IASLC HISTORY

CELEBRATING 50 YEARS IASLC 1974–2024

ADVANCES IN THORACIC ONCOLOGY TREATMENT AND RESEARCH

LEGACY OF IMPACT, FUTURE OF PROMISE

Edited by Fred R. Hirsch, MD, PhD and Paul A. Bunn, Jr., MD

IASLC HISTORY

ADVANCES IN THORACIC ONCOLOGY TREATMENT AND RESEARCH

LEGACY OF IMPACT, FUTURE OF PROMISE

Edited by Fred R. Hirsch, MD, PhD and Paul A. Bunn, Jr., MD

Published for the
International Association of the Study of Lung Cancer
By Editorial Rx Press

IASLC Headquarters
1775 N. Sherman Street
Suite 1600, Denver, USA
80203-4317
IASLC CEO: Karen Kelly, MD

Editorial Rx Press
Bee Communication, LLC
PO Box 974
N. Eastham, USA
02651

Copyright © International Association of the Study of Lung Cancer
All rights reserved

ISBN 978-1-947768-03-1

First printing September 2024
10 9 8 7 6 5 4 3 2 1

Printed in the United States of America
Original cover and book layout design by Biographics
Managing Editor and Publisher: Deb Whippen, Editorial Rx Press
IASLC Headquarters Publisher: Jan Mazotti

CONTENTS

PART I. ABOUT IASLC

1 50-YEAR OVERVIEW OF IASLC 3
2 IASLC GOVERNANCE 14
3 THE IASLC WORLD CONFERENCE ON LUNG CANCER 17
4 IASLC AWARDS, FELLOWSHIPS, AND RESEARCH GRANTS. 30
5 OTHER IASLC MEETINGS/WEBINARS 47
6 IASLC JOURNALS. 54
7 IASLC PUBLICATIONS 61
8 PATHOLOGY COMMITTEE 65
9 STAGING AND PROGNOSTIC FACTORS COMMITTEE 86
10 LUNG CANCER PATIENT ADVOCACY AT THE IASLC. 101

PART II. ADVANCES IN THORACIC ONCOLOGY TREATMENT AND RESEARCH

11 LUNG CANCER CAUSATION AND PREVENTION 109
12 EARLY DETECTION IN LUNG CANCER: A HISTORICAL OVERVIEW 127
13 BIOLOGY. 159
14 PATHOLOGY AND BIOMARKERS 194
15 SURGICAL ADVANCES AND SURGERY 209
16 ADVANCES IN RADIATION ONCOLOGY 230
17 CHEMOTHERAPY FOR METASTATIC NON-SMALL CELL LUNG CANCER 239
18 PROGRESS IN SMALL CELL LUNG CANCER: CELEBRATING 50 YEARS 259
19 ADVANCES IN MOLECULAR THERAPY. 272
20 LUNG CANCER - ADVANCES IN IMMUNOTHERAPY 294
21 ADVANCES IN COMBINED MODALITY THERAPY FOR NSCLC 324
22 LUNG CANCER - ADVANCES IN SUPPORTIVE CARE 335
23 MESOTHELIOMA. 351
24 ADVANCES IN THE TREATMENT OF THYMIC MALIGNANCIES 361
25 NURSE AND ALLLIED HEALTH PROFESSIONALS 372

DEDICATION

To those who fought before against lung cancer through research and care, those who are dedicated today to eradicating thoracic malignancies, and those who will lead us into tomorrow as we strive to conquer this disease.

To the patients and survivors who inspire us always.

PART I

ABOUT IASLC

ABOUT IASLC

IASLC MISSION

Be the multidisciplinary world authority on lung and other thoracic cancers through collaborative science, education, and advocacy in order to ensure optimal prevention and patient care.

1

50-YEAR OVERVIEW OF IASLC

In the early 1970s the International Association for the Study of Lung Cancer (IASLC) embarked on its member-driven mission to study and eradicate lung cancer and other thoracic malignancies. Inspired by its members across the globe and guided by the Board of Directors and executive leaders (Box 1), for the past half a century IASLC has led international efforts to reduce lung cancer mortality rates by hosting global conferences and funding cutting-edge research and training; by publishing journals, books, guidelines; and by supporting patient advocates and the patient community.

IASLC is now celebrating 50 years of impact, which has included offering education for the health care community and the public about thoracic cancers. As the global leader in lung cancer information and education, IASLC programs, publications, and policy statements have been designed, ultimately and always, to alleviate the burden lung cancer places on patients, families, and communities.

WHY IS IT IMPORTANT TO COMMEMORATE IASLC'S 50-YEAR HISTORY?

IASLC's membership includes the leaders and professional worldwide community involved in the historic development of lung cancer therapy and management. As a global medical society, IASLC collectively has a shared identity and sense of purpose and commitment. To continue the efforts to decrease mortality from thoracic cancers it is important to understand what has worked well and not as well.

Pia Hirsch
Historical Executive Staff Leader, 2003-2018

In this publication IASLC members share the story of progress in the field of thoracic oncology over the last half century, with a focus on the most recent history in our rapidly evolving field, a story that parallels and often is driven by the organizational growth of the IASLC and its mission in action.

IASLC MISSION

Be the multidisciplinary world authority on lung and other thoracic cancers through collaborative science, education, and advocacy in order to ensure optimal prevention and patient care.

Box 1. IASLC Executive Leaders 1994-Present

Karen Kelly, MD
Chief Executive Officer, 2022-present

Dave Mesko, MBA
Chief Executive Officer, 2018-2022

Fred R. Hirsch, MD, PhD
Chief Executive Officer, 2013-2018

Paul A. Bunn, Jr., MD
Executive Director, 2003-2013

Heine Høi Hansen, MD
Executive Director, 1994-2003

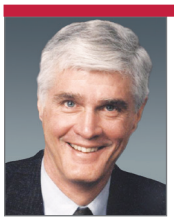
BOARD OFFICERS 2023-2025

President: Paul Van Schil, Belgium
President-Elect: Caicun Zhou, China
Past President: Heather Wakelee, USA
Chief Executive Officer: Karen Kelly, USA
Secretary: Ming-Sound Tsao, Canada
Treasurer: Joachim Aerts, Netherlands

BOARD MEMBERS 2023-2025

Directors: Joe Chang, USA
Carlos Gil Moreira Ferreira, Brazil
Jhanelle Gray, USA
Young Tae Kim, South Korea
Natasha Leighl, Canada
Morten Quist, Denmark
Antoni Rosell, Spain
Lecia Sequist, USA
Benjamin Solomon, Australia
Paula Ugalde, USA
Ignacio Wistuba, USA
Wen-Zhao Zhong, China

› *Visit https://www.iaslc.org/about-us/board-directors for the listing of past IASLC Officers and Board Members.*



Paul Bunn, Jr., MD
IASLC President 1994-1997;
IASLC Executive Director 2003-2013

"The IASLC's organizational vision of conquering lung and other thoracic cancers worldwide looks ahead to the future of lung cancer medicine and to continuing the global progress in lung cancer through research, education, prevention, and treatment in a multidisciplinary manner."

CURRENT COMMITTEES AND CHAIRS (2023-2025 TERM)

Basic & Translational Science Committee Chair:
Celine Mascaux, France

Career Development Committee Chair:
Tindara Franchina, Italy

Communications Committee Chair:
Jarushka Naidoo, Ireland

Education Committee Chair:
Pranshu Mohindra, USA

Global Multidisciplinary Practice Standards Committee (GMPSC) Chair:
Nir Piled, Israel

Global Policy and Partnerships Committee Chair:
Andreas Charalambous, Cyprus

Membership Committee Chair:
Sudish Murthy, USA

Multidisciplinary Clinical Science Committee Chair:
Tom Stinchcombe, USA

Nurses & Allied Health Professionals Committee Chair: Michelle Turner, USA

Pathology Committee Chair:
Sanja Dacic, USA

Patient Advocates Committee Chair:
Shani Shilo, Israel

Rare Tumors Committee Chair:
Paul Bass, Netherlands

Screening & Early Detection Committee Chair:
Annette McWilliams, Australia

Tobacco Control & Smoking Cessation Committee Chair: Joelle Fathi, USA

› *Visit https://www.iaslc.org/about-us/iaslc-committees for the listing of current committee members and past IASLC Committee Chairs.*

IASLC MEMBERSHIP. Over the last decade since the publication of IASLC's 40-year history anniversary,[1] the IASLC membership has increased considerably (Figure 1). During Dr. Hirsch's leadership as Executive Director, the membership increased from 3,200 members (2012) to a peak of more than 11,300 members in 2023. Not only did the number of members increase, but also the representation of different disciplines. Patient advocacy groups became much more involved in IASLC activities over this period of time, and in 2016 a coalition (LCAM) was formed consisting of IASLC in partnership with a number of patient advocacy groups to better promote Lung Cancer Awareness Month in November. During the same time period the IASLC 's financial assets also increased significantly (Figure 2), which allowed IASLC to expand the IASLC Headquarters; the number of IASLC employees increased from 5 (2013) to 23 (2018) and in 2024 further expanded to 35 staff, offering members more member benefits and delivering IASLC's mission further even further across the globe. Most lately in 2020 IASLC's offices moved to a new Headquarter in downtown Denver, USA, to better facilitate organizational operations.

Heather Wakelee, MD
IASLC Immediate Past-President
2021-2023

"The IASLC provides forums for intellectual exchange of new data and offers opportunity to engage with others doing similar work in a way that few other societies can. We are also truly multidisciplinary and international."

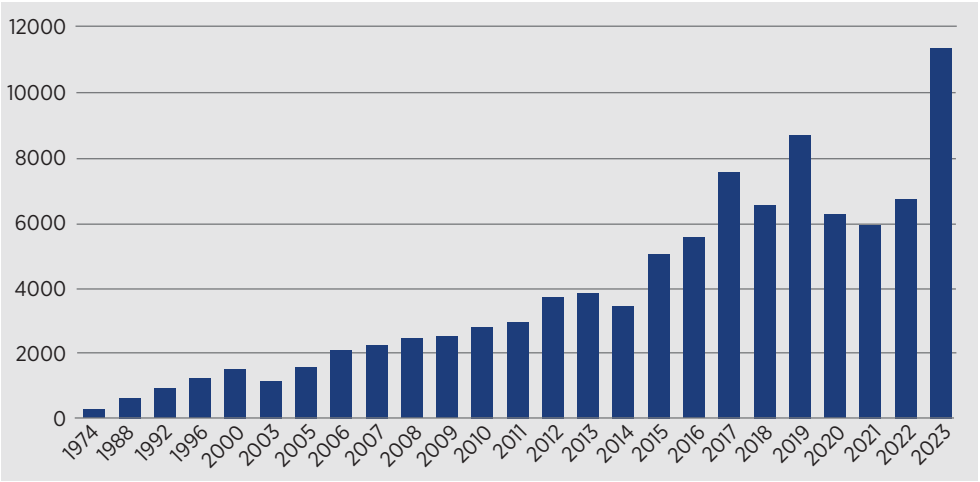


Figure 1. Growth in Membership.
Source: IASLC headquarters.

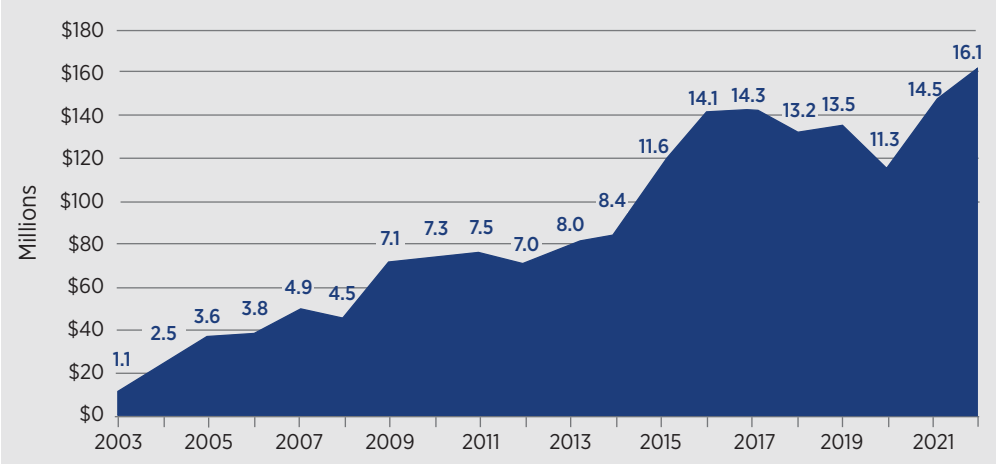


Figure 2. IASLC Assets 2012-2021.
Source: IASLC headquarters.

WORLD CONFERENCE ON LUNG CANCER. Several other significant changes were made during those years, which has shaped the organization's progress. Among these achievements were turning the World Conference on Lung Cancer (WCLC) into a successful annual event from being held as bi-annual meetings. Some skepticisms were put to rest when WCLC could host about 8,000 participants at peak in Toronto 2018. Also, the number of abstract presentations were increased similarly. Thus, the annual WCLC made IASLC the main lung cancer event of the year (further details provided in Chapter 2).

Heine Høi Hansen, MD
IASLC President 1988-1991; IASLC first Executive Director, 1994-2003

"In October 1972, the First International Workshop for Therapy of Lung Cancer was held at Airlie Conference Center in Virginia. This conference, sponsored by the US National Cancer Institute (NCI), drew together 115 individuals from 15 countries, representing all disciplines of medicine involved in lung cancer. The interchange of ideas among this multi-disciplinary international group was both productive and stimulating. At the concluding meeting, held on October 20, 1972, Dr. David T. Carr, USA, introduced the idea of forming an international organization to continue this fruitful exchange of ideas."

JOURNAL OF THORACIC ONCOLOGY. IASLC's official journal, the *Journal of Thoracic Oncology* (JTO), underwent a significant strategic change in 2015 as the IASLC decided to change publishers from Lippincott to Elsevier and at the same time expand the journal's scientific breadth and reach, including electronically (Figure 3). In 2013, Editor-in-Chief, Dr. Alex Adjei, who succeeded Dr. James Jett, set goals to increase the JTO impact factor, which he did, as it's risen from 4.0 to >20. This impressive feat has lifted the IASLC journal to one of the most recognized and impactful oncology journals. Its sister open access journal, *JTO Clinical and Research Reports*, led by Editor-in-Chief Dr. Emily Stone, was launched in January 2020, and is now fully indexed with its own impact factor (first impact factor 1.4). Also, during the last decade an IASLC news magazine (later electronically distributed as *IASLC Lung Cancer News* [ILCN]) was established under the editorship of Dr. Corey Langer to better inform the membership of the organization's activities.

Figure 3. JTO Cover.

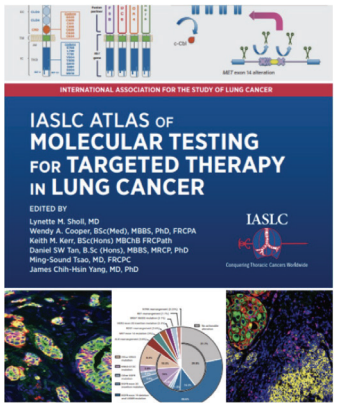


Figure 4. *Atlas of Molecular Testing for Targeted Therapy in Lung Cancer* Cover.

IASLC STAGING PUBLICATIONS AND ATLASES. Following publication in 2009 of the first edition of the *IASLC Staging Manual in Thoracic Oncology*, IASLC produced several atlases dealing with a range of lung cancer biomarker testing topics, including ALK, ROS1, EGFR, and PD-L1, and an atlas on immunohistochemistry for lung cancer diagnosis. The most recent, the 2023 *IASLC Atlas of Molecular Testing for Targeted Therapy in Lung Cancer*, provides a comprehensive overview of all current and emerging molecular targets, specimen acquisition, available assays, and reporting and interpretation of molecular testing results from both a diagnostic and clinical perspective (Figure 4).

IASLC FOUNDATION. In 2015 the IASLC Board of Directors decided to establish an IASLC Foundation.[2] The purpose was to focus on increasing the number of IASLC grants and fellowships and to have a dedicated forum for these purposes. In 2023, the IASLC Foundation awarded nine research grants totaling $750,000. This year's grant recipients represent another diverse group of researchers from around the world. IASLC Foundation Research Grants are made possible by donations from individual donors, foundation partners, and pharmaceutical companies and foundations.

GLOBAL MEETINGS. Under Dr. Paul Bunn's leadership, IASLC regional scientific and educational meetings were established, such as the IASLC Latin America Conference on Lung Cancer (2004),[3] Asia Conference on Lung Cancer (2004),[4] the North America Conference on Lung Cancer (2001),[5] and the European Lung Cancer Congress (2008).[6] Organized by the IASLC with the European Society of Medical Oncology, this latter meeting is a collaborative effort of the most important multidisciplinary societies representing thoracic oncology specialists, working together to advance science, disseminate education and improve the practice of lung cancer specialists worldwide. All of these meetings are of significant importance for collaborations and have grown significantly over the last decade, sparking vital developments in lung cancer research and education in the respective regions.

Fred R. Hirsch, MD, PhD
IASLC CEO 2013-2018

"Through bringing young and more established investigators from different disciplines and with different expertise from different nations together in one 'family'—that is what leads to fruitful collaborations and scientific progress. That is how IASLC, over 50 years, has succeeded to the benefit of our patients."

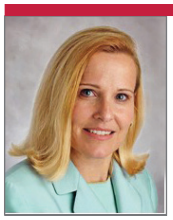
FUTURE DIRECTIONS

As we relish in the many accomplishments the IASLC has made over the past fifty years, we recognize that there is more work to be done to accomplish our vision. While nations like the United States have witnessed a significant decline in lung cancer mortality over the past 30 years due to effective tobacco control, comprehensive screening programs, and innovative treatments, the worldwide statistics are less encouraging with GLOBOCAN 2020 reporting a 30% rise in lung cancer mortality by 2030.[7] Disturbingly, 70% of these deaths are concentrated in low- and middle-income nations.[8] Consequently, the economic burden of lung cancer healthcare far exceeds that of other cancers.[9]

The IASLC is uniquely positioned to alter the trajectory of lung cancer mortality. The new 2024-2029 strategic plan to conquer lung cancer and other thoracic malignancies in the 21st century is a bold testimony to this goal. Fostering an environment conducive to swift research advances and prompt educational dissemination and clinical implementation, reinforced through local community-driven actions and policy-level changes was central to designing our strategic plan. The plan is cemented in three pillars: 1) collaborative science—advancing scientific knowledge of thoracic cancers to improve all aspects of prevention and patient care; 2) global education—delivering leading edge knowledge worldwide to effectively prevent and combat thoracic cancers and 3) promote accessible multidisciplinary care—transforming scientific advancements into actionable patient-centered interventions. Our diverse member base, drawn from every corner of the globe and representing a myriad of disciplines, are key to enact and realizing the goals. By creating new committees in basic and translational science, multidisciplinary clinical science that

includes our highly valued TNM staging project, rare tumors, global multidisciplinary standards and global policy and partnership and refreshing our existing committees in pathology, education, communication, early detection and screening, tobacco control and smoking cessation, nursing and allied health, and patient advocacy we are better positioned to cater to the dynamic needs of the worldwide thoracic cancer community, propelling us closer to our vision. Essential to propagating our mission and vision requires attention to our members career journey from early, mid, and late phases therefore we have reimagined our career development committee, charging them with creating and sustaining initiatives across this journey. Assisting this committee is the IASLC Foundation, whose members are dedicated to expanding their fundraising activities for research projects.

The revised strategic plan prominently highlights four fundamental elements that are woven into its core: global inclusion, member support, multidisciplinary collaboration, and commitment to patients (Figure 5). The IASLC is proud to be an early adopter of valuing diversity, as well as consistently prioritizing gender, regional, and specialty representation in all our endeavors. However, our commitment doesn't end there. With a record number of 10,000+ IASLC members, we must delve deeper into the realms of diversity, inclusion, and equity (DEI). To this end, we've established a dedicated DEI taskforce. This team is set to engage with our members to gain insights and chart a path forward with continuous monitoring for adaptability. The IASLC is determined to channel its efforts, particularly where the stakes are highest - in low- and middle-income countries. We've taken concrete steps by launching member-driven regional taskforces ensuring we're tailoring our approach based on regional characteristics. Simultaneously, we're amplifying our initiatives in Latin America. The IASLC is a leader in consistently championing patient's rights, needs, and voices by integrating and elevating patient perspectives into our research, education and clinical



Karen Kelly, MD
IASLC CEO 2022-present

"Today there is so much going on in the world of thoracic oncology. We have the largest arsenal of tools to defeat lung cancer than we've ever had.... The challenge is how do we implement these great advances on a global scale? That is what I and the IASLC, is committed to—increasing our global presence. Making sure the patient and the doctor have all the tools they need to find the best opportunity to cure. And to continue to work with our advocates to raise awareness about all the facets of this disease. It does truly take a village to conquer thoracic cancers worldwide."

Figure 5. Revised IASLC Strategic Plan.

practice. The exchange of experiences and knowledge between patients and members is deeply inspiring, they are the reasons behind our endeavors. That's why our updated strategic plan places patients at the heart of our initiatives.

Our aspirations require collective efforts. Recognizing this, we're broadening our partnership portfolio to include international and diverse professional entities, advocacy groups, industry stakeholders, and governmental agencies. Together, with collective resolve and actionable strategies, we can accelerate worldwide progress in combating thoracic cancers.

In summary, the journey of the IASLC over the past half-century underscores the relentless pursuit of excellence, innovation, and genuine care for patients. As we move forward, guided by our renewed strategic plan and driven by our diverse membership, it's imperative to remember the challenge of thoracic cancers remains a global one, and it demands our consistent collaboration, adaptability, and unwavering commitment. Through unity, tenacity, creativity, and the collective wealth of experience and knowledge among our members, we stand poised to make an even greater impact in the next chapter of our story. The IASLC remains steadfast in its mission, ever motivated by the lives we touch and the profound difference we can make in the global battle against thoracic cancers.

Paul Van Schil, MD, PhD
IASLC President 2023-2025

"These are fascinating times for thoracic surgeons. Sublobar resections for the smallest lung cancers and neoadjuvant treatment including immunotherapy have almost become part of our daily practice although many questions remain to be answered."

Tetsuya Mitsudomi, MD
IASLC President 2019-2021

"I think this is an exciting time in thoracic oncology. There has been so much progress over the last 30-40 years. No one can predict what is happening after 5 years or what will become the standards for our patients. IASLC meetings help organize your knowledge about lung cancer, and also you make friends at these meetings, which is a very important aspect of the IASLC. Without the IASLC, my life as a doctor would be very different."

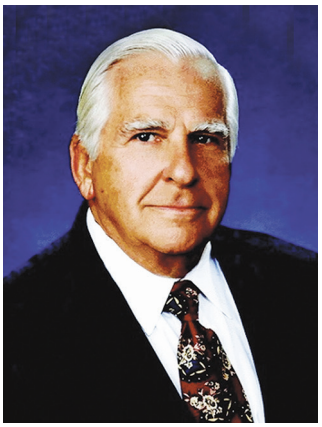
References

1. Bunn PA, Hirsch FR, editors. IASLC Progress in Lung Cancer: Celebrating 40 Years 1974-2013. IASLC Press. Aurora, CO. 2013
2. International Lung Cancer Foundation. International Association for the Study of Lung Cancer. Accessed October 18, 2022. https://www.iaslc.org/international-lung-cancer-foundation
3. IASLC Latin America Conference on Lung Cancer. International Association for the Study of Lung Cancer. Accessed October 18, 2022. https://lalca2023.iaslc.org/
4. IASLC Asian Conference on Lung Cancer. International Association for the Study of Lung Cancer. Accessed October 18, 2022. https://aclc2022.iaslc.org/
5. IASLC North America Conference on Lung Cancer. International Association for the Study of Lung Cancer. Accessed October 18, 2022. https://www.iaslc.org/meetings-webinars/iaslc-2023-north-america-conference-lung-cancer
6. European Lung Cancer Congress. International Association for the Study of Lung Cancer. Accessed October 18, 2022. https://www.iaslc.org/meetings-webinars/2023-european-lung-cancer-congress
7. Sung H, Ferlay F, Seigel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide from 36 Cancers in 185 Countries. *CA Cancer J Clin.* 2021; 71:209-249.
8. WHO International Agency for Research on Cancer. Estimated number of deaths in 2020, all cancers, both sexes, all ages. Cancer today. Published 2020. Accessed April 7, 2024. https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=population&modepopulation=income&population=900&populations=900&key=total&sex=0&cancer=39&type=1&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmsc=1&include_nmsc_other=1&half_pie=0&donut=0
9. Chen S, Cao Z, Prettner K, et al. Estimates and Projections of the Global Economic Cost of 29 Cancers in 204 Countries and Territories From 2020 to 2050. *JAMA Oncology*. 2023;9:465-472.

IASLC PRESIDENTS

Oleg Selawry
1974-1976

David Carr
1976-1977



Clifton Mountain
1977-1978

George Higgins
1978-1980

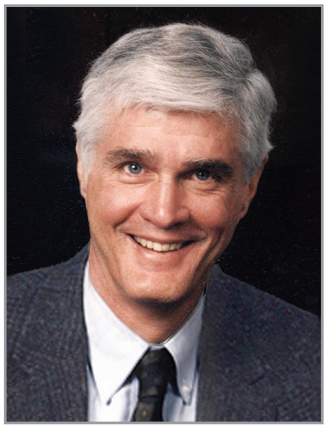
Pierre Alberto
1980-1982

Shiohiro Ishikawa
1982-1985

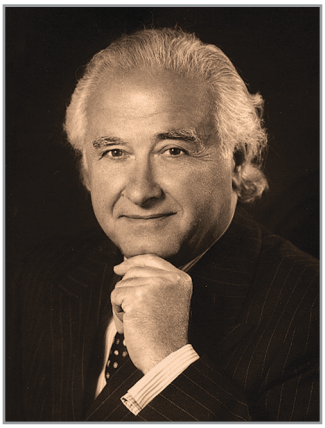
Ronald Vincent
1985-1988

Heine Hansen
1988-1991

Yoshihiro Hayata
1991-1994



Paul Bunn, Jr.
1994-1997



Giovanni Motta
1997-2000

Harubui Kato
2000-2003

Frances Shepherd
2003-2005

Desmond Carney
2005-2007

Nagahiro Saijo
2007-2009

David Gandara
2009-2011

Peter Goldstraw
2011-2013

Tony Mok
2013-2015

David Carbone
2015-2017

Georgio V. Scagliotti
2017-2019

Tetsuya Mitsudomi
2019-2021

Heather Wakelee
2021-2023

Paul Van Schil
2023-2025

Caicun Zhou
2025-2027

IASLC COMMITTEES

IASLC organizational committees contribute to the effective operation and development of IASLC programs. Comprising every specialty in lung cancer including patient advocacy, IASLC committees are at the heart of the society. IASLC committee members contribute their specialized skills and talents to help shape the work of the organization, develop educational content, shape the association's messaging, plan annual meetings, contribute to publications authored by the IASLC and more.

In addition to the historical profiles provided by leaders of the Pathology Committee, Staging Committee, and Patient Advocates Committee in the chapters that follow, here is listing of current IASLC Committees, which represent both the breath of IASLC activities as well as the past and present accomplishments of IASLC volunteer leaders.

ADVANCED RADIATION TECHNOLOGY COMMITTEE

The Advanced Radiation Technology (ART) Committee focuses on educating members about emerging techniques, technologies, and strategies for treating thoracic malignancies.

CAREER DEVELOPMENT AND FELLOWSHIP COMMITTEE

The Career Development and Fellowship Committee focuses on supporting the next generation of lung cancer specialists.

COMMUNICATIONS COMMITTEE

The Communications Committee develops campaigns to increase IASLC brand recognition and credibility while educating the public about complex lung and thoracic cancer issues. The committee also reviews articles for publication in the *Journal of Thoracic Oncology* and determines which pieces to promote to the media.

CONTINUING MEDICAL EDUCATION COMMITTEE

The Continuing Medical Education (CME) Committee oversees the educational program of IASLC to ensure that activities are planned and implemented in compliance with all ACCME Accreditation Requirements, including the ACCME Standards for Commercial Support℠. The CME Committee is also responsible for ensuring that IASLC's CME activities meet the requirements of the American Medical Association Physician's Recognition Award (AMA PRA).

EDUCATION COMMITTEE

The Education Committee plans and implements educational activities in accordance with IASLC's mission of providing education and information about lung cancer and other thoracic malignancies to IASLC members, to the medical community at large, and to the public.

MEMBERSHIP COMMITTEE

The Membership Committee reviews and recommends membership status requirements and benefits for all IASLC members. Members of this committee also strategize and implement tactics to increase and retain association membership in their area of specialty and region.

COMMITTEES

MESOTHELIOMA COMMITTEE

Mesothelioma is a rare tumor with limited options that has seen several research updates in 2020, many of which were spearheaded by members of this committee.

NURSES AND ALLIED HEALTH PROFESSIONALS COMMITTEE

The Nursing & Allied Health Professionals Committee (NAHP) within IASLC is comprised of multidisciplinary clinicians and researchers each with a unique perspective, committed to advancing the education of both practitioners and patients in thoracic oncology. Their goal is to improve and optimize outcomes for oncology patients and families across the cancer trajectory through diagnosis, treatment, survivorship, and end-of-life.

PATHOLOGY COMMITTEE

For more than 35 years, the IASLC Pathology Committee has played a fundamental role in fulfilling core aspects of the association's mission. See Chapter 8.

PATIENT ADVOCATES COMMITTEE

The Patient Advocates Committee ensures that the IASLC addresses the informational needs of the public, advocates, and patients living with lung and thoracic cancers. This committee also comprehensively addresses the educational and related needs of the public as an important constituency in the work of the association. See Chapter 10.

SCREENING AND EARLY DETECTION COMMITTEE

The Screening and Early Detection Committee provides leadership and oversight of IASLC activities in these areas. The committee works with appropriate internal committees to enhance the quality and quantity of IASLC cancer prevention initiatives and provides leadership in partnership with other societies in the area of cancer prevention and screening.

STAGING AND PROGNOSTIC FACTORS COMMITTEE

Staging lung cancer and other thoracic malignancies accurately is critical in deciding treatment regimens and ensures best standardized care for patients worldwide. The IASLC Staging Project is a global effort to study and improve the current staging system for lung cancer, as well as for thymic and esophageal cancers and mesothelioma. See Chapter 9.

TOBACCO CONTROL AND SMOKING CESSATION COMMITTEE

Improving patient care by raising awareness of cessation-related data and by provision of information regarding the latest and most successful cessation techniques for patients with lung cancer.

2

IASLC GOVERNANCE

The International Association for the Study of Lung Cancer (IASLC), headquartered in Denver, USA since 2003, operates within the regulatory framework of the state of Colorado. Its journey began with the formalization of its legal status as a nonprofit entity, a process initiated by filing and obtaining approval of its articles of incorporation. Since its inception in 1974, the IASLC has adhered to its bylaws, which serve as the cornerstone of its operations. These bylaws outline the organization's structure, defining roles, responsibilities, and processes crucial for ensuring adherence to its mission.

During its 50-year history the purpose and mission of the IASLC have continued unchanged, with a more detailed description approved by the Board of Directors in 2013 that remains today:

a) Advancing the study, prevention, diagnosis, and treatment of lung cancer and thoracic malignancies.

b) Disseminating knowledge about these diseases to its members, the broader medical community, and the public.

c) Employing all available means to eradicate lung cancer and thoracic malignancies as significant health threats worldwide.

Recognizing the need to address systemic disparities that impact access to research funding and healthcare for patients with lung cancer and thoracic malignancies, the IASLC expanded its mission in 2021. This expansion led to the establishment of a dedicated Diversity, Equity, and Inclusion (DEI) Task Force charged with identifying and overcoming barriers hindering progress in these areas. Consequently, access to care was elevated as a key priority for the IASLC in the 2024 strategic plan.

Regular reviews and amendments to the governing articles of incorporation and bylaws historically have been and are undertaken to address the dynamic needs of the organization. In 2019, this review included updates, clarifications, additions, and deletions to these governing documents as proposed by the Governance Committee and subsequently approved by the members for the purpose of providing clearer policies and procedures around membership, the Board of Directors, officers, and indemnification. A Conflict-of-Interest Policy, Document Retention Policy, and Whistleblower Policy were added.

The governance structure of the IASLC is characterized by several groups, each playing a vital role in organizational oversight and decision-making:

The **Board of Directors** consists of a minimum of 10 and a maximum of 20 members who are elected by the membership and who serve a 4-year term. The President, President-Elect, and Past President serve 2-year terms each for a total of 6 years. The President is the Chair of the Board and the Executive Committee. Board members are required to attend all Board meetings, which are regularly held on a quarterly basis. They are responsible for ensuring that the IASLC abides by its bylaws and creates and implements a strategic vision. The "majority rule" for approval or dissention applies to all voting measures and are recorded.

The **Executive Committee**, comprising key leadership positions including the President, President-Elect, Past President, Secretary, Treasurer, and Chief

Executive Officer (CEO), is entrusted with transacting routine business between Board meetings, guided by the principle of majority rule.

To ensure prudent self-regulation, the bylaws established several committees composed of members of the Board:

The **Governance Committee** maintains the integrity of the association's governing documents, proposing revisions, as needed, to align with evolving governance standards and the diverse needs of its international membership. Moreover, the committee oversees the implementation of the Conflict of Interest Policy.

The **Finance Committee** meticulously evaluates the annual budget crafted in collaboration with the Chief Financial Officer, ensuring financial prudence and sustainability. Additionally, the Committee reviews the performance of the association's investment portfolio and advises on necessary adjustments.

The **Audit Committee** safeguards the integrity of the organization's internal controls, risk management practices, and financial reporting. It liaises with independent audit firms, facilitating comprehensive audits and ensuring compliance with legal and ethical standards.

The **Nominating Committee** is tasked with identifying and recommending qualified candidates for leadership positions within the organization, ensuring robust representation and diverse perspectives.

In addition to these governing bodies, the IASLC has several working committees, comprising experts with multidisciplinary expertise in thoracic malignancies. These committees convene to address a wide array of pertinent topics, leveraging collective knowledge and consensus-building to drive progress in the field. Additional task forces and panels are established at the discretion of the Board.

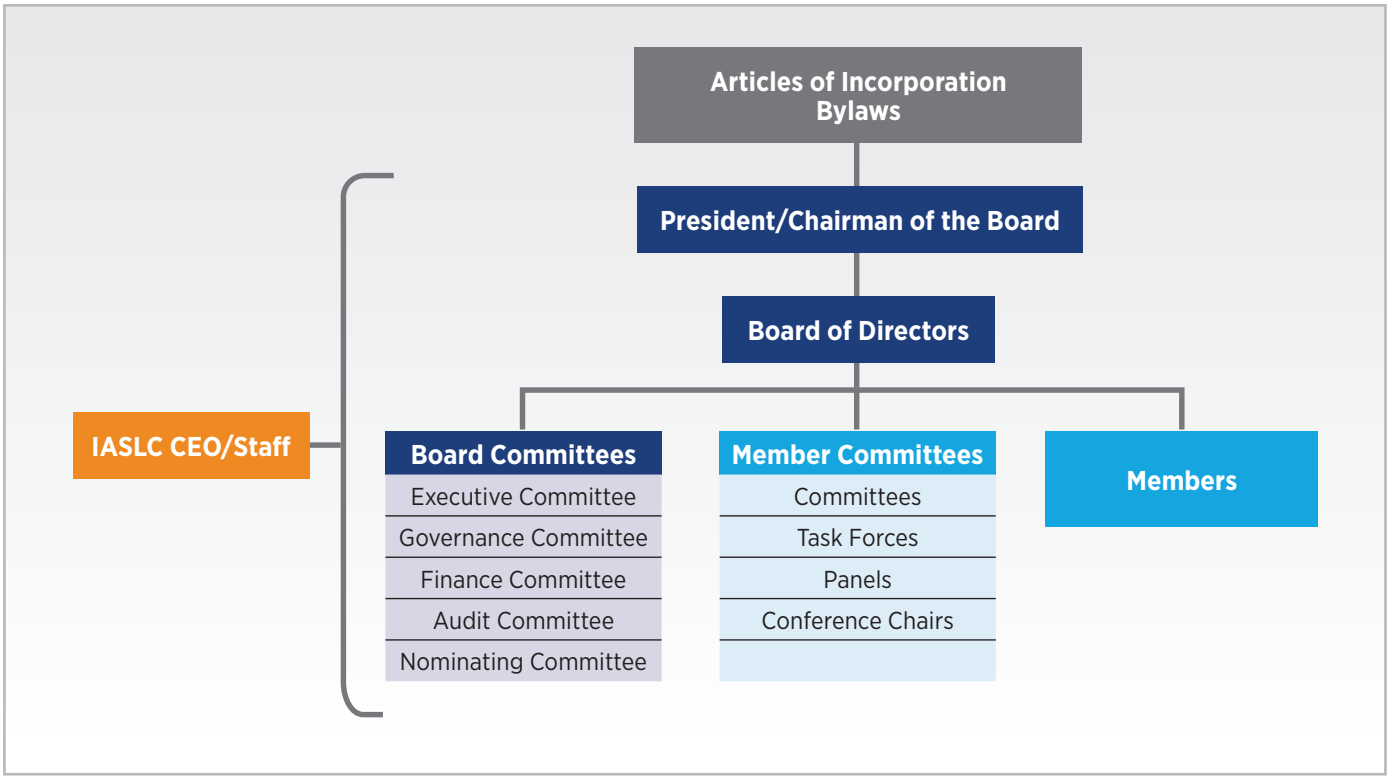


Figure. IASLC Governance and Organizational Structure.

At the heart of the IASLC are its members, who form a vibrant community dedicated to the shared goal of combating thoracic malignancies. To accommodate the diverse needs and interests of its membership base, the Association offers various membership categories and dues structures. Active members enjoy numerous privileges, including eligibility for leadership roles, participation in conferences, speaking engagements, and voting rights in all elections.

Under the stewardship of the CEO, the IASLC's strategic direction is realized through effective staff management and implementation of the strategic plan. This plan, revisited every five years, serves as a roadmap for organizational growth and impact. Notably, the strategic plan underwent significant revisions in 2018 and 2023, reflecting the evolving landscape of thoracic oncology and the organization's strategic priorities. The CEO, supported by a dynamic leadership team and staff, ensures alignment between organizational objectives and operational initiatives.

Over the past decade, the IASLC has experienced fluctuations in its staffing levels, driven by various factors. However, under the leadership of CEO Dr. Karen Kelly, operational restructuring efforts have yielded substantial staff growth and retention. The executive team, comprising the Chief Operating Officer, Chief Scientific Officer, Chief Financial Officer, and Chief Development Officer, collaborates seamlessly to advance the association's mission. Additionally, the establishment of a dedicated Department of Information Technology (IT) and the hiring of a Director of Strategic Initiatives underscore the organization's commitment to innovation and strategic foresight. Furthermore, the appointment of a Director of Human Resources in 2019 has ensured a supportive work environment conducive to staff well-being and professional development.

In summary, the IASLC remains steadfast in its commitment to advancing the study and treatment of thoracic malignancies, guided by a robust governance framework and an engaged membership. Through strategic planning, effective governance, and dedicated leadership, the Association continues to make significant strides in its mission to eliminate lung cancer and thoracic malignancies as global health threats.

3

THE IASLC WORLD CONFERENCE ON LUNG CANCER

Since the inception of the IASLC, its premier and most important event has been the World Conference on Lung Cancer (WCLCs). The goals of this conference are to disseminate education and research progress on thoracic cancers worldwide. Also, the WCLC has been the forum where younger and more established investigators from different specialties and different countries have come together in order to establish an international collaborative culture. Furthermore, the WCLC has become an important event for industry and academia to meet and exchange ideas and to establish collaborations. The programmatic topics have typically been prevention, screening, diagnosis, staging, therapy, supportive care, basic research, and multidisciplinary care including surgery, radiation therapy, medical oncology, nursing, psychosocial support, patient advocacy, and related studies.

From a very modest beginning with several hundred participants at the first WCLC in the USA in 1978, the meeting has grown to the largest worldwide meeting on thoracic cancers. For the first WCLC in Hilton Head, SC, USA, in 1978 until the 10th meeting in Vancouver, Canada, in 2003, the meeting was held every 3 years, which was felt to be sufficient to accommodate presentations of the most important research advances. Over time, the increasing rapidity of medical advances in all fields, the increasing number of disciplines involved in thoracic cancer research, the increasing number of submitted abstracts, the increasing number of attendees, the increasing number of countries submitting abstracts sending attendees all justified more frequent meetings. The WCLCs were transformed to biannual (from 2003-2015) and from 2015 onward to annual WCLCs. Table 1 shows the locations, dates,

Table 1. IASLC WCLCs and Conference Presidents/Chairs from 2011 through 2024

WCLC	Location	Conference Presidents/Chairs	Date
14	Amsterdam	Prof. Postmus, Dr. van Zandwijk	July 3-7, 2011
15	Sydney	Dr. Boyer, Dr. Fong	October 27-30, 2013
16	Denver	Dr. Hirsch	September 6-10, 2015
17	Vienna	Dr. Pirker	December 4-7, 2016
18	Yokohama	Dr. Park, Dr. Asamura	October 15-18, 2017
19	Toronto	Dr. Shepherd, Dr. Leighl, Dr. Bezjak, Dr. Darling	September 23-26, 2018
2019 (20th)	Barcelona	Dr. Rami-Porta, Dr. Rosell, Dr. Felip	September 7-10, 2019
2020 (21st)	Singapore (virtual)	Dr. Wu, Dr. Soo, Dr. Tan	January 28-31, 2021
2021 (22nd)	Denver (virtual)	Dr. Harpole, Dr. Higgins, Dr. Stinchcombe	September 8-14, 2021
2022 (23rd)	Vienna	Dr. Pirker, Dr. Lim, Dr. Mornex, Dr. Novello, Dr. Prosch	August 6-9, 2022
2023 (24th)	Singapore	Dr. P. Lee, Dr. C. Lee, Dr. Hegi-Johnson	September 9-12, 2023
2024 (25th)	San Diego	Dr. Patel, Dr. Martin, Dr. Florez, Dr. Moraes	September 7–10, 2024

and Congress Presidents/Chairs of each WCLC from 2011 through 2024. The number of attendees and the number of abstracts for each WCLC are shown in Figure 1, and Figure 2 shows the number of countries represented.

The history of the WCLCs during the first 40 years of the IASLC was well documented in the 35- and 40-year History of the IASLC books. The international make-up of the IASLC led the Board to rotate the physical location of the WCLCs to different regions of the world. These regions were defined as the Americas, Europe, and Asia/Rest of world. The location of each WCLC since 2011 is shown in Table 1. In recognition that travel to distant parts of the world would limit in-person attendance at distant locations, the IASLC Board also instituted regional meetings in North America, Europe, Latin America, and Asia to be held yearly or at least in years when the IASLC's WCLC was held in other regions. Descriptions of these regional meetings are provided in Chapter 5.

In early years, as the site of the WCLCs rotated, the IASLC Board would solicit applications for the site city to hold the WCLC in the region of the meeting. Members submitted applications to hold the meeting in their home city. The IASLC Board then selected the best sites and held site visits to each of the selected sites. Many of these site visits were remarkable in their variety and competition. Select members of the IASLC Board of Directors and Chief Executive Officer participated in many site visits, which often included several local dignitaries, i.e., meetings with London's Mayor, Boris Johnson, later the United Kingdom Prime Minister, Professor Lord Darzi, the United Kingdom Health Minister, and an invited visit at the Hofburg Palace in Vienna with the Chancellor/President of Austria, Dr. Heinz Fisher. Over time, these site visits and city rotations became quite expensive and contentious. Thus, the Board decided to limit the number of sites, especially in North America and Europe, focusing on Denver, USA, and San Diego, USA, and Vienna, Austria, and Barcelona, Spain, in Europe. Members from the region could submit applications to serve as the Conference Chairs. Previously, The Board of Directors usually invited an established IASLC member to serve as Conference President, who also had a seat at the Board of Directors. Later, the IASLC Board selected Conference Chairs who in turn selected the Organizing Committee.

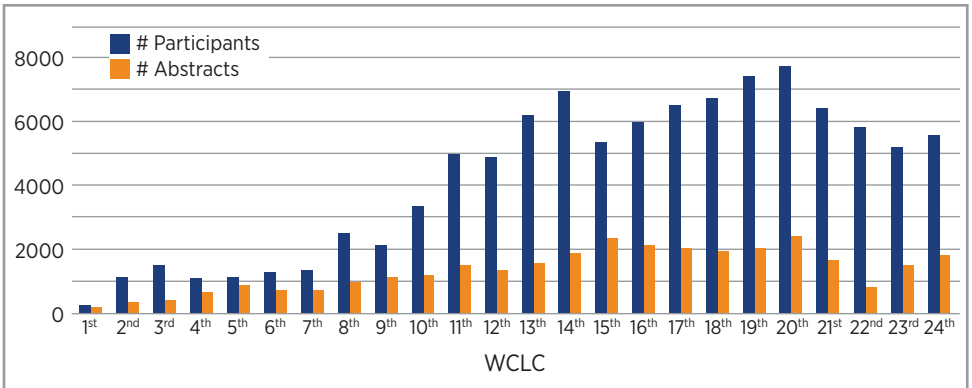


Figure 1. 1st-24th IASLC World Conference on Lung Cancer: Number of participants and abstracts for each meeting.

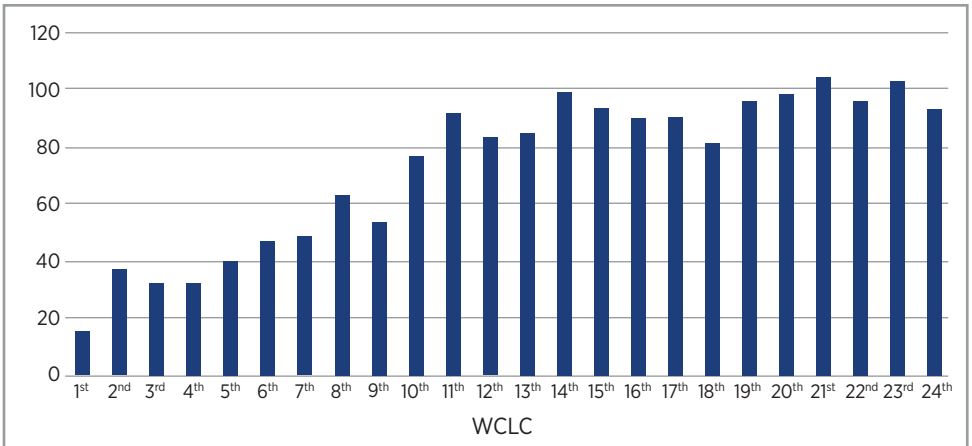


Figure 2. 1st-24th IASLC World Conference on Lung Cancer: Number of countries represented at each meeting.

In this chapter we focus on the WCLCs that were held since 2011, from the 14th WCLC in Amsterdam in 2011 to the 24th WCLC held in San Diego in September 2024 (Table 1). Beginning with the 16th WCLC in Denver, USA, the Board decided to limit the number of host sites and to select the Conference Presidents in an open solicitation. This solicitation is held annually for the WCLC to be held 3 years later. As a result, 5 individuals were selected as Organizing Chairs for the 23rd WCLC in 2022, 3 individuals for the 24th WCLC in 2023, and 4 individuals for the 25th WCLC in 2024. In addition to the Conference Presidents, an Organizing Committee consisting of a multidisciplinary group also is selected with Board approval.

Members of each unique WCLC Organizing Committees review for their meeting all submitted abstracts for publication, for presentation as posters, poster discussion, mini-oral, oral or plenary presentations. The Organizing Committee also assists in selection of some of the regional award recipients. Recipients of the IASLC Awards are presented at each of the WCLCs. Those individuals who received IASLC Awards, Fellowships, and Research Grants at each WCLC are listed in Chapter 4.

Originally, the WCLCs were held over 4 days, which allowed for some very special social events including a horse race, a rodeo, train rides to wine country, visits to museums and other sites, and so on. Over time, pressure grew to limit the length of the WCLC meeting and the Board elected to eliminate these social days so that the conference length became 3 days beginning in 2015.

Many important events continued to be held at each WCLC. These included a Board dinner for Board members, staff, past Presidents, and invited individuals; an IASLC Foundation dinner; an opening reception; and a faculty dinner. There are no social events during the day. Pharmaceutical companies are allowed to hold sponsored educational meetings on the day before or after the meeting or at meal breaks and evenings. Content of these meetings is reviewed and approved by the Organizing Committee.

In these years through 2023, attendance peaked at 7,755 attendees at the 20th WCLC in Barcelona (Fig 2). Due to the COVID epidemic the 21st and 22nd WCLC in 2020 and 2021 were held virtually and attendance declined. The first post-pandemic WCLC in 2022 was both in-person and virtual and was held in Vienna as described below. Subsequent WCLCs continued to include both in-person and virtual registrants.

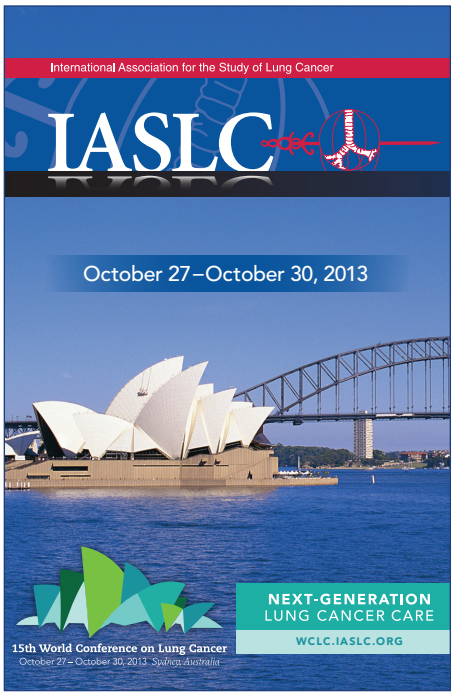
14TH WCLC / Amsterdam, The Netherlands / July 3-7, 2011

The 2011 14th WCLC was held in Amsterdam, The Netherlands, with Dr. Pieter Postmus as Conference President and Dr. Nico van Zandwijk as Conference Co-President. Once again, records were set for the number of submitted abstract—1,880. The number of registrants was 6,989. The Opening Ceremony was held at the Rai Convention Center, featured a "live version" of the famous Dutch painting "the Nightwatch," and featured the famous Dutch Singer Karin Bloemen who wrote a song especially for the occasion. The Gala dinner finished with a performance by Caro Emerald, a rising star in Europe, whose grooving jazz, infectious mambos, and banging beats filled the dance floor. IASLC Awards and Research Grants presented at this meeting are shown in Chapter 4. Highlights of the scientific sessions included presentations by Dr. Richard

Peto, masterly revealing novel data of the smoking epidemic including the favorable effects of cessation of smoking at advanced age and by Dr. Scagliotti who demonstrated the positive effects of pemetrexed in a randomized study, leading to the approval of pemetrexed as first-line therapy for patients with non-squamous NSCLC. In addition, the Amsterdam meeting provided major reviews of the role of PET scanning in surgical candidates, the role of surgery in malignant pleural mesothelioma, and updates of targeted treatments for mutation-positive NSCLC. For the first time multiple sessions were included for lung cancer nurses, as well as a 'hands-on' (endoscopy) session, and a multi-disciplinary introduction in statistics.

15TH WCLC / Sydney, Australia / October 27-30, 2013

The 15th WCLC was held at the Darling Harbour Convention Center in Sydney, Australia. There were a record number of submitted abstracts—2,319. The Conference President was Dr. Michael Boyer with Dr. Kwun Fong as Co-Conference President. The meeting featured increased input from advocates and from nursing and allied health professionals. The Opening Ceremony, which was preceded by a tobacco cessation session, featured a keynote presentation by The Honourable Nicola Roxon, former Health Minister of Australia, as well as an overview of the research in lung cancer and IASLC's 40-year history presented by Dr. Fred R. Hirsch. Meeting scientific highlights included results of the RTOG 0617 study presented by Dr. Jeff Bradley showing that 74Gy of chest RT was not superior and was more toxic than 60GY. Dr. Mark Kris presented the results of a Lung Cancer Mutation Consortium trial showing that treatment with therapies matched to oncogenic drives improved survival. Dr. Valerie Beral presented data showing the important risk reduction associated with smoking cessation and Dr. Charles Swanton presented data on tumor heterogeneity as an obstacle to immune therapy efficacy. As the meeting was held near Asia, there was an increase in the number of Chinese attendees and there was a special session for Chinese in Mandarin. This was the first WCLC with presentations on checkpoint inhibitor therapy. The Gala dinner program included an amazing journey through Australia including regional cuisine, indigenous culture, and live music. IASLC Awards and Research Grants presented during the meeting are shown in Chapter 4.



16TH WCLC / Denver, CO, USA / September 6-10, 2015

The 16th WCLC was held in Denver, USA under the Conference Presidency of Dr. Fred R. Hirsch, MD, PhD. The Planning Committee consisted of members of various disciplines including Dr. Laurie Gaspar (radiation), Dr. John Mitchell (thoracic surgery), Dr. Wilbur Franklin (pathology), Dr. York Miller (pulmonary), Dr. D. Ross Camidge (medical oncology), and Ms. Janet Freeman-Daily (advocacy). The meeting was attended by approximately 6,000 participants from 90 countries. There were 2,120 abstracts submitted and of these 253 were presented in oral sessions, 434 in mini-oral sessions, 1,212 as posters and 11 in plenary sessions. The oral sessions were divided into standard oral sessions with 10-minute presentations and mini-oral sessions with 5-minute presentations. There was a plenary session on a different topic each day. IASLC Awards and Research Grants given and awardees are listed in Chapter 4.

Scientific highlights during the conference were presentation of the Eight Edition of the UICC/IASLC Staging Classification (presented by Dr. Ramon Rami-Porta, Spain) based on data from 94,708 patients diagnosed around the world from 1999-2010. Furthermore, a new WHO Classification of Thoracic Tumors was presented by Dr. William Travis, USA. The 2015 WHO classification captured a decade of remarkable advances in all lung cancer specialties. The rapid development of molecular and immunohistochemistry tools provided a strong foundation for the new classification.

Other scientific highlights included a phase III study comparing carboplatin/pacltaxel or carboplatin/paclitaxel/bevacizumab with or without cetuximab in patients with advanced NSCLC (SWOG 0819) presented by Dr. Roy Herbst, USA and adjuvant chemotherapy with or without bevacizumab in resected NSCLC (ECOG 1505) presented by Dr. Heather Wakelee, USA. Multi-region whole exome and transcriptome sequencing of EGFR-mutated NSCLC and novel mechanisms for resistance to EGFR-directed therapies (EGFR TKIs) was presented by Dr. Daniel Tan from Singapore. Several important studies on smoking globally were presented and Dr. Ugo Pastorino from Italy presented study showing that stopping smoking reduces mortality in low-dose CT screened population. Dr. Christine Berg, USA gave an update on lung cancer screening with low-dose CT based on NLST and PLCO studies. Dr. Jean-Charles Soria from France gave a plenary review of the rapid scientific progress in advanced NSCLC focusing on EGFR- and ALK-positive NSCLC studies and two studies with new ALK-inhibitors, brigatinib and repotrectinib (later FDA-approved for ROS-1–positive NSCLC), were presented. Dr. Anton Berns from the Netherlands made a plenary review of progress in developing mouse models for studies in lung cancer.

Also, during the 16th WCLC, the IASLC released a new global statement on Tobacco Control and Smoking Cessation that called for higher taxes on tobacco products, comprehensive advertising, and promotion bans and product regulation, including pack warnings.

The patients' advocacy groups had at this conference a strong voice—more than ever previously—with personal testimony from advocate Ms. Janet Freeman-Daily. At the 16th WCLC Opening Ceremony, testimony was given by Ms. Emily Bennet Taylor, a 28-year old former athlete and never-smoker, who was diagnosed

with stage 4 lung cancer and treated successfully.

While presentations of the scientific developments are the primary goal of the World Conferences, another purpose of the WCLC is to bring investigators from all over the world together under the umbrella of the IASLC. Thus, social arrangements have also been a landmark for many WCLCs and the 16th WCLC in Denver was no exception. For the "Gala Dinner," several thousand delegates danced to the music from the famous band the "Kool & the Gang."

17TH WCLC / Vienna, Austria / December 4-7, 2016

The 17th WCLC was held in Vienna, Austria, and chaired by Dr. Robert Pirker and the local Organizing Committee was comprised of 19 Core Program Committee members and 15 Regional Organizing Committee members. The meeting was attended by 6,541 individuals representing 90 countries. There were 2,044 abstracts submitted and of these 150 were presented in oral sessions, 149 in mini-oral sessions, 8 in plenary sessions, and 1,522 as posters. IASLC Awards and Research Grants given and awardees are listed in Chapter 4.

Highlights of the presentations included a presentation by the President of Uruguay, Dr. Tabaré Vázquez, who described the successful case the Uruguayan Government made against the tobacco industry. The meeting was also attended by the President of Austria, Dr. Heinz Fischer, and the former Chancellor of Austria, Dr. Alfred Gusenbauer. The Keynote Lecture was presented by Nobel Laureate Prof. Dr. Harald zur Hausen on "Risk factors for lung cancer" during the Opening Plenary. There were many scientific highlights including the presentation of the changes in the 8th edition of the TNM staging classification. The results of the AURA trial comparing osimertinib to combination chemotherapy in patients with EGFR T790M mutations showing superiority for osimertinib cemented the first line role of osimertinib in these patients. The ASCEND-4-4 trial results demonstrated the superiority of ceritinib over chemotherapy in patients with ALK fusions. The quality of life (QOL) results from the KEYNOTE-024 trial showed that single agent pembrolizumab was associated with superior QOL compared to platinum doublet chemotherapy, cemented the routine use of single agent immunotherapy in NSCLC patients with high PDL1 levels (TPS >50%). The results of the BRAIN trial were presented and demonstrated that icotinib was superior to the combination of whole brain radiation and chemotherapy in patients with brain metastases harboring *EGFR* mutations. The results of the GALAXY-2 trial were presented showing no benefit for the addition of ganetespib to docetaxel in NSCLC patients who had progressed after first line therapy. The results of the OAK trial showing superiority of atezolizumab immunotherapy to docetaxel chemotherapy cemented the role of immunotherapy in lung cancer therapy.

Left to right: Dr. Fred Hirsch, Dr. Tabaré Vázquez, and Dr. Robert Pirker.

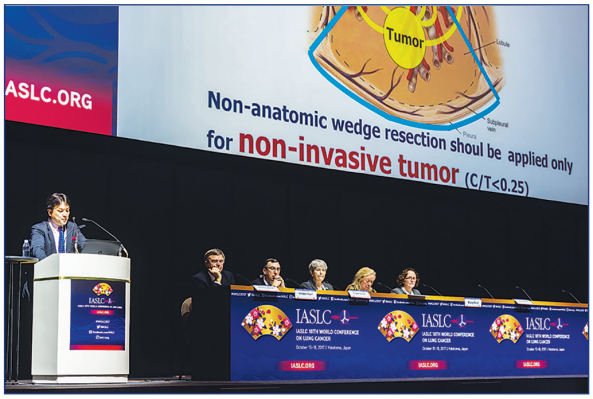
18TH WCLC / Yokohama, Japan / October 15-18, 2017

The 18th World Conference on Lung Cancer was held in Yokohama (the Pacifico Yokohama), Japan in 2017. This was the first conference after the change from biannual to annual organization of the IASLC. The Conference was held under the leadership of Dr. Hisao Asamura and Dr. Keunchil Park as Conference Co-Chairs. The IASLC Awards and Research Grants given and awardees are listed in Chapter 4. The meeting was attended by 7,443 individuals from 96 countries.

With the rapidly expanding application of immune checkpoint inhibitors (ICIs), biomarkers of ICIs were actively discussed at the WCLC 2017. Presentation on the Blueprint 2 study in the plenary session impacted the direction of PD-L1 Immunohistochemistry. The results of the PACIFIC trial, which used durvalumab after chemoradiation in locally advanced, unresectable non-small cell carcinoma was published in 2017. Patient-reported outcomes of the PACIFIC study were presented in the WCLC 2017. In addition to ICI, molecular diagnostics and targeted therapy were also impactful topics, and many presentations and discussions were made in symposiums, educational lectures, and oral sessions. The use of the 8th edition of the TNM Classification for thoracic malignancies started in 2017 (except in North America where it started in 2018). The concept and practical use of the new TNM Classification was lectured in the educational session. CT screening was one of the major themes of the conference, and prevention, screening, and management of screen-detected lung cancer were also discussed in a plenary session.

The conference motto was "Synergy to Conquer Lung Cancer." There were 1,970 submitted abstracts. Of these, 3 were selected for plenary presentation, 151 for oral presentation, 274 for mini-oral presentation, and 1,397 for poster presentation. Highlights included the presence of the Japanese Crown Prince, Emperor of Japan.

Dr. Hisao Asamura, Conference Co-Chair.



Naruhito, Emperor of Japan.

19TH WCLC / Toronto, Canada / September 23-26, 2018

The 19th WCLC was held in Toronto, Canada, in the Metro Toronto Convention Centre. The Conference was led by Co-Chairs Dr. Frances Shepherd, Dr. Andrea Bezjak, Dr. Gail Darling, and Dr. Natasha Leighl. These leaders oversaw the meeting's purposeful focus on multidisciplinary research and care in thoracic oncology. They also represent the increasing focus on diversity, including gender diversity. At this WCLC, the IASLC Board held a dinner in the "quintessentially Canadian" Hockey Hall of Fame, where the Board members were able to show off (or test) both their offensive and goalie skills before dinner.

Over 7,400 individuals traveled from 96 countries and 2,005 scientific abstracts were accepted for inclusion and discussion in the meeting in a range of scientific session formats. Of these, 4 were selected for plenary presentation, 104 for oral presentation, 329 for mini-oral presentation, and 1,450 for poster presentation. IASLC Awards and Research Grants given and awardees are listed in Chapter 4.

Highlights included the presentation of IMPower 133, a randomized trial demonstrating improved outcomes in extensive-stage SCLC in response to the addition of atezolizumab to the regimen of standard carboplatin and etoposide vs the addition of placebo. Also at this meeting, among other abstract data, the results from the KLN 189 trial were presented, showing the benefits of adding pemetrexed to pemetrexed/carboplatin in stage 4 lung adenocarcinoma.

IASLC Board dinner with the Stanley Cup.

20TH WCLC / Barcelona, Spain / September 7-10, 2019

The 20th WCLC was held in Barcelona, Spain, under the leadership of Drs. Ramon Rami-Porta, Enriqueta Felip, and Antoni Rosell as Co-Chairs. IASLC Awards and Research Grants given and awardees are listed in Chapter 4. The meeting was attended by 7,755 individuals from 99 countries. This was the all-time largest number of attendees.

There were 2,403 submitted abstracts. This was the largest number of abstracts ever submitted (Fig 1). Of these, 18 were selected for plenary presentation, 132 for oral presentation, 298 for mini-oral presentation, and 1,760 for poster and e-poster presentation.

Highlights included a presentation of KEYNOTE 021 showing the results of the addition of pembrolizumab to doublet chemotherapy, presented by Dr. Corey Langer, from the USA; the mutations that were associated with sensitivity or resistance to durvalumab immunotherapy in the MYSTIC trial, presented by Dr. Naiyer Rizvi, from the USA; and evaluations of the best criteria for selection of individuals for screening CT scans, presented by Dr. Stephen Lam, from Canada, Dr. F. Sullivan, from the UK, and Dr. Ugo Pastorino, from Italy. Additionally, the results of the VIOLET trial comparing thoracotomy and video-assisted (VATS) approach for lung cancer resection was presented by Dr. Eric Lim, from the UK. In essence, the VATS approach was associated with significantly lower in-hospital complications and shorter length of stay compared with thoracotomy, without compromising the completeness of resection or the upstaging of mediastinal lymph nodes. Dr. Tamás Molnár, from Hungary, delivered a most inspiring presentation on the parallel lives of tuberculosis and lung cancer during which he masterfully intertwined science, history and literature. Also of note, was a presentation by Ms. Jenny Mitchell, RN, from the UK, who presented a nurse-led follow-up service for patients undergoing lung resection for early stage lung cancer that showed the degree of specialization and implication in the management of patients with lung cancer of British nurses, a service that should be paradigmatic for other countries.

Another important event was the launching of the new journal of the IASLC. Dr. Alex A. Adjei, Editor-in-Chief of the *Journal of Thoracic Oncology*, presented the online open access *JTO Clinical and Research Reports*. As Dr. Adjei explained in a press conference, the main objective of this new IASLC journal is to publish articles that deserve publication but do not fit in the limited space of the JTO.

Delegation from Tata Memorial Hospital, Mumbai, India. Left to right: Dr. Virendra Tiwari, Dr. Devayani Niyogi, Dr. Sabita Jiwnani, and Dr. C. S. Prames.

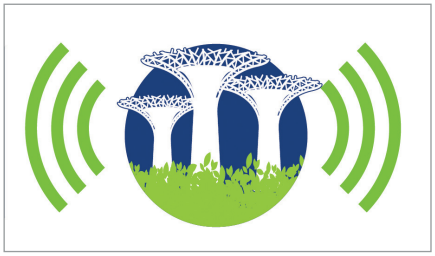
Closing ceremony (left to right): Dr. Ramon Rami-Porta, Ms. Pat Vigués, Dr. Enriqueta Felip, and Dr. Antoni Rosell.

21ST WCLC VIRTUAL EVENT / Singapore / January 28-31, 2021

The Conference Chair for the 21st WCLC was Dr. Yi-long Wu, China, and the Organizing Committee was led by Dr. Daniel Tan, Conference Co-Chair, Singapore, with Dr. Ross Soo, Conference Co-Chair, Singapore. Unfortunately, the world and the Organizing Committee were faced with the COVID pandemic from early 2020. This pandemic led to the cancellation of holding the WCLC in person. Because of the uncertainty, the meeting was held virtually in two parts. The first part consisted of the plenary sessions that were delivered on August 19, 2020. The remainder of the abstract presentations were given virtually and in poster presentations held from January 28-31, 2021. Overall, there were 1,601 submitted abstracts. Of these, 6 were selected for plenary presentation, 45 for oral presentation, 101 for mini-oral presentation, and 1,015 for featured poster and e-poster presentation.

This meeting and the challenges of creating a full scale virtual meeting for the first time put a tremendous strain on the IASLC staff as well as the supporting staff from International Conference Services. These individuals were up to the challenge and the meeting was highly successful with 6,422 virtual attendees from around the globe. In addition, many individuals were able to view the presentation virtually after the meeting dates. This conference underscored the continued importance of WCLC in bringing together the thoracic oncology community and the feasibility of the virtual meeting format in enabling the timely delivery of science at the highest level to a global audience.

Highlights of the meeting included the impact of the COVID



pandemic on management of thoracic malignancies, targeted options, and sequencing issues involving KRAS, HER2 & ALK, treatment approaches in the EGFR-mutated setting, an update report from KEYNOTE-189, and a report on nivolumab as a new option in patients with relapsed malignant mesothelioma. The non-scientific highlights included the first successful conduct and execution of a large scale virtual conference for a global audience and the WCLC 2020 Virtual Presidential symposium.

IASLC Awards and Research Grants given and awardees are listed in Chapter 4.

22ND WCLC VIRTUAL EVENT / Denver, CO, USA / September 8-14, 2021

The 22nd WCLC was held virtually from Denver under the leadership of Dr. David Harpole with Drs. Kristin Higgins and Thomas Stinchcombe as Co-Chairs. IASLC Awards and Research Grants given and awardees are listed in Chapter 4. Overall, there were 817 submitted abstracts. The COVID epidemic and the resulting inability to travel undoubtedly accounted for the reduction in the number of abstracts and attendees. Of these, 5 were selected for plenary presentation, 71 for oral presentation, 99 for mini-oral presentation, and 530 for featured poster and e-poster presentation. The virtual attendance at the time of the meeting was 5,816 from 96 countries. Of course, many members and individuals had the opportunity to view the presentations after the meeting dates.

Highlights of the presentations included: phase III results from the POSEIDON trial showing the role of durvalumab +/- tremilimumab

in first-line therapy of NSCLC; the results of Impower 010 in the adjuvant setting demonstrating that adjuvant atezolizumab could improve event-free and overall survival in resected early-stage patients; the negative results from the ATLANTIS trial showing equivalence of CAV to lurbinectedin/doxorubicin to CAV or topotecan in relapsed SCLC; global variability in lung cancer deaths attributable to air pollution; and, an IASLC study of the impact of the COVID-19 pandemic on clinical trials.

Between the 22nd and 23rd WCLC there was a change in the IASLC leadership. Karen Kelly, MD, a long-time IASLC member, was selected as the new IASLC Chief Executive Officer. She was immediately charged with planning for the 23rd WCLC, which was to be held in person for the first time since the COVID pandemic began as well as virtually since many people from around the globe were still unable to travel to Austria. The IASLC staff and the ICS staff worked diligently with the organizing committee to ensure the success of the 23rd WCLC meeting.

23RD WCLC / Vienna, Austria / August 6-9, 2022

The 23rd WCLC was held in Vienna, Austria under the leadership of Dr. Robert Pirker, as Honorary Chair, and Drs. Eric Lim, Francoise Mornex, Silvia Novello, and Helmut Prosch as Co-Chairs. There were 1,469 submitted abstracts submitted from 63 countries. The meeting was attended by 5,216 individuals and was offered in a hybrid format including recorded virtual participation. These participants were from 103 countries. IASLC Awards and Research Grants given and awardees are listed in Chapter 4.

Highlights of the meeting included presentation of the survival results from the IMpower010 trial comparing adjuvant atezolizumab with best supportive care following platinum-based chemotherapy in patients with completely resected stage IB (≥4 cm)-IIIA NSCLC. Atezolizumab demonstrated a trend towards increased overall survival for stage II-IIIA patients with PD-L1 positive tumors. Another randomized trial demonstrated the ability of individual tobacco counselling to increase quit rates in women (but not in men) undergoing CT screening. The results of trial CALGB 140503 were presented, indicating that sublobar resection was not inferior to lobectomy with respect to disease-free survival, and overall survival was similar with the two procedures in stage I NSCLC. The results of the neoadjuvant NADIM II randomized trial in which resectable patients received 2 or 3 cycles of neoadjuvant chemotherapy and immunotherapy were presented, raising the issue of the best number of preoperative cycles and, when discussed with the results of the CheckMate 816 trial, whether postoperative immunotherapy is necessary.

For the first time the International Lung Cancer Foundation sponsored a "STEPS" competition to raise funds for research. This was highly successful. The IASLC officers presented many important awards (see Chapter 4). There were 10 Developing Nation awardees who had their trips to the 23rd WCLC paid for by the IASLC, allowing them to attend the conference. There were 10 Early Career Education Awards providing funding for the early research of these young investigators. Awards also presented at this WCLC included 15 WCLC Academy Participant Awards, four Nurse and Allied Health Awards, and three Patient Advocacy awards. As well, there were three Cancer Care Team awards presented to The Instituto Nacional del Thorax in Chile, the Shanghai Pulmonary Hospital affiliated to Tongji University, Shanghai, People's Republic of China, and the Baptist Cancer Center, Memphis, TN, USA.

24TH WCLC / Singapore / September 9-12, 2023

The 24th WCLC was held in Singapore on Sept 9-12, 2023. The conference chairs were Drs. Pyng Lee, Chee Lee, and Fiona Hegi-Johnson. IASLC Awards and Research Grants given and awardees are listed in Chapter 4. There were over 5,622 attendees and 300 speakers from 94 countries. This is the first in-person WCLC post-Covid pandemic when the world stood still for 3 years. Over the 4 days of the meeting the program was a crafted integration of in-person only and live-streamed sessions to which onsite and virtual delegants participated. More than 1,831 abstracts were submitted, of which four were selected for plenary presentation, 92 for oral presentation, 160 for mini-oral presentation, and 1,155 for featured poster and e-poster presentation. This meeting also had the best attended CT screening pre-conference symposium.

Highlights from the 24th WCLC included a presentation by Dr. Eric Lim of the MARS 2 randomized trial in malignant mesothelioma, indicating that patients with mesothelioma who received surgical resection had a similar survival compared to those with no surgical resection. This controversial result is under further investigation. The early results of the FLAURA 2 trial comparing osimertinib alone to platinum chemotherapy plus osimertinib in advanced NSCLC patients with EGFR mutations was presented by Dr. Pasi Jänne. The early results showed superior PFS in patients receiving the combination, but there were no differences in early evaluation of overall survival. Patients with poor prognostic markers such as p53 mutations seemed to have less benefit.

Dr. Huang presented the results of the Taiwan National screening program that included never-smokers. The trial showed that the CT screening detected early cancers and improved survival in all subjects including never-smokers. This trial will stimulate continuing efforts to identify patients at highest risk. Asia shoulders the highest burden

Left to right: Dr. Stephen Lam, Dr. Lee Pyng, Dr. Marjolein Heuvelmans, and Dr. Chi-Fu Yang.

Conference Chairs (left to right) Drs. Chee Lee, Fiona Hegi-Johnson, and Pyng Lee.

of lung cancer with the majority diagnosed in advanced stages without screening. Asian lung cancer also has molecular signatures that are distinctly different from the western population. The Taiwan lung screening program sheds light on extending eligibility criteria for low-dose CT screening to never-smokers with family history, individuals with significant exposure to environmental pollution whether it is high cooking index, and exposure to second-hand smoke or air pollution. Lung cancer screening trials achieve the fundamental goal of stage shift which will enable us to conquer lung cancer in the near future.

In a Special Plenary Session chaired by Dr. Paul Van Schil, President of the IASLC, and Dr. Ramón Rami-Porta, acting Past-Chair of the IASLC Staging and Prognostic Factors Committee (SPFC), the innovations proposed by the IASLC SPFC for the 9th edition of the tumor, node and metastasis (TNM) classification were presented for the first time.

Dr. Asamura, Chair of the SPFC and Chair of its Lung Cancer Domain, presented the proposals for lung cancer. Dr. Valerie Rusch, Chair of the SPFC Pleura Mesothelioma Domain, presented those for pleural mesothelioma. Finally, Dr. Enrico Ruffini, Chair of the Thymic Epithelial Tumors Domain, presented the innovations for thymic tumors. This session was well attended because there was great expectation in the thoracic oncology community around the world about the changes that would be incorporated into the 9th edition TNM of thoracic malignancies that will be enacted in 2025.

25TH WCLC / San Diego / September 7-10, 2024

WCLC 2024 Co-Chairs

Sandip Patel, MD
University of California, USA

Linda Martin, MD
University of Virginia, USA

Narjust Florez, MD
Dana-Farber Cancer Institute, USA

Fabio Ynoe de Moraes, MD, PhD, MBA
Queens University, Canada

4

IASLC AWARDS, FELLOWSHIPS, AND RESEARCH GRANTS

IASLC Awards, Fellowships, and Research Grants are integral to the delivery of the IASLC mission. Recognition of leaders and mentors, and support of those new to the field doing critical thoracic oncology research, are two components of this vital and unique program. As well, through its Awards programs, IASLC honors both those providing invaluable care to patients and those who are advocates for patients.

EARLY AWARDS

The first official IASLC award given in IASLC's history was the IASLC Merit Award given to Dr. Clifton Mountain in 1991. At the 7th WCLC in Colorado Springs in 1994, other IASLC Distinguished Service Awards were launched. It was at this meeting that the first Mary Matthews Pathology Award was presented to Dr. Geno Saccamanno, a pathologist, whose work paved the way to understanding of lung cancer pathology, etiology, and biology through extensive research, particularly on bronchial cytology. The first IASLC Scientific Award was also presented to Dr. Robert Ginsberg, MD, thoracic surgeon from Toronto, Canada, for his contributions to the surgical treatment of early-stage lung cancer. And in this year, Dr. Jesse Steinfeld, former U.S. surgeon general and antitobacco crusader, received the Joseph W. Cullen Prevention/Early Detection Award, which recognizes an IASLC scientist for a lifetime achievement in the prevention of thoracic malignancies.

GROWTH AND CHANGE

The IASLC Awards, Fellowships, and Research Grants programs have grown in scope, volume, and impact since those early and important recognitions. Changes and growth points include those listed below. All are continuing programs that are highlights of each annual WCLC. The following are examples of developments of Awards/Lectureships:

2000 – The first IASLC Fellowship Grant is awarded; these are for a one-year research project. They were first established in collaboration with Bristol Myers Squibb and facilitated by patient advocate Bo Aldige. Dr. Jun Zhang (2000) and Dr. Fred R. Hirsch and Mr. Yunfei Wang (2001) were the first IASLC Fellows to receive this award.

2004 – The first IASLC Young Investigator Award is given - grants that provide support to young investigators for independent research studies. Dr. Benjamin Solomon of Peter MacCallum Cancer Center in Australia was this award's first recipient.

2009 – The Young Investigator's Award becomes the Young Investigator's Travel Award.

2011 - The IASLC Scientific Award becomes the Paul A. Bunn, Jr. Scientific Award.

2016 – The first James D. Cox Lectureship Award for Radiation Oncology is presented.

2016 – The Patient Advocacy Award is renamed Patient Advocate Educational Travel Award.

2017 – The Nurse or Allied Health Professional Awards are established.

2017 – The IASLC Academy program is established.

2018 – The first LCFA/BMS/ILCF Young Investigator Research Grant in Translational Immuno-oncology is first awarded. This grant supports research in translational immuno-oncology undertaken by early-career investigators that aim to improve the care and treatment of individuals with lung cancers. The first recipients of this prestigious award were Katheryn Beckermann, USA, and Dr. Zoltan Lohinai of the National Koranyi Institute of Pulmonology, Hungary.

2019 - The Adi F. Gazdar IASLC Merit Award is established (previously the IASLC Merit Award) and the Fred R. Hirsch, Lectureship Award for Translational Research was established (previous Adi F. Gazdar Lectureship), honoring Dr. Hirsch role as researcher and former CEO of the IASLC.

2017 – The IASLC Lectureship Award for Nurses and Allied Health is first awarded; now called the IASLC Lectureship Nurses and Health Professionals Award.

2019 – The collaborative IASLC Supportive Training for Advocates on Research & Science (STARS) and Patient Research Advocates (PRAs) program launched.

2019–2020 – The Young Investigator's Travel Award was renamed the Early-Career Travel Award (2019), and then in 2020 was renamed as the Early-Career Education Award.

2021 – The first IASLC Lectureship Award for Tobacco Control and Smoking Cessation is presented.

2022 – The Developing Nations Award name is changed to the Developing Nation Education Award.

2023 – The Developing Nation in Tobacco Control and Smoking Cessation Awards are established.

CURRENT CATEGORIES OF IASLC AWARDS, FELLOWSHIPS, AND RESEARCH GRANTS

IASLC DISTINGUISHED SERVICE AWARDS

IASLC Distinguished Service Awards recognize investigators in the field of lung and thoracic cancers—those who are established in their careers—for their outstanding contributions to the field and to the IASLC. These individuals are "luminaries" in their field of work and have made significant life-time accomplishments.

Mary J. Matthews Pathology/Translational Research Award (1994–present)

The Mary J. Matthews Pathology/Translational Research Award recognizes an IASLC scientist for a lifetime achievement in pathology and translational research of thoracic malignancies. Dr. Matthews served as a senior investigator and pathologist at the National Cancer Institute's Medical Oncology Branch. She was pioneer in the foundation of the histologic subtypes of lung cancer and the relationship between those subtypes and the clinical course of lung cancer. Geno Saccommano, MD, PhD, a physician and cancer researcher who dedicated his life to developing a pioneering technique to assist in the early detection of lung cancer was the first to receive the award in 1994.

2023: Fernando Lopez-Rios, Spain
2022: Rafael Rosell, Spain
2021: Deepali Jain, India
2020: Caroline Dive, UK
2019: Andrew Nicholson, UK
2018: Ignacio Wistuba, USA
2017: Yasushi Yatabe, Japan
2016: Keith Kerr, UK
2015: Ming Tsao, Canada
2013: Tetsuya Mitsudomi, Japan
2011: Philip Hasleton, UK
2009: Masayuki Noguchi, Japan
2007: Fred R. Hirsch, USA
2005: Elisabeth Brambilla, France
2003: Adi Gazdar, USA
2000: Yukio Shimosato, Japan
1997: William D. Travis, USA
1994: Gene Saccomanno, USA

Adi F. Gazdar IASLC Merit Award (formerly the IASLC Merit Award) (1991-present)

In 2019, the IASLC Board of Directors unanimously voted to elevate its recognition of Dr. Adi F. Gazdar to one of its highest honors by renaming the IASLC Merit Award for Dr. Gazdar. The Adi F. Gazdar IASLC Merit Award proudly recognizes and honors Dr. Gazdar's lifelong dedication to lung cancer research through his pioneering work in molecular pathology. The recipient of the annual Adi F. Gazdar IASLC Merit Award is chosen by the IASLC Executive Committee and is announced and recognized at the annual World Conference on Lung Cancer. The first recipient of the IASLC Merit Award was Clifton F. Mountain in 1991.

2023 Myung-Ju Ahn, South Korea
2022 Valerie Rusch, USA
2021: Michael Boyer, Australia
2020: Alex Adjei, USA
2019: Hisao Asamura, Japan
2018: Francoise Mornex, France
2017: Ramon Rami-Porta, Spain
2016: Keunchil Park, South Korea & Sumitra Thongprasert, Thailand
2015: Harvey Pass, USA
2013: James Jett, USA
2011: David Ball, Australia
2009: Giorgio V. Scagliotti, Italy
2007: Peter Goldstraw, UK
2005: Harubumi Kato, Japan
2003: Paul A. Bunn Jr., USA
2000: Desmond N. Carney, Ireland
1997: Heine H. Hansen, Denmark
1994: Norman Bleehen, UK; Yukio Shimosato, Japan
1991: Clifton F. Mountain, USA

Joseph W. Cullen Prevention/Early Detection Award

The Joseph W. Cullen Prevention/Early Detection Award recognizes an IASLC scientist for a lifetime achievement in the prevention of thoracic malignancies. Dr. Cullen served as the Deputy Director of the National Cancer Institute's (NCI) Division of Cancer Prevention and Control. He created the Smoking, Tobacco, and Cancer Program at the NCI in 1982. The winner of the first award in 1994 was Jesse Steinfeld, MD, the U.S. Surgeon General when the American National Cancer Act of 1971 was enacted into federal law.

2023: William Evans, Canada
2022: Edward F. Patz Jr., USA
2021: Gabriella Sozzi, Italy
2020: Pan-Chyr Yang, Taiwan
2019: Denise Aberle, USA
2018: Nise Yamaguchi, Brazil; Fadlo Khuri, Lebanon
2017: Carolyn Dresler, USA
2016: Ugo Pastorino, Italy
2015: Jacek Jassem, Poland
2013: Pieter Postmus, Netherlands
2011: John Field, UK
2009: Stephen Lam, Canada
2007: James Mulshine, USA
2005: Nigel Gray, Australia
1997: Clifford Douglas, USA
1994: Jesse Steinfeld, USA

Paul A. Bunn, Jr. Scientific Award (formerly the IASLC Scientific Award) (1994-present)

The Paul A. Bunn, Jr. Scientific Award recognizes an IASLC scientist for a lifetime achievement of scientific contributions to thoracic cancer research. Dr. Paul Bunn's studies set worldwide standards for the treatment of lung cancer and identified issues of natural history and biomarkers of prognosis and therapy selection. Robert Ginsberg, MD, a thoracic surgeon from Toronto, Canada, earned the first award in 1994 for his contributions to the surgical treatment of early-stage lung cancer. Initially named the IASLC Scientific Award, the IASLC renamed the award in honor of Dr. Bunn after he served as executive director and CEO for 10 years.

2023: Suresh Ramalingam, USA
2022: James Yang, Taiwan
2021: David P. Carbone, USA
2020: Joan Schiller, USA
2019: Charles Rudin, USA
2018: Charles Swanton, UK
2017: Tony Mok, Hong Kong
2016: Roy Herbst, USA
2015: Yi-Long Wu, China
2013: David R. Gandara, USA
2011: Nagahiro Saijo, Japan
2009: Bruce Johnson and Thomas J. Lynch, USA
2007: Frances Shepherd, Canada
2005: Thierry LeChevalier, France
2003: Paul van Houtte, Belgium
2000: Daniel C. Ihde, USA
1997: John D. Minna, USA
1994: Robert Ginsberg, Canada

IASLC LECTURESHIP AWARDS

IASLC Lectureship Awards are recognized at each WCLC and focus on the areas of radiation oncology, medical oncology, small cell lung cancer, nursing/allied health, translational research, thoracic surgery, staging, and tobacco control. They are given largely to younger/mid-career investigators who have demonstrated specific focused research projects in the different research categories. All Lectureship Award winners are asked to deliver a scientific lecture in a Plenary Session at WCLC. IASLC Lectureship Awards include:

- **James D. Cox Lectureship Award for Radiation Oncology**

  2023: Rafal Dziadziuszko, Poland
  2021: Yuko Nakayama, Japan
  2021: Cecile Le Pechoux, France
  2020: Walter Curran, USA
  2019: Corinne Favire-Finn, UK
  2018: Hak Choy, USA

- **Daniel C. Ihde Lectureship Award for Medical Oncology**
  - 2023: D. Ross Camidge, USA
  - 2022: Patrick Forde, USA
  - 2021: Fabrice Barlesi, France
  - 2020: Myung-Ju Ahn, South Korea
  - 2019: Daniel Tan, Singapore
  - 2018: David Carbone, USA
  - 2017: Dirk De Ruysscher, Netherlands
  - 2016: Krista Wink, Netherlands
  - 2015: John Edwards, UK
  - 2013: Suresh Ramalingam, USA
  - 2011: Vidya Setty, USA
  - 2009: Jin Soo Lee, Republic of Korea
  - 2007: Nasser Hanna, USA

- **Heine H. Hansen Lectureship Award for Small Cell Lung Cancer**
  - 2023: Jie Wang, China
  - 2022: Stephen Liu, USA
  - 2021: Trudy Oliver, USA
  - 2020: Lauren Byers, USA
  - 2019: Caroline Dive, UK
  - 2018: Charles Rudin, USA
  - 2017: Taofeek Owonikoko, USA
  - 2016: Marianna Christodoulou, UK
  - 2015: Charles Rudin, USA
  - 2013: Michael Seckl, UK
  - 2011: Joachim von Pawel, Germany
  - 2009: David Spigel, USA
  - 2007: Ben Slotman, Netherlands

- **IASLC Lectureship Award for Nurses and Allied Health Professionals**
  - 2023: Melissa Culligan, USA
  - 2022: Anne Fraser, Australia
  - 2021: Pippa Labuc, Australia
  - 2020: Mary Duffy, Australia
  - 2019: Kahren M. White, Australia
  - 2018: Kim Rohan, USA
  - 2017: Morten Quist, Denmark

- **Fred R. Hirsch Lectureship Award for Translational Research**
  - 2023: Wendy Cooper, Australia
  - 2022: Lukas Bubendorf, Switzerland
  - 2021: Lynette Scholl, USA
  - 2020: Sanja Dacic, USA
  - 2019: Roman K. Thomas, Germany
  - 2018: Matthew Meyerson, USA
  - 2017: Katey Enfield, Canada
  - 2016: Jonathan Riess, USA
  - 2015: Lynette Fernandez-Cuesta, France (formerly Adi F. Gazdar)

- **Robert J. Ginsberg Lectureship Award for Surgery**
  - 2023: Jessica Donington, USA
  - 2022: Isabelle Opitz, Switzerland
  - 2022: Shun-Ichi Watanabe, Japan
  - 2020: Eric Lim, UK
  - 2019: Giulia Veronesi, Italy
  - 2018: Valerie Rusch, USA
  - 2017: Francesco Guerrera, Italy
  - 2016: Aki Kobayashi, Japan
  - 2015: Virginie Westeel, France
  - 2013: Meinoshin Okumura, Japan
  - 2011: Kelvin Lau, UK
  - 2009: Enriqueta Felip, Spain
  - 2007: Aokage Keiju, Japan

- **Clifton F. Mountain Lectureship Award for Staging**
  - 2023: Navneet Singh, India
  - 2022: Clarissa Mathias, Brazil
  - 2021: Ayten Cangir, Turkey
  - 2020: Enrico Ruffini, Italy
  - 2019: Paula Ugalde, USA
  - 2018: Johan Vansteenkiste, Belgium
  - 2017: Herbert Decaluwe, Belgium
  - 2016: Hao-Ran Zhai, UK
  - 2015: Edward Robbins, USA
  - 2013: Min Kim, South Korea
  - 2011: Richard Peto, UK
  - 2009: Junji Yoshida, Japan

- **Tsuguo Naruke Lectureship Award for Surgery**
  - 2023: Alan Sihoe, Hong Kong
  - 2022: Wen-Zhao Zhong, China
  - 2021: James Huang, USA
  - 2020: Samina Park, Republic of Korea
  - 2019: Raja M. Flores, USA
  - 2018: Hisao Asamura, Japan
  - 2017: Matthew Smeltzer, USA
  - 2016: Ryuichi Waseda, Japan
  - 2015: Ryutaro Kakinuma, Japan
  - 2013: Junji Yoshida, Japan
  - 2011: Marcin Zielinski, Poland
  - 2009: Matthew Ninan, USA

- **IASLC Lectureship Award for Tobacco Control and Smoking Cessation**
  - 2023: Silvia Novello, Italy
  - 2022: Ray Osarogiagbon, USA
  - 2021: Graham Warren, USA
  - 2020: Wanda de Kanter, Netherlands
  - 2019: Emily Stone, Australia

OTHER AWARDS AND AWARDS PROGRAMS

- **Developing Nation Education Awards (formerly Developing Nation Award)**

Another vital IASLC Award is the **Developing Nation Education Awards**, which began in 2007. The Developing Nation Education Awards are available for trainees and residents of countries listed on the IASLC Membership Guidelines webpage. This award provides the opportunity for presenters of high-rated abstracts from developing nations to grow professionally by attending educational sessions, networking, and developing professional relationships with colleagues from around the world. Award Recipients include:

2023:
Nour Al-Bzour, Jordan
Jia-Yi Deng, China
Muhammed Elfaituri, Libya
Chinmay Satish Haridas, India
Yang-Si Li, China
Yin Li, China
Si-Cong Ma, China
Zhenbin Qiu, China
Du Xu, China
Chao Zhang, China

2022:
Amiya Agrawal, India
Leen Al-kraimeen, Jordan
Rui Fu, China
Chenchen Guo, China
Chinmay Haridas, India
Debapriya Mondal, India
Amber Rathor, India
Sebawe Syaj, Jordan
Saurav Verma, Canada

2021:
Aruna Nambirajan, India
Hanna Lianti, Indonesia
Luis Roberto Basbus, Argentina
Mei-Mei Zheng, China

2020:
Zhong-Yi Dong, China
Jinghua Chen, China
Wen-Fang Tang, China
Jia-Tao Zhang, China
Alfredo Chua, Philippines
Venkata Pradeep Babu, India
Piyakarn Watcharenwong, Thailand
Ilavarasi Vanidassane, India
Ece Çakıroğlu, Turkey
Matias Cerini, Argentina
Mohamed Ait Erraisse, Morocco
Eby Aluckal, India
Fredrick Asirwa, Kenya
Charu Bahl, India

2019:
Anna Basharina, Russia
Yue Cheng, China
Voc Dang, Vietnam
Evgeny Denisov, Russia
Atit Dewi, Indonesia
Diego Armando Diaz-Garcia, Colombia

2018:
Luciene Bonan, Brazil
Liang-liang Cai, China
Shruti Kate, India
Natalia Khranovska, Ukraine
Milica Kontic, Serbia
Tahir Mehmood, Pakistan
Orestes Santos Morales, Cuba
Dongrong Situ, China
Qi Song, China
Malcolm Tagbarha, Philippines

2017:
Pedro Aguiar Jr., Brazil
Sharif Ahmed, Bangladesh
Marisol Arroyo Hernandez, Mexico
Feliciano Barron, Mexico
Gulrukh Botiralieva, Uzbekistan
Gamze Çetinkaya, Turkey
Tatiana Ionova, Russia
Akhil Kapoor, India
Sze Shyang Kho, Malaysia
Hengrui Liang, China
Qianwen Liu, China
Hüseyin Melek, Turkey
Mangesh Patil, India
Amrita Singh, India

Apichat Tantraworasin, Thailand
Ana Paula Teixeira, Portugal
Lin Tong, China
Natthay Triphuridet, Thailand
Dongsheng Yue, China
Fei Zhou, China

2016:
Andrey Akopov, Russia
Weijing Cai, China
Arun Chandrasekharan, India
Zhong-Yi Dong, China
Alok Goel, India
Gaurav Kumar, India
Denisse Lee, Mexico
Tatiane Montella, Brazil
Isis Nascimento, Brazil
Viktoriia Nikulina, Sweden
Shengxiang Ren, China
Ahmed Salem, UK
Ayaz Shahid, India
Navneet Singh, India
Chandrashekhar Sreeramareddy, Malaysia
Ana Paula Teixeira, Portugal
Dawei Yang, China
Shuang Zhao, China
Yue, Zhao China

2015:
Blessing Obiazi-Odiase, Nigeria
Xiankun Han, China
Satya Narayan , India
Qi Wang, China
María Castillo, Guatemala
Malcolm Tagbarha, Nigeria
GK Mini
Bernadette Reyna Asuncion, Singapore
Cristina Perez, UK
Emmanuel Odiase, Nigeria
Tomi Kovacevic, Serbia

2013:
Ning Cheng, China
Neekkan Dey, India
Alexander Kabakov, Russia
Urvashi Kaushik, India
Natalia Khranovska, Ukraine
Yubo Liu, China
CS Pramesh, India
Cinthya Sternberg, Brazil
Natthaya Triphuridet, Thailand
Subrata Saha, India

2011:
Yijun Gao, China
Tanawat Jirakulaporn, Thailand
Andreia Melo, Mexico
Emmanuel Odiase, Nigeria
Subrata Saha, India
Chunxia Su, China
Lei Yu, China
Yong Zhang , China
Xiao Zhao, China
Qinghua Zhou, China

2009:
Bakhrom, Akhmedov, Uzbekistan
CS Pramesh, India
Ji Eun Uhm, South Korea
Bojan Zaric, Serbia
Amelia Szymanowska, Poland
Bi Nan, China
Emmanuel Odiase, Nigeria
Adam Szpechcinski, Poland
Ana Patané, Italy
Ilker Iskender, Turkey
P Sankpal, India
Smiti Sripathi, India
Kashif Iqbal, India
Lei Yu, China
Claudia Poleri, Italy

2007:
Digambar Behera, India
Kashif Iqbal, Pakistan
Polina Gervas, Russia
Sreeja Leelakumari, Canada
Qinghua Zhou, China
Bernadette Asuncion, Philippines
Alena Mikhalenka, Belarus
Shambhu Dutta Joshi, India
Shankpal Pramod, India
Jaime Guachalla, Chile

- **Early-Career Education Awards**

The Early-Career Education Awards are available for fellows, students, trainees, or post-doctoral researchers with a professional degree within three years of initial faculty appointment. This award provides the opportunity for presenters of high-rated abstracts to grow professionally by attending educational sessions, networking, and developing professional relationships with colleagues from around the world. In 2007 this award was named the Young Investigator's Award; in 2009, the name was changed to the Young Investigator's Travel Award. In 2019, the Award was again renamed to the Early-Career Travel Award, and then in 2020 was renamed as the Early-Career Education Award. Award Recipients include:

2023:
Jacqueline Aredo, USA
Xiaoshuang Feng, China
Patrick Goodley, UK
Adam Grippin, USA
Ilias Houda, Morocco
Matthew Lee, USA
Anlin Li, China
Seshiru Nakazawa, Japan
Priyanka Senthil, India
Neil Wallace, Australia

2022:
Nicolas Alcala, Spain
Marta Casarrubios, Spain
Kevin Chua, Singapore
Laurent Dercle, France
Simon Heeke, Germany
Arvind Kumar, India
Jennifer Marks, USA
Emilie Mathian, France
Alberto Traverso, Italy
Hana Zahed, France

2021:
Aakash Desai, USA
Arvind Kumar, India
Biagio Ricciuti, Italy
Ilyas Yambayev
Jason Liu, China
Jiaqing Liu, China
Joseph Chan, USA
Karin Schelch, Austria
Luca Cantini, Italy
Mark Jaradeh, USA
Martina Aineseder, Argentina
Nikhil Yegya-Raman, India
Peixin Chen, China
Ranjan Pathak, India
Samuel Kareff, USA

2020:
Lawson Eng, Singapore
Nobuyuki Takahashi, Japan
Biagio Ricciuti, Italy
Prantesh Jain, India
Aaron C. Tan, Singapore
Xue Bai, China
Yoen Wook Kim, South Korea
Afaf Abed, Australia
Satya Padmaja, India
Saskia Cooke, USA
Isabelle Milner, USA
Milena Cavic, Serbia

2019:
Dennis Adeegbe, USA
Francesca Ambrosi, Italy
Kathryn Arbour, USA
Kathryn Banfill, UK
Joseph Barnett, UK
Kaustav Bera, USA
Lawek Berzenji, Belgium
Daniel Breadner, UK
Milena Cavic, Serbia
Jiae Koh, Republic of Korea

2018:
Arpita Desai, USA
Arooj Fatima, Pakistan
Giovanni Fucà, Italy
Silvia Garcia-Roman, Spain
Marjolein Heuvelmans, Netherlands
Fang Hu, China
Adam Januszewski, UK
Tao Jiang, China
Jenny Turcott, Mexico
Natalie Vokes, USA
Zyanya Lucia Zatarain-Barrón, Mexico

2017:
Haval Balata, UK
Joshua Bauml, USA
Kezhong Chen, China
Hanbo Chen, Netherlands
Bhagirathbhai Dholaria, USA
Katey Enfield, Canada
Roberto Ferrara, Italy
Meredith Giuliani, Canada
Francesco Guerrera, Italy
Tomonari Kinoshita, Japan
Gillianne Lai, Singapore
Marcin Nicoś, Poland
Ji Soo Park, Republic of Korea
Alexandre Reuben, USA
Sara Ricciardi, Italy
Katharine See, Australia
Michael Sharpnack, USA
Yaakov Tolwin, Israel
Joan Elias Walter, Netherlands
Marissa Williams, Australia

2016:
Daiana Becker-Santos, Canada
Ji An Hwang, Republic of Korea
Takahiro Karasaki, Japan
Elly Marcq, Belgium
Sandra Ortiz-Cuaran, France
Sara Ricciardi, Italy
Kadir Sarun, Australia
Kyle Wang, USA
Krista Wink, Netherlands
Hao-ran Zhai, China

2015:
Lynnette Fernandez-Cuesta, France
Brandon S. Sheffield, Canada
Kenichi Suda, Japan
Dawei Yang, China
Clara Pérez-Rambla
Wenjing Zhang , China
Tomasz Powrózek, Poland
Yoshihisa Kobayashi, USA
Ji Yun Lee, Republic of Korea
Dana Tsui, USA

2013:
Kathryn Gold, USA
Vinai Gondi, USA
Jill Larsen, Austalia
Yu Liu, China
Tatsuo Maeyashiki, Japan
Victor Martinez, Canada
Geoffrey Oxnard , USA
Tai Sun Park, Republic of Korea
Jessica Sieren, USA

2011:
Jamie Chaft, USA
Katey Enfield, Canada
Maxim Freidin, UK
Jian-mei Hou, China
Hyojin Kim, Republic of Korea
Marie Loh, Singapore
Gunita Mitera, Canada
Larissa Pikor, Canada
Yoshihisa Shimada, Japan
Neeta Somaia, USA
James Sullivan, USA
Kelsie Thu, Canada
Robert van Boerdonk, Netherlands
Naomi Verstegen, Netherlands
Emily Ann Vucic, Canada

2009:
James Sullivan, USA
William Lockwood, Canada
Toby Campbell, USA
Yukihiro Yoshida, Japan
Loretta Erhunmwunsee, USA
Ryu Kanzaki, Japan
Judith van Loon, Netherlands
Nicolas Girard, France
Raymond Jang, Canada
Linna Li, China

2007:
Digambar Behera, India
Kashif Iqbal, Pakistan
Polina Gervas, UK
Sreeja Leelakumari, Canada
Qinghua Zhou, China
Bernadette Asuncion, USA
Alena Mikhalenka, Belarus
Shambhu Dutta Joshi, India
Shankpal Pramod, India
Jaime Guachalla, Chile

- **Nurse or Allied Health Professional Education Awards**

Started in 2017, the Nurse or Allied Health Professional awards consist of up to five awards offered in two categories: Early Career (started in 2017) and Developing Nations (2023). The number of awards in each category is approximately equal to the final numbers determined by the quality of applications received. The awards provide opportunities for Nurse and Allied Health presenters of high-rated abstracts to grow professionally by attending educational sessions, networking, and developing professional relationships with colleagues from around the world. Award Recipients include:

2022:
Lakedia Banks, USA
Imanuely Borchardt, Brazil
Amanda Moore, USA
Andreja Sajnic, Croatia

2019:
Somaya Abouabdou, Egypt
Gisele Moreira, Brazil
Carolyn Roberts, Canada

2018:
Csaba Laszlo Degi, Romania
Barbara Gutierres, Brazil

2017:
Zhi Xuan Lin, Taiwan
Laerke Winther, Denmark

- **Patient Advocate Educational Travel Awards (formerly Advocacy Award)**

The IASLC Patient Advocate Educational Awards provide an opportunity for patients/survivors, carers/caregivers, and patient advocates to be a part of IASLC's most anticipated global conference: the IASLC WCLC. The number of educational awards is limited to a maximum of five. Fewer than the maximum amount can be awarded, depending on interest, qualifications of the applicants, and the review process. Special consideration is given to applicants who have never been awarded a Patient Advocate Educational Award (formerly the Patient Advocate Travel Award). In 2011, the award was called the Advocacy Award. In 2016 the award name was changed to the Patient Advocate Educational Travel Award. Award Recipients include:

2023:
Aditya Manna, India
Yvonne Diaz, UK
Annabelle Gurwitch, USA
Graham Hall, Australia
Joseph Isaac, Nigeria
Miryana Pérez Vela, Mexico

2022:
MaryAnn Bradley, Canada
Seamus Cotter, Ireland
Dusty Donaldson, USA

2019:
Christine Qiong Wu, Canada
Csaba Laszlo Degi, Romania
Gina Hollenbeck, USA
Paul Brown, Australia
Weini Qiu, China

2018:
Caleb Egwuenu, Nigeria
Nabanita Mandal, India
Erin Sarauer, USA
Juanita Segura, USA
Vivek Tomar, India

2017:
Anne Marie Cerato, Canada
Annie Cacciato, USA
Aditya Manna, India
Andrea Prias, Peru
Csaba László Dégi, Romania

2016:
Kazuo Hasegawa, Japan
Lillian Leigh, Australia
Ide Mills, USA
Ewelina Szmytke, Poland

2011:
Darby Anderson, USA
Linda Wenger, USA
Alexandra Butcher, Australia
V.P. Shankpal, India
Kim Norris, USA

- **Early Career in Tobacco Control and Smoking Cessation Awards**

Established in 2023, the Early Career in Tobacco Control and Smoking Cessation Awards are available for fellows, students, trainees, or post-doctoral researchers with a professional degree within three years of initial faculty appointment. This award provides the opportunity for presenters of high-rated abstracts to grow professionally by attending educational sessions, networking, and developing professional relationships with colleagues from around the world. Award Recipients include:

2023: Xinan Wang, USA

- **Developing Nation in Tobacco Control and Smoking Cessation Awards**

Established in 2023, the Developing Nation in Tobacco Control and Smoking Cessation Awards are available for trainees and residents of nations listed on the IASLC Membership Guidelines webpage.* The individual must submit a high-quality abstract addressing epidemiological data from their country or have undertaken educational or policy development activities aimed at tobacco control. Award Recipients include:

2023: Silvia Novello, Italy

- **IASLC International Mentorship Program**

The IASLC International Mentorship Program is a time-honored professional development program dedicated to the principles of education, mentorship, and collaboration for early-career thoracic malignancies-focused physicians and researchers from economically developing countries globally. The IASLC International Mentorship Program is an initiative designed to develop today's young investigators into tomorrow's thoracic oncology leaders. Each year's participants are assigned well-established mentors who live and work in the region where the IASLC's annual WCLC is taking place. Mentees meet their mentors on-site at the conference and then following the WCLC, they travel to their mentor's institution for a week to learn from the mentor and meet, interact, and share ideas with other multidisciplinary cancer care and research teams there.

2023:
Rui Fu, China
Edwin Nugroho Njoto, Indonesia
Jayson Paragas, Philippines
Raghda Taleb, Egypt
Yang Wo, China
Meimei Zheng, China

2019:
Puji Raharja Santosa, Indonesia
Rachel Freeman, USA
Jinghua Chen, China
Wannisa Laosuangkoon, Thailand
Jitendra Meena, India

2018:
Banu Atalar, Turkey
Manoj Gowda, India
Nehemiya Igulu Bandese, Uganda
Yangsi Li, China
Brooklyn Mazure, Canada
Valliappan Muthu, India
Julieta Pandolfi, Argentina
Kuruswamy Prasad, India
Teerada Siripoon, Thailand
Jelena Spasic, Serbia
Shuyuan Wang, China
Jia-Tao Zhang, China
Chao Zhang, China

2017:
Noor Alsaadoun, Canada
Aseem Rai Bhatnagar, India
Wandee Chanprasertpinyo, Thailand
Valeria Denninghoff, Argentina
Jin Kang, China
Madiha Kanwal, Czech Republic
Sze Shyang Kho, UK
Milica Kontic, Serbia
Wenhua Liang, China
Fariz Nurwidya, Indonesia
Abhishek Shankar, India
Voralak Vichapat, Thailand
Mian Xie, China

2016:
Sandhya C. Acharya, Nepal
Ihsan Alloubi, Morocco
Marisol Arroyo Hernandez, Mexico
Silvia Josefina Ayala León, Paraguay
Chanchai Charonpongsuntorn, Thailand
Fábio Chaves, Brazil
Kezhong Chen, China
May Myat Cho, Thailand
Paola De la Iglesia, Argentina
Carolina Gabay, Argentina
Shaodong Hong, China
Omer Giray Intepe, Turkey
Deepali Jain, India
Ashish Jakhetiya, India
Milica Kontic, Serbia
Tomi Kovacevic, Serbia
Vinaya Kumar, India
Delfin Lovelina Francis, India
Rosa Luz, Luna Palencia, Mexico
Jose Nicolas Minatta, Argentina
Xiaomin Niu, China
Pierpaolo Pastina, Italy
Sandra Perdomo, Colombia
Fawaz Pullishery, Saudi Arabia
Xiaohua Shi, China
Chunxia Su, China
Adam Szpechcinski, Poland
Vikas Talreja, India

Satheesh Thungappa, India
Fengying Wu, China
Daniela Xhemalaj, Albania
Yi-Chen, Zhang, China

2015:
Rafael Bitton, Brazil
Saul Campos Gomez, Mexico
Juliano Coelho, Brazil
Rania Gaber, Egypt
Maria Jose Labanca, Argentina
Zoltan Lohinai, Hungary
Daniela Morales-Espinosa, Spain
Ahmed Nagy, Egypt
Ren Shengxiang, China
Soumyajit Roy, India
Phannin Tiraswasdichai, Thailand
Long Jiang, China
Raharam Burrah, India

2013:
Natthaya Triphuridet, Thailand

- **IASLC Academy**

The IASLC Academy is a prestigious program geared towards early-career physicians worldwide aspiring to pursue academic careers in thoracic oncology. Guided by leading experts, participants benefit from mentorship, research opportunities, and career development insights. The Academy mentors are seasoned professionals who offer guidance and assistance to mentees undertaking research projects within diverse realms of medical and radiation oncology, pathology, and thoracic surgery. Through their extensive experience, mentors serve as invaluable resources, imparting knowledge and expertise to early career professionals. They facilitate the development of essential skills, such as communication, presentation abilities, grant writing, and navigating the complexities of funding. Additionally, mentors help mentees tackle global challenges by fostering problem-solving abilities tailored to the unique landscape of their respective fields. In essence, these mentors play a pivotal role in shaping the next generation of professionals by equipping them with the tools and insights necessary for success in their careers.

2023:
Marina Baine, USA
Mariana Brandao, Belgium
Ferdinando Cerciello, Switzerland
Francesco Cortiula, Italy
Alessandro Di Federico, Italy
Kathryn Engelhardt, USA
Marjolein Heuvelmans, Netherlands
Melinda Hsu, USA
Yiqing Huang, China
Aditya Juloori, USA
Yeon Wook Kim, Republic of Korea
Alessandro Leonetti, Italy
Melina Marmarelis, USA
Vanessa Menezes, Brazil
Shrinidhi Nathany, India
Federica Pecci, Italy
Pedro Rocha, USA
Khvaramze Shaverdashvili, USA
Misty Shields, USA
Nathan Yu, USA

2021 & 2022:
Brian S Henick, USA
Manglio Rizzo, Argentina
Coral Olazagasti , USA
Carlos Cabrera-Gálvez, Argentina
Hashim Ismail, India
Guilherme Harada, Brazil
Stephanie Saw, USA
Giovanni Rossi, Italy
Barliz Waissengrin, USA
Ilit Turgeman, Israel
Keigo Kobayashi, Japan
Nicole Carriel, Chile
Konstantinos Leventakos, USA
Mihaela Aldea, France
Joseph Murray, USA

2019 & 2020:
Mehmet Altan, USA
Shahed Badiyan, USA
Andrew Bang, Canada
Sabina Berezowska, Switzerland
Fábio de Figueirêdo Chaves, Brazil
Carlo Genova, Italy
Maria Aime Giorlando, Argentina
Mohamed Gouda, USA
Manoj Gowda, India
Jin Kang, China
Victoria Lai, USA
Rebecca Moor, Australia
Alessandro Russo, Italy
Yu Yang Soon, Singapore
Aaron Tan, Singapore
Jamal Zaini, Indonesia

2017 & 2018:
Surein Arulananda, Australia
Ahmed Badawy, Egypt
Marta Honorio, Portugal
Jennifer Lewis, USA
Jessica Lin, USA
Tan Ling, Singapore
Benjamin Lok, Canada
Alexander Louie, UK
Deebya Mishra, Nepal
Fabio Moraes, Canada
Pablo Munoz, Chile
Francesco Passiglia, Italy
Erin Schenk, USA

- **STARS, STARS Scholars, STARS Mentors, and PRAs**

The STARS Scholar Program is for people who have or had lung cancer and their family members. People who do not have this personal connection to a person who has or had lung cancer are not eligible to apply. Applicants must be active patient research advocates (PRAs). Previous participants in the STARS Scholar program may apply to participate in the Scholar Program again. Successful completion of the STARS PRA program is desirable, but is not required and does not guarantee acceptance into the Scholar Program.

STARS 2019:
Susan McCullough, Australia
Kimberley MacIntosh, Canada
Caleb Egwuenu, Nigeria
Shelly Engfer-Triebenbach, USA
Laura Greco, USA
Lillian Leigh, Australia
Jill Hamer-Wilson, Canada
Dusty Donaldson, USA
Upal Basu Roy, USA
Jill Feldman, USA

STARS Scholars:
Dave Bjork, USA
Emi Bossio Bell, Canada
Bruce Dunbar, USA
Caleb Egwuenu, Nigeria
Michel Itel, Australia
Angus Pratt, Canada
Lorraine Tyler, Australia
Wayne Yeung, USA

STARS Mentors:
Anne-Marie Baird, Ireland
Upal Basu Roy, USA
Andrew Ciupek, USA
Jill Feldman, USA
Lillian Leigh, Australia

STARS PRA:
Chris Conneran, USA
Elizabeth Dols, USA
Laura Floyd, Canada
Deborah Friedman, USA
Larry Gershon, USA
Tiffini Joseph, USA
Tarunima Malik Grover, India
Barbara Martin, USA
Oonagh McArdle, Ireland
Tim Monds, Canada
Aileen Murgatroyd, UK
Pierre Onda, USA
Deirdre Russo, USA
Oskar Torberger, Sweden
Lorraine Tyler, Australia

Patient Advocate Educational Award:
Joseph Isaac, Nigeria
Graham Hall, Australia
Yvonne Diaz, UK
Annabelle Gurwitch, USA
Aditya Manna, India
Miryana Pérez Vela, Mexico

IASLC RESEARCH GRANTS AND FELLOWSHIPS

Adequate research funding is key to furthering developments in lung cancer treatment. By partnering with foundations, nonprofits, corporations, and individual donors, the IASLC has provided several Research Grants each year since the first IASLC Fellowship was awarded in 2000.

The IASLC Research Grants Program funds the training of researchers who wish to pursue careers in lung cancer diagnosis, treatment, or laboratory research as well as other aspects of the study of lung tumors. To support investigators in throughout their career continuum, the IASLC offers three distinct types of Research Grants:

- **Fellowships:** IASLC Fellowships support individuals who will be in fellowship training or its equivalent for the duration of the grant funding. Fellowship candidates must be mentored by a Principal Investigator (PI) who agrees to supervise the candidate and oversee the proposed project. Recipients receive this support during a pivotal and early time in their career when fellowship support has an important role for the continuation of careers as well as the successful completion of targeted research.

- **Young Investigator Grants:** IASLC Young Investigator Grants support individuals who are within five years of their initial faculty appointment and who serve as the Principal Investigator of the proposed project.

- **Mid-Career/Junior Faculty Grants:** IASLC Mid-Career/Junior Faculty Grants support individuals who are within 5-10 years of their initial faculty appointment.

Following is a selection of awarded IASLC Research Grants:

- **IASLC Young Investigator Grant**

Started in 2004, this grant is for investigators who are ready to begin independent research studies. The IASLC Foundation offers numerous grants on an annual cycle, dependent on geographic region of applicant. These one-year grants are for $50,000 in research funding. Past recipients include:

2023:
Amy Cummings, University of California, United States
Adrien Constantini, Université Paris, France

2022:
Dr. Zsolt Megyesfalvi, National Koranyi Institute of Pulmonology, Hungary
Dr. Lawson Eng, Princess Margaret Cancer Centre, Canada
Dr. Molly Siu Ching Li, The Chinese University of Hong Kong, Hong Kong SAR China
Dr. Gavitt Woodard, Yale University School of Medicine, United States
Dr. Stephanie Saw, National Cancer Centre Singapore, Singapore
Dr. Colin Lindsay, The Christie NHS Foundation Trust, United Kingdom

2021:
Dr. Kelsie Thu, St. Michaels, Hospital, University of Toronto, Canada
Dr. Miriam Jamal-Hanjani, University College London Cancer Institute, United Kingdom
Dr. Rachel Dodd, The University of Sydney, Australia
Dr. Chiara Ambrogio, University of Turin, Italy
Dr. Andrew Chow, Memorial Sloan Kettering Cancer Center, United States

2020:
Dr. Hua Zhang, New York University School of Medicine, United States
Dr. Cleo Goyvaerts, Vrje Universiteit Brussels, Belgium
Dr. Wencai Zhang, University of Central Florida, United States

2019:
Dr. Roberto Ferrara, I.R.C.C.S. National Cancer Institute, Italy
Dr. Ashanya Malalaserkera, Concord Cancer Centre, Australia
Dr. Ashwin Somasundaram, UPMC Hillman Cancer Center, United States

2018:
Dr. Benjamin Lok, Princess Margaret CC, Toronto
Dr. John Charles Rotondo, University of Ferrara Italy, Italy
Dr. Aaron Tan, National Cancer Centre Singapore, Singapore

2017:
Dr. Paolo Ceppi, Interdisciplinary Center for Clinical Research (IZKF) Friedrich-Alexander University Erlangen, Germany
Dr. William Lockwood, British Columbia Cancer Agency, Canada
Dr. Pedro Medina | University of Granada, Spain

2016:
Dr. Esra Akbay, UT Southwestern Medical Center at Dallas, United States
Luiz Araujo, Brazilian National Cancer Institute, Brazil
Dr. Julie George, University of Cologne, Germany

2015:
Dr. Mark Awad, Dana-Farber Cancer Institute, United States
Dr. Jill Larsen, QIMR Berghofer Medical Research Institue, Australia
Dr. Adrian Sacher, Princess Margaret Cancer Centre, Canada
Dr. Kenichi Suda, Kinki University, Japan
Dr. Silvestre Vicent, Center for Applied Medical Research, Spain

2013:
Dr. Narendra Wajapeyee, Yale University, United States

2012:
Dr. Anne-Marie Baird, St. James Hospital/Trinity College, Ireland
Dr. Alexander Drilon, Memorial Sloan-Kettering Cancer Center, United States
Dr. Jih-Hsiang Lee, National Taiwan University Hospital, Taiwan
Dr. Don Nguyen, Yale University, United States

2011:
Dr. Milind Suraokar, University of Texas MD Anderson Cancer Center, United States

2010:
Dr. Tanawat Jirakulaporn, Siriraj Hospital, Thailand

2009:
Dr. Yuichi Machida, May Rochester dba Mayo Clinic College of Medicine, United States
Ms. Monica Spinola, The University of Texas Southwestern Medical Center, United States

2008:
Dr. Prasad Adusumilli, Memorial Sloan Kettering Cancer Center, New York, United States
Dr. D. Ross Camidge, University of Colorado Comprehensive Cancer Center, United States
Dr. Boone Goodgame, Washington University School of Medicine, United States

2007:
Mr. Mohammed Hoque, John Hopkins University, United States
Dr. Mark Klein, University of Minnesota, United States

2004:
Assoc. Professor Benjamin Solomon, Peter MacCallum Cancer Center, Australia

- **IASLC Fellowship Grants**

Exclusive to fellows, these grants provide $50,000 for a one-year research project. Opportunities are numerous and based on the geographic region of the applicant.

2023:
Luis Prieto, Mayo Clinic, United States
Griselda Awanis, Cancer Research UK Manchester Institute, United Kingdom
Regina Hoo, National Cancer Center Singapore, Singapore

2022:
Dr. Amila Suraweeera, Queensland University of Technology, Australia
Dr. Elena Torreggiani, University of Ferrara, Italy
Dr. Ting-Yu Shih, Boston University, United States
Dr. Marco Tagliamento, Gustave Roussy, France
Dr. Adithya Basasubramanian, Walter & Eliza Hall of Medical Research, University of Melbourne, Australia
Dr. Diego Serrano, Universidad de Navarra, Spain
Dr. Lavanya Sivapalan, Sidney Kimmel Cancer Center, Johns Hopkins University, United States

2021:
Dr. Joao Victor Alessi, Dana-Farber Cancer Institute, United States
Dr. Mohammad Aarif Siddiqui, University of Southern Denmark, Denmark
Dr. Claudia Freitas, Centro Hospitalar e Universitário de São João e Faculty of Medicine, University of Porto, Portugal
Dr. Afaf Abed, Edith Cowan University, Australia
Dr. Adithya Balasubramanian, Walter & Eliza Hall Institute of Medical Research, University of Melbourne, Australia
Dr. Jose Carlos Benitez, Insitut Gustave Roussy, France
Dr. Misty Shields, University of South Florida, Moffitt Cancer Center, United States

2020:
Dr. Karmele Valencia, University of Navarra, Spain
Dr. Kasey Cargill, UT MD Anderson Cancer Center, United States
Dr. Biagio Ricciuti, Dana-Farber Cancer Institute, United States

2019:
Dr. Mark Adams, Translational Research Institute, Queensland University of Technology, Australia
Dr. Hanbo Chen, VU University Medical Center, Amsterdam

2018:
Dr. Anastasios Dimou, University of Colorado, United States
Dr. Laura Mezquita, Gustave Roussy, France
Dr. Sanghyuk Song, Kangown National Univ. Hospital, Republic of Korea

2017:
Dr. Hou Guo, First Hospital of Shanxi Medical University, China
Dr. Masaoki Ito, The Health and Sciences Research Institute of the "Germans Trias I Pujo" Foundation (IGTP), Japan

2016:
Dr. Siddhartha Devarakonda, Washington University School of Medicine, United States
Dr. Nicolas Reynoird, INSERM, France

2015:
Dr. Puey Ling Chia, Olivia Newton-John Cancer Research Institute, Australia
Dr. Colin Lindsey, Manchester Cancer Research Centre, UK
Dr. Yoichiro Mitsuishi, Juntendo University Hospital, Japan
Dr. Sara Pilotto, University of Verona, Italy

2014:
Dr. Samuel Rowbotham, Boston Children's Hospital, United States
Dr. Steffen Sorensen, Aarhus University Hospital, Denmark

2013:
Dr. Peter Choi, Dana-Farber Cancer Institute, United States
Dr. Daniela Morales Espinosa, Trias and Pujol Brothers University Hospital, Spain

2011:
Dr. Martin Sos, Max Planck Institute for Neurological Research, Germany
Dr. Yang Wang, Guangdong Lung Cancer Institute and Cancer Center, China

2010:
Dr. Daniel Chistoph, University of Colorado Health Science Center, Germany
Dr. Dawn Stults, Vanderbilt-Ingram Medical Center, United States

2009:
Dr. Don Gibbons, University of Texas MD Anderson Cancer Center, United States
Dr. Celine Mascaux, Hospitaux Universitaires de Strasbourg, France
Dr. Meredith Tennis, University of Colorado Denver Health Science Center, United States
Dr. Luca Toschi, Clinico Humanitas, Italy

2008:
Dr. Shantanu Banerji, CancerCare Manitoba, Canada
Dr. Khaled Hassan, University of Michigan, United States
Dr. M. Naomi Horiba, University of Maryland Marlene and Stewart Greenebaum Cancer Center, United States
Professor Sebahat Ocak, UC Louvain, Belgium
Professor Nir Peled, Soroka Medical Center, Israel
Dr. Ilse Valencia, UT Southwestern Medical Center at Dallas, United States

2007:
Dr. Romulo (Martin) Brena, The Ohio State University, United States
Dr. Grace Dy, Mayo Clinic-Department of Oncology, United States
Dr. Tanguy Lim-Seiwert, The University of Chicago, United States
Dr. David Shames, The University of Texas Southwestern Medical Center, United States

2006:
Dr. Daniela Basseres, University of North Carolina at Chapel Hill, Brazil
Dr. Rafal Dziadziuszko, Medical University of Gdansk, Poland
Dr. Hiromichi Ebi, Nagoya University Graduate School of Medicine, Japan
Dr. David Jackman, Dana-Farber Cancer Institute, United States
Assoc. Professor Thomas John, University Health Network, Ontario Cancer Institute, Princess Margaret Hospital, Australia
Professor Stefano Landi, University of Pisa, Italy
Dr. Jill Larsen, The Prince Charles Hospital, Australia
Dr. Elena Levantini, Beth Israel Deaconess Medical Center, United States
Professor Roman Thomas, Dana-Farber Cancer Institute, Harvard Medical School and Broad Institute of M.I.T. and Harvard, United States
Dr. Glen Weiss, University of Colorado Health Sciences Center, United States

2005:
Dr. Jeffrey Engelman, Dana-Farber Cancer Institute (Applicant), Harvard Medical School and Beth Israel Deaconess Medical Center (Supervisor), United States
Dr. Ten Hoang, University of Wisconsin Medical School Madison, United States
Dr. Remy Pedeux, Universite de Rennes, France

2004:
Dr. Christopher Lyon, Lovelace Respiratory Research Institute, United States
Dr. Julian Molina, Department of Oncology Mayo Clinic, United States
Dr. Maria Jose Pajares, University of Navarra, Spain
Dr. Samir Witta, Mountain Blue Cancer Care Center, United States

2003:
Ms. Federica Gemignani, International Agency for Research on Cancer (IARC), France

2002:
Dr. Zdravko Kosjerina, Institute for Pulmonary Diseases of Vojvodina, Serbia

2001:
Dr. Fred Hirsch, University of Colorado Denver, United States
Dr. Yunfei Wang, Dana-Farber Cancer Institute, United States

2000:
Dr. Jun Zhang, University of Kansas Medical Center, United States

- **LCFA/BMS/IASLC Disparities in Clinical Oncology Research Grants**

2022:
Dr. Jonathan Villena-Vargas, Weill Cornell Medicine, United States

- **LCFA/BMS/ILCF Young Investigator Research Grant in Translational Immuno-oncology**

To support research in translational immuno-oncology undertaken by early-career investigators that aim to improve the care and treatment of individuals with lung cancers. Up to two grants may be given in this funding cycle, and each will be $100,000 per year for up to two years.

2023:
Aparna Sharma, All India Institute of Medical Sciences, India

2022:
Dr. Adrian Sacher, Princess Margaret Cancer Center, Canada
Dr. Vincent Lam, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, United States
Dr. Jon Zugazagoitia, Hospital 12 de Octubre, Spain
Dr. Triparna Sen, Mount Sinai, United States

2019:
Dr. Jarushka Naidoo, Johns Hopkins University, United States
Dr. Daniel Spakowicz, The Ohio State University, United States

2018:
Dr. Katheryn Beckerman, Vanderbilt Health, United States
Dr. Zoltan Lohinai, National Koranyi Institute of Pulmonology, Hungary

- **LCFA/ILCF Lori Monroe Fellowship in Translational Lung Cancer Research Grant**

To support research in translational immune-oncology by early career investigators who aim to improve the care of individuals with lung cancer and reduce the burden of these diseases.

2019:
Dr. Haiying Cheng, Albert Einstein College of Medicine, United States
Dr. Kellie Smith, Johns Hopkins University, United States

2018:
Dr. Alice Berger, Fred Hutchinson Cancer Research Center, United States
Dr. Christine Lovly, Vanderbilt University School of Medicine, United States

2017:
Dr. Carla Martins, University of Cambridge, United Kingdom
Dr. Kellie Smith, Johns Hopkins University, United States

- **Boehringer Ingelheim IASLC Foundation Chinese Research Fellowship Award**

2019:
Dr. Sumei Lu, Ohio State University Medical Center, United States

2017:
Dr. Deshui Jia, Shanghai General Hospital, China
Dr. Shengxiang (Harry) Ren, Tongji University, China

2015:
Dr. Yayi He, Shanghai Pulmonary Hospital, China

2014:
Dr. Xiangkun Han, Institute of Biomchemistry and Cell Biology, China

2013:
Dr. Lulu Yang, Guangdong General Hospital & Guangdong Academy of Medical Sciences, China

- **Prevent Cancer Foundation and the IASLC Foundation Joint Research Grant**

2019:
Dr. Keshav Raj Paudel, University of Newcastle, Australia

2018:
Dr. Atiqur Rahman, Hunter Medical Research Institute, University of Newcastle, Australia

2015:
Dr. Valsamo Anagnostou, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, United States

2013:
Dr. Patrick Forde, Johns Hopkins University, United States

- **LCFA Fellowship Grant**

2019:
Dr. Daniel Costa, Beth Israel Deaconess Medical Center, United States

2010:
Dr. Jessica Donington, New York University School of Medicine, United States
Dr. Geoffrey Liu, Princess Margaret Cancer Hospital, Canada

- **Addario Lung Cancer Foundation Young Investigator Grant**

2017:
Dr. Evgeny Izumchenko, University of Chicago, United States

2016:
Robin Mjelle, Norwegian University of Science and Technology NTNU, Norway

- **IASLC/Lung Ambition Alliance Junior Faculty Research Grant for the Study of COVID-19 and Lung Cancer**

2020:
Dr. Mattia Boeri, Fondazione IRCCS Istituto Nazionale Tumori Milano, Italy
Dr. Jun-Chieh Tsay, New York University Medical Center, United States
Dr. Jeremias Sulam, Johns Hopkins Univeristy, United States
Dr. Amit Kulkarni, University of Minnesota, United States

- **APLCC Fellowship Grant**

2016:
Dr. Apichat Tantraworasin, Chiang Mai University, Thailand

2017:
Dr. Piyada Sitthideatphaiboon, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thailand

- **Free ME From Lung Cancer (FMFLC) and ILC Foundation (ILCF) Joint Fellowship Grant for the Early Detection of Lung Cancer**

2018:
Dr. Eva Koziolek, UCLA, United States

- **IASLC John Fisher's Legacy Fellowship Grant**

2020:
Dr. Robert Smyth, Boston Medical Center, United States

2019:
Dr. Tejas Patil, University of Colorado Denver, United States

- **Simon Chan Shang Whai - IASLC - LFA Cancer Research Travel Award**

2013:
Dr. Jiayu Li, Shanghai Pulmonary Hospital, China
Dr. Yuanyuan Li, Gleneagles Hospital, Hong Kong
Dr. Qixue Wang, Tianjin Medical University General Hospital, China

5

OTHER IASLC MEETINGS/WEBINARS

In addition to holding the WCLC, the IASLC has throughout history arranged smaller, topic-focused workshops and seminars to spread information about thoracic neoplasms, basic and clinical research, standards of care, advocacy, and more. Some workshops have been held with the sole purpose of gathering smaller groups of experts in the field to discuss and interpret the newest research in the field (e.g., EGFR, Small-Cell Lung Cancer, Prevention, Combined Treatment Modalities, Mesothelioma, Immunotherapy, and more).

Over the last decades regional conferences were developed in order to educate (younger) regional investigators and focus on specific regional issues related to lung cancer. The Latin American Lung Cancer Conference (LALCA) was developed in collaboration with local lung cancer investigators and initiated by Drs. Bunn, Yamaguchi, Hirsch, and Scagliotti in Sao Paulo, Brazil in 2004. The Asian-Pacific Lung Cancer (APLC) Conferences followed the same model and were initiated by Dr. Sumitra Tongprasert from Chiang Mai University in Thailand in collaboration with Drs. Bunn, Hirsch, and Scagliotti. The first APLC was held in Chiang Mai, Thailand in 2004. The inaugural European Lung Cancer Conference, was developed in partnership with the European Society for Medical Oncology (ESMO) and was held in Geneva in 2008 and was initiated by Drs. Bunn, Stahel, and Hirsch. Hosted in Chicago, IL, the North American Lung Cancer Conference (NACLC) was initially established with ASCO and ASTRO, but was later solely organized by the IASLC. Efforts to establish a similar regional conference in the Middle East and African regions included The IASLC Africa Conference on Lung Cancer held in Tangier, Morocco in 2018 initiated by Drs. David Carbone and Fred Hirsch.

Special acknowledgment is given to Mrs. Pia Hirsch, who with colleagues in the IASLC Headquarters Office worked tirelessly during much of this earlier history of IASLC meetings, overseeing their tremendous growth and deliveries worldwide. Throughout its 50-year history, on all continents but Antarctica, IASLC activities have included regional conferences, joint events offered in cooperation with other leading organizations, as well as endorsed events. The international identity of the IASLC recognizes and taps into the network of international experts, practitioners, and others in the global lung cancer community to share advances made and delivered in every area of the world.

The development of digital communications and capabilities in the last 25 years has added virtual opportunities to join colleagues together in learning from each other and thought leaders across the world not just those in the same room. The global pandemic forced the IASLC, like most organizations, to redefine meetings with colleagues from gatherings in which attendees sit together to events in which attendees greet each other via a screen in their respective offices or homes. Because of its history of hosting an ongoing global exchange of ideas, the IASLC was well-positioned to move into this digital meeting arena and thrive.

Tables 1 and 2 list, respectively, IASLC meetings held singly or jointly, or endorsed since 2015, and webinars since 2017. IASLC webinars are distinct from live meetings in which an attendee can participate virtually.

Educational Events. Today when describing its educational events, the IASLC organizes and lists them alongside the detailed list of IASLC conferences. Accredited by the Accreditation Council on Continuing Medical Education (ACCME) in 2012 to be a provider of continuing medical education, the IASLC expanded its roster of educational offerings since that time. The ability to deliver educational events live, digitally, or in a hybrid fashion, also has enabled a wider platform of IASLC educational activities for participants to choose from and later transition the information learned into the clinic. In addition, following a survey of the IASLC membership in the early 2010s regarding the need for educational materials for paramedical professionals, the IASLC formed new committees to support the increase of educational activities available to nurses and allied health professionals.

MEETINGS

Table 1. IASLC Meetings 2024-2015

IASLC Conferences & Meetings	Meeting Name	Location	Date
Endorsed	Artificial Intelligence for Oncology	Milan, Italy	5/10/2024
Endorsed	1st Annual AGILE Conference	Madrid, Spain	5/9/2024
Endorsed	3rd International Summit on Lung Cancer	Rome, Italy	5/5/2024
Endorsed	2024 Texas Lung Cancer Conference	Austin, TX	4/18/2024
Endorsed	All Ireland Lung Cancer Conference	Dublin, Ireland	4/12/2024
Endorsed	European Lung Cancer Congress	Prague, Czech Republic	3/20/24-3/23/24
	Targeted Therapies of Lung Cancer	Santa Monica, CA	2/21-2/24/24
Endorsed	II International Thoracic Cancer Debates 2024	Canary Islands, Spain	2/2-2/3/24
	The Basics of Pain Management for Cancer Patients from Diagnosis to Palliative Care – Thoracic Cancer Edition	Chicago, IL	12/1/2023
	North America Conference on Lung Cancer	Chicago, IL	12/1-12/3/23
Endorsed	SBOC XXIV Congress 2023	Rio de Janiero, Brazil	11/16-11/19/23
	Hot Topics in Basic & Translational Science: Resistance to IO in NSCLC	Brussels, Belgium	11/10-11/12, 2023
Endorsed	5th International Lung Cancer Summit	Lausanne, Switzerland	11/10/2023
Endorsed	Best of WCLC 2023 Korea	Seoul, Korea	10/28/2023
Endorsed	DC Lung Cancer Conference 2023	Washington, DC	10/7/2023
Endorsed	Best of WCLC 2023 San Francisco	San Francisco, CA	9/30/2023
Endorsed	Best of WCLC 2023 Italy	Online	9/20-9/21/23
	CT Screening Symposium	Singapore	9/9/2023
Endorsed	24th Annual PER Internaltional Lung Cancer Congress	Huntington Beach, CA	7/27-7/29/23
Endorsed	2023 TOGA Annual Scientific Meeting	Melbourne, Australia	7/19-7/21/23
Endorsed	44th International Conference on the Screening for Lung Cancer & 12th Conference on Research for Early Lung Cancer Treatment	Verona, Italy	6/28-6/30/23
Endorsed	iMig International conference	Lille, France	6/26/2023
Endorsed	Great Debates & Updates in Lung Cancers Conference	Chicago, IL	5/4/2023
	Hot Topic Meeting: Small Cell Lung Cancer	New York, NY	4/5-4/7/23
Endorsed	Texas Lung Cancer Conference	Austin, TX	3/31/2023
Joint Event	European Lung Cancer Congress	Copenhagen, Denmark	3/29-4/1/23

Table 1 cont.

IASLC Conferences & Meetings	Meeting Name	Location	Date
	Targeted Therapies of Lung Cancer	Santa Monica, CA	2/22-2/25/23
	Latin America Conference on Lung Cancer	Montevideo, Uruguay	1/25-1/27/23
Endorsed	3rd Oncobroncho MDT Meeting: Creation & Innovation	Cairo, Egypt	1/19-1/20/23
Endorsed	DC Lung Cancer Conference 2022	Washington, DC	10/29/2023
	Asia Conference on Lung Cancer	Nara, Japan	10/27-10/29/22
	North America Conference on Lung Cancer	Chicago, IL	9/23-9/25/22
	CT Screening Symposium	Vienna, Austria	8/5/2022
Joint Event	ESTS-IASLC Annual Meeting	The Hague, Netherlands	6/19-6/21/22
Joint Event	ESTRO-IASLC: Advances in Radiotherapy for Lung Cancer	Copenhagen, Denmark	5/6-5/10/22
	Targeted Therapies of Lung Cancer	Santa Monica, CA	2/22-2/26/22
Endorsed	2nd Onco-Bronchology Multidisciplinary Meeting		1/20-1/21/22
	Latin America Conference on Lung Cancer	Online	12/3-12/4/21
Endorsed	Best of WCLC 2021 Japan	Yokohama, Japan	11/27/2021
Endorsed	Best of WCLC 2021 Korea	Virtual	11/13/2021
Endorsed	Simpoia Nacional GBOT 2021	Virtual	11/5-11/6/21
Endorsed	Quantitative Imaging Workshop	Virtual	11/4-11/5/21
Endorsed	Best of WCLC 2021 San Francisco	Virtual	10/30/2021
	Hot Topic Meeting: Small Cell Lung Cancer	Virtual	10/29-10/30/21
Endorsed	IV International Workshop on Genomic Testing in Cancer: Facing a New Era in Personalized Medicine	Virtual	10/27-10/29/21
Endorsed	9th International Pulmo-Delta (PD9) Conference of the Egyptian Society of Chest Diseases & Tuberculosis	Cairo, Egypt	9/30/2021
Endorsed	Best of WCLC 2021 Brazil	Virtual	9/23/2021
Endorsed	PER 22nd Annual International Lung Cancer Congress	Virtual	7/29-7/31/21
Joint Event	IASLC-ESTS Joint Session: 29th European Coference on General Thoracic Surgery	Virtual	6/20-6/22/21
	2021 CT Screening Symposium	Virtual	5/7-5/8/21
Endorsed	Oncology Update: Treatment Paradigm in 2021 & Beyond	Virtual	4/23-4/24/21
Joint Event	European Lung Cancer Congress 2021	Virtual	3/25-3/27/21
Endorsed	Best of WCLC Korea	Virtual	3/20/2021
	Targeted Therapies of Lung Cancer	Virtual	3/3-3/4/21
Endorsed	8th Lung Cancer Network Virtual Symposium: Bridging Science to Practice	Virtual	2/20/2021
Endorsed	Physician's Education Resource 18th Annual Winter Lung Cancer Conference	Virtual	2/5/2021
Joint Event	IASLC-ESTRO 2020	Virtual	11/28-12/1/20
Endorsed	Pulmonary Oncology: From Prevention to Advanced Disease Despite COVID-19	Virtual	11/9/2020
Endorsed	ECO Lung Summit	Virtual	10/29/2020
	North America Conference on Lung Cancer	Virtual	10/16-10/17/20
Endorsed	Arab-African International Cancer Congress (AAICC)	Virtual	10/8-10/9/20

Table 1 cont.

IASLC Conferences & Meetings	Meeting Name	Location	Date
	Hot Topic Meeting: Liquid Biopsy	Virtual	10/2-10/3/20
	WCLC Singapore Virtual Presidential Symposium	Virtual	8/7/2020
Endorsed	EACR 2020 Congress: Innovative Cancer Science	Virtual	6/18-6/19/20
Endorsed	III International Workshop on Genomic Testing in Cancer: Towards an Immune-Genomic Approach for Cancer Treatement	Virtual	5/14/2020
Joint Event	European Lung Cancer Congress	Cancelled	4/15-4/18/2020
Endorsed	From Tissue Sample Collection to Biomarker Testing	Colombia	3/4-3/6/20
	FDA-AACR-IASLC Workshop to Address the Criticality of Tobacco Use Assessment in Oncology Therapeutic Trials	Silver Spring, MD	2/28/2020
Endorsed	Australian Lung Cancer Conference	Australia	2/19-2/21/20
	Targeted Therapies of Lung Cancer	Santa Monica, CA	2/19-2/22/20
Endorsed	Lung Cancer 360 3rd Edition: Understanding the Lung Cancer Management Updates	Ismalia, Egypt	2/13-2/14/20
Endorsed	17th Annual Winter Lung Cancer Conference	Miami, FL	2/7-2/9/20
Joint Event	AACR-IASLC International Joint Conference: Lung Cancer Translational Science from the Bench to the Clinic	San Diego, CA	1/11-1/14/20
	Best of WCLC 2019: San Francisco	San Francisco, CA	11/23/2019
	Best of WCLC 2019: Hungary	Budapest, Hungary	11/21-11/23/2019
	Latin America Conference on Lung Cancer	Mexico City, Mexico	10/17-10/19/2019
	North America Conference on Lung Cancer	Chicago, IL	10/10-10/11/2019
	Best of WCLC 2019: India	New Delhi, India	9/22/2019
Endorsed	20th Annual International Lung Cancer Congress	Huntington Beach, CA	7/25-7/27/2019
	2019 Mesothelioma Meeting	New York, NY	7/10-7/12/2019
Joint Event	European Lung Cancer Conference	Geneva, Switzerland	4/10-4/13/2019
	Hot Topic Meeting: Small Cell Lung Cancer	New York, NY	4/3-4/5/2019
	Targeted Therapies of Lung Cancer	Santa Monica, CA	2/20-2/22/2019
	Evolution of Therapeutic Decision-Making for Advanced Squamous Cell Lung Cancer (SqCLC)	Virtual	12/3/2018
	Asia Conference on Lung Cancer	Guangzhou, China	11/8-11/10/2018
	Lessons Learned from Neoadjuvant Studies in Lung Cancer	Virtual	11/7/2018
	Latin America Conference on Lung Cancer	Cordoba, Argentina	8/15-8/18/2018
Joint Event	European Lung Cancer Congress	Geneva, Switzerland	4/11-4/14/2018
	Lung Cancer Immunotherapy Meeting	Madrid, Spain	3/22-3/24/2018
Joint Event	IASLC-FDA Lung Cancer Neoadjuvant Meeting	Bethesda, MD	3/1-3/2/2018
	Targeted Therapies of Lung Cancer	Santa Monica, CA	2/21-2/24/2018
Joint Event	AACR-IASLC International Joint Conference: Lung Cancer Translational Science from the Bench to the Clinic	San Diego, CA	1/8-1/11/2018
	ESMO 2017: Lung Cancer Highlights	Virtual	10/9/2017
	Chicago Multidisciplinary Symposium in Thoracic Oncology	Chicago, IL	9/14/2017
	Screening for Lung Cancer: What Clinicians Need to Know	Online	9/6/2017

Table 1 cont.

MEETINGS

IASLC Conferences & Meetings	Meeting Name	Location	Date
	Management of Squamous Cell Carcinoma of the Lung	Online	8/16/2017
	Proton Therapy for Lung Cancer	Online	8/8/2017
	Management of Immunotherapy Side Effects	Online	8/1/2017
	Advances in the Treatement of Lung Cancer: ASCO 2017 Update	Online	7/12/2017
	Biology & Treatment of Thoracic Neuroendocrine Tumors	Online	6/21/2017
	Immunotherapy: A New Standard of Care in NSCLC	Online	5/15/2017
Joint Event	European Lung Cancer Conference	Geneva, Switzerland	5/5-5/8/2017
	NSCLC: Management of Brain Metastases	Online	4/19/2017
	Side Effects of Immunce Checkpoint Inhibitors	Online	3/21/2017
	Management of Squamous Cell Carcinoma of the Lung	Online	3/16/2017
	Small Cell Lung Cancer Workshop	New York, NY	3/15-3/17/2017
	Immunotherapy for NSCLC: What's Next?	Online	2/7/2017
	Chicago Multidisciplinary Symposium in Thoracic Oncology	Chicago, IL	9/22-9/24/2016
	Latin America Conference on Lung Cancer	Panama City, Panama	8/25-8/27/2016
Joint Event	European Lung Cancer Conference	Geneva, Switzerland	4/13-4/16/2016
Joint Event	AACR-IASLC International Joint Conference	San Diego, CA	1/4-1/7/2016
Joint Event	European Lung Cancer Conference	Geneva, Switzerland	4/15-4/18/2015

WEBINARS

Table 2. IASLC Webinars 2024-2017

IASLC Webinars	Meeting Name	Date
	Best of TTLC 2024	3/29/2024
	Bronchoscopic Ablation Therapy for Lung Malignancies	2/15/2024
	2023 NACLC Highlights	12/7/2023
	2023 ESMO Highlights	11/15/2023
	2023 Radiation Oncology Updates Webinar	11/8/2023
	From WCLC23 to You: Presented by Lung Cancer Research Advocates	10/30/2023
Endorsed Webinar	KOL Knockout™: Cancer Pain Management Edition	10/30/2023
	2023 WCLC Highlights	10/13/2023
	Current Approaches and Future Directions in Radiotherapy for Small Cell Lung Cancer	8/29/2023
	Finding the Right Dose: Using Patient-Reported Data in Early Phase Clinical Trials	8/24/2023
	Emerging ADCs and Their Role in Advanced Lung Cancer Treatment	8/22/2023
	2023 ASCO Highlights	7/6/2023
	The Impact of Lung Cancer on Intimate Relationships	6/13/2023
	ESMO 2022 NSCLC Highlights	11/3/2022
	Real-World Data (RWD) Leading to Real-World Evidence (RWE)	10/28/2022
	ASCO 2022 - Meeting Highlights	8/1/2022
	Emerging Perioperative Treatment Using Immune Checkpoint Inhibitors in Patients with Resectable NSCLC	4/26/2022

Table 2 cont.

IASLC Webinars	Meeting Name	Date
	Updates on Liquid Biopsy for Advanced NSCLC: A Consensus Statement from the IASLC	1/11/2022
	World Conference on Lung Cancer 2021 Highlights	10/1/2021
	Global Access to Radiotherapy for Lung Cancer	9/22/2021
	What Do All Those Lines and Colors Mean? Interpreting Cancer Data Plots.	8/26/2021
	Prehabilitation: Optimizing Patients to Improve Outcomes - Part 2	7/13/2021
	Prehabilitation: Optimizing Patients to Improve Outcomes - Part 1	5/19/2021
	Challenging Cases in Lung SBRT	4/22/2021
	IASLC 2020 WCLC Singapore: Highlights	2/21/2021
	State-of-the-Art in Combination Immuno/Radiotherapy for Non-Small Cell Lung Cancer	1/20/2021
	Managing Clinical and Translational Research During COVID	1/15/2021
	Supportive Care of Lung Cancer Patients during COVID-19	12/8/2020
	Artificial Intelligence and Cost Effectiveness in Lung CT Screening	11/11/2020
	Cancer Drug Development in the Era of Precision Medicine	11/2/2020
	IV Propulmão360 - Liquid Biopsy for Cancer Detection	10/20/2020
	Treatment of Lung Cancer: 2020 ASCO Highlights	7/31/2020
	Exclusive Webinar: Treatment of Lung Cancer | 2020 ASCO Highlights	7/31/2020
	Impact of COVID-19 on the Diagnostic Workup of Lung Cancer	5/11/2020
	Systemic Therapy for Advanced Stage Lung Cancer During the COVID-19 Pandemic	4/29/2020
	Impact of COVID-19 on Treatment of Patients with Lung Cancer with Local or Locoregional Disease	4/28/2020
	Practical Practice Recommendations for Lung Cancer Radiotherapy During the COVID-19 Pandemic: An ESTRO-ASTRO Consensus Statement	4/20/2020
	Radiotherapy Highlights from WCLC & ASTRO 2019	12/11/2019
	Women & Lung Cancer: Screening, Treatment, and Beyond	8/29/2019
	A Special Webinar for Patient Research Advocates (PRA)	7/22/2019
	Multidisciplinary Management of Immune-Mediated Adverse Events in Lung Cancer	7/17/2019
	How to Interpret the Outcomes of Comparative Effeciveness Studies in Early Stage NSCLC: A Primer for Radiation Oncologists	6/25/2019
	Portuguese Language Webinar to Review the Updated Molecular Testing Guidelines	5/22/2019
	Spanish Language Webinar to Review the Updated Molecular Testing Guidelines	5/8/2019
	Biomarkers in Lung Cancer Screening	4/23/2019
	Lung Cancer Screening Using Low Dose Computed Tomography	3/28/2019
	The Implementation of Lung Cancer Screening: The Poland Experience	3/5/2019
	Management of Malignant Pleural Effusions: An Official ATS/STS/STR Clinical Practice Guideline	1/25/2019
	Local & Regional Recurrances Following SABR in Stage I NSCLC: Diagnosis & Management	12/18/2018
	Radiographic Assessment and Radiation Therapy for Malignant Pleural Mesothelioma	11/27/2018
	Radiotherapy Highlights from 2018 WCLC and ASTRO 2018 Annual Meeting	11/20/2018
	IASLC 19th WCLC Highlights	10/16/2018
	Surgery for Mesothelioma	10/3/2018

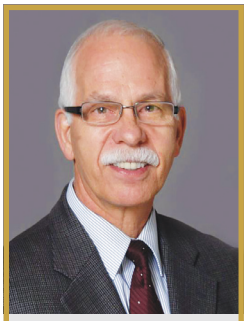
Table 2 cont.

IASLC Webinars	Meeting Name	Date
	New Approaches to the Treatment of Recurrent Small Cell Lung Cancer	9/19/2018
	Immunotherapy for Mesothelioma: Current Status & Future Directions	9/11/2018
	Locally Advanced NSCLC: Finally Progress	8/21/2018
	Treatement of Lung Cancer: 2018 ASCO Highlights	7/18/2018
	Treatment of ALK-Positive NSCLC: Current Status & Future Directions	6/26/2018
	EGFR–Mutant Lung Cancer in 2018	5/8/2018
	Thymoma Update: 2018	4/24/2018
	Genomic Analysis of Plasma Cell-Free DNA for Lung Cancer Management: An Imperfect Biomarker, But We Love It Anyway	4/10/2018
	Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment with Targeted Tyrosine Kinase Inhibitors: 2018	3/29/2018
	Immunotherapy for Early & Locally-Advanced NSCLC	3/13/2018
	Mesothelioma Update	2/27/2018
	Treatment Strategies for ROS1 NSCLC	2/6/2018
	Promising Novel Approaches to Lung Cancer	1/23/2018
	Spanish Language Webinar to Review the Updated Molecular Testing Guidelines	1/16/2018
	Liquid Biopsy for the Management of Non-Small Cell Lung Cancer	1/16/2018
	Small Cell Lung Cancer: Is It Time for Biomarker-Directed Therapy?	1/11/2018
	Smoking Cessation Within Tobacco Control: “Probably Not What You’re Thinking”	12/20/2017
	Evolution of SCLC Therapy: Chemotherapy & Beyond	12/6/2017
	Management of Stage III NSCLC	12/4/2017
	ASTRO 2017: Lung Cancer Highlights	11/15/2017
	IASLC Atlas of PD-L1 Testing in Lung Cancer	11/9/2017
	NSCLC Pathology & Molecular Testing: What Should Clinicians Know?	10/10/2017
	IASLC Atlas of ALK and ROS1 Testing in Lung Cancer	9/21/2017
	Radiotherapy Options in Patients with Brain Metastases from NSCLC	9/15/2017
	PD-L1 Assessment and Biomarkers for Immunotherapy	7/12/2017
	Adjuvant Therapy of Lung Cancer: New Perspectives	6/20/2017
	Locally Advanced NSCLC: Where Are We, Were Do We Go From Here?	5/9/2017
	Is There an Oligometastatic State in NSCLC	5/3/2017

6

IASLC JOURNALS

Today the *Journal of Thoracic Oncology* (JTO), IASLC's flagship medical journal, is the association's central publication vehicle for advancing new knowledge vital to the understanding and management of lung cancer and related thoracic neoplasms. Reporting the latest research in thoracic oncology, the JTO functions as an ambassador of the IASLC mission. The JTO's stands today as the dynamic journal of record in thoracic oncology, which is the result of historical achievements and decision of the Society and its ongoing editorial leadership (Figure 1).



Dr. James Jett, Founding JTO Editor, 2006-2012.

Mary Todd, JTO Managing Editor, 2006-2022.

Dr. James Jett, a pulmonologist from Mayo Clinic in the USA, with the support of Mary Todd, Managing Editor, oversaw the first JTO issue, which was published in January 2006 with an international Board of Associate Editors. JTO was a new journal at that time, revamped from its predecessor journal, *Lung Cancer*, which continues to publish today. After its first nine issues were released in 2006, JTO began to publish on a monthly in 2007. In March 2007, JTO was accepted by the National Library of Medicine for inclusion and indexing in MEDLINE and Pub Med.

From the start, JTO emphasized a multidisciplinary approach with a focus on original research (clinical trials and translational or basic research), reviews, and opinion pieces. The IASLC membership is the journal's core audience, in addition to those also involved in the research and treatment of lung malignancies including epidemiologists, medical oncologists, radiation oncologists, thoracic surgeons, pulmonologists, radiologists, pathologists, and research scientists with a special interest in thoracic oncology.

At the completion of Dr. Jett's term as Editor at the end of 2012, following an international search, Dr. Alex Adjei was appointed to be the second editor of JTO effective January 2013. Dr. Adjei quickly built on the journal's foundation and mission created by Dr. Jett and has led the journal to expand its impact and reach globally with the latest thoracic

Figure 1. Representative covers of the *Journal of Thoracic Oncology* 2006-2024.

oncology research and education. His goals included updating and aligning the editorial board membership to meet the challenges of the future to include representation from specialties such as genomics, genetic epidemiology, quality of life, symptom control, survivorship, outcomes research, health economics, and public policy. He emphasized that the new membership of the editorial board would continue to represent the multidisciplinary nature of thoracic oncology as well as the large international membership of IASLC. Even at this early stage of his editorship, he recognized the disparity between the amount of high quality scientific material to be published and the space constraints of the journal. Strict page limits were imposed and online only publication of some manuscript materials was implemented. In addition, some content, such as case reports and letters to the editor, were published online only. After several initial years in partnership with the publisher Lippincott (Wolters Kluwer), the IASLC office under Dr. Hirsch's leadership together with the Editor-in-Chief, Dr. Adjei, made a significant change in the journal's lay out, and the IASLC Board of Directors accepted the change of publisher to Elsevier in 2015.

The Board of Directors of the IASLC and the editorial office of the JTO, with the support of the publisher Elsevier, decided that JTO would become an electronic-only publication, starting January 2024. In addition to reducing the carbon footprint, this transition also aligned with the shift in how the journal was accessed. "The use of the JTO journal online increased dramatically over the course of the pandemic, with 1.4 million full-text downloads on the ScienceDirect platform in 2021 alone. In addition, from 2017 to 2021, full-text downloads on jto.org almost tripled from 800,000 to 2.1 million," said Dr. Adjei in his editorial.

Dr. Alex Adjei, JTO Editor-in-Chief, 2013-present.

Today JTO is the primary educational and informational publication for topics relevant to the prevention, detection, diagnosis, and treatment of all thoracic malignancies. In 2017 JTO's impact factor was over 10 for the first time (10.366), and in 2023 it doubled that (21.0) (Figure 2). Articles and topics of interest to Dr. Adjei and the JTO Editors are listed in Table 1, and a list of JTO articles published from the journal's launch up to January 2024 that make the top 15 most cited list are provided in Table 2.

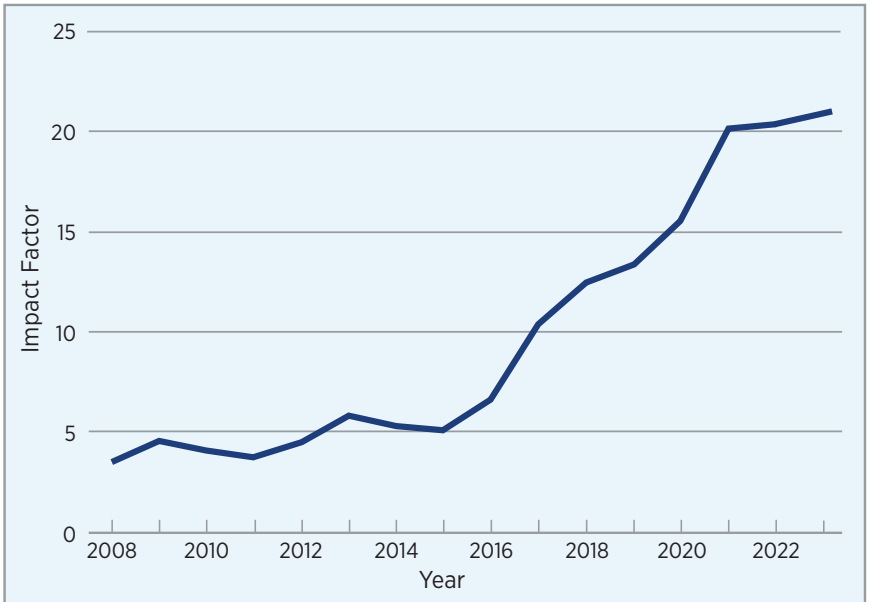


Figure 2. *Journal of Thoracic Oncology* Impact Factor 2008-2023.

Table 1. JTO Breadth and Reach: Topics and Articles of Interest

- Manuscripts dealing with epidemiology, prevention, screening, early detection, staging, cure, and treatment of thoracic malignancies.
- Submissions on tobacco control and cessation, particularly where there is direct relevance to lung cancer epidemiology and therapeutic outcomes.
- Submissions on pathologic and histologic classification and novel imaging and bronchoscopic approaches.
- Submissions regarding novel systemic therapies, particularly in the fields of biomarker targets, genomics, immunology, and cellular therapies.
- Novel radiotherapy and surgical techniques.
- Randomized phase II and phase III trials, as well as meta analyses of individual participant data.
- Basic science studies that have direct clinical and translational relevance.

Table 2. Lifetime Most Cited Articles. Articles Published From the Launch of JTO Up to January 2024 That Makes the Top 15 Most Cited List.

Article Title	Scopus Lifetime Citations
International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma › Travis W.D., Brambilla E., Noguchi M., et al.	3816
The 2015 World Health Organization Classification of Lung Tumors: Impact of genetic, clinical and radiologic advances since the 2004 classification › Travis W.D., Brambilla E., Nicholson A.G., et al.	2992
The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours › Goldstraw P., Crowley J., Chansky K., et al.	2992
The IASLC Lung Cancer Staging Project: Proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer › Goldstraw P., Chansky K., Crowley J., et al.	2871
Receiver operating characteristic curve in diagnostic test assessment › Mandrekar J.N.	2095
A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER) › Shi Y., Au J.S.-K., Thongprasert S., et al.	1062
PD-L1 immunohistochemistry assays for lung cancer: Results from phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project › Hirsch F.R., McElhinny A., Stanforth D., et al.	1020
Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer › Tian S., Hu W., Niu L., Liu H., Xu H., Xiao S.-Y	1019
The IASLC Lung Cancer Staging Project: A proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer › Rusch V.W., Asamura H., Watanabe H., Giroux D.J., Rami-Porta R., Goldstraw P.	933
Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: Updated results of 257 patients in a Japanese multi-institutional study › Onishi H., Shirato H., Nagata Y., et al.	826
Introduction to the 2015 World Health Organization Classification of Tumors of the Lung, Pleura, Thymus, and Heart › Travis W.D., Brambilla E., Burke A.P., Marx A., Nicholson A.G	702
Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology › Lindeman N.I., Cagle P.T., Beasley M.B., et al.	691
The international epidemiology of lung cancer: Geographical distribution and secular trends › Youlden D.R., Cramb S.M., Baade P.D.	649
The IASLC Lung Cancer Staging Project: Proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer › Rami-Porta R., Ball D., Crowley J., et al.	638
Checkpoint inhibitors in metastatic EGFR-mutated non–small cell lung cancer—A meta-analysis › Lee C.K., Man J., Lord S., et al.	620

JTO HIGHLIGHTS

- Editors and Editorial Board. Dr. Adjei has recruited global leaders to lead an expanded editorial board.
- Editorial Initiatives, such as "Lung Cancer Worldwide" and "Controversies in Thoracic Oncology."
- JTO response to the pandemic with publication of COVID articles. This includes the first reported pulmonary pathology article in the literature.
- Staging classification articles and representation of the IASLC research and data collection.
- Increase publication of randomized clinical trial results. (since Vienna).
- Different language editions over the years.

JTO MILESTONES

2013-2014

- Dr. Alex Adjei started his term as the second Editor-in-Chief of JTO
- New features introduced:
  1. The JTO Editor's Choice, a collection of articles that highlight certain topics of interest or importance each month. These articles are made freely available for a period of three months following their online publication.
  2. Each issue has sections called "In This Issue," "Research Watch" and "News-in-Brief," which summarize important thoracic oncology research findings and news within JTO and across other journals.
  3. There is also a monthly "Tobacco Control" column contributed by Dr. Emily Stone on behalf of the IASLC Tobacco Control Committee, reporting on research updates and news around the world related to tobacco control.
  4. Enhanced editorials: Editorials are soli by Dr. Adjei or Associate Editors to discuss important subjects corresponding with published JTO articles, which ultimately raise awareness, interest, and readership of the publications.

2015

- Elsevier was contracted to publish JTO starting with the January 2016 issue. The IASLC's partnership with Elsevier combined with Dr Adjei's clear vision has led to steady growth for the JTO.

2019

- The "Lung Cancer Worldwide" series was launched and offers insights into the epidemiology, screening and diagnosis, surgical management, radiation management, and systemic management of lung cancer in different countries around the globe. There are more than 45 articles published to date.

2020

- We curated a collection of articles on COVID-19 through a robust and expedited review process.
- The first article from the collection was published in March 2020, which demonstrated the first reported pulmonary pathology of COVID-19 in patients with lung cancer.[1] This is one of the most cited articles today.
- Highest number of submissions of all time: 2,007.
- In October 2020, Dr. Adjei was invited by Elsevier Research Academy to lead a webinar on "How to publish with the *Journal of Thoracic Oncology*."

2021

- Dr. Adjei is the inaugural recipient of the Adi F. Gazdar IASLC Merit Award in recognition of his accomplishments and contributions to cancer drug development and the lung cancer community.
- A new series called "Controversies in Thoracic Oncology" was introduced in March 2021. These are "Pro and Con" opinion pieces from experts dealing with topics that are open to debate. Currently, 28 articles have been published.

2022-2023

- Bailey Creamer, BFA, joined us in April 2022 as Editorial Assistant, providing support for the editorial office of the IASLC journals.
- In January 2023, Dr. Vun-Sin Lim was officially contracted as the Managing Editor of JTO.
- The "Tobacco Control" column celebrated its 10th year of reporting on tobacco control and smoking cessation around the world in March 2023. Dr. Emily Stone, the column editor, highlighted the topics she covered over the last decade in a special edition of the March issue.
- The IASLC Staging Articles is a collection of important publications from the IASLC Staging and Prognostic Factors Committee on staging classification and representation of the IASLC research and data collection. We have also curated a collection of articles for the Proposals for the Ninth Edition of TNM Stage Classification of Thoracic Tumors from this committee.
- New feature: "Graphical Abstracts" was introduced in 2023 to accompany a published article online, providing visual summary of key contents and findings to enhance readers' experiences.

Bailey Creamer, BFA, JTO and JTO CRR, 2022-present.

Dr. Vun-Sin Lim, Editorial Consultant, JTO CRR, 2020-2022; Managing Editor, JTO, 2023-present.

2024

- JTO is published online only, eliminating printed publications. Read Dr. Adjei's editorial "The Coming of a New Age: The *Journal of Thoracic Oncology* Goes Electronic in 2024."[2]
- As of April 2024, the Editorial Board has expanded to 80 editors and Editorial Board members from 26 countries, with 30% of female members.

JTO CLINICAL AND RESEARCH REPORTS

JTO's companion Open Access journal—JTO Clinical and Research Reports (JTO CRR)—was launched in response to the tremendous growth in submissions to JTO. This growth was driven by the burgeoning research in thoracic oncology as well as advances in genomics and the use of the programmed death-ligand 1 and programmed cell death protein 1 inhibitors. Many articles not accepted by JTO deserved publication nonetheless. In fact, these research results are of high interest by the practice community to provide optional clinical care. Recognizing this need as well as the opportunity, Dr Adjei in partnership with Ms Anne Lloyd of Elsevier proposed the establishment of a second journal in 2019. The IASLC Board of Directors endorsed this proposal and a new, second journal, JTO CRR, was established with Dr Adjei as the founding Editor-in-Chief. The first online issue was published in February 2020. JTO CRR complements JTO by offering authors a gold open-access publication option, ensuring that its articles are immediately and permanently free to access by everyone.

Dr. Adjei established an Editorial Board for JTO CRR that was comprised of 21 well-established JTO associate editors and together the complementary identity of this second IASLC journal was formed. Dr Vun-Sin Lim was contracted as the Editorial Consultant to manage the day-to-day operation and editorial and scientific development of the journal in 2020. In its first year, the journal published quarterly with a total of four issues and 67 articles. Like the JTO, the IASLC has also curated a collection of articles on COVID-19. The first article from the collection was published in April 2020.[3]

In January 2021, the journal transitioned from a quarterly to a monthly publication as the volume of manuscripts increased substantially over the first year. Additionally, the journal moved away from the traditional Issue Based Publishing model to

Article Based Publishing model, in which an article post-production is immediately published online with all citable information and articles appear in an issue on a rolling basis. These changes align with the goal of getting important research findings published and reaching the readers in a timely manner.

Dr. Emily Stone, JTO Clinical and Research Reports Editor-in-Chief, 2023-present.

In January 2023, Dr. Emily Stone was named JTO CRR's new Editor-in-Chief. Read special editorials entitled "Our work is done, and you are in good hands" by Dr. Adjei,[4] and "Building on a legacy" by Dr. Stone,[5] published in the 2023 January Issue of JTO CRR in celebration of this milestone. Expert in respiratory medicine, multidisciplinary team care, tobacco control and smoking cessation, and translational research, Dr. Stone, with the support of her Editorial Board and the current Editorial Office team, leads JTO CRR to fulfill its intent to publish high-quality thoracic oncology research relating to clinical trials, outcome analyses, translational research, cost utility analyses, and related topics (Table 3). The journal is indexed in the Directory of Open Access Journals, Scopus, PubMed and Web of Science. JTO CRR is off to a strong start with its first impact factor at 3.0.

Together JTO and JTO CRR feature novel research about the prevention, detection, diagnosis, and treatment of all thoracic malignancies. Leaders in the field of scholarly periodicals publishing, these two journals are ambassadors for the IASLC mission to ensure optimal thoracic neoplasm prevention and patient care through collaborative science, education, and advocacy.

Table 3. JTO CRR Breadth and Reach: Topics and Articles of Interest

- Phase I trials
- Well-performed single-arm phase II trials
- Subset analyses of published trials
- Impactful retrospective studies
- Database analysis
- Large institutional series
- High-quality case reports
- Region-specific clinical trials
- Subspecialty thoracic oncology studies
- Selected high-quality meeting reports

IASLC REVIEWER WORKSHOP

The IASLC recognizes the limited or lack of formal training opportunities for early- and mid-career physicians and physician-scientists in peer review, which is a vital element of academic publishing and research. To improve reviewer performance and quality of manuscript reviews, the IASLC, JTO, and JTO CRR conducted a formalized workshop to train reviewers. It was a one-day workshop held before the annual World Conference on Lung Cancer (WCLC) to train these IASLC members in manuscript review, particularly the ability to make judgements of impacts of manuscripts.

The workshop director is Dr. Alex Adjei. Dr. Vun-Sin Lim leads workshop planning and coordination, facilitated by Mary Todd,

2021 Workshop Participants | Virtual

Rania Aly
Egypt

Amarendra Amar
India

Ashish Jakhetiya
India

Jih-Hsiang Lee
Taiwan

Aaron Tan
Singapore

Aleksei Tikhonov
France

Bailey Creamer and the IASLC. The workshop accepts participants from the regions where the WCLC takes place. The inaugural workshop was held virtually in 2021 due to the COVID-19 pandemic. Six participants from Asia and Rest of the World attended the online workshop, joined by four faculty members with didactic lectures and discussion of reviewed articles. In conjunction with the 2022 WCLC, the first in-person, one-day workshop took place in Vienna, Austria, with 16 participants from Europe. The 2024 workshop was held in San Diego, CA, United States in conjunction with the WCLC, with 20 participants from the Americas.

References

1. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. *J Thorac Oncol.* 2020;15:700-704. doi:10.1016/j.jtho.2020.02.010
2. Adjei AA. The Coming of a new age: The Journal of Thoracic Oncology goes electronic in 2024. *J Thorac Oncol.* 2023;18:1257. doi:10.1016/j.jtho.2023.08.006
3. Tu Y, Fang J, Yin M, Yu W, Li Y. A Cured Coronavirus Disease 2019 Case of an 86-Year-Old With 13 Chronic Diseases: A Case Report. *JTO Clin Res Rep*. 2020;1:100038. doi:10.1016/j.jtocrr.2020.100038
4. Adjei AA. Our work is done, and you are in good hands. *JTO Clin Res Rep*. 2022;4:100447. doi:10.1016/j.jtocrr.2022.100447
5. Stone E. Building on a Legacy. *JTO Clin Res Rep*. 2023;4:100445. doi:10.1016/j.jtocrr.2022.100445

2022 Workshop Participants | Vienna, Austria

Haval Balata
UK

Martin Barr
Ireland

Maristella Bungaro
Italy

Jules Derks
Netherlands

Francesca Jacobs
Italy

Laura Moliner
UK

Filiz Oezkan
Germany

Samina Park
Switzerland

Periklis Perikleous
UK

Anne Marie Quinn
Ireland

Jo Raskin
Belgium

Maria Lucia Reale
Italy

Pedro Rocha
Spain

Seyer Safi
Germany

Tiziana Vavala
Italy

Gerard Walls
UK/Ireland

7

IASLC PUBLICATIONS

IASLC ATLAS SERIES

In 2013, the IASLC Pathology Committee convened a panel of experts to develop a guide regarding multiple diagnostic platforms available to detect ALK gene rearrangements or fusion proteins, recognizing the need for standardization of these assays (Figure 1). The result of this effort was publication of the *IASLC Atlas of ALK Testing in Lung Cancer*, a resource designed to help pathologists, laboratory scientists, and practicing physicians better understand the background, protocol, and interpretation of ALK testing results in patients with advanced NSCLC (Figure 2).

The success of this first IASLC Atlas publication laid the groundwork for development by the Pathology Committee of an ongoing Atlas series. The series has continued to provide guidance regarding dynamic immunohistochemical and molecular topics over the last 10+ years (Table 1) (see Chapter 8).The IASLC's latest Atlas, the IASLC Atlas of Molecular Testing for Targeted Therapy in Lung Cancer, provides a comprehensive overview of all current and emerging molecular targets, specimen acquisition, available assays, and reporting and interpretation of molecular testing results from both a diagnostic and clinical perspective.

Figure 1. IASLC ALK Testing Workshop attendees, Sorrento, Italy, 2013. **Front row** (left to right): Y. Yatabe, M. Varella-Garcia, E. Brambilla, S. Lantéujoul, R. Gaspo (Pfizer Oncology), J-H Chung. **Back row** (left to right): A. Yoshida, I. Wistuba, F. R. Hirsch, M. S. Tsao, E. Thunnissen, L. Bubendorf, K. Kerr.

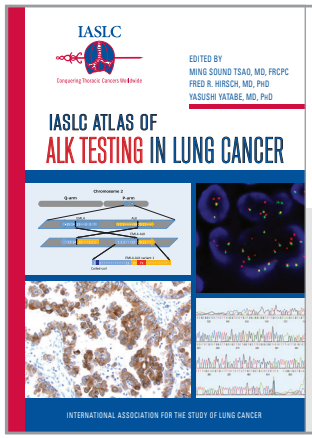


Figure 2. *IASLC Atlas of ALK Testing in Lung Cancer* (2013), first publication in the IASLC Atlas series.

Table 1. IASLC Atlas Publications 2016-2023

2013	*IASLC Atlas of ALK Testing in Lung Cancer*
2016	*IASLC Atlas of ALK and ROS1 Testing in Lung Cancer*
2017	*IASLC Atlas of PD-L1 Immunohistochemistry Testing in Lung Cancer*
2017	*IASLC Atlas EGFR Testing in Lung Cancer*
2020	*IASLC Atlas of Diagnostic Immunohistochemistry*
2023	*IASLC Atlas of Molecular Testing for Targeted Therapy in Lung Cancer*

IASLC NEWSLETTERS AND TABLOID COMMUNICATIONS

Communications with members has always been a priority for the IASLC in the delivery of its mission. Early on (1975) an IASLC newsletter was established with Lawrence Broder, MD as the editor, to better inform the frowing membership about the activities of the Association. This IASLC newsletter was the only official IASLC publication until the launch of the journal, *Lung Cancer,* in 1985, the forebear of today's *Journal of Thoracic Oncology* and *JTO Clinical and Research Reports* (see Chapter 5). Revived in early 2004 by the IASLC Communications Committee and Dr. Fred Hirsch, the IASLC Newsletter was established as a regular communication between the Executive Office, the Board of Directors, and IASLC members. The Newsletter provided regular updates about IASLC events, resources, and benefits. The Newsletter also communicated to members the latest IASLC news and announcements, including election results, award program activities, meetings and workshop proceedings, and the most recent research published in the *Journal of Thoracic Oncology* (see Chapter 6). New IASLC members were regularly announced in IASLC Newsletters, which fulfilled its mission to publish information of general interest to IASLC members that would not necessarily be found in peer-review journals.

In 2016, the IASLC continued and expanded the mission of the IASLC Newsletter with the launch of *IASLC Lung Cancer News*, or ILCN. Dr. Corey Langer was appointed as Editor (Figure 3), a role he continues today through many changes and growth of this publication, including its shift from a print tabloid to an online publication.

Columns established in the inaugural ILCN that continue to provide the latest information to IASLC members and others in the thoracic oncology commnity include Meeting Highlights and Previews, the NCI and FDA Corners in which important up-to-date developments in clinical treatments are discussed by the leaders involved, Global Research Reports, Evolving Standards of Care, Survivorship contributions by patient advocates and survivors, Names in the News– brief news about professional accomplishments and changes, and invited perspectives from thought leaders in the field.

While the focus of ILCN has remained constant—highlighting updates on thoracic malignancy research, including diagnostics, screening, tobacco control, therapeutic interventions, quality of life, symptom management, and survivorship—this publication has evolved over the past 8 years, since its inception. It is now a 100% digital publication, no longer distributed in print. In addition robust Editorial Group was appointed with additional members added over time to support and deepen the ILCN's editorial breadth and content. Currently, the ILCN Editorial Board consists of three Associate Editors, Mary Jo Fidler from

Figure 3. Corey J. Langer, MD, Editor, *IASLC Lung Cancer News*.

Welcome to ILCN from Dr. Corey Langer, Editor
April 2016

"It is my privilege to introduce the *IASLC Lung Cancer News* (ILCN)....ILCN is a new tabloid publication that will highlight updates on thoracic malignancy research, including diagnostics, screening, tobacco control, therapeutic interventions, quality of life, symptom management, and survivorship. This tabloid will acknowledge the complex interplay that exists between these investigational realms and between all stakeholders in the research and care of individuals with thoracic cancers and will feature expert commentary from thoracic oncology leaders, industry, and regulators. The target audience for this publication encompasses researchers, physicians, and other specialists, including allied health professionals, involved in the care of patients with thoracic malignancy."

Chicago, Suresh Senan from the Netherlands, and Wytold Rzyman from Poland, and Editorial Board members who are physicians, nurses, and patient research advocates. This composition of editorial leadership ensures that ILCN coverage is not only multidisciplinary, geographically varied, and timely but also nuanced and practical. Since the onset of the pandemic, the board meets virtually, every other week, and reviews all relevant literature pertaining to thoracic malignancy with a focus on meeting highlights and presentations that often fall outside the purview of the IASLC. These meetings have been orchestrated by the managing editors, first Deborah Whippen at the tabloid's inception, then Joy Curzio, and now, as of 2024, Erin Jungmeyer. Without the contributions of these three, the ILCN would not exist.

IASLC TEXTBOOKS

The necessity of spreading information about lung cancer has also been supported by IASLC textbooks. The IASLC has developed or supported a number of textbooks over the last 25 years (Table 2), since the early publication of *Lung Cancer Therapy Annual* (2000-2008), which briefed the oncology community about the most recent developments in lung cancer by reviewing the literature from the previous year.

In 2014, first chapters of *The IASLC Multidisciplinary Approach to Thoracic Oncology* (Editors, Dr. Harvey Pass, Executive Editor, and Drs. Giorgio Scagliotti and David Ball, Editors) were made available at the Sydney WCLC with the entire book released for distribution in late spring 2014. In this book, Editor Dr. Pass assembled the world's leading experts on all aspects of lung cancer to provide an up-to-date and authoritative summary of the current status of lung cancer etiology, pathogenesis, biology, molecular biology, pathology, early detection, diagnosis, staging, treatment, and supportive care.

About the publication of *IASLC Thoracic Oncology* in 2017, Dr. Pass said, "This endeavor calls for one international society and one book or information source that is born and keeps on growing, just like the Society."

Table 2. IASLC Textbooks 1999-2017

1999	*IASLC Textbook of Lung Cancer* (English 1999, Chinese 2000) (Hansen, Ed)
2005	*IASLC Textbook of Prevention and Detection of Early Lung Cancer* (Hirsch, Bunn, Kato, Mulshine, Eds)
2014	*The IASLC Multidisciplinary Approach to Thoracic Oncology* (Pass, Ball, Scagliotti, Eds.)
2017	*IASLC Thoracic Oncology* (Pass, Ball, Scagliotti, Eds.)

IASLC STAGING MANUAL AND CARDS

Led by the efforts of then-Staging Committee Chair, Dr. Peter Goldstraw, in 2009 the IASLC published the new 7th edition classification for lung cancer in the *IASLC Staging Manual in Thoracic Oncology* and its companion *IASLC Staging Handbook*, the first-ever site-specific cancer staging publications in thoracic oncology. These publications and their accompanying educational materials were launched during the 13th World Conference on Lung Cancer to support the study and preparation for the new staging system prior to its implementation in January 2010.

The success of the global distribution of this important IASLC educational resource led to its publication again in a new edition in parallel with the new 8th edition staging system with Dr. Ramon Rami-Porta as Editor. Updated Staging Classification Cards were distributed by IASLC at the 2015 World Conference, along with cards for the 2015 WHO Classification (Figure 4).

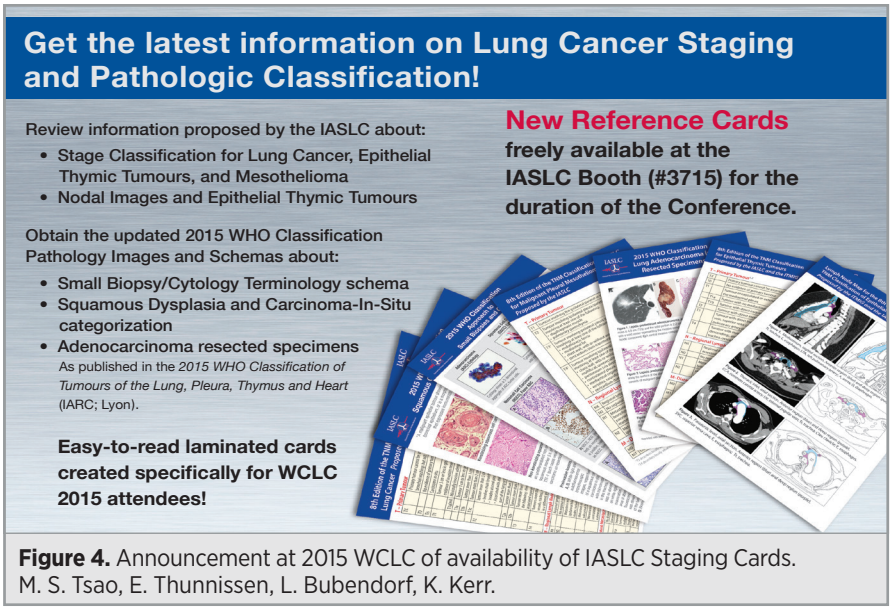


Figure 4. Announcement at 2015 WCLC of availability of IASLC Staging Cards. M. S. Tsao, E. Thunnissen, L. Bubendorf, K. Kerr.

Currently a third edition of the *IASLC Staging Manual* is in final development under the leadership of Dr. Hisao Asamura, to be launched at the 2024 World Conference in San Diego, CA. See Chapters 8 and 9 for further details about the IASLC Staging and Pathologic Classification programs.

8

PATHOLOGY COMMITTEE

William D. Travis,[1] **Elisabeth Brambilla,**[2] **Wendy A. Cooper,**[3] **Fred R. Hirsch,**[4] **Keith M. Kerr,**[5] **Andrew G. Nicholson,**[6] **Masayuki Noguchi,**[7] **Ming-Sound Tsao,**[8] **Ignacio I. Wistuba,**[9] **and Yasushi Yatabe**[10] | [1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]University Grenoble Alpes, INSERM, Grenoble, France; [3]NSW Health Pathology, Royal Price Alfred Hospital, Camperdown, NSW, Australia; [4]Center for Thoracic Oncology/Tisch Cancer Institute; Mount Sinai Health System, New York, NY, USA; [5]Aberdeen Royal Infirmary, Aberdeen, Scotland, UK; [6]Royal Brompton and Harefield Hospitals, Guy's and St Thomas' NHS Foundation Trust, London, UK; [7]Narita-Tomisato Tokushukai; Chiba, Japan; [8]Princess Margaret Cancer Center, Toronto, Canada; [9]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [10]National Cancer Center, Tokyo, Japan

One of the greatest strengths of the IASLC is the overarching multidisciplinary approach to addressing thoracic cancers. With this focus, over the past 50 years, the leadership of the IASLC has wisely invested invaluable resources and support for thoracic pathologists within the framework of the Pathology Committee. This approach has enabled IASLC pathologists to meet consistently to discuss and work on projects, often with multidisciplinary collaboration, that have led to major advances in lung-cancer classification, diagnosis, and management.

It has been 40 years since the Pathology Panel was officially recognized by the IASLC Board in 1982. The IASLC Board of Directors approved the formation of an IASLC Pathology Panel after the publication of the 1981 World Health Organization (WHO) classification of lung tumors as recommended by Dr. Mary Matthews, Dr. Fred R. Hirsch, Dr. Adi Gazdar, and Dr. Raymond Yesner. This group was initially called the "Pathology Panel." Later, when the IASLC formalized multiple committees, the name was changed to the "Pathology Committee." The purpose of the Pathology Committee has evolved somewhat over the years, but its constant priorities have been to help the IASLC maintain a leadership role in the lung-cancer field, a critical role in the mission of the IASLC to provide leadership in the clinical and scientific aspects of lung cancer pathology, with a multidisciplinary approach (Table 1).

The work of the Pathology Committee has evolved with the emergence of new technologies and therapies, such as immunohistochemistry, molecular biology, targeted therapy, and immunotherapy. The Pathology Committee has been highly productive in generating key publications in the form of scientific investigations, classification guidelines, and educational documents. Consequently, these activities and accomplishments have allowed for the IASLC and Pathology Committee members to play leadership roles in the lung-cancer field, particularly in developing the 1981,[1] 1999,[2] 2004,[3] 2015,[4] and 2021[5] WHO classifications.

This chapter provides an update to the previous book on the 40-year history of the IASLC, including a special article in the *Journal of Thoracic Oncology* led by Ming-Sound Tsao that reviews the 40-year history and accomplishments of the Pathology Committee.[6,7]

PATHOLOGY COMMITTEE MEMBERS AND PROJECTS 1982-2023

The chairs of the Pathology Committee between 1982 and 2023 are illustrated in Figure 1, and many of the historical figures in the early years are illustrated in Figure 2. The history of the membership of the Pathology Committee from 1982 through

Table 1. The Purpose of the IASLC Pathology Panel/Committee

1983	• Encourage research activities concerning surgical and experimental pathology of lung cancer. • Define a more exact histopathologic interpretation and classification of lung tumors within IASLC during slide circulation and workshops. • Offer individuals and study groups a panel evaluation of histologic/cytologic material from lung cancer to make a uniform basis for comparing clinical and paraclinical studies from the several investigations within IASLC. • Provide postgraduate training education in lung-cancer pathology.
2005	• Provide international leadership in the clinical and scientific aspects of lung-cancer pathology. • Support the organization of IASLC: its projects, publications, and meetings. • Integrate with other specialties: surgery, oncology, radiation therapy, and molecular biology. • Play a central role in major publications (especially WHO classification efforts) in the field of lung cancer and other thoracic tumors.
2015	**1. DIAGNOSTIC** • Lead classification of thoracic tumors in conjunction with the WHO. • Develop new ideas on improving the pathological classification of thoracic malignancies. • Ensure that this classification of tumors is thorough, globally applicable, reproducible, and dynamic. **2. EDUCATION** • Improve the skills of pathologists in relation to the diagnosis of thoracic cancers. • Improve knowledge of pathology in all disciplines involved in patient management of thoracic cancers, lung cancer, mesothelioma, and thymic epithelial tumors. **3. RESEARCH AND SERVICE DEVELOPMENT** • Be involved in pre-clinical research and its translation into clinical practice. • Conduct studies and develop criteria that can lead to greater accuracy of tumor diagnosis by pathologists worldwide. • Develop standards or reference materials for molecular testing that are becoming necessary for personalizing patient treatment with new targeted therapies in lung cancer.
2022	• Publish, review, and write papers on cutting-edge issues in pathology of thoracic tumors and biomarker testing. • Conduct studies to improve the diagnosis and pathological classification of lung cancer. • Offer guidance for the organization's annual slate of meetings. • Help establish the IASLC as an international leader in the clinical and scientific aspects of lung-cancer pathology.

Abbreviation: WHO, World Health Organization.

2023 is summarized in Tables 3 through 13.

One measure of the impact of the Pathology Committee is reflected by the high number of citations for the articles published. Although the WHO Blue Book classifications are some of the most highly cited publications (Figure 3),[2-5] Pathology Committee members have led or collaborated on many scientific efforts that have been published in individual journals. Table 2 summarizes some of the most highly cited articles published in the *Journal of Thoracic Oncology*, in which members of the Pathology Committee were major contributors.

The number of active projects undertaken by the Pathology Committee is summarized in part B of Tables 3 through 13. These tables also cite the numerous publications that resulted from work by Pathology Committee members during each period. In addition to these WHO Blue Books and many publications, the Pathology Committee has published multiple educational IASLC Atlases on key molecular and immunohistochemical topics (Figure 4).[8-13]

1982-1991
Mary Matthews

1991-1999
Fred R. Hirsch

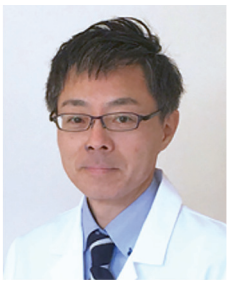
1999-2005
William D. Travis

2005-2009
Elisabeth Brambilla

2009-2011
Masayuki Noguchi

2011-2013
Ming-Sound Tsao

2013-2015
Andrew G. Nicholson



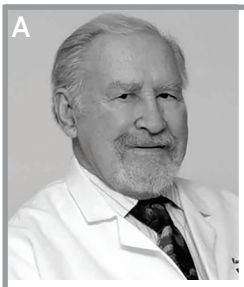
2015-2017
Yasushi Yatabe

2017-2019
Ignacio Wistuba

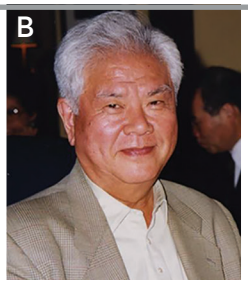
2019-2021
Keith Kerr

2021-2023
Wendy A. Cooper

Figure 1. IASLC Pathology Committee Chairs 1982-2023



Raymond Yesner



Yukio Shimosato

Adi Gazdar

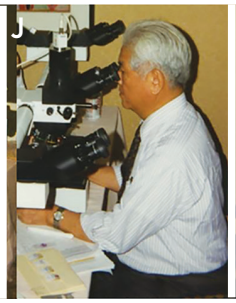
Philip Hasleton

Emilio Alvarez-Fernandez

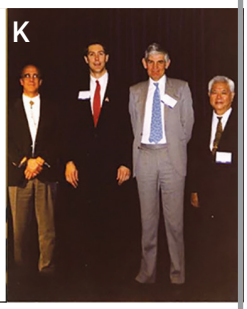
Bryan Corrin

Bruce Mackay Richard Steele

Neuroendocrine Tumor Slide Review, 1996 Washington DC: **Row 1.** Tom Colby, Elisabeth Brambilla, Sam Hammar **Row 2.** Mary Shepard, Fred Hirsch, Richard Steele **Row 3.** Philip Hasleton, Adi Gazdar, Yoshihiro Matsuno



Neuroendocrine Slide Review, 1996: Yukio Shimosato



WHO Presentation, 1998, Nice, France: Tom Colby, William Travis, Bryan Corrin, Yukio Shimosato

Figure 2. Historical Members of the Pathology Committee

Table 2. Top-Cited Articles by the Pathology Panel in the *Journal of Thoracic Oncology*

Year	Manuscript title	Citation number*
2011[37]	The New International Association for the Study of Lung Cancer/American Thoracic Society/ European Respiratory Society International Multidisciplinary Lung Adenocarcinoma classification	5998
2015[39]	The 2015 World Health Organization Classification of Lung Tumors: impact of genetic, clinical and radiologic advances since the 2004 classification	4458
2015[40]	Introduction to The 2015 World Health Organization Classification of Tumors of the Lung, Pleura, Thymus, and Heart	3162
2013[38]	Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology	1923
2018[51]	Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: guideline from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology	1465
2017[41]	PD-L1 immunohistochemistry assays for lung cancer: results from phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project	1269
2021[65]	The 2021 WHO classification of lung tumors: impact of advances since 2015	630
2018[50]	PD-L1 immunohistochemistry comparability study in real-life clinical samples: results of Blueprint phase 2 project	681
2020[52]	A Grading System for Invasive Pulmonary Adenocarcinoma: A Proposal From the International Association for the Study of Lung Cancer Pathology Committee.	280
2020[54]	IASLC Multidisciplinary Recommendations for Pathologic Assessment of Lung Cancer Resection Specimens After Neoadjuvant Therapy	258

*From Google Scholar (April 16, 2024).

Table 3A. Pathology Panel Members, **1983-1994**

Mary J. Matthews, USA*† (Chair, 1983-1991)
Fred R. Hirsch, Denmark* (Secretary, 1982-1991; Chair, 1991-1998)
Seena Aisner, Newark, USA*
Onofrio Campopbasso, Italy*†
Bryan Corrin, UK
J.D. Elema, The Netherlands*
Adi Gazdar, USA
Samuel P. Hammar, USA
Bruce Mackay, USA*
Magnus Nasiell, Sweden*
Mary Sheppard, England
Yukio Shimosato, Japan* (Board of Directors, 1991-1997)
Richard H. Steele, Australia*
Raymond Yesner, USA*† (Chair, 1981 WHO panel)
L. Zettergren, Sweden*

Abbreviation: WHO, World Health Organization.
*Original IASLC Pathology Panel Members recorded in IASLC Newsletter, April 1983.
†Members of the 1981 WHO lung tumor expert committee on lung cancer.

Table 3B. Publications, **1983-1994**

Small cell carcinoma[14,15]

Table 4A. Pathology Panel Members, **1994-1999**

Fred R. Hirsch, Denmark (Chair, 1991-1998)
Seena Aisner, USA
Emilio Alvarez-Fernandez, Spain
Elisabeth Brambilla, France
Thomas V. Colby, USA
Bryan Corrin, UK
Adi Gazdar, USA
Samuel P. Hammar, USA
Philip S. Hasleton, UK
Bruce Mackay, USA
Helmut Popper, Austria
Mary Sheppard, England
Yukio Shimosato, Japan (Board of Directors, 1991-1997)
Richard Steele, Australia
William D. Travis, USA

Table 4B. Publications and Projects, **1994-1999**

Publications

1999 WHO classification: histologic typing of tumors of the lung and pleura[2,70]

Neuroendocrine tumors[71]

Project

Adenocarcinoma

Abbreviation: WHO, World Health Organization.

Table 5A. Pathology Panel Members, **1999-2005**

William D. Travis, USA (Chair)
Seena Aisner, USA
Emilio Alvarez-Fernandez, Spain
Elisabeth Brambilla, France
Thomas V. Colby, USA
Bryan Corrin, UK
Wilbur Franklin, USA
Adi Gazdar, USA, (Board of Directors, 2000-2005)
Fred R.Hirsch, USA
Samuel P. Hammar, USA
Philip S. Hasleton, UK
Bruce Mackay, USA
Masayuki Noguchi, Japan
Helmut Popper, Austria
Richard H. Steele, Australia

Observers

Douglas B. Flieder, USA
Kim R. Geisinger, USA
Douglas W. Henderson, Australia
Keith Kerr, UK
Yuko Minami, Japan
Andrew G. Nicholson, UK
Victor L. Roggli, USA
FBJM Thunnissen, The Netherlands
Ming-Sound Tsao, Canada
Madeline F. Vazquez, USA
Ignacio I. Wistuba, USA
T. Yokose, Japan
Maureen F. Zakowski, USA

Table 5B. Publications and Projects, **1999-2005**

Publications

2004 WHO classification of tumors of the lung, thymus, pleura and heart[3,70]

Adenocarcinoma, including a major contribution to the 2004 IASLC Meeting on Bronchioloalveolar carcinoma in New York[16,17]

Neuroendocrine lung tumors: atypical carcinoid and small cell carcinoma[72,73]

IASLC Lung Cancer Staging Project: AJCC Cancer Staging Manual: Lung Cancer (sixth edition)[74]

Project

Squamous preinvasive lesions

Abbreviation: AJCC, American Joint Committee on Cancer; WHO, World Health Organization.

Table 6A. Pathology Panel Members, **2005-2009**

Elisabeth Brambilla, France (Chair and IASLC Board of Directors, 2007-2011)
Douglas B. Flieder, USA
Wilbur Franklin, USA
Adi Gazdar, USA
Kim R. Geisinger, USA
Philip S. Hasleton, UK
Douglas Henderson, Australia
Fred R. Hirsch, USA
Bruce E. Johnson, USA
Andrew G. Nicholson, England
Masayuki Noguchi, Japan (Chair-elect, 2005-2009)
Victor L. Roggli, USA
F.B.J.M. Thunnissen, The Netherlands
William D. Travis, USA
Ming-Sound Tsao, Canada

Table 6B. Publications and Projects, **1999-2005**

Publications

Neuroendocrine lung tumors: proceedings of 2007 IASLC Workshop in London[18]

IASLC Lung Cancer Staging Project: AJCC Cancer Staging Manual: lung;[75] T descriptors;[76] M descriptors,[77] carcinoids,[27] visceral pleural invasion[28]

Adenocarcinoma classification: beginning of the IASLC/ATS/ERS Lung Adenocarcinoma Classification[78]

Abbreviation: AJCC, American Joint Committee on Cancer

Pathology Panel (1983-1989)

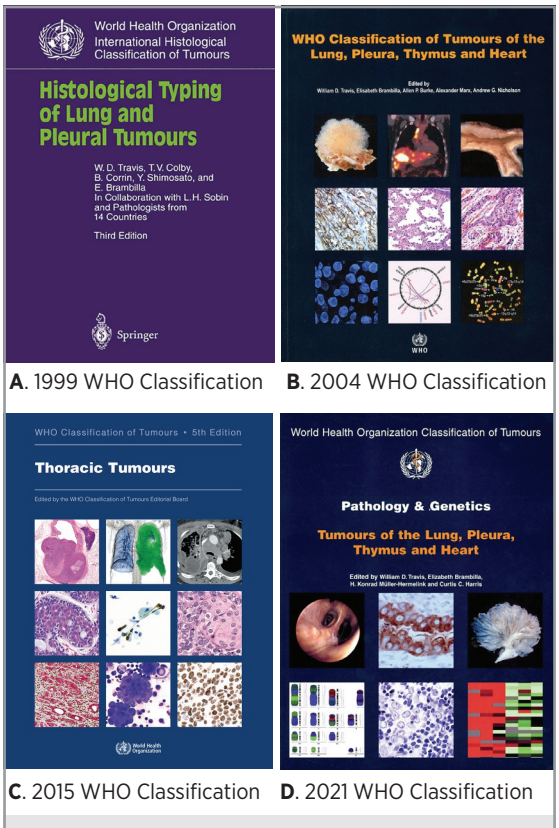
After publication of the 1981 WHO classification (the WHO committee members are illustrated in Figure 5), the IASLC Pathology Panel was chaired by Dr. Matthews from 1983 through 1994 (Table 3A). During this time, the main focus was classification of small cell lung cancer and its subtypes (Table 3B). The proposed classification included the classic "lymphocyte-wlike, oat-cell subtype (22) and intermediate subtype with large cells mixed with lymphocyte-like cells (22/40) and mixed subtypes with mixtures of small cells with adenocarcinoma"[14,15] (Table 3B).

Pathology Panel (1990-2000)

From 1991 through 1998, the Pathology Panel was chaired by Dr. Hirsch (Tables 4A and 4B). In 1996, Dr. William D. Travis, a panel member, was asked by the WHO to coordinate a revision of the international classification of lung tumors. This effort led to the publication of the 1999 WHO Classification: Histologic Typing of Lung and Pleural Tumours (Figure 3A).[2] The revised classification created new subcategories of adenocarcinomas and neuroendocrine tumors. The 1999 WHO classification committee met in Nice, France, at the 1998 International Academy of Pathology meeting (Figure 6), where the main editors presented the classification in a plenary session (Figure 2K). During this time, the panel collected a cohort of pulmonary neuroendocrine tumors with slides and blocks, which resulted in multiple papers on atypical carcinoid, small cell carcinoma, and comparative molecular features (Tables 4B and 5B). A set of slides from 100 lung adenocarcinomas was also circulated among the panel for review and discussion.

Pathology Panel (2000-2009)

From 1999 through 2005, the Pathology Panel was chaired by Dr. Travis (Tables 5A and 5B), and from 2005 through 2009 by Dr. Elisabeth Brambilla (Tables 6A and 6B). In 2003, the IASLC Pathology Panel was well represented in the leadership and



A. 1999 WHO Classification **B**. 2004 WHO Classification

C. 2015 WHO Classification **D**. 2021 WHO Classification

Figure 3. WHO Thoracic Bluebooks with Major Contributions by IASLC Pathology Committee

2013 2016 2017

2017 2020 2023

Figure 4. IASLC Atlases on Key Molecular and Immunohistochemical Topics

Table 7A. Pathology Panel Members, **2009-2011**

Masayuki Noguchi, Japan (Chair)

Board Liaisons

Johan Vansteenkiste, Belgium
Seena Aisner, USA
Elisabeth Brambilla, France (Board of Directors)
Federico Cappuzzo, Italy
Lucian R. Chirieac, USA
Rafal Dziadziuszko, Poland
Fred R. Hirsch, USA
Kim Geisinger, USA
Keith Kerr, UK
Iver Petersen, Germany
Andrew G. Nicholson, UK
Masayuki Noguchi, Japan
Victor L. Roggli, USA
Erik Thunnissen, The Netherlands
William D. Travis, USA
Ming-Sound Tsao, Canada
Ignacio I. Wistuba, USA
Yasushi Yatabe, Japan

Observers

Yoshihiro Matsuno, Japan
Yuichi Ishikawa, Japan
Giuseppe Pelosi, Italy
Sylvie Lantuejoul, France
Maureen F. Zakowski, USA
Andre L. Moreira, USA
Mary Beth Beasley, USA

Table 7B. Publications and Projects, **2009-2011**

Publications

IASLC/ATS/ERS Lung Adenocarcinoma Classification[34, 37]

Diagnosis of lung cancer in small biopsies and cytology[79]

Projects

Adenocarcinoma reproducibility
Neuroendocrine tumors
Squamous cell carcinoma
Large cell carcinoma
Molecular classification

Table 8A. Pathology Panel Members, **2011-2013**

Ming-Sound Tsao, Canada (Chair, 2011-2013)
Elizabeth Brambilla, France
Kim R. Geisinger, USA
Andrew G. Nicholson, UK
Masayuki Noguchi, Japan
Seena Aisner, USA
Lucian R. Chirieac, USA
Sanja Dacic, USA
Rafal Dziadziuszko, Poland
Kim Geisinger, USA
Fred R. Hirsch, USA
Keith Kerr, UK
Yuichi Ishikawa, Japan
Iver Petersen, Germany
Victor L. Roggli, USA
Erik Thunnissen, The Netherlands
Kafai To, China/Hong Kong
William D. Travis, USA
Ignacio I. Wistuba, USA
Yasushi Yatabe, Japan

Table 8B. Publications and Projects, **2011-2013**

Publications

Review articles about the 2011 IASLC/ATS/ERS Lung Adenocarcinoma Classification[29-37]

IASLC Atlas of ALK Testing in Lung Cancer[9]

Projects

Adenocarcinoma reproducibility

Beginning of 2015 WHO classification project with focus on adenocarcinoma, neuroendocrine tumors, squamous cell carcinoma, sarcomatoid/large cell carcinoma, and molecular classification and database

Biomarker and bioassay standardization

Abbreviation: WHO, World Health Organization.

writing committee for the 2004 WHO classification (Figure 3B).[3] The writing committee for the 2004 WHO classification met at the International Agency for Research on Cancer in Lyon, France, in March 2003 (Figure 7).

In November 2004, a workshop on bronchioloalveolar carcinomas (BAC), sponsored by the IASLC and American Society of Clinical Oncology, was held to address the problems in the classification of BAC, including the radiologic and clinical issues. The chairs were Dr. Travis and Dr. Wilbur Franklin, with radiologic input from Dr. Kavita Garg (USA) and clinical input from Dr. F. Cappuzzo (Italy). To prepare for this meeting, a group of pathologists accompanied by Dr. Bruce Johnson, a medical oncologist, met to review lung adenocarcinoma slides contributed by the participants (Figure 8). This project resulted in 2 papers.[16,17] In December 2007, the IASLC held an International Workshop on Advances in Pulmonary Neuroendocrine Tumors that included several members of the Pathology Panel. This workshop resulted in a paper in the *Journal of Thoracic Oncology*.[18] The Panel also began working on changes to the pathologic classification of lung adenocarcinomas and

Figure 5. 1981 WHO Committee. **Standing** (right to left): Raymond Yesner, Chairman (USA); Dr. Wong (WHO); Roger Seal (Wales); WHO Representative; Herbert Spencer, M.D. (England); Leslie Sobin (WHO), Leiv Kreyberg (Norway); Yukio Shimosato (Japan); P. Mirejovsky (Czechoslovakia); E. Chaves (Brazil); J. Chretien (France); K. Shanmugaratnam (Singapore). **Seated** (right to left): Dr. Sobin's secretary; L.G. Olchovskaya (USSR); Mary Matthews (USA); L. Hochholzer (USA); O. Campobasso (Italy).

Figure 6. IASLC Pathology Panel 1998 and 1999 WHO Committee, Nice, France. **Back row** (left to right): William D. Travis, Bryan Corrin, Helmut Popper, Thomas V. Colby, Richard Steele, Fred R. Hirsch. **Front row**: Bruce Mackay, Samuel P. Hammar, Yukio Shimosato, Adi F. Gazdar, Elisabeth Brambilla, Seena Aisner, Philip Hasleton, Emilio Alvarez Fernandez.

Figure 7. 2004 WHO Writing Committee at Consensus Meeting, March 2003, Lyon, France. **Back row** (left to right): Keith Kerr, Henry Tazelaar, Robert Loire, Alan Burke, David Dail, Elisabeth Brambilla, Allen Gibbs, Francoise Galateau-Salle, Francoise Bijuit-Thivolet, Paul Kleihues, Mojgan Devouassoux-Shisheboran, Michael O. Kurrer, Peter Möller, Bryan Corrin, Andrew Nicholson. **Middle row:** Victor Roggli, Andrew Churg, Alex Marx, Fabio Menestrina, Masayuki Noguchi, Douglas Flieder, Adi Gazdar, Philip Haselton, Konrad Muller-Hermelink, Thomas Colby. **Front row:** Wilbur Franklin, Leslie Sobin, Yukio Shimosato, Nancy Harris, Tseng-tong Kuo, Philip Cagle, Fred Hirsch, William Travis.

Table 9A. Pathology Panel Members, **2013-2015**

Andrew G. Nicholson, UK (Chair)
Keith Kerr, UK (Board Liaison)
Seena Aisner, USA
Mary Beth Beasley, USA
Johan Botling, Sweden
Elisabeth Brambilla, France
Lucian R. Chirieac, USA
Sanja Dacic, USA
Rafal Dziadziuszko, Poland
Kim Geisinger, USA
Fred R. Hirsch, USA
Yuichi Ishikawa, Japan
Nirush Lertprasertsook, Thailand
Andre L. Moreira, USA
Masayuki Noguchi, Japan
Guiseppe Pelosi, Italy
Iver Petersen, Germany
Victor L. Roggli, USA
Erik Thunnissen, The Netherlands
Kai Fai To, Hong Kong
William D. Travis, USA (Board of Directors)
Ming-Sound Tsao, Canada
Ignacio I. Wistuba, USA
Yasushi Yatabe, Japan

Table 9B. Publications and Projects, **2013-2015**

Publications

2015 WHO classification of tumors of the lung, pleura, thymus, and heart[4]

IASLC Atlas of ALK and ROS1 Testing in Lung Cancer[10]
PD-L1 – Blueprint project[80]

Poorly differentiated non-small cell lung cancer reproducibility[42]

College of American Pathologists, IASLC, Association for Molecular Pathology molecular testing guideline[38,81,82]

IASLC Strategic Screening Advisory Committee[83]

Projects

Adenocarcinoma grading
Immunohistochemistry Atlas and review article

Neuroendocrine tumor immunohistochemistry and reproducibility

Multiple tumor nodules pathology, reproducibility, and multidisciplinary consensus in support of the ninth edition of the TNM classification

Abbreviations: PD-L1, programmed death ligand 1; ROS1, reactive oxygen species 1; WHO; World Health Organization.

Table 10A. Pathology Panel Members, **2015-2017**

Yasushi Yatabe, Japan (Chair)
Keith Kerr, UK (Board Liaison)
Mary Beth Beasley, USA
Alain Borczuk, USA
Johan Botling, USA
Lukas Bubendorf, Switzerland
Gang Chen, China
Lucian R. Chirieac, USA
Teh-Ying Chou, Taiwan
Jin-Haeng Chung, South Korea
Sanja Dacic, USA
Kim Geisinger, USA
Fred R. Hirsch, USA
Sylvie Lantuejoul, France
Mari Mino-Kenudson, USA
Andre L. Moreira, USA
Andrew G. Nicholson, England
Masayuki Noguchi, Japan
Giuseppe Pelosi, Italy
Claudia Poleri, Argentina
Prudence A. Russell, Australia
Erik Thunnissen, The Netherlands
William D. Travis, USA (Board of Directors)
Ming-Sound Tsao, Canada
Arne Warth, Germany
Ignacio I. Wistuba, USA

Emeritus members

Elisabeth Brambilla, France

Observers

Natasha Rekhtman, USA
Alberto Marchevsky, USA
Noriko Motoi, Japan
Akihiko Yoshida, Japan
Kelly Butnor, USA
Douglas Flieder, USA
Wendy Cooper, Australia
Yuko Minami, Japan
Kenzo Hiroshima, Japan
Deepali Jain, India
David Hwang, Canada
Julien Adam, France
John Longshore, USA
Yuan Li, China
Lynette M. Sholl, USA

pulmonary neuroendocrine tumors. The work on lung adenocarcinoma varied from prior classifications, as it included radiologists and clinicians like the BAC workshop (Table 5B).

During these years, an enormous effort was put into developing the 2011 IASLC/ATS/ERS Lung Adenocarcinoma Classification. This effort was stimulated by (1) discoveries that *EGFR* mutations and *ALK* rearrangements were effective therapeutic molecular targets in patients with advanced lung adenocarcinoma,[19-23] (2) the observation by Dr. Masayuki Noguchi and Dr. Yukio Shimosato, that pure BAC without invasion or only small amounts of invasion have a 100% disease-free survival,[24] and (3) the recognition that ground-glass opacities by computed tomography generally correlate with a BAC pattern histologically.[25] Thus, the time appeared appropriate for a complete multidisciplinary reevaluation of the classification and terminology used for lung adenocarcinoma. This international multidisciplinary classification project was proposed to and approved by the IASLC Board of Directors at the 2007 12th World Conference on Lung Cancer (WCLC) meeting, and it subsequently received support from the American Thoracic Society (ATS) and European Respiratory Society (ERS). The first meeting of this lung adenocarcinoma classification occurred at Memorial Sloan Kettering Cancer Center (MSKCC, New York) in 2008 (March 28-31). More than 50 experts in lung cancer participated,

Figure 8. Pathology Panel meeting for International Association for the Study of Lung Cancer/American Society of Clinical Oncology meeting on Bronchioloalveolar Carcinoma, August 2004 at Armed Forces Institute of Pathology, Washington, DC. **Back row** (left to right): Wilbur Franklin, Erik Thunnissen, Philip Hasleton, Douglas Henderson, Ming-Sound-Tsao, Kim Geisinger, Douglas Flieder, William Travis, Bruce Johnson, Victor Roggli, and Robert Padera (Pathologist, Brigham & Women's Hospital, Boston, MA). **Front row:** Masayuki Noguchi, Y Minami (Thoracic Pathology Fellow, Tsukuba, Japan), Elisabeth Brambilla, Ignacio Wistuba, Sanaa Hussein (Thoracic Pathology Fellow, Memorial Sloan Kettering Cancer Center).

Table 10B. Publications and Projects, **2015-2017**

Publications

2015 WHO review articles for the *Journal of Thoracic Oncology*[39,40]

Multiple tumor nodules[84]
IASLC Atlas of EGFR Testing in Lung Cancer[8]
IASLC Atlas of ALK and ROS1 Testing in Lung Cancer[10]
PD-L1 immunohistochemistry (Blueprint 2)[41]
Reproducibility on neuroendocrine tumors[43]

IASLC Lung Cancer Staging Project: eighth edition: AJCC Cancer Staging: lung[85]; T-descriptors[86]; subsolid/lepidic nodules[48]; small cell carcinoma[87]; multiple lung nodules[44-47]

IASLC small cell carcinoma meeting[49]

Projects

PD-L1 Atlas project
Molecular database
Diagnostic immunohistochemistry
Grading of lung cancer

Abbreviations: PD-L1, programmed death ligand 1; ROS1, reactive oxygen species 1; WHO, World Health Organization.

creating an international multidisciplinary group of pathologists, medical oncologists, pulmonologists, thoracic surgeons, radiologists, and molecular biologists. Twenty-five pathologists were involved at this meeting (Figure 9). The ATS required the project to include a systematic review, which created a strong literature-based foundation for the recommendations made in the classification. During a second International Multidisciplinary Lung Adenocarcinoma meeting in March 2009 at MSKCC, the concepts of "adenocarcinoma in situ" and "minimally invasive adenocarcinoma" emerged. In addition, it became apparent that the term "BAC" needed to be replaced, as it was being used to refer to at least 5 different entities, 2 of which were adenocarcinoma in situ and minimally invasive adenocarcinoma. For resected lung adenocarcinomas, the approach of histologic classification according to the predominant subtype was adopted as previously suggested.[26] Invasive adenocarcinomas were classified by predominant pattern (lepidic, acinar, papillary, solid, and micropapillary). The concept of lepidic versus invasive growth led to a new concept for lung adenocarcinoma that used invasive size rather than total size in lepidic nonmucinous lung adenocarcinomas.

Also, the Pathology Panel supported the IASLC Staging Project in developing the seventh edition lung cancer TNM classification. The panel recommended the use of TNM staging for bronchial carcinoids in addition to standardizing the use of elastic stains to evaluate visceral pleural invasion and classify it as PL0, PL1, PL2, and PL3 depending on the depth of pleural invasion.[27,28]

Pathology Committee (2009-2013)

Dr. Noguchi became the Pathology Committee Chair from 2009 through 2011 (Tables 7A and 7B), followed by Dr. Ming-Sound Tsao from 2011 through 2013 (Tables 8A and 8B). Dr. Noguchi continued to

Figure 9. Pathology Meeting at MSKCC in March 2009 to Develop 2011 IASLC/ATS/ERS Adenocarcinoma Classification. **Back row** (left to right): James Suh, Charu Deshpande, Yuichi Ishikawa, Iver Petersen, Lucian Chirieac, Ming Tsao, Erik Thunnissen, William D. Travis, Andrew Nicholson, Keith Kerr, and Giuseppe Pelosi. **Front row:** Noriko Motoi, Fred Hirsh, Yasushi Yatabe, Yuko Minami, Adi Gazdar, Wilbur Franklin, Elisabeth Brambilla, Ignacio Wistuba, Masayuki Noguchi, Douglas Flieder, Alain Borczuk, Philip Hasleton, Daisuke Nonaka, and Natasha Rekhtman.

Table 11A. Pathology Panel Members, 2017-2019

Ignacio I. Wistuba, USA (Chair)
Masayuki Noguchi, Japan (Board Liaison)
Mary Beth Beasley, USA
Alain Borczuk, USA
Johan Botling, Sweden
Lukas Bubendorf, Switzerland
Gang Chen, China
Teh-Ying Chou, Taiwan
Jin-Haeng Chung, South Korea
Wendy A. Cooper, Australia
Sanja Dacic, USA
David Hwang, Canada
Deepali Jain, India
Keith Kerr, Scotland
Sylvie Lantuejoul, France
Fernando Lopez-Rios, Spain
Yuko Minami, Japan
Mari Mino-Kenudson, USA
Andre L. Moreira, USA
Noriko Motoi, Japan
Andrew G. Nicholson, England
Mauro Papotti, Italy
Giuseppe Pelosi, Italy
Claudia Poleri, Argentina
Natasha Rekhtman, USA
Anja Roden, USA
Lynette M. Sholl, USA
Erik Thunnissen, The Netherlands
Ming-Sound Tsao, Canada
Yasushi Yatabe, Japan
Akihiko Yoshida, Japan

Emeritus members
Elisabeth Brambilla, France
Fred R. Hirsch, USA
William D. Travis, USA

Observers
Dongmei Lin, China
John Longshore, USA

coordinate the IASLC Pathology Committee during the critical period of finalizing the IASLC/ATS/ERS Lung Adenocarcinoma Classification. Many of the final challenging discussions occurred during a meeting of the writing committee at the Bellagio Center of the Rockefeller Foundation in Bellagio, Italy, in October 2009 (Figures 10 and 11). This new classification was followed by articles highlighting implications of the classification for radiology,[29] thoracic surgery,[30,31] small biopsies and cytology specimens,[32-34] resected specimens,[35] and staging.[36] Articles were also published in the primary journals of the other sponsoring societies: European Respiratory Society[30] and ATS.[34]

After presentations of the new IASLC/ATS/ERS Lung Adenocarcinoma Classification at the 13th WCLC (August 2009, San Francisco, CA), ATS (May 2009, San Diego, CA), and ERS meetings (September 2009, Vienna, Austria), the manuscript was finally published in the February 2011 issue of the *Journal of Thoracic Oncology*.[37]

After the IASLC/ATS/ERS Lung Adenocarcinoma Classification was finally accepted for publication in the *Journal of Thoracic Oncology*, Dr. Noguchi held a meeting at his home institution in Tsukuba, Japan, in January 2011 (Figure 12). Realizing that a revision of the WHO classification was coming, this meeting addressed all major types of lung cancer, including adenocarcinoma, neuroendocrine tumors, squamous cell carcinoma, large cell carcinoma, and the concept of a molecular classification of lung cancer.

Figure 10. Writing Committee Meeting for 2011 IASLC/ATS/ERS Adenocarcinoma Classification at The Bellagio Center, Rockefeller Foundation, Bellagio Italy, October, 2009. **Back row** (left to right): Paul van Schil, Masahiro Tsuboi, Charles Powell, Kim Geisinger, Andrew Nicholson, William Travis, David Beer, Giorgio Scagliotti. **Front row:** Masayuki Noguchi, Elisabeth Brambilla, Greg Riely, Tetsuya Mitsudomi, Kavita Garg, Fred Hirsch, John Austin, Yasushi Yatabe.

Figure 11. The Pathology Team of the Writing Committee Meeting for 2011 IASLC/ATS/ERS Adenocarcinoma Classification at The Bellagio Center, Rockefeller Foundation, Bellagio Italy, October, 2009. **Back row** (left to right): Fred R. Hirsch, William D. Travis. **Front row:** M Masayuki Noguchi, Andrew Nicholson, Elisabeth Brambilla.

Members of the IASLC Pathology Committee participated in the development of the molecular testing guideline for selecting patients with lung cancer for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors in collaboration with the College of American Pathology (CAP) and the Association for Molecular Pathology.[38] The guideline provides 15 recommendations for molecular testing.

Pathology Committee (2013-2017)

Dr. Andrew G. Nicholson became the Pathology Committee

Figure 12. IASLC Pathology Committee Meeting, Tsukuba Japan, January 2011, organized by Masayuki Noguchi. **Back row** (left to right): Ming-Sound Tsao, Yoshihiro Matsuno, Kenzo Hiroshima, Andre Moreira, Keith Kerr, William D. Travis, Kim R. Geisinger, Iver Petersen, Lucian Chirieac, Giuseppe Pelosi, Yasushi Yatabe, Toshiro Niki, Yuichi Ishikawa, Yukio Nakatani, Ka-fai To, Rafal Dziadziuszko, Erik Thunnissen, Se-jin Jang. **Front row:** Gang Chen, Mary Beth Beasley, Hisao Asamura, Fred R. Hirsch, Masayuki Noguchi, Elisabeth Brambilla, Seena Aisner, Yuko Minami, Koji Tsuta, Chiho Ohbayashi, Sylvie Lantuejoul, Naoe Itoguchi, Akiko Maeshima, Teh-Ying Chou, Noriko Motoi, Jin-Haeng Chung, Satomi Noguchi.

Chair from 2013 through 2015 (Tables 9A and 9B), followed by Dr. Yasushi Yatabe from 2015 through 2017 (Tables 10A and 10B). The initial major work during these years was to develop the 2015 WHO classification (Figure 3C).[4] This classification was a major change from the previous 2004 WHO classification, particularly due to implementation of the 2011 IASLC/ATS/ERS Lung Adenocarcinoma Classification. This classification added a new focus on small biopsies and cytologies and greatly expanded focus on molecular testing and the implications for classification of other major tumors, such as squamous cell carcinoma, large cell carcinoma, and adenosquamous carcinoma. In addition to lung adenocarcinoma, these tumors were the topic of important discussions to formulate updated diagnostic criteria. The 2015 WHO classification writing committee had a consensus meeting in Lyon, France, in April 2014 (Figure 13). After the WHO Blue Book was published, a series of articles that summarize the new changes in lung-cancer classification were published in the *Journal of Thoracic Oncology*.[39,40]

Other major projects that were published during this time included (1) the IASLC Atlas of ALK Testing in Lung Cancer,[9] with a follow-up IASLC Atlas of ALK and ROS1

Figure 13. 2015 WHO Classification Writing Committee, Lyon Meeting April, 2014. **Back row** (left to right): Alain Borczuk, Nicolas Girard, Philippe Stroebel, Leendert Looijenga, Christina Basso, Yuichi Ishikawa, Giuseppe Pelosi, Alberto Marchevsky, Ignacio Wistuba, Keith Kerr, Marc Ladanyi, Brian Rous. **Middle row:** Andre Moreira, Masayuki Noguchi, Edwina Duhig, Sanja Dacic, Francoise Galateau-Salle, Mary Beth Beasley, Ming-Sound Tsao, Yasushi Yatabe, Joseph Maleszewski, Fabio Tavora, Fred Hirsch. **Front row:** William D. Travis, Andrew G. Nicholson, Alexander Marx, Allen Burke, Elisabeth Brambilla, Elain S. Jaffe, Hiroko Ohgaki, Robert Jakob.

Testing in Lung Cancer 2016;[10] (2) The IASLC Atlas of EGFR Testing in Lung Cancer;[8] (3) the programmed death ligand 1 (PD-L1) Blueprint project;[41] (4) a poorly differentiated non-small cell lung cancer reproducibility project;[42] and (5) a project on how immunohistochemistry improves the diagnosis of small cell carcinoma.[43] Projects also began to develop a grading system for lung adenocarcinoma and to write Atlases and review articles on PD-L1 staining and the role of immunohistochemistry in the pathologic evaluation of lung cancer.

In support of the ninth edition TNM classification, a multidisciplinary working group of pathologists, surgeons, oncologists, and radiologists prepared a series of articles to address clinical, pathologic, and molecular features for distinguishing separate primary lung cancers from intrapulmonary metastases for staging purposes. This led to a series of special articles focused on ground-glass/lepidic features and pneumonic-type lung adenocarcinomas.[44-47] In addition, as a consequence of the 2011 IASLC/ATS/ERS Lung Adenocarcinoma Classification, the use of invasive size rather than total size to determine the T-factor tumor size was proposed by an international multidisciplinary group of experts led by the IASLC Pathology Committee. This approach was implemented in the ninth edition TNM classification.[48] Additional discussions were held about developing a molecular database that could become an important part of the IASLC lung-cancer staging project in the future.

With the rapid molecular advances in the understanding of small cell carcinoma, the IASLC held an international multidisciplinary meeting at Memorial Sloan Kettering in April 2015. A summary of this meeting was published in the *Journal of Thoracic Oncology* in 2016.[49]

Pathology Committee (2017-2021)

Dr. Ignacio Wistuba was the Pathology Committee Chair from 2017 through 2019, followed by Dr. Keith Kerr from 2019 through 2021. During these years, a number of projects came to fruition, with publications on (1) the IASLC Atlas on PD-L1 immunohistochemistry in lung cancer,[11] (2) the Blueprint 2 project on PD-L1 immunohistochemistry,[50] (3) the updated molecular testing guideline for selecting patients with lung cancer,[51] (4) a proposed IASLC lung adenocarcinoma grading system for nonmucinous lung adenocarcinomas,[52] (5) recommendations on processing surgical resection specimens following neoadjuvant therapy,[53,54] (6) a review of the challenges of tumor mutational burden as an immunotherapy biomarker,[55] (7) the IASLC Atlas of Diagnostic Immunohistochemistry,[12] (8) a review article on best practice recommendations in diagnostic immunohistochemistry in the *Journal of Thoracic Oncology*,[56] (9) a summary of lung-cancer staging issues for pathologists,[57] and (10) perspectives on PD-L1 immunohistochemistry.[58] In addition, in support of the IASLC Staging Project, there was Pathology Committee representation in articles on the topic of the R factor and molecular database.[59,60]

In collaboration with the Federal Drug Administration, the IASLC had a meeting on the current status and future perspectives on neoadjuvant therapy in lung cancer. This meeting was summarized in the *Journal of Thoracic Oncology*.[61] Another IASLC meeting on small cell carcinoma that summarized new approaches to treatment based on new laboratory advances was held at MSKCC in 2019. This meeting led to a review article summarizing the presentations published in 2020 in the *Journal of Thoracic Oncology*.[62]

Due to the growing number of important topics that needed to be addressed by the Pathology Committee, a formal structure of working groups (Tables 11B and 12B) was established with a composition depending on the various types of expertise and interests of the participating members. One result of this expansion in various projects was a diversification of the committee membership beyond traditional histopathology and cytopathology skills to include molecular biology and diagnostics.

The last pre-pandemic Pathology Committee meeting with attendance of virtually all

Table 11B. Pathology Committee Working Groups, **2017-2019**

Publications

IASLC Atlas of PD-L1 Immunohistochemistry Testing in Lung Cancer[11]

PD-L1 immunohistochemistry: Blueprint 2[50]

IASLC and Federal Drug Administration meeting summary: current status and future perspectives on neoadjuvant therapy in lung cancer[61]

Updated molecular testing guideline for selection of patients with lung cancer[51]

Lung cancer staging review of eighth edition staging for pathologists[57]

Working Groups

Lung cancer invasion

Adenocarcinoma grading
Tumor mutational burden
Assessment of immune-related markers
Cytology
Major pathological response
Neuroendocrine tumors
Staging of multiple nodules using molecular tools
Staging Committee and R factor
Spread through air spaces
DLL3 immunohistochemistry
IASLC lung cancer synoptic reporting

Abbreviations: DLL3, delta-like 3.

Table 12B. Pulications and Working Groups, **2019-2021**

Publications

Adenocarcinoma grading† [52]
Tumor mutational burden† [55]
Assessment of immune-related markers† [58]
Major pathological response† [53,54]

Best practice recommendations for diagnostic immunohisto-chemistry in lung cancer[56]

IASLC Atlas of Diagnostic Immunohistochemistry[12]
IASLC Staging Project: R factor[60]; molecular database[59]
IASLC small cell carcinoma meeting proceedings[62]

Working Groups

Lung cancer invasion
Cytology
Neuroendocrine tumors
Staging of multiple nodules using molecular tools
Staging Committee and R factor
Spread through air spaces

†Ongoing working group.

Table 12A. Pathology Panel Members, **2019-2021**

Keith Kerr, UK (Chair)
Masayuki Noguchi, Japan (Board Liaison)
Erik Thunnissen, The Netherlands (Alternate Board Liaison)

Active Members

Mary Beth Beasley, USA
Sabina Berezowska, Switzerland
Alain Borczuk, USA
Lukas Bubendorf, Switzerland
Teh-Ying Chou, Taiwan
Jin-Haeng Chung, South Korea
Wendy A. Cooper, Australia
Sanja Dacic, USA
Yuchen Han, China
David Hwang, Canada
Deepali Jain, India
Sylvie Lantuejoul, France
Fernando Lopez-Rios, Spain
Yuko Minami, Japan
Mari Mino-Kenudson, USA
Andrew G. Nicholson, UK
Masayuki Noguchi, Japan
Mauro Papotti, Italy
Claudia Poleri, Argentina
Natasha Rekhtman, USA
Anja Roden, USA
Kurt Schalper, USA
Lynette M. Sholl, USA
Ming-Sound Tsao, Canada
Ignacio I. Wistuba, USA
Yasushi Yatabe, Japan
Akihiko Yoshida, Japan

Emeritus members

Elisabeth Brambilla, France
Fred R. Hirsch, USA
William D. Travis, USA

Observers

Philippe Joubert, Canada
Dongmei Lin, China
John Longshore, USA
Daisuke Matsubara, Japan

panel members was at the WCLC in Barcelona, Spain, in September 2019 (Figure 14). In February 2020, the Pathology Committee met in Los Angeles, California (Figure 15), but the members from Asia were unable to attend because of the emerging COVID-19 pandemic.

Pathology Committee (2021-2023)

Dr. Wendy Cooper was the current Pathology Committee Chair from 2021 through 2023. During her time as chair, the major work of the 2021 WHO classification was completed (Figures 3D and 16).[5]

In addition, review articles about the 2021 WHO classification were published in the *Journal of Thoracic Oncology*.[63-65] A major effort led by Dr. Erik Thunnissen and Dr. Noguchi to refine criteria for invasion in nonmucinous lung adenocarcinomas was published in

Figure 14. IASLC Pathology Committee, at WCLC, Barcelona, Spain, September, 2019. **Back row** (left to right): David Hwang, Fernando Lopez-Rios, Giuseppe Pelosi, Johan Botling, Lynette Sholl, Alain Borczuk, John Longshore, William D. Travis, Lukas Bubendorf, Fred R. Hirsch, Akihiko Yoshida, Teh-Ying Chou. **Middle row:** Wlodzimierz Olszewski, Andre Moreira, Yuko Minami, Sabina Berezowska, Deepali Jain, Jin-Haeng Chung, Sylvie Lantuejoul, Mary Beth Beasley, Sanja Dacic, Anja Rodin, Mari Mino-Kenudson, Wendy Cooper, Masayuki Noguchi, Dongmei Lin, Philippe Joubert. **Front row:** Elisabeth Brambilla, Andrew Nicholson, Ignacio Wistuba, Keith Kerr, Ming-Sound Tsao, Yasushi Yatabe, Mary Redman, Erik Thunnissen.

Figure 15. The IASLC Pathology Committee meeting, Los Angeles, California, February 2020. **Back row** (left to right): Erik Thunnissen, Ming Tsao, Mauro Papotti, William D. Travis, Lynette Sholl, Fernando Lopez-Rios, David Hwang, Alain Borczuk, Kurt Schalper. **Middle row:** Lukas Bubendorf, Sanja Dacic, Anja Roden, Ignacio Wistuba, Sylvie Lantuejoul, Wendy Cooper. **Front row:** Natasha Rekhtman, Claudia Poleri, Mari Mino-Kenudson, Deepali Jain, Wendy Cooper, Keith Kerr.

the *Journal of Thoracic Oncology*.[66] In addition, a study about subtyping non-small cell lung cancer in conventional cytology was published by the cytology working group.[67] The *IASLC Atlas of Molecular Testing for Targeted Therapy in Lung Cance*r was published in 2023 (Figure 4).[13] IASLC supported major projects led by Dr. Sanja Dacic on pathology assessment of major pathologic response to neoadjuvant therapy in lung cancer including an international reproducibility project[68] and use of artificial intelligence to assess pathologic response.[69] Under Dr. Cooper's leadership, there continued to be a great deal of hard work and activity in each of the working groups outlined in Table 13B. Each of these working groups were involved with projects that are anticipated to result in multiple publications in the near future. As the Pathology Committee has done throughout its existence, in the spirit of exploring new technologies, a new artificial intelligence working group has just been established.

Pathologists Role on the IASLC Board of Directors

Previously, Dr. Gazdar (2000-2005) and Dr. Brambilla (2007-2011) served on the IASLC Board of Directors. However, after a period (2011-2013) with no pathologist on the Board, it was recognized that the Board needed consistent representation by a pathologist

Figure 16. 2021 WHO Classification, Writing Committee, October, 2019, Lyon, France. **Back row** (left to right): Yasushi Yatabe, Sigurd Lax (SM), Brian Rous (SM), Anthony Gill (SM), John Chan (SM/EM), Sunil Lakhani (SM), Alain Borczuk, Keith Kerr, Sylvie Lantuejoul, Esther Olivia (SM), Alexander Lazar (SM), Joseph Maleszewski, Fernando Augusta Soares (SM). **Middle row:** Reiko Watanabe (O), John Srigley (SM), Lester Thompson (SM), Kay Washington (SM), Giorgio Scagliotti, Erika Denton, Sanja Dacic, Atsushi Ochiai, Deepali Jain, Wendy Cooper. **Front row:** Francoise Galateau, Andrew Nicholson, Valerie White (O/TE), Ian Cree, Dilani Lokohetty (O), Fatima Carneiro (SM), Masayuki Noguchi, Ming-Sound Tsao (SM/EM), Toyonori Tsuzuki (SM).
SM= standing member, EM=expert member, O=observer, TE-technical editor

Table 13A. Pathology Panel Members, **2021-2023**

Wendy A. Cooper, Australia (Chair)
Ming-Sound Tsao, Canada (Board Liaison)
Erik Thunnissen, The Netherlands (Board Liaison)
Mary Beth Beasley, USA
Sabina Berezowska, Switzerland
Alain Borczuk, USA
Lukas Bubendorf, Switzerland
Teh-Ying Chou, Taiwan
Jin-Haeng Chung, South Korea
Sanja Dacic, USA
Yuchen Han, China
David Hwang, Canada
Deepali Jain, India
Philippe Joubert, Canada
Keith Kerr, UK
Sylvie Lantuejoul, France
Dongmei Lin, China
Fernando Lopez-Rios, Spain
Yuko Minami, Japan
Mari Mino-Kenudson, USA
Mauro Papotti, Italy
Paul Hofman, France
Claudia Poleri, Argentina
Natasha Rekhtman, USA
Anja C. Rodin, USA
Kurt Schlalper, USA
Lynette M. Sholl, USA
Annikka Weissferdt, USA
Yasushi Yatabe, Japan

Emeritus members
Fred R. Hirsch, USA
Andrew G. Nicholson, London
Masayuki Noguchi, Japan
William D. Travis, USA
Ignacio I. Wistuba, USA

Observers
John Le Quesne, UK
Daisuke Matsubara, Japan
Anjali Saqi, USA
Hyo Sup Shim, Korea
Jan Von Der Thűsen, The Netherlands

who would serve as a board liaison. During the time that Dr. Kerr and Dr. Travis served on the Board of Directors (2013-2017), Dr. Kerr represented the board liaison to the Pathology Committee. Since that time, Dr. Noguchi served on the Board of Directors from 2017 through 2021. Dr. Thunnissen joined the Board in 2019, and Dr. Tsao joined in 2021, and they are currently the 2 pathologists on the IASLC Board of Directors. Having a pathologist consistently on the Board of Directors, who can serve as a board liaison to the Pathology Committee, will help not only the effectiveness of the Pathology Committee but also the effectiveness of the IASLC in our efforts to combat lung cancer.

Mary J. Matthews Pathology/Translational Research Award

This award is one of the distinguished service awards given annually at the WCLC that recognizes professionals who have made major contributions to the field of thoracic cancers. The Mary J. Matthews Pathology/Translational Research Award is given to an IASLC scientist for a lifetime achievement in pathology and translational research of thoracic malignancies. Dr. Matthews served as a senior investigator and pathologist at the National Cancer Institute's Medical Oncology Branch. She was a pioneer in the foundation of the histologic subtypes of lung cancer and the relationship between those subtypes and the clinical course of lung cancer. Dr. Geno Saccommano, a physician and cancer researcher who dedicated his life to developing a pioneering technique to assist in the early detection of lung cancer, was the first to receive the award in 1994. The list of people given this award is summarized in Chapter 4, "IASLC Awards, Fellowships, and Research Grants."

SUMMARY

Over the past 40 years, the IASLC Pathology Committee has played an important role in providing leadership in the lung-cancer field. The ongoing support of this committee by the IASLC has allowed for the world's leading pathologists to work together and have consistent, multidisciplinary interactions. Because of the IASLC, not only its pathology committee work, but also through participation on the IASLC Staging and Prognostic Factors Committee and other IASLC committees, service on the IASLC Board of Directors and participation in many IASLC-sponsored conferences, particularly the WCLC, has given pathologists many opportunities to make major contributions to the lung-cancer field. The scope of the Pathology Committee's work has increased remarkably over the past 4 decades, and with the many advances in new technology, such as molecular testing and artificial intelligence, the importance of this committee will only continue to grow.

Table 13B. Publications and Working Groups, **2021-2023**

Publications
2021 WHO Classification of Thoracic Tumours[5]
Journal of Thoracic Oncology review articles 63-65,[88]
Cytology† [67]
Invasion† [66]
IASLC Atlas of Molecular Testing in Targeted Therapy for Lung Cancer[13]
Working Groups
Cytology
Lung cancer grading
Immune biomarkers
Invasion
Pathologic response to neoadjuvant therapy
Molecular
Multiple tumor nodules
Neuroendocrine tumors
R factor
Spread through air spaces
Synoptic template for lung cancer
Artificial intelligence

Abbreviation: WHO, World Health Organization.

References

1. World Health O. Histological typing of lung tumors. 1st ed. Geneva: World Health Organization; 1981.
2. Travis WD, Colby TV, Corrin B, et al. Histological Typing of Lung and Pleural Tumors. 2nd ed. Berlin: Springer; 1999.
3. Travis WD, Brambilla E, Muller-Hermelink HK, et al. WHO Classification of Tumors 2004: Pathology and Genetics: Tumours of the Lung, Pleura, Thymus and Heart. 3rd ed. Lyon: IARC; 2004.

4. Travis WD, Brambilla E, Burke AP, et al. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. 4th ed. Lyon: International Agency for Research on Cancer; 2015.
5. WHO.Classification.Editorial.Board. WHO Classification of Tumours: Thoracic Tumours. 5th ed. Lyon (France): International Agency for Research on Cancer; 2021.
6. Tsao MS, Travis WD, Brambilla E, et al. Forty years of the international association for study of lung cancer pathology committee. *J Thorac Oncol*. 2014;9:1740-9.
7. Bunn P, Asamura H, Ball D, et al. Progress in Lung Cancer; Celebrating 40 years of the IASLC and Research Advancements. Denver, CO: International Association for the Study of Lung Cancer; 2013.
8. Mok TS, Carbone DP, Hirsch FR. IASLC Atlas of EGFR Testing in Lung Cancer. North Ft. Myers, FL: International Association for the Study of Lung Cancer; 2017.
9. Tsao MS, Hirsch FR, Yatabe Y. IASLC Atlas of ALK Testing in Lung Cancer. Aurora, CO: International Association for the Study of Lung Cancer; 2013.
10. Tsao MS, Hirsh FR, Yatabe Y. IASLC Atlas of ALK and ROS1 Testing in Lung Cancer. 2nd ed. North Fort Myers, FL: International Association for the Study of Lung Cancer; 2016.
11. Tsao MS, Kerr KM, Dacis S, et al. IASLC Atlas of PD-L1 Immunohistochemistry Testing in Lung Cancer. North Fort Myers, FL: International Association for the Study of Lung Cancer; 2018.
12. Yatabe Y, Borczuk A, Cooper WA, et al. IASLC Atlas of Diagnostic Immunohistochemistry. North Ft. Myers, FL: International Association for the Study of Lung Cancer; 2020.
13. Sholl LM, Cooper W, Tan D, et al. IASLC Atlas of Molecular Testing for Targeted Therapy in Lung Cancer: IASLC; 2023.
14. Hirsch FR, Matthews MJ, Yesner R. Histopathologic classification of small cell carcinoma of the lung: comments based on an interobserver examination. Cancer. 1982;50:1360-6.
15. Hirsch FR, Matthews MJ, Aisner S, et al. Histopathologic classification of small cell lung cancer. Changing concepts and terminology. *Cancer*. 1988;62: 973-7.
16. Travis WD, Garg K, Franklin WA, et al. Evolving concepts in the pathology and computed tomography imaging of lung adenocarcinoma and bronchioloalveolar carcinoma. *J Clin Oncol*. 2005;23:3279-87.
17. Travis WD, Garg K, Franklin WA, et al. Bronchioloalveolar carcinoma and lung adenocarcinoma: the clinical importance and research relevance of the 2004 World Health Organization pathologic criteria. *J Thorac Oncol*. 2006;1:S13-S9.
18. Lim E, Goldstraw P, Nicholson AG, et al. Proceedings of the IASLC International Workshop on Advances in Pulmonary Neuroendocrine Tumors 2007. *J Thorac Oncol*. 2008;3:1194-201.
19. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004;350:2129-39.
20. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004;304:1497-500.
21. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad* Sci. 2004;101:13306-11.
22. Inamura K, Takeuchi K, Togashi Y, et al. EML4-ALK fusion is linked to histological characteristics in a subset of lung cancers. *J Thorac Oncol*. 2008;3:13-7.
23. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol*. 2009;27:4247-53.
24. Noguchi M, Morikawa A, Kawasaki M, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. *Cancer*. 1995;75:2844-52.
25. Park CM, Goo JM, Lee HJ, et al. Nodular ground-glass opacity at thin-section CT: histologic correlation and evaluation of change at follow-up. *Radiographics*. 2007;27:391-408. tk
26. Motoi N, Szoke J, Riely GJ, et al. Lung adenocarcinoma: Modification of the 2004 WHO mixed subtype to include the major histologic subtype suggests correlations between papillary and micropapillary adenocarcinoma subtypes, EGFR mutations and gene expression analysis. *Am J Surg Patho*l. 2008;32:810-27.
27. Travis WD, Giroux DJ, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the inclusion of broncho-pulmonary carcinoid tumors in the forthcoming (seventh) edition of the TNM Classification for Lung Cancer. *J Thorac Oncol*. 2008;3:1213-23.
28. Travis WD, Brambilla E, Rami-Porta R, et al. Visceral pleural invasion: pathologic criteria and use of elastic stains: proposal for the 7th edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2008;3:1384-90.
29. Austin JH, Garg K, Aberle D, et al. Radiologic implications of the 2011 classification of adenocarcinoma of the lung. *Radiology*. 2013;266:62-71.
30. Van Schil PE, Asamura H, Rusch VW, et al. Surgical implications of the new IASLC/ATS/ERS adenocarcinoma classification. *Eur Respir J.* 2012;39:478-86.
31. Van Schil PE, Sihoe AD, Travis WD. Pathologic classification of adenocarcinoma of lung. *J Surg Oncol*. 2013;108:320-6.
32. Travis WD, Brambilla E, Noguchi M, et al. Diagnosis of lung cancer in small biopsies and cytology: implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification. *Arch Pathol Lab* Med. 2013;137:668-84.
33. Travis WD, Brambilla E, Riely GJ. New pathologic classification of lung cancer: relevance for clinical practice and clinical trials. *J ClinOncol*. 2013;31:992-1001.
34. Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society: international multidisciplinary classification of lung adenocarcinoma: executive summary. Proceedings of the American Thoracic Society. 2011;8:381-5.
35. Travis WD, Brambilla E, Noguchi M, et al. Diagnosis of Lung Adenocarcinoma in Resected Specimens: Implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society Lung Classification. *Arch Pathol Lab Med*. 2013;137:685-705.
36. Brambilla E, Travis WD. Clinical relevance and TNM implications of the new concept of minimally-invasive adenocarcinomas in situ with a lepidic pattern. *Eur J Cardiothorac Surg*. 2013;43:932-3.
37. Travis WD, Brambilla E, Noguchi M, et al. The New IASLC/ATS/ERS international multidisciplinary lung adenocarcinoma classification. *J Thoracic Oncol*. 2011;6: 244-85.
38. Lindeman NI, Cagle PT, Beasley MB, et al. Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors:

Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol*. 2013;8:823-59.
39. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. *J Thorac Oncol*. 2015;10:1243-60.
40. Travis WD, Brambilla E, Burke AP, et al. Introduction to The 2015 World Health Organization Classification of Tumors of the Lung, Pleura, Thymus, and Heart. *J Thorac Oncol.* 2015;10:1240-2.
41. Hirsch FR, McElhinny A, Stanforth D, et al. PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project. *J Thorac Oncol*. 2017;12:208-22.
42. Thunnissen E, Noguchi M, Aisner S, et al. Reproducibility of histopathological diagnosis in poorly differentiated NSCLC: an international multiobserver study. *J Thorac Oncol*. 2014;9:1354-62.
43. Thunnissen E, Borczuk AC, Flieder DB, et al. The Use of Immunohistochemistry Improves the Diagnosis of Small Cell Lung Cancer and Its Differential Diagnosis. An International Reproducibility Study in a Demanding Set of Cases. *J Thorac Oncol*. 2017;12:334-46.
44. Detterbeck FC, Nicholson AG, Franklin WA, et al. The IASLC Lung Cancer Staging Project: Summary of Proposals for Revisions of the Classification of Lung Cancers with Multiple Pulmonary Sites of Involvement in the Forthcoming Eighth Edition of the TNM Classification. *J Thorac Oncol*. 2016;11:639-50.
45. Detterbeck FC, Marom EM, Arenberg DA, et al. The IASLC Lung Cancer Staging Project: Background Data and Proposals for the Application of TNM Staging Rules to Lung Cancer Presenting as Multiple Nodules with Ground Glass or Lepidic Features or a Pneumonic Type of Involvement in the Forthcoming Eighth Edition of the TNM Classification. *J Thorac Oncol*. 2016;11:666-80.
46. Detterbeck FC, Franklin WA, Nicholson AG, et al. The IASLC Lung Cancer Staging Project: Background Data and Proposed Criteria to Distinguish Separate Primary Lung Cancers from Metastatic Foci in Patients with Two Lung Tumors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol*. 2016;11:651-65.
47. Detterbeck FC, Bolejack V, Arenberg DA, et al. The IASLC Lung Cancer Staging Project: Background Data and Proposals for the Classification of Lung Cancer with Separate Tumor Nodules in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol*. 2016;11:681-92.
48. Travis WD, Asamura H, Bankier AA, et al. The IASLC Lung Cancer Staging Project: Proposals for Coding T Categories for Subsolid Nodules and Assessment of Tumor Size in Part-Solid Tumors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer. *J Thorac Oncol*. 2016;11:1204-23.
49. Bunn PA, Jr., Minna JD, Augustyn A, et al. Small Cell Lung Cancer: Can Recent Advances in Biology and Molecular Biology Be Translated into Improved Outcomes? *J Thorac Oncol*. 2016;11:453-74.
50. Tsao MS, Kerr KM, Kockx M, et al. PD-L1 Immunohistochemistry Comparability Study in Real-Life Clinical Samples: Results of Blueprint Phase 2 Project. *J Thorac Oncol*. 2018;13:1302-11.
51. Lindeman NI, Cagle PT, Aisner DL, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. *J Thorac Oncol*. 2018;13:323-58.
52. Moreira AL, Ocampo PSS, Xia Y, et al. A Grading System for Invasive Pulmonary Adenocarcinoma: A Proposal From the International Association for the Study of Lung Cancer Pathology Committee. *J Thorac Oncol*. 2020;15:1599-610.
53. Travis WD, Dacic S, Sholl LM, et al. Pathologic Assessment of Lung Squamous Cell Carcinoma After Neoadjuvant Immunotherapy. *J Thorac Oncol*. 2021;16:e9-e10.
54. Travis WD, Dacic S, Wistuba I, et al. IASLC Multidisciplinary Recommendations for Pathologic Assessment of Lung Cancer Resection Specimens After Neoadjuvant Therapy. *J Thorac Oncol*. 2020;15:709-40.
55. Sholl LM, Hirsch FR, Hwang D, et al. The Promises and Challenges of Tumor Mutation Burden as an Immunotherapy Biomarker: A Perspective from the International Association for the Study of Lung Cancer Pathology Committee. *J Thorac Oncol*. 2020;15:1409-24.
56. Yatabe Y, Dacic S, Borczuk AC, et al. Best Practices Recommendations for Diagnostic Immunohistochemistry in Lung Cancer. *J Thorac Oncol*. 2019;14:377-407.
57. Nicholson AG, Tsao MS, Travis WD, et al. Eighth Edition Staging of Thoracic Malignancies: Implications for the Reporting Pathologist. *Arch Pathol Lab Med*. 2018;142:645-61.
58. Lantuejoul S, Sound-Tsao M, Cooper WA, et al. PD-L1 Testing for Lung Cancer in 2019: Perspective From the IASLC Pathology Committee. *J Thorac Oncol*. 2020;15:499-519.
59. Osarogiagbon RU, Rami-Porta R, Tsao MS, et al. The International Association for the Study of Lung Cancer Molecular Database Project: Objectives, Challenges, and Opportunities. *J Thorac Oncol*. 2021;16:897-901.
60. Edwards JG, Chansky K, Van Schil P, et al. The IASLC Lung Cancer Staging Project: Analysis of Resection Margin Status and Proposals for Residual Tumor Descriptors for Non-Small Cell Lung Cancer. *J Thorac Oncol*. 2020;15:344-59.
61. Blumenthal GM, Bunn PA, Jr., Chaft JE, et al. Current Status and Future Perspectives on Neoadjuvant Therapy in Lung Cancer. *J Thorac Oncol*. 2018;13:1818-31.
62. Poirier JT, George J, Owonikoko TK, et al. New Approaches to SCLC Therapy: From the Laboratory to the Clinic. *J Thorac Oncol.* 2020;15:520-40.
63. Tsao MS, Nicholson AG, Maleszewski JJ, et al. Reprint of "Introduction to 2021 WHO Classification of Thoracic Tumors." *J Thorac Oncol.* 2022;17:337-40.
64. Tsao MS, Nicholson AG, Maleszewski JJ, et al. Introduction to 2021 WHO Classification of Thoracic Tumors. *J Thorac Oncol.* 2022;17:e1-e4.
65. Nicholson AG, Tsao MS, Beasley MB, et al. The 2021 WHO Classification of Lung Tumors: Impact of Advances Since 2015. *J Thorac Oncol*. 2022;17:362-87.
66. Thunnissen E, Beasley MB, Borczuk A, et al. Defining morphologic features of invasion in pulmonary non-mucinous adenocarcinoma with lepidic growth-A proposal by the IASLC Pathology Committee. *J Thorac Oncol.* 2023; 18:447-462.
67. Jain D, Nambirajan A, Chen G, et al. NSCLC Subtyping in Conventional Cytology: Results of the International Association for the Study of Lung Cancer Cytology Working Group Survey to Determine Specific Cytomorphologic Criteria for Adenocarcinoma and

Squamous Cell Carcinoma. *J Thorac Oncol.* 2022;17:793-805.
68. Dacic S, Travis W, Redman M, et al for the IASLC Pathology Committee. International Association for the Study of Lung Cancer study of reproducibility in assessment of pathologic response in resected lung cancers after neoadjuvant therapy. *J Thorac Oncol.* 2023;18:1290-130.
69. Dacic S, Travis WD, Giltnane JM, et al. Artificial intelligence-powered assessment of pathologic response to neoadjuvant atezolizumab in patients with NSCLC: Results from the LCMC3 study. *J Thorac Oncol.* 2023;S1556-0864(23)02415-2.
70. Brambilla E, Travis WD, Colby TV, et al. The new World Health Organization classification of lung tumours. *Eur Respir J*. 2001;18:1059-68.
71. Onuki N, Wistuba II, Travis WD, et al. Genetic changes in the spectrum of neuroendocrine lung tumors. *Cancer*. 1999;85:600-7.
72. Beasley MB, Thunnissen FB, Brambilla E, et al. Pulmonary atypical carcinoid: Predictors of survival in 106 cases. Hum Pathol. 2000;31:1255-65.
73. Nicholson SA, Beasley MB, Brambilla E, et al. Small Cell Lung Carcinoma (SCLC): A Clinicopathologic Study of 100 Cases With Surgical Specimens. *Am J Surg Pathol*. 2002;26:1184-97.
74. Rusch VW, Appelman HD, Byhardt R, et al. Lung. In: Greene FL, Page DL, Fleming ID, et al., eds. AJCC Cancer Staging Manual. New York: Springer-Verlag; 2002:167-81.
75. Rusch VW, Appleman HD, Blackstone E, et al. Lung. In: Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. AJCC Cancer Staging Manual. Chicago: American Joint Commision on Cancer; Springer; 2009:253-70.
76. Rami-Porta R, Ball D, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol.* 2007;2:593-602.
77. Postmus PE, Brambilla E, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the M descriptors in the forthcoming (seventh) edition of the TNM classification of lung cancer. *J Thorac Oncol.* 2007;2:686-93.
78. Travis WD, Brambilla E, Noguchi M, et al. The New IASLC/ATS/ERS International Multidisciplinary Lung Adenocarcinoma Classification. *J Thorac Oncol.* 2009;4:S86-S9.
79. Travis WD, Rekhtman N, Riley GJ, et al. Pathologic diagnosis of advanced lung cancer based on small biopsies and cytology: a paradigm shift. *J Thorac Oncol.* 2010;5:411-4.
80. Kerr KM, Tsao MS, Nicholson AG, et al. Programmed Death-Ligand 1 Immunohistochemistry in Lung Cancer: In what state is this art? *J Thorac Oncol.* 2015;10:985-9.
81. Lindeman NI, Cagle PT, Beasley MB, et al. Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors: Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *Arch Path Lab Med*. 2013;137:828-60.
82. Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Mol Diagn*. 2013;15:415-53.
83. Field JK, Aberle DR, Altorki N, et al. The International Association Study Lung Cancer (IASLC) Strategic Screening Advisory Committee (SSAC) response to the USPSTF recommendations. *J Thorac Oncol.* 2014;9:141-3.
84. Nicholson AG, Torkko K, Viola P, et al. Interobserver Variation among Pathologists and Refinement of Criteria in Distinguishing Separate Primary Tumors from Intrapulmonary Metastases in Lung. *J Thorac Oncol.* 2018;13:205-17.
85. Rami-Porta R, Asamura H, Travis WD, et al. Lung. In: Amin MB, ed. AJCC Cancer Staging Manual. 8th ed. Chicago: American Joint Committee on Cancer; 2017:431-56.
86. Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol.* 2015;10:990-1003.
87. Nicholson AG, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the Clinical and Pathologic Staging of Small Cell Lung Cancer in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol*. 2016;11:300-11.
88. Nicholson AG, Scagliotti G, Tsao MS, et al. 2021 WHO Classification of Lung Cancer: A Globally Applicable and Molecular Biomarker-Relevant Classification. *J Thorac Oncol.* 2022;17:e80 - e3.

9

STAGING AND PROGNOSTIC FACTORS COMMITTEE

Ramón Rami-Porta,[1,2] **Hisao Asamura,**[3] **Paul A. Bunn Jr,**[4] **John Crowley,**[5] **Gail Darling,**[6] **Frank C. Detterbeck,**[7] **Dorothy J. Giroux,**[5] **Peter Goldstraw,**[8,9] **Fred R. Hirsch,**[10] **and Valerie W. Rusch**[11] | [1]Hospital Universitari Mútua Terrassa, University of Barcelona, Terrassa, Barcelona, Spain; [2]Network of Centers for Biomedical Research in Respiratory Diseases (CIBERES) Lung Cancer Group, Terrassa, Barcelona, Spain; [3]Keio University School of Medicine, Tokyo, Japan; [4]University of Colorado Cancer Center, Aurora, USA; [5]Cancer Research And Biostatistics, Seattle, USA; [6]Dalhousie University, Nova Scotia Health, Halifax, NS, Canada; [7]Yale University, New Haven, USA; [8]National Heart and Lung Institute, Imperial College, London, United Kingdom; [9]Royal Brompton Hospital, London, United Kingdom; [10]Tisch Cancer Institute, Icahn School of Medicine, Mount Sinai Health System, New York, USA; [11]Memorial Sloan Kettering Cancer Center, New York, USA

HISTORICAL NOTE ON TUMOR CLASSIFICATION AND STAGING

For more than five decades, the determination of the anatomic extent of malignant tumors has been based on the size, location, and invasion of the primary tumor (T), the involvement and location of the regional lymph nodes (N), and the presence and location of the distant metastases (M)—the so called TNM classification. Tumors of similar prognosis classified by the TNM system are grouped in stages.

This classification and its staging system were developed by Pierre Denoix, a French surgical oncologist, in a series of articles that he published from 1943 to 1952. The Union for International Cancer Control (UICC) adopted this classification and published brochures for individual tumors from 1960 to 1967, with the one for lung cancer appearing in 1966. Two years later, the UICC published the first edition of the *TNM Classification of Malignant Tumours* in pocket-book format, as we know it today. The American Joint Committee on Cancer (AJCC) also adopted the TNM classification, and published its first staging manual in 1977.[1]

That first UICC edition was followed by five more with innovations, those concerning lung cancer being derived from the analyses of a North American database collected and managed by Clifton F. Mountain, a thoracic surgeon at the MD Anderson Cancer Center and a former president of the International Association for the Study of Lung Cancer (IASLC). That database of 5319 surgically treated patients with lung cancer from North America, important as it was, lacked international character and representation of other therapeutic modalities. The system it informed was called International Staging System, but it was based on a national database.[2]

ORIGIN OF THE IASLC STAGING AND PROGNOSTIC FACTORS COMMITTEE

The limitations of the North American database prompted an initiative in the IASLC that was formulated during the International Workshop on Intrathoracic Staging, organized by Peter Goldstraw, a thoracic surgeon at the Royal Brompton Hospital in London. Sponsored by the IASLC, the 2-day Workshop took place in the National Heart and Lung Institute in London in October 1996 (Figure 1).

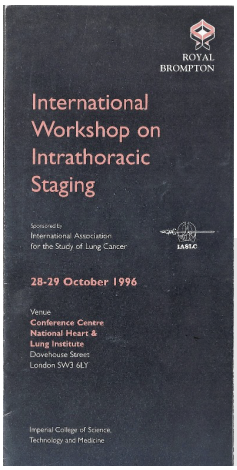


Figure 1. Front page of the program of the International Workshop on Intrathoracic Staging.

Specialists from Asia, North America, and Europe gathered at the Workshop to discuss, among other issues, the limitations of the 5th edition of the TNM classification of lung cancer that was about to be published and that was presented by Clifton F. Mountain himself, who was one of the invited speakers.[3]

During the Workshop, several decisions were made: a) to propose a name, a definition, and the minimal requirements of the intraoperative nodal assessment in lung cancer operations; b) to revise the TNM classification periodically to overcome the limitations of the North American database, for which a truly international database would be necessary; c) to propose a new regional lymph node map that reconciles the differences of the two lymph node maps commonly used worldwide, which are the Naruke and the Mountain and Dresler; and d) to propose an international and multidisciplinary definition of complete resection for lung cancer.[4,5,1]

The members of the IASLC Staging Committee, renamed IASLC Staging and Prognostic Factors Committee (SPFC) in 2013, would carry out all these activities within the frame of the IASLC Staging Project. The IASLC Board approved the SPFC in 1998 and provided some funding for the initiation of the activities. The members of the SPFC were selected to represent all involved specialties and geographic regions, and they met in 1999 and 2000 for subsequent meetings, during which potential data contributors were identified, a timeline was agreed upon, and a budget was outlined.

In 2001, Eli Lilly and Company provided an unrestricted grant to finance the SPFC activities. Cancer Research And Biostatistics (CRAB), a biostatistics agency in Seattle with ample experience in managing and analyzing cancer databases from collaborative studies in North America, was incorporated into the SPFC. In collaboration with CRAB, members of the SPFC selected the data elements and defined the dictionary that would be used to register data of retrospective cases in the IASLC database that would inform the 7th edition of the TNM classification of lung cancer. The first phase of the IASLC Staging Project, that would last until the publication of the 7th edition of the TNM classification in 2009, had begun.[6]

ACTIVITIES AND ACHIEVEMENTS

The First Phase of the IASLC Staging Project, 1996 to 2009

Systematic nodal dissection

The first objective of the 1996 London Workshop was to name and define the minimal requirements for the removal of lymph nodes that accompanied lung cancer resections since the early 1950s.[7] The agreed-upon name was "systematic nodal dissection," chosen for its brevity and the implication of a standardized approach to resection. The terms "radical" and "mediastinal" were considered, but not chosen—"radical" was avoided to prevent linking the surgical procedure solely to its therapeutic effect, and "mediastinal" was not included because the surgical maneuver should not be limited to the lymph nodes of the mediastinum. Rather, it should also include the hilar and the intrapulmonary nodes. Consequently, the resultant definition consisted of two steps:

"**Step one:** Excision of the mediastinal fat and enclosed lymph nodes which are dissected and identified in accordance with an internationally accepted nodal chart. After macroscopic assessment, the nodes are sent separately for histological examination. Complete dissection of all mediastinal tissues is desirable, but at least three mediastinal nodal stations should be excised, one of which should be those nodes in the subcarinal position."

"**Step two:** The excision of hilar and intrapulmonary lymph nodes and their identification in accordance with an internationally accepted nodal chart. After macroscopic assessment they are

sent separately for histological examination. Dissection should proceed in a centrifugal manner until the extent of resection has been determined."[3]

Definition of complete resection in lung cancer surgery

As a parallel project, during periodical meetings of the SPFC, the definition of complete resection was discussed. After revising the previous definitions of complete, or radical resection, as it was sometimes called, the different forms of intraoperative nodal evaluation, the requirements for pathologic N0, and the impact of positive pleural lavage cytology, the SPFC proposed a definition of complete resection, which, by extension, led to definitions of incomplete and uncertain resections. Peter Goldstraw and Ramón Rami-Porta provided final touches, leading to its completion in early October 2004. Remarkably, the two did so on an express train to Saint Petersburg, having just come from Moscow, where they had participated in a Russo-Japanese thoracic surgery meeting. The article was published in 2005.[8]

Complete resection implies that no residual tumour (R0) is left behind but goes beyond the definition of R0. As an important innovation, it includes systematic nodal dissection, as described in the 1996 London Workshop,[3] or lobe-specific systematic nodal dissection. The latter assigns three specific mediastinal nodal stations depending on the lobar location of the primary tumor, always including the subcarinal nodes regardless of the lobe involved. In addition to negative resection margins, there should not be extracapsular invasion of lymph nodes removed separately or located at the margin of the main lung specimen; and the highest mediastinal lymph node removed should be negative. Its counterpart, incomplete resection is the equivalent of the R1 and R2 categories of the residual tumour, and it is defined by involved margins, extracapsular nodal invasion, involved nodes left unremoved, and positive pleural or pericardial effusions. A single condition is enough to define it.

A definition was also needed to qualify resections in which no residual tumor is left but all requirements of complete resection are not fulfilled. That is, the margins are free of tumor, but the intraoperative lymph node evaluation does not reach the standards of systematic nodal dissection or lobe-specific systematic nodal dissection; the highest mediastinal lymph node removed is involved by cancer; carcinoma in situ is present at the bronchial margin; or the pleural lavage cytology is positive. Thus, such terms as "relatively complete" and "relatively incomplete" were considered. However, it was David Ball, a forward-thinking radiotherapist from Melbourne, Australia, who proposed the term "uncertain resection," which the members of the SPFC unanimously accepted. Although the definition for uncertain resection had no equivalent among the R categories, the UICC accepted it and coded it as R0(un) in the 7th edition TNM for all tumors as a resection with healthy margins but with an inadequate intraoperative nodal assessment; and, specifically for lung cancer, when the highest mediastinal lymph node removed is positive.[9] Carcinoma in situ and positive pleural lavage cytology were excluded from the UICC definition of R0(un) because they already were considered R1 conditions.

The IASLC definitions have been used in different parts of the world and have remained unchallenged up to now. Four different groups from different countries have validated the prognostic relevance of the three types of resection using their own databases, including the IASLC database of the 8th edition TNM.[10-13] This has reinforced the clinical impact of the definitions and provided them with practical value in surgical practice. The definitions were never thought to be definitive. The concept of complete resection has evolved over the decades, and they will further evolve when the determination of minimal residual disease and its impact on cancer management are more available and better understood, respectively.[14,15]

The 7th edition of the TNM classification for lung cancer

When the initial Staging Committee met in Barcelona for the first week of July in 2005, it had

a simple focus for structure: form Subcommittees to convene the day prior to the beginning of the IASLC's World Conference on Lung Cancer (WCLC), when the database would close for analyses. These Subcommittees were charged with making recommendations for changes that were introduced in the 7th edition of the lung cancer TNM. There were Subcommittees for the T, the N, and the M components of the classification, as well as for prognostic factors, small cell lung cancer, validation and methodology, and nodal chart. Peter Goldstraw, as chair of the SPFC, and John Crowley, as representative of CRAB's statisticians, were members of all the Subcommittees, and they provided the committees with sound clinical and methodological guidance (Figure 2). There were 28 members, three additional biostatisticians from CRAB (Figure 3), and four observers to the SPFC. All are duly listed and acknowledged in the appendix of all the IASLC staging articles, together with the institutions that contributed cases to the IASLC Staging Project.

Data from 100,869 patients diagnosed from 1990 to 2000 were submitted from Asia, Australia, Europe, and North America to the IASLC database. After exclusions, 81,495 were available for analyses. Most patients were from Europe, and over half underwent resection alone or combined with chemo-radiotherapy (Table 1).

Figure 3. Statisticians Dorothy Giroux (sitting, left), Vanessa Cilento (sitting, right), and Kari Chansky (standing) with Ramón Rami-Porta at CRAB's meeting room, June 8th-10th, 2006.

Figure 2. Peter Goldstraw (left) and John Crowley, clinical and methodological pillars of the IASLC Staging Project, at one of the SPFC meetings in CRAB's meeting room in Seattle, WA, USA, June 8th-10th, 2006, when the recommendations for the forthcoming 7th edition of the TNM classification of lung cancer were finalized and prepared for publication.

Table 1. Number of Cases in the Databases Used to Inform the Revisions of the TNM Classification of Thoracic Malignancies.

	Number of evaluable patients		
Tumors	**First phase 7th edition**	**Second phase 8th edition**	**Third phase[a] 9th edition**
Lung cancer - NSCLC - SCLC - Other - Molecular data	81,495[b] 68,463 (84%) 13,032 (16%)	77,156[b] 70,967 (92%) 6,189 (8%)	87,043[b] 73,197 (84%) 5,530 (6%) 8,316 (10%) 9,931 (14%)*
Malignant pleural mesothelioma	3,101[b]	2,414[b]	3,598[b]
Thymic epithelial tumors	N/A	7,314[c]	9,147[d]
Esophagus and esophago-gastric junction	N/A	22,654[e]	>12,000[f]

[a]Definitive number of patients.
[b]Registered by the International Association for the Study of Lung Cancer (IASLC) and analyzed by Cancer Research And Biostatistics (CRAB).
[c]Registered by the International Thymic Malignancies Interest Group (ITMIG) and analyzed by CRAB.
[d]Registered by the ITMIG and the IASLC and analyzed by CRAB.
[e]Registered by the Worldwide Esophageal Cancer Collaboration and analyzed at the Cleveland Clinic, Cleveland, OH, USA.
[f]Registered and analyzed by the International Esophageal Study Group. Resected cases, only.
*Percentage relative to NSCLC.
Abbreviations: NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; N/A: not available.

The granularity of the database allowed thorough analyses of the T, N, and M descriptors. Tumor size was found to have more prognostic relevance than the previous editions of the classification showed. Furthermore, subcategories for T1 (T1a: ≤2cm; and T1b: >2-≤3cm) and T2 (T2a: >3-≤5cm; and T2b: >5-≤7cm) were created, and tumors >7cm in size were reclassified as T3. The N descriptors did not change, but quantifying nodal disease by the number of involved nodal zones was found to be prognostic. The concept of nodal zone—a group of neighboring nodal stations—was proposed to facilitate nodal classification, especially for those patients who would not undergo resection. The more nodal zones involved, the worse the prognosis: single N1 zone had better prognosis than multiple N1 zones, but these had similar prognosis to that of single N2 zone, while the involvement of multiple N2 zones had the worst prognosis. These results were evident with the analysis of postoperative data, yet they were not found at clinical staging, which precluded the incorporation of N subcategories based on the number of involved nodal zones into the 7th edition of TNM. In the M component, intrathoracic and extrathoracic metastases were assigned different M categories: M1a and M1b, respectively. Some tumors changed from one stage to another, otherwise there were no changes in the number of stages.[16]

Other innovations of the 7th edition TNM were: the definition of visceral pleura invasion as the invasion of its elastic layer and its categorization as PL0 (no involvement), PL1 (involvement of the elastic layer) and PL2 (involvement of the lung surface), and PL1 and PL2 classify the tumour as T2a; the classification of separate tumor nodules as T3 if located in the same lobe of the primary tumor, T4 if in another ipsilateral lobe, and M1a if in the contralateral lung; and the validation of the TNM in surgical and non-surgical small cell lung cancer and in bronchopulmonary carcinoids, the latter being included in the TNM classification for the first time in the history of this staging system.

All the recommendations proposed by the IASLC SPFC were accepted by the UICC and the AJCC, and they were incorporated into their respective 7th edition staging manuals (Figure 4).

The robustness of the presented data and the methodology used for the analyses of the database[17] made the IASLC the main provider of evidence to the UICC and AJCC for the 7th and for future editions of the TNM classification of lung cancer and other thoracic malignancies, as these were progressively incorporated into the IASLC Staging Project.

All the articles presenting evidence for the innovations recommended for the 7th edition lung cancer TNM, namely, the

Figure 4. The SPFC Core Group that finalized the recommendation for changes for the 7th edition TNM for lung cancer. From top to bottom and left to right: James Jett, Zeba Shaikh (Peter Goldstraw's research assistant), Ramón Rami-Porta and Leslie Sobin; Mark Krasnik, Eric Vallières and Masahiro Tsuboi; Jung-Gi Im, Elisabeth Brambilla, Dorothy Giroux and David Ball; Pieter Postmus, Patti Groome, Jan Van Meerbeeck, Paul Van Houtte, Catherine Kennedy and Bill Travis; Vanessa Cilento, Kari Chansky, Peter Goldstraw, John Crowley and Jean-Paul Sculier. Terrace of the Sorrento Hotel in Seattle, WA, USA, June 8th-10th, 2006.

articles on the T, the N, the M, the stages, the validation, the surgical and non-surgical small cell lung cancer, the visceral pleura invasion, the bronchopulmonary carcinoids, the lymph node chart, and the additional prognostic factors were published in the *Journal of Thoracic Oncology*, the official journal of the IASLC, from 2007 to 2009.[16]

The IASLC lymph node chart

Thirteen years after the 1996 London Workshop, during which the need for a new lymph node map was discussed and the general guidelines for its design were outlined, the IASLC presented a nodal chart that was the result of an international and multidisciplinary consensus.[18] Its main new features were the enlargement of the supraclavicular and subcarinal nodal stations, the shift of the anatomic midline to the left paratracheal margin, and the new borders separating mediastinal from hilar lymph nodes (the lower rim of the azygos vein on the right, and the upper rim of the pulmonary artery on the left). All nodal stations have clear anatomic landmarks (Figure 5).

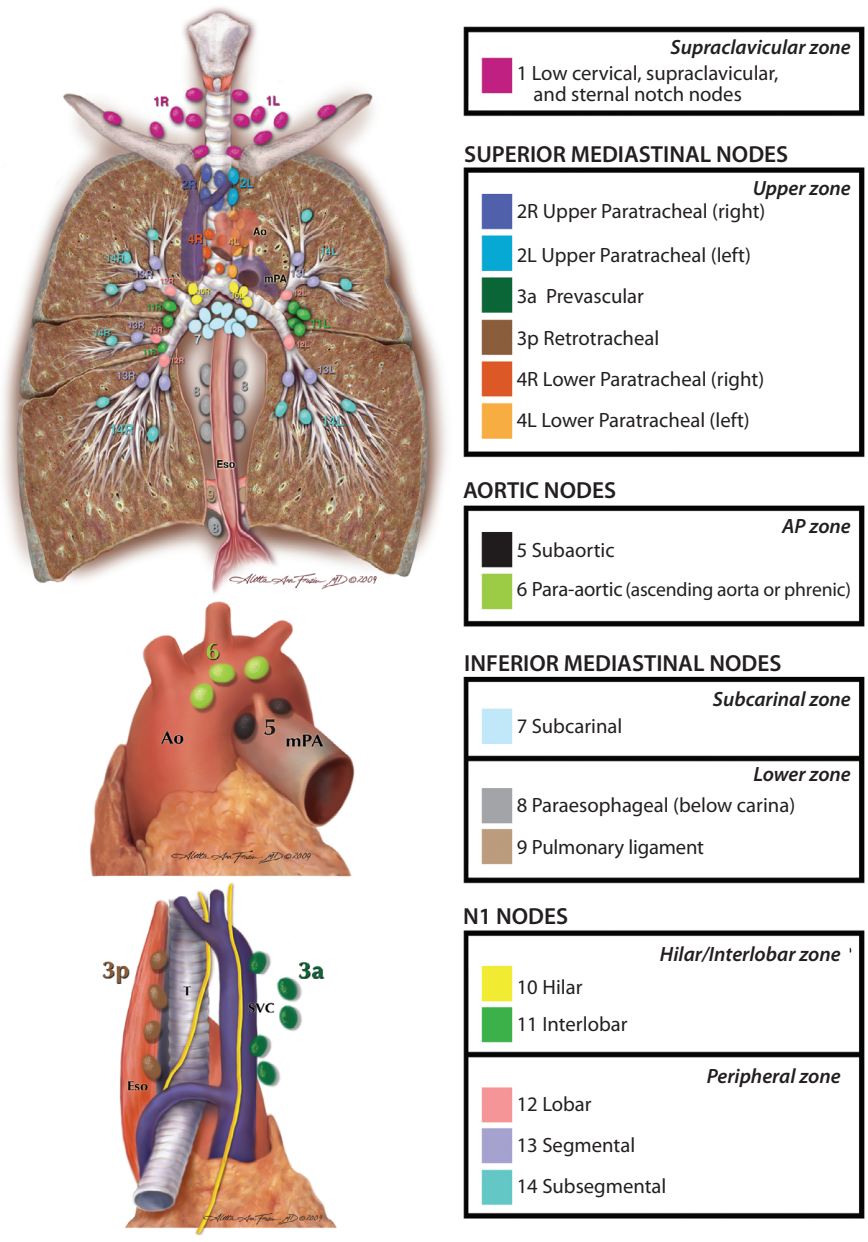


Figure 5. International Association for the Study of Lung Cancer lymph node map. Taken from reference 18 with permission. Copyright ©2008 Aletta Ann Frazier, MD.

The 7th edition of the TNM classification and prognostic factors for malignant pleural mesothelioma

Originally planned for lung cancer only, it soon became obvious that the scope of the IASLC Staging Project should encompass other thoracic malignancies as well, and malignant pleural mesothelioma was the first to be incorporated into the Project. Work on malignant pleural mesothelioma started during the first phase of the IASLC Staging Project and was carried out into the second phase.

The IASLC, in collaboration with the International Mesothelioma Interest Group (IMIG), collected a series of 3,101 surgically treated patients from 1995 to 2009, originating from 15 institutions in four continents. The objective of their analyses was to identify conflictive issues in the classification of malignant pleural mesothelioma that could prompt

further research based on a larger database of surgically and non-surgically treated patients. This would be developed in the second phase of the IASLC Staging Project.[20] This database was also useful to develop prognostic models based on staging, clinical, biological, and therapeutic data.[21] Additional collaboration between the IASLC SPFC and IMIG resulted in a consensus document on the definitions of extrapleural pneumonectomy, extended pleurectomy/decortication, pleurectomy/decortication, and partial pleurectomy intended for use in the forthcoming activities of the IASLC Mesothelioma Staging Project.[22]

In the 7th edition TNM for malignant pleural mesothelioma, the 6th edition categories, descriptors and stages were kept unchanged.

The IASLC Staging Manual and Handbook in Thoracic Oncology

Once the UICC and the AJCC accepted the revisions proposed by the IASLC SPFC, the Committee thought that a manual containing the TNM classification of lung cancer and of mesothelioma, together with the site-specific rules for each tumor, would be a good means to disseminate the new information and have it ready in a single source. The manual would also contain chapters on the general rules of the TNM classification that apply to all cancers, on survival analyses, on prognostic factors, and a list of frequently asked questions and their answers. The *IASLC Staging Manual in Thoracic Oncology* and the *IASLC Staging Handbook in Thoracic Oncology*, a pocketsize condensed version of the former, were edited by Peter Goldstraw and published in 2009 (Figure 6). Derivatives were subsequently published in many formats and in other languages, including Spanish, Italian, Chinese, and Japanese.

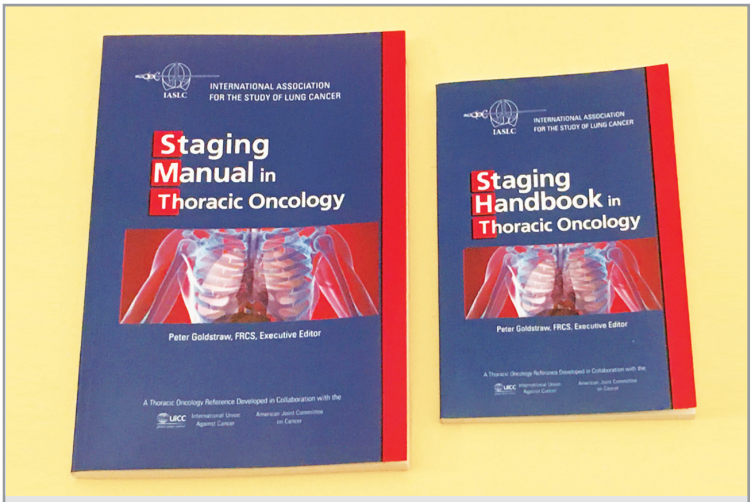


Figure 6. First edition of the *IASLC Staging Manual in Thoracic Oncology* and of the *IASLC Staging Handbook in Thoracic Oncology*.

The Second Phase of the IASLC Staging Project, 2009 to 2016

The 2009 World Conference on Lung Cancer that took place in San Francisco, USA, marked the end of the first phase of the IASLC Staging Project. Peter Goldstraw became the Past-Chair of the Committee and Ramón Rami-Porta replaced him as Chair. During the next few months, the Committee membership was revised, some members rotated off, and others were incorporated to represent all specialties related to the management of thoracic malignancies and as many geographic regions as possible.

The scope of the IASLC Staging Project widened. With malignant pleural mesothelioma already incorporated into the Project, the second group of malignancies to be added to the project was thymic epithelial tumors.

The International Thymic Malignancies Interest Group (ITMIG), created in 2009, shared some objectives with the IASLC Staging Project, thus the two groups agreed to collaborate on the development of a new TNM classification for thymic epithelial tumors.[23] Thomas W. Rice, a thoracic surgeon from the Cleveland Clinic, in Cleveland, USA, played an integrative role in this joint effort. That included a memorandum of understanding to promote and disseminate the forthcoming TNM classification of esophageal and esophago-gastric junction cancers based on the large international database of the Worldwide Esophageal Cancer Collaboration (WECC).

The simple structure of the IASLC SPFC that served well to achieve the objectives of the first phase of the IASLC Staging Project had to be modified to accommodate the incorporation of the new tumors and the

growing number of Committee members. The four malignancies were organized in domains (lung cancer, malignant pleural mesothelioma, thymic epithelial tumors, and esophageal cancer domains), and the Committee members were distributed among the four domains. Each domain had a chairperson and as many subcommittees as necessary for the development of the specific tasks of the domain. It was Peter Goldstraw's idea to create the Advisory Boards with the objective to add more specialists to the domains without increasing the number of SPFC members.

The 8th edition of the TNM classification for lung cancer

Due to time limitations in the first phase of the IASLC Staging Project, the collected data used to inform the 7th edition of the TNM classification for lung cancer were exclusively retrospective. For the 8th edition, the objective was to register as much prospective data as possible, in addition to the retrospective data that would be submitted. CRAB created a system called electronic data capture (EDC). It allowed for the online registration of cases using an updated dataset that included demographic, clinical, biological, pathologic, staging, therapeutic, and follow-up data. Even though only 5% of cases were registered through the EDC system, the detail provided proved very useful, especially when the number and location of metastases were analyzed. After exclusion, 77,156 cases diagnosed between 1999 and 2010 and were available for analyses (Table 1).

The analyses of the new database increased understanding of the prognostic impact of tumor size. More T categories based on tumor size were found to separate tumors with significantly different prognosis: T1 was divided into T1a, T1b and T1c at one cm intervals; T2 was divided into T2a (>3-≤4 cm) and T2b (>4-≤5 cm); tumors >5-≤7 cm were reclassified as T3, and those >7 cm as T4. Endobronchial location <2 cm from the carina and total atelectasis were reclassified as T2a; mediastinal pleura invasion was deleted as a T descriptor; and invasion of the diaphragm was reclassified as T4. In the 7th edition, the quantification of nodal disease during pathologic staging enabled the subclassification of the N categories based on the number of involved nodal zones. In the 8th edition, quantification of nodal disease was based on the number of involved nodal stations. However, these subclassifications could not be replicated during clinical staging, resulting in no changes to the N categories, and their descriptors remained unchanged. In the M component, data submitted through the EDC allowed the reclassification of extrathoracic metastases into single and multiple, coded as M1b and M1c. The number of stages increased: stage IA was subdivided into stages IA1, IA2 and IA3 to include the new T1a, T1b and T1c N0 and M0 tumors, respectively; stage IIIC was added to include T3 and T4 tumors with N3 M0; and stage IV was subdivided into IVA (M1a and M1b) and IVB (M1c).[24]

For the first time in the history of the TNM classification of lung cancer, instructions were given on how to measure tumor size at clinical staging, and at pathologic staging after induction therapy had caused some objective tumor response and regression. Codes were assigned to the new adenocarcinomas: Tis (AIS) for adenocarcinoma in situ and T1mi for minimally invasive adenocarcinoma.[25]

Given the increasing number of lung cancers presenting with multiple lesions at the time of diagnosis and the confusion and discrepancies during staging, the ad hoc Multiple Pulmonary Sites Workgroup was established under the leadership of Frank Detterbeck. After a thorough review of the available evidence and several multidisciplinary discussions, the Workgroup recommended uniform clinical and pathologic classifications of second primaries, separate tumor nodules, multifocal non-mucinous adenocarcinomas with ground glass/lepidic features, and pneumonic-type adenocarcinoma.[26]

The 8th edition of the TNM classification for malignant pleural mesothelioma

International collaboration was essential to collect data from nearly 2,500 evaluable patients with malignant pleural meso-

thelioma with clinical and/or pathologic staging information diagnosed between 1995 to 2013 from 29 centers in four continents (Table 1).[27] The analyses of this database allowed the recommendation to combine the 7th edition T1a (parietal pleura invasion) and T1b (visceral pleura invasion) into the 8th edition T1. The observation of the prognostic impact of pleural thickness was thought to deserve further study in the forthcoming edition of the classification as a potential T descriptor. For the N component, the analyses showed no survival differences between N1 and N2, so these were combined into the 8th edition N1, and the 7th edition N3 was reclassified into the 8th edition N2. Metastatic disease had worse prognosis than locally advanced tumors and was kept alone in stage IV. In the 8th edition, stage IA includes T1N0M0 tumors, only, while stage IB includes T2-T3N0M0. The new stage II includes T1-T2N1M0; stage IIIA includes T3N1M0; and stage IIIB, T4N0-1M0 and all N2M0 tumors.[28]

The first TNM classification for thymic epithelial tumors approved by the UICC and the AJCC

Although societies and various institutions proposed more than a dozen different TNM and non-TNM classifications for thymic epithelial tumors, none made their way into the official UICC and AJCC staging manuals, thus none have received official international recognition.[29] The collaboration between ITMIG and IASLC allowed for the collection of more than 10,000 patient records from 105 sites worldwide. Of these, more than 7,000 cases were suitable for analyses (Table 1). This was a retrospective database, following the model of the initial ITMIG database, and including data from patients with thymoma, thymic carcinoma, and thymic carcinoid.[30-31]

The analyses of the IASLC/ITMIG database allowed for the definition of a T1 category divided in two subcategories based on the invasion of the mediastinal pleural: T1a when there is no invasion, and T1b when there is. T1a tumors can be encapsulated or not, and the mediastinal fat may or may not be involved. T2 category implies the involvement of the pericardium, and the T3 and T4 categories define involvement into the lung, chest wall, and mediastinal organs. Contrary to the Masaoka-Koga classification, involvement of these structures must be confirmed histopathologically at pathologic staging. Nodal involvement is described by the N1 and N2 categories, representing involved anterior perithymic nodes and deep intrathoracic or cervical nodes, respectively. These categories align with a regional lymph node map specifically devised for thymic malignancies.[32] Distant metastases were divided into pleural and pericardial nodules (M1a) and any other location, including the lung and distant organs (M1b). The stage grouping is simple: stages I, II, IIIA, and IIIB include T1N0M0, T2N0M0, T3N0M0, and T4N0M0 tumors, respectively. Stage IV is divided into IVA for N1 and M1a tumors, as well as IVB for N2 and M1b tumors.[33]

This is the first official TNM classification of thymic epithelial tumors. It is based on a large series of patients, and it is applicable to thymomas, thymic carcinomas, and thymic carcinoids, as subgroup analyses show. The classification marks a significant advancement from the Masaoka and Masaoka-Koga classifications, which, despite the fact that they were based on less than 100 cases, stood the test of time and served us well for four decades. Let's hope that this TNM classification will continue to evolve with necessary refinements as more data are generated and additional cases are submitted to the new database that will inform the 9th edition TNM.

The ITMIG also contributed recommendations on the handling of resected specimens, the radiologic assessment of tumor response, and a new proposal for mediastinal compartments.[34-36]

The 8th edition of the TNM classification for esophageal and esophago-gastric junction cancers

Led by Thomas W. Rice, the 8th edition of the TNM classification of esophageal and esophago-gastric junction cancers derives from the analyses of data from more than 22,000 patients (Table 1) whose tumors had clinical, pathologic, and post-induction pathologic classification and staging. Compared to the 7th edition, the

8th made important innovations. It continued with the harmonization of the classification of esophageal and esophago-gastric junction cancers, which was initiated in the 7th edition TNM. However, in the 8th, the distance of the tumor's epicenter reduced from 5 cm (7th edition) to 2 cm (8th edition) from the esophago-gastric junction to classify cancers of the esophago-gastric junction as esophageal cancers. The 8th edition also has different clinical and pathologic stage groupings for squamous carcinomas and adenocarcinomas. In the case of squamous carcinoma, pathologic prognostic groupings have been revised to consider both tumor grade and anatomic location. Conversely, for adenocarcinomas, only tumor grade was taken into account in the updates. Furthermore, with the 8th, for the first time in the TNM classification of esophageal and esophago-gastric junction cancers, there is a post-induction pathologic staging identical for squamous carcinoma and adenocarcinoma.[37] This post-induction pathologic classification was accepted by the AJCC, but not by the UICC.

This TNM classification, featured in both the second edition of the *IASLC Staging Manual in Thoracic Oncology* and the *IASLC Staging Handbook in Thoracic Oncology*, is accessible in pocket-size plasticized cards, published by the IASLC, together with the classification for lung cancer, malignant pleural mesothelioma, and thymic epithelial tumors. This arrangement fulfills the agreement between the IASLC and Thomas W. Rice to disseminate the 8th edition of the TNM classification for esophageal and esophago-gastric junction cancers with the other thoracic malignancies.

The IASLC Staging Manual and Handbook in Thoracic Oncology

In 2016, the publication of the 8th edition of the TNM by the UICC and the AJCC, along with the second edition of both the *IASLC Staging Manual in Thoracic Oncology* and the *IASLC Staging Handbook in Thoracic Oncology*, both edited by Ramón Rami-Porta, marked the culmination of the second phase of the IASLC Staging Project (Figures 7 and 8).

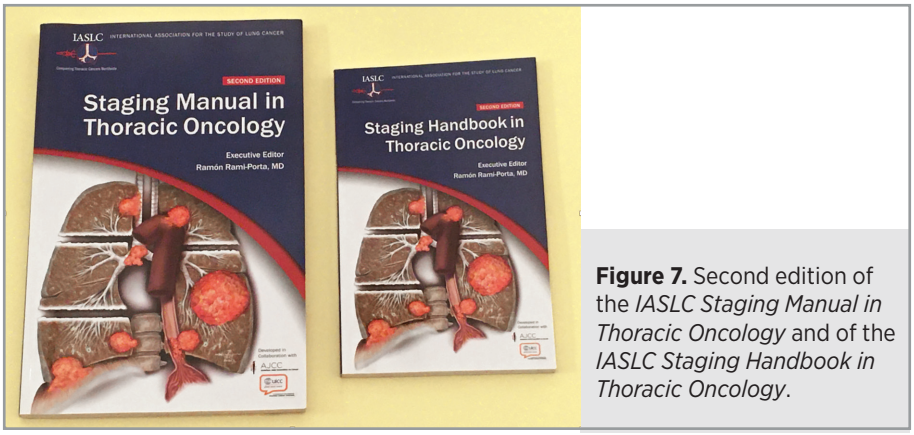


Figure 7. Second edition of the *IASLC Staging Manual in Thoracic Oncology* and of the *IASLC Staging Handbook in Thoracic Oncology*.

Figure 8. Mission accomplished. The members of the IASLC SPFC met in Vienna on December 4th, 2016. The 8th edition of the TNM classifications for lung cancer, malignant pleural mesothelioma, thymic epithelial tumors, and esophageal and esophago-gastric junction cancers were published and ready for enactment on January 1st, 2017, except in the USA, where they were enacted a year later. The third phase of the IASLC Staging Project started under the leadership of Hisao Asamura (first row center, in white pullover), who replaced Ramón Rami-Porta (standing on his right) as Chair of the IASLC SPFC.

THE PRESENT AND BEYOND

At the time of this writing, the IASLC Staging Project and the activities of the SPFC have spanned for more than 25 years since its conception in 1996, and is near completion of the third phase of the IASLC Staging Project (2016-2024). AstraZeneca provided an unrestricted grant for the development of this phase of the IASLC Staging Project.

Chaired by Hisao Asamura, a thoracic surgeon from Keio University in Tokyo, Japan, the SPFC continues to be structured in four domains, but it has grown in complexity to accommodate its ever expanding members and projects. The SPFC Steering Committee was created to coordinate all the activities of the SPFC and meets once a month via teleconference (Figure 9).

Data on new patients with lung cancer and epithelial thymic tumors were collected until December 31, 2021, when the new database containing EDC and batch data was closed for analyses. Data on malignant pleural mesothelioma submitted to the EDC system was collected until May 31, 2022. The new database is comparable in size to those used for the 7th and the 8th editions of the TNM classifications of thoracic malignancies. Additionally, it contains biomarkers, which is a new feature (Table 1). To handle the complexities of this initiative, the Molecular Markers Subcommittee, co-chaired by David Carbone and Fred R. Hirsch, was added to the other Lung Cancer Domain

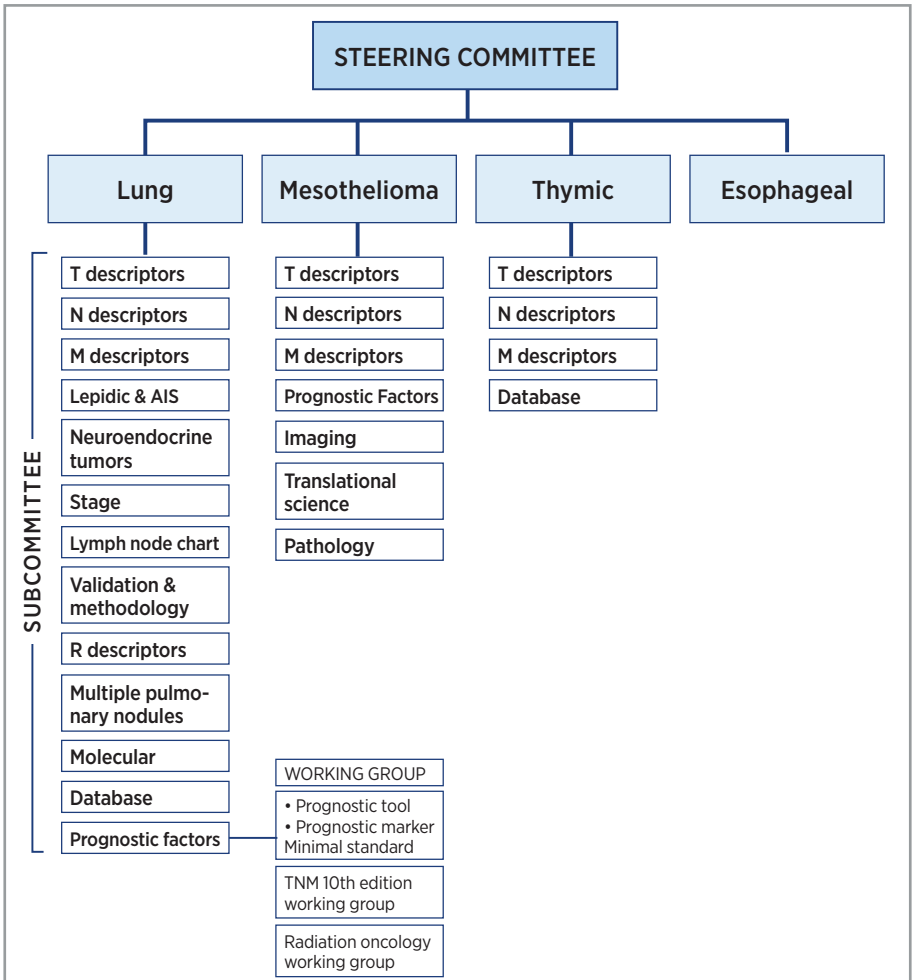


Figure 9. Structure of the IASLC Staging and Prognostic Factors Committee for the third phase of the IASLC Staging Project; 2016 to 2024.

Subcommittees.[38] The members of the different SPFC Domains, Subcommittees and CRAB statisticians analyzed the database according to the objectives of each Subcommittee, following a predefined methodology.[39]

In the past few months, the original articles supporting the innovations that the IASLC SPFC suggested for the 9th edition of the TNM classification of thoracic malignancies were published. The definitive databases used for the revision of the TNM classification of lung cancer, pleural mesothelioma, and thymic epithelial tumors were described in detail for future reference.[40-42] The core articles providing the background, the methods used and the results of the analyses of the T, the N and the M components of the classification as well as the stage groups of the three thoracic malignancies included in the IASLC Staging Project are already available in print or online.[43-52] Additionally, an article summarizing the results of the analyses

of patients whose lung cancers had tumor cells spread through air spaces (STAS), in support of the inclusion of STAS as a histologic descriptor, was also published.[53] The residual tumor classification for lung cancer was revised to make it more descriptive and clinically relevant.[54] An article on the potential use of molecular data of nearly 10,000 registered patients in the 9th edition database, in combination with anatomic tumor extent, highlighted the objectives and the possibilities of the IASLC database to achieve this objective.[55] Although the lymph node map of thymic epithelial tumors remains unchanged, a new article provides clarifications and updated figures to facilitate its clinical use.[56] Finally, the modeling of prognostic factors in pleural mesothelioma was also updated.[57] Table 2 summarizes the innovations introduced in the 9th edition of the TNM classification of thoracic malignancies.

Table 2. Innovations in the 9th edition of the TNM classification of thoracic malignancies.

Malignancy	T, N, M, stages	Innovations
Lung cancer	T	No changes
	N	N2a: involvement of a single N2 nodal station N2b: involvement of multiple N2 nodal stations
	M	M1c1: multiple extrathoracic metastases in a single organ system M1c2: multiple extrathoracic metastases in multiple organ systems
	Stages	T1N1: moved from stage IIB to stage IIA T1N2a: moved from stage IIIA to stage IIB T2N2b: moved from stage IIIA to stage IIIB T3N2a: moved from stage IIIB to stage IIIA
	STAS	New histopathologic descriptor
Pleural mesothelioma	T	The sum of maximum pleural thickness measured at three fixed levels and fissure thickness are incorporated as new clinical T1, T2 and T3 descriptors
	N	No changes
	M	No changes
	Stages	Stage I: T1N0M0 Stage II: T1N1M0 and T2N0M0 Stage IIIA: T1N2M0, T2N1-2M0, T3N0-2M0 Stage IIIB: T4N0-2M0 Stage IV: any T, any N, M1
Epithelial thymic tumors	T	T1a: ≤5cm in largest dimension T1b: >5cm in largest dimension Mediastinal pleura: deleted from the T classification and added as additional histologic descriptor Lung and phrenic nerve involvement is reclassified as T2
	N	No changes
	M	No changes
	Stages	No changes
Esophagus and esophagogastric junction		No revisions were made to the 8th edition TNM

T: primary tumor; N: nodal involvement; M: distant metastases; STAS: spread through air spaces

The TNM classification and staging explains about 60% of prognosis of lung cancer,[24] but there are many other prognostic factors different from the anatomic tumor extent. These prognostic factors include aspects related to the tumor itself, such as the TNM classification and molecular changes to the patient, and to the environment. The UICC categorizes these factors as essential, additional, and new and promising. Prognostic factor grids for resectable and advanced or metastatic non-small cell lung cancer and for small cell lung cancer, were added to the lung cancer chapter of the 8th edition of the *UICC TNM Classification of Malignant Tumours*.

The database compiled by the IASLC to inform the 9th edition of the TNM classification of lung cancer contains most of these prognostic factors, and for the first time, it collects biomarkers, encompassing genetic biomarkers, copy number alterations, and protein alterations. The objective is to combine anatomic extent with all the other prognostic factors to build prognostic groups, thereby enhancing prognosis beyond what is provided by anatomic tumor

extent alone. This comprehensive approach aids in treatment planning. This is a complex process that will require adherence to a sound methodology.[58] How this will be incorporated into the TNM classification is still a matter of debate because the UICC and the AJCC hold different views on this issue. While the UICC stages are exclusively defined by parameters of anatomic tumor extent, the newly introduced prognostic stage groupings of the 8th edition of the AJCC include both anatomic and non-anatomic prognostic factors. Probably, how we call them will not really matter as long as we understand the meaning of the terms that we use to communicate.[59]

The Lung Cancer Domain is also working on the definition of the Essential TNM for this tumor. The Essential TNM is meant to simplify the staging process in low- and middle-income countries. It starts with the exploration of distant metastases, and if there are metastases, the tumor is classified as stage IV (distant) and no further explorations are required. If no metastases are found, the staging process continues to examine regional lymph nodes; if present, the disease is classified as stage III (either regional limited or regional extended). Finally, if there are no regional lymph nodes, the primary tumor is examined and the disease is classified as stage I (localized limited) or stage II (localized advanced), depending of the characteristic of the primary tumor.

The third edition of the *IASLC Staging Manual in Thoracic Oncology*, edited by Hisao Asamura, was distributed during the World Conference on Lung Cancer that took place in San Diego, USA, in September 2024, culminating the third phase of the IASLC Staging Project. It is also planned to have a smooth transition from the 9th to the 10th edition.

At the start of the third phase of the IASLC Staging Project, the newly created Database Subcommittee, co-chaired by Paula Ugalde and Pietro Bertoglio, began revising the data elements to simplify the included items, add the necessary new ones, and delete those that are seldom registered and used. In addition, the new 10th Edition Working Group is in charge of planning the activities of the fourth phase of the IASLC Staging Project and chaired and vice-chaired by Valerie W. Rusch and Raymond U. Osarogiagbon, respectively, well before the end of the third phase in 2024.

CONCLUSION

In these past 25 years, the IASLC Staging Project not only achieved all the objectives that had been outlined during the London Workshop of 1996—mainly centered in lung cancer—but widened them to include malignant pleural mesothelioma and epithelial thymic tumors into the project, and cooperated in the dissemination of the TNM classification of esophageal and esophago-gastric junction cancers. The proposed revisions of the TNM classifications of these thoracic malignancies were based on robust evidence, and the UICC and the AJCC accepted them and included them in their respective staging manuals. This unprecedented evidence-based process put the IASLC at the front line of the periodic revisions of the TNM classifications of thoracic malignancies, and consolidated its position as the principal provider of evidence to the UICC and the AJCC.

The widening of the scope of the SPFC to include other prognostic factors opened new horizons for the IASLC Staging Project and the activities of the SPFC. The era of personalized medicine requires prognostic refinement. The combination of anatomic tumor extent and other factors will certainly improve prognosis for the individual patient. The challenge of this objective is big and possible to attain with the collaboration of individuals and institutions around the world that share their data with the IASLC, enabling the achievement of the objectives of the IASLC Staging Project, the activities of which have spanned for more than 25 of the 50 years of the IASLC history.

References

1. Goldstraw, P. The history of TNM staging in lung cancer. In: Rami-Porta R, ed; *IASLC Staging Manual in Thoracic Oncology*, 2nd ed; Editorial Rx Press: North Fort Myers, United States of America, 2016; pp. 67-78.
2. Mountain CF. A new international staging system for lung cancer. *Chest*. 1986; 89 (4 Suppl):225S-233S.
3. Goldstraw P. Report on the International workshop on intrathoracic staging, London, October 1996. *Lung Cancer*. 1997;18:107-111.

4. Naruke T, Suemasu K, Ishikawa S. Lymph node mapping and curability at various levels of metastasis in resected lung cancer. *J Thorac Cardiovasc Surg*. 1978; 76:832-839.
5. Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. *Chest*. 1997; 111:1718-1723.
6. Goldstraw P, Crowley JJ. The International Association for the Study of Lung Cancer International Staging Project on Lung Cancer. *J Thorac Oncol*. 2006;1:281-286.
7. Cahan WG, Watson WL, Pool JL. Radical pneumonectomy. *J Thorac Surg*. 1951; 22:449-473.
8. Rami-Porta R, Wittekind C, Goldstraw P, International Association for the Study of Lung Cancer (IASLC) Staging Committee. Complete resection in lung cancer surgery: proposed definition. *Lung Cancer*. 2005;49: 25-33.
9. Wittekind Ch, Comptom CC, Brierley J, Sobin LH, eds. *UICC TNM Supplement. A Commentary on Uniform Use*, 4th ed.; Wiley-Blackwell: Oxford, United Kingdom, 2012.
10. Gagliasso M, Migliaretti G, Ardissone F. Assessing the prognostic impact of the International Association for the Study of Lung Cancer proposed definitions of complete, uncertain, and incomplete resection in non-small cell lung cancer surgery. *Lung Cancer*. 2017;111:124-130.
11. Edwards JG, Chansky K, Van Schil P, et al. The IASLC Lung Cancer Staging Project: analysis of resection margin status and proposals for residual tumor descriptors for non-small cell lung cancer. *J Thorac Oncol*. 2020;15:344-359.
12. Osarogiagbon RU, Faris NR, Stevens W, et al. Beyond margin status: population-based validation of the proposed International Association for the Study of Lung Cancer residual tumor classification recategorization. *J Thorac Oncol*. 2020;15:371-382.
13. Yun JK, Lee GD, Choi S, et al. A validation study of the recommended change in residual tumor descriptors proposed by the International Association for the Study of Lung Cancer for patients with pN2 NSCLC. *J Thorac Oncol*. 2021;16:817-826.
14. Rami-Porta R, Wittekind C, Goldstraw P. Complete resection in lung cancer surgery: from definition to validation and beyond. *J Thorac Oncol*. 2020; 15:1815-1818.
15. Rami-Porta R. The evolving concept of complete resection in lung cancer surgery. *Cancers*. (Basel) 2021;13:2583. DOI: 10.3390/cancers13112583.
16. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol*. 2007; 2:706-714.
17. Groome PA, Bolejack V, Crowley J J, et al. The IASLC Lung Cancer Staging Project: validation of the proposals for revision of the T, N, and M descriptors and consequent stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol*. 2007; 2:694-705.
18. Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P. The IASLC Lung Cancer Staging Project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2009; 4:568-577.
19. Goldstraw P ed. *IASLC Staging Manual in Thoracic Oncology*, 1st ed. Editorial Rx Press: North Fort Myers, United States of America, 2009.
20. Rusch VW, Giroux D, Kennedy K, et al. Initial analysis of the International Association for the Study of Lung Cancer mesothelioma database. *J Thorac Oncol*. 2012;7:1631-1639.
21. Pass HI, Giroux D, Kennedy C, et al. Supplementary prognostic variable for pleural mesothelioma. A report from the IASLC Staging Committee. *J Thorac Oncol*. 2014;9:856-864.
22. Rice D, Rusch V, Pass H, et al. Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma. A consensus report of the International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group. *J Thorac Oncol*. 2011;6:1304-1312.
23. Detterbeck F. International Thymic Malignancies Interest Group. A way forward. *J Thorac Oncol*. 2010;5:S365-S370.
24. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11:39-51.
25. Travis WD, Asamura H, Bankier AA, et al. The IASLC Lung Cancer Staging Project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2016; 11:1204-1223.
26. Detterbeck FC, Nicholson AG, Franklin WA, et al. The IASLC Lung Cancer Staging Project: summary of proposals for revisions of the classification of lung cancers with multiple pulmonary sites of involvement in the forthcoming eighth edition of the TNM classification. *J Thorac Oncol*. 2016; 11:639-650.
27. Pass H, Giroux D, Kennedy C, et al. The IASLC Mesothelioma Staging Project: improving staging of a rare disease through international participation. *J Thorac Oncol*. 2016;11:2082-2088.
28. Rusch VW, Chansky K, Kindler HL, et al. The IASLC Mesothelioma Staging Project: proposals for the M descriptors and for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for mesothelioma. *J Thorac Oncol*. 2016;11:2112-2119.
29. Filosso P, Ruffini E, Lausi P, Oliaro A, Detterbeck F. Historical perspectives: the evolution of the thymic epithelial tumors staging system. *Lung Cancer*. 2014;83:126-132.
30. Detterbeck FC, Asamura H, Crowley J, et al. The IASLC/ITMIG Thymic Malignancies Staging Project. Development of a stage classification for thymic malignancies. *J Thorac Onco*l. 2013;8:1467-1473.
31. Huang J, Ahmad U, Antonicelli A, et al. Development of the International Thymic Malignancy Interest Group international database: an unprecedented resource for the study of a rare group of tumors. *J Thorac Oncol*. 2014;9:1573-1578.
32. Bhora FY, Chen DJ, Detterbeck FC, et al. The ITMIG/IASLC Thymic Epithelial Tumors Staging Project: a proposed lymph node map for the thymic epithelial tumors in the forthcoming 8th edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2014;9:S88-S96.
33. Detterbeck FC, Stratton K, Giroux D, et al. The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposal for an evidence-based stage classification system for the forthcoming (8th) edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2014;9:S65-S72.
34. Detterbeck FC, Moran C, Huang J, et al. Which way up? Policies and procedures for surgeons and pathologists regarding resection specimens of thymic malignancy. *J Thorac Oncol*. 2011;6: S1730-S1738.
35. Carter BW, Tomiyama N, Bhora FY, et al. A modern definition of mediastinal compartments. *J Thorac Oncol*. 2014;9:S97-S101.

36. Benveniste MF, Korst RJ, Rajan A, Detterbeck FC, Maron EM. A practical guide from the International Thymic Malignancy Interest Group (ITMIG) regarding the radiographic assessment of treatment response of thymic epithelial tumors using modified RECIST criteria. *J Thorac Oncol*. 2014;9:S119-S124.
37. Rice TW, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P. Cancer of the esophagus and esophagogastric junction: an eighth edition staging primer. *J Thorac Oncol.* 2017;12:36-42.
38. Osarogiagbon RU, Rami-Porta R, Tsao MS et al. The International Association for the Study of Lung Cancer Molecular Database Project: objectives, challenges, and opportunities. *J Thorac Oncol.* 2021;16:897-901.
39. Detterbeck FC, Nishimura KK, Cilento VJ, et al. The IASLC Lung Cancer Staging Project: methods and guiding principles for the development of the 9th edition TNM classification. *J Thorac Oncol.* 2022;17:806-815.
40. Asamura H, Nishimura KK, Giroux DJ, et al. IASLC Lung Cancer Staging Project: the new database to inform revisions in the ninth edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2023;18:564-575.
41. Wolf AS, Eisele M, Giroux DJ, et al. The International Association for the Study of Lung Cancer Pleural Mesothelioma Staging Project: expanded database to inform revisions in the ninth edition of the TNM classification of pleural mesothelioma. *J Thorac Oncol*. 2024; https://doi.org/10.1016/j.jtho.2024.01.018
42. Rimner A, Ruffini E, Cilento V, et al. The International Association for the Study of Lung Cancer Thymic Epithelial Tumors Staging Project: an overview of the central database informing revision of the forthcoming (ninth) edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2023;18:1386-1398.
43. Van Schil PE, Asamura H, Nishimura KK, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals for the revisions of the T-descriptors in the forthcoming ninth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2024;19:749-765.
44. Huang J, Osarogiagbon RU, Giroux DJ, et al. The International Association for the Study of Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming ninth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2024; 19:766-785.
45. Fong KM, Rosenthal A, Giroux DJ, et al. The International Association for the Study of Lung Cancer Staging Project for Lung Cancer: proposals for the revision of the M descriptors in the forthcoming ninth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2024;19:786-802.
46. Rami-Porta R, Nishimura KK, Giroux DJ, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals for revision of the TNM stage groups in the forthcoming (ninth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2024; https://doi.org/10.1016/j.jtho.2024.02.011
47. Okumura M, Marino M, Cilento V, et al. The International Association for the Study of Lung Cancer Thymic Epithelial Tumor Staging Project: proposals for the T component for the forthcoming (ninth) edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2023;12:1638-1654.
48. Fang W, Girard N, Cilento V, et al. The International Association for the Study of Lung Cancer Thymic Epithelial Tumors Staging Project: proposals for the N and the M components for the forthcoming (ninth) edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2024;19:52-70.
49. Ruffini E, Huang J, Cilento V, et al. The International Association for the Study of Lung Cancer Thymic Epithelial Tumors Staging Project: proposals for a stage classification for the forthcoming (ninth) edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2023;18:1655-1671.
50. Gill RR, Nowak AK, Giroux DJ, et al. The International Association for the Study of Lung Cancer Mesothelioma Staging Project: proposals for revisions of the "T" descriptors in the forthcoming ninth edition of the TNM classification for pleural mesothelioma. *J Thorac Oncol*. 2024; https://doi.org/10.1016/j.tho.2024.03.007
51. Bille A, Ripley RT, Giroux DJ, et al. The International Association for the Study of Lung Cancer Mesothelioma Staging Project: proposals for the "N" descriptors in the forthcoming ninth edition of the TNM classification for pleural mesothelioma. *J Thorac Oncol*. 2024; https://doi.org/10.1016/j.jtho.2024.05.003
52. Nowak AK, Giroux DJ, Eisele M, et al. The International Association for the Study of Lung Cancer Pleural Mesothelioma Staging Project: proposal for revision of the TNM stage groupings in the forthcoming (ninth) edition of the TNM classification for pleural mesothelioma. *J Thorac Oncol*. 2024; https://doi.org/10.1016/j.jtho.2024.05.002
53. Travis WD, Eisele M, Nishimura KK, et al. The International Association for the Study of Lung Cancer (IASLC) Staging Project for Lung Cancer: recommendations to introduce spread through air spaces as a histologic descriptor in the ninth edition of the TNM classification of lung cancer. Analysis of 4061 pathologic stage I NSCLC. *J Thorac Oncol*. 2024; https://doi.org/10.1016/j.jtho.2024.03.015
54. Detterbeck FC, Ostrowski M, Hoffmann H, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals for revision of the classification of residual tumor after resection for the forthcoming (ninth) edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2024; https://doi.org/10.1016/j.jtho.2024.03.021
55. Osarogiagbon RU, Rami-Porta R, Tsao MS, et al. The International Association for the Study of Lung Cancer Molecular Database Project: objectives, challenges, and opportunities. *J Thorac Oncol*. 2021;16:897-901.
56. Marom EM, Fang W, Ruffini E, et al. The International Association for the Study of Lung Cancer Thymic Epithelial Tumor Staging Project: a re-assessment of the international Thymic Malignancy Interest Group/International Association for the Study of Lung Cancer lymph node map for thymic epithelial tumors for the forthcoming ninth edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2023;18:1672-1688.
57. Wolf AS, Rosenthal A, Giroux DJ, et al. The International Assocaition for the Study of Lung Cancer Pleural Mesothelioma Staging Project: updated modeling of prognostic factors in pleural mesothelioma. *J Thorac Oncol*. 2023;18:1689-1702.
58. Detterbeck F. Developing a prognostic prediction model for lung cancer. In: Rami-Porta R, ed; *IASLC Staging Manual in Thoracic Oncology*, 2nd ed; Editorial Rx Press: North Fort Myers, United States of America, 2016; pp: 237-258.
59. Rami-Porta R, Asamura H, Brierley J, Goldstraw P. Staging, tumor profile, and prognostic groups in lung cancer or the new Tower of Babel. *J Thorac Oncol*. 2016; 8:1201-1203.

10

LUNG CANCER PATIENT ADVOCACY AT THE IASLC

Upal Basu Roy,[1] **Jesme Fox,**[2] **Kristin Ito,**[3] **Lillian Leigh,** [4]**Kim Norris,**[5] **and Janet Freeman-Daily,**[6] **team lead** | [1]LUNGevity Foundation, Bethesda, USA; [2]Roy Castle Lung Cancer Foundation, Liverpool, United Kingdom; [3]International Association for the Study of Lung Cancer, Denver, USA; [4]Thoracic Oncology Group of Australasia, Thornbury, Australia; [5]Lung Cancer Foundation of America, Los Angeles, USA; [6]The ROS1ders, Inc, Sacramento, USA

While cancer patient advocacy first arose in the 1970s, when individual breast cancer patients shared their stories, lung cancer patient advocacy did not begin to develop until the late 1990s. Patient advocates became involved with the IASLC around 2003, when the annual National Cancer Institute (NCI) lung cancer SPORE (Specialized Programs of Research Excellence) workshop was held concurrently with the IASLC Targeted Therapies meeting. Lung cancer SPORE patient advocates who attended that meeting became aware of the IASLC and wanted to get involved.

In years since, lung cancer treatments and research have rapidly evolved because of numerous advancements, especially those in the last decade. These developments have enabled more patients to survive longer and with better quality of life, often inspiring them and their caregivers to become active lung cancer advocates. There are now dozens of individual lung cancer patient advocates and advocacy organizations around the globe, each with their own unique character, skills, and focus based on their country of residence.[1-3]

Today, lung cancer patient advocacy consists of five general areas (Figure 1): outreach and education, patient support, fundraising, policy advocacy, and research advocacy.

- **Outreach and education** involves telling patient stories, raising awareness, and informing patients, caregivers, and the public about lung cancer.
- **Patient support** involves helping patients and their caregivers navigate the healthcare system where they live.
- **Fundraising** raises money for research and advocacy efforts.
- **Policy** advocacy involves working to change legislation and regulations in order to improve outcomes.
- **Research** advocacy involves sharing the patient perspective with researchers and institutions with the goal of advancing cancer research.

This chapter focuses on the IASLC patient advocacy activities in outreach and education, fundraising, and research advocacy. The IASLC does not provide direct patient support nor engage in policy advocacy.

Figure 1. Types of lung cancer patient advocacy.

OUTREACH AND EDUCATION

IASLC Patient Advocates Committee

In 2012, in recognition of the growing influence of the lung cancer patient advocate community, IASLC created the IASLC Patient Advocates Committee (PAC) with the goal of creating unified messaging through the advocate community for Lung

Cancer Awareness Month (LCAM). The resulting LCAM Coalition created resource materials for use by all patient advocates and advocacy groups (the IASLC transferred stewardship of the LCAM Coalition to GO2 Foundation for Lung Cancer in 2021 to further build the global movement). The PAC, which involves advocates from around the globe, continues to meet on a regular basis and pursue lung cancer advocacy projects.

Jill Feldman (research advocate, co-founder of the EGFR Resisters, and 2022 Chairperson of the PAC) worked through the PAC to create a Language Guide.[4] Its purpose is to help educate and encourage the lung cancer research and clinical community to use respectful spoken and written language that is inclusive, equitable, and free of stigma. For example, the language "the treatment failed the patient" is preferable to "the patient failed treatment." The Language Guide has been overwhelmingly accepted and utilized by the lung cancer community, and beyond.

Advocate Participation in IASLC Communications

Patient advocates have been involved in several aspects of IASLC communications. Advocates sit on the *IASLC Lung Cancer News* (ILCN) Editorial Board and have been involved at various times with other committees that generate IASLC communications. In these positions they provide patient perspective on content that may be of particular interest to patients, comment on content for publication, and co-author articles that share the patient view on lung cancer research developments and clinical care. Advocates have been moderators, presenters, and panelists for IASLC podcasts and webinars, and co-authored IASLC publications such as biomarker testing guidelines. The IASLC also collaborates with advocacy organizations to communicate lung cancer science and research to the broader lung cancer community.

Patient Advocate Education

For nearly 20 years, the IASLC has welcomed patient advocates as part of the World Conference on Lung Cancer (WCLC). Nowadays, the WCLC is an annual conference focused uniquely on thoracic oncology, including lung cancer detection, treatment, and survivorship. These meetings are the largest global gathering of lung cancer researchers and doctors. To recognize and encourage individual lung cancer patient advocates who have demonstrated their interest in learning more about lung cancer, in 2013 the IASLC instituted a Patient Advocacy Award for advocates who are early in their advocacy journey. These awards, now called Patient Advocacy Education Awards, enable five advocates each year to travel to the WCLC, where they can network with international advocates, meet practicing thoracic oncology clinicians and researchers, and learn the latest information about lung cancer care and research. The IASLC also helped initiate the "Hope with Answers" project at its 2018 Targeted Therapies meeting with the Lung Cancer Foundation of America (LCFA). The project continues under management of LCFA and generates podcasts and videos of interviews with advocates, clinicians, and researchers who discuss key lung cancer topics of interest to patients (e.g., clinical trials) in patient-friendly language.[6]

Awards for Excellence in Patient Care

The IASLC makes annual awards in areas that impact patients. In 2017, the IASLC initiated its Cancer Care Team Award.[7] This award recognizes exceptional care for patients with lung cancer that goes beyond interactions with any one specialist or care center. This award acknowledges that sometimes delivery of patient care is at its best when multidisciplinary team members offer the patient seamless and informed communication, as well as an individualized treatment plan based on not just the patient's needs but the patient's wishes.

COLLABORATIVE FUNDRAISING FOR RESEARCH

The IASLC has partnered with various lung cancer advocacy organizations to raise awareness and funds for research. Below are two examples of long-term collaborations.

The International Lung Cancer Foundation (ILCF) Young Investigator Research Grant

In November of 2009, the IASLC partnered with Lung Cancer Foundation of America (LCFA) to create the ILCF Young Investigator Grant, which focuses on (but not limited to) junior investigators in the international lung cancer research community. Since its inception, the program has awarded 19 grants for a total of over $9 million in lung cancer research funding. Many of the grant recipients have become leaders in the research community and have leveraged their grant to obtain additional funding from other sources, including two National Institutes of Health (NIH) MERIT awards. The success of this program spawned additional grant partnerships with other advocacy organizations.

The Lung Ambition Alliance

The Lung Ambition Alliance (LAA) launched in 2019 with four founding partners: IASLC, Global Lung Cancer Coalition, AstraZeneca, and Guardant Health.[8] The goal of this alliance is to accelerate advances in lung cancer survival and improve patient outcomes. Blending the partners' varied expertise and resources has generated several initiatives[9] spread across more than 50 countries, with focus on increasing screening and early diagnosis, advancing innovative therapies, and improving quality of care. A flagship program is Initiatives in Lung Cancer Care (ILC2) program, which supports patient and career organizations to deliver transformative projects focused on addressing gaps in lung cancer service delivery.[10] Over the initial three funding rounds, a total of 39 ILC2 grants have been awarded.

RESEARCH ADVOCACY

Research advocates are volunteers with a personal connection to lung cancer who are passionate about helping research translate into meaningful outcomes for patients and their families. Research advocacy infuses the patient perspective into research to make scientific and medical advances more patient-centered.[11] The IASLC aims to help equip research advocates with the knowledge of science and research processes, which they can combine with their own and other patients' experiences to increase the benefit of lung cancer research for patients. Skilled research advocates can provide a patient perspective in activities, such as grant reviews, research protocol design, and regulatory activities.

Advocate Attendance at WCLC

In recent years, the IASLC has provided the growing number of patients, advocates, and caregivers complimentary Society membership and conference registration. The advent of the COVID-19 pandemic resulted in IASLC conferences becoming virtual, which enabled more advocates to attend conference sessions and keep current on the latest lung cancer science. The IASLC plans to keep the hybrid aspect of future conferences to continue providing broader advocate access. Since the 10th WCLC in 2003, IASLC has hosted a joint session with the GLCC, an alliance of 40 not-for-profit and charitable organizations from 30 countries, each focused on advocating for better outcomes for lung cancer patients.[12] This joint session has provided an opportunity for lung cancer advocates to learn from global key opinion leaders and has also provided a platform for the lung cancer clinicians to learn what is important to patients. To encourage collaborations, the GLCC Annual Members Meeting coincides with the WCLC each year.

Advocacy Presentations at IASLC Conferences

Possibly the first patient advocate presentation at an IASLC meeting occurred in 2003 in Vilnius, Lithuania, when Jesme Fox presented on the concept of lung cancer patient advocacy (which was just getting started), the importance of informed consent, and the need for policy advocacy in lung cancer. Every WCLC now includes an advocate track as a formal part of the conference program. Each year, two international patient advocates are selected to chair the Advocacy Track Committee and are responsible for creating the agenda for the session, reviewing abstracts (including inviting

other reviewers), and spearheading the abstract peer review process. Experienced research advocates also review abstracts for scientific tracks. This provides advocates the experience of participating in a scientific conference at the planning level, and it also encourages advocates from all over the world to submit abstracts to each annual WCLC. An increasing number of patient advocates each year are also invited speakers and involved in planning and reviewing abstracts for other IASLC conferences.

Supportive Training for Advocates on Research and Science (STARS) Program

The latest addition to the research advocacy offerings from the IASLC is the STARS Program (Figure 2).[13] Initiated in 2019, STARS offers patient advocates the training and mentoring needed to evolve into Patient Research Advocates (PRAs), with the goal of increasing the number of international PRAs equipped with the knowledge, resources, and connections to accurately communicate science and research to a variety of stakeholders within the lung cancer community, and to bring their patient and caregiver perspective to lung cancer research and policy. The curriculum considers the global nature of advocacy, and involves interactive presentations with lung cancer advocates, clinicians, and researchers about the research process, standard of care and latest scientific breakthroughs.

PRAs are selected through a competitive process and receive guidance from experienced research advocate mentors throughout the program. PRAs start their online training several months before the WCLC, attend the WCLC sessions, and afterwards present to the STARS community a research advocacy project on a topic of their choice, which varies with research advocacy opportunities in the PRA's home country. As of 2022, the IASLC STARS Program has supported 53 participants (including 10 mentors) from eleven countries: Australia, Canada, Germany, Greece, India, Ireland, Nigeria, Netherlands, New Zealand, United Kingdom, and United States. PRAs who complete STARS training and demonstrate involvement in research advocacy may apply to have their travel to future WCLCs covered by the program.

Figure 2. The PRAs, Mentors, and staff of the inaugural IASLC STARS program at WCLC 2019 in Barcelona, Spain.

References

1. LungCAN member organizations. The Lung Cancer Action Network (LungCAN). Accessed October 14, 2022. https://lungcan.org/our-members/
2. Global Lung Cancer Coalition membership. Global Lung Cancer Coalition. Accessed October 14, 2022. https://www.lungcancercoalition.org/about-glcc/membership/
3. Lung Cancer Europe members. Lung Cancer Europe. Accessed October 14, 2022. https://www.lungcancereurope.eu/our-members/
4. IASLC Language Guide. International Association for the Study of Lung Cancer. Accessed October 14, 2022. https://www.iaslc.org/IASLCLanguageGuide
5. Advocacy Awards. International Association for the Study of Lung Cancer. Accessed October 14, 2022. https://www.iaslc.org/patient-advocacy/advocacy-awards
6. Hope With Answers: Living With Lung Cancer Podcast. Lung Cancer

Foundation of America. Accessed October 14, 2022. https://lcfamerica.org/lung-cancer-info/hope-with-answers-podcast/
7. IASLC Cancer Care Team Award. International Association for the Study of Lung Cancer. Accessed October 14, 2022. https://www.iaslc.org/CCTA-nominations
8. The Lung Ambition Alliance. Accessed October 14, 2022. https://www.lungambitionalliance.com/
9. Lung Ambition Alliance Initiatives. The Lung Ambition Alliance. Accessed October 14, 2022. https://www.lungambitionalliance.com/our-initiatives.html
10. Initiatives in Lung Cancer Care (ILC2). The Lung Ambition Alliance. Accessed October 14, 2022. https://www.lungambitionalliance.com/our-initiatives/initiatives-in-lung-cancer-care.html
11. Research Advocacy Network, Inc. Roadmap to Research Advocacy in Translational Science. Accessed October 14, 2022. https://researchadvocacy.org/sites/default/files/docs/
12. Global Lung Cancer Coalition. Accessed October 14, 2022. https://www.lungcancercoalition.org/about-glcc/membership/
13. IASLC Supportive Training for Advocates on Research & Science (STARS) program. International Association for the Study of Lung Cancer. Accessed October 14, 2022. https://www.iaslc.org/patient-advocacy/stars

PART II

ADVANCES IN THORACIC ONCOLOGY TREATMENT AND RESEARCH

TREATMENT RESEARCH

11

LUNG CANCER CAUSATION AND PREVENTION

Jonathan M. Samet,[1] **K. Michael Cummings,**[2] **Eva Szabo,**[3] **Graham W. Warren,**[4] **York E. Miller,**[5] **and Steven M. Dubinett**[6] | [1]Colorado School of Public Health, Aurora, USA; [2]Medical University of South Carolina, Charleston, USA; [3]National Cancer Institute, National Institutes of Health, Bethesda, USA; [4]Medical University of South Carolina, Charleston, USA; [5]Denver Veterans Affairs Medical Center, and University of Colorado Denver, Denver, USA; [6]David Geffen School of Medicine at UCLA, and Greater Los Angeles VA Health System, Los Angeles, USA.

The study of lung cancer causation and prevention has been a major focus of the IASLC. Multidisciplinary collaborations worldwide have facilitated the IASLC mission of discovery and prevention implementation. This chapter covers many of the IASLC advances in causation, lung cancer prevention, tobacco control, and smoking cessation.

CAUSAL JUDGMENTS AND TOBACCO CONTROL

The conclusions that active and passive smoking cause lung cancer have had powerful consequences for tobacco control, motivating actions to reduce an avoidable cause of a highly lethal malignancy. Quoting the 2004 Surgeon General's report on smoking and health, "The statement that an exposure 'causes' a disease in humans represents a serious claim, but one that carries with it the possibility of prevention."[1] And, "A causal conclusion conveys the inference that changing a given factor will actually reduce a population's burden of disease, either by reducing the overall number of cases or by making the disease occur later than it would have."[2] This section addresses how causal conclusions have been reached around smoking and lung cancer, providing a historical perspective.

The rising numbers of clinical cases of lung cancer and the rate of death from this malignancy across the first half of the 20th century motivated epidemiological studies of the causes of the steep increase in lung cancer, particularly among men.[3] By 1950, the results of the first epidemiological studies, all based in the case-control design, were reported, and all showed a strong association of smoking with lung cancer.[4-6] At the time, this design, which involves comparison of smoking by people with lung cancer with smoking by comparable controls without lung cancer, was questioned because of its retrospective nature and novelty. By 1954, the findings of initial prospective cohort studies, undertaken because of the perception of greater validity, were published with similar findings.[7-9] In this approach, study participants were enrolled with a collection of information on their smoking on entry into the cohort; they were then followed for lung cancer incidence and/or mortality and the lung cancer rate in smokers compared to that in never-smokers. In the 1950s, complementary work was initiated to understand how tobacco smoke could cause lung cancer, including animal experiments and characterization of the components of tobacco smoke. Over time, these studies documented numerous known carcinogens in tobacco smoke, including tobacco-specific nitrosamines.

The epidemiological studies on smoking and lung cancer were part of a paradigmatic shift in the discipline that began in the early decades of the 20th century. By then, epidemiology was an established discipline, but its focus had been on infectious diseases, seeking links between infectious agents and diseases and testing control strategies. As microscopy and laboratory methods advanced,

Robert Koch and others sought to determine which pathogens caused particular diseases, such as the Vibrio cholerae organism and cholera. For judging whether a causal association existed, guidelines were promulgated—the Henle-Koch postulates—which had an experimental basis (Box 1).[10]

The emerging evidence on smoking and lung cancer did not fit within the infectious disease paradigm and the Henle-Koch postulates. Much of the key evidence was obtained with epidemiological designs that were considered novel at the time, and in the studies generating the evidence, the critical exposure—tobacco smoking—was not subject to the control brought by randomization. In fact, the first randomized trials were implemented in the late 1940s, contemporaneously with the observational studies. One oft-repeated criticism posited that smokers were different from nonsmokers in ways that increased lung cancer risk, i.e., the association of smoking with lung cancer was subject to confounding by other factors. The noted statistician, Sir Ronald Fisher, codified this suggestion in his "constitutional hypothesis."[11] The tension around interpreting the evidence on smoking and lung cancer and other diseases was reflected in publications across the 1950s.

The role of the tobacco industry and its surrogates in this discussion needs to be acknowledged. The industry's campaign to discredit scientific research on smoking and health can be dated formally to 1953 and a meeting of the industry's lawyers at the Plaza Hotel in New York City.[12] The surrogates included Fisher and another prominent statistician from the Mayo Clinic, Joseph Berkson. The industry's overall strategy was intended to create doubt via a multi-pronged strategy that has since been well described through the industry's internal documents and that led to the major tobacco companies being found guilty of fraudulent activity and racketeering under the Racketeer Influenced and Corrupt Organizations (RICO) Act.

Box 1. Henle-Koch Postulates

1. The microorganism must be found in abundance in all organisms suffering from the disease, but should not be found in healthy organisms.
2. The microorganism must be isolated from a diseased organism and grown in pure culture.
3. The cultured microorganism should cause disease when introduced into a healthy organism.
4. The microorganism must be re-isolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent.

While across the 1950s the scientific evidence became increasingly convincing as to causation of lung cancer by smoking, the 1964 report on smoking and health by an advisory committee to the Surgeon General provided a firm conclusion on causation based on a transparent process.[13] In 1962, the UK Royal College of Physicians had also concluded that smoking caused lung cancer, but through a less well-defined process.[14] The 1964 report established a framework for making determinations on the strength of evidence for causation of adverse consequences of tobacco products that remains in use today with little modification. With more than 50 years of application of the framework, its utility and validity have been established and the general approach has reached into other sectors where causal determinations are a basis for action. The report was developed by an Advisory Committee to Surgeon General Terry that was selected with objectivity in mind. The following quotes describe the approach:

- "A plan was adopted at the first meeting…"
- "…a major general requirement was that of making the information available…"
- "…(The committee—added) made decisions or judgments at three levels…": 1) validity of a publication or report; 2) validity of interpretations and conclusions of authors; and 3) conclusions of the committee.

Additionally, the committee adopted a set of guidelines for evaluating the evidence holistically for causal inference, often referred to as the Surgeon General's criteria (Table 1). These criteria were developed by committee ith the help of an epidemiology consultant, Dr. RA Stallones.[15] Similar guidelines

were published a year later by Sir Austin Bradford Hill (Table 1).[16] Both sets of guidelines supported evidence integration, bringing together observational evidence and considerations related to biological plausibility. These were not checklists but guidance for expert judgement. There was only one absolute—temporality; putative cause necessarily precedes the effect. The 2004 report of the Surgeon General returned to this methodology and the guidelines, adding a standardized classification for the strength of evidence for causation.[1]

Table 1. Guidelines for Causal Inference: Surgeon General Report's Criteria Versus Hill's Criteria

Surgeon General Report's Criteria	Hill's Criteria
Consistency of association	Strength
Strength of association	Consistency
Specificity of association	Specificity
Temporal relationship of association	Temporality
Coherence of association	Biological gradient
	Coherence
	Experiment

Sources : Smoking and health: Report of the Advisory Committee to the Surgeon General, 1964[13] and Hill AB, 1965.[16]

The 1964 report concluded that smoking caused lung cancer in men; the evidence on women was limited at the time, but the causal conclusion was subsequently expanded to women. The 1986 report of Surgeon General Everett Koop stated, as its first conclusion, "Involuntary smoking is a cause of disease, including lung cancer, in healthy nonsmokers."[17] Together, the conclusions on active and passive smoking and lung cancer have had broad impact, reaching a global level. Grounded in the framework advanced in the 1964 Surgeon General's report, these conclusions have held in the face of the tobacco industry's efforts to diminish them and have been the anchor for lung cancer control for more than half a century.

The ever-strengthening evidence on smoking and lung cancer led to two key methodological advances related to causation: addressing the quantification of the increase in lung cancer risk associated with smoking and estimating the burden of lung cancer caused by smoking. The motivation for these two advances is evident. If an agent causes a disease, then the increase in risk for individuals exposed to the cause is of interest, as is the amount of disease caused by the agent in a population. The odds ratio was described by Cornfield in a 1951 paper for quantifying association in a 2 by 2 table, as generated by a case-control study; and the attributable risk statistic was described by Levin in a 1953 paper.[18,19] Both advances were motivated by the observational evidence on smoking and lung cancer. Data from the case-control studies published in 1950 did not describe the strength of association but did use statistical significance testing. Using some of the early case-control study data, Levin showed that the majority of lung cancer cases was attributable to smoking. His notion of the attributable risk makes a comparison to exposure in the world as it is, for example, the actual pattern of smoking to a counterfactual world absent the exposure, a world without smoking, or to some other comparison exposure level. Levin's approach underlies disease burden estimation generally, and the attributable risk estimates made in the Surgeon General's reports, such as that 480,000 deaths per year were attributable to smoking in 2014.[20]

This same general approach—integration of epidemiological evidence with other lines of evidence—was generalized to other potential respiratory carcinogens, leading to causal conclusions for other environmental and occupational agents. As a historical note, radon was causally linked to lung cancer even before these methods led to the causal finding of the 1964 Surgeon General's report. The conclusion on radon was based on observations of underground miner populations exposed to high levels of radon and to understandings about the

dosimetry of radon and its progeny in the lung.[21] Indoor radon is now considered a ubiquitous lung carcinogen for the general population. The World Health Organization's International Agency for Research on Cancer (IARC) evaluates potential carcinogens using a transparent protocol that examines the epidemiological, toxicological, and mechanistic evidence, and it integrates the evidence streams to determine the strength of evidence. Over time, IARC has expanded the list of Group 1 (known carcinogens) to include many well-known lung carcinogens: asbestos, nickel compounds and other agents, along with specific occupations and industries.[22]

In 2013, the IARC classified outdoor air pollution generally and airborne particulate matter specifically as Group 1 carcinogens based on epidemiological evidence, the presence of carcinogens in the air pollution mixture, the mutagenic activity of particulate matter collected in outdoor air, and other mechanistic considerations.[23] One potential mechanism for air pollution to cause lung cancer was proposed by Hill and colleagues based on the observation that within epidemiological cohorts, EGFR-driven adenocarcinomas were associated with estimated exposures to fine particulate matter.[24] In a preclinical mouse model with induced expression EGFR, exposure to fine particulate matter increased incidence of early-lung neoplasia. The authors concluded that fine particulate matter may have a tumor promoting role in lung carcinogenesis.

Outdoor air pollution is of broad public health concern because of its ubiquity and growing severity in some low- and middle-income countries. For 2021, 18.6% of lung cancer deaths were attributable to ambient air pollution.[25] While the IARC classification was for particulate matter generally, research based in the Multi-Ethnic Cohort in California found mixed evidence for increased lung cancer risk associated with the ultrafine particulate matter (less than 0.1 microns in aerodynamic diameter) generated around airports.[26] The strong association was for squamous cell carcinoma. Another publication based on this cohort documented positive associations of lung cancer risk with indicators for traffic-related pollution.[27]

The methods that were developed for characterizing the association of smoking with lung cancer continue to have impact. Prevention measures based on the resulting causal conclusions have had global benefit.

TOBACCO CAUSATION AND PREVENTION

Determinants of Tobacco Use

The primary reason people use tobacco on a persistent daily basis for years and decades is to obtain nicotine, which causes addiction.[20,28-31] While there is little doubt that nicotine dependence sustains tobacco use in most users, the response to nicotine varies widely in the population.[32] The biological, likely hereditary, affinity to nicotine most likely explains why some people who try a tobacco product do not need to use it every day or at all, while others crave nicotine and find it difficult to go more than a few hours without using tobacco and struggle to refrain from using it in some cases even after experiencing serious health problems such as cancer.[32,33]

In 2020, global sales of nicotine-containing products were estimated at $853 billion, with factory-made cigarettes dominating the market (84.2%), followed by other smoked tobacco products, including roll-your-own and pipe tobacco, cigars and cigarillos (8.9%), nicotine vaping products (2.5%), heated tobacco products (2.4%), oral tobacco products (1.7%), and medicinal nicotine products (0.3%).[34] Tobacco dependence can develop with use of all forms of nicotine containing tobacco and even with prescription nicotine-containing medications.[4] However, the way different tobacco products are designed can influence the bioavailability of nicotine and associated downstream health problems people experience.[35,36] Cigarettes and their variants, such as roll-your-own cigarettes and mass-produced cigars, pose the highest risks for lung cancer and chronic obstructive pulmonary disease because the design of these products involves the inhalation of tobacco smoke, which contains a toxic mixture of chemicals, including more than 60 carcinogens in every puff.[36]

Interventions to Reduce the Harms Caused by Tobacco Use

The global effort to reduce the harms caused by tobacco use led to the creation and adoption of the Framework Convention on Tobacco Control (FCTC), the first global health treaty negotiated under the auspices of the World Health Organization (WHO).[37] The FCTC is an attempt by the WHO to have countries adopt the same set of comprehensive regulations regarding tobacco, rather than having legislation vary from country to country. Currently, there are 182 Parties to the FCTC covering more than 90% of the world population (https://fctc.who.int/who-fctc/overview/parties). The FCTC commits countries to implement a suite of tobacco harm minimization measures intended to accomplish three goals: 1) Reduce the demand for tobacco; 2) Reduce the supply of tobacco; and 3) Reduce the harm caused by tobacco products. Demand reduction interventions have the goal of reducing consumer interest in using tobacco, while supply reduction attempts try to reduce tobacco use by limiting the supply of tobacco to the population. Harm reduction assumes that people will continue to use tobacco and thus seeks to minimize the harm caused by using tobacco products by altering their potential to cause disease and disability to both users and nonusers.[38] Table 2 gives examples of demand, supply, and harm reduction interventions.

The effectiveness of the FCTC in minimizing the harms of tobacco depends on how each national government chooses to implement the policies and programs recommended in the FCTC protocols. Evidence to date shows wide variability in implementation of FCTC protocols across countries with some governments moving aggressively to reduce tobacco use among its citizens, whereas other countries have been slow to adopt policies that will dramatically alter the trajectory of tobacco use.[39] Also, with 80% of the world's smokers now residing in low- and middle-income countries, it is debatable as to whether the relatively slow incremental approach to tobacco control utilized by high income countries over the past 50 years will substantially reduce the projected 1 billion tobacco related deaths worldwide in the 21st century.[40,41]

Research has shown that the programs and policies that have the greatest chances for minimizing the harms caused by tobacco are those that impact the greatest number of people in the population.[42] Highly efficacious interventions, such as stop-smoking clinics, that reach only a tiny fraction of the target population will not have a sizeable impact on reducing smoking prevalence. This is one of the reasons that past research has shown that the most potent interventions are those that impact the entire population repeatedly, such as product regulations, higher taxes on tobacco products, comprehensive advertising bans, pack warnings, mass media campaigns, and smoke-free policies.[42] While clinical practice guidelines for the treatment of tobacco dependence have been widely disseminated by various governments and medical organizations, their impact on tobacco use at the population level has been minimal, since the guidelines have been mostly voluntary and promoted without the kind of financial support necessary to ensure wide access to recommended treatments.[43]

Product regulations have the greatest potential to dramatically and rapidly reduce the harms caused by tobacco products, but they also have been politically difficult to implement due to the enormous lobby power of tobacco companies.[41,44] A common misconception about

Table 2. Examples of Demand, Supply, and Harm Reduction Interventions

Demand Reduction	Supply Reduction	Harm Reduction
Tobacco taxation	Product bans	Smoke-free laws
Advertising bans	Youth access laws	Product regulation
Consumer education	Licensing	Access to lower-risk products
Tobacco cessation	Trade policies	
Smoke-free laws		

tobacco use is that the most dangerous component of the product is nicotine; however, while nicotine can be addictive, it is the other toxicants in tobacco, especially burned tobacco, that are the true causes of tobacco-related diseases.[45-47] The vast majority of cigarette brands on the market in the United States today contain more than 8 milligrams (mgs) of nicotine in the tobacco, of which about 10% is absorbed when smoked, yielding an average delivery of 0.8 mgs or more of nicotine per cigarette.[48] However, cigarette manufacturers have long had the technical capability to control the nicotine content in cigarettes to minimize product-abuse liability.[49]

In 1994, Benowitz and Henningfield proposed the idea of establishing a ceiling for the amount of nicotine allowed in a cigarette to reduce nicotine dependence.[50] These authors suggested a potential maximum level of 0.5 mg of nicotine per gram of tobacco in a cigarette, which would yield 0.05 mg/cigarette available to the smoker. Research conducted since 1994 combined with evidence from cigarette company documents made public in the late 1990s, shows that establishing a very low nicotine standard for smokeable tobacco products may br able to prevent nicotine dependence in most new users while allowing nicotine dependent smokers to markedly reduce their cigarette consumption, leading to higher rates of smoking cessation.[51-53] Simulation modelling studies suggest that such a product regulation could dramatically and rapidly reduce future projected smoking related diseases and premature deaths.[54,55]

Recently, both the United States and the New Zealand governments have proposed the idea of setting a limit on the nicotine content of smokeable tobacco products while at the same time making access to lower risk non-combustible forms of nicotine a priority.[56-58] Studies suggest that access to consumer acceptable alternatives to cigarettes could also help smokers transition away from cigarettes while at the same time discouraging consumer participation in the sale of illicitly produced normal nicotine cigarettes.[59-61] However, the question remains as to whether smokers may be willing to abandon smoked tobacco products for a delivery system that is substantially different, albeit with much lower health risks (see Figure 1). Until smokers are given enough information to allow them to choose for themselves, the status quo will remain. Government policies can help move this process

Figure 1. Nicotine product continuum of risk. Reprinted with permission from Neal L. Benowitz, MD, Professor of Medicine Emeritus, University of California San Francisco.

along by allowing for differential regulation of product marketing and taxation rates linked to product risk.[41,44] The natural experiment in Sweden, where the use of oral tobacco (i.e., snus) displaced cigarettes as the main source of nicotine delivery resulting in less cancer, provides evidence that smoking harm reduction works, although it is unclear if this result in Sweden can be replicated elsewhere.[62,63] However, the rapid growth of nicotine vaping products (both e-cigarettes and heat-tobacco products) in selected countries over the past decade suggests that cigarette smokers are willing to adopt alternative nicotine tobacco products.[41]

Businesses will respond to market conditions when their profits are at stake. In the United States, when e-cigarettes started impinging on cigarette sales, cigarette manufacturers quickly developed their own products, and they also began acquiring popular e-cigarette brands (e.g., Juul, Logic) in an effort to exert control of the market. Some cigarette companies have even acknowledged that they are attempting to position themselves for a future when cigarettes may not be as predominant in the marketplace as they are today.[64,65] However, expecting cigarette manufacturers to voluntarily transition out of the cigarette business is unrealistic in much the same way as gas and oil companies are unlikely to transform away from petroleum even though there are obvious public health benefits. Prohibition of all nicotine containing tobacco products is not feasible nor necessary to solve the health problems caused by tobacco use disorder, which stems primarily from the use of smokeable tobacco.[66] Adopting tobacco product regulations and taxation policies which will favor lower-risk alternative nicotine products over smokeable products can help accelerate a decline in the use of smokeable tobacco and the diseases that they cause, including lung cancer.

PREVENTION OF LUNG CANCER

Principles of Cancer Prevention

Despite seminal improvements in the understanding of the biology of lung cancer and the introduction of targeted and immune therapies that have revolutionized the care of patients with lung cancer, this disease remains a major source of morbidity and mortality worldwide. Prevention and interception of the development of invasive and metastatic disease is an appealing way to alter cancer's dire natural history. Previously referred to as 'chemoprevention' that relied on dietary or pharmacologic interventions to slow or reverse the process of carcinogenesis,[67] prevention now encompasses a variety of strategies (e.g., immunoprevention) that have broadened its scope and are focusing on a precision approach. Even though no agents have been approved for the prevention of lung cancer thus far, recognition of the complexities of the multiple diseases, encompassed by the terms 'non-small cell lung cancer' and 'small cell lung cancer,' and the principles guiding the development of preventive agents are paving the way for a more personalized approach in the new generation of prevention clinical trials.

Fundamental to the concept of cancer prevention is the recognition that lung cancer development is a lengthy evolutionary process that occurs over decades in response to carcinogen-induced cellular damage and that the entire exposed epithelium is at-risk due to those exposures, resulting in field carcinogenesis.[68,69] The sequence of histologic changes is well described in the central lung that gives rise to squamous cell carcinoma, but it is not as well understood for peripheral adenocarcinomas, and even less so for other histologic subtypes. Seminal studies of sputum exfoliated cells by Saccomanno et al. demonstrated that squamous cell carcinoma develops through a series of stages from mild through severe dysplasia to carcinoma in situ and invasive carcinoma, over many years.[69] The corresponding histologic lesions in the bronchial epithelium (bronchial dysplasias of varying severity) have been studied via sequential bronchoscopies, demonstrating that only approximately one-third of patients with bronchial dysplasia develop cancer, with 40% of the cancers arising from the actual dysplastic sites and the rest arising elsewhere in the lung.[70] Intensive molecular and immunologic characterization

of dysplastic and carcinoma in situ lesions is revealing specific characteristics of progressive lesions, such as high mutational burden, specific methylation patterns, chromosomal instability, and immune dysregulation.[71-74] These data provide a rationale for targeting individuals with these preinvasive bronchial lesions for systemic (or regional, delivered to the lung only) preventive interventions using sequential bronchoscopies to follow progress during early phase clinical trials addressing squamous carcinogenesis, and they identify rational targets for intervention trials.

The understanding of the histologic and molecular development adenocarcinomas arising in the peripheral lung is less advanced, partially due to the inaccessibility of the peripheral lung to repeated longitudinal tissue sampling. The histologic evolutionary sequence of at least some invasive adenocarcinomas is thought to include atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), and minimally invasive adenocarcinoma (MIA).[75] AAH can appear as ground glass opacities (GGOs) on CT scans, although only 25-60% of resected GGOs are histologic AAH lesions, and in one prospective trial, only 7% of such lesions eventually became AIS, MIA, or invasive carcinomas with a median follow-up of 4.3 years.[76-78] Since the majority of GGOs are not resected, the true prevalence of AAH is not known. Molecular, immunologic, and metabolomic characterization of these adenocarcinoma precursors is limited by the inability to determine which lesions are progressive versus regressive, since AAHs are mainly identified at the time of resection for a concurrent suspected invasive adenocarcinoma. Nevertheless, accumulating data suggest AAHs can be mutationally complex and can exhibit known drivers (e.g., *EGFR, KRAS, BRAF*), although the drivers may not be the same as those in the synchronous adenocarcinomas.[79] Metabolic and immune dysregulation, with evidence of the presence of neoantigens and an adaptive immune response to those neoantigens, have also been identified in AAHs.[79-81] These emerging data have led to the development of prevention clinical trials specifically addressing adenocarcinoma prevention by focusing on GGOs in high-risk smokers, with CT scans pre- and post-intervention assessing efficacy over time.

The selection of targets for preventive intervention requires a thorough understanding of the efficacy and safety profiles of potential interventions. Evidence of efficacy comes from knowledge of mechanism of action, *in vitro* and *in vivo* animal carcinogenesis or transgenic experimental models, epidemiologic studies, and secondary endpoint analyses from trials performed for other indications.[82] Efficacy needs to be balanced with toxicity, given that the majority of at-risk individuals are not likely to develop cancer in the short term or possibly ever. Rare major toxicities, such as increased cardiovascular disease with prolonged rofecoxib use in a colon cancer prevention trial, must be avoided.[83] Additionally, minor side effects (e.g., low grade abdominal discomfort or bloating) may also have a major impact on long term compliance and thus must be carefully considered as well. For these reasons, agents that potentially prevent multiple histologic and molecular subtypes of lung cancer, multiple types of cancers and/or multiple chronic diseases are especially appealing. The selection of cohorts for prevention clinical trials should mirror the population that will be offered effective interventions. Several risk prediction models have been developed, primarily for application to lung cancer screening but equally applicable to identification of high-risk cohorts targeted for interventions.[84] One such model, developed by Tammemagi et al., based on a large population cohort from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), is reasonably robust and has been incorporated into the eligibility criteria of an ongoing prevention clinical trial (NCT04931017).[85]

Given that lung cancer development occurs over many years, cancer incidence is an appropriate endpoint only for phase III clinical trials that require lengthy follow-up and large sample sizes. Earlier phase trials depend on intermediate endpoints that are theoretically predictive of patient outcomes by evaluating a bio-

logic event that occurs between a carcinogenic exposure and the subsequent development of cancer. Requirements for useful intermediate markers include: 1) integral involvement in the process of carcinogenesis, such that expression correlates with disease course, 2) differential expression between normal and at-risk epithelium, 3) readily reproducible measurement in biospecimens that can be realistically obtained in clinical trials, and 4) modulation only by effective interventions.[82] Validation in prospective clinical trials is required for a marker to become a validated surrogate endpoint; no marker has achieved this status thus far. Premalignant lesions, as discussed above, are among the most commonly used intermediate endpoint biomarkers, given their role in the development of invasive malignancy. However, a wide variety of molecular abnormalities, including gene expression profiles, have been used to identify signals of efficacy.[86,87]

Past and Present Clinical Trials

Historically, phase III clinical trials attempting prevention in high-risk smokers (the Alpha Tocopherol Beta Carotene Study (ATBC) and the Beta-Carotene and Retinol Efficacy Trial (CARET), both using beta-carotene either alone or with vitamin E or vitamin A) or prevention of second primary cancers after curative treatment of initial lung cancer (Lung Intergroup Trial with low-dose 13-cis retinoic acid and ECOG5597 with selenium), have not been positive.[88-91] Instead, the beta-carotene trials showed increased lung cancer risk and mortality, while the 13-cis retinoic acid trial showed possible increased recurrence and mortality in current smokers. Table 3 summarizes the salient features of completed trials; additional data with other vitamins, aspirin, and micronutrients, all negative, are summarized in a recent Cochrane Review.[94]

As a result, subsequent clinical efforts have turned to phase II trials, which have the potential

Table 3. Phase III Lung Cancer Chemoprevention Trials

Trial Name (Reference)	Cohort	Sample Size	Intervention	1° Endpoint	Effect
ATBC (88)	Male smokers, 50-69 yo	29,133	AT 50 mg/d vs BC 20 mg/d vs both vs neither x 5-8 yrs	1° lung cancer: BC ↑18% AT ↓2%	Harmful
CARET (89)	Smokers (current/former) and asbestos workers	18,314	BC 30 mg/d + retinol 25,000 IU/d vs placebo x 5 yrs	1° lung cancer: RR=1.28; lung cancer mortality; RR=1.46	Harmful
Isotretinoin Intergroup Trial (90)	Resected stage I NSCLC	1,166	Isotretinoin 30 mg/d vs placebo x 3 yrs	SPT: HR 1.08; mortality HR 1.07	Null
ECOG 5597 (91)	Resected stage I NSCLC	1,772	Selenium 200 ug/d vs placebo x 48 mth	SPT: lung cancer SPT: 1.62 v 1.30 per 100 person-yrs (Se/placebo); overall SPT=3.54 vs 3.39 per 100 person years	Null
Physicians' Health Study (92)	Male physicians, 40-84 yo	22,071	BC 50 mg qod vs ASA 325 vs both vs placebo x 12 yrs	BC: lung cancer incidence *Current: RR=0.90 *Former: RR=1.0, *Never: RR=0.78	Null
EUROSCAN (93)	Resected NSCLC or H&N cancer	2,592	RP 300,000 IU/d x 1 yr, then 150,000 IU/d x 1 yr vs NAC 600 mg/d x 2 yr vs both vs no intervention	5-yr OS: 71% vs 72% (NAC vs no NAC); 70% vs 73% (RP vs no RP); no effect on second primary cancer	Null

AT=alpha-tocopherol; BC=beta carotene; ASA=aspirin; RR=relative risk; IU=international units; RP= retinyl palmitate; *=Smoker; NAC=N-acetylcysteine; OS=overall survival; SPT=second primary tumor; HR=hazard ratio; Se=selenium

to identify efficacious agents more rapidly in shorter duration trials (e.g., 6 months) enrolling a smaller number of participants (e.g., 80-150). The prototype of these trials is the study of inhaled budesonide in individuals with bronchial dysplasia.[95] Based on abundant data implicating inflammation in lung carcinogenesis and animal models as well as epidemiologic data, this trial monitored both the central airway via bronchoscopy and the peripheral lung via CT screening.[96] Although the 6-month intervention did not result in significant dysplasia regression, there was increased regression of CT-detected nodules (a secondary endpoint). This led to the development of a new clinical trial model, focusing on individuals with indeterminate pulmonary nodules undergoing CT screening. The first such trial used inhaled budesonide for one year in individuals with solid or subsolid indeterminate nodules. Although initially negative, the long-term follow-up showed a statistically significant, albeit small, persistent decrease in the size of ground glass, but not solid, nodules.[97,98] The relevance of this finding to subsequent development of cancer is not clear. A subsequent trial focused only on subsolid indeterminate nodules and used low-dose aspirin, based on preclinical, epidemiologic, and secondary endpoint analyses of prior cardiovascular trials.[99] This study was also negative, although it helped to establish the methodology for performing adenocarcinoma prevention trials.

Table 4 summarizes ongoing and recently finished early phase trials that have not yet reported results. This new generation of trials includes a greater focus on immune therapies, including checkpoint inhibitors, that reflects the increasing understanding of the importance of immune dysregulation during lung cancer development. Similarly, the experience of phase III trials showing worse outcomes in current vs. former smokers is reflected on the exclusive focus on former smokers in several trials. Some of these trials are also examining gene expression profiles from the abnormal field and developing predictive biomarkers to enable

Table 4. Ongoing Early Phase Lung Cancer Chemoprevention Trials

Agent	NCT Number	Cohort	1° Endpoint
Canakinumab (CanPrevent-Lung Trial)	NCT04789681	High-risk pulmonary nodules	Nodule regression
EGF-rP64K/montanide ISA 51 (CIMAvax-EGF) vaccine	NCT04298606	High-risk for lung cancer, or lung cancer survivors	Antibody response, safety, molecular biomarkers
Inhaled iloprost	NCT02237183	Sputum atypia or history of bronchial dysplasia (former smokers)	Toxicity, compliance
Black raspberry nectar (BE WELL)	NCT04267874	Current/former smokers	Feasibility, effect on inflammatory biomarkers (nasal brushings) and stool microbiome
MUC1 Peptide-Poly-ICLC Vaccine	NCT03300817	Current/former smokers undergoing CT screening	Immunogenicity, safety
Pembrolizumab (IMPRINT-Lung Trial)	NCT03634241	Indeterminate pulmonary nodules, with or without history of lung cancer	Regression of high-risk nodules
Nivolumab	NCT03347838	Current/former smoker with sputum atypia or history NSCLC or HNSCC	Improvement in endobronchial histology
Sulforaphane	NCT03232138	Former smokers	Bronchial dysplasia, cell proliferation, apoptosis
Metformin	NCT04931017	Overweight/obese former smokers	PD-1 expression on pulmonary Treg cells
Lovaza and Curcumin C3 complex	NCT03598309	Current/former smokers undergoing CT screening, with lung nodules	Change in nodule size, rate of > 4mm nodules

better delivery of interventions to the at-risk individuals who are most likely to benefit.

Recent studies suggest that the host immune response is capable of both recognizing and preventing the outgrowth of invasive malignancy at the earliest points of cancer development.[100] Immunosurveillance and immunoediting are operative in pulmonary premalignancy, giving rise to novel immunoprevention strategies. For example, nivolumab is under investigation for reversal of squamous dysplasia in high-risk current and former smokers (NCT03347838). Although immune recognition is evident in the earliest stages of disease, immunosuppressive networks may dominate as pulmonary premalignancy progresses to invasive lung cancer.[101,102] Thus, the interrogation of the immune contexture in developing premalignancy could enable cancer interception, a strategy that seeks to block the progression of premalignancy to invasive cancer.[72]

Future Opportunities

The past 50 years have witnessed a rapidly increasing understanding of the process of carcinogenesis and the development of highly sophisticated new technologies to study the epithelium of at-risk individuals. These insights are providing new opportunities for a precision approach for cancer prevention. New risk assessment models are helping to identify the highest risk smokers who should be targeted for early detection and prevention efforts. Although many challenges exist, clear progress offers hope that lung cancer will become a preventable disease.

SMOKING CESSATION TO IMPROVE CANCER TREATMENT OUTCOMES

Reframing Smoking and Cancer Care: The Clinical Effects of Smoking and Smoking Cessation on Cancer Treatment

Smoking has traditionally been viewed as a significant risk factor for several health conditions, including 13 different cancers, and causing over 80% of lung cancers.[20] However, the adverse effects of smoking continue after a cancer diagnosis. Reviewing over 400 studies, including over 500,000 patients between 1990-2012, the 2014 Surgeon General's Report from the USA concluded that smoking by cancer patients and survivors increases overall mortality by a median of 50% and cancer-related mortality by a median of 60%.[20] Continued smoking also increases the risk for second primary cancers and has strong associations with increased cancer treatment toxicity. A review of studies between 2013 and 2017 confirmed the increased risks of overall mortality and further observed a doubling in risk of mortality for patients who continued to smoke at follow-up, following their cancer treatment.[103] Cost estimates for second-line cancer treatment for patients who fail first-line treatment due to smoking have been estimated at $3.4 billion annually in the USA and $239 million annually in Canada.[104,105]

Smoking cessation remains the optimal method to prevent the adverse effects of smoking, both prior to and following a cancer diagnosis.[106] Across disease sites and treatment, smoking cessation after a cancer diagnosis is associated with a 45% median reduction in overall mortality. A recent systematic review of lung cancer studies between 1980 and 2021 observed that quitting smoking within 12 months prior to diagnosis reduced risk of overall mortality by 26%.[107] However, restricting analyses to studies reporting on quitting smoking after a cancer diagnosis observed a 35% risk reduction in overall mortality. These benefits of quitting smoking are readily understood when recognizing that smoking cessation benefits survival for both cancer and non-cancer related health outcomes. Collectively, these findings reframe smoking cessation as a core component of cancer care.

Practice Patterns, Advocacy, Guidelines, and National Initiatives

Significant advances have occurred over the past decade to increase awareness of the effects of smoking on cancer treatment. Parallel surveys of oncology physicians by the IASLC and American Society of Clinical Oncology demonstrated similar observations that approximately 90% of oncologists regularly ask

about tobacco use and approximately 80% advise patients to quit smoking.[108] In contrast, less than 40% regularly assisted patients with quitting. Though smoking affects survival, cancer control, and toxicity, a small minority of nationally funded cooperative group trials assessed smoking as a part of research, and little information was available to assess the impact of smoking on clinical trial outcomes.[110-112]

Most large cancer organizations now advocate for smoking cessation across the continuum of cancer care.[113] In 2015, the National Comprehensive Cancer Network (NCCN) developed smoking cessation guidelines for patients with cancer using the core evidence-based approaches of behavioral counseling and pharmacotherapy to increase success in quitting smoking.[114,115] The Cancer Centers Cessation Initiative supported by the National Cancer Institute (NCI) in the USA funded 52 NCI-designated cancer centers to implement clinical smoking cessation programs for cancer patients.[116] The Canadian Partnership Against Cancer worked with all jurisdictions across Canada to increase access to smoking cessation resources, showing a change from 26% of cancer centers in 2016 to 87% of centers by 2020.[117]

In 2022, the American College of Surgeons Commission on Cancer implemented the Just ASK initiative to begin addressing smoking in cancer care, with access to over 1,500 cancer centers that provide care to approximately 70% of patients across the USA.[116] These highlight broad national initiatives that are disseminating access to evidence-based care and represent significant progress over the past decade.

Delivering Evidence-Based Smoking Cessation to Patients with Cancer

The fundamental principles of evidence-based care include identifying patients who smoke and providing counseling and pharmacotherapy to assist patients in quitting. The two most recognized models are the 5A's (Ask-Advise-Assess-Assist-Arrange) or 3A's/AAC/AAR (Ask-Advise-Assist, Ask-Advise-Connect, or Ask-Advise-Refer) approach.[113,119] Figure 2 describes the steps of both models and lists features

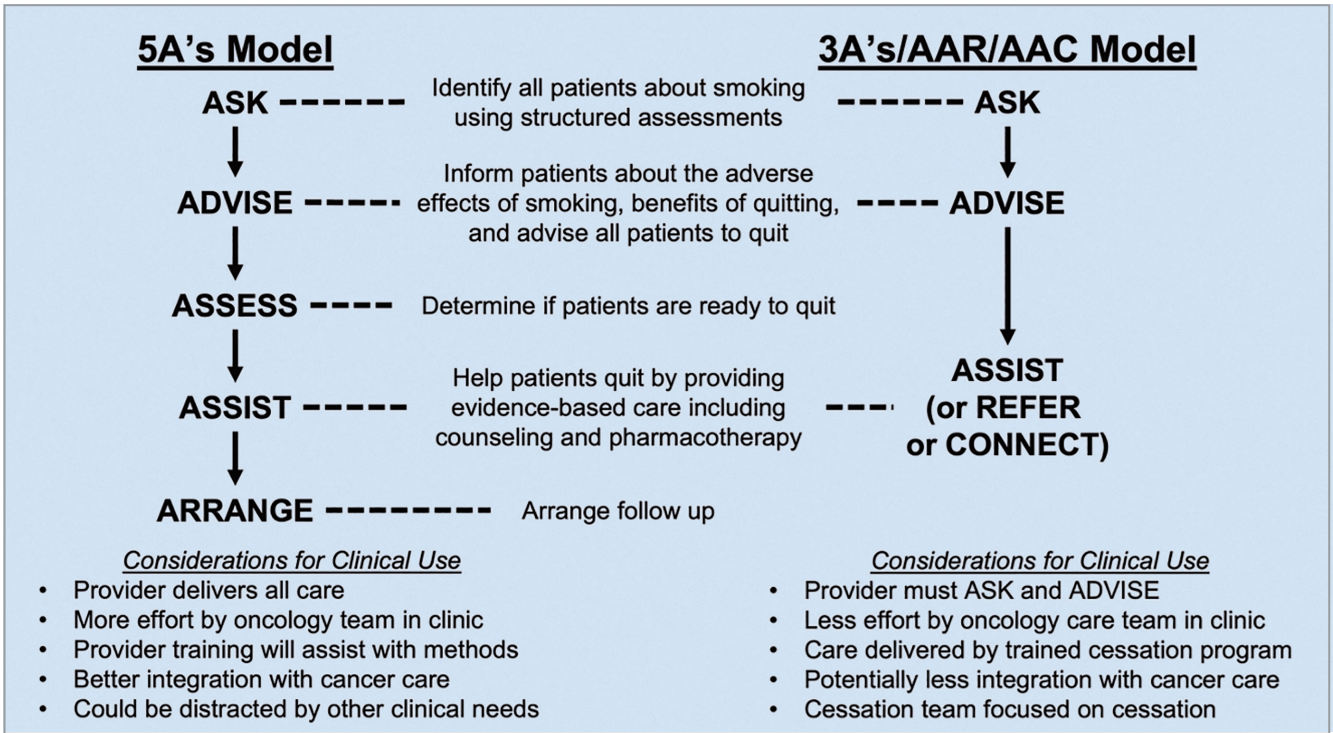


Figure 2. Models for Smoking Cessation Support

that can be considered to fit each clinical scenario. In general, the 5A's approach frequently relies on delivery of cessation support by individual clinical providers, while the 3A's approach frequently relies upon delivery of cessation support by referring to trained counselors or providers who provide evidence-based care. The approaches discussed are applicable across the continuum of cancer care, including screening for cancer through patient diagnosis, treatment, and follow-up. However, it is critical to understand that successful approaches depend on developing institution- or clinic-specific approaches that coordinate or develop resources to identify patients who need support and deliver evidence-based care.[118]

Asking involves accurately identifying patients who smoke. The following cognitively tested core question, supported by the NCI,[119,120] can be an efficient question used during initial consultation and at follow-up:

How long has it been since you smoked a cigarette (even one or two puffs)?

a. I smoked a cigarette today (at least one puff)
b. 1-7 days
c. Less than 1 month
d. Less than 1 year
e. More than 1 year
f. Don't know/don't remember

Any patients who report smoking within the past 30 days should receive support to quit smoking and prevent relapse.[112,113]

Advising patients consists of empathetic communication that smoking cessation can improve survival and cancer treatment outcomes.[113] Clinicians at all levels can deliver consistent support to encourage patients to quit smoking by using empathetic approaches.[121] Patients who receive consistent support from multiple treatment team members, such as physicians, nurses, therapists, etc., better recognize the importance of quitting smoking as a part of cancer care.[113,120] However, it is critical to understand that smoking is an addiction that starts early in life and can be very difficult to overcome. Many patients will require repeated attempts before successfully quitting, and all clinicians should recognize reductions in smoking as a progressive success by patients with the ultimate goal of achieving patient abstinence.

Assisting patients in quitting smoking is best accomplished through use of evidence-based approaches. Behavioral counseling and pharmacotherapy are proven methods that significantly increase chances that patients will quit.[115] Some clinicians may decide to provide direct assistance to patients, and numerous online and in-person resources are available to train clinicians in evidence-based methods to assist patients with smoking cessation. Whereas most oncologists do not regularly provide assistance with quitting,[108,109] oncologists can provide focused advice and actively refer patients to dedicated cessation programs. Dedicated programs that provide in-person interventions can usually deliver higher intensity treatments that have been reported to increase quit rates to as high as 45%.[124] Phone-based cessation interventions have shown to have high participation by cancer patients[125,126] and improve survival.[127] Using existing trained smoking cessation resources, such as trained counselors, dedicated tobacco treatment programs, quit lines, and other community resources, can improve the multidisciplinary approach to integrating smoking cessation into cancer treatment.[120] However, it is critical to identify what existing resources are available for a specific institution or clinic, and after, implement a standard of practice to provide cessation support to all patients who report smoking.

Future Directions

Smoking cessation can benefit both cancer and non-cancer related outcomes and should clearly be a standard of cancer care.[128] Traditional keys to future success include methods to increase delivery of evidence-based care access to all eligible cancer patients, improving targeted approaches to increase individual quit rates, and comprehensively linking smoking and cessation with clinical outcomes and research. However, optimal cancer treatment strategies have yet to be defined for patients who smoke. As an example, patients with a current or recent smoking history

treated with poly adenosine diphosphate-ribose polymerase (PARP) inhibitors appear to have better outcomes as compared to chemotherapy alone.[129,130] Future success is critically dependent upon identifying optimal cancer treatment strategies for patients who smoke as well as universal adoption of smoking cessation in the same manner as multidisciplinary treatment with surgery, radiotherapy, or systemic therapy.

SUMMARY

The IASLC has been an international proponent of tobacco smoking elimination. This will have the greatest impact at the societal level for the prevention of lung cancer. Additional environmental exposures, including second-hand smoke, radon, arsenic, beryllium, silica, and air pollution, are responsible for a smaller but significant fraction of the total lung cancer burden. The risk of lung cancer in never-smokers is less well understood, but exposure to household air pollution from domestic solid fuel use is associated with increased risk for incident lung cancer.[131] On the individual level, the priority intervention for lung cancer prevention for smokers is smoking cessation. Bronchial epithelial cells cultured from current smokers demonstrate a high mutational burden compared to never-smokers. Former smokers demonstrate expansion of a population of epithelial cells with a mutational burden similar to that of age matched never-smokers, which provides evidence for a reparative capacity.[132] We now understand more of the associations between immune function and the fate of premalignant lesions in the central and peripheral airways, leading to testable hypotheses for the medical prevention of lung cancer in former smokers that are beginning to be explored in clinical trials. Lung cancer is strongly associated with pulmonary diseases characterized by inflammation and dysfunctional tissue repair, such as chronic obstructive lung disease and pulmonary fibrosis. In the future, early detection of these diseases and interventions to slow their progression may have significant impact on the lung cancer burden in former smokers. Vulnerability of never-smokers to lung cancer requires further investigation. If common characteristics, such as reparative or immune dysfunction, are identified, it may be possible to identify high risk individuals who could benefit from early detection or medical prevention. Lung cancer was a rare disorder prior to widespread cigarette smoking. Progress in research, clinical care, and public health measures all provide opportunities for the mitigation of this leading cause of lung cancer morbidity and mortality.

References

1. U.S. Department of Health and Human Services. *The Health Consequences of Smoking : A Report of the Surgeon General*. Atlanta, GA. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 2004.
2. Robins J, Greenland S. The probability of causation under a stochastic model for individual risk. *Biometrics*. Dec 1989;45(4):1125-38.
3. Samet JM. Carcinogenesis and lung cancer: 70 years of progress and more to come. *Carcinogenesis*. Oct 15 2020;41(10):1309-1317. doi:10.1093/carcin/bgaa094
4. Levin ML, Goldstein H, Gerhardt PR. Cancer and tobacco smoking; A preliminary report. *JAMA*. May 27 1950;143(4):336-8. doi:10.1001/jama.1950.02910390008002
5. Doll R, Hill AB. Smoking and Carcinoma of the Lung - Preliminary Report. *British Medical Journal*. 1950;2(4682):739-748. doi:DOI 10.1136/bmj.2.4682.739
6. Wynder EL, Graham EA. Tobacco Smoking as a Possible Etiologic Factor in Bronchiogenic Carcinoma - A Study of 684 Proved Cases. *JAMA*. 1950;143(4):329-336. doi:DOI 10.1001/jama.1950.02910390001001
7. Doll R, Hill AB. The Mortality of Doctors in Relation to Their Smoking Habits - a Preliminary Report. *BMJ*. 1954;1(4877):1451-1455. doi:DOI 10.1136/bmj.1.4877.1451
8. Hammond EC, Horn D. The Relationship between Human Smoking Habits and Death Rates - a Follow-up Study of 187,766 Men. *JAMA*. 1954;155(15):1316-1328. doi:DOI 10.1001/jama.1954.03690330020006
9. Dorn HF. The Relationship of Cancer of the Lung and the Use of Tobacco. *The American Statistician*. 1954;8(8):7-13.
10. Glass TA, Goodman SN, Hernan MA, Samet JM. Causal inference in public health. *Annu Rev Public Health*. 2013;34:61-75. doi:10.1146/annurev-publhealth-031811-124606
11. Fisher RAS. *Smoking. The cancer controversy. Some attempts to assess the evidence*. Edinburgh; London: Oliver & Boyd, [1959].
12. *The cigarette century :The rise, fall, and deadly persistence of the product that defined America*. Basic Books; 2007.
13. United States. Department of Health, Education, Welfare. Public Health Service. *Smoking and Health Report of the Advisory Committee to the Surgeon General of the Public Health Service*. USGPO; 1964.
14. Royal College of Physicians of London. *Smoking and Health. A Report of The Royal College of Physicians of London on Smoking in Relation to Cancer of the*

Lung and Other Diseases. [Preceded by a summary of the report.]. Pitman Medical Publishing Co; 1962.
15. Stallones L. Commentary: Teaching causal thinking (Commentary on 'The association between tobacco and coronary heart disease'). *Int J Epidemiol*. Jun 2015;44(3):748-9. doi:10.1093/ije/dyv125
16. Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med*. May 1965;58:295-300.
17. U.S. Department of Health and Human Services. *The Health Consequences of Involuntary Smoking: A Report of the Surgeon General*. 1986- : DHHS. U.S. Dept. of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Health Promotion and Education, Office on Smoking and Health; 1986:xix. 359 pages: illustrations.
18. Cornfield J. A method of estimating comparative rates from clinical data; applications to cancer of the lung, breast, and cervix. *J Natl Cancer Inst*. Jun 1951;11(6):1269-75.
19. Levin ML. The occurrence of lung cancer in man. *Acta Unio Int Contra Cancrum*. 1953;9(3):531-41.
20. U.S. Department of Health and Human Services. Office of the Surgeon General, United States. Department of H, Human S. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General; 2014.
21. *Health Risks of Radon and Other Internally Deposited Alpha-Emitters: Beir IV*. 1988.
22. *List of classifications by cancer sites with sufficient or limited evidence in humans*. Vol. 1-132. 2022.
23. Loomis D, Grosse Y, Lauby-Secretan B, et al. The carcinogenicity of outdoor air pollution. *Lancet Oncol*. Dec 2013;14(13):1262-3. doi:10.1016/s1470-2045(13)70487-x
24. Hill W, Lim EL, Weeden CE, et al. Lung adenocarcinoma promotion by air pollutants. *Nature*. Apr 2023;616(7955):159-167. doi:10.1038/s41586-023-05874-3
25. Institute for Health Metrics and Evaluation. https://vizhub.healthdata.org/gbd-compare/#
26. Bookstein A, Po J, Tseng C, et al. Association between Airport Ultrafine Particles and Lung Cancer Risk: The Multiethnic Cohort Study. *Cancer Epidemiol Biomarkers Prev*. 2024;33(5):703-711.
27. Cheng I, Yang J, Tseng C, et al. Traffic-related Air Pollution and Lung Cancer Incidence: The California Multiethnic Cohort Study. *Am J Respir Crit Care Med*. Oct 15 2022;206(8):1008-1018. doi:10.1164/rccm.202107-1770OC
28. U.S. Department of Health and Human Services. *The Health Consequences of Smoking : Nicotine Addiction: A report of the Surgeon General*. Atlanta, GA. U.S. Department of Health and Human Services, Centers for Disease Control and Preventio; 1988.
29. U.S. Department of Health and Human Services. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. 2010. Publications and Reports of the Surgeon General.
30. Association AP. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. 2022.
31. Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *Annu Rev Pharmacol Toxicol*. 2009;49:57-71. doi:10.1146/annurev.pharmtox.48.113006.094742
32. Senkus M. *Smoking Satisfaction*. Truth Tobacco Industry Documents. R.J. Reynolds Tobacco Company; 1976.
33. Liu MZ, Jiang Y, Wedow R, et al. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nature Genetics*. Feb 2019;51(2):237-+. doi:10.1038/s41588-018-0307-5
34. Global trends in nicotine. Foundation for a Smoke-Free World. https://www.smokefreeworld.org/advancing-industry-transformation/global-trends-nicotine/
35. Orleans CT, Slade J. *Nicotine addiction: principles and management*. Oxford University Press; 1993.
36. *Tobacco and cancer: The science and the Story*. World Scientific Publishing; 2022.
37. *World Health Organization Framework Convention on Tobacco Control*. 2003.
38. O'Connor RJ, Cummings KM. *Tobacco Harm Minimization*. 2nd ed. Science Direct; 2017:169-77.
39. Gravely S, Giovino GA, Craig L, et al. Implementation of key demand-reduction measures of the WHO Framework Convention on Tobacco Control and change in smoking prevalence in 126 countries: an association study. *Lancet Public Health*. Apr 2017;2(4):e166-e174. doi:10.1016/S2468-2667(17)30045-2
40. Hoffman SJ, Poirier MJP, Rogers Van Katwyk S, Baral P, Sritharan L. Impact of the WHO Framework Convention on Tobacco Control on global cigarette consumption: quasi-experimental evaluations using interrupted time series analysis and in-sample forecast event modelling. *BMJ*. Jun 19 2019;365:l2287. doi:10.1136/bmj.l2287
41. Bates C. How to Save 100 Million Lives. Tobacco Reporter 2022.
42. *Methods for Evaluating Tobacco Control Policies*. vol 12. International Agency for Research on Cancer World Health Organization; 2008.
43. Nilan K, Raw M, McKeever TM, Murray RL, McNeill A. Progress in implementation of WHO FCTC Article 14 and its guidelines: A survey of tobacco dependence treatment provision in 142 countries. *Addiction*. Nov 2017;112(11):2023-2031. doi:10.1111/add.13903
44. Cummings KM, Ballin S, Sweanor D. The past is not the future in tobacco control. *Prev Med* Nov 2020;140:106183. doi:10.1016/j.ypmed.2020.106183
45. Cummings KM, Hyland A, Giovino GA, et al. Are smokers adequately informed about the health risks of smoking and medicinal nicotine? *Nicotine & Tobacco Research*. Dec 2004;6:333-340. doi:10.1080/14622200412331320734
46. O'Brien EK, Nguyen AB, Persoskie A, Hoffman AC. US adults' addiction and harm beliefs about nicotine and low nicotine cigarettes. *Preventive Medicine*. Mar 2017;96:94-100. doi:10.1016/j.ypmed.2016.12.048
47. Steinberg MB, Bover Manderski MT, Wackowski OA, et al. Nicotine risk misperception among US physicians. *J Gen Intern Med*. Dec 2021;36(12):3888-3890. doi:10.1007/s11606-020-06172-8
48. Administration USFaD. *Advance notice of proposed rulemaking: Tobacco product standard for nicotine level of combusted cigarettes*. 2018.
49. Havermans A, Pieper E, Henkler-Stephani F, Talhout R. Feasibility of Manufacturing Tobacco with Very Low Nicotine Levels. *Tobacco Regulatory Science*. Nov 2020;6(6):405-415. doi:10.18001/Trs.6.6.4
50. Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. *N Engl J Med*. Jul 14 1994;331(2):123-5. doi:10.1056/NEJM199407143310212

51. Macqueen DA, Heckman BW, Blank MD, et al. Transient compensatory smoking in response to placebo cigarettes. *Psychopharmacology (Berl)*. Sep 2012;223(1):47-54. doi:10.1007/s00213-012-2685-1
52. Smith TT, Koopmeiners JS, White CM, et al. The Impact of Exclusive Use of Very Low Nicotine Cigarettes on Compensatory Smoking: An Inpatient Crossover Clinical Trial. *Cancer Epidemiol Biomarkers Prev*. Apr 2020;29(4):880-886. doi:10.1158/1055-9965.EPI-19-0963
53. Donny EC, White CM. A review of the evidence on cigarettes with reduced addictiveness potential. *Int J Drug Policy*. Jan 2022;99:103436. doi:10.1016/j.drugpo.2021.103436
54. Apelberg BJ, Feirman SP, Salazar E, et al. Potential Public Health Effects of Reducing Nicotine Levels in Cigarettes in the United States. *N Engl J Med*. May 3 2018;378(18):1725-1733. doi:10.1056/NEJMsr1714617
55. Wilson N, Hoek J, Nghiem N, Summers J, Grout L, Edwards R. Modelling the impacts of tobacco denicotinisation on achieving the Smokefree 2025 goal in Aotearoa New Zealand. *N Z Med J*. Jan 21 2022;135(1548):65-76.
56. Gottlieb S, Zeller M. A Nicotine-focused framework for public health. *N Engl J Med*. Sep 21 2017;377(12):1111-1114. doi:10.1056/NEJMp1707409
57. Prater E. Tobacco companies will be forced to reduce nicotine in U.S. cigarettes until they're non-addictive, if the Biden administration has its way: report. *Fortune* 2022.
58. McClure T. New Zealand to ban smoking for next generation in bid to outlaw habit by 2025. New Zealand. 2021.
59. Benowitz NL, Donny EC, Hatsukami DK. Reduced nicotine content cigarettes, e-cigarettes and the cigarette end game. *Addiction*. Jan 2017;112(1):6-7. doi:10.1111/add.13534
60. White CM, Hatsukami DK, Donny EC. Reducing the relative value of cigarettes: Considerations for nicotine and non-nicotine factors. *Neuropharmacology*. Sep 15 2020;175:108200. doi:10.1016/j.neuropharm.2020.108200
61. Freitas-Lemos R, Keith DR, Tegge AN, et al. Estimating the impact of tobacco parity and harm reduction tax proposals using the experimental tobacco marketplace. *Int J Environ Res Public Health*. Jul 23 2021;18(15)doi:10.3390/ijerph18157835
62. Ramstrom L, Borland R, Wikmans T. Patterns of smoking and Snus use in Sweden: Implications for public health. *Int J Environ Res Public Health*. Nov 9 2016;13(11)doi:10.3390/ijerph13111110
63. Rodu B, Cole P. The burden of mortality from smoking: comparing Sweden with other countries in the European Union. *Eur J Epidemiol*. 2004;19(2):129-31. doi:10.1023/b:ejep.0000017703.13810.97
64. Perrone M. Altria expands sales of heated-cigarette as revenue slides. *The Washington Post*. https://www.washingtonpost.com/business/altria-expands-sales-of-heated-cigarette-as-revenue-slides/2020/07/28/edc29878-d0db-11ea-826b-cc394d824e35_story.html
65. Company RJRT. Transforming Tobacco. https://rjrt.com/transforming-tobacco/our-mission-and-vision/
66. Fairchild A, Healton C, Curran J, Abrams D, Bayer R. Evidence, alarm, and the debate over e-cigarettes. *Science*. Dec 13 2019;366(6471):1318-1320. doi:10.1126/science.aba0032
67. Sporn MB, Dunlop NM, Newton DL, Smith JM. Prevention of chemical carcinogenesis by vitamin A and its synthetic analogs (retinoids). *Fed Proc*. May 1 1976;35(6):1332-8.
68. Auerbach O, Stout AP, Hammond EC, Garfinkel L. Changes in bronchial epithelium in relation to cigarette smoking and in relation to lung cancer. *N Engl J Med*. Aug 10 1961;265:253-67. doi:10.1056/NEJM196108102650601
69. Saccomanno G, Archer VE, Auerbach O, Saunders RP, Brennan LM. Development of carcinoma of lung as reflected in exfoliated cells. *Cancer*. 1974;33(1):256-270. doi:Doi 10.1002/1097-0142(197401)33:1<256::Aid-Cncr2820330139>3.0.Co;2-G
70. van Boerdonk RA, Smesseim I, Heideman DA, et al. Close surveillance with long-term follow-up of subjects with preinvasive endobronchial lesions. *Am J Respir Crit Care Med*. Dec 15 2015;192(12):1483-9. doi:10.1164/rccm.201504-0822OC
71. Teixeira VH, Pipinikas CP, Pennycuick A, et al. Deciphering the genomic, epigenomic, and transcriptomic landscapes of pre-invasive lung cancer lesions. *Nat Med*. Mar 2019;25(3):517-525. doi:10.1038/s41591-018-0323-0
72. Beane JE, Mazzilli SA, Campbell JD, et al. Molecular subtyping reveals immune alterations associated with progression of bronchial premalignant lesions. *Nat Commun*. Apr 23 2019;10(1):1856. doi:10.1038/s41467-019-09834-2
73. Mascaux C, Angelova M, Vasaturo A, et al. Immune evasion before tumour invasion in early lung squamous carcinogenesis. *Nature*. Jul 2019;571(7766):570-575. doi:10.1038/s41586-019-1330-0
74. Pennycuick A, Teixeira VH, AbdulJabbar K, et al. Immune surveillance in clinical regression of preinvasive squamous cell lung cancer. *Cancer Discov.* Oct 2020;10(10):1489-1499. doi:10.1158/2159-8290.CD-19-1366
75. Kerr K. *Adenomatous hyperplasia and the origin of peripheral adenocarcinoma of the lung*. Pathology of Lung Tumors. Churchill Livingstone; 1997.
76. Nakajima R, Yokose T, Kakinuma R, et al. Localized pure ground-glass opacity on high-resolution CT: Histologic characteristics. *J Comput Assist Tomogr*. May-Jun 2002;26(3):323-9. doi:10.1097/00004728-200205000-00001
77. Ohtsuka T, Watanabe K, Kaji M, Naruke T, Suemasu K. A clinicopathological study of resected pulmonary nodules with focal pure ground-glass opacity. *Eur J Cardiothorac Surg*. Jul 2006;30(1):160-3. doi:10.1016/j.ejcts.2006.03.058
78. Kakinuma R, Noguchi M, Ashizawa K, et al. Natural History of Pulmonary Subsolid Nodules: A Prospective Multicenter Study. *J Thorac Oncol*. Jul 2016;11(7):1012-28. doi:10.1016/j.jtho.2016.04.006
79. Sivakumar S, Lucas FAS, McDowell TL, et al. Genomic Landscape of Atypical Adenomatous Hyperplasia Reveals Divergent Modes to Lung Adenocarcinoma. *Cancer Res*. Nov 15 2017;77(22):6119-6130. doi:10.1158/0008-5472.CAN-17-1605
80. Nie M, Yao K, Zhu X, et al. Evolutionary metabolic landscape from preneoplasia to invasive lung adenocarcinoma. *Nat Commun*. Nov 10 2021;12(1):6479. doi:10.1038/s41467-021-26685-y10.1002/1097-0142(197401)33:1<256::Aid-Cncr2820330139>3.0.Co;2-G
81. Krysan K, Tran LM, Grimes BS, et al. The Immune Contexture Associates with the Genomic Landscape in Lung Adenomatous Premalignancy. *Cancer Res*. Oct 1 2019;79(19):5022-5033. doi:10.1158/0008-5472.CAN-19-0153
82. Szabo E. Phase II cancer prevention clinical trials. *Semin Oncol*. Aug 2010;37(4):359-66. doi:10.1053/j.seminoncol.2010.06.015
83. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J*

Med. Mar 17 2005;352(11):1092-102. doi:10.1056/NEJMoa050493
84. Ten Haaf K, van der Aalst CM, de Koning HJ, Kaaks R, Tammemagi MC. Personalising lung cancer screening: An overview of risk-stratification opportunities and challenges. *Int J Cancer*. Jul 15 2021;149(2):250-263. doi:10.1002/ijc.33578
85. Tammemagi MC, Katki HA, Hocking WG, et al. Selection criteria for lung-cancer screening. *N Engl J Med*. Feb 21 2013;368(8):728-36. doi:10.1056/NEJMoa1211776
86. Szabo E. Biomarkers in phase I-II chemoprevention trials: lessons from the NCI experience. *Ecancermedicalscience*. 2015;9:599. doi:10.3332/ecancer.2015.599
87. Garland LL, Guillen-Rodriguez J, Hsu CH, et al. Effect of intermittent versus continuous low-dose aspirin on nasal epithelium gene expression in current smokers: A randomized, double-blinded trial. *Cancer Prev Res (Phila)*. Nov 2019;12(11):809-820. doi:10.1158/1940-6207.CAPR-19-0036
88. Alpha-Tocopherol BCCPSG. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med*. Apr 14 1994;330(15):1029-35. doi:10.1056/NEJM199404143301501
89. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med*. May 2 1996;334(18):1150-5. doi:10.1056/NEJM199605023341802
90. Lippman SM, Lee JJ, Karp DD, et al. Randomized phase III intergroup trial of isotretinoin to prevent second primary tumors in stage I non-small-cell lung cancer. *J Natl Cancer Inst*. Apr 18 2001;93(8):605-18. doi:10.1093/jnci/93.8.605
91. Karp DD, Lee SJ, Keller SM, et al. Randomized, double-blind, placebo-controlled, phase III chemoprevention trial of selenium supplementation in patients with resected stage I non-small-cell lung cancer: ECOG 5597. *J Clin Oncol*. Nov 20 2013;31(33):4179-87. doi:10.1200/JCO.2013.49.2173
92. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med*. 1996; 334(18):1145-9. doi: 10.1056/NEJM199605023341801. PMID: 8602179.
93. Van Zandwijk N, Dalesio O, Pastorino U, de Vries N, van Tinteren H. EUROSCAN, a randomized trial of vitamin A and N-acetylcysteine in patients with head and neck cancer or lung cancer. For the European Organization for Research and Treatment of Cancer Head and Neck and Lung Cancer Cooperative Groups. *J Natl Cancer Inst*. 2000; 92(12):977-86. doi: 10.1093/jnci/92.12.977. PMID: 10861309.
94. Cortes-Jofre M, Rueda JR, Asenjo-Lobos C, Madrid E, Bonfill Cosp X. Drugs for preventing lung cancer in healthy people. *Cochrane Database Syst Rev*. Mar 4 2020;3:CD002141. doi:10.1002/14651858.CD002141.pub3
95. Lam S, leRiche JC, McWilliams A, et al. A randomized phase IIb trial of pulmicort turbuhaler (budesonide) in people with dysplasia of the bronchial epithelium. *Clin Cancer Res*. Oct 1 2004;10(19):6502-11. doi:10.1158/1078-0432.CCR-04-0686
96. Kelloff GJ, Lippman SM, Dannenberg AJ, et al. Progress in chemoprevention drug development: The promise of molecular biomarkers for prevention of intraepithelial neoplasia and cancer-a plan to move forward. *Clin Cancer Res*. Jun 15 2006;12(12):3661-97. doi:10.1158/1078-0432.CCR-06-1104
97. Veronesi G, Szabo E, Decensi A, et al. Randomized phase II trial of inhaled budesonide versus placebo in high-risk individuals with CT screen-detected lung nodules. *Cancer Prev Res* (Phila). Jan 2011;4(1):34-42. doi:10.1158/1940-6207.CAPR-10-0182
98. Veronesi G, Lazzeroni M, Szabo E, et al. Long-term effects of inhaled budesonide on screening-detected lung nodules. *Ann Oncol*. May 2015;26(5):1025-1030. doi:10.1093/annonc/mdv064
99. Bonanni B, Serrano D, Maisonneuve P, et al. Low-dose aspirin in high-risk individuals with screen-detected subsolid lung nodules: A randomized phase II trial. *JNCI Cancer Spectr*. Dec 2020;4(6):pkaa096. doi:10.1093/jncics/pkaa096
100. Stanton SE, Castle PE, Finn OJ, Sei S, Emens LA. Advances and challenges in cancer immunoprevention and immune interception. *J Immunother Cancer*. Mar 21 2024;12(3)doi:10.1136/jitc-2023-007815
101. Krysan K, Tran LM, Dubinett SM. Immunosurveillance and regression in the context of squamous pulmonary premalignancy. *Cancer Discov*. Oct 2020;10(10):1442-1444. doi:10.1158/2159-8290.CD-20-1087
102. Yanagawa J, Tran LM, Salehi-Rad R, et al. Single-cell characterization of pulmonary nodules implicates suppression of immunosurveillance across early stages of lung adenocarcinoma. *Cancer Res*. Oct 2 2023;83(19):3305-3319. doi:10.1158/0008-5472.CAN-23-0128
103. Warren G. When Analyzing Meaningful Progress We Can't Ignore the Obvious. 2021.
104. Warren GW, Cartmell KB, Garrett-Mayer E, Salloum RG, Cummings KM. Attributable failure of first-line cancer treatment and incremental costs associated with smoking by patients with cancer. *JAMA Netw Open*. Apr 5 2019;2(4):e191703. doi:10.1001/jamanetworkopen.2019.1703
105. Iragorri N, Essue B, Timmings C, Keen D, Bryant H, Warren GW. The cost of failed first-line cancer treatment related to continued smoking in Canada. *Curr Oncol*. Dec 2020;27(6):307-312. doi:10.3747/co.27.5951
106. U.S. Department of Health and Human Services. Office of the Surgeon General. *Smoking Cessation: A Report of the Surgeon General*. U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General; 2020:xx, 675 pages.
107. Caini S, Del Riccio M, Vettori V, et al. Quitting smoking at or around diagnosis improves the overall survival of lung cancer patients: A systematic review and meta-analysis. *J Thorac Oncol*. May 2022;17(5):623-636. doi:10.1016/j.jtho.2021.12.005
108. Warren GW, Marshall JR, Cummings KM, et al. Practice patterns and perceptions of thoracic oncology providers on tobacco use and cessation in cancer patients. *J Thorac Oncol*. May 2013;8(5):543-8. doi:10.1097/JTO.0b013e318288dc96
109. Warren GW, Marshall JR, Cummings KM, et al. Addressing tobacco use in patients with cancer: A survey of American Society of Clinical Oncology members. *J Oncol Pract*. Sep 2013;9(5):258-62. doi:10.1200/JOP.2013.001025
110. Gritz ER, Dresler C, Sarna L. Smoking, the missing drug interaction in clinical trials: Ignoring the obvious. *Cancer Epidemiol Biomarkers Prev*. Oct 2005;14(10):2287-93. doi:10.1158/1055-9965.EPI-05-0224

111. Peters EN, Torres E, Toll BA, et al. Tobacco assessment in actively accruing National Cancer Institute Cooperative Group Program Clinical Trials. *J Clin Oncol*. Aug 10 2012;30(23):2869-75. doi:10.1200/JCO.2011.40.8815
112. Peters EN, Warren GW, Sloan JA, Marshall JR. Tobacco assessment in completed lung cancer treatment trials. *Cancer.* Nov 15 2016;122(21):3260-3262. doi:10.1002/cncr.30223
113. Warren GW, Simmons VN. *Tobacco Use and the Cancer Patient*. 11th ed. DeVita, Hellman, and Rosenberg's Cancer : Principles & Practice of Oncology. Wolters Kluwer Health; 2018.
114. Shields PG, Herbst RS, Arenberg D, et al. Smoking Cessation, Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. Nov 2016;14(11):1430-1468. doi:10.6004/jnccn.2016.0152
115. Clinical Practice Guideline Treating Tobacco U, Dependence Update Panel L, Staff. A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. *Am J Prev Med*. Aug 2008;35(2):158-76. doi:10.1016/j.amepre.2008.04.009
116. Croyle RT, Morgan GD, Fiore MC. Addressing a core gap in cancer care-The NCI Moonshot Program to help oncology patients stop smoking. *N Engl J Med*. Feb 7 2019;380(6):512-515. doi:10.1056/NEJMp1813913
117. Smoking Cessation in Cancer Care Across Canada. Canadian Partnership Against Cancer; 2020. https://www.partnershipagainstcancer.ca/topics/smoking-cessation-cancer-care/
118. Just ASK Quality Improvement Project & Clinical Study. American College of Surgeons; 2022. https://www.facs.org/quality-programs/cancer-programs/pdsa-just-ask/
119. *Treating Smoking in Cancer Patients: An Essential Component of Cancer Care*. National Cancer Institute Tobacco Control Monograph Series. 2022.
120. Warren GW, Ward KD. Integration of tobacco cessation services into multidisciplinary lung cancer care: rationale, state of the art, and future directions. *Transl Lung Cancer Res*. Aug 2015;4(4):339-52. doi:10.3978/j.issn.2218-6751.2015.07.15
121. Land SR, Toll BA, Moinpour CM, et al. Research priorities, measures, and recommendations for assessment of tobacco use in clinical cancer research. *Clin Cancer Res*. Apr 15 2016;22(8):1907-13. doi:10.1158/1078-0432.CCR-16-0104
122. Land SR, Warren GW, Crafts JL, et al. Cognitive testing of tobacco use items for administration to patients with cancer and cancer survivors in clinical research. *Cancer*. Jun 1 2016;122(11):1728-34. doi:10.1002/cncr.29964
123. Banerjee SC, Haque N, Schofield EA, et al. Oncology care provider training in empathic communication skills to reduce lung cancer stigma. *Chest*. May 2021;159(5):2040-2049. doi:10.1016/j.chest.2020.11.024
124. Cinciripini PM, Karam-Hage M, Kypriotakis G, et al. Association of a comprehensive smoking cessation program with smoking abstinence among patients with cancer.*JAMA Netw Open*. Sep 4 2019;2(9):e1912251. doi:10.1001/jamanetworkopen.2019.12251
125. Warren GW, Marshall JR, Cummings KM, et al. Automated tobacco assessment and cessation support for cancer patients. *Cancer*. Feb 15 2014;120(4):562-9. doi:10.1002/cncr.28440
126. Notier AE, Hager P, Brown KS, et al. Using a quitline to deliver opt-out smoking cessation for cancer patients. *JCO Oncol Pract*. Jun 2020;16(6):e549-e556. doi:10.1200/JOP.19.00296
127. Dobson Amato KA, Hyland A, Reed R, et al. Tobacco cessation may improve lung cancer patient survival. *J Thorac Oncol*. Jul 2015;10(7):1014-9. doi:10.1097/JTO.0000000000000578
128. Evans WK, Warren GW, Dresler C. Ignoring the obvious: Smoking cessation improves survival. *J Thorac Oncol*. May 2022;17(5):596-598. doi:10.1016/j.jtho.2022.03.008
129. Reck M, Blais N, Juhasz E, et al. Smoking history predicts sensitivity to PARP inhibitor veliparib in patients with advanced non-small cell lung cancer. *J Thorac Oncol*. Jul 2017;12(7):1098-1108. doi:10.1016/j.jtho.2017.04.010
130. Ramalingam SS, Novello S, Guclu SZ, et al. Veliparib in combination with platinum-based chemotherapy for first-line treatment of advanced squamous cell lung cancer: A randomized, multicenter phase iii study. *J Clin Oncol*. Nov 10 2021;39(32):3633-3644.
131. Cheng ES, Chan KH, Weber M, et al. Solid fuel, secondhand smoke, and lung cancer mortality: a prospective cohort of 323,794 chinese never-smokers. *Am J Respir Crit Care Med*. 2022 Nov 1;206(9):1153-1162. doi: 10.1164/rccm.202201-0114OC.
132. Yoshida K, Gowers KHC, Lee-Six H, et al. Tobacco smoking and somatic mutations in human bronchial epithelium. *Nature*. 2020 Feb;578 (7794):266-272. doi: 10.1038/s41586-020-1961-1.

12

EARLY DETECTION IN LUNG CANCER: A HISTORICAL OVERVIEW

James L. Mulshine,[1] **Denise R. Aberle,**[2] **Matthijs Oudkerk,**[3] **Takashi Ohtsuka,**[4] **Masao Naruke,**[5] **and Ugo Pastorino**[6] | [1]Rush University, Chicago, USA; [2]David Geffen School of Medicine at UCLA, Los Angeles, USA; [3]University of Groningen, Groningen, the Netherlands; [4]The Jikei University, Tokyo, Japan; [5]International Goodwill Hospital, Kanagawa, Japan; [6]Fondazione IRCCS Istituto Nazionale Tumori Milano, Milan, Italy.

NCI LUNG CANCER EARLY DETECTION TRIALS LEADING UP TO THE NATIONAL LUNG SCREENING TRIAL

Although the first epidemiological papers indicating that "smoking is connected with the shortening of life span" were published in the first half of the 20th century, not until the 1950s did Hill and Doll in Great Britain and Wynder and Graham in USA convincingly show a statistically significant correlation between cigarettes smoking and lung cancer occurrence.[1-3] Other epidemiological data, such as reported by Dr. Mort Levin, supported the causal relationship of smoking to lung cancer.[4]

In response to the recognition of a causal relationship between smoking and the development of lung cancer, a number of systematic efforts to address the high lethality of lung cancer were launched. Notable in this regard was the Philadelphia Pulmonary Neoplasm Research Project which was a major effort started in 1951 and funded in part by the US Public Health Service as well as the American Cancer Society. This study was designed to elucidate the natural history of lung cancer using chest X-ray using a non-randomized, biannual evaluation of a cohort of male participants, 45 years and older. For ten years, this cohort of 6,136 male volunteers was screened every six months with chest X-ray along with a survey of potential lung cancer symptoms.[5] Over those 10 years, 121 cases of lung cancer was detected with a five-year survival rate of 8%. There was no objective evidence that the cases of lung cancer detected by the bi-annual chest X-ray screening survived longer than the cancers detected by clinical symptoms.[6]

The rapid rise in lung cancer incidence from 1930 forward coincided with the global increase in uptake of cigarette smoking, which spurred sustained research on improving lung cancer detection to improve health outcomes. Innovations included better chest X-ray technique and the introduction of fiberoptic bronchoscopy.[7-9] Perhaps the most promising of these developments was the improved cytological method for lung cancer detection devised by Dr. Gino Saccomanno, who worked with a large uranium mining cohort in the Colorado Plateau.[10] Saccomanno adapted the cytological approach pioneered by cervical cancer cytologist, Georgios Papanikolaou, MD, for application in early lung cancer diagnosis. Through a sustained effort, Saccomanno devised a process to reliably recover exfoliated bronchial epithelial cells from sputum samples to allow cytologic detection of the presence of malignant cells.[10] The emergence of this promising new approach for early lung cancer detection led to enthusiasm for combining chest x-ray with sputum cytology to enable routine detection of curable lung cancer.

The timing for further evaluation of the combination of chest

x-ray and sputum cytology was favorable in the United States as the National Cancer Act was just signed into law.[11] Provisions of this legislation provided funding to rapidly evaluate this new approach to early lung cancer detection. The Director of the NCI, Division of Cancer Biology and Diagnosis, at that time, Dr. Nathaniel Berlin, developed a structure called the Cooperative Early Lung Cancer Detection Program.[12] This organization was comprised of four consortial partners, including John Hopkins, Memorial Sloan Kettering, and Mayo Clinic, Rochester, Minnesota, for patient accrual; and the University of Cincinnati for data management and analysis of the trial data. The goal was to conduct a randomized trial to determine the benefit of adding sputum cytological evaluation to regular chest X-ray for the early detection of lung cancer. The prospects for success with the combined chest X-ray and sputum cytology approach was further improved by reports of improved lung cancer outcomes with refinement of the thoracic surgery approach.[13]

Unfortunately, the outcome of the NCI-sponsored randomized trial evaluating for mortality benefit of lung cancer screening with chest X-ray and sputum cytology compared to best practice did not demonstrate a statistically significant mortality reduction.[12] This result has been extensively reanalyzed but a clear consensus emerged that the combination of chest X-ray and sputum cytology did not result in a meaningful improvement in lung cancer outcomes.[14] Despite objective improvement in survival, the critical requirement of definitively reducing lung cancer mortality in a randomized trial was not achieved.[15] This was a challenging trial result. However, emerging from that negative screening trial experience was a clearer picture of the performance requirements of a successful early detection tool.

It was now recognized that it was necessary for an effective lung cancer screening tool to advance the diagnosis of lung cancer within a screening trial, to a time prior to metastatic dissemination in order to avoid the influence of lead time and length biases (earlier awareness of still lethal cancer and overestimation of survival duration related to accretion of more indolent cancers, respectively). These biases result in a non-significant screening trial outcome when more "earlier" cancer cases are detected but those cancer cases are not detected "early" enough to be actual "curative" cases of early lung cancer. Therefore, the gold standard of objectively demonstrating a successful screening tool is by significantly reducing lung cancer-related mortality.[16] This dynamic underscored the need for a meaningful early lung cancer detection tool to actually routinely detect highly curable, Stage I lung cancer cases.

The disappointing result of combined chest X-ray and sputum lung cancer screening detection trial would stand for the next fifteen years, despite extensive lung cancer research. Fortunately, the results of an NCI-supported R01 grant were reported in 1999 by Claudia Henschke and her study team using a low- dose thoracic computed tomography scanning integrated with a defined management work-up approach. This approach did improve the detection rate of Stage I lung cancers.[17] This seminal study, published in *Lancet,* involved parallel analysis of a smoking cohort of 1,000 screening subjects using both chest X-ray and low-dose CT in each study participant. This dual evaluation revealed that lung cancer was detected in 27 cases by CT compared to only 7 cases of malignancy detected by chest X-ray. The CT-detected lung cancers were found to be clinically Stage 1 in 85% of the positive cases.[17]

This report ultimately led to the initiation of the National Cancer Institute, National Lung Screening Trial, as well as the Dutch/Belgian NELSON trial to validate this important finding, as will be discussed later in this chapter.[18,19] An underappreciated factor in the success of chest CT compared to chest X-ray screening is the rapid improvement of CT technology over the last 25 years, allowing for much improved detection of smaller primary lung cancers. In Figure 1A, the graph shows a rapid

evolution from large slice thickness, from 10 mm to under 2 mm over the period from 1996 to 2001, which was just a year before the start of the National Lung Screening Trial. The National Lung Screening Trial used multi-detector scanners (usually with 4 detectors) that were able to acquire 1.0 to 2.5 mm slice thickness. As shown in Figure 1A, the thinner slice images, usually at 2.0 mm as indicated by the dotted line, allowed for improved visualization and measurement of more subtle abnormalities with nodule detection compared to chest X-ray.[20]

The 3D resolution performance of CT scanners in characterizing small lung nodules continues to improve as shown in Figure 1B. The data in Figure 1B is derived from quality control data acquired from CT scanners used in chest imaging from a number of global screening sites over the time interval from the completion of the NLST to 2024.[21] In parallel, with the trend for using finer slice thickness and related measures to optimize nodule detection resolution, corresponding improvements in computer capabilities has vastly improved rapid and economical image analysis and image storage capabilities.

The combined contributions of these technical innovations have profoundly improved the performance and scalability of global lung cancer screening implementation. In addition, the routine ability of chest CT scans to acquire detailed anatomic data has set the stage for more robust analyses with Artificial Intelligence and other innovations to sustain remarkable progress in advancing the detection and care of early thoracic disease consistent with the mission of the International Association of Lung Cancer in reducing the mortality burden of lung cancer.

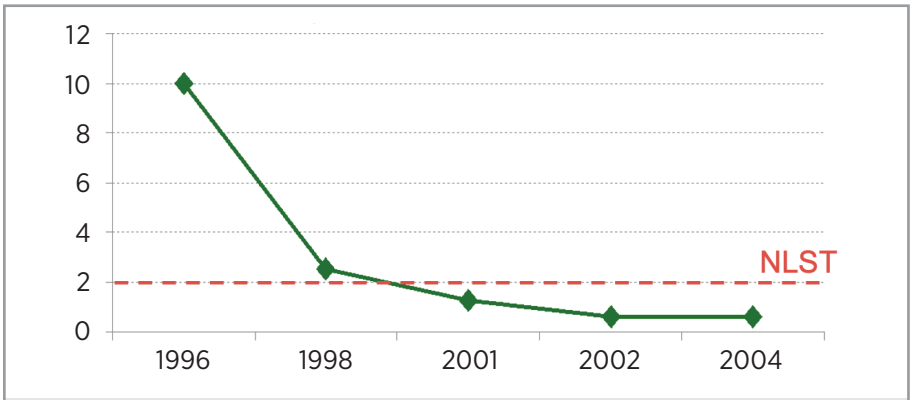


Figure 1A. Width of Chest CT slice thickness (in millimeters) over the interval from 1996-2004. Courtesy of Riccardo S. Avila, Accumetra, LLC.

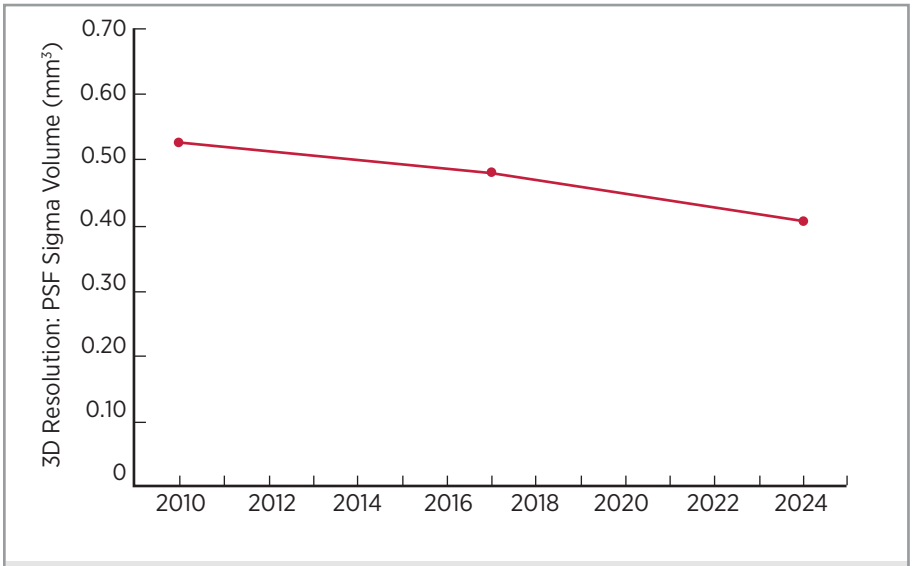


Figure 1B. Aggregate analysis of CT scanners used for nodule assessment for lung cancer screening from 2010 to 2024. Resolution is measured in 3D and expressed as the point-spread function volume with lower values indicating improved 3D resolution. Courtesy of Ricardo S. Avila, Accumetra, LLC.

THE AMERICAN AND CANADIAN SCREENING EXPERIENCE USING LOW DOSE COMPUTED TOMOGRAPHY

Early Trials of CXR Screening for Lung Cancer

Reasoning that lung cancer survival is more favorable with early stage diagnosis, four randomized trials of lung cancer

screening with chest radiography (CXR) were conducted in the United States and Europe[22-25] during 1960-1980, to determine whether screening could improve outcomes. Each trial used various combinations and frequencies of CXR and sputum cytology to screen high-risk individuals. Perhaps the most widely known of these is the Mayo Lung Project, which randomized 9,211 male smokers, 45 years or older, who were initially determined to be cancer free by baseline screening. The intervention arm received intensive screening by CXR and sputum cytology every four months for 6 years.[22] The participants assigned to the control arm received no trial-related screening, but were advised to receive annual CXR and sputum cytology. At trial's end in 1983, there were increased numbers of early stage lung cancers and longer survival in participants in the intervention arm. However, the numbers of advanced stage lung cancers and lung cancer mortality rates were the same in the screening and control arms, indicating that there was no favorable stage shift to earlier stage cancers with CXR screening. Extended follow-up of the participants through 1996 also showed no mortality benefit from screening.

Some critics have ascribed the lack of mortality benefit in these early CXR trials to low sample sizes insufficient to detect small benefits with CXR screening, as well as contamination due to participants in the control arm who received CXR or sputum screening outside of the trial. A critical caveat is that improved survival is insufficient evidence of the benefit of screening interventions.[26] Lead time in diagnosis can improve the length or survival (time between diagnosis and death) independent of improving longevity (delaying the time of death). For this reason, as well as other well-known biases associated with observational studies, the benefits of screening require the observation of improved mortality, specifically in the context of a randomized trial with a contemporaneous control arm.

Lingering ambiguity over whether there might be a benefit to CXR screening provided the impetus to include lung cancer screening in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial sponsored by the National Cancer Institute. Initiated in 1993, the PLCO trial enrolled 77,464 men and women aged 55-74 years, across the United States, and randomized them to receive screening with a baseline and three annual CXR screens in the intervention arm and no screening in the control arm.[27] After follow-up for a median of nearly 12 years, there was no significant difference in mortality rates between the CXR-screened and non-screened arms. A subset analysis performed in 30,321 older, heavy smokers in the PLCO also showed no mortality benefit. The PLCO trial has reinforced the observation that CXR screening provides no significant decrease in death rates from lung cancer in individuals at high risk.[28]

EARLY CONSIDERATIONS OF LOW DOSE CT IN THE UNITED STATES

Interest in the use of low dose computed tomography (LDCT) as a potential screening tool for early lung cancer detection increased in the United States following the publication of early results from a Japanese study in 1996 in which LDCT was compared with CXR in 1369 individuals.[29] Kaneko and colleagues found an increase in the detection rate of lung cancer to 0.43% with LDCT versus 0.12% with CXR; 93% (14 of 15 lung cancers) detected with LDCT were stage I. The encouraging results of this study showed the potential sensitivity LDCT for early detection and led to the planning and initiation of observational studies as well as clinical trials in the United States and Canada. This review highlights only the larger clinical studies on lung cancer screening in North America. The Early Lung Cancer Action Program (ELCAP) was the largest such study, had a single arm design, and served to inspire later, larger randomized controlled trials on the use of LDCT for lung cancer detection.[30]

THE EARLY LUNG CANCER ACTION PROJECT

The ELCAP study involved a cohort of 1,000 asymptomatic individuals who were 60 or younger and who had no

history of cancer (other than non-melanoma skin cancer), had a minimum 10-pack-year smoking history and were surgically resectable in the event of a lung cancer diagnosis. All participants received both helical CT scans and posteroanterior chest radiographs (CXR) at baseline screen.[30,31] Helical LDCT scans were acquired at 140 kVp and 40 mA with 10 mm slice thickness at 5 mm overlapping increments with a medium sharp (bone) reconstruction kernel.

Management recommendations were developed trial-wide, but were not required per protocol so long as a diagnosis was established. Recommendations were based on nodule size, but always involved an initial standard-dose, high-resolution CT (HRCT) scan of 1 mm slice thickness for the evaluation of any nodules seen on screening exams. For persistent indeterminate nodules lacking a benign appearance (benign calcifications) on HRCT, management recommendations were based on nodule size and included follow-up HRCT at regular intervals and/or histologic sampling using percutaneous, bronchoscopic or video-assisted thoracoscopic approaches.[30,31]

Comparing baseline LDCT scans to CXR, indeterminate lung nodules were observed in 23% (N = 233) and 7% (N = 68) of participants, respectively.[30,31] On LDCT, solitary nodules were observed in 68% of participants with positive screens, while the remainder had multiple (2-6) nodules. Malignancies were four-fold more commonly diagnosed on LDCT (2.7% vs. 0.7%). Of 27 CT-detected lung cancers, 96% (26/27) were resectable, 85% (23/27) were stage I, and 19 (83%) were not visible on CXR.

Incidence screens were acquired in 841 participants (84%) within 6-18 months following baseline screens; 461 (46%) underwent subsequent incidence screens, with roughly 75% of second incidence occurring within 6-18 months of the prior screen.[32] A positive incidence screen was defined as a newly detected lung nodule or one that exhibited interval growth. All positive screens underwent initial diagnostic dose HRCT. The subsequent management of nodules that did not completely resolve were based on size criteria and included repeat HRCT at regular intervals for the smallest nodules or histologic sampling for nodules that showed interval growth, had a subsolid consistency that developed solid components, or grew in size. Among a total of 1,184 incidence screens, new indeterminate nodules were ultimately observed in 30 patients on LDCT screening. Among 30 patients, two patients died of cardiac disease unrelated to the lung nodule prior to further work-up, and in 12 cases the nodules resolved. Of the remaining 16 indeterminate nodules, 8 patients underwent biopsy to establish a diagnosis of lung cancer in seven. There were 2 interval endobronchial cancers, meaning symptom-based cancers diagnosed after a negative baseline screen and prior to an annual incidence screen.[32]

In a later ELCAP publication involving a larger cohort of 10,056 participants, differences between baseline and incidence screen-detected lung cancers were described.[33] Eligibility criteria were the same as in the original ELCAP study, although a subset of individuals had a minimum age of 40 years with any history of personal smoking, passive smoking exposure, or a family history of lung cancer who could undergo curative surgical resection. A total of 250 individuals had screen-detected lung cancer, 202 from baseline screens and 48 from annual incidence screens. Five symptom-based interval cancers diagnosed prior to incidence screening were excluded from analyses.

Of baseline screen-detected cancers, 76% (N = 153) were adenocarcinomas, including 9 cases of adenocarcinoma in situ (AIS). Nine percent (N = 19) were squamous cell histology, and 12% (N = 24) were of neuroendocrine origin, including 7 typical carcinoid tumors, 9 small cell lung cancers, 6 large cell neuroendocrine tumors, and 2 atypical carcinoid tumors. In contrast, among annual incidence screens, 50% (N = 24) were adenocarcinoma (with only 1 adenocarcinoma in situ), 15% (N = 7) were of squamous histology, and 31% (N = 15) were of neuroendocrine histology, including 1 atypical carcinoid, 10 small cell lung cancers, and 4 large cell neuroendocrine tumors.

Baseline screens had higher proportions of adenocarcinoma, AIS, and typical carcinoids, which are slower growing than squamous cell lung carcinomas. At incidence screens, the shift towards squamous and poorly differentiated neuroendocrine tumors suggests that incidence cancers are more rapidly growing. Nodules of subsolid CT consistency were more common in baseline screens, whereas lung cancers on incidence screens were smaller in diameter, more commonly solid consistency, and invasive.

With their first publication in 1999, the ELCAP investigators ignited interest in the potential of LDCT screening and served to stimulate North American investigators to pursue randomized trials that could confirm and quantify the mortality benefits of LDCT screening.

THE ORIGINS OF THE NATIONAL LUNG SCREENING TRIAL

In 1998, the National Cancer Institute (NCI) invited applications for a new program focused on oncologic imaging, which was awarded to the American College of Radiology Imaging Network (ACRIN). Among the protocols submitted as part of the application was a small randomized trial comparing annual LDCT screening to no screening. Although not powered to address a mortality difference, the trial was designed to show proof of concept while measuring differential quality of life between the two arms; establish a biospecimen archive that could be used to validate molecular markers of lung cancer; and analyze the cost effectiveness of LDCT screening from a societal perspective.

In parallel with the ACRIN trial proposal, six screening sites associated with the ongoing PLCO trial initiated a study called the Lung Screening Study (LSS).[34] Intended to show feasibility, the LSS accrued 3,000 individuals at high risk of lung cancer and convincingly showed that such individuals would agree to be randomized to receive LDCT or CXR. The LSS investigators proposed a larger randomized trial that would enroll additional subjects with the aim of assessing for mortality reduction with LDCT screening.

NLST STUDY DESIGN AND PARTICIPANT CHARACTERISTICS

The ACRIN and LSS trial concepts were independently presented to the Board of Scientific Advisors of the National Cancer Institute and ultimately merged to form a single trial, named the National Lung Screening Trial (NLST), in which 50,000 high risk individuals would be randomized to either LDCT or CXR screening for three annuals screens, with follow-up for an average of 6.5 years (maximum follow-up of 7.4 years). The trial involved 23 ACRIN sites and 10 LSS sites. Trial procedures, image acquisition protocols for LDCT, interpretation guidelines, and data elements were harmonized between the ACRIN grant and LSS contract.

For the comparator arm to the LDCT screening arm, posteroanterior CXR rather than no screen was chosen for several reasons. Foremost, the ongoing PLCO trial was comparing CXR screening with usual care during the design phase of the NLST. The NLST investigators reasoned that if the PLCO trial was to show a lung cancer-specific mortality reduction with CXR, then CXR screening would become the new standard of care against which LDCT should be compared. Secondly, although no lung cancer screening test was officially endorsed in the US, some primary and subspecialty care providers performed periodic CXR on their heavy smokers as an unofficial screening test; individuals who received CXR as part of their customary preventive health care could result in contamination in the control arm and mask mortality benefits. Finally, given considerable press coverage of LDCT screening in the US and aggressive advertising by several entrepreneurial medical facilities nationwide, it could have been challenging to communicate equipoise between LDCT and usual care (non-screening) arms.

The primary endpoint of the NLST was differential lung cancer mortality reduction with LDCT.[35,36] Several secondary endpoints included lung cancer incidence, stage distribution, screening performance, treatment-related morbidities, and all-cause mortality.

The ACRIN investigators retained several secondary aims: to assess associations between COPD and lung cancer, establish a biospecimen repository for future validation of potential molecular markers of early lung cancer, compare quality of life between the two arms, and measure the cost-effectiveness of screening.

The NLST eligibility criteria were designed to include those at highest risk of lung cancer based on age and smoking history who would tolerate surgical resection of the lung. Criteria included: asymptomatic individuals aged 55 to 74 years who were current or former smokers of ≥ 30 pack-years. Former smokers must have quit within the preceding 15 years. Individuals who had a prior diagnosis of lung cancer, had undergone chest CT within 18 months of enrollment, or who had unexplained hemoptysis or weight loss ≥15 lb. (6.8 kg) were excluded. Targeted recruitment of underrepresented minorities was implemented at specific sites based on regional demographic data and site-specific strategies.[37]

Low dose CT screens were performed on scanners certified for use in the NLST by a medical physics oversight committee. NLST scans had to meet protocol requirements, which included 18 imaging parameters on 14 scanner platforms from four manufacturers.[38] Maximum reconstructed slice thickness was 2.5 mm (preferably 1 -1.25 mm slice thickness); low dose technique based on CT dose index volume (CTDIvol) of 2-3 mGy, and a smooth reconstruction algorithm. Similarly, standards were established for the performance of CXR.[38]

Screening exams were performed annually for a total of three annual screens per participant; participants with the diagnosis of lung cancer were removed from active screening and followed institutional algorithms for imaging assessment and lung cancer treatment. Adherence to the screening protocol across three rounds was 95% in the LDCT arm and 93% in the CXR arm.

Participants completed detailed demographic and medical history questionnaires at baseline. At semiannual (ACRIN) or annual (LSS) intervals, participant vital status and interval cancer diagnoses were recorded. Death certificates were obtained for participants known to have died; the names and social security numbers of participants lost to follow-up were submitted to the National Death Index to ascertain probable vital status. Deaths due to lung cancer or following diagnostic or treatment interventions in lung cancer patients were included as lung cancer deaths in the primary endpoint analysis.

The results of screening LDCT and CXR exams were reported by trained radiology investigators for both trial arms. All downstream diagnostic tests, results, and complications were obtained from medical records by certified medical abstractors.

Enrollment for the NLST began September 2002 and was completed in April 2004, 4 months in advance of the target completion date.[35] In total, 53,456 participants were enrolled and equally randomized to the LDCT or CXR arm. Of all participants, 34,614 (65%) were accrued by the LSS and 18,842 (35%) from ACRIN sites.[39] Comparison of the ACRIN and LSS study cohorts showed that the two groups were similar with respect to demographics: 13630 (72%) or ACRIN participants were < 65 years of age vs. 25,604 (74%) of LSS participants; 8440 (45%) of ACRIN and 12483 (39%) of LSS subjects were women; and 9514 (50%) of ACRIN and 16,265 (47%) of LSS participants were current smokers. Randomization was stratified by sex and 5-year age group, ensuring virtually identical numbers for these variables across study arms.[39]

The characteristics of the NLST population were compared with the overall NLST-eligible US population as measured with the Tobacco Use Supplement (TUS) of the US Census Bureau Current Population Surveys.[38] In both populations, 59% were men; however, the NLST participants were younger, fewer were current smokers, and more than twice as many had a college degree or higher (Table 1).

SCREENING RESULTS AND TEST PERFORMANCE

Screen positivity on LDCT screening was defined as a nodule ≥ 4 mm of any consistency.

Table 1. Demographic Features of the NLST Cohort Relative to the NLST-Eligible US Population[1]

Characteristic	LDCT Arm	CXR Arm	Tobacco Use Supplement[1]
Male (%)	15770 (59.0%)	15,763 (59.0%)	58.5%
Smoking History			
Median pack-years	48.0	48.0	47.0
Former smoker (%)	13,853 (51.8%)	13,823 (51.7%)	42.9%
Age group (%)			
55-59 yrs.	11,440 (42.8%)	11,421 (42.7%)	35.2%
60-64 yrs.	8170 (30.6%)	8198 (30.7%)	29.3%
65-69 yrs.	4756 (17.8%)	4762 (17.8%)	20.8%
70-74 yrs.	2352 (8.8%)	2345 (8.8%)	14.7%
Race | Ethnicity %			
White	24,289 (90.9%)	24,260 (90.7%)	
Black or African American	1196 (4.5%)	1182 (4.4%)	5.5%
Hispanic or Latino	479 (1.8%)	456 (1.7%)	2.4%
Education Status			
Less than high school	1642 (6.2%)	1610 (6.1%)	21.3%
College degree or higher	8433 (31.6%)	8406 (31.4%)	14.4%

Abbreviations: LDCT = low-dose CT; CXR = Chest x-ray
[1]Estimates were derived from the Tobacco Use Supplement of the US Census Bureau Current Population survey for the years of NLST enrollment, restricting the survey population to those respondents who met the NLST criteria of age and smoking eligibility.

Diagnostic algorithms were incorporated into the ACRIN NLST protocol, but institutions were allowed to follow local practices.[40] Nodules 4-10 mm diameter of any consistency were recommended to undergo repeat LDCT surveillance imaging at 3-6 months, depending upon the nodule size and level of suspicion of the radiologist. Stable nodules could be reassessed at 12 and 24 months from the positive screen to confirm stability or resolution; growing nodules < 7 mm underwent repeat 3-month LDCT surveillance. Nodules > 10 mm, enlarging nodules ≥ 7 mm, or subsolid nodules exhibiting changes in consistency to solid components were recommended for early repeat surveillance LDCT, F18-fluorodeoxyglucose positron emission tomography (FDG-PET), or histologic sampling. Positive CXR screens were defined as any visible lung nodule. Diagnostic pathways for CXR-detected nodules depended upon nodule size and included repeat CXR with special views, LDCT, PET-CT, or biopsy.

The rate of screen positivity was 24.2% with LDCT and 6.9% with CXR across all screens. In both arms, screen positivity dropped on the third and final screen to 16.8% and 1.5%, respectively, because the NLST protocol allowed stable nodules to be categorized as negative. Positive screens were observed at some point in 39.1% of participants in the LDCT arm and in 16.0% of those in the CXR arm.

In the LDCT screening arm, sensitivity at T0 was 93.8%, specificity was 73.4%, positive predictive value (PPV) was 3.8% (increasing to 52.9% for a positive screen that led to a biopsy procedure), and negative predictive value (NPV) was 99.9%.[41] At the T1 and T2 incidence screens, sensitivity was 94.4% and 93.0%, specificity was 72.6% and 83.9%, PPV was 2.4% and 5.2%, and the NPV was 99.9% and 99.9%, respectively.[42]

In the CXR arm, sensitivity at T0 was 73.5%, specificity was 91.3%, PPV was 5.7% (increasing to 70.2% for a positive screen that led to a biopsy procedure), and NPV was 99.8%.[41] At the T1 and T2 incidence screens, sensitivity was 59.6% and 63.9%, specificity was 94.1% and 95.3%, PPV was 4.4% and 6.7%, and NPV was 99.8% and 99.8%, respectively.[42]

LUNG CANCER DIAGNOSES–STAGE DISTRIBUTION–CANCER HISTOLOGY IN THE NLST

There were 1,060 lung cancers (645 per 100,000 person-years) diagnosed in the LDCT arm (Table 2), of which 649 (61.2%) were screen-detected (35). Forty-four lung cancers (4.2%) were diagnosed following a negative screen (interval cancers) and 367 (34.6%) were diagnosed absent any screening, most occurring

Table 2. Lung Cancers Diagnosed in the NLST by Screen Result and Time Period

Screen Result and Time Period	CT Arm (%)	CXR Arm (%)
Screen-detected lung cancers T0-T2	649 (61.2%)	279 (29.6%)
Interval lung cancers T0-T2 (Screen negative)[1]	44 (4.2%)	137 (14.6%)
NO screen cancers[2]	367 (34.6%)	525 (55.8%)
Total lung cancers in screening arm	1060 (100.0%)	941 (100%)

[1]Interval cancers refer to lung cancer diagnoses following a negative screen.
[2]Lung cancers in the NO screen arm included 802 lung cancers diagnosed in the post-screening period (90%), 35 diagnosed in participants who were never screened (4%) and 55 lung cancers in those due for screening (6%).

during the post-screening phase of observation. In contrast, of 941 lung cancers (572 per 100,000-person years) observed in the CXR arm, 279 (29.6%) were screen-detected, 525 (55.8%) occurred during the post-screening phase of observation, and 137 (14.6%) were interval cancers following a negative screen.

In the LDCT arm (Figure 2), 1,040 (of 1,060 total) lung cancers were of known stage based on the sixth edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer.[43] Of 1,040 lung cancers of known stage, 635 were LDCT screen-detected and 520 (50.0%) were stage I. Among the LDCT-detected lung cancers, 400 of 635 (63.0%) were stage I. Advanced stage (stage III, IV) accounted for 447 (43.0%) lung cancers in the LDCT arm; interval cancers following a negative screen were diagnosed in 44 (4.2%). In the LDCT arm, the increase in early-stage cancers was associated with a decrease in late-stage cancers, resulting in a favorable stage shift.

In contrast, in the CXR arm (Figure 2), 929 lung cancers of known stage were diagnosed. Of these, 275 were detected by CXR screening and 289 (31.1%) were stage I; 131 of 275 (47.6%) CXR-detected cancers were stage I. In the CXR arm, 566 (60.9%) of all cancers were stage III-IV and 135 (14.5%) were interval cancers following a negative CXR screen.

The most common histologic cell type of lung cancer was adenocarcinoma, observed in 490 (46.8%) of 1,048 LDCT screenees and 363 (39%) of 931 CXR screenees.[35] This included bronchoalveolar cell carcinoma, seen in 110 (10.5%) of LDCT screenees and 35 (3.8%) of CXR screenees. Bronchoalveolar cell carcinoma, a term no longer used, included adenocarcinoma in situ; minimally invasive adenocarcinoma; and invasive lepidic adenocarcinoma, which are now classified separately. Few bronchoalveolar cell carcinomas were observed in the CXR arm, largely because they are typically subsolid in consistency and not visible on CXR. Squamous cell carcinoma was the second most common histology in both the LDCT and CXR arms, accounting for 23.2% and 22.1% of lung cancers, respectively. Non-small

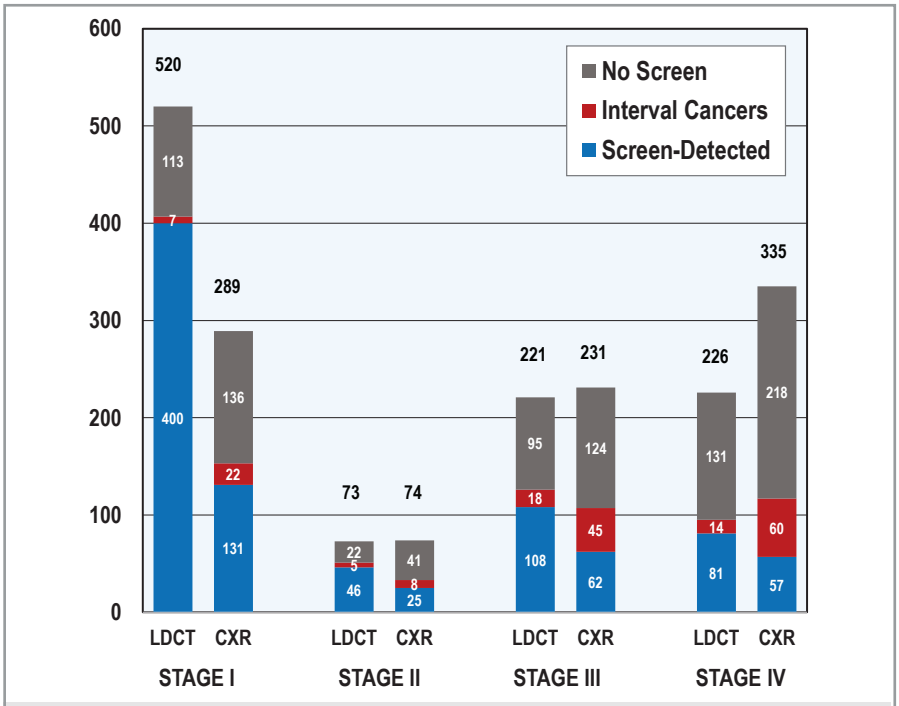


Figure 2. Stage distribution of lung cancers by screening arm and time point. In the LDCT arm, the increase in early stage cancers was associated with a decrease in late stage cancers, resulting in a favorable stage shift. Abbreviations: LDCT = low dose computed tomography, CXR = chest radiography.

cell lung cancer (NSCLC), which included adenosquamous, sarcomatoid, and unclassified/not otherwise specified histologies, was the third most frequent histology, seen in 12.5% and 17.0% of LDCT and CXR arms, respectively. Small cell lung cancer was diagnosed in 13.1% and 17.1% of LDCT and CXR arms, respectively.

DIAGNOSTIC EVALUATION AND ADVERSE EVENTS IN POSITIVE SCREENS

At the baseline screen, more than 90% of positive LDCT screens led to some form of diagnostic evaluation; lower rates of follow-up were seen on later rounds.[35] The most common diagnostic evaluation was further imaging, of which early repeat CT was most common (Table 3). Invasive procedures were uncommon in both arms at all screening time points. Of these, surgical interventions were most common (4.0%). Thoracotomy accounted for the most common surgical intervention (2.9%), likely because thoracoscopic procedures were only becoming mainstream during the time of the NLST.

Complications following diagnostic procedures were categorized as major, intermediate, and minor.[35] Events occurring within 60 days of an invasive procedure, or of a screening exam if no invasive procedures were performed, were included based on the timing of the complication independent of whether it was considered definitely or likely related to an intervention. Representative major complications included cardiopulmonary arrest, myocardial infarction, stroke, death, or surgical complications such as empyema, wound dehiscence, bronchopulmonary fistula, and chylous effusion. Intermediate complications included cardiac arrhythmia requiring intervention, sepsis, fever or infection requiring antibiotics, transfusion requirement, or pneumothorax requiring tube placement. Minor complications included atelectasis, pneumothorax without chest tube, bronchospasm, allergic reaction, or vasovagal reaction.

Adverse events from the screening examinations themselves were very few and minor.[35] The rate of at least one type of complication was 1.4% in the LDCT arm and 1.6% in the CXR arm. In the LDCT arm, major complications in individuals with lung cancer were observed in 75 (11.6%) of 649 patients and in 12 (< 0.01%) of 17,053 individuals without lung cancer. Deaths occurred in 10 (1.5%) of 649 LDCT

Table 3. Diagnostic Follow-up of Positive Screens in the Three Screening Rounds of the NLST

Variable	Low Dose CT				Chest Radiography			
	T0	T1	T2	Total	T0	T1	T2	Total
Total positive tests	7191 (100%)	6901 (100%)	4054 (100%)	18,146 (100%)	2387 (100%)	1482 (100%)	1174 (100%)	5043 (100%)
Confirmed lung cancer	270 (3.8%)	168 (2.4%)	211 (5.2%)	649 (3.6%)	136 (5.7%)	65 (4.4%)	78 (6.6%)	279 (5.5%)
Any diagnostic follow-up	6369 (90.4%)	3866 (57.4%)	2522 (64.5%)	12,757 (72.1%)	2176 (92.7%)	1078 (74.0%)	957 (83.3%)	4211 (85.0%)
Clinical procedure	5089 (72.2%)	3190 (47.3%)	2151 (55.0%)	10,430 (58.9%)	1414 (60.2%)	723 (49.7%)	658 (57.3%)	2795 (56.4%)
Imaging examination	5717 (81.1%)	2520 (37.4%)	2009 (51.3%)	10,246 (57.9%)	2010 (85.6%)	968 (66.5%)	906 (78.9%)	3884 (78.4%)
Chest radiography	1284 (18.2%)	613 (9.1%)	650 (16.6%)	2547 (14.4%)	867 (36.9%)	381 (26.2%)	365 (31.8%)	1613 (32.6%)
Chest CT	5153 (73.1%)	2046 (30.4%)	1608 (41.1%)	8807 (49.8%)	546 (65.8%)	745 (51.2%)	712 (62.0%)	3003 (60.6%)
FDG-PET ± CT	728 (10.3%)	350 (5.2%)	393 (10.0%)	1471 (8.3%)	179 (7.6%)	105 (7.2%)	113 (9.8%)	397 (8.0%)
Percutaneous Sampling	155 (2.2%)	74 (1.1%)	93 (2.4%)	322 (1.8%)	83 (3.5%)	37 (2.5%)	52 (4.5%)	172 (3.5%)
Bronchoscopy ± Sampling	306 (4.3%)	178 (2.6%)	187 (4.8%)	671 (3.8%)	107 (4.6%)	56 (3.8%)	62 (5.4%)	225 (4.5%)
Surgical procedure	297 (4.2%)	197 (2.9%)	219 (5.6%)	713 (4.0%)	121 (5.2%)	51 (3.5%)	67 (5.8%)	239 (4.8%)
Mediastinoscopy	60 (0.9%)	32 (0.5%)	25 (0.6%)	117 (0.7%)	22 (0.9%)	12 (0.8%)	21 (1.8%)	55 (1.1%)
Thoracoscopy	82 (1.2%)	56 (0.8%)	96 (2.5%)	234 (1.3%)	22 (0.9%)	11 (0.8%)	20 (1.7%)	53 (1.1%)
Thoracotomy	197 (2.8%)	148 (2.2%)	164 (4.2%)	509 (2.9%)	96 (4.1%)	44 (3.0%)	44 (3.8%)	184 (3.7%)
Other procedures	168 (2.4%)	96 (1.4%)	63 (1.6%)	327 (1.8%)	55 (2.3%)	33 (2.3%)	34 (3.0%)	122 (2.5%)

Abbreviations: T0 = Baseline screen, T1 = First incidence screen performed at 12 months from baseline screen, T2 = Final incidence screen performed at 24 months from baseline screen, CT = computed tomography, FDG-PET = F18-fluorodeoxyglucose positron emission tomography. Sampling refers to either cytology or tissue biopsy. NOTE: Percentages of diagnostic procedures performed at any screening timepoint do not sum to 100% because more than one procedure could be performed on a participant following a positive screen.

arm participants with lung cancer and 11 (< 0.01%) without lung cancer; of those without lung cancer, 5 deaths were reported in LDCT arm participants who underwent no invasive procedures. In the CXR arm, major complications were reported in 24 (8.6%) of 279 participants with lung cancer and 4 (<0.01%) of 4,674 participants without lung cancer; deaths were reported in 11 (3.9%) of CXR arm participants with lung cancer and in 3 (< 0.01%) without lung cancer, the latter being in CXR arm participants who underwent no invasive procedures.

Table 4. Cause of Death According to Screening Group Based on Death Certificates*

Cause of Death	LDCT Arm	CXR Arm	Total
Neoplasm of lung and bronchus	427/1865 (22.9%))	503/1991 (25.3%)	930/3856 (24.1%)
Other neoplasm	416/1865 (22.3%)	442/1991 (22.5%)	858/3856 (22.3%)
Cardiovascular illness	486/1865 (26.1%)	470/1991 (23.6%)	956/3856 (24.8%)
Respiratory illness	175/1865 (9.4%)	226/1991 (11.4%)	401/3856 (10.4%)
Complications of medical or surgical care	12/1865 (0.6%)	7/1991 (0.4%)	19/3856 (0.5%)
Other	349/1865 (18.7%)	343/1991 (17.2%)	692/3856 (17.9%)

*Of 1877 participants in the LDCT arm, cause of death was unknown in 12 participants; of 1988 participants in the CXR arm, cause of death was unknown in 7 participants. Denominators represent deaths for which cause was known. These numbers are not equal to the number of lung cancer deaths in the mortality analysis; the latter included information from all medical sources and review by an end-point verification team. Causes of death were coded using the International Classification of Diseases, 10th Revision (ICD-10).

MORTALITY RATES IN THE NLST

Mortality rates in the NLST were based on data censored through January 2009 to allow thorough review by an end-point verification committee. In the LDCT arm, 356 deaths from lung cancer occurred over 144,103 person-years, resulting in 247 deaths per 100,000 person-years. In the CXR arm, 443 deaths from lung cancer occurred over 143,368 person-years, resulting in 309 deaths per 100,000 person-years. There was a relative reduction in the rate of death from lung cancer in the LDCT arm of 20.0% (95% CI, 6.8 to 26.7; P=0.004). The number needed to screen to prevent one death was 320.[35]

Using data from death certificates through December 2009 (Table 4), there were 1,877 deaths from all causes in the LDCT arm and 2,000 deaths in the CXR arm, resulting in a significant reduction in all-cause mortality of 6.7% (95% CI, 1.2 to 13.6; P = 0.02) in the LDCT arm. Lung cancer accounted for 24.1% of all deaths in the NLST; 60.3% of excess deaths in the CXR arm were due to lung cancer. If deaths from lung cancer were excluded, the reduction in all-cause mortality with the use of LDCT was not significant (P = 0.28).[35]

EFFECTS OF SCREENING ON QUALITY OF LIFE

To determine the effects of screening result on health-related quality of life (HRQoL) and anxiety, a subset of 2,812 participants across both arms of the NLST completed the Short Form Health Survey (SF-36),[44] a measure of physical and mental function. The State Trait Anxiety Inventory (STAI Form Y-1) was used to measure state anxiety.[45] Questionnaires were administered at baseline and at 1-month and 6-months following each of the three screening exams to assess both short term effects, after participants knew their screening results, and longer-term effects. Analyses considered four types of screening results: true positive, false positive, negative, and screens with significant other findings unrelated to potential lung cancer. After adjusting for potential confounders, in 62 (2.2%) participants with true positive screens (diagnosed with lung cancer within 12 months of the index screen), both physical and mental HRQoL fell; as well, these participants reported substantially higher levels of anxiety.[46] False positive results were seen in 1,024 (36.4%) participants, significant incidental findings in 344 (12.2%) participants, and negative screens in 1,381 (49.1%) participants. Short-term and long-term HRQoL and state anxiety did not differ across participants with false positive screens, significant other findings, or negative screens. There were

no differences across study arms. Overall, there was no association between global HRQoL and screen results, whether the results were negative, false positive, or identified significant other findings.

COST-EFFECTIVENESS OF LDCT SCREENING IN THE NLST

Given that costs are a major consideration for US health policy decisions regarding LDCT screening for lung cancer, the NLST-ACRIN investigators conducted a cost-effectiveness analysis.[47] Estimates of life-years were based on the number of deaths observed during the trial and the projected survival of persons alive at the end of the trial. The investigators used data on a subset of participants who had completed the SF-36 to derive quality adjustments to life expectancy, as well as more detailed information related to diagnostic procedures and lung cancer treatments. Costs were based on utilization rates and Medicare reimbursements. Total per-person costs were calculated as the sum of direct medical costs and indirect costs based on 2009 US pricing, including time and travel for participants and caregivers. Subgroup analyses were performed based on age, sex, smoking history, and risk of lung cancer; sensitivity analyses involved changes in base case assumptions regarding the effects of LDCT on mortality from causes other than lung cancer, degrees of overdiagnosis, the effectiveness of CXR screening, and both optimistic and pessimistic assumptions about long-term survival of participants with early stage disease.

Relative to no screening, LDCT screening cost an additional $1,631 per person, provided an additional 0.316 life-years per person, and provided 0.0201 quality-adjusted life-years (QALY) per person. The incremental cost-effectiveness ratio was $52,000 per life-year gained and $81,000 per QALY. Discounted per-person costs were much higher in the CT arm, owing largely to the much higher cost of chest CT relative to a CXR ($285 vs. $24). Per-person costs for diagnostic workups and surgery were higher in the LDCT arm, but per-person costs for chemotherapy and radiotherapy were lower. Future medical costs were slightly higher in the LDCT arm because a higher proportion of participants were still alive at the end of the trial. Sensitivity analyses showed that modest changes in base assumptions would greatly affect these calculations, moreover, that the way in which LDCT screening is implemented would ultimately determine whether it is cost-effective outside of a clinical trial.

ASSOCIATIONS BETWEEN COPD AND LUNG CANCER

Secondary analyses by NLST-ACRIN investigators of associations between airflow obstruction and lung cancer were completed using results of baseline spirometry performed on all ACRIN participants in both arms. Pre-bronchodilator airflow limitation was sub-grouped according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades.[48] Consistent with previous observations, screening participants with spirometric COPD had a two-fold increase in lung cancer incidence (incident rate ratio, 2.15; P<0.001) relative to those with no airflow limitation.[49] Moreover, incidence rates of lung cancer increased linearly with increasing airflow obstruction (effect size=0.34, P<0.0001).[50,51] The risk of dying from lung cancer also increased with more severe airflow limitation (effect size=0.35, P< 0.0001). Among those with COPD, there were no "excess" early stage lung cancers, as defined by the adenocarcinoma spectrum of in situ, minimally invasive, or invasive, lepidic predominant histologies; these histologies were largely observed in individuals without airflow limitation.[49] Relative to participants with no COPD, adenocarcinomas overall were fewer and surgical resection rates were lower in those with COPD, despite comparable staging. For those with severe or very severe airflow limitation (GOLD 3-4), there was no apparent favorable stage shift or reduction in lung cancer mortality, suggesting potentially limited benefit of screening in individuals with severe COPD. These observations warrant further research.

BIOREPOSITORY

A central interest of the NLST ACRIN investigators was the creation of a biorepository that could be used to develop biomarkers to determine high-risk cohorts, distinguish benign from malignant lung nodules detected on LDCT screening, and validate biomarker candidates predictive or prognostic of tumor behavior.[52] Biospecimens were collected on approximately 10,300 NLST-ACRIN participants at each of three screening time points. The biorepository consists of > 100,000 samples each of buffy coat and plasma, 54,000 urine samples, and 37,000 sputum cell pellet specimens. In addition, paraffin-embedded tissues from roughly 204 participants who underwent surgical resection for lung cancer were requested for the creation of tissue microarrays. The biospecimens are archived at the ECOG-ACRIN Central Biorepository and Pathology Facility at the University of Texas MD Anderson Cancer Center. Biospecimens can be requested through an application process that undergoes scientific review.

IMPLICATIONS OF THE NLST FINDINGS

The NLST was the first randomized trial to show a 20% lung cancer-specific mortality reduction with LDCT. The LDCT arm had a greater than three-fold increase in positive screens, most of which were false positive. With LDCT, the false positivity rate at T0 baseline screen was 26.6%, dropping to 16.1% at the third (T2) screen; the false discovery rate was 96% at T0 and 95% at T2. Using the knowledge gained from the NLST, contemporary US practice, based on the ACR Lung-RADS Version 2.0 guideline[53] now scores solid or part-solid nodules < 6 mm and ground glass nodules < 30 mm diameter as negative (with recommendations to complete annual incidence screens). More detailed recommendations for nodules above these thresholds and for nodules at incidence screens are provided. These modifications to screening interpretation have substantially reduced overall positivity rates, false positivity rates, and downstream procedures with LDCT screening. In the NLST, complications from invasive diagnostic procedures were uncommon, and deaths or severe complications were rare, particularly among participants without lung cancer.

The NLST participants differ in some ways from the eligible US population in that they were younger, better educated, more often former smokers, and whites were disproportionately represented; the NLST findings may have been affected by a "healthy volunteer" effect. A high proportion of participating sites were academic centers with subspecialty expertise in screening and its management, which may not represent community practice. Although surgical mortality in the NLST was lower than in the general US population (1% vs. 4%), thoracotomy was performed as the most common surgical procedure; less invasive thoracoscopic resections are increasingly the norm, which should reduce mortality in current practice. There have been concerns that CT, even LDCT, will increase the risk of radiation-induced cancers. Although this was not measurable in the NLST, contemporary scanners are capable of adequately imaging the chest at lower radiation doses and the benefit to risk ratio with screening is high. Overdiagnosis remains a concern, particularly for the lesions classified histologically as bronchoalveolar cell carcinoma. Although overdiagnosis cannot be directly measured, the initial rates of overdiagnosis from the NLST were estimated to be 18%,[54] due largely to lung cancers classified as bronchoalveolar cell carcinoma, which has since been subdivided into more granular histologies. That said, an extended analysis (11.3 – 12.3 years) of the NLST estimated overdiagnosis to be 3%.[55] This is not surprising given that rates of overdiagnosis are highly sensitive to the post-screening follow-up time. Finally, the NLST provided for only three annual screens; the effects of continuous screening may well influence differential mortality rates.

PAN-CANADIAN EARLY DETECTION OF LUNG CANCER PROJECT (PANCAN)

In 2008, The Pan-Canadian Early Detection of Lung Cancer Project (PanCan) established a Pan-Canadian single arm prospective

study designed to combine risk modeling, autofluorescence bronchoscopy, and serum biomarkers with LDCT screening for early lung cancer detection.[56] The study premise was that the inclusion of low-cost risk modeling and biomarkers to select population cohorts at highest risk of lung cancer could provide a cost-effective application of relatively expensive, yet effective detection methods. Their focus was on detection rates and costs, comparing their results with randomized trials in the US and Europe to establish a knowledge base for lung cancer screening in Canada.

There were three study objectives: 1) To develop a multi-modal screening strategy and integrated methods to detect early lung cancer such that screening could become affordable within the Canadian health care system; 2) To evaluate the impact of screening on quality of life of participants in the screening study; and 3) To develop a decision analytic framework for determining costs and effectiveness of lung cancer screening, leveraging the results of international randomized trials. The primary outcome of the study was lung cancer incidence; the secondary outcome was stage distribution compared to the NLST and Canadian cancer statistics. The study was not designed to provide information on the mortality benefit of lung cancer screening, but was intended to complement large randomized trials in the US and EU that would be released in roughly similar time frames.

THE USE OF RISK PREDICTION MODELING TO IDENTIFY A HIGH-RISK SCREENING COHORT

The PanCan study was among the first to prospectively recruit individuals for lung cancer screening based on an estimated 6-year lung cancer risk ≥ 2%. They used a novel risk assessment model called the PanCan model,[57] which was a precursor to the validated PLCOm2012 model developed in the Prostate Lung Colorectal and Ovarian Cancer Screening Trial (PLCO).[58] The PanCan risk model included eight predictor variables: Age (in ordinal levels 1-4), education level (dichotomous; high school completion or less and beyond high school), family history of lung cancer (no vs. yes), body-mass index (dichotomous; less than 30 kg/m^2 vs. greater), CXR in prior three years (ordinal as 0, 1, and on more than one occasion), smoking duration in years, pack-years smoked, and self-reported history of chronic obstructive pulmonary disease (COPD) (yes vs. no).

Based on the PanCan risk model, 2,537 eligible ever-smokers aged 50-75 years with no self-reported history of lung cancer were enrolled from September 2008 to December 2010 across eight Canadian centers. Participants provided blood specimens and received a LDCT screen at three time points: baseline (T0), 1 year (T1) and 4 years (T4). Low dose CT scans were acquired with ≤1.25 mm slice thickness at contiguous intervals using both intermediate and high frequency reconstruction kernels. Baseline spirometry was performed on all participants. From among the first half of entrants, autofluorescence bronchoscopy was also performed at T0; 1,300 participants underwent both LDCT screening and autofluorescence bronchoscopy. Participants were followed for a median of 5.5 years (interquartile range (IQR) 3.2-6.1); median follow-up after the final T4 screen was 1.9 years (IQR 1.5-2.5 years).

During follow-up, there were 172 lung cancers diagnosed among 164 participants, including 10 interval lung cancers (9 occurring between T1 and T4 screens). Of 137 surgical resections, 16 (12%) were for benign disease. The cumulative incidence of lung cancer in PanCan was 6.5%, significantly higher than that observed in the NLST (4.0%; p<0.0001). Moreover, 133 (77%) of 172 lung cancers were Stage I-II vs. 57% in the NLST. The PanCan model underestimated the observed risk of lung cancer by 30%, yet yielded a higher proportion of participants at high risk of lung cancer than existing studies, establishing the premise that risk-based models outperform rule-based (categorical) models in determining the optimal screening cohorts.

THE ROLE OF AUTOFLUORESCENCE BRONCHOSCOPY

Autofluorescence bronchoscopy (AFB) was offered to the first enrolled PanCan participants at the time of baseline LDCT,

which resulted in endobronchial biopsies in 1,300 (25.6%) participants.[59] Of these, dysplastic or higher-grade lesions were detected in 5.3% of participants (n = 68) and included mild dysplasia (n = 36), moderate dysplasia (n = 25), severe dysplasia (n = 3), carcinoma in situ (n = 1), and carcinoma (n = 4). Only one CIS lesion and one typical carcinoid were detected solely by AFB, yielding an occult cancer rate of 0.15% (95% CI, 0.0%-0.6%), whereas 56 (4.3%) prevalence cancers were observed on LDCT. The lower rate of detection of central cancers in PanCan is likely multifactorial, relating to the shift in prevalence of NSCLC from squamous cell carcinoma to adenocarcinoma, the inclusion of women in PanCan, and the fact that AFB candidates were not selected based on known sputum atypia, COPD, prior or synchronous lung cancers, or aerodigestive cancers. Overall, the low yield of AFB to LDCT screening in a high-risk cohort detected too few CT-occult cancers to merit its incorporation into a lung cancer screening program.[59]

EXPLORATION OF COPD IN A SCREENING COHORT

Emphysema, one of the common causes of COPD, is evaluable on CT; however, COPD is defined by physiologic airflow limitation, which necessitates spirometry to establish the diagnosis.[60] Spirometry was performed at baseline in PanCan participants, which allowed investigators to evaluate the frequency of diagnosed and undiagnosed COPD, as well as to correlate airflow obstruction with CT-defined emphysema. Of 2,514 participants who completed spirometry, 527 (21%) self-reported a prior diagnosis of COPD and 1,987 (79%) did not. Overall, spirometry defined COPD in 1,136 individuals (45.2%); 833 individuals (73%) had no prior diagnosis of COPD, accounting for 41.9% of those with no self-reported prior diagnosis. Conversely, 170 individuals (32.2%) of those who did self-report COPD did not meet spirometric criteria.[61]

The LDCT screening exams were visually scored for the extent of emphysema on a five-point Likert scale from none to severe emphysema. There was a poor relationship between emphysema severity and spirometry-based COPD (Weighted Kappa = 0.16). Using backward selection, a multivariable model to predict spirometry-based COPD included: age, current smoking status, pack-years, dyspnea, wheeze, participation in a high-risk occupation, and emphysema extent on LDCT. The discriminatory ability using c-statistic was 0.627 (95% CI = 0.607 to 0.650); although poorly discriminating, all deciles of predicted risk had a high prevalence of COPD, underscoring the high prevalence of COPD in a lung cancer screening population.[61]

LIQUID ASSAYS FOR LUNG CANCER PREDICTION

Blood specimens obtained in 2,485 individuals at baseline in the PanCan cohort were used to measure pro-surfactant protein B (Pro-SFTPB) as a predictor of lung cancer.[62] Samples were analyzed using pro-SFTPB enzyme-linked immunosorbent assay (ELISA). They found that pro-DFTPB (log-transformed) is significantly and independently associated with lung cancer and adds to prediction beyond that contributed by established risk factors such as age, sex, body mass index, personal history of cancer, family history of lung cancer, forced expiratory volume in one second percent predicted, cigarettes smoked per day, and smoking duration. Pro-SFTPB (log-transformed) had an odds ratio of 2.220 (95% CI, 1.727 to 2.853; $P < .001$). Full models with and without pro-SFTPB were 0.741 (95% CI, 0.696 to 0.783) and 0.669 (95% CI, 0.620 to 0.717; $P < .001$), respectively. These models underwent external validation using the Carotene and Retinol Efficacy Trial (CARET). CARET was a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of daily supplementation with 30 mg of beta-carotene and 25,000 IU retinyl palmitate on primary lung cancer prevention in ever smokers.[63] When comparing lung cancer cases with controls in CARET, the use of pro-SFPTB in risk modeling yielded an AUC of 0.683 (95% CI, 0.604 to 0.761).

HEALTH-RELATED QUALITY OF LIFE IN THE PANCAN COHORT

In the PanCan study, 1,237 participants underwent LDCT screening without AFB. The 12-item short-form (SF-12)[64] and the EuroQoL questionnaire (EQ-5D-3L (three-level version of EQ-5D)) were used to determine HRQoL; the State Trait Anxiety Inventory (STAI Form Y-1) was used to measure state anxiety.[45] Questionnaires were administered in person at the time of study enrolment (baseline), by phone within 1 month after participants received their LDCT results, 1 month after any downstream diagnostic testing for a positive screen (post-investigations), and prior to the first annual repeat LDCT (12 months post-baseline).[65] Overall, there were no clinically significant differences in HRQoL outcomes between baseline and each of the subsequent survey time points. However, more participants experienced a clinically significant increase (vs. decrease) in anxiety following baseline LDCT, which was more pronounced among women and participants who were concerned about their lung cancer risk at baseline. Paradoxically, participants with positive baseline screens reported decreased anxiety, although this did not reach statistical significance in multivariate analysis. Some of the excess increased anxiety persisted over time. As observed in the NLST and some European trials, lung cancer screening was associated with little or no adverse physical or psychological long-term impacts on participants; however, the PanCan findings differed from the NLST in that the latter observed a short-term increase in anxiety following a positive screening result.

RESOURCE UTILIZATION AND COSTS IN THE PAN-CANADIAN STUDY

The PanCan investigators analyzed resource utilization and the costs of screening for two years of follow-up after the treatment of screen-detected cancers.[66] For each participant, demographic information, screening results, resource utilization data, and complications were collected from the point of enrollment to the point of data censoring on December 31, 2012. For participants without lung cancer, data were recorded from the T0 baseline screen for 18 months; data on participants with lung cancer were collected if the diagnosis occurred within 30 months of the T0 screen and prior to December 31, 2012. Data were divided into four phases: 1) diagnostic work-up: from T0 to data of 1st date of first treatment), 2) first-line treatment: from first treatment start date to final day, or 30 days following surgery, including complications until their resolution or participant death; 3) Follow-up year 1, and 4) Follow-up year 2. Follow-up phases occurred 365 days from the previous transition and included relapsed lung cancers prior to December 31, 2012, as well as resources used for participants who received supportive care only. The cost analysis was based on the Canadian public payer's perspective; unit costs for resource utilization were based on the provincial 2013 reimbursement schedules from the Medical Service Plan in the province of British Columbia.

In total, data on 2,059 participants were analyzed, including 1,961 without lung cancer and 83 (4%) with a lung cancer diagnosis. The average per-person cost of screening with LDCT was $453 (95% CI, $400-505). Of 83 lung cancer cases; 62 (75%) were stage I or II. Among 83 patients, 67 underwent first-line surgery and 16 (19%) received non-surgical treatments. Differences in costs between those who did or did not undergo surgery were significant, averaging $33,244 for surgical patients and $47,792 for non-surgical patients.[33] Differences in costs between surgically and non-surgically managed patients were largely due to higher costs of bronchoscopy, physician time, and imaging resources in the latter, although the costs of complications were higher in those who had first line surgery. Of note, only cytotoxic chemotherapy was factored into the cost analysis, excluding targeted agents and immunotherapies that are more expensive. The entire program, including LDCT screening and treatment costs averaged $1,880 per person. Although this analysis did not

provide an estimate of cost-effectiveness, the cost analysis was analyzed based on real world data in a Canadian cohort and had comparable costs to those calculated in the NLST.

NODULE PREDICTION MODELING

Among the most consequential products of the PanCan study was the creation of a predictive tool to estimate the probability of lung cancer in nodules detected on screening LDCT, called the Brock model.[67] The model was first developed in the PanCan cohort, and included 1,871 individuals with 7,008 nodules (102 malignant), then externally validated on 1,090 participants with 5,021 nodules (42 malignant) who participated in chemoprevention trials at the British Columbia Cancer Agency (BCCA). The presence or absence of nodule spiculation was not recorded in the BCCA studies. As such, parsimonious and full logistic-regression models were developed that did and did not include nodule spiculation (Table 5). The performance of the final parsimonious and full models without spiculation as a variable showed excellent discrimination and calibration, with areas under the receiver-operating characteristic curve (AUC) > 0.90 for both development and validation cohorts; for nodules ≤ 10 mm the AUCs were ≥0.89 in both cohorts (Table 6). After comparison with other nodule-prediction models, the Brock model has been recommended for initial assessment of IPNs in both screened and non-screened individuals by the British Thoracic Society[68] and is used by some institutions in complement to standard nodule classification variables.

SUMMARY OF FINDINGS FROM THE PAN-CANADIAN EARLY DETECTION OF LUNG CANCER PROJECT

The PanCan study was a multicenter study across Canada designed to integrate multiple different methods of LDCT, AFB, and serum biomarkers as a strategy for early lung cancer detection. The use of a risk prediction model rather than a rule-based approach based on age and smoking criteria to determine eligibility was successful in identifying those at greater risk of lung cancer. They observed a significantly higher cumulative incidence of lung cancer relative to the NLST (6.5% vs 4.0%, respectively). Although AFB was not found to improve cancer detection rates, the addition of a serum biomarker, Pro-SFTPB, was significantly and independently associated with lung cancer; the log-transformed Pro-SFTPB had an odds ratio of 2.220 and improved the performance of prediction models. As has been observed in other studies, HRQoL was not significantly adversely impacted by LDCT screening. A cost analysis based on real-world data in the PanCan cohort yielded LDCT and treatment costs that were comparable to those observed in the NLST. Finally, the PanCan investigators established a nodule prediction model, the Brock model, which has been validated in a number of external cohorts and has been recommended by some professional organizations to be included as part of the assessment of positive screens.

EUROPEAN LUNG CANCER SCREENING TRIALS WITH LOW-DOSE COMPUTED TOMOGRAPHY (LDCT)

NELSON Trial

The NELSON trial, a Dutch acronym for "Dutch-Belgian lung cancer screening trial," was designed to determine whether LDCT screening reduces lung cancer mortality by ≥25% versus no screening after a follow-up of 10 years.[69] Men and women between the ages of 50 and 75 were screened by a questionnaire on health, smoking, cancer history, and other health and lifestyle factors.[1,2] After the required sample size was determined, participants included current smokers and former smokers with ≤10 years of cessation, who smoked >15 cigarettes a day for >25 years or >10 cigarettes a day for >30 years.[69-70]

Between 2004 and 2012, 15,822 participants were randomized to receive four LDCT screenings or no screening. LDCT screenings took place at baseline, 1 year, 3 years, and 5.5 years with a 10 year follow-up (Table 7).[69] In total, 13,195 men were included in the primary analysis and 2,594

Table 5. Parsimonious and Full Logistic Regression Models for the Probability of Lung Cancer in Pulmonary Nodules

	Parsimonious Model No Spiculation		Full Regression Model No Spiculation	
Predictor Variable	**Odds Ratio (95% CI)**	**P-value**	**Odds Ratio (95% CI)**	**P-value**
Age, per year			1.03 (0.99-1.07)	0.11
Sex (female vs. male)	1.79 (1.13-2.82)	0.01	1.76 (1.09-2.83)	0.02
Family history of lung cancer (Yes vs. No)			1.35 (0.84-2.16)	0.21
Emphysema (Yes vs. No)			1.41 (0.82-2.42)	0.21
Nodule size		<0.001†		<0.001†
Nodule consistency				
Solid			Reference	
Part-solid			1.40 (0.72-2.74)	0.32
Ground-glass			0.74 (0.40-1.35)	
Nodule location (upper vs. middle or lower lobes)	1.90 (1.78-3.08)	0.009	2.04 (1.22-3.41)	0.007
Nodule count per scan (per each additional nodule)			0.92 (0.85-1.00)	0.05
Model constant (Beta coefficient)	-6.5929	-6.8071		
	Parsimonious Model With Spiculation		**Full Regression Model With Spiculation**	
Age, per year			1.03 (0.99-1.07)	0.16
Sex (female vs. male)	1.91 (1.19-3.07)	0.008	1.82 (1.12-2.97)	0.02
Family history of lung cancer (Yes vs. No)			1.34 (0.83-2.17)	0.23
Emphysema (Yes vs. No)			1.34 (0.78-2.33)	0.29
Nodule size		< 0.001†		< 0.001†
Nodule consistency				
Solid			Reference	
Part-solid			1.46 (0.74-2.88)	0.28
Ground-glass			0.88 (0.48-1.62)	0.68
Nodule location (upper vs. middle or lower lobe)	1.82 (1.12-2.98)	0.02	1.93 (1.14-3.27)	0.02
Nodule count per scan (per each additional nodule)			0.92 (0.85-1.00)	0.049
Spiculation (Yes vs. No)	2.54 (1.45-4.43)	0.001	2.17 (1.16-4.05)	0.02
Model constant	-6.6144	-6.7892		

Age is centered on the mean of 62 years, nodule size is centered on 4 mm, and nodule count is centered on 4. As such, 62 is subtracted from the actual age, 4 mm is subtracted from the actual nodule size, and 4 is subtracted from the actual number of nodules).
†Nodule size (measured in millimeters) had a nonlinear relationship with lung cancer and was transformed in all models. Adapted from reference 63 with permission.

Table 6. Performance Characteristics of Parsimonious Models for Nodule Prediction from the Canadian Studies Using Receiver Operating Characteristic Curves

Model	PanCan Development Cohort AUC (95% CI)	BCCA Validation Cohort AUC (95% CI)
Parsimonious Model, No Spiculation (All Nodules)	0.941 (0.911-0.962)	0.960 (0.927-0.980)
Parsimonious Model, No Spiculation (Nodules ≤ 10 mm)	0.894 (0.833-0.937)	0.907 (0.822-0.963)
Full Model, No Spiculation (All Nodules)	0.942 (0.909-0.966)	0.970 (0.945-0.986)
Full Model, No Spiculation (Nodules ≤ 10 mm)	0.891 (0.825-0.942)	0.938 (0.872-0.978)

Adapted from reference 63 with permission.

Table 7. Screening-Test Results in Each Screening Round for Male Participants in the Screening Group of the NELSON Trial.

Screening	Screening Uptake		Indeterminate Test	Positive Test	Detection of Lung Cancer	Positive Predictive Value
	Men Eligible for Screening	Men Undergoing Randomization				
	number/total number (%)					*%*
Round 1	6309/6583 (95.8)	63/90/6583 (95.8)	1241/6309 (19.7)	147/6309 (2.3)	56/6309 (0.9)	38.1
Round 2	6086/6459 (94.2)	6086/6583 (92.5)	357/6086 (5.9)	95/6096 (1.6)	45/6086 (0.7)	47.4
Round 3	5768/6285 (91.8)	5768/6583 (87.6)	385/5768 (6.7)	136/5768 (2.4)	65/5758 (1.1)	47.8
Round 4	4437/5771 (76.9)	4437/6583 (67.4)	86/4437 (1.9)	89/4437 (2.0)	37/4437 (0.8)	41.6
Total	22,600/25,098 (90.0)	22,600/26,332 (85.8)	2069/22,600 (9.2)	467/22,600 (2.1)	203/22600 (0.9)	43.5

Adapted from reference 71 with permission.

women in the subgroup analysis.[71] In the primary analysis, 90% of participants adhered to LDCT screening, and a mean of 9% had at least one additional CT. The referral rate for suspicious nodules was 2.1%. At 10-year follow-up, the cumulative lung cancer incidence was 5.58 in the screening arm versus 4.91 in the control arm (rate ratio, 1.14; 95% CI, 0.97 to 1.33) (Table 8).[71] Furthermore, 156 people in the screening arm died of lung cancer compared to 206 people

Table 8. Lung-Cancer Stage and Histologic Type of All First-Detected Lung Cancers in Male Participants of the NELSON Trial at 10 Years of Follow-up or on December 31, 2015.

Variable	Screening Group			Control Group
	Screening-Detected Lung Cancer (N=203)†	Non—Screening-Detected Lung Cancer (N=141)	Any Lung Cancer (N=344)	Any Lung Cancer (N=304)
	number of participants (%)			
Stage				
IA	95 (46.8)	10 (7.1)	105 (30.5)	21 (6.9)
IB	24 (11.8)	10 (7.1)	34 (9.9)	20 (6.6)
IIA	8 (3.9)	4 (2.8)	12 (3.5)	13 (4.3)
IIB	11 (5.4)	6 (4.3)	17 (4.9)	17 (5.6)
IIIA	20 (9.9)	14 (9.9)	34 (9.9)	43 (14.1)
IIIB	13 (6.4)	14 (9.9)	27 (7.8)	34 (11.2)
IV	19 (9.4)	73 (51.8)	92 (26.7)	139 (45.7)
Unknown	13 (6.4)	10 (7.1)	23 (6.7)	17 (5.6)
Histologic type‡				
Adenocarcinoma	123 (60.6)	56 (39.7)	179 (52.0)	133 (43.8)
Squamous-cell carcinoma	39 (19.2)	38 (27.0)	77 (22.4)	94 (30.9)
Small-cell carcinoma	13 (6.4)	27 (19.1)	40 (11.6)	46 (15.1)
NSCLC	8 (3.9)	8 (5.7)	16 (4.7)	13 (4.3)
Other	20 (9.9)	12 (8.5)	32 (9.3)	18 (5.9)

Note: Percentages may not total 100 because of rounding. NSCLC, non--small cell lung carcinoma.
†Data on three screening-detected lung cancers were not available in the national cancer registry (date of diagnosis unknown).
‡Cases of lung cancer were classified into five main histologic types: adenocarcinoma, squamous-cell carcinoma, small-cell carcinoma, NSCLC, and other (*International Classification for Diseases for Oncology*, third edition). Adapted from reference 71 with permission.

in the control arm (cumulative rate ratio for death, 0.76; 95% CI, 0.61 to 0.94), corresponding to a 24% reduction in lung cancer deaths. The cumulative rate ratio for death among women after 8 years follow up was even lower at 0.41 (95% CI, 0.19 to 0.84)[3] and statistically significant corresponding to a 59% reduction in lung cancer deaths. After 10 years the mortality reduction decreased to a rate ratio at 0.67 (95% CI, 0.38 to 1.14) which was not significant showing the effect of stopping a screening program after 4 rounds (Figure 3).

To determine whether lung cancer screening of high-risk individuals affects their health-related quality-of-life (HRQoL), 1,466 participants received questionnaires up to 2-years following randomization. HRQoL was measured as generic HRQoL (12-item questionnaire and EuroQoL questionnaire), anxiety (Spielberger State-Trait Anxiety Inventory), and lung cancer-specific distress (impact of event scale). At 2-year follow-up, no differences were observed in health-related quality-of-life between groups.[72]

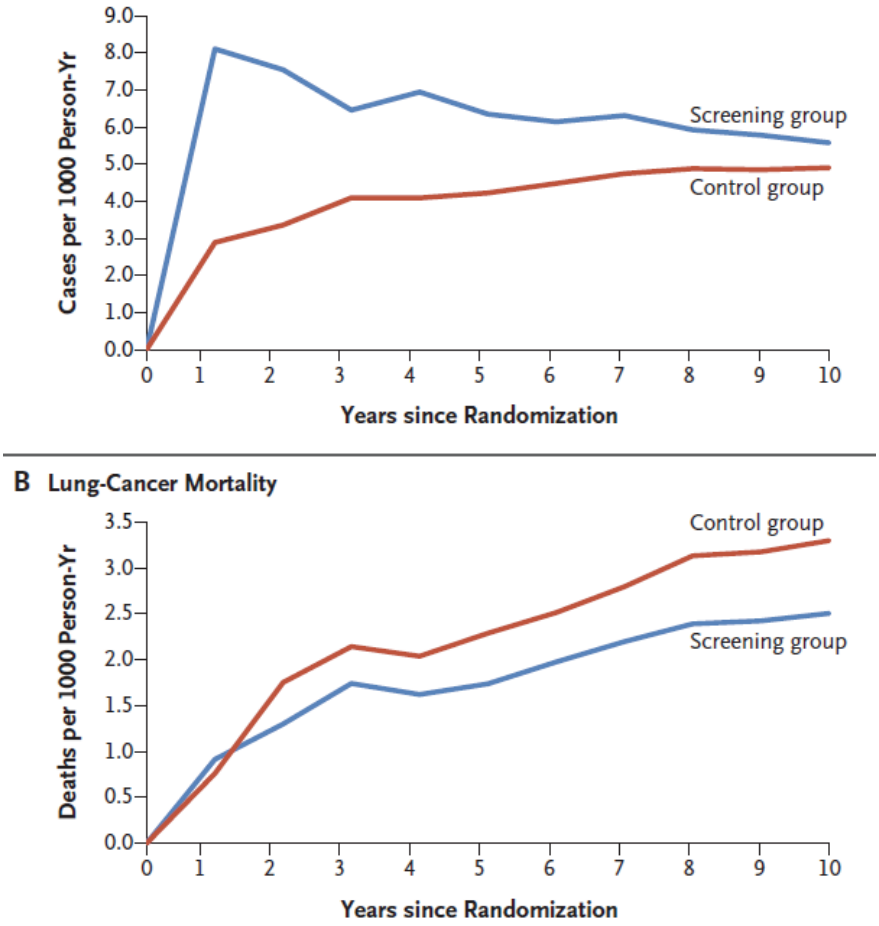


Figure 3. Lung cancer-incidence and lung-cancer mortality among male participants of the NELSON Trial. Reprinted with permission from reference 71.

Danish Lung Cancer Screening Trial (DLSCT)

The primary objective of the Danish Lung Cancer Screening Trial (DLSCT) was to assess if annual LDCT screening can reduce lung cancer mortality by >25%.[73] Individuals volunteered for the study by responding to advertisements in local and regional newspapers. To be included in the study, participants were required to be 50 to 70 years old, current smokers or former smokers with <10 years of cessation and who quit after the age of 50 and have a history ≥20 pack years.[73] From 2004 to 2006, the DLSCT randomized 4,104 individuals to five annual LDCT screenings or no screening. Adherence was high in both groups, with 96% adherence in the screening group and 93% adherence in the control group. The lung cancer detection rate was 0.83% at baseline and the mean annual detection rate was 0.67% at incidence rounds. At the end of screening, 69 lung cancers were diagnosed in the screening group compared to 24 lung cancers in the control group (P<.001). At 5-year follow-up, 100 cancers were found in the screening group compared to 53 cancers in the control group. There was no difference observed in lung cancer mortality, as 39 participants died of lung cancer in the screening group compared to 38 partici-

pants in the control group (hazard ratio, 1.03; 95% CI, 0.66 to 1.6).[74]

German Lung Cancer Screening Intervention (LUSI) Trial

The German Lung Cancer Screening Intervention (LUSI) trial was launched in 2007 and included 4,052 individuals aged 50 to 69 years old with a history of smoking ≥15 cigarettes per day for ≥25 years or ≥10 cigarettes per day for ≥30 years. Participants were recruited from the general population between 2007 and 2011 and were randomized to five annual LDCT screenings or a control arm with 5 annual questionnaires.[75] Smoking cessation was offered to all participants, including former smokers, at randomization.[76] After a mean follow-up of 8.8 years, 85 lung cancers were detected in the LDCT arm compared to 67 in the control arm. Furthermore, there were 29 lung cancer deaths in the LDCT arm versus 40 in the control arm. The hazard ratio for lung cancer mortality was 0.74 (95% CI: 0.46-1.19; p = 0.21) among men and women combined, which was a statistically nonsignificant difference. Modeling by sex, however showed a statistically significant reduction in lung cancer mortality among women (HR = 0.31 [95% CI: 0.10-0.96], p = 0.04), but not among men (HR = 0.94 [95% CI: 0.54-1.61], p = 0.81)[77] A follow-up analysis of the study results suggested a risk of overdiagnosis, especially in individuals with comparatively shorter life expectancies.[78]

The United Kingdom Lung Screen (UKLS) Trial

The United Kingdom Lung Screen (UKLS) trial was the last of the European lung cancer screening trials launched. The overall goal of the UKLS trial was to contribute data required to make informed decisions regarding the introduction of population screening for lung cancer. Since the UKLS trial was not powered to show a decrease in lung cancer deaths, another objective was to provide results for pooling with other European lung screening trials.[79] To identify high-risk participants, individuals between 50 and 75 years old were contacted by a questionnaire based on the Liverpool Lung Project (LLP).[79] After analyzing the responses to the questionnaire, those with an LLPv2 risk score ≥4.5% for developing lung cancer over the next 5 years were included in the study.[80] From October 2011 to February 2013, 4,055 participants were randomized to a single-screen LDCT with predefined management protocols, or to usual care. After a median follow-up of 7.3 years, 86 cancers were diagnosed in the LDCT arm and 75 in the control arm. Although not significant, there was a trend in reduction of lung cancer mortality in the LDCT arm with 30 lung cancer deaths reported compared to 46 deaths in the control arm (relative risk, 0.65; 95% CI, 0.41 to 1.02).[80] To assess the long-term impact of cancer screening on psychosocial measures such as cancer distress, anxiety, depression and decision satisfaction, participants filled out the six-item Cancer Worry Scale, Hospital Anxiety and Depression Scale, and the six-item Satisfaction with Decision Scale up to two years after being recruited to the study. An analysis of the questionnaires did not find a clinically significant long-term psychosocial impact on these high-risk patients.[81]

Summary

Several European randomized controlled trials have been performed to study the benefit of lung cancer screening on lung cancer mortality in a high-risk population. These include NELSON, LUSI, DLCST, and UKLS.[82] They each have different thresholds for smoking history, age, and risk factors for screening selection. Although the majority were small in size and statistically underpowered, the results of all of the European studies are contributing to the implementation of CT screening in Europe.[82]

LUNG CANCER EARLY DETECTION TRIALS IN EAST ASIA

The 2011 National Lung Screening Trial (NLST) in the United States showed that low-dose computed tomography (LDCT) screening reduced mortality from lung cancer in high-risk individuals.[83] The 2020 Dutch and Belgian study (Nederlands–Leuvens Longkanker Screenings Onderzoek, NELSON) showed that in high-risk individuals, lung

cancer mortality was significantly lower among those who underwent volume CT screening than among those who did not undergo screening.[84] These two studies indicate that LDCT may be effective in reducing lung cancer mortality in high-risk individuals in the United States and Europe. However, the results for lung cancer screening may be different in the Asian population due to variations in prevalence. For example, lung cancer is more common in women and non-smokers in Asia than in western countries.[85] This chapter describes previous and ongoing research on screening for early lung cancer in East Asia.

In Japan, a retrospective cohort study in Hitachi City was performed between 1998 and 2006.[86] Citizens aged 50–74 years who underwent LDCT screening and chest X-ray screening were investigated. Among the citizens who underwent LDCT screening (17,935 residents; 9,790 males and 8,145 females), 273 cases of lung cancer (1.5%), 72 cases of lung cancer death (0.4%), and 885 cases of all-cause death (4.9%) were detected. Among the citizens who underwent X-ray screening (15,548 residents; 6,526 males and 9,022 females), 164 cases of lung cancer (1.1%), 80 cases of lung cancer death (0.5%), and 1,188 cases of all-cause death (7.6%) were detected. The hazard ratios of the CT group to the X-ray group were 1.23 for lung cancer incidence rate, 0.49 for lung cancer mortality rate, and 0.57 for all-cause mortality rate. Remarkably, more than 90% of female participants were non-smokers; therefore, this study suggests that LDCT-based screening can decrease lung cancer-related mortality, even in non-smokers. Currently, a randomized controlled trial of non/light smokers is being conducted in Japan (Japanese randomized trial for evaluating the efficacy of low-dose thoracic CT screening for lung cancer: JECS study).[87] This study evaluated 35,000 participants aged 50–64 years with a smoking history of less than 30 pack-years who were randomly assigned to two groups. The intervention group underwent LDCT in the first and sixth years, while the control group underwent chest X-ray screening in the first year. The participants in both groups were encouraged to undergo routine annual chest X-ray screening for lung cancer. After 10 years of follow up, lung cancer mortality rates were compared. The results of this JECS study are awaited.

The National Korean Lung Cancer Screening Project (K-LUCAS), a single-arm trial of 256 (how does this number relate the 5592 number mentioned later in the paragraph?) high-risk individuals, used the same inclusion criteria as the NLST. The K-LUCAS was a two-year trial conducted from February 2017 to December 2018. The screening results were reported using the Lung Imaging Reporting and Data System (Lung-RADS) algorithm. Among 5592 high risk participants, 336 (5.9%) had category 4 (suspicious of lung cancer) and 42 (0.7%) had confirmed lung cancer. The interim results showed that lung cancer screening targeting high-risk populations is promising for detecting early stage lung cancer in Korea.[88]

In China, the Rural People's Republic of China Screening Program (RuraCSP) was conducted in 2010 among a rural population at high risk of developing cancer.[89] Through the RuraCSP, lung cancer screening has been directed in six provinces with approximately 13,000 high-risk individuals who have been assessed by LDCT scan, with a lung cancer detection rate of 1%. Recently, a multicenter population-based prospective cohort study was performed in 12 cities in eight provinces across China, recruiting individuals aged 40–74 years who were asymptomatic for lung cancer with no history of lung cancer. The participants were classified as high- or low-risk.[90] Participants at high-risk were invited for a one-off LDCT and classified into screened and non-screened groups. Among the 223,302 participants at high risk, 79,581 (35.6%) had an LDCT scan (screened group) and 143,721 (64·4%) did not (non-screened group). Lung cancer incidence was 47.0% higher, lung cancer mortality was 31.0% lower, and all-cause mortality was 32.0% lower for participants in the screened group compared with those in the non-screened group.

In Taiwan, the Taiwan Lung Cancer Screening for Never-Smoker Trial (TALENT) study enrolled 12,011 individuals between 2015 and 2019.[91] The participants were between 55 and 75 years of age and had never smoked. The participants had one of the following risk factors for lung cancer: family history of lung cancer within the third degree of relations, passive smoking exposure, tuberculosis or chronic obstructive pulmonary disease, a cooking index of 110 or greater, and absence of ventilation during cooking. Of the 12,011 participants, 6,009 (50 %) had a family history of lung cancer and 2,094 (17.4%) were considered positive on screening. Of these, 395 participants (3.3%) underwent lung biopsy or surgery. Lung cancer was diagnosed in 313 patients (2.6%), with 255 (2.1%) diagnosed with invasive lung cancer. The prevalence of lung cancer was 3.2% and 2.0% ($p < 0.001$) in participants with and without lung cancer family history, respectively.

Next-generation sequencing (NGS) has markedly decreased the detection threshold and can be used for lung cancer screening. Clinical trials evaluating the potential application of ctDNAs in lung cancer screening are ongoing.[92] In China, a study of a diagnostic model based on targeted DNA methylation sequencing had an accuracy of 80% in the discrimination of benign and malignant pulmonary nodules.[93] The results of these NGS-based studies are promising.

In conclusion, many clinical studies on the early detection of lung cancer have been conducted in East Asia. Given the background of low smoking rates among Asian women, high-risk individuals should be identified from past and ongoing clinical studies to create an appropriate early detection screening model.

PERSONALIZED SCREENING STRATEGIES IN ITALY: THE MILD AND BIOMILD TRIALS

The first randomized screening trial conducted in Italy was the DANTE (Detection and Screening of Early Lung Cancer by Imaging Technology and Molecular Essays), that started in 2001 and enrolled 2,472 male smokers of 60-75 years, with a median smoking exposure of 45 pack-years. The Dante trial failed to demonstrate a significant mortality reduction at 3 years, despite the higher proportion of lung cancers detected (4,7% vs 2,8%, p=0,016 overall, and 2,6% vs 1,0%, p=0,004 in stage I).[94] A later analysis with 8-year follow-up confirmed these results.[95]

The ITALUNG trial enrolled from 2004 to 2006 had a total of 3,206 smokers of 55-69 years, with a median smoking exposure of 39 pack-years. The results published in 2017 revealed a non-significant 30% reduction of LC-specific mortality (RR=0.70; 95% CI 0.47 to 1.03).[96]

The research activity of the Istituto Nazionale Tumori of Milan (INTM) in the field of lung screening has focused on the identification of individual risk and the development of personalized screening strategies, conducting three prospective screening studies with low-dose CT (LDCT) in 9,196 heavy smokers: the MILD study enrolled 4,099 people from 2005 to 2011,[97,98] BioMILD 4119 from 2016 to 2019[99] and SMILE 978 from 2019 to 2020.[100]

Higher Cut-Offs for Solid Nodules

The first pilot study published in the *Lancet* in 2003 already defined a minimum threshold of 5 mm for suspicious nodules and the use of PET to reduce false positives.[101] In subsequent studies, the analysis of nodules was based on the automatic calculation of volumetry and the threshold for defining indeterminate nodules was progressively raised to 60 mm^3 in MILD and 113 mm^3 in BioMILD.

Thanks to this high threshold, which would later be adopted by the international LungRads guidelines in 2019, the majority (88%) of BioMILD participants were classified as negative at the first low-dose CT (LDCT) examination and repeated the exam after three years.[99]

The choice of a high threshold without risks of underestimation of the diagnosis was possible thanks to the development of artificial intelligence (AI) programs developed in collaboration with the University of Nijmegen, which allowed an accurate measurement of the volume of each nodule, solid or sub-solid, and its growth at LDCT control after three months or a year.[102-104] If we consider that

13,046 solid, 1,109 partially solid and 2,803 non-solid nodules were analyzed among the 4,119 participants in BioMILD, we realize the practical value of AI programs in lung screening. In fact, with volumetric analysis, false positives, useless checks, and unnecessary interventions have been drastically reduced.[105]

LONGER SCREENING INTERVALS

The MILD trial demonstrated for the first time with a randomized comparison the safety and efficacy of longer screening intervals in individuals with negative baseline LDCT. In fact, the lung cancer mortality at 10 years was the same for biennial and annual LDCT arms.[106] In addition, the MILD design of prolonged screening beyond five years achieved a statistically significant reduction not only of lung cancer mortality but also of overall mortality (Pastorino - Figure 4).

The adoption of intervals of 2 or 3 years made it possible to extend the screening intervention up to 10 years in low-risk subjects, without compromising the beneficial effects associated with screening.

Indeed, the long-term results of BioMILD demonstrated that a screening protocol personalized according to the individual risk level made it possible to obtain a high percentage of lung cancers in the early stage and reduce the number of unnecessary tests, with a lower impact on instrumental resources and staff commitment.[6] The total number of LDCTs performed in the first six years of BioMILD was less than half that expected, with an annual range of 14,334, instead of 28,833.

Ultra-Low-Dose CT

Over the years, it has been possible to progressively reduce the radiation exposure of each single LDCT exam from 2 mSV with the 16slice scanner in the MILD trial to 1.5 mSV with the 128slice of the BioMILD. The acquisition of a new 192slice dual-source scanner in 2019 made it possible to further reduce the dose to 0.4 mSV, little different from that of a chest x-ray. To develop the best ultra-low dose CT (ULDCT) protocol, it was necessary to conduct a randomized study on 361 volunteers, which compared four different ULDCT protocols in terms of diagnostic accuracy for solid and subsolid pulmonary nodules.[107] On the basis of this such trial results, a new ULDCT protocol was implemented in 2020 for all screening participants at INTM.

Surveillance of Sub-Solid Nodules

The active surveillance program of sub-solid nodules (SSN) started in 2005 with the MILD trial, using AI analysis programs specific for low-density nodules[108] has allowed us to avoid a huge number of unnecessary lung

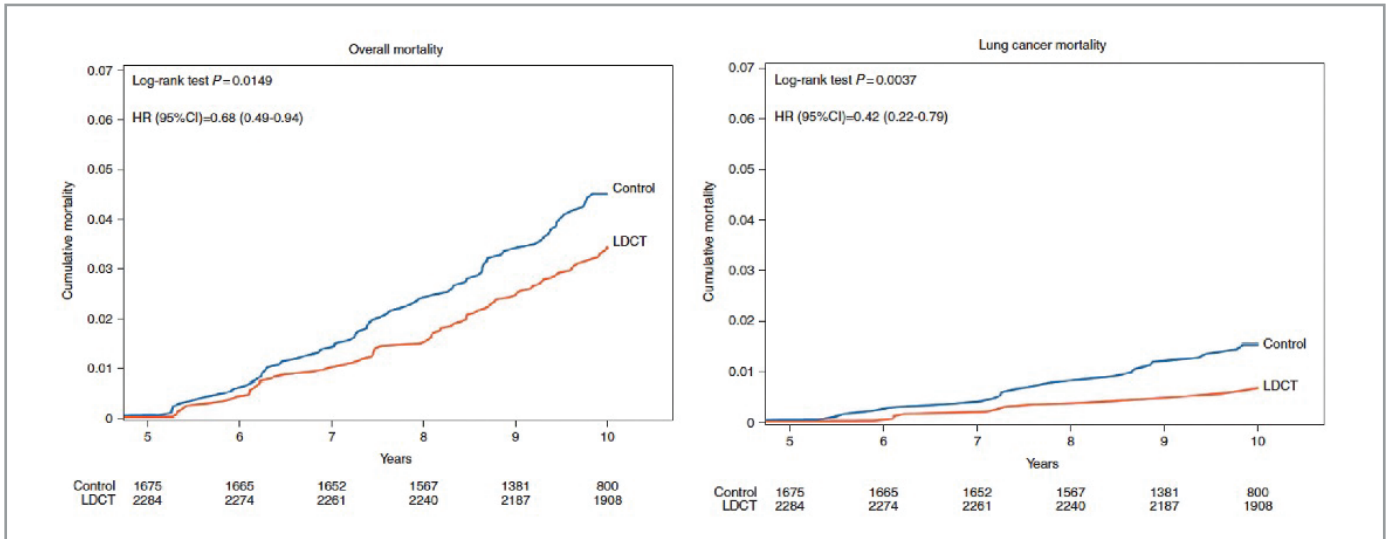


Figure 4. Landmark analysis of cumulative overall mortality and lung cancer mortality, by arm beyond 5 years.

resections.[109] In fact, sub-solid lesions are very frequent in heavy smokers (>10%), but only a small part develops an invasive component, which is easy to identify by the appearance of a solid component. Thanks to the active surveillance program, in the MILD trial it was possible to avoid all lung resections for in situ tumors and reduce the risk of operations for benign diseases to below 5%.[110]

More recently, the benefits of SSN surveillance have been confirmed in the BioMILD trial, with a total of 1,085 SSNs (844 nonsolid-NSNs and 241 partsolid-PSNs) detected in 18.6% (758/4071) of participants. After a median follow-up of 8.6 years, LC was diagnosed only in 4.4% on SSNs, with higher frequency in PSNs (7.1%) and prevalent SSNs (8.4%), a 8-year cumulative survival of 93.8% and no LC-related deaths.[111]

Blood Biomarkers

An area of research that has characterized all screening programs in INTM has been the identification, development, and clinical evaluation of biomarkers in blood. From the first studies on the quantification of circulating DNA,[112] we moved on to the examination of microRNAs and the development of a diagnostic and predictive test based on a combination of 24 microRNAs.[113,114] BioMILD was the first screening program to prospectively evaluate the clinical value of a circulating biomarker in combination with LDCT. The five-year results of BioMILD showed that in subjects with indeterminate or positive nodules, the microRNA blood test was able to identify individuals with a much higher risk of lung cancer, who should be subjected to more frequent and thorough checks[99] (Figure 5). At the same time, the analysis of indeterminate nodules with machine-learning techniques revealed that the radiomics profile could improve the differential diagnosis between benign and malignant nodules,[115] and that a specific examination of the blood immune profile (immunoscore) could reduce the frequency of false negatives to the microRNA test.[116] Based on these results, a prospective study on the diagnostic value of the three combined tests is underway at INTM, financed by the Ministry of Health and the European 4-ITLR project.

The value of blood biomarkers, particularly of small RNAs, in screening is strengthened by recent reports.[117]

Individual Risk Factors

Analysis of individual risk factors in LDCT screening cohorts has shown that interstitial lung disease,[118] reduced lung function,119 elevated levels of C-reactive protein in the blood,[120] or the presence of coronary calcifications[121] have a significant impact on long-term mortality and limit the potential benefit of screening. Recently, the availability of internationally validated AI software for the analysis of pulmonary nodules, the automatic quantification of coronary artery calcifications (CAC) without electrocardiographic synchronization (ECG-gating) and the level of pulmonary emphysema,[122] has made it possible to re-evaluate all LDCT performed in INTM for the last twenty years, with amazing

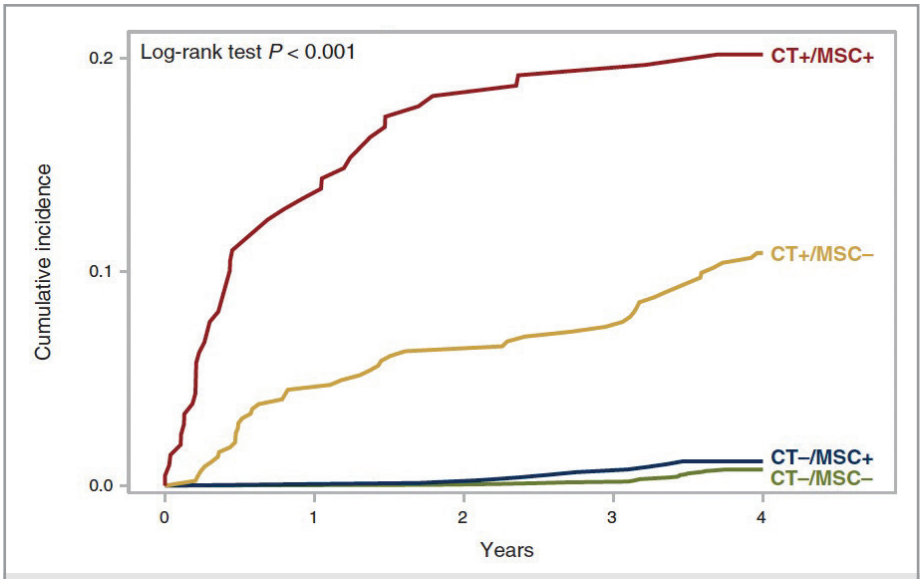


Figure 5. Four-year cumulative lung cancer incidence, stratified by four risk groups: CT+/MSC+, CT+/MSC-, CT-/MSC+, and CT-/MSC-. CT= computed tomography, MSC= micro RNA signature classifier. Reprinted from reference 99, © 2022 The Author(s).

results. Quantification of CAC on baseline LDCTs has been shown to predict all-cause mortality at 6 years in BioMILD[123] and at 12 years in MILD,[124] regardless of the type of scanner (16slice or 128slice). In particular, in MILD subjects with a CAC score higher than 400, 12-year mortality was over 15% and only a small proportion had a positive history of cardiovascular disease. These results open new perspectives for the prevention and early diagnosis of chronic cardiovascular and pulmonary disease in asymptomatic heavy smokers.

Gender Differences

Gender differences were explored in a pooled cohort of 2,368 females and 4,127 males from MILD and BioMILD trials. Cumulative LC incidence and proportion of Stage I were not different in the two genders, but LC survival from the time of diagnosis was significantly higher in females (72.3% vs. 51.7%; p=0.0005). On the other hand, the coronary artery calcification (CAC) score was much lower in females than males (8.7 vs. 41, p<0.0001). As consequence of both factors, the all-cause mortality at 12 years was 4.1% in females and 7.7% in males (p<0.0001) (Figure 6).[125] These results prompt further insights into the gender-related biology of lung cancer and offer new prospects for targeted prevention by gender.

Smoking Cessation

It has been known for years that smoking cessation reduces mortality in subjects undergoing LDCT screening compared to those who continue to smoke,[126] and a multicentric pilot study showed that the administration of Varenicline during LDCT screening significantly improved the quit rate.[127] Ultimately, the results of a randomized study combining primary prevention and early diagnosis is finally available. The SMILE randomized study conducted in INTM on 869 active smokers screened with ULDCT demonstrated that the use of a natural and low-cost drug, such as citisine, increases the probability of quitting smoking sixfold in one year compared to "only" counseling"[128] (Figure 7). Taking into account that the study was conducted during the pandemic,[129] it is reasonable to estimate that the success rate under normal conditions could exceed 40%. The SMILE study provides strong scientific evidence that primary prevention can be associated with lung screening with a potential benefit on all smoking-related diseases.[130]

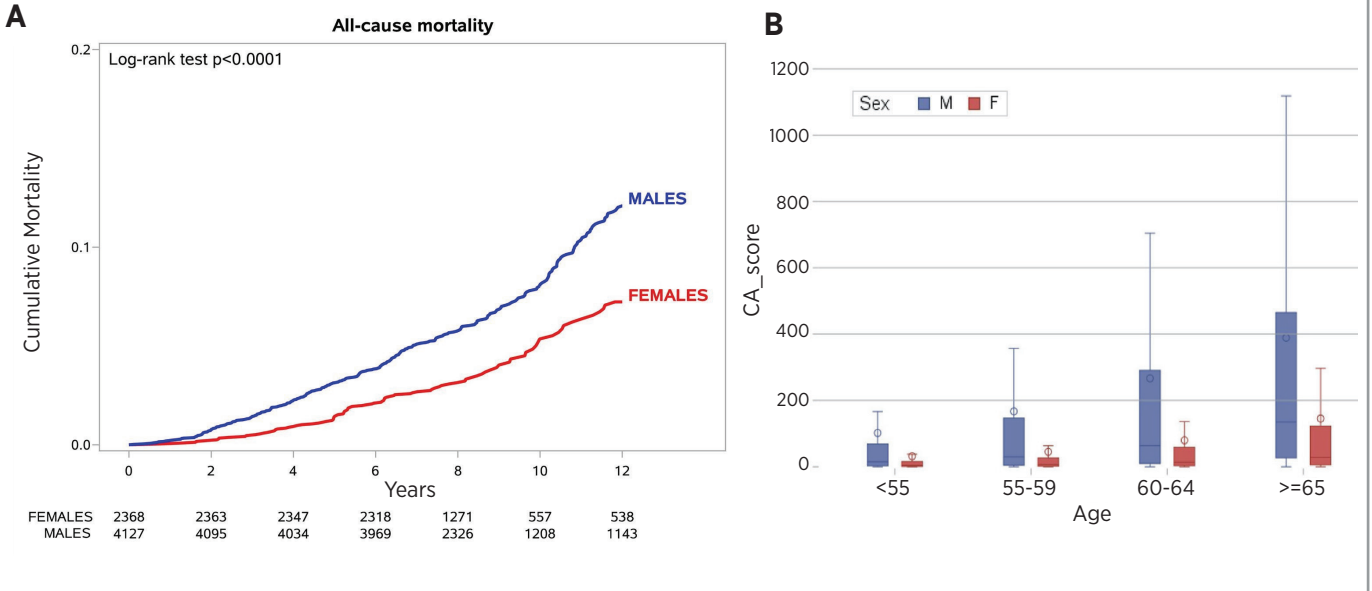


Figure 6. Twelve-year mortalitycurves stratified by sex: all-cause mortality (A) and noncancer mortality (A), and boxplots of the distribution of CAC score by sex and age (B). Reprinted from reference 125, © 2022 The Author(s).

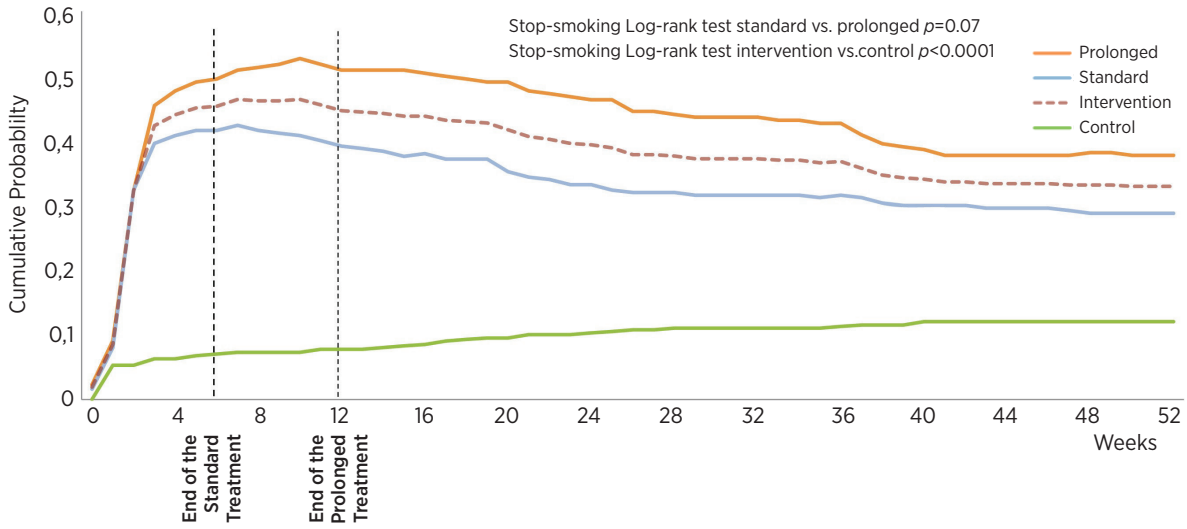


Figure 7. Cumulative probablilty and smoking cessation trend in the intervention and control arms. Reprinted from reference 128, © 2022 The Author(s).

European Screening Networks

In 2019, the European Commission has funded a European multicenter program called 4-IN-THE-LUNG-RUN (4ITLR) aimed at the development and validation of optimal techniques for the early diagnosis of lung cancer in heavy smokers, in which participants are randomized to annual vs. biennial LDCT, and INTM has the specific task of assessing the value of blood biomarkers.

Concurrently, in 2021 the Italian Ministry of Health funded a national multicenter screening program called Italian Pulmonary Screening Network (RISP), including 18 national centers with high multidisciplinary clinical expertise to recruit 10,000 smokers ≥35 pack/years, aged 55 to 75. The RISP program includes smoking cessation intervention by cytisine tablets and offered free of charge to all active smokers. RISP aims to demonstrate the feasibility and efficacy of a national LDCT screening program, its ability to reduce mortality from lung cancer and increase smoking cessation with pharmacological support. RISP also aims to evaluate the potential benefit in other chronic diseases such as emphysema, COPD and coronary artery calcifications (CAC) through the automatic quantification (AI) of individual LDCT images. The ultimate objective of RISP is to include lung screening and pharmacological prevention with citisine in the essential levels of care (LEA), through a network of reference centers that provide national coverage and quality levels comparable to breast, cervix and colon screening programs.

Finally, in April 2023 the European Union within the EU4HEALTH program 2021–2027 launched the SOLACE project (Strengthening the screening of Lung Cancer in Europe), and coordinated by The European Institute for Biomedical Imaging Research (EIBIR) and involving 34 Institutions around Europe. SOLACE aims at developing, testing, and disseminating tools to help overcome identified bottlenecks and specifically address the health inequalities in different European countries in the setting of lung cancer screening. Specific objectives are: a) Facilitate and support the implementation of structured low-dose CT lung cancer screening programs in Europe, b) Improve the quality of lung cancer screening across Europe, c) Improve the accessibility, benefit-harm balance, and cost effectiveness of lung cancer screening programs, and d) Bring together, for the first time, all key stakeholders needed to design, plan, and implement LCS in member states on a sustainable basis (https://europeanlung.org/solace/).

Summary
Italian trials support the benefit of long-term LDCT screening to reduce lung cancer as well as all-cause mortality in heavy smokers. The most effective strategy was focused on the identification of individual risk, based on measurable damage, to implement personalized screening programs. In a holistic approach, blood biomarkers and radiomic profiles can be integrated by AI instruments to further improve the results of primary and secondary prevention.

CONCLUDING REMARKS

The last two decades have provided the undisputable evidence that LDCT screening can reduce lung cancer mortality, with limited radiation damage, avoidance of unnecessary treatments, and sustainable costs.

The synergy between early lung cancer detection by LDCT, AI assessment of coronary calcification and emphysema, coupled with drug-sustained smoking cessation, can boost the benefits of preventive programs in life-long heavy smokers, vastly exceeding the results of screening for other cancers.

Nonetheless, large-scale implementation of LDCT screening in all countries and the achievement of durable compliance will require the overcoming of major cultural barriers, lack of confidence in prevention, and fear of potential harm, all of which are still widespread among high-risk individuals, as well as their physicians.

From the very beginning, the International Association for the Study of Lung Cancer has supported scientific advances in lung cancer prevention and will continue to be a crucial world-wide player in this field.

Acknowledgments

The authors endorse the importance of the contributions of the pioneers of lung cancer screening research who are mentioned in this chapter and also acknowledge that many more talented clinicians and researchers from across the world contributed to progress in this area than space allows for full recognition. Ricardo S. Avila and Accumetra LLC are thanked for assistance in preparing the figures contained in this manuscript. Dr. Paul Bunn and Fred Hirsch are also thanked for their efforts to celebrate the 50th year of IASLC with such a comprehensive book.

References

1. Doll R, Hill AB. Smoking and carcinoma of the lung; preliminary report. Br Med J. 1950;2:739–748.
2. Daff ME, Doll R, Kennaway EL. Cancer of the lung in relation to tobacco. *Br J Cancer*. 1951;5:1–20. doi: 10.1038/bjc.1951.1 PMCID: PMC2007759 PMID: 14839198
3. Wynder EL, Graham EA. Landmark article May 27, 1950: Tobacco Smoking as a possible etiologic factor in bronchiogenic carcinoma. A study of six hundred and eighty-four proved cases. By Ernest L. Wynder and Evarts A. Graham. *JAMA*. 1985;253:2986-2994. doi: 10.1001/jama.253.20.2986. PMID: 3889389.
4. Mulshine JL. Reflections on early cancer control efforts. *J Surg Oncol*. 1999.70:207-208.PMID: 10219014
5. Boucot KR, Cooper DA, Weiss W. The Philadelphia Pulmonary Neoplasm Research Project. *Med Clin North Am*. 1970;54:549- 553.
6. Boucot KR, Weiss W. Is curable lung cancer detected by semiannual screening? *JAMA*. 1973;224:1361-1365. doi:10.1001/jama.1973.03220240015004). PMID: 4739985
7. Rimington J. Smoking, sputum and lung cancer. *Br Med J*. 1968;1:732-734.
8. Marsh BR, Frost JK, Erozan YS, et al: Flexible fiberoptic bronchoscope-its place in the search for lung cancer. *Ann Otol Rhinol Laryngol*. 1973;53:101-110.
9. Hayata Y, H Kato, J Ono, et al. Fluorescence fiberoptic bronchoscopy in the diagnosis of early-stage lung cancer. Recent results. *Cancer Res*. 1982;82:121-130. doi: 10.1007/978-3-642-81768-7_11. PMID: 7111834 DOI: 10.1007/978-3-642-81768-7_11
10. Saccomanno G, Archer VE, Auerbach 0, et al: Development of carcinoma of the lung as reflected in exfoliated cells. Cancer 1974; 33:256-270.
11. Mulshine JL, Hirsch FR. National Cancer Act and Lung Cancer Screening: An example of intended impact September 15, 2021. https://dailynews.ascopubs.org/do/10.1200/ADN.21.200712/full/
12. Berlin NI, Buncher CR, Fontana RS, et al. The National Cancer Institute cooperative early lung cancer detection program. *Am Rev Respir Dis*. 1984;130:545-549
13. Baker RR, Marsh BR, Ball WC Jr, et al: Screening for bronchogenic carcinoma. The surgical experience. *J Thorac Cardiovasc Surg*. 1979;78:876-882.
14. Carter D, Screening for lung cancer. *Yale J Biol Med*. 1981;54;381-385.
15. Fontana RS, Sanderson DR, Woolner LB, et al. Screening for lung cancer. A critique of the Mayo Lung Project. *Cancer*. 1991; 67(4 Suppl):1155-1164. doi:10.1002/1097-0142(19910215)67:4+<1155::aid-cncr2820671509>3.0.co;2-0. PMID: 1991274.
16. Mulshine JL, Tockman MS, Smart CS. Considerations in the development of lung cancer screening tools. *Review J Natl Cancer Inst*. 1989;81:900-906. doi: 10.1093/jnci/81.12.900. PMID: 2659802 DOI: 10.1093/jnci/81.12.900
17. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: Overall design and findings from baseline screening. *Lancet*. 1999;354:99–105.
18. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD,

et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365:395-409. doi: 10.1056/NEJMoa1102873. Epub 2011 Jun 29. PMID: 21714641
19. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med*. 2020;382:503-513. doi: 10.1056/NEJMoa1911793. Epub 2020 Jan 29. PMID: 31995683
20. National Lung Screening Trial Research Team; Aberle DR, Berg CD, Black WC, et al. The National Lung Screening Trial: Overview and study design. *Radiology*. 2011;258:243-53. doi: 10.1148/radiol.10091808. Epub 2010 Nov 2. PMID: 21045183; PMCID: PMC3009383.
21. Rydzak CE, Armato SG, Avila RS, Mulshine JL, Yankelevitz DF, Gierada DS. Quality assurance and quantitative imaging biomarkers in low-dose CT lung cancer screening. *Br J Radiol*. 2018;91:20170401. doi: 10.1259/bjr.20170401. Epub 2017 Oct 27. PMID: 28830225; PMCID: PMC6350468.
22. Fontana RS, Sanderson DR, Woolner LB, et al. Lung cancer screening: the Mayo program. *J Occup Med*. 1986;28:746–750.
23. Melamed MR, Flehinger BJ, Zaman MB, et al. Screening for early lung cancer: Results of the Memorial Sloan-Kettering study in New York. *Chest*. 1984;86:44–53.
24. Frost JK, Ball WC Jr, Levin ML, et al. Early lung cancer detection: Results of the initial (prevalence) radiologic and cytologic screening in the Johns Hopkins study. *Am Rev Respir Dis*. 1984;130:549–554.
25. Kubik A, Kubik A, Parkin DM, et al. Lack of benefit from semi-annual screening for cancer of the lung: follow-up report of a randomized controlled trial on a population of high-risk males in Czechoslovakia. *Int J Cancer*. 1990;45(1):26–33.
26. Black WC. Computed tomography screening for lung cancer: Review of screening principles and update on current status. *Cancer*. 2007;110:2370-2384.
27. Hocking WG, Hu P, Oken MM, et al for the PLCO Project Team. Lung cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. *J Natl Cancer Inst*. 2010;102:722-731.
28. Oken MM, Hocking WG, Kvale PA, et al for the PLCO Project Team. Screening by chest radiograph and lung cancer mortality. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Randomized Trial. *JAMA*. 2011;306:1865-1873.
29. Kaneko M, Eguchi K, Ohmatsu H, et al. Peripheral lung cancer: Screening and detection with low-dose spiral CT versus radiography. *Radiology*. 1996;201:798–802.
30. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: Overall design and findings from baseline screen. *Lancet*. 1999;354: 99 – 105.
31. Henschke CI. Early Lung Cancer Action Project. Overall design and findings from baseline screen. *Cancer.* 2000;89:2474-2482.
32. Henschke CI, Naidich DP, Yankelevitz DF, et al. Early Lung Cancer Action Project. Initial findings on repeat screening. *Cancer*. 2001;92:153-159.
33. Carter D, Vazquez M, Flieder DB, et al. Comparison of pathologic findings of baseline and annual repeat cancers diagnosed on CT screening. *Lung Cancer*. 2007;56:193-199.
34. Gohagan J, Marcus P, Fagerstrom R, et al. for the Lung Screening Study Research Group. Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs. chest radiograph. The Lung Screening Study of the National Cancer Institute. *Chest*. 2004;126:114-121.
35. The National Lung Screening Trial Research Team. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365:295-409.
36. National Lung Screening Trial Research Team; Aberle DR, Berg CD, Black WC, et al. The National Lung Screening Trial: Overview and study design. Radiology. 2011; 258:243-253.
37. Duda C, Mahon I, Chen MH, et al. Impact and costs of targeted recruitment of minorities to the National Lung Screening Trial. *Clin Trials*. 2011;8:214-23.
38. Cagnon CH, Cody DD, McNitt-Gray MF, Seibert JA, Judy PF, Aberle DR. Description and implementation of a quality control program in an imaging-based clinical trial. *Acad Radiol*. 2006;13:1431-1441.
39. National Lung Screening Trial Research Team; Aberle DR, Adams AM, Berg CD, et al. Baseline characteristics of participants in the randomized national lung screening trial. *J Natl Cancer Inst*. 2010;102:1771-1779.
40. Aberle DR, Black WC, Goldin JG, Patz E, Gareen I, Gatsonis C. American College of Radiology Imaging Network. ACRIN #6654. Contemporary Screening for the Detection of Lung Cancer. Version Date 2004. https://www.acr.org/-/media/ACR/NOINDEX/Research/ACRIN/Legacy-Trials/ACRIN-6654.pdf
41. National Lung Screening Trial Research Team; Church TR, Black WC, Aberle DR, et al. Results of initial low-dose computed tomographic screening for lung cancer. *N Engl J Med*. 2013;368:1980-1991.
42. Abesrle DR, DeMello S, Berg CD, et al. National Lung Screening Trial Research Team. Results of the two incidence screenings in the National Lung Screening Trial. *N Engl J Med.* 2013;369:920-931.
43. Greene FL, Page DL, Fleming ID, et al. AJCC Cancer Staging Manual. 6th ed. New York: Springer-Verlag, 2002.
44. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ*. 2002;21:271-292.
45. Spielberger CD, Gorsuch RL, Lushene RE. Test Manual for the State Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press, 1970.
46. Gareen IF, Duan F, Greco EM, Snyder BS, Boiselle PM, et al. Impact of lung cancer screening results on participant health-related quality of life and state anxiety in the National Lung Screening Trial. *Cancer*. 2014;20:3401-3409.
47. Black WC, Gareen IF, Soneji SS, Sicks JD, Keeler EB, et al. Cost-effectiveness of CT screening in the National Lung Screening Trial. *N Engl J Med*. 2014;371:1793-1802.
48. Global Initiative on Chronic Obstructive Lung Disease (GOLD). 2023 GOLD REPORT. https://goldcopd.org/2023-gold-report-2/; accessed 1/23/2023.
49. Young RP, Duan F, Chiles CM, et al. Airflow limitation and histology shift in the National Lung Screening Trial. *Am J Respir Crit Care Med*. 2015;192:1060-1067.
50. Hopkins RJ, Duan F, Chiles C, et al. Reduced expiratory flow rate among heavy smokers increases lung cancer risk. Results from the National Lung Screening Trial-American College of Radiology Imaging Network cohort. *Ann Am Thorac Soc*. 2017;14:392-402.
51. Young RP, Ward RC, Scott RJ, Gamble GD, Silvestri G. Airflow limitation and mortality during cancer screening in the National Lung Screening Trial: Why

quantifying airflow limitation matters. *Thorax*. 2022;0:1-9.
52. Patz, Jr EF, Caporaso NE, Dubinett SM, Massion PP, Hirsch FR, et al. National Lung Cancer Screening Trial American College of Radiology Imaging Network specimen biorepository originating from the Contemporary Screening for the Detection of Lung Cancer Trial (NLST, ACRIN 6654). Design, intent and availability of specimens for validation of lung cancer biomarkers. *J Thorac Oncol*. 2010;5:1502-1506.
53. Lung-RADS ® 2022. https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/Lung-RADS-2022.pdf
54. Patz Jr, EF, Pinsky P, Gatsonis C, Sicks JD, Kramer BS, et al. Overdiagnosis in low-dose computed tomographic screening for lung cancer. *JAMA Intern Med*. 2014;174:269-274.
55. National Lung Screening Trial Research Team. Lung cancer incidence and mortality with extended follow-up in the National Lung Screening Trial. *J Thorac Oncol*. 2019;14:1732-1742.
56. Early Detection of Lung Cancer – A Pan Canadian Study. Version 9, Dec 14, 2010. Available at: https://brocku.ca/lung-cancer-screening-and-risk-prediction/pan-can/
57. Tammemagi MC, Schmidt H, Martel S, et al. Participant selection for lung cancer screening by risk modelling (the Pan-Canadian Early Detection of Lung Cancer [PanCan] study): a single arm, prospective study. *Lancet Oncol*. 2017;18:1523-1531.
58. Tammemagi MC, KatkiHA, Hocking WG, Church TR, Caporaso N, et al. Selection criteria for lung-cancer screening. *N Engl J Med*. 2013;368:728-736.
59. Tremblay A, Taghizadeh N, McWilliams AM, MacEachern P, Stather DR, et al. Low prevalence of high-grade lesions detected with autofluorescence bronchoscopy in the setting of lung cancer screening in the Pan-Canadian Lung Cancer Screening Study. *Chest*. 2016;150:1015-1022.
60. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD executive summary. *Am J Respir Crit Care Med*. 2017;195:557-582.
61. Goffin JR, Pond GR, Puksa S, et al. Chronic obstructive pulmonary disease prevalence and prediction in a high-risk lung cancer screening population. *BMC Pulm Med*. 2020;16;20:300. doi: 10.1186/s12890-020-01344-y.
62. Sin DD, Tammemagi M, Lam S, Barnett MJ, Duan X, et al. Pro-surfactant protein B as a biomarker for lung cancer prediction. *J Clin Oncol*. 2013;31:4536-4543.
63. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, et al. Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. *J Natl Cancer Inst*. 1996;88:1550-1559.
64. Jenkinson C, Layte R, Jenkinson D, et al. A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? *J Public Health Med*. 1997;19:179–186.
65. Taghizadeh N, Tremblay A, Cressman, S, et al. Health-related quality of life and anxiety in the Pan-CAN lung cancer screening Cohort. *BMJ Open*. 2019; 9: e024719. doi: 10.1136/bmjopen-2018-024719.
66. Cressman S, Lam S, Tammemagi MC, et al. Resource utilization and costs during the initial years of lung cancer screening with computed tomography in Canada. *J Thorac Oncol*. 2014;9:1449-1458.
67. McWilliams A, Tammemagi MC, Mayo JR, et al. Probability of cancer in pulmonary nodules detected on first screening CT. *N Engl J Med*. 2013;369:910-919.
68. Callister MEJ, Baldwin DR, Akram AR, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules. *Thorax*. 2015;70:ii1-ii54.
69. van Iersel CA, de Koning HJ, Draisma G, et al. Risk-based selection from the general population in a screening trial: Selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). *International Journal of Cancer*. 2007;120:868-874. doi:10.1002/ijc.22134
70. Zhao YR, Xie X, de Koning HJ, Mali WP, Vliegenthart R, Oudkerk M. NELSON lung cancer screening study. *Cancer Imaging*. 2011/10/03/2011;11(1A):S79-S84. doi:10.1102/1470-7330.2011.9020
71. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume ct screening in a randomized trial. *N Engl J Med*. 2020;382:503-513. doi:10.1056/NEJMoa1911793
72. van den Bergh KA, Essink-Bot ML, Borsboom GJ, Scholten ET, van Klaveren RJ, de Koning HJ. Long-term effects of lung cancer computed tomography screening on health-related quality of life: The NELSON trial. *Eur Respir J*. 2011;38:154-61. doi:10.1183/09031936.00123410
73. Pedersen JH, Ashraf H, Dirksen A, et al. The Danish randomized lung cancer CT screening trial--overall design and results of the prevalence round. *J Thorac Oncol*. 2009;4:608-614. doi:10.1097/JTO.0b013e3181a0d98f
74. Wille MM, Dirksen A, Ashraf H, et al. Results of the Randomized Danish Lung Cancer Screening Trial with Focus on High-Risk Profiling. *Am J Respir Crit Care Med*. 2016;193:542-51. doi:10.1164/rccm.201505-1040OC
75. Field JK, Duffy SW, Baldwin DR, et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. *Health Technol Assess*. 2016;20:1-146. doi:10.3310/hta20400
76. Field JK, Vulkan D, Davies MPA, et al. Lung cancer mortality reduction by LDCT screening: UKLS randomised trial results and international meta-analysis. *Lancet Reg Health Eur*. 2021;10:100179. doi:10.1016/j.lanepe.2021.100179
77. Brain K, Lifford KJ, Carter B, et al. Long-term psychosocial outcomes of low-dose CT screening: results of the UK Lung Cancer Screening randomised controlled trial. *Thorax*. 2016; 71:996-1005. doi:10.1136/thoraxjnl-2016-208283
78. Becker N, Motsch E, Gross ML, et al. Randomized study on early detection of lung cancer with MSCT in Germany: Study design and results of the first screening round. *J Cancer Res Clin Oncol*. 2012;138:1475-1486. doi:10.1007/s00432-012-1228-9
79. Bade M, Bähr V, Brandt U, et al. Effect of smoking cessation counseling within a randomised study on early detection of lung cancer in Germany. *J Cancer Res Clin Oncol*. 2016;142:959-968. doi:10.1007/s00432-015-2105-0
80. Becker N, Motsch E, Trotter A, et al. Lung cancer mortality reduction by LDCT screening-Results from the randomized German LUSI trial. *International Journal of Cancer*. 2020; 146:1503-1513. doi:10.1002/ijc.32486
81. González Maldonado S, Motsch E, Trotter A, et al. Overdiagnosis in lung cancer screening: Estimates from the German Lung Cancer Screening Intervention Trial. *International Journal of Cancer*. 2021; 148:1097-1105. doi:10.1002/ijc.33295
82. Oudkerk M, Devaraj A, Vliegenthart R, et al. European position statement on

lung cancer screening. *Lancet Oncol*. 2017;18:e754-e766. doi:10.1016/s1470-2045(17)30861-6
83. National Lung Screening Trial Research T, Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365: 395-409.
84. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume ct screening in a randomized trial. *N Engl J Med*. 2020;382:503-13.
85. Cheng YI, Davies MPA, Liu D, Li W, Field JK. Implementation planning for lung cancer screening in China. *Precis Clin Med*. 2019;2:13-44.
86. Nawa T, Fukui K, Nakayama T, Sagawa M, Nakagawa T, Ichimura H, et al. A population-based cohort study to evaluate the effectiveness of lung cancer screening using low-dose CT in Hitachi city, Japan. *Jpn J Clin Oncol*. 2019;49:130-6.
87. Sagawa M, Sugawara T, Ishibashi N, Koyanagi A, Kondo T, Tabata T. Efficacy of low-dose computed tomography screening for lung cancer: The current state of evidence of mortality reduction. *Surg Today.* 2017;47:783-8.
88. Lee J, Kim Y, Kim HY, et al. Feasibility of implementing a national lung cancer screening program: Interim results from the Korean Lung Cancer Screening Project (K-LUCAS). *Transl Lung Cancer Res*. 2021;10:723-736.
89. Zhou Q, Fan Y, Wu N, et al. Demonstration program of population-based lung cancer screening in China: Rationale and study design. *Thorac Cancer*. 2014;5:197-203.
90. Li N, Tan F, Chen W, et al. One-off low-dose CT for lung cancer screening in China: A multicentre, population-based, pros*pective cohort study.* Lancet Respir Med. 2022;10:378-91.
91. Yang P. PS01.02 National Lung Cancer Screening Program in Taiwan: The TALENT Study. *Journal of Thoracic Oncology*. 2021;16(3, supplement):S58.
92. Li C, Wang H, Jiang Y, et al. Advances in lung cancer screening and early detection. *Cancer Biol Med*. 2022;19:591-608.
93. Liang W, Chen Z, Li C, et al. Accurate diagnosis of pulmonary nodules using a noninvasive DNA methylation test. *J Clin Invest*. 2021;131.
94. Infante M, Cavuto S, Lutman FR, et al. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. *Am J Respir Crit Care Med*. 2009;180:445-53.
95. Infante M, Cavuto S, Lutman FR, et al. Long-term follow-up results of the DANTE trial, a randomized study of lung cancer screening with spiral computed Tomography. *Am J Respir Crit Care Med*. 2015;191:1166-1175.
96. Paci E, Puliti D, Lopes Pegna A, et al. Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. *Thorax*. 2017;72:825-831. doi: 10.1136/thoraxjnl-2016-209825.
97. Pastorino U, Rossi M, Rosato V, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. *Eur J Cancer Prev*. 2012;21:308-315.
98. Pastorino U, Silva M, Sestini S, et al. Prolonged lung cancer screening reduced 10-year mortality in the MILD trial: New confirmation of lung cancer screening efficacy. *Ann Oncol*. 2019;30:1162-1169.
99. Pastorino U, Boeri M, Sestini S, et al. Baseline computed tomography screening and blood microRNA predict lung cancer risk and define adequate intervals in the BioMILD trial. *Ann Oncol*. 2022;33:395-405.
100. Milanese, G., Sabia, F., Sestini, S., et al. feasibility and safety of lung cancer screening and prevention program during the COVID-19 Pandemic. *Chest*. 2021;160, e5–e7. https://doi.org/10.1016/j.chest.2021.02.072
101. Pastorino U, Bellomi M, Landoni C, et al. Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. *Lancet*. 2003;362:593-597.
102. Ciompi F, Chung K, van Riel SJ, et al. Towards automatic pulmonary nodule management in lung cancer screening with deep learning. *Sci Rep*. 2017;7:46878. doi: 10.1038/srep46878.
103. Schreuder A, Jacobs C, Lessmann N, et al. Combining pulmonary and cardiac computed tomography biomarkers for disease-specific risk modelling in lung cancer screening. *Eur Respir J*. 2021: 2003386. doi: 10.1183/13993003.03386-2020.
104. Schreuder A, Jacobs C, Lessmann N, et al. Scan-based competing death risk model for re-evaluating lung cancer computed tomography screening eligibility. *Eur Respir J.* 2022;59:2101613. doi: 10.1183/13993003.01613-2021.
105. Milanese G, Sabia F, Ledda RE, et al. Volumetric measurements in lung cancer screening reduces unnecessary low-dose computed tomography scans: Results from a single-center prospective trial on 4119 subjects. *Diagnostics*. 2022;12:229. doi: 10.3390/diagnostics12020229.
106 Pastorino U, Sverzellati N, Sestini S, et al. Ten-year results of the Multicentric Italian Lung Detection trial demonstrate the safety and efficacy of biennial lung cancer screening. *Eur J Cancer*. 2019;118:142-148.
107. Milanese G, Ledda RE, Sabia F, et al. Ultra-low dose computed tomography protocols using spectral shaping for lung cancer screening: Comparison with low-dose for volumetric LungRADS classification. *Eur J Radiol*. 2023;161:110760. doi: 10.1016/j.ejrad.2023.110760.
108. Silva M, Schaefer-Prokop CM, Jacobs C, et al. Detection of subsolid nodules in lung cancer screening: Complementary sensitivity of visual reading and computer-aided diagnosis. *Invest Radiol*. 2018;53:441-449.
109. Long-term surveillance of ground-glass nodules. Evidence from the MILD trial. *J Thorac Oncol*. 2012;7:1541-1546.
110. Silva M, Prokop M, Jacobs C, et al. Long-term active surveillance of screening detected subsolid nodules is a safe strategy to reduce overtreatment. *J Thorac Oncol*. 2018;13:1454-1463. doi: 10.1016/j.jtho.2018.06.013.
111. Balbi M, Sabia F, Ledda RE, et al. Surveillance of subsolid nodules avoids unnecessary resections in lung cancer screening: Long-term results of the prospective BioMILD trial. *ERJ Open Research*. 2024. DOI: 10.1183/23120541.00167-2024
112. Sozzi G, Roz L, Conte D, et al. Plasma DNA quantification in lung cancer computed tomography screening: Five-year results of a prospective study. *Am J Respir Crit Care Med*. 2009;179:69-74.
113. Boeri M, Verri C, Conte D, et al. MicroRNA signatures in tissues and plasma predict development and prognosis of computed tomography detected lung cancer. *Proc Natl Acad Sci U S A.* 2011;108:3713-3718.
114. Sozzi G, Boeri M, Rossi M, et al. Clinical utility of a plasma-based miRNA signature classifier within computed tomography lung cancer screening: A correlative MILD trial study. *J Clin Oncol*. 2014;32:768-773.
115. Rundo L, Ledda RE, di Noia C, et al. A low-dose ct-based radiomic model to

improve characterization and screening recall intervals of indeterminate prevalent pulmonary nodules. *Diagnostics (Basel)*. 2021;11:1610. doi: 10.3390/diagnostics11091610.
116. Fortunato O, Huber V, Segale M, et al. Development of a Molecular Blood-Based Immune Signature Classifier as Biomarker for Risks Assessment in Lung Cancer Screening. *Cancer Epidemiol Biomarkers Prev*. 202;31:2020-2029. doi: 10.1158/1055-9965.EPI-22-0689.
117. Sozzi G, Pastorino U. Small RNAs do it better. Editorial. *J Thorac Oncol*. 2023;18:1428-1430. doi: 10.1016/j.jtho.2023.08.019.
118 Sverzellati N, Guerci L, Randi G, et al. Interstitial lung diseases in a lung cancer screening trial. *Eur Respir J*. 2011;38:392-400.
119. Calabrò E, Randi G, La Vecchia C, et al. Lung function predicts lung cancer risk in smokers: a tool for targeting screening programs. *Eur Respir J*. 2010;35:146-151.
120. Pastorino U, Morelli D, Marchianò A, et al. Inflammatory status and lung function predict mortality in lung cancer screening participants. *Eur J Cancer Prev*. 2018;27:289-295.
121. Sverzellati N, Cademartiri F, Bravi F, et al. Relationship and Prognostic Value of ModiMILDfied Coronary Artery Calcium Score, FEV1, and Emphysema in Lung Cancer Screening Population: The MILD Trial. *Radiology*. 2012 Feb;262:460-467.
122. Kang HW, Ahn WJ, Jeong JH, et al. Evaluation of fully automated commercial software for Agatston calcium scoring on non-ECG-gated low-dose chest CT with different slice thickness. *Eur Radiol*. 2022;33:1973-1981.
123. Balbi M, Sabia F, Ledda RE, et al. Automated coronary artery calcium and quantitative emphysema in lung cancer screening: Association with mortality, lung cancer incidence, and airflow obstruction. *J Thorac Imaging*. 2023;38:W52-W63.
124. Sabia F, Balbi M, Ledda RE, et al. Fully automated calcium scoring predicts all-cause mortality at 12 years in the MILD lung cancer screening trial. *PLoS One*. 2023;18:e0285593. doi: 10.1371/journal.pone.0285593.
125. Ruggirello M, Valsecchi C, Ledda RE, et al. Long-term outcomes of lung cancer screening in male and female. *Lung Cancer*. 2023;185:107387. doi: 10.1016/j.lungcan.2023.107387
126. Gallus S, Lugo A, Suatoni P, et al. Effect of Tobacco Smoking Cessation on C-Reactive Protein Levels in A Cohort of Low-Dose Computed Tomography Screening Participants. *Sci Rep*. 2018;8:12908. doi: 10.1038/s41598-018-29867-9.
127. Pozzi P, Munarini E, Bravi F, et al. A combined smoking cessation intervention within a lung cancer screening trial: A pilot observational study. Tumori. 2015; 101:306-311.
128. Pastorino U, Ladisa V, Trussardo S, et al. Cytisine therapy improved smoking cessation in the randomized screening and multiple intervention on lung epidemics lung cancer screening trial. *J Thorac Oncol*. 2022;17:1276-1286.
129. Milanese G, Sabia F, Sestini S, et al. Feasibility and safety of lung cancer screening and prevention program during the COVID-19 pandemic. *Chest*. 2021;160:e5-e7. doi: 10.1016/j.chest.2021.02.072. Epub 2021 Mar 18.
130. Dresler C, Evans WK. Breathing life into lung cancer screening trials. *J Thorac Oncol*. 2022;17:1244–1246.

13

BIOLOGY

Raghav Chandra,[1] **Michele Carbone,**[2] **John V. Heymach,**[3] **Tetsuya Mitsudomi,**[4] **Rolf A. Stahel,**[5] **and John D. Minna**[1] | [1]University of Texas Southwestern Medical Center, Dallas, USA; [2]University of Hawaii Cancer Center, Honolulu, USA; [3]The University of Texas MD Anderson Cancer Center, Houston, USA; [4]Kindai University, Osaka-Sayama, Japan; [5]University of Zurich, Zurich, Switzerland.

CELLULAR AND MOLECULAR BIOLOGY AS A KEY COMPONENT OF LUNG CANCER PATHOGENESIS AND BEHAVIOR

Lung cancer is the leading cause of cancer-related mortality worldwide, comprised of a group of clinically and biologically distinct tumor types, including non-small cell lung cancer (NSCLC), small cell lung cancer, (SCLC) (Figure 1) and respective histologic subtypes within these two major classifications.[1] Work by a large cadre of IASLC investigators have shown the important connections of lung cancer biologic features with clinical-pathologic characteristics and pathogenesis. Thus, a key insight coming from these IASLC investigations was that a detailed understanding of lung cancer cellular and molecular biology would lead to a "roadmap" for the better understanding of lung cancer early detection, prevention, prognosis, and therapeutic approaches. These studies also led to an appreciation of both inter-tumor heterogeneity in lung cancer molecular and cellular biology and also information on heterogeneity

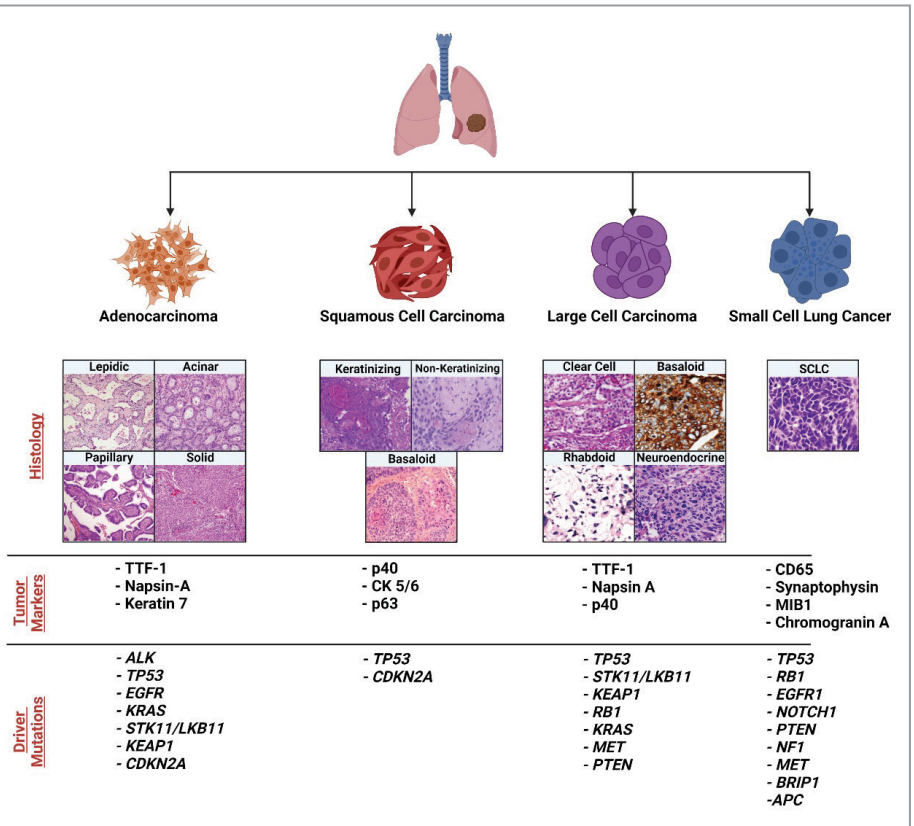


Figure 1. Lung cancers are stratified into two major subtypes: NSCLC, which includes adenocarcinoma and squamous cell carcinoma, and SCLC. Large cell carcinomas are a rare heterogenous subtype of lung cancer identified as diagnoses of exclusion. Between these subtypes, distinct histologic patterns have been documented, and specific tumor markers can be used to distinguish lung cancer subtypes from each other. Several key driver mutations associated with carcinogenesis and tumor progression for each subtype have been identified, and several are potential therapeutic targets.[6,342-347]

within individual lung cancers. Thus, underlying molecular and cellular biology drives and influences clinical behavior. These "behaviors" include local growth, invasion, metastases, initial evasion of immune responses, responses to therapy of all types, and the development of therapeutic resistance, gene/protein expression programs, genetic and epigenetic alterations (oncogenome), and the tumor microenvironment, all of which dramatically impact patient outcomes and survival.

Therefore, a fundamental understanding of lung cancer's cellular and molecular biology is essential to rationally approach optimal lung cancer prevention, early diagnosis, determination of prognosis, and treatment selection for individual patients ("precision medicine"). With the molecular changes involved in lung cancer pathogenesis, the overarching concept is that understanding these mechanisms will provide the roadmap to both develop precision medicine biomarkers, but also identify "acquired vulnerabilities" (differences between tumor and normal cells) that have developed or were exposed during lung cancer pathogenesis that can be attacked for prevention ("early interception") and therapy. The long term goal of such interception of lung cancer at multiple stages is to return patients to normal lives. These molecular and cellular biologic studies also identified that lung cancers exhibited all of the well-known "hallmarks of cancer."[2] As part of this review we also identify current Major Knowledge Gaps in the areas discussed.

MOLECULAR AND CELLULAR BIOLOGY OF LUNG CANCER

NSCLC Subtypes and Tumor Biology

NSCLCs reflect a biologically and clinically heterogeneous subset of tumors, including lung adenocarcinoma (LUAD) and lung squamous cell carcinomas (LUSC), as well as large cell carcinomas, including large cell neuroendocrine cancers (LCNECs), mixed histologic types, and uncommon variants discussed in detail in other chapters.[3] Biomarkers representative of LUAD include thyroid transcription factor 1 (TTF1), napsin A, and keratin 7.[4,5] Molecular markers representative of LUSC include p40, CK5/6, and p63.[6]

NSCLC early pathogenesis

NSCLC develops through a series of pathologic molecular changes and genetic mutations arising from premalignant lesions. These progenitor cells are ill-defined, but preclinical studies suggest that bronchioalveolar stem cells and type II alveolar cells (LUAD) and tracheal basal cells (LUSC) may be implicated (see Chapter 14).[7] Several risk factors for lung cancer have been identified, including intake of alcohol, cured meats, deep-fried foods, and exposure to respiratory toxins like polycyclic aromatic hydrocarbons, silicates, asbestos, and nuclear materials.[8] However, cigarette smoking, whether primary or secondhand exposure, remains the strongest independent risk factor for lung cancer, with 85% to 90% of all lung cancer patients having a history of smoking.[8,9]

Recently, the importance of exposure to pollution with small 2.5 micron air particles (e.g., identified from zip codes) and their lung carcinogenic effect has been identified and appears to be of major importance as a risk factor and a new target for lung cancer prevention.[10-12] Defining the quantitative importance of exposure to 2.5-micron particles is a Major Knowledge Gap.

Molecular and cellular biology of lung cancer preneoplasia

The airway field of injury theory, illustrated in Figure 2, posits that toxin-induced injury to the respiratory epithelium results in genetic mutations and epigenetic changes resulting in malignant transformation. This could be due to clonal expansion of a single mutant clone that propagates across the epithelial respiratory lining, from polyclonal stem cells arising from host responses to toxin damage, each with genetically diverse mutational profiles, or from paracrine effects from the malignant cells and their TME.[9]

Recently there have been major advances and molecular studies of lung cancer preneoplasia.[13-19] These have identified many key events, including progression-specific methylation changes on

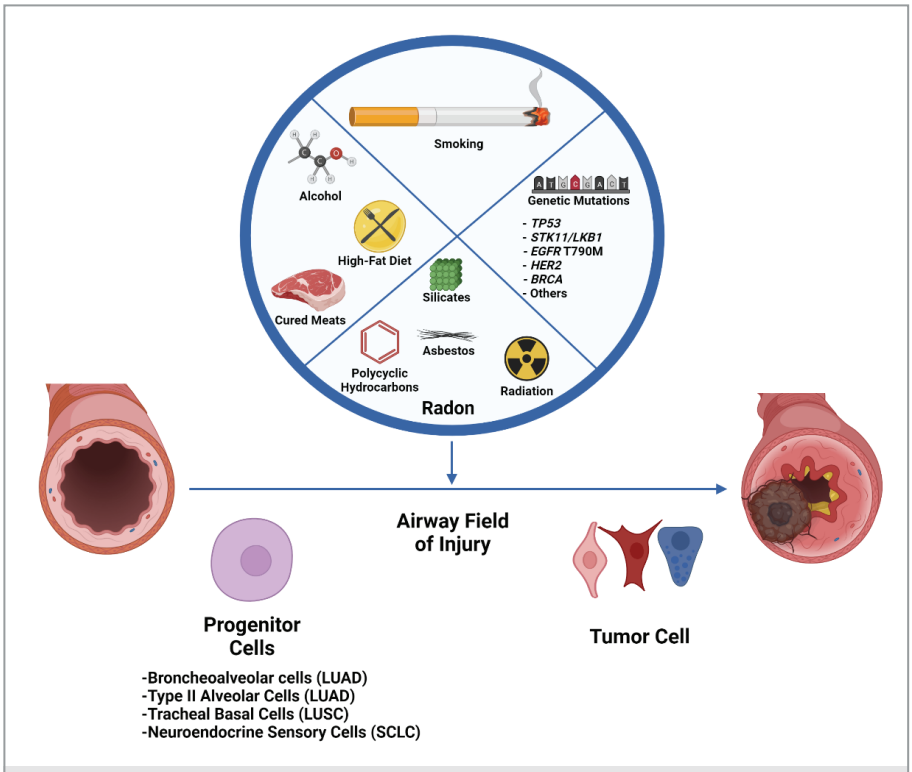


Figure 2. The "airway field of injury" hypothesis suggests that lung cancers arise from benign progenitor cells exposed to carcinogenic substances like cigarette smoking, certain diets, exposure to toxins like polycyclic hydrocarbons and asbestos, radiation, or from underlying genetic mutations. These progenitor cells develop genetic mutations, become dysplastic, and ultimately, undergo malignant transformation.

a background of widespread heterogeneity and chromosomal instability signature[19]; potential immune escape mechanisms, such as impaired antigen presentation by genomic and epigenetic and immunomodulators expression changes, which occur in the precancer lesions and not stroma (see later section on "Mechanisms of immune checkpoint blockade escape in lung cancer")[18]; driver mutations, chromosomal copy number aberrations and aberrant DNA methylation that impact host immune responses and facilitate immune evasion, promoting the outgrowth of fit subclones in preneoplasia into dominant clones in invasive LUAD[17]; perturbed metabolic pathways that emerge early in premalignant lesions[16]; and minimal somatic mutations in pivotal driver mutations and essential proliferative factors are the only detectable somatic mutations in the very early-stage of adenocarcinoma in situ lesions (AIS), followed by copy number changes and global DNA hypomethylation at later stages.[15]

Complicating all of these studies is the recent discovery in persons who do not have lung cancer, of multiple mutations in genes known to be involved in lung cancer pathogenesis in the lung epithelium of persons with chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) in a manner similar to that found in clonal hematopoiesis of indeterminate potential (CHIP) in the peripheral blood.[20,21] Clearly, how to integrate our understanding of lung cancer pathogenesis of these large scale and frequent presence of such mutations in persons who do not have lung cancer, particularly with regard to their use in early detection and prevention efforts, represents a Major Knowledge Gap. In addition, the field of injury needs to include studies relating to the "field of immune escape" of precancerous and cancerous lesions, as this represents another Major Knowledge Gap.

Molecular Alterations in NSCLC With Respect to Identifying Lung Cancer Vulnerabilities With Associated Biomarkers to Facilitate Precision Medicine

Identifying lung cancer vulnerabilities through detailed molecular analyses

Developing new lung cancer therapies involves several major requirements, including identifying a lung cancer vulnerability, finding a drug that targets this vulnerability, identifying the target of this drug, identifying precision medicine biomarkers in the tumor cells (e.g., mutation or some other molecular change, mRNA or protein expression), and establishing a therapeutic window for targeting the vulnerability that such lung cancer

cells are preferentially killed over normal cells. After the discovery of targeting oncogene addiction in many never-smoking lung cancers via mutant EGFR through the use of tyrosine kinase inhibitors (TKIs), there was great hope that a detailed molecular characterization of lung cancer would identify other such vulnerabilities (oncoproteins with known activities that could be "drugged") and provide all the other essential ingredients for new, potentially curative therapies. While this has been true for a handful of genes (e.g., mutant EGFR), by and large, this is still a work in progress. Over the past 20 years there have been a large number of studies with detailed molecular analyses, including protein coding (whole exome), whole genome sequencing, mRNA transcriptomic expression, and proteomics expression analyses of large number of NSCLC tumor specimens. This information is deposited and available for study in accessible databases, such as The Cancer Genome Atlas (TCGA) project.[22-29]

Several activating and inactivating oncogenic driver mutations have been identified in LUAD, including *EGFR, ALK, KRAS, TP53, KEAP1, STK11*, *HER2,* and *NF1*. Frequent mutations in LUSC include *CDK2NA* and *TP53*.[3] Dominant oncogenes include *EGFR, ALK, KRAS, RET*, and *BRAF*. Frequently mutated tumor suppressor genes include *TP53, CDKN2A, STK11*, and *KEAP1* (Figure 1). Several of these oncogenes are potential therapeutic targets for which targeted therapies have gained FDA approval or are under active preclinical and clinical investigation and are discussed in detail elsewhere in this publication (see Chapters 11, 12, and 14). While tumor suppressor genes (TSGs) as co-mutations may influence response to therapies, no therapies targeting TSGs alone have moved into the clinic. These mutations, copy number changes (amplifications and deletions), epigenomic changes, mRNA, and protein expression changes found in patient tumors have been integrated with those found in preclinical models to try to identify new lung cancer acquired vulnerabilities and potential therapeutic targets.[30-35]

Only a few of these (all "dominant oncogenes") have been found through a series of clinical translational studies to be applicable for developing precision medicine targeted therapy of NSCLC, with key examples being EGFR, ALK, KRAS, RET, ROS 1, BRAF, NRG1, MET discussed in detail elsewhere in this volume.[36] Thus, a Major Knowledge Gap is how to determine both the functional role of the many molecular alterations that have been described in lung cancer, beyond those already known for the current small group of targetable mutated oncoproteins identified by molecular studies as oncogenes or tumor suppressor genes, as well as potential lung cancer therapeutic vulnerabilities these changes are postulated to create. Advances in functional genomics provide a way to fill in the knowledge gap of the importance of individual and combinations of genes in lung cancer pathogenesis and vulnerabilities (discussed later in preclinical model studies).

Identification of NSCLC molecular characteristics predicting response to chemotherapy

While there have been multiple attempts to identify oncogenotypes, mRNA, and protein expression signatures that predict the response to clinically available chemotherapy, none have progressed to be routinely employed in clinical practice, representing another Major Knowledge Gap. Of interest, there have been chemical library screens in a "chemistry first" approach that identified small molecules with selective toxicity for certain patient-derived NSCLC cell lines. These studies have identified mutational or expression correlates predicting responses to new therapies and targets for NSCLC.[37,38] Similarly, studies of drug response phenotypes in large, annotated patient-derived tumor cell-line collections provide a preclinical stratification scheme for anticancer agents. These generate genetic predictions of drug response in the preclinical setting, leading to clinical trial testing to facilitate the development of personalized medicine approaches, which are later elaborated in the discussion of preclinical models.[31]

A key issue for all of these studies is while multiple small

molecules with potent and highly selective anti-lung cancer activity can be identified, finding the targets of these molecules and the mechanisms of action that they use for their anti-cancer activity remains a formidable challenge and a Major Knowledge Gap. Likewise, it is important to have a "therapeutic window" so that the new therapies have selective toxicity for lung cancers over normal cells. In this regard, the current screens have identified many compounds that selectively kill subsets of NSCLCs but not normal lung epithelial cells.[37,38]

Finally, while there was hope that each new therapy would have a mRNA or protein expression signature predicting which lung cancers would be primarily sensitive or resistant to the new therapies, even extending this to other features such as copy number variation or tumor metabolomics, there was no one consistent parameter that identified the large majority of new lung cancer vulnerabilities or responses to currently available chemotherapy agents.[38] In fact, these studies showed that even within one histologic type of NSCLC, specifically LUAD, there were many different previously unappreciated subgroups. Thus, defining subgroups within the major known types of lung cancer that are of clinical translational/therapeutic importance remains a Major Knowledge Gap.

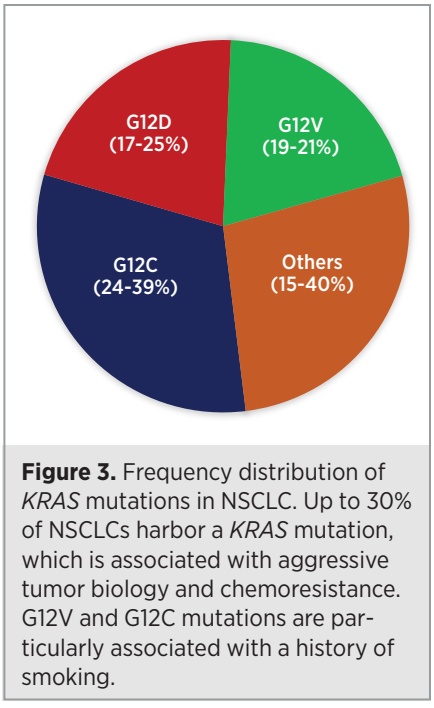


Figure 3. Frequency distribution of *KRAS* mutations in NSCLC. Up to 30% of NSCLCs harbor a *KRAS* mutation, which is associated with aggressive tumor biology and chemoresistance. G12V and G12C mutations are particularly associated with a history of smoking.

Identification of NSCLC molecular characteristics predicting response to immune checkpoint blockade (ICB) immunotherapy and potential acquired resistance mechanisms

With the discovery of the dramatic clinical response to ICB therapy in a subset (approximately 15% to 20%) of patients with NSCLC, including long-term relapse-free survival, there has been intense work to try to identify tumor molecular predictors of which patients would have or not have such responses; understand the mechanisms of immune evasion that generated these clinically important different patient groups (see clinical trials discussed in detail in other chapters); and identify the cancer-associated antigens or neoantigens that elicited these anti-tumor immune responses, all representing Major Knowledge Gaps in the field of anti-lung cancer immunotherapy.[39-41]

Ultimately these anti-tumor immune responses are related to the development of immune responses against tumor-related or neoantigens related to the tumor mutation burden (TMB) and neoantigen burden.[42-44] While there are several host factors (blood neutrophil/lymphocyte ratio, microbiome) we focus here on tumor molecular changes.[43,45,46] TMB and tumor PD-L1 expression are independently associated with durable clinical benefit, while copy number alterations, EGFR, and LKB1/STK11 mutations were associated with lack of benefit.[43-49]

In second-line therapy for NSCLC, immune checkpoint inhibitors (ICIs) were associated with prolonged overall survival (OS) compared with docetaxel in *EGFR* wild-type but not *EGFR* mutant groups. Conversely, they prolonged overall survival in the *KRAS*-mutant subgroup but not in the *KRAS* wild-type subgroup.[50] Consistently, there is a known lack of response compared to chemotherapy and increased toxicity of ICB in tumors with never-smoking lung cancer-associated oncoprotein mutations such as *EGFR* that have available *TKI* targeted therapy.[50,51] Tumor-associated immune cell populations (infiltrating CD8+ T cells, genetic signatures of immune cell activation, and indications of DNA mismatch repair abnormalities such as microsatellite instability, which is uncommon) are associated with ICB responses.[46,48] The relative treatment benefits were similar according to smoking status,

performance status, age, histology (LUAD, LUSC), or sex.[50]

A real-world study identified PD-L1 expression, disease burden, and STK11 and JAK2 alterations as features associated with a higher likelihood of early progression on ICB-monotherapy, while CDKN2A alterations were associated with worse long-term outcomes in ICB-chemotherapy treated patients.[52] Recently, a database and a web platform were established to investigate biomarkers of immunotherapy response in a large cohort of solid tumor samples, including NSCLC, which will facilitate identifying patients likely to respond or be resistant to ICB therapy.[53]

To determine potential mechanisms of acquired resistance to ICB therapy, pre- and post-treatment/relapse tumor biopsies were molecularly compared for patients with NSCLC treated with ICB with or without chemotherapy, those treated with chemotherapy alone, and those treated only with a TKI. The genomic alterations found at the time of acquired ICB resistance included: activating mutations in PDGFRA, ERBB2; loss-of-function mutations in STK11, B2M, NF1/2, APC, CDKN2A/B, MAP3K1, KEAP1, MAP2K4, and JAK1; and copy number loss of B2M, STK11, SMARCA4, KEAP1, CD274/PDCD1LG2, and JAK1.[54,55] This study found the mechanisms of acquired resistance to ICB therapy to be heterogeneous, indicating the need for both tumor rebiopsy at the time of identification of acquired resistance and the need for personalized post-ICB treatment approaches, which represents a Major Knowledge Gap.[54,55]

SCLC Subtypes and Tumor Biology

SCLC early pathogenesis

SCLC is biologically and clinical distinct from NSCLC and represents 16% of lung cancer cases.[56] SCLC is an extremely aggressive malignancy with early metastatic spread precluding curative resection in most cases and rapid development of chemoresistance, resulting in a dismal prognosis. Five-year relative survival rates have remained poor, ranging from 4.9% to 6.4%.[57] SCLCs express neuroendocrine (NE) markers, including calcitonin-gene related peptide, NCAM1, Myc, achaete-scute complex homolog-like 1 (ASCL1), neurogenic differentiation factor 1 (NEUROD1), synaptophysin, TTF1, MIB1, CD65, and chromogranin A (Figure 1).[58,59]

Smoking is the most significant risk factor associated with SCLC (up to 97% of cases), leading to the high level of somatic mutations identified in these tumors.[58,60] Large numbers of both early-stage resected SCLC and later-stage metastatic tumors have now been sequenced for mutations and profiled for mRNA expression, with the results deposited in accessible databases.[61,62] These studies show a very high tumor mutation burden in SCLCs and smoking-associated mutational signatures. The most frequently identified mutations in SCLC include *TP53, RB1, CYLD, EGFR1, BRIP1, NOTCH1, PTEN, APC, NF1, MET*, as well as overexpression and amplifications of myc family members c-myc (MYC), MYCL, and MYCN.[60,63] Unlike NSCLC, mutations in tumor suppressor genes dominate the genetic landscape of SCLC.[64] Indeed, at least 90% of SCLCs harbor *TP53* and *RB1* mutations.[64,65]

Recently, SCLC arising in never-smokers has also been identified. These occur in younger patients with female predominance and have lower tumor mutation burden, no smoking mutational signatures, and fewer TP53 mutations, indicating a different tumor biology.[66] Importantly, proteomic analyses of SCLCs are now available and provide new biologic insights and identify potential therapeutic targets like the GNAS/PKA/PP2A axis in SCLC and PARP inhibitor-induced degradation of lineage-specific oncoproteins.[67-70] Despite all of this detailed molecular information, a Major Knowledge Gap is whether the histologic normal epithelium contains similar changes that could be used for early diagnosis, including identification of patients at the highest risk for developing SCLC, and potentially used for studying the impact of early interception of SCLC before it becomes clinically evident.

Molecular and biologic classification of SCLC subtypes

Investigation of epigenetic and

genetic features distinguished two major subtypes based on differential expression of key NE markers.[65] These were historically classified as "classic" SCLC (*ASCL1^{high}/NEUROD1^{low}*) or "variant" SCLC (*ASCL1$^{low/variable}$/NEUROD1^{high}*).[65] Exploration of the epigenetic and transcriptomic landscape of SCLC in patient samples, cells, genetically engineered mouse models, and patient-derived xenografts (PDXs) has been synthesized into four major proposed lineage transcription factor-defined SCLC subtypes: Neuroendocrine (SCLC-A and SCLC-N) and Non-Neuroendocrine, or non-NE, (SCLC-Y and SCLC-P).[65,71-73] To meaningfully distinguish between SCLC-A and SCLC-N tumors, a "neuroendocrine score" has been established based on the top 25 strongly and least strongly associated with NE differentiation.[74] It is important to note that recent investigations demonstrate that these may not be distinct entities, but rather reflections of different stages of disease which may be heterogeneously present in individual patient tumors.[75] A Major Knowledge Gap is whether any classification, such as those defined by A, N, Y, and P transcription factor subtypes, provides useful information on selection of the best therapies for individual patients. Thus, while this classification system describes tumor biology, the translational impact of these subtypes, including whether they identify clinically impactful therapeutic targets, is not yet clear (Figure 4).[76-79]

ASCL1: Some of downstream *ASCL1* targets may be potentially therapeutically actionable. Prominent examples include *Delta-like protein (DLL3)*, which suppresses Notch signaling and promotes tumor growth in NE tumors.[80] As DLL3 is highly and specifically expressed in SCLC cells, a variety of DLL3 inhibitors (Rovalpituzumab, AMG757, AMG119) are currently in various stages of clinical trials for SCLC with mixed clinical response.[80,81]

SCLC-N: Overexpression of *NEUROD1* is associated with increased tumor cell survival and migratory capacity in SCLC through activation of several downstream potential therapeutic targets, including *TrkB, NCAM, Aurora Kinase A (AURKA)*, and others.[76,82]

SCLC-P: SCLCs in this category are non-NE and are defined by high expression of *POU class 2 homeobox 3 (POU2F3)* and low expression of *ASCL1* and *NEUROD1*.[65,76] These represent the least common subtype of SCLC and are classified as having a "tuft cell-like" appearance.[71] These lesions may be susceptible to insulin-like growth factor 1 (IGFR1) inhibition, as recent CRISPR screens have demonstrated SCLC-P tumors to be dependent on IGFR1 for growth.[71] SCLC-P tumors are also enriched for immune-related genes.[83]

SCLC-Y: SCLC-Y tumors are defined by high expression of

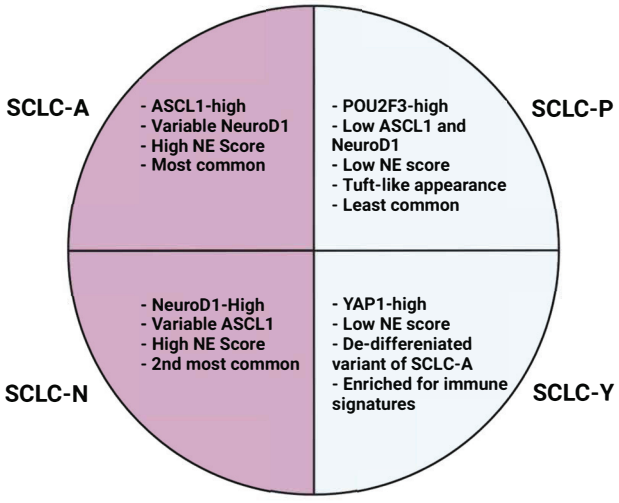


Figure 4. Recent consolidation of transcriptomic and epigenetic data from preclinical models and patients has yielded four major SCLC subtypes. SCLC-A and SCLC-N are enriched for NE markers, while SCLC-P and SCLC-Y are not. SCLC-A tumors are the most commonly identified, while SCLC-P lesions are the least common. SCLC-Y tumors may reflect a de-differentiated variant of SCLC-A tumors via *MYC*-mediated upregulation of Notch signaling. These tumors are particularly enriched for immune gene signatures.

Yes-associated protein 1 (YAP1), a transcriptional co-activator regulated by the Hippo pathway.[65,84] *YAP1* expression is among the top 25 genes not associated with NE differentiation on the scoring algorithm established by Zhang and colleagues.[74] Nuclear translocation of *YAP1* is associated with cell growth and metastasis in several cancers and may be associated with chemoresistance in SCLC.[85] YAP1 expressing tumors may be particularly sensitive to immunotherapy and are enriched for high expression of *MTOR, CD38, LAG-3, PD-L1*, interferon-γ-associated genes, genes associated with T-cell inflammation, *HLA*, and T-cell receptor genes.[76,86] Recently, tumors expressing YAP1 previously thought to be SCLC are probably best classified as a SMARCA4-deficient undifferentiated thoracic malignancies.[87]

Molecular and biologic correlates of SCLC response and resistance to chemotherapy

While the majority of SCLC patients respond to initial standard platin-etoposide chemotherapy, ultimately over 90% of patients develop resistance to multimodal chemotherapy.[88] Precision medicine biomarkers identifying which SCLC before treatment will be sensitive or resistant to platin-etoposide therapy, and the mechanisms underlying primary and acquired resistances represent Major Knowledge Gaps. Several mechanisms for how SCLCs rapidly develop chemoresistance have been identified using patient-derived preclinical models, including DNA damage repair, glutathione-mediated inhibition of drug-DNA interactions, aberrant DNA methylation, and others.[88,89] Overexpression of numerous genes is associated with acquired chemoresistance in SCLC, including *EZH2, NRBF2, MYC,* and *YAP*.[89-92] Downregulation of SLFN11 expression in SCLC is highly correlated with platin-etoposide resistance.[89,93] Recently, ecDNA leading to high levels of myc amplification has been found in a subset of SCLCs.[94,95] These ecDNA MYC amplifications, particularly those involving c-MYC (MYC), lead to tumor plasticity and a high degree of tumor heterogeneity. Importantly, ecDNA of MYC and other MYC family members, MYCL and MYCN, are associated with the development of resistance to platin-etoposide chemotherapy and cross-resistance to other clinically used cancer chemotherapies.[94,95]

Molecular biologic correlates of SCLC response to immunotherapy

Given the large TMB found in SCLC and occasional autoimmune reactions found in SCLC patients, there was an expectation that ICB therapy would lead to dramatic results (and potential toxicities) in SCLC patients. However, while ICB is beneficial as frontline therapy for SCLC, the overall survival benefits are modest (a few months).[78,96] Nevertheless, more patients are alive at three years when treated with ICB + etoposide platinum chemotherapy compared to chemotherapy alone.[96] These results identified a Major Knowledge Gap in understanding the molecular biologic correlates of SCLC responses and lack of responses to ICB therapy.

Downregulation of MHC and tumor cell autonomous immune expression is seen in ASCL1/neuroendocrine expressing "classic" SCLC, while re-expression of these programs is found with loss of NE features.[97] The identification of a group of SCLCs with low expression of all three transcription factors, ASCL1, NEUROD1, and POU2F3, or low expression of all three transcription factor signatures accompanied by an inflamed gene signature (SCLC- I), identified patients deriving the greatest benefit from the addition of immunotherapy to chemotherapy.[98] There is also a distinct subset of non-NE SCLCs that re-express MHC and are associated with ICB benefit.[99]

Also identified was a PLCG2-high expressing SCLC phenotype associated with stem like pro-metastatic features, worse survival, and less immune infiltration with T-cell dysfunction, and a profibrotic, immunosuppressive monocyte/macrophage population.[100] Molecular analyses of pretreatment SCLC specimens annotated by patient responses identified both neuroendocrine (NE) and non-NE SCLC subsets that showed ICB responses.[101] NE tumors with low tumor-associated macrophage (TAM) but high effector T-cell signals demonstrated longer overall

survival with PD-L1 blockade and CE versus platin-etoposide alone than non-NE tumors with high TAM and high T-effector signal.[101] Recently, a telomere-targeting drug, 6-Thio-2′-deoxyguanosine, depleted cancer initiating cells and promoted anti-tumor immunity in SCLC.[102]

Large Cell Neuroendocrine Cancers (LCNECs) and Related Pulmonary Neuroendocrine Tumors

LCNECs, considered a subtype of NSCLC, make up 1-3% of primary lung cancers, usually occurring in older male heavy cigarette smokers, and express neuroendocrine features such as chromogranin-A, synaptophysin, and CD56.[103,104] These are aggressive tumors, often metastatic, and have a high recurrence rate even after presumably curative surgical resection, with an overall five-year survival rate of 35%.[103,104] There is no standard chemotherapy or immunotherapy treatment with documented survival or quality of life benefit for LCNEC patients, representing a Major Knowledge Gap.[103]

George's comprehensive genomic and transcriptomic analysis of LCNECs identified two molecular subgroups:

- Type I LCNECs (37% of all LCNECs) had a NE profile of ASCL1(high)/DLL3(high)/Notch(low) expression phenotype with biallelic TP53 and STK11/KEAP1 changes.[105]
- Type II LCNECs (42% of all LCNECs) had biallelic inactivation of TP53 and RB1 and a NE profile of ASCL1(low)/DLL3(low)/Notch(high) and also showed upregulated expression of immune-related pathways.[105]

Whether these two groups have common or distinct therapeutic vulnerabilities is another Major Knowledge Gap. A "real-world" retrospective survival analysis of 125 advanced LCNEC patients treated with (41) or without (84) ICIs showed median overall survival of 12.4 months associated with ICI treatment, compared to 6 months for patients not receiving ICI therapy, suggesting a potential positive impact of ICI on overall survival of LCNECs.[106] Thus, a Major Knowledge Gap is identifying the molecular characteristics of LCNECs which will benefit from ICI.

Pulmonary carcinoids including "atypical" (more aggressive carcinoids) are reviewed in detail elsewhere in this volume and in the recent literature, including their molecular genetics.[104,107] Recent molecular analyses of typical and atypical carcinoids and LCNECs have identified a group of "supra-carcinoids." These supra-carcinoids have mRNA expression patterns more aligned with SCLC than carcinoids.[107] Importantly these supra-carcinoids expressed high levels of immune checkpoint genes, interferon-gamma, and MHC class I and II genes, indicating they may respond to ICI therapy.[107] Biobanks of patient derived pulmonary neuroendocrine organoids were created for carcinoids of all types and LCNECs, and they showed the dependencies of these on epidermal growth factor (EGF) as a potential therapeutic vulnerability.[108]

Lung Cancer Cell Proteogenomics and Their Surface Expression as New Cancer Therapeutic Targets Lead to the Development of Antibody Drug Conjugates (ADCs) and Bispecific Antibodies as Novel Therapies

Comprehensive molecular analyses of lung cancers for changes in mutations, copy number variation, methylation, and mRNA and microRNA expression have recently been combined and complemented with proteomics analyses, providing proteogenomic analyses.[67,109-114] These studies highlight the importance of associating genomics with their functional proteomic outcome.[112] Importantly for the development of new therapeutic approaches, proteogenomic studies are providing detailed lung cancer cell surface protein expression profiles coupled with knowledge of cancer-specific expression ("therapeutic window"), and thus, the potential for antibody targeting of these lung cancer-associated surface phenotypes using antibody drug conjugates (ADCs) and bispecific antibodies.[115-122]

ADCs represent a new therapeutic class made up of an antibody directed at a tumor epitope, connected by a linker to a cytotoxic payload, showing anti-tumor

activity in many malignancies, including lung cancer. Current examples of antigenic targets for ADCs with potential activity in NSCLC include *HER2* (Famtrastuzumab deruxtecan and Sacituzumab govitecan), *HER3* (Patritumab deruxtecan), *TROP2* (Datopotamab-deruxtecan), and MET (Telisotuzumab vedotin), and in SCLC, *B7H3* (Ifnatamab deruxtecan), and *SEZ6* (ABBV-1011).[122] Bispecific antibodies are designed to bind two different antigens, either on the tumor cell providing added specificity and targeted therapy, or by enabling them to connect immune cells with cancer cells, resulting in enhanced tumor cell killing.[123] Bispecific antibodies target sites in the tumor cell and an interaction with tumor and T-cells. An example of a bispecific antibody targeting two antigens on the surface of lung cancer cells, such as MET and EGFR, is amivantamab.[123] An example of a bispecific T-cell engager (BiTE) is tarlatamab which targets DLL3 expression on SCLCs and CD3 on T cells leading to T-cell–mediated tumor lysis.[123,124]

Molecular Evolution of Lung Cancer Over Time

While there are numerous studies molecularly characterizing lung cancers at one point in time (usually at diagnosis or relapse), a Major Knowledge Gap exists in detailed molecular observations of lung cancers from individual patients over the course of their illness. Recently, the first results of the "TRACERx project" have been released, providing the first detailed tumor and biospecimen molecular analyses of a larger number of NSCLC patients over the course of their illness.[14,125-129] In TRACERx 421, NSCLC patients in the United Kingdom were profiled genomically for 1,644 tumor regions, analyzed for circulating tumor DNA (ctDNA) in their peripheral blood, and studied for immune cells targeting lung cancer, providing a picture for each patient from diagnosis until relapse.[128] TRACERx objectives were to study the relationship of intra-tumor heterogeneity to clinical outcomes, understand the effects of platin-doublet chemotherapy, understand cancer metastatic behavior, and track dynamics of intratumor mutational heterogeneity.[128] As part of these studies, they found that genetic changes common to all tumor cells in a patient ("truncal events"), such as MYC and receptor TKI pathways, were different than "subclonal events" (found in only some tumor cells) and included common changes, such as in LKB1/STK11, TP53, and KRAS.[127,128] They also found different types of molecular changes associated with metastases ("early and late divergence") and metastases that were either monoclonal or polyclonal.[126] In addition, standard chemotherapy with platin doublets played a role in tumor evolution and intratumor heterogeneity.[126] The most highly expressed mutant, or amplified, genes contributed to clonal selection.[129]

Finally, TRACERx, using blood samples from the patients, found that anti-tumor B-cell responses resulted in anti-tumor antibodies and that antibodies against human endogenous retroviruses promotes lung cancer immunotherapy.[130]

Molecular Correlates of Lung Cancer Metabolism

Metabolic phenotypes in lung cancer give rise to both inter-tumor and intra-tumor differences that can potentially be therapeutically targeted.[131] Lung cancers exhibit considerable inter-tumor heterogeneity for metabolism.[132] Many NSCLCs activate an NRF2-dependent transcriptional program-regulating serine and glycine metabolism, which is also related to clinical aggressiveness.[133] Enhanced glycolysis and glucose oxidation are common in NSCLCs; oxidation of multiple nutrients is found including lactate as a carbon source.[134] Metabolically heterogeneous regions are found in individual tumors, with potential contribution of non-glucose nutrients in well-perfused lung tumor areas.[132]

Relating to specific oncogenotypes, fatty acid oxidation mediated by acyl-CoA synthetase long chain 3 is required for mutant KRAS lung tumorigenesis.[135] Also, targeting de novo lipogenesis and the Lands cycle induced ferroptosis in KRAS-mutant LUAD.[136] Metabolomics profiling has the potential to predict efficacy of chemo-immunotherapy in NSCLC.[137] A combination of

KRAS and LKB1/STK11 mutations in NSCLC imposes a metabolic vulnerability related to a dependence on a cross-compartmental pathway of pyrimidine metabolism in an aggressive subset of NSCLC.[138] Similarly, LKB1 and KEAP1/NRF2 pathways were found to cooperatively promote metabolic reprogramming with enhanced glutamine dependence in KRAS-mutant LUADs.[139] A distinct metabolic phenotype of lung squamous cell carcinoma identified a selective vulnerability to glycolytic inhibition.[140] Many of the patient-derived NSCLC lines have extensive metabolomic annotation, which allows correlation to oncogenotype and RNA expression phenotypes.[141] Therapeutic approaches are possible since targeting pathways involved in detoxification of reactive metabolites arising from increased glucose metabolism in cancer can potentially be targeted.[142] Likewise, it is possible that targeting MYC-enhanced glycolysis can be used for the treatment of SCLC.[143] Recently, preclinical findings demonstrated that sirpiglenastat (DRP-104), already in clinical trials, suppressed tumor growth and increased responses to ICB therapy in KEAP1 mutant NSCLCs.[144]

Molecular Correlates of Lung Cancer Cachexia

While lung cancer can be associated with several paraneoplastic syndromes, including tumor-secreted endocrine syndromes and tumor-associated auto-immunity, perhaps the most important such paraneoplastic syndrome is lung cancer-associated cancer cachexia. Cancer cachexia is a common problem associated with advanced lung cancer and dramatically impacts patients' quality of life.[145] Of great importance, cancer-related cachexia impacts nutritional status, muscle mass, the efficacy of immunotherapy, and survival in NSCLC patients.[146] There have been recent advances for this Major Knowledge Gap in identifying the mechanisms underlying lung cancer cachexia.[147,148] In the TRACERx study, blood proteomic biomarkers found a significant association between circulating GDF15 and loss of body weight, skeletal muscle, and adipose tissue at tumor relapse, suggesting potential therapeutic targeting of GDF15 for cancer cachexia treatment.[147] A direct relationship to the tumor oncogenotype for lung cancer cachexia was identified when tumor loss-of-function mutations in STK11/LKB1 were found to induce cachexia.[148]

ROLE OF THE TUMOR MICROENVIRONMENT IN LUNG CANCER BIOLOGY AND THERAPY RESPONSE

The TME is a complex array of stroma, endothelial cells, fibroblasts, and immune cells surrounding cancer cells in the tumor, as illustrated in Figure 5. In the context of lung cancer biology, the TME is implicated in all facets of tumor progression, metastasis, and treatment resistance.[149] Lung cancers both influence and are, in turn, influenced by the TME. These include impacts on malignant behavior and response to chemotherapy, targeted therapy, and immunotherapy. While insight into the role of the NSCLC TME is extensive, comparatively little is known about the SCLC TME and its impact on tumor biology. The current Major Knowledge Gaps surrounding the TME in lung cancer include:

- Mechanistically, how does an individual tumor influence the TME to promote tumor growth?
- How does the tumor oncogenotype impact and influence the TME?
- How does the TME mechanistically impact and influence the behavior of individual lung cancers?
- Does the composition of the TME provide information regarding an individual lung cancer prognosis or as a guide to treatment?
- Can elements of the TME be therapeutically targeted to kill lung cancer cells or to enhance responses to chemotherapy, targeted therapy, immunotherapy, and radiation therapy?

LUNG CANCER TUMOR STROMA

Cancer-Associated Fibroblasts (CAFs)

Cancer-associated fibroblasts (CAFs) maintain the extracellular matrix (ECM) and contribute to tumor fibrosis, angiogenesis,

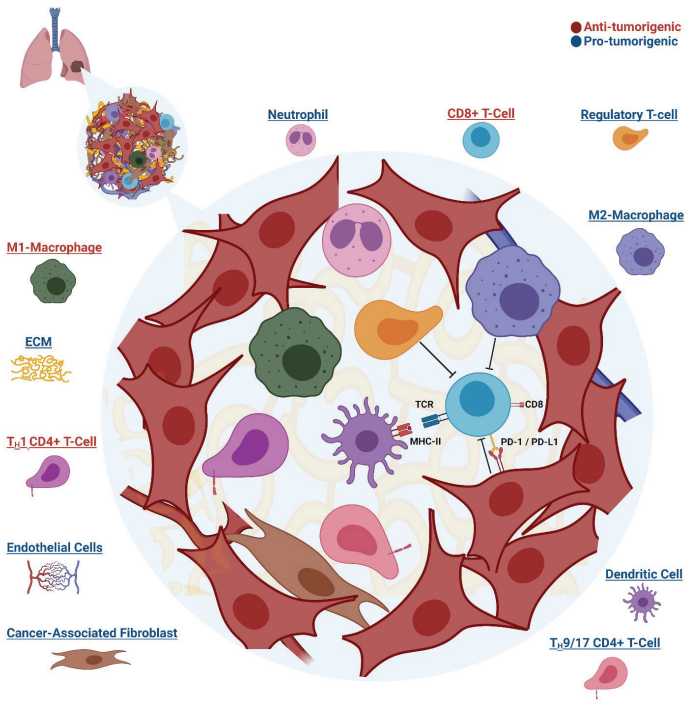


Figure 5. Components of the TME in lung cancer. Cells in the TME may have pro-tumorigenic (**blue**) or anti-tumorigenic (**red**) impacts on cancer cells. Cancer-associated fibroblasts remodel the ECM, promote desmoplasia, and contribute to immune evasion and metastasis. The ECM is a complex network of structural proteins that provides both a mechanical framework for the TME and engages in paracrine and autocrine signaling cascades. Endothelial cells form the tumor vasculature, and hypoxia-driven angiogenesis is a key facet of tumor progression. Tumor-associated macrophages exist on a spectrum between a pro-inflammatory, anti-tumorigenic, immunostimulatory M1 phenotype and an anti-inflammatory, immunosuppressive, pro-tumorigenic M2 phenotype. Neutrophils promote immunosuppression, EMT, and hypoxia, and are inversely associated with CD8+ T-cell infiltration. Regulatory T-cells potently induce immunosuppression and inhibit CD8+ T-cell activity. T_H1 polarized CD4+ T-helper cells promote an inflammatory response and are associated with increased response to ICI, while anti-inflammatory $T_H9/17$ polarized CD4+ T-cells may drive metastasis. Dendritic cell function is hijacked by tumor cells, contributing to immune tolerance. CD8+ T-cell are primary effector cells that can target and destroy tumor cells, but their activity is suppressed through numerous mechanisms including expression of PD-L1 by tumor and stromal cells, secretion of immunosuppressive cytokines by regulatory T-cells, impaired dendritic cell antigen presentation, and arginase-1 expression by M2-macrophages.

metastasis, immune evasion, epithelial-mesenchymal transition (EMT), and chemoresistance.[150] The types of CAFs found in individual lung cancers profoundly impact patient outcomes, response, and resistance to all types of therapy.[151-155] In the context of NSCLC, significant advances have been made in terms of understanding the multifaceted roles of CAFs, with individual studies suggesting biologic context-specific subtypes. Unlike the globally defined CAF phenotypes identified in pancreatic ductal adenocarcinoma or colorectal cancer, universal definitions of heterogenous CAF subtypes have not yet been characterized in NSCLC, representing a Major Knowledge Gap.[150,156,157]

A recent meta-analyses and systematic review of 44 studies, including 7,582 patients, identified five major CAF markers: podoplanin, CAIX, α-SMA, periostin, and FAP.[156] Of these, podoplanin and α-SMA have been found to be significantly associated with poorer prognosis, most prominently in LUAD.[156] Major functions of CAFs in NSCLC include ECM remodeling, EMT, migration and invasion, angiogenesis, modulation of tumor metabolism, and immunosuppression.[156,158] CAF function in SCLC is not as well-elucidated. A recent study demonstrated that high levels of transforming growth factor-β (TGFβ) in CAFs are associated with superior overall survival in SCLC, reduced tumor growth, radiosensitivity, and antitumor immunity.[159] CAF secretion of TGFβ is associated with immunosuppressive FoxP3+ regulatory T-cell infiltration and immunosuppression in NSCLC.

Extracellular Matrix (ECM)

The role of the ECM in lung cancer growth, metastases, response to therapy, and how it can be therapeutically targeted, represents a Major Knowledge Gap. The ECM is comprised of the network of TME cellular components, as well as a complex network of structural proteins, including collagens, laminins, proteoglycans, hyaluronan, matrix metalloproteinases, and endothelial cells. These components provide the mechanical

framework of the tumor and contribute to the complex autocrine and paracrine signaling cascades in the TME, which contribute to tumor proliferation, metabolism, invasion, immune evasion, EMT, and therapy resistance.[7] CAFs are prominent contributors to the production and maintenance of these structural support proteins in lung cancer.[7] The ECM responds dynamically to various stimuli and stressors to permit and facilitate tumor progression.

Collagen, the most abundant ECM protein, contributes to ECM stiffness, promotion of inflammation, invasion, and metastasis through modulation of tensile strength and posttranslational modifications (i.e., lysyl oxidization).[7] Lysyl oxidase-mediated ECM remodeling is dysregulated with *LKB1* deficiency found in many LUADs, and reactive lysyl oxidase activity has been implicated in post-resection recurrence in NSCLC.[160,161] Other components, including proteoglycans, laminins, syndecans, and others, have been shown to contribute to cell migration, invasion, tumor growth, and resistance to chemotherapy and ICI.[7,162-164]

The ECM contributes significantly to SCLC progression. SCLC tumors are highly desmoplastic with a robust surrounding ECM, which may contribute to the rapid development of resistance to chemotherapy-induced apoptosis and chemo-radioresistance.[165,166] CXCL12-induced integrin activation has been demonstrated to be a key mediator of this pronounced adhesion between SCLC cells and the surrounding ECM proteins.[167]

Angiogenic Endothelial Cells

Angiogenesis is a key hallmark of carcinogenesis.[149] Despite investigation and extensive clinical trials, the role of angiogenesis and how to effectively target it to significantly improve lung cancer therapy remains a Major Knowledge Gap. As lung tumor cells proliferate, an ever-increasing microvascular supply is needed to sustain and augment progression. Major cellular players include endothelial cells, pericytes, immune cells, and CAFs, which facilitate the angiogenic process through modulation of the ECM and secretion of key pro-angiogenic factors like vascular endothelial growth factors (VEGF), basic fibroblast growth factor, stroma cell-derived factor-1, and others.[168,169]

Hypoxia is frequently identified in the NSCLC-TME and drives the production of hypoxia-inducible factor 1-α, a potent stimulator of angiogenesis through activation of VEGF.[170] VEGF-A/C expression in tumor cells is correlated with worse survival, and elevated VEGF-B levels are associated with metastasis in NSCLC.[171,172] As such, anti-VEGF therapies like bevacizumab and ramucirumab have been extensively investigated in numerous clinical trials, ultimately resulting in FDA approval for bevacizumab (in combination with platinum-doublet chemotherapy) and ramucirumab (in combination with erlotinib for *EGFR*-mutant tumors or with docetaxel for metastatic disease with progression on or after platinum-based therapy).[168]

While angiogenesis is not well-studied in SCLC, information coming from the occasional resected SCLC has demonstrated that microvessel count and VEGF expression are associated with worse survival.[173]

The Immune Microenvironment

Given the recent advances in the use of immune checkpoint blockade/inhibition (ICB) immunotherapy for the majority of lung cancers it essential we identify and begin to fill in the Major Knowledge Gaps concerning the lung cancer immune microenvironment (including tumor-associated macrophages, neutrophils, dendritic cells (DCs), T-cells of all types) to understand both how immune evasion occurs allowing lung cancer development, identifying which immune micro-environments will allow response or conversely resistance to ICB therapy, and potential ways to modify the immune microenvironment to improve anti-tumor immune therapies.

Tumor-Associated Macrophages

Tumor-associated macrophages (TAMs) are highly abundant in the TME and contribute to NSCLC tumor progression through promotion of invasion, resistance to therapy, metastasis, angiogenesis, and immunomodulation

through paracrine and autocrine interactions with other cells in the TME.[174-176] These TAMs are derived from circulating monocytes, as well as resident alveolar macrophages. Historically, macrophage phenotype was classified into two subtypes: an immunosuppressive, "M2-like" state, as well as an inflammatory "M1-like" state. M1-like TAMs reflect classically activated pro-inflammatory macrophages associated with immunostimulatory anti-tumor response.[177] M1-TAMs may comprise up to 30% of NSCLC-TAMs, and a higher density of these M1-TAMs is inversely associated with pathologic stage and is an independent predictor of longer survival.[178,179] Conversely, an elevated density of M2-like TAMs in the NSCLC stroma is associated with a worse prognosis compared to M1-like TAMs, and preclinical studies have demonstrated that M2-like TAMs contribute to tumor cell growth, invasion, and chemoresistance.[177,180] In reality, macrophages exist on a spectrum between these two states, and recent molecular profiling studies have suggested several phenotypically distinct macrophage populations in murine models of lung cancer.[181]

Neutrophils

Polymorphonuclear leukocytes (PMNs), or neutrophils, are first responders to sites of injury or infection and participate in phagocytosis, secretion of lytic enzymes and cytokines, and maintenance of the inflammatory response.[182] In NSCLC, PMNs are highly prevalent in the TME and promote tissue hypoxia, immunosuppression, and EMT.[183,184] High PMN density is negatively correlated with CD4+ and CD8+ T-cell density in the TME and is associated with suppressed CD8+ T-cell activity and a poorer response to ICI therapy.[184-186] Clinically, neutrophilia has been associated with a worse prognosis and decreased locoregional and distant metastatic disease control in cisplatin-based chemoradiation-treated stage III disease. A high neutrophil ratio (routinely available from blood counts) is associated with lymph node metastasis and poorer disease free survival (DFS) and OS.[187-189] High neutrophil ratio is similarly associated with advanced stage, liver metastasis, smoking status, and poor prognosis in SCLC.[190]

Dendritic Cells

Dendritic cells are professional antigen-presenting cells stratifying into myeloid or plasmacytoid phenotypes.[191] While DCs are crucial for antitumor immunity, their functions can be "hijacked" by lung cancer to promote immune tolerance.[191-194] In NSCLC, DCs facilitate tumor progression through the production of heparin binding EGF-like growth factor, impaired antigen presentation, exclusion from the TME, and polarization into an immunosuppressive plasmacytoid state.[195] Indeed, high density of plasmacytoid DCs is associated with advanced stage, lung squamous cancer (LUSC) histology, and smoking status.[196] Little has been investigated regarding the role of DCs in SCLCs. CD1a+ and CD83+ DCs have been identified in SCLC tumor specimens, and tumor-derived factors may be responsible for suppressing DC maturation.[197]

Regulatory T-Cells

Regulatory T-cells (Tregs) potently induce immunosuppression in the NSCLC TME and are associated with resistance to ICB.[198] These CD4+/FoxP3+ cells regulate the inflammatory immune response in physiologic states. In NSCLC, Tregs facilitate immune evasion through expression of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and subsequent inhibition of T-cell co-stimulation, the expression of programmed death-ligand 1 (PD-L1), further reduces co-stimulation and inactivating effector T-cells, and the production of immunosuppressive cytokines like IL-10.[198] Circulating FoxP3+ Treg cell concentration is associated with advanced disease, and infiltrating FoxP3+ Treg levels are associated with smoking status, diminished response to ICI, poorer OS, and recurrence after resection.[199-202] The prognostic impact of FoxP3 expression in SCLC is controversial. Previous investigations report that presence of FoxP3+ Tregs is associated with longer relapse-free survival (RFS), which may reflect the concurrent expression of other immune biomarkers in the TME.[203] However, some reports indicate that high ratio of FoxP3+

cells is associated with worse lung cancer survival, potentially due to secretion of IL-15 by SCLC cells promoting immunosuppressive IL-10 secretion by Tregs in the TME.[204]

CD4+ T-Cells

CD4+ T-cells are key players in the adaptive immune response, functioning as "helper" cells. These cells are activated by binding the B2 domain of MHC-II protein to CD4 co-receptor and can polarize into inflammatory T_H1 (secretion of IFN-ϒ, TNF-α), anti-inflammatory T_H2 (IL-4, IL-13), and other phenotypes.[205] Anti-tumorigenic functions of CD4+ T-cells include stimulation of CD8+ cytotoxic T-cells, direct antitumor activity through secretion of IFN-ϒ and TNF-α, as well as stimulation of B-cells for the production of antibodies against tumor antigens.[205] As such, presence of T_H1 CD4+ T-cells is associated with increased response to ICI and prolonged progression-free survival (PFS).[202] Conversely, immunosuppressive T_H9/$T_H17$lymphocytes are associated with metastasis and poor prognosis.[206] Furthermore, EMT is associated with increased expression of immunosuppressive cytokines and exclusion of CD4+ T-cells in LUAD and both CD4+ and CD8+ T-cells in LUSC.[207] While the SCLC-TME is generally immune-depleted and CD4+ T-cell positivity in these tumors range from 22% to 37%, increased metabolic activity noted on positron-emission tomography is inversely associated with CD4 and CD8+ T-cell infiltration.[83,98,208]

CD8+ T-Cells

CD8+ cytotoxic T-lymphocytes (CTLs) are the primary effector cells in the NSCLC-TME. As activated CD8+ T-cells target and destroy tumor cells, infiltration of CTLs is associated with better prognosis in NSCLC.[209,210] CTLs interact with MHC-1 molecules on the surfaces of antigen-presenting cells, such as dendritic cells and macrophages, resulting in activation of the T-cell receptor complex. These are fully co-stimulated by binding of the CD28 receptor to CD80/86 ligands from activated B-cells, macrophages, and other antigen-presenting cells (APCs).[211] Once activated, CTLs recruit natural killer (NK) cells and promote pore formation in target tumor cells and induce through secretion of granzymes, cathepsin C, perforin, and other cytolytic granules.[211] CTLs respond to the presence of tumor neoantigens, which are indirectly measured by total mutational burden (TMB), which is associated with superior response to ICI in NSCLC.[212]

MECHANISMS OF IMMUNE CHECKPOINT BLOCKADE ESCAPE IN LUNG CANCER

In addition to previously discussed interactions with TAMs, CAFs, and other TME cells to promote immune evasion, NSCLC cells hijack self-regulatory immune checkpoints to escape the antitumor immune response. NSCLC tumors and stromal cells express PD-L1 and B7.1, which bind to PD-1 receptors and CTLA-4 receptors, respectively, on CTLs, inhibiting their activation.[211] PD-L1 is not only secreted by tumor cells, but also other cells in the TME, including monocytes, TAMs, and PMNs.[184] As such, inhibition of the PD-L1/PD-1 axis or CTLA4 activity to ameliorate CTL inhibition by tumor cells has become the foundations of immunotherapy. Four anti-PD-1/PD-L1 axis agents are FDA-approved for NSCLC (pembrolizumab, nivolumab, durvalumab, and atezolizumab), with remarkable clinical benefit and ever-expanding indications (see other chapters for detailed discussion). These proteins have become both biomarkers for tumor behavior and response to immunotherapy. Some studies suggest that high expression of PD-L1 is associated with worse prognosis in NSCLC.[213] At the same time, stromal PD-1 immune cell infiltration predicts superior response after anti-PD-1 therapy.[210] Tumor PD-L1 expression has also been demonstrated to predict both post-chemotherapy durable response to nivolumab and is associated with better clinical outcomes, even at low expression levels.[210,214]

It is important to note that *EGFR*-mutant NSCLC may be associated with reduced PD-L1 expression, lower TMB, and an immune-exclusive, or "immune cold," TME, which is likely responsible for the very reduced levels of response to ICI in *EGFR*-mutant

NSCLCs.[215] CTL activity and proliferation are profoundly depleted in SCLC, and increased magnitude of proliferating circulating CTLs is associated with better PFS.[216] Recent gene expression analyses of SCLC patient-derived lines, PDXs, and tumor specimens identified that while high NE scores inversely correlated with immune infiltration, immunotherapy is not necessarily more effective for these tumors, despite a high TMB.[83,97,217] Inhibition of NK cell activity through decreased activating ligands may be implicated in this process.[217] Transcriptomic analyses of SCLC-Y tumors show that these tumors may be particularly enriched for innate immune response gene expression.[73] Overall, tumors with low expression of all classic markers (ASCL1, NeuroD1, POU2F3) denote a recently identified inflammatory "SCLC-I" subtype, which is most enriched for immune-related signatures. These lesions may be particularly sensitive to ICB therapy.[98,101]

MECHANISMS OF INVASION, METASTASIS, LINEAGE PLASTICITY, WITH RESISTANCE TO CHEMOTHERAPY AND TARGETED THERAPY IN LUNG CANCER

Molecular and Biologic Correlates of Mechanisms of Lung Cancer Metastases

Mortality in lung cancer is intimately tied to invasion and metastasis.[218] The most common sites of extranodal metastasis are contralateral or ipsilateral lung, brain, liver, bone, and adrenal glands.[219] LUAD-NSCLC is more likely to metastasize to the brain, liver, adrenals, and bone compared to LUSC-NSCLC, and SCLC is more likely to metastasize to the liver.[218,219] A Major Knowledge Gap is: what are the molecular and biologic features of lung cancer that determine both the presence and sites of metastases?

Differences in primary tumor and target-organ specific microenvironments may play a role in metastatic spread. The study of patient samples has been limited by logistical concerns of rebiopsy, timing of metastasis diagnosis, and limited availability of tumor samples.[220] The metastatic process begins with remodeling and degradation of the ECM (e.g., by CAFs), migration and invasion of tumor cells through the basement membrane, intravasation into lymphatic vessels or the bloodstream, and deposition of these tumor cells at target metastatic organs.[220]

In assuming a metastatic phenotype, NSCLC cells and their surrounding microenvironment undergo several morphologic and functional changes, modulated by the stromal and immune components of the TME.[221,222] In NSCLC cells, EMT is a cornerstone of this process. EMT involves the loss of classic epithelial features, such as cell polarity and cell-cell adhesion, and reduced expression of E-cadherin. It also involves the assumption of a mesenchymal phenotype, characterized by increased metalloproteinase activity, expression of mesenchymal markers like vimentin, and increased migratory and invasive potential.[221] Expression of ZEB1 and expression of TGF-β in tumor cells are key drivers of EMT.[223] Activation of the TGF-β signaling pathway results in downstream activation of transcription factors *SNAIL, ZEB*, and *TWIST*, which upregulate mesenchymal markers and suppress epithelial markers.[159,221] Overall, NSCLCs with an EMT phenotype are more invasive, resistant to therapy, and exhibit stem-cell-like features.[221]

SCLC is nearly always highly metastatic, and what functionally drives this metastatic behavior is a Major Knowledge Gap. While the mechanisms of metastasis in this tumor are incompletely understood, recent advances in murine models established from genetic engineering, patient-derived tumors, or circulating tumor cells have catalyzed investigation into the mechanisms of metastasis in this cancer.[224-226] Recently discovered major mechanisms using preclinical models and patient specimens include cell fate changes, upregulation of NFIB expression, NFIB-independent mechanisms, NE with non-NE cell-cell interactions, vascular mimicry, notch signaling, EMT, use of neuronal neurite programs, and evasion of innate immunity.[100,217,226] Brain metastases, which are very frequent in SCLC, may be associated with tumor cell cross-talk with astrocytes that mimic brain development.[227] As with NSCLC, EMT in

SCLC may contribute to metastatic behavior and is implicated with the development of chemoresistance.[226,228] Furthermore, tumoral heterogeneity and cell-cell interactions between NE and non-NE SCLC cells may be a key driver in SCLC metastasis.[226]

Resistance Mechanisms, Cancer Stem Cells, Drug Tolerant Persisters, Intra-tumor Heterogeneity, Resistance to Targeted Therapy, and Lineage Plasticity

Another Major Knowledge Gap(s) in lung cancer biology are the mechanism(s) of primary and acquired resistance to standard chemotherapy combinations (e.g. "platin doublets"), targeted, and ICB-based therapies.[36, 229] Despite substantial advancements in the treatment of NSCLC with targeted and immunotherapy, the vast majority of patients rapidly develop resistance to chemotherapy, targeted therapy, and ICB therapy, and succumb to metastatic disease. Several tumor features, including the activity of many of the aforementioned TME cells, such as CAFs, the ECM, TAMs, and Tregs, contribute to such resistance in NSCLC, in addition to inherent or acquired drug resistance pathways in primary tumor cells.

A major factor contributing to chemoresistance is the inherent inter-patient, inter-tumoral heterogeneity of NSCLCs with respect to tumor mutation burden, clonal variation, activated pathways, tumor metabolism, and the TME. This results in significant variability in response to standard chemotherapy, specific targeted therapies, and ICI therapy.[230] As discussed, having molecular makers of the tumor or the TME that identify which lung cancers are sensitive or resistant to specific therapies is a Major Knowledge Gap. Specific mutational profiles of previously discussed oncogenotypes are inherently chemoresistant. Indeed, the presence of *KRAS* mutations is associated with a reduced disease control rate after first-line platinum therapy, and *EGFR*-mutant tumors with concomitant *KRAS* mutations are more resistant to TKI therapy.[231,232]

Specific "on target" oncogene mutations are associated with overcoming targeted inhibition of the driver oncogene. The *EGFR* T790M site mutation is classically associated with anti-EGFR (TKI) therapy resistance due to a larger methionine side chain in the ATP-binding pocket, which inhibits drug binding.[233] This has been extended to a structure-based classification that predicts drug response in EGFR-mutant NSCLC.[234,235] With the development of mutant KRAS-targeted therapy for lung cancer, specific "on target" mutations are now found for KRAS-targeted therapies and can be identified in patient-derived lung cancer cell-line biologic models.[236] A Major Knowledge Gap is the role of lineage plasticity in lung cancer development, evolution, metastatic behavior, and development of resistance to chemotherapy, targeted therapy and immunotherapy.[237] Besides the acquisition of resistance-conferring genetic mutations, reversible mechanisms that lead to drug tolerance have emerged. Lung cancer cells can change their "identity" by dedifferentiating into a progenitor-like state or by transdifferentiating to a different lineage (e.g., lung adenocarcinoma to lung squamous, or lung adenocarcinoma to SCLC histology).[238] This "plasticity" in tumour cells also can transform tumor cells to a different phenotypic state that no longer depends on the drug-targeted pathway.[239] A dramatic example is resistance to EGFR TKI therapy in LUADs arising by transformation into a SCLC.[240-243] In mouse LUAD models, epigenomic changes provide state transitions that result in tumor progression.[244] These changes appear to arise out of a high plasticity cell state (HPCS) that develops with lung cancer evolution that result in cancer cells progressively adopting alternate lineage identities.[245]

Intra-Tumor Heterogeneity

New technological advances such as single cell RNAseq (scRNAseq), deep sequencing for mutational allele frequencies, multiomics-enhanced immune histochemical approaches, spatial transcriptomics, and new artificial intelligence (AI)/computational biology-enhanced image analyses have shown that many lung cancers have significant intra-tumor heterogeneity that play significant roles in

tumor behavior and response to therapy.[14,126,127,246-253] Intra-tumor heterogeneity includes both clonal and polyclonal changes, involving truncal and subclonal mutations, copy number changes, and gene expression differences. Several studies demonstrate that some aspects of intra-tumor heterogeneity are associated with survival differences.[14,126,127,247,248,254] The mechanisms, functional role, and their impact on therapy responses of the multiple types of intra-tumor heterogeneity in lung cancer represent a Major Knowledge Gap.

Another Major Knowledge Gap in intra-tumor heterogeneity is the role that cancer stem cells (CSCs), also referred to as cancer initiating cells, play in both tumor biology and responses to therapies.[255-257] These make up only a small fraction of the tumor cell populations in individual patients (e.g., approximately 0.5% to 10% in NSCLCs, and 10% to 30% in SCLCs) but appear highly correlated with response to therapy and development of therapy resistance.[255,257-261] CSCs are a rare but highly tumorigenic fraction of tumor cells that regulate tumor initiation and progression. They substantially contribute to intra-tumoral heterogeneity and are highly resistant to traditional therapies due to their low proliferation rate, expression of drug efflux proteins like ATP-binding cassette transporters, mesenchymal phenotype, and accelerated DNA repair.[262]

Furthermore, tumor cells acquire resistance to first-line cisplatin-based chemotherapy through numerous mechanisms including expression of anti-apoptotic proteins, upregulation of DNA repair processes, growth factor independence, expression of ABC transporters, and development of resistance to cisplatin-DNA adduct expression.[263] Another Major Knowledge Gap is the role that drug tolerant persister cells, also called DTPs, have within individual tumors in resistance to chemotherapy and targeted therapies.[264-266] DTPs appear to arise stochastically as "drug tolerant" cells, are transient and do not carry resistance mutations, and can either progress towards irreversible resistance or become drug sensitive again.[266] Currently, there are no accepted biomarkers to aid in identification of DTPs, but they appear to play a major role in lung cancers' resistance to multiple types of therapy and can develop through epigenomic, transcriptional, metabolomic, and TME interactions.[265]

PRECLINICAL MODELS TO STUDY LUNG CANCER BIOLOGY

Preclinical models are widely used to study lung cancer biology, identify mechanisms underlying lung cancer pathogenesis, and uncover key potential therapeutic vulnerabilities, providing necessary information for clinical translation of these findings. In addition, because the same models can be distributed to multiple investigators, they are important tools for both stimulating lung cancer translational research and permitting multiple investigators to validate findings.[267-269] These models include patient-derived tumor and normal lung epithelial cell lines, PDXs, and tumor xenografts from circulating tumor cells (CDXs), mouse tumors and their derived cell lines arising spontaneously after carcinogen exposure and in genetically engineered mouse models (GEMMs) of lung cancer. There are also less commonly used lung tumor line models from other sources, such as rats and canines. Each of the preclinical model has particular advantages and disadvantages, and often studies in one preclinical model type, such as patient tumor cell lines, leads to studies in other models for confirmation, for example, PDXs. While all of these preclinical models are widely used, a Major Knowledge Gap is how to efficiently use and integrate the results from these different models in a manner that provides the most useful information to facilitate successful clinical translation of their findings.

Patient-Derived Tumor Cell Lines

Human lung cancer cell lines have been widely distributed and used throughout the world for studies of lung cancer biology, pathogenic mechanisms, and discovery and testing of new therapeutics.[267] Importantly, the majority of these have undergone molecular characterization, including genome DNA sequencing to detect mutations and RNAseq/

microarray profiling to determine gene expression profiles. Additionally, functional genomic testing has been conducted, and these data are deposited in widely accessible databases such as the Cancer Cell Line Encyclopedia (CCLE), Catalogue of Somatic Mutations in Cancer (COSMIC), and the Cancer Dependency Map (DepMap).[30-34]

Patient-Derived Xenografts (PDXs)

Tumor cell lines in the large majority of cases can generate xenograft tumors growing in immunodeprived mice. These include immunodeficient models. For example, Nod-scid gamma (NSG), lack mature B, T, and NK cells, or athymic nude mice. Over the past several years, a large number of lung tumors of all histologic types have been implanted directly from patients into immunodeprived mice without intervening cell culture, and in approximately 30% to 50% of cases, this process generates replicating tumor xenografts that maintain the properties of the tumors from which they were generated.[224,270] Despite being more difficult to maintain, PDXs usually reflect clinically consistent tumor cell behavior and molecular heterogeneity. They can be used for a personalized approach to individual patient tumors and may predict patient-specific anti-tumor therapeutic responses.[271] While engraftment rates range from 20% to 90%, several international groups have made steady progress in establishing numerous available NSCLC and SCLC PDX models.[271,272] PDX models grown in immunodeprived mice lack any immune system. Humanized immunocompetent mouse models, established through engrafting of CD34+ hematopoietic stem or precursor cells, have emerged as a promising approach to address this issue. Meraz et al. recently developed a humanized PDX model that demonstrated anti-tumor response to anti-PD1 ICI therapy.[273] Likewise, Li et al. were able to show that targeting Axl in dendritic cells led to anti-LUAD immune responses in humanized mouse models.[274] Overall, PDX models have paved the way for many clinical trials and FDA-approved targeted therapies currently being used to treat lung patients.

Lung Tumor Organoid Cultures

Patient-derived tumor lines and fresh tumor samples can also be used in three-dimensional (3D) "organoid" type models with other cell lines from the TME to better simulate tumor cell behavior in a physiologically concordant fashion.[268,269,275-283] They have been used to assess drug response phenotypes for individual patients, as well as examine the impact of the TME on co-cultured lung cancer cells.[268,277,278,283] While there is an urgent need to develop "biobanks" of lung tumor organoids from individual patients, a major problem with primary lung cancer organoid cultures compared to other lineage tumors is that normal cells, such as normal epithelial cells and fibroblasts, often outgrow tumor cells.[275,280,281] In addition, the logistics for distributing such primary organoid cultures to multiple other labs to validate results have not yet been solved.

Mouse Models of Lung Cancer Including Genetically Engineered Mouse Models (GEMMs)

Spontaneously arising and carcinogen induced mouse lung cancer models, essentially all NSCLC, have been used for decades and are often driven by acquired KRAS mutations.[269,284,285] More complex models, such as genetically engineered mouse models or GEMMs for short, utilize genetic engineering to activate or inactivate key genes (e.g., *TP53, KRAS, myc*) to explore the effects of specific oncologic pathways and have been developed for both NSCLC and SCLC.[269] Indeed, many of the key lung genotypes can be recapitulated in mouse models to further study targeted therapy, TME interactions and metastatic patterns.[286] SCLC GEMMS were created decades ago by inactivation of TP53 and RB1 (RP model), and later RB P130 (RPP model).[285] Newer SCLC GEMMS are being developed to allow rapid genetic manipulation for exploration of the functional role of multiple genes using CRISPR technologies, such as genes involved in metastatic behavior.[226,285] Importantly, these GEMMs have shown that inter-

tumoral heterogeneity in SCLC is influenced by the cell type of origin.[287]

Human Lung Epithelial Cells for Preclinical Model Studies

It is possible to culture normal lung epithelial cells from large and small airways to study the impact of various carcinogens and tumor promoters to generate lung cancer in both 2D and 3D culture systems. The ability to routinely immortalize human bronchial epithelial cells (HBECs) and human small airway epithelial cells (HSAECs) using genetic manipulation of cdk4 expression (to overcome upregulation of p16) and telomerase to allow for cell immortality has generated a large array of normal human lung cells to study the pathogenesis of lung cancer.[288-294] Well-known lung cancer oncogenes and tumor suppressor genes, such as KRAS, TP53, myc, LKB1/STK11, and ZEB1, have been genetically manipulated in these cells and eventually can lead to the development of invasive lung cancers.[223,295,296] Of interest, it turns out that normal HBECs and HSAECs are extremely resistant to full oncogenic transformation, requiring multiple genetic alterations, despite the use of these potent cancer-causing genes.[295,296] These human preclinical models are being used to explore the impact of carcinogens and specific oncogenic changes in lung tumor pathogenesis. In addition, they can be used to compare the results of such changes in normal lung cells compared to tumor cells taken from the same patient to identify tumor-specific vulnerabilities.[37] They are also useful for forward genetic screens to identify new potential oncogenes and tumor suppressor genes that can convert them to a more malignant phenotype.[297]

Functional Genomic Studies

The advent of multiple new ways to manipulate individual and combinations of genes in lung cancer cells, normal lung epithelial cells, and in GEMMs has revolutionized our ability to determine the importance of a gene's role in lung cancer pathogenesis, biological behavior, as a therapeutic target, or as a therapy "sensitizer." These include both *in vitro* and *in vivo* approaches and include exogenously expressing, or "knocking down/knocking out" a gene to determine their impact on lung tumor biology. Classic examples include replacing a mutant or missing tumor suppressor gene with a wild-type copy to determine if that inhibits tumor growth, or knocking down/out a potential driver oncogene to determine if that inhibits tumor growth. These approaches are so common that a large fraction of lung cancer molecular and cell biology studies now reported have some components related to such functional genomics approaches. Results of whole genome or multiple gene screens are deposited in large accessible databases to facilitate future research. A widely used example is DepMap, which contains data on the impact of knocking down/out nearly every human gene on the *in vitro* growth of a large panel of approximately 70 patient-derived lung cancer cell lines.[34] These functional genomic studies can be used to identify new drug targets by identifying genes that are both "druggable" and whose expression has to be maintained for the lung cancer cell to keep growing. In this case the clone used to manipulate the gene, such as a CRISPR targeting guide, "drops out" in the growing lung cancer cell population, while those guides directed at genes that do not impact lung cancer growth remain. Such functional genomic screens are in the process of revolutionizing the search for new therapeutic targets, chemical and natural product library screens, drug sensitizers, and the discovery of associated molecular biomarkers predicting responses in lung cancer.[298-301] By including normal lung epithelial cells, it is possible to determine the presence and size of a "therapeutic window" (the targeted protein is required for lung cancer but not normal lung cell survival).[38] Finally, it is possible to perform these screens *in vivo* by introducing libraries of genes or clones targeting specific genes into a tumor cell population such that each cell has only one gene targeted and then injecting large numbers of such cells (approximately 10^7), allowing xenograft or syngeneic tumors to form and

then determining which genes targeted were retained or could be done away with by the tumor *in vivo*.[302] While the creation of each GEMM of lung cancer represents a functional genomics study, for example introducing TP53 loss of function and oncogenic KRAS to create a LUAD, new technologies allow testing of multiple genes at the same time in tumor creation. By studying the composition of genes in each, the multiple new lung cancers arising in an individual mouse, large numbers of genes can be tested for their role in generating new lung cancers.[303,304]

MESOTHELIOMA

This malignancy is discussed in detail in Chapter 23. Here we focus on the Major Knowledge Gaps that have recently emerged.

Major Knowledge Gap 1: Did the asbestos ban work?

The short answer is yes; the incidence of mesothelioma per 100,000 persons has decreased, providing evidence that the ban worked. In the 1980s, asbestos use was banned in Europe and Australia, and it was significantly restricted in the US, before being entirely banned in 2024. In the past decade, the incidence of mesothelioma has decreased, yet the number of mesothelioma deaths per year in the US (3,000 deaths per year) and the rest of the Western world has not significantly changed.[305-307] Why? For several reasons:

1) The population increased in most countries during the past decades, therefore the overall number of cancer patients increased.

2) There is a 30 to 50+ year latency between exposure to asbestos and the development of mesothelioma; therefore, most asbestos workers develop mesothelioma when they are older.[307,308] As the fraction of the population that reaches old age has increased, the number of workers most susceptible to develop mesothelioma has also increased.[309,310]

3) An increasing fraction of mesotheliomas are developing in carriers of germline mutations that may cause or predispose to mesothelioma; presumably, in the past these were all attributed to asbestos.[311,312]

4) An increasing number of mesotheliomas are developing in cancer patients who were treated with radiation therapy to the chest and abdomen and who, several years later, developed sarcomas and mesotheliomas.[311,313]

5) As we develop rural areas, we inevitably encroach on terrain containing asbestos and other carcinogenic mineral fibers, such as erionite and antigorite. Workers first, and residents later, are exposed to these carcinogenic mineral fibers and may develop mesothelioma.[312] It is hoped that in coming years, rural areas will be tested for the possible presence of naturally occurring carcinogenic fibers in the terrain before, and not after, they have been developed.

Major Knowledge Gap 2: What is happening in Asia, Africa, and South America, where, except for rare exceptions, asbestos is not banned and its use has significantly increased in recent years?

The short answer is that we do not know, but it is reasonable to expect a significant increase in the number of mesotheliomas in coming years.[309] For example, China and India—countries that have used increasing amounts of asbestos—did not report mesothelioma cases, and the reason for this reporting deficit is not clear. A recent study estimated an incidence of mesothelioma in China of 1.4 persons per million in 2016, projected to become 1.9 persons per million in 2030.[314,315] One major problem is the lack of reliability of mesothelioma diagnoses in China and other developing countries.[311] For example, a US/Chinese team of pathologists jointly reviewed mesothelioma diagnoses made in a major university hospital in China and confirmed only 50% of them.[314] Inadequate training to diagnose this rare cancer and lack of supporting immune stains to document the diagnosis were the most common problems.[311,314] Similar concerns were raised for diagnoses of mesothelioma in South America and African countries.[311] Consequently, accurately estimating mesothelioma incidence in these countries and continents remains impossible.[311] However, given the increasing use of asbestos in developing countries, it is reasonable to

predict that the number of deaths due to mesotheliomas will also increase.[311] Given the success of the asbestos ban in reducing the incidence of mesothelioma, the challenge in coming years will be to convince the rest of the world to introduce an asbestos ban, before, and not after, they are confronted with a mesothelioma epidemic.[305-307]

Major Knowledge Gap 3: How does asbestos cause mesothelioma?

Recent work demonstrated that asbestos causes mesothelioma by promoting and sustaining a chronic inflammatory process that, over time, promotes tumor growth.[311] The NLRP3 inflammasome and HMGB1 were identified as possible key mediators of asbestos-mediated inflammation and carcinogenesis.[311,316,317] Experiments in transgenic mice deficient in NLRP3 and in mice lacking HMGB1, injected with asbestos, showed that HMGB1-deficient mice had a significantly reduced incidence of mesothelioma, whereas NLRP3 deficiency did not influence the incidence of mesothelioma.[318,319] These findings proved that HMGB1 is a key mediator of asbestos carcinogenesis.[319] HMGB1 is also a key mediator of mesothelioma in carriers of germline BAP1 mutations, because BAP1, through its interaction with HDAC1, modulates the transfer of HMGB1 from the nucleus to the cytoplasm and extracellularly, where HMGB1 promotes inflammation and mesothelioma.[320] Aspirin, a non-specific inhibitor of HMGB1, significantly decreased the incidence of mesothelioma in mice exposed to asbestos.[321] The challenge in coming years is to identify and develop more specific HMGB1 inhibitors for clinical use to reduce the incidence of mesothelioma among asbestos-exposed individuals and carriers of germline BAP1 mutations.

Major Knowledge Gap 4: Do mesotheliomas developing in carriers of germline mutations of BAP1 and of other genes require a different medical approach?

The short answer is yes, the details are being developed. Briefly, individuals carrying heterozygous germline mutations of BAP1 are at high risk of developing mesothelioma, and when they do, their tumor cells show biallelic inactivation of this gene, providing evidence of causation.[311,312,319] About 30% to 50% of family members carrying germline BAP1 mutations will develop mesothelioma; all will develop some, often several, different cancer types.[311,312] In addition, mesothelioma has been observed in families affected by other tumor predisposition syndromes, such as families carrying heterozygous germline mutations of BARD1, BLM, TP53, BRCA1, BRCA2, etc.[322-326] It has been estimated that about 16% of mesotheliomas develop in carriers of germline mutations of BAP1, the most common mutation, or of other tumor suppressor genes.[327] These mesotheliomas, at least those developing in carriers of heterozygous germline mutations of BAP1, BARD1, and possibly other genes, are always of the epithelioid type, except recurrences after therapy, with a tubulopapillary or trabecular architecture. They are multifocal and remain indolent for several years, showing minimal invasion.[328] Median survival is about 5 to 7 years, an average that includes invasive mesotheliomas diagnosed after several years of recurrent pleural effusions, as well as mesotheliomas diagnosed at an early stage via thoracoscopy conducted because of high suspicion in families affected by multiple cases of mesothelioma or during surgery for other conditions.[328] The latter have a much-prolonged survival and seem to respond well to surgery and other therapies; several patients survived more than 20 years and/or died of other causes.[328] Carriers of germline BAP1 mutations are at high risk of developing additional malignancies, which for the most part will also respond to therapy when detected at an early stage.[328] To study mesothelioma in carriers of heterozygous germline BAP1 mutations, the NCI has opened two clinical trials at the Bethesda Medical Center directed by Dr. R. Hassan (non-surgical protocol NCT03830229) and Dr. D. S. Schrump, (surgical protocol NCT04431024). These trials which focus on early detection of mesothelioma and other cancers in these subjects, have signifi-

cantly improved our ability to study the mechanisms and the clinical presentations of early stage malignancies in this syndrome and to identify the most effective screening and therapeutic approaches. The results of the surgical trial will be published soon and we anticipate that it will have a radical impact on how we screen, diagnose, and treat these patients. The challenge in coming years will be to understand why these patients can survive mesothelioma or at least can live for several years with this diagnosis: is it because their tumors are less aggressive or because their immune system/tumor microenvironment, which contains cells with only 1 intact BAP1 allele, is able to keep mesothelioma from infiltrating nearby organs? The latter hypothesis is supported by the finding that over 60% of sporadic (for the most part asbestos-induced) mesotheliomas contain biallelic BAP1 inactivating mutations in their tumor cells, yet these sporadic mesotheliomas are aggressive and show only a minimally improved survival and response to therapy.[328-330] The challenge in the coming years it to figure out the underlying mechanisms responsible for the much-improved prognosis of mesotheliomas developing in carriers of germline mutations of BAP1 and of other genes, and to determine whether we can target these same mechanisms in patients with sporadic mesotheliomas to improve their survival.

Major Knowledge Gap 5: Is there a role for immunotherapy in mesothelioma?

The success of checkpoint inhibitors therapy in melanoma prompted investigators to test this type of immunotherapy in other cancers, including mesothelioma. The initial high hopes that immunotherapy might represent a better option for mesothelioma patients compared to chemotherapy were tempered by recent findings showing that immunotherapy had much more serious side effects and comparable survival to chemotherapy in patients with pleural mesothelioma of the epithelioid type.[331-336] This issue has been recently debated in the *Journal of Thoracic Oncology* by those advocating the use of immunotherapy for mesothelioma and those arguing against it. We refer readers to these articles for in-depth analyses of this issue.[337,338] However, it appears that all agree that immunotherapy may increase median survival of about 4 months for patients with sarcomatoid mesothelioma, the more aggressive variant of mesothelioma that is resistant to chemotherapy.[337,338] The challenge in coming years is to validate these findings and confirm that patients with sarcomatoid mesothelioma benefit from immunotherapy.

Major Knowledge Gap 6: Is there a role for surgery in mesothelioma?

The possible benefit of surgery for mesothelioma has been debated for years, with strong advocates in the past, but no randomized clinical trials to support its use. Recently, however, there has been a shift away from the more invasive extrapleural pneumonectomy to pleurectomy decortication. Several studies have shown that pleurectomy decortication is associated with reduced mortality and better overall survival compared to extrapleural pneumonectomy.[339] Very recently, in the MARS 2 trial, Dr. Lim and colleagues compared the clinical benefit and cost-effectiveness of pleurectomy decortication and chemotherapy vs. chemotherapy alone for patients with pleural mesothelioma: 169 participants were randomly assigned to surgery, and 166 were randomly assigned to chemotherapy alone.[340] The study's primary outcome, which has now been accepted for publication, showed that extended pleurectomy decortication for mesothelioma was associated with a 28% increase in the risk of death in the first 42 months (P = .03). Additionally, this study found that the global quality of life was reduced with surgery and that every statistically significant outcome was worse with surgery in all measures of the EORTC QLQ-C30 scale. These findings confirmed similar concerns expressed in the past by the Dr. Jablons and colleagues, who have been arguing that surgery had no role in mesothelioma, except for palliative purposes.[341] Is there a future for surgery in mesothelioma?

An article coordinated by Dr. HI Pass, in which Dr. Lim and Jablons debated on the "no surgery side" and Drs. Bueno, Opitz, and others debated on the "pro-surgery" side, then these authors together analyze and discuss these issues, will be published soon in the *Journal of Thoracic Oncology*, and we refer readers to this forthcoming article.

Summary: Much has been happening in the world of mesothelioma in the recent past. The studies summarized above provided better ways to prevent and treat mesothelioma, and, finally, we are able to save some patients' lives. The answers to the open questions listed in the "Major Knowledge Gaps" will further improve our ability to help them. Mesothelioma patients should always be tested for germline mutations to identify the estimated 16%, who, along with their affected family members, can benefit from annual screenings. These screenings help with early detection which can be often followed by curative resection of those minimally invasive mesotheliomas developing in carriers of germline mutations of BAP1 and of other genes. However, mesotheliomas caused by asbestos or, less frequently, by other carcinogenic fibers and radiation therapy, and mesotheliomas not linked to any detectable cause, remain resistant to current therapies, therefore prevention is of outmost importance.

Improvements in radiation therapy and consequent narrowing of fields of exposure should reduce the number of radiation-induced mesotheliomas in coming years. It is hoped that the asbestos ban will soon be adopted by the many countries in Africa, Asia, and South America that continue to use asbestos for commercial purposes. Moreover, as rural areas are developed, the terrain should be tested for the possible presence of natural occurring asbestos and other carcinogenic fibers to prevent exposure to workers first, and later to residents, as has occurred in some US states, Turkey, Italy, New Caledonia, and others.

CONCLUSION

Through multiple decades of research, much of it led by the IASLC member investigators, there has been tremendous development in understanding of the molecular and cellular biology of lung cancer and mesothelioma. The development of a wide range of preclinical models has been crucial to studying the role of molecular changes in lung cancer with respect to its pathogenesis and identification of tumor-acquired vulnerabilities. These, molecular and cell biologic studies have gone hand in hand with clinical trials and changes in lung cancer treatment and clinical care delivery. Routinely, all newly diagnosed lung cancer patients have their tumor specimens assessed for a large panel of genomic and expression markers as part of helping plan for their clinical care. However, while these molecular and cell biologic studies have played a substantial role in the treatment of lung cancer improving patient outcomes, as discussed, "Major Knowledge Gaps" indicate that considerable progress is still needed. This is particularly true for developing new approaches for the early detection and prevention ("interception") of lung cancer. It also involves extending findings related to cigarette smoking-induced lung cancer to other environmental pathogens, such as air pollution and the recent large epidemic of SARS-CoV-2 infection that affected millions of individuals' lung epithelial cells. Furthermore, it is critical for more precisely selecting the best available chemotherapy, targeted therapy, immune therapy, and radiotherapy for individual patients. It also includes integrating systemic therapies with both surgery (particularly in neoadjuvant fashion) and radiotherapy, and enhancing available targeted therapies to achieve durable long-term remissions and potential cures. Additionally, it focuses on significantly increasing anti-tumor immune responses to provide very long-term remissions and potential cures. Efforts should also be made to prevent and ameliorate metastatic disease, even if a cure is not achieved, and to alleviate tumor-induced paraneoplastic syndromes, such as cancer cachexia, as well as immediate and long-term-related toxicities.

Acknowledgements

This chapter is dedicated to the memory of our long-term IASLC colleague and pioneer in lung cancer cellular and molecular biology, Distinguished Professor of Pathology, Adi F. Gazdar, M.D., who led the way in many of these fields. It also is dedicated to our patients who stimulated much of this research, and to the many members of the National Cancer Institute of Veterans Affairs (NCI-VA) and the National Cancer Institute of the Navy Medical Oncology Branches, the Hamon Center, and the University of Texas Special Program of Research Excellence in Lung Cancer, who scientifically contributed to these fields. We apologize for any original publications of importance not cited because of our use of articles reviewing various areas. Supported by Grants: P50 CA070907, CA213274, CA224065, CA260560, CA142543, and TARDIS Fellowship for RC.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.* 2021;71: 209-249.
2. Hanahan D. Hallmarks of Cancer: New Dimensions. *Cancer discovery*. 2022;12:31-46.
3. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. *Nature.* 2018;553:446-454.
4. Chen Z, Fillmore CM, Hammerman PS, et al. Non-small-cell lung cancers: a heterogeneous set of diseases. *Nature reviews Cancer.* 2014;14:535-546.
5. Turner BM, Cagle PT, Sainz IM, et al. Napsin A, a new marker for lung adenocarcinoma, is complementary and more sensitive and specific than thyroid transcription factor 1 in the differential diagnosis of primary pulmonary carcinoma: evaluation of 1674 cases by tissue microarray. 2012;136:163-171.
6. Zheng M. Classification and Pathology of Lung Cancer. *Surg Oncol Clin N Am.* 2016;25:447-468.
7. Gotte M, Kovalszky I. Extracellular matrix functions in lung cancer. *Matrix Biol.* 2018;73:105-121.
8. Molina JR, Yang P, Cassivi SD, et al. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. *Mayo clinic proceedings*. Elsevier; 2008;83:584-594.
9. Steiling K, Ryan J, Brody JS, Spira A. The field of tissue injury in the lung and airway. *Cancer Prev Res (Phila)*. 2008;1:396-403.
10. Liu Y, Wang Y, Zhang R, et al. Transcriptomics profile of human bronchial epithelial cells exposed to ambient fine particles and influenza virus (H3N2). *Scientific reports*. 2023;13:19259.
11. Hill W, Lim EL, Weeden CE, et al. Lung adenocarcinoma promotion by air pollutants. Nature 2023;616:159-167.
12. Balmain A. Air pollution's role in the promotion of lung cancer. *Nature*. 2023;616:35-36.
13. Han G, Sinjab A, Rahal Z, et al. An atlas of epithelial cell states and plasticity in lung adenocarcinoma. *Nature*. 2024;627:656-663.
14. Karasaki T, Moore DA, Veeriah S, et al. Evolutionary characterization of lung adenocarcinoma morphology in TRACERx. *Nat Med.* 2023;29:833-845.
15. Haga Y, Sakamoto Y, Kajiya K, et al. Whole-genome sequencing reveals the molecular implications of the stepwise progression of lung adenocarcinoma. *Nature communications.* 2023;14:8375.
16. Nie M, Yao K, Zhu X, et al. Evolutionary metabolic landscape from preneoplasia to invasive lung adenocarcinoma. *Nature communications.* 2021;12:6479.
17. Dejima H, Hu X, Chen R, et al. Immune evolution from preneoplasia to invasive lung adenocarcinomas and underlying molecular features. *Nature communications.* 2021;12:2722.
18. Pennycuick A, Teixeira VH, AbdulJabbar K, et al. Immune Surveillance in Clinical Regression of Preinvasive Squamous Cell Lung Cancer. *Cancer discovery.* 2020;10:1489-1499.
19. Teixeira VH, Pipinikas CP, Pennycuick A, et al. Deciphering the genomic, epigenomic, and transcriptomic landscapes of pre-invasive lung cancer lesions. *Nat Med.* 2019;25:517-525.
20. Yun JH, Khan MAW, Ghosh A, et al. Clonal Somatic Mutations in Chronic Lung Diseases Are Associated with Reduced Lung Function. *Am J Respir Crit Care Med.* 2023;208:1196-1205.
21. Yan X, Kaminski N. Somatic Mutations: The Next Frontier in Demystifying Chronic Obstructive Pulmonary Disease and Idiopathic Pulmonary Fibrosis? *Am J Respir Crit Care Med.* 2023;208: 1150-1151.
22. Zhang XC, Wang J, Shao GG, et al. Comprehensive genomic and immunological characterization of Chinese non-small cell lung cancer patients. *Nature communications.* 2019;10:1772.
23. Hu X, Fujimoto J, Ying L, et al. Multi-region exome sequencing reveals genomic evolution from preneoplasia to lung adenocarcinoma. *Nature communications.* 2019;10:2978.
24. Taylor AM, Shih J, Ha G, et al. Genomic and Functional Approaches to Understanding Cancer Aneuploidy. *Cancer cell*. 2018;33:676-689 e673.
25. Lee WC, Diao L, Wang J, et al. Multiregion gene expression profiling reveals heterogeneity in molecular subtypes and immunotherapy response signatures in lung cancer. *Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc.* 2018;31:947-955.
26. Campbell JD, Alexandrov A, Kim J, et al. Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas. *Nature genetics*. 2016;48:607-616.
27. Berger AH, Brooks AN, Wu X, et al. High-throughput Phenotyping of Lung Cancer Somatic Mutations. *Cancer cell.* 2016;30:214-228.
28. Cancer Genome Atlas Research N. Comprehensive molecular profiling of lung adenocarcinoma. *Nature.* 2014;511:543-550.
29. Imielinski M, Berger AH, Hammerman PS, et al. Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. *Cell.* 2012;150:1107-1120.
30. Ghandi M, Huang FW, Jane-Valbuena J, et al. Next-generation characterization of the Cancer Cell Line Encyclopedia. *Nature.* 2019;569:503-508.
31. Barretina J, Caponigro G, Stransky N, et al. The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity. *Nature*. 2012;483:603-607.
32. Tate JG, Bamford S, Jubb HC, et al. COSMIC: the Catalogue Of Somatic

Mutations In Cancer. *Nucleic Acids Res*. 2019;47:D941-D947.
33. Vazquez F, Boehm JS. The Cancer Dependency Map enables drug mechanism-of-action investigations. *Mol Syst Biol.* 2020;16:e9757.
34. Tsherniak A, Vazquez F, Montgomery PG, et al. Defining a Cancer Dependency Map. *Cell*. 2017;170:564-576 e516.
35. Nusinow DP, Szpyt J, Ghandi M, et al. Quantitative Proteomics of the Cancer Cell Line Encyclopedia. *Cell.* 2020;180:387-402 e316.
36. Wang M, Herbst RS, Boshoff C. Toward personalized treatment approaches for non-small-cell lung cancer. *Nat Med*. 2021;27:1345-1356.
37. Kim HS, Mendiratta S, Kim J, et al. Systematic identification of molecular subtype-selective vulnerabilities in non-small-cell lung cancer. *Cell*. 2013;155:552-566.
38. McMillan EA, Ryu MJ, Diep CH, et al. Chemistry-First Approach for Nomination of Personalized Treatment in Lung Cancer. *Cell*. 2018;173:864-878 e829.
39. Brahmer JR, Lee JS, Ciuleanu TE, et al. Five-Year Survival Outcomes With Nivolumab Plus Ipilimumab Versus Chemotherapy as First-Line Treatment for Metastatic Non-Small-Cell Lung Cancer in CheckMate 227. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology.* 2023;41:1200-1212.
40. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. *N Engl J Med*. 2022;386:1973-1985.
41. Reck M, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in metastatic non-small cell lung cancer: CheckMate 9LA 2-year patient-reported outcomes. *Eur J Cancer*. 2023;183:174-187.
42. Pu X, Wu L, Su D, et al. Immunotherapy for non-small cell lung cancers: biomarkers for predicting responses and strategies to overcome resistance. *BMC cancer*. 2018;18:1082.
43. Liang S, Wang H, Tian H, et al. The prognostic biological markers of immunotherapy for non-small cell lung cancer: current landscape and future perspective. *Front Immunol*. 2023;14:1249980.
44. Rizvi H, Sanchez-Vega F, La K, et al. Molecular Determinants of Response to Anti-Programmed Cell Death (PD)-1 and Anti-Programmed Death-Ligand 1 (PD-L1) Blockade in Patients With Non-Small-Cell Lung Cancer Profiled With Targeted Next-Generation Sequencing. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology.* 2018;36:633-641.
45. Prelaj A, Tay R, Ferrara R, et al. Predictive biomarkers of response for immune checkpoint inhibitors in non-small-cell lung cancer. *Eur J Cancer*. 2019;106:144-159.
46. Ushio R, Murakami S, Saito H. Predictive Markers for Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer. *J Clin Med*. 2022;11.
47. Blons H, Garinet S, Laurent-Puig P, Oudart JB. Molecular markers and prediction of response to immunotherapy in non-small cell lung cancer, an update. *J Thorac Dis*. 2019;11:S25-S36.
48. Memmott RM, Wolfe AR, Carbone DP, Williams TM. Predictors of Response, Progression-Free Survival, and Overall Survival in Patients With Lung Cancer Treated With Immune Checkpoint Inhibitors. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer.* 2021;16:1086-1098.
49. Pabst L, Lopes S, Bertrand B, et al. Prognostic and Predictive Biomarkers in the Era of Immunotherapy for Lung Cancer. *International journal of molecular sciences.* 2023;24.
50. Lee CK, Man J, Lord S, et al. Clinical and Molecular Characteristics Associated With Survival Among Patients Treated With Checkpoint Inhibitors for Advanced Non-Small Cell Lung Carcinoma: A Systematic Review and Meta-analysis. *JAMA oncology.* 2018;4:210-216.
51. Adderley H, Blackhall FH, Lindsay CR. Toxicity with small molecule and immunotherapy combinations in non-small cell lung cancer. *Cancer immunology, immunotherapy: CII*. 2021;70:589-595.
52. Hong L, Aminu M, Li S, et al. Efficacy and clinicogenomic correlates of response to immune checkpoint inhibitors alone or with chemotherapy in non-small cell lung cancer. *Nature communications.* 2023;14:695.
53. Kovacs SA, Fekete JT, Gyorffy B. Predictive biomarkers of immunotherapy response with pharmacological applications in solid tumors. *Acta Pharmacol Sin*. 2023;44:1879-1889.
54. Ricciuti B, Lamberti G, Puchala SR, et al. Genomic and Immunophenotypic Landscape of Acquired Resistance to PD-(L)1 Blockade in Non-Small-Cell Lung Cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology.* 2024;42:1311-1321.
55. Henick BS, Herzberg BO, Concepcion-Crisol CP, Taylor AM. Controlled Chaos: Parsing Acquired Immunoresistance in Lung Cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology.* 2024;42:1211-1214.
56. Bunn PA, Minna JD, Augustyn A, et al. Small cell lung cancer: can recent advances in biology and molecular biology be translated into improved outcomes? *Journal of Thoracic Oncology.* 2016;11:453-474.
57. Wang S, Tang J, Sun T, et al. Survival changes in patients with small cell lung cancer and disparities between different sexes, socioeconomic statuses and ages. *Scientific reports*. 2017;7:1-13.
58. Karachaliou N, Pilotto S, Lazzari C, et al. Cellular and molecular biology of small cell lung cancer: an overview. *Translational lung cancer research.* 2016;5:2-15.
59. Fruh M, De Ruysscher D, Popat S, et al. Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology: official journal of the European Society for Medical Oncology.* 2013;24 Suppl 6:vi99-105.
60. Cardona AF, Rojas L, Zatarain-Barron ZL, et al. Multigene Mutation Profiling and Clinical Characteristics of Small-Cell Lung Cancer in Never-Smokers vs. Heavy Smokers (Geno1.3-CLICaP). *Front Oncol*. 2019;9:254.
61. George J, Lim JS, Jang SJ, et al. Comprehensive genomic profiles of small cell lung cancer. *Nature*. 2015;524:47-53.
62. George J, Maas L, Abedpour N, et al. Evolutionary trajectories of small cell lung cancer under therapy. *Nature*. 2024;627:880-889.
63. Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. *Nat Rev Dis Primers.* 2021;7:3.
64. Wistuba II, Gazdar AF, Minna JD. Molecular genetics of small cell lung carcinoma. *Seminars in oncology. Elsevier*. 2001;28:3-13.
65. Rudin CM, Poirier JT, Byers LA, et al. Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data. *Nature Reviews Cancer.* 2019;19:289-297.

66. Thomas A, Mian I, Tlemsani C, et al. Clinical and Genomic Characteristics of Small Cell Lung Cancer in Never Smokers: Results From a Retrospective Multicenter Cohort Study. *Chest.* 2020;158:1723-1733.
67. Liu Q, Zhang J, Guo C, et al. Proteogenomic characterization of small cell lung cancer identifies biological insights and subtype-specific therapeutic strategies. *Cell.* 2024;187:184-203 e128.
68. Szeitz B, Megyesfalvi Z, Woldmar N, et al. In-depth proteomic analysis reveals unique subtype-specific signatures in human small-cell lung cancer. *Clin Transl Med*. 2022;12:e1060.
69. Coles GL, Cristea S, Webber JT, et al. Unbiased Proteomic Profiling Uncovers a Targetable GNAS/PKA/PP2A Axis in Small Cell Lung Cancer Stem Cells. *Cancer cell.* 2020;38:129-143 e127.
70. Kim C, Wang XD, Liu Z, et al. Induced degradation of lineage-specific oncoproteins drives the therapeutic vulnerability of small cell lung cancer to PARP inhibitors. *Science advances*. 2024;10:eadh2579.
71. Huang YH, Klingbeil O, He XY, et al. POU2F3 is a master regulator of a tuft cell-like variant of small cell lung cancer. *Genes Dev*. 2018;32:915-928.
72. Pongor LS, Tlemsani C, Elloumi F, et al. Integrative epigenomic analyses of small cell lung cancer cells demonstrates the clinical translational relevance of gene body methylation. *iScience.* 2022;25:105338.
73. Tlemsani C, Pongor L, Elloumi F, et al. SCLC-CellMiner: A Resource for Small Cell Lung Cancer Cell Line Genomics and Pharmacology Based on Genomic Signatures. *Cell reports*. 2020;33:108296.
74. Zhang W, Girard L, Zhang YA, et al. Small cell lung cancer tumors and preclinical models display heterogeneity of neuroendocrine phenotypes. *Translational lung cancer research.* 2018;7:32-49.
75. Ireland AS, Micinski AM, Kastner DW, et al. MYC Drives Temporal Evolution of Small Cell Lung Cancer Subtypes by Reprogramming Neuroendocrine Fate. *Cancer cell*. 2020;38:60-78 e12.
76. Schwendenwein A, Megyesfalvi Z, Barany N, et al. Molecular profiles of small cell lung cancer subtypes: therapeutic implications. *Mol Ther Oncolytic*s. 2021;20:470-483.
77. Ding XL, Su YG, Yu L, et al. Clinical characteristics and patient outcomes of molecular subtypes of small cell lung cancer (SCLC). *World J Surg Oncol.* 2022;20:54.
78. Petty WJ, Paz-Ares L. Emerging Strategies for the Treatment of Small Cell Lung Cancer: A Review. *JAMA oncology.* 2023;9:419-429.
79. Poirier JT, George J, Owonikoko TK, et al. New Approaches to SCLC Therapy: From the Laboratory to the Clinic. *Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer*. 2020;15:520-540.
80. Owen DH, Giffin MJ, Bailis JM, et al. DLL3: an emerging target in small cell lung cancer. *J Hematol Oncol*. 2019;12:61.
81. Blackhall F, Jao K, Greillier L, et al. Efficacy and safety of rovalpituzumab tesirine compared with topotecan as second-line therapy in DLL3-high SCLC: results from the phase 3 TAHOE study. *Journal of Thoracic Oncology*. 2021;16:1547-1558.
82. Osborne JK, Larsen JE, Shields MD, et al. NeuroD1 regulates survival and migration of neuroendocrine lung carcinomas via signaling molecules TrkB and NCAM. *Proceedings of the National Academy of Sciences of the United States of America*. 2013;110:6524-6529.
83. Chen Y, Jin Y, Hu X, Chen M. Infiltrating T lymphocytes in the tumor microenvironment of small cell lung cancer: a state of knowledge review. *J Cancer Res Clin Oncol*. 2022;148:881-895.
84. Pocaterra A, Romani P, Dupont S. YAP/TAZ functions and their regulation at a glance. *Journal of cell science*. 2020;133:jcs230425.
85. Song Y, Sun Y, Lei Y, et al. YAP1 promotes multidrug resistance of small cell lung cancer by CD74-related signaling pathways. *Cancer medicine*. 2020;9:259-268.
86. Owonikoko TK, Dwivedi B, Chen Z, et al. YAP1 Expression in SCLC Defines a Distinct Subtype With T-cell-Inflamed Phenotype. *Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer.* 2021;16:464-476.
87. Ng J, Cai L, Girard L, et al. Molecular and Pathologic Characterization of YAP1-Expressing Small Cell Lung Cancer Cell Lines Leads to Reclassification as SMARCA4-Deficient Malignancies. *Clinical cancer research: an official journal of the American Association for Cancer Research.* 2024;30:1846-1858.
88. Chen P, Kuang P, Wang L, et al. Mechanisms of drugs-resistance in small cell lung cancer: DNA-related, RNA-related, apoptosis-related, drug accumulation and metabolism procedure. *Translational lung cancer research*. 2020;9:768-786.
89. Gardner EE, Lok BH, Schneeberger VE, et al. Chemosensitive Relapse in Small Cell Lung Cancer Proceeds through an EZH2-SLFN11 Axis. *Cancer cell*. 2017;31:286-299.
90. Shen W, Luo P, Sun Y, et al. NRBF2 regulates the chemoresistance of small cell lung cancer by interacting with the P62 protein in the autophagy process. *iScience*. 2022;25:104471.
91. Grunblatt E, Wu N, Zhang H, et al. MYCN drives chemoresistance in small cell lung cancer while USP7 inhibition can restore chemosensitivity. *Genes & development.* 2020;34:1210-1226.
92. Wu Q, Guo J, Liu Y, et al. YAP drives fate conversion and chemoresistance of small cell lung cancer. *Science advances.* 2021;7:eabg1850.
93. Murai J, Thomas A, Miettinen M, Pommier Y. Schlafen 11 (SLFN11), a restriction factor for replicative stress induced by DNA-targeting anti-cancer therapies. *Pharmacol Ther*. 2019;201:94-102.
94. Pal Choudhuri S, Girard L, Lim JYS, et al. Acquired Cross-Resistance in Small Cell Lung Cancer due to Extrachromosomal DNA Amplification of MYC Paralogs. *Cancer discovery*. 2024;14:804-827.
95. Pongor LS, Schultz CW, Rinaldi L, et al. Extrachromosomal DNA Amplification Contributes to Small Cell Lung Cancer Heterogeneity and Is Associated with Worse Outcomes. *Cancer discovery*. 2023;13:928-949.
96. Paz-Ares L, Chen Y, Reinmuth N, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. *ESMO Open.* 2022;7:100408.
97. Cai L, Liu H, Huang F, et al. Cell-autonomous immune gene expression is repressed in pulmonary neuroendocrine cells and small cell lung cancer. *Commun Biol.* 2021;4:314.
98. Gay CM, Stewart CA, Park EM, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. *Cancer cell*. 2021;39:346-360 e347.
99. Mahadevan NR, Knelson EH, Wolff JO, et al. Intrinsic Immunogenicity of Small Cell Lung Carcinoma Revealed by Its Cellular Plasticity. *Cancer discovery*. 2021;11:1952-1969.

100. Chan JM, Quintanal-Villalonga A, Gao VR, et al. Signatures of plasticity, metastasis, and immunosuppression in an atlas of human small cell lung cancer. *Cancer cell.* 2021;39:1479-1496 e1418.
101. Nabet BY, Hamidi H, Lee MC, et al. Immune heterogeneity in small-cell lung cancer and vulnerability to immune checkpoint blockade. *Cancer cell*. 2024;42:429-443 e424.
102. Eglenen-Polat B, Kowash RR, Huang HC, et al. A telomere-targeting drug depletes cancer initiating cells and promotes anti-tumor immunity in small cell lung cancer. *Nature communications*. 2024;15:672.
103. Ferrara MG, Stefani A, Simbolo M, et al. Large Cell Neuro-Endocrine Carcinoma of the Lung: Current Treatment Options and Potential Future Opportunities. *Front Oncol*. 2021;11:650293.
104. Rekhtman N. Lung neuroendocrine neoplasms: recent progress and persistent challenges. *Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc.* 2022;35:36-50.
105. George J, Walter V, Peifer M, et al. Integrative genomic profiling of large-cell neuroendocrine carcinomas reveals distinct subtypes of high-grade neuroendocrine lung tumors. *Nature communications*. 2018;9:1048.
106. Dudnik E, Kareff S, Moskovitz M, et al. Real-world survival outcomes with immune checkpoint inhibitors in large-cell neuroendocrine tumors of lung. *J Immunother Cancer.* 2021;9.
107. Alcala N, Leblay N, Gabriel AAG, et al. Integrative and comparative genomic analyses identify clinically relevant pulmonary carcinoid groups and unveil the supra-carcinoids. *Nature communications*. 2019;10:3407.
108. Dayton TL, Alcala N, Moonen L, et al. Druggable growth dependencies and tumor evolution analysis in patient-derived organoids of neuroendocrine neoplasms from multiple body sites. *Cancer cell.* 2023;41:2083-2099 e2089.
109. Stewart PA, Welsh EA, Slebos RJC, et al. Proteogenomic landscape of squamous cell lung cancer. *Nature communications*. 2019;10:3578.
110. Chen YJ, Roumeliotis TI, Chang YH, et al. Proteogenomics of Non-smoking Lung Cancer in East Asia Delineates Molecular Signatures of Pathogenesis and Progression. *Cell*. 2020;182:226-244 e217.
111. Gillette MA, Satpathy S, Cao S, et al. Proteogenomic Characterization Reveals Therapeutic Vulnerabilities in Lung Adenocarcinoma. *Cell*. 2020;182:200-225 e235.
112. Yanovich-Arad G, Geiger T. Across the Globe: Proteogenomic Landscapes of Lung Cancer. *Cell*. 2020;182:9-11.
113. Satpathy S, Krug K, Jean Beltran PM, et al. A proteogenomic portrait of lung squamous cell carcinoma. *Cell*. 2021;184:4348-4371 e4340.
114. Chen H, Drapkin BJ, Minna JD. Proteomics: A new dimension to decode small cell lung cancer. *Cell*. 2024;187:14-16.
115. Drago JZ, Modi S, Chandarlapaty S. Unlocking the potential of antibody-drug conjugates for cancer therapy. *Nat Rev Clin Oncol*. 2021;18:327-344.
116. Fu Z, Li S, Han S, et al. Antibody drug conjugate: the "biological missile" for targeted cancer therapy. *Signal Transduct Target Ther.* 2022;7:93.
117. Dumontet C, Reichert JM, Senter PD, et al. Antibody-drug conjugates come of age in oncology. *Nat Rev Drug Discov.* 2023;22:641-661.
118. Tsuchikama K, Anami Y, Ha SYY, Yamazaki CM. Exploring the next generation of antibody-drug conjugates. *Nat Rev Clin Oncol.* 2024;21:203-223.
119. Labrijn AF, Janmaat ML, Reichert JM, Parren P. Bispecific antibodies: a mechanistic review of the pipeline. *Nat Rev Drug Discov.* 2019;18:585-608.
120. Szijj P, Chudasama V. The renaissance of chemically generated bispecific antibodies. *Nat Rev Chem.* 2021;5:78-92.
121. Klein C, Brinkmann U, Reichert JM, Kontermann RE. The present and future of bispecific antibodies for cancer therapy. *Nat Rev Drug Discov.* 2024;23:301-319.
122. Coleman N, Yap TA, Heymach JV, et al. Antibody-drug conjugates in lung cancer: dawn of a new era? *NPJ Precis Oncol.* 2023;7:5.
123. Khosla AA, Jatwani K, Singh R, et al. Bispecific Antibodies in Lung Cancer: A State-of-the-Art Review. *Pharmaceuticals (Basel)*. 2023;16.
124. Paz-Ares L, Champiat S, Lai WV, et al. Tarlatamab, a First-in-Class DLL3-Targeted Bispecific T-Cell Engager, in Recurrent Small-Cell Lung Cancer: An Open-Label, Phase I Study. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology.* 2023;41:2893-2903.
125. Abbosh C, Frankell AM, Harrison T, et al. Tracking early lung cancer metastatic dissemination in TRACERx using ctDNA. *Nature*. 2023;616:553-562.
126. Al Bakir M, Huebner A, Martinez-Ruiz C, et al. The evolution of non-small cell lung cancer metastases in TRACERx. *Nature*. 2023;616:534-542.
127. Frankell AM, Dietzen M, Al Bakir M, et al. The evolution of lung cancer and impact of subclonal selection in TRACERx. *Nature*. 2023;616:525-533.
128. Hayes TK, Meyerson M. Molecular portraits of lung cancer evolution. *Nature*. 2023;616:435-436.
129. Martinez-Ruiz C, Black JRM, Puttick C, et al. Genomic-transcriptomic evolution in lung cancer and metastasis.*Nature*. 2023;616:543-552.
130. Ng KW, Boumelha J, Enfield KSS, et al. Antibodies against endogenous retroviruses promote lung cancer immunotherapy. *Nature*. 2023;616:563-573.
131. DeNicola GM, Shackelford DB. Metabolic Phenotypes, Dependencies, and Adaptation in Lung Cancer. *Cold Spring Harb Perspect Med.* 2021;11.
132. Hensley CT, Faubert B, Yuan Q, et al. Metabolic Heterogeneity in Human Lung Tumors. *Cell*. 2016;164:681-694.
133. DeNicola GM, Chen PH, Mullarky E, et al. NRF2 regulates serine biosynthesis in non-small cell lung cancer. *Nature genetics.* 2015;47:1475-1481.
134. Faubert B, Li KY, Cai L, et al. Lactate Metabolism in Human Lung Tumors. *Cell.* 2017;171:358-371 e359.
135. Padanad MS, Konstantinidou G, Venkateswaran N, et al. Fatty Acid Oxidation Mediated by Acyl-CoA Synthetase Long Chain 3 Is Required for Mutant KRAS Lung Tumorigenesis. *Cell reports*. 2016;16:1614-1628.
136. Bartolacci C, Andreani C, Vale G, et al. Targeting de novo lipogenesis and the Lands cycle induces ferroptosis in KRAS-mutant lung cancer. *Nature*. communications 2022;13:4327.
137. Mei L, Zhang Z, Li X, et al. Metabolomics profiling in prediction of chemo-immunotherapy efficiency in advanced non-small cell lung cancer. *Front Oncol*. 2022;12:1025046.
138. Kim J, Hu Z, Cai L, et al. CPS1 maintains pyrimidine pools and DNA synthesis in KRAS/LKB1-mutant lung cancer cells. *Nature*. 2017;546:168-172.
139. Galan-Cobo A, Sitthideatphaiboon P, Qu X, et al. LKB1 and KEAP1/NRF2 Pathways Cooperatively Promote Metabolic Reprogramming with Enhanced Glutamine Dependence in KRAS-Mutant Lung Adenocarcinoma. *Cancer research*. 2019;79:3251-3267.

140. Goodwin J, Neugent ML, Lee SY, et al. The distinct metabolic phenotype of lung squamous cell carcinoma defines selective vulnerability to glycolytic inhibition. *Nature communications*. 2017;8:15503.
141. Chen PH, Cai L, Huffman K, et al. Metabolic Diversity in Human Non-Small Cell Lung Cancer Cells. *Mol Cell*.2019;76:838-851 e835.
142. Luengo A, Abbott KL, Davidson SM, et al. Reactive metabolite production is a targetable liability of glycolytic metabolism in lung cancer. *Nature communications*. 2019;10:5604.
143. Cargill KR, Stewart CA, Park EM, et al. Targeting MYC-enhanced glycolysis for the treatment of small cell lung cancer. *Cancer Metab*. 2021;9:33.
144. Pillai R, LeBoeuf SE, Hao Y, et al. Glutamine antagonist DRP-104 suppresses tumor growth and enhances response to checkpoint blockade in KEAP1 mutant lung cancer. *Science advances*. 2024;10:eadm9859.
145. Zhu R, Liu Z, Jiao R, et al. Updates on the pathogenesis of advanced lung cancer-induced cachexia. *Thorac Cancer*. 2019;10:8-16.
146. Madeddu C, Busquets S, Donisi C, et al. Effect of Cancer-Related Cachexia and Associated Changes in Nutritional Status, Inflammatory Status, and Muscle Mass on Immunotherapy Efficacy and Survival in Patients with Advanced Non-Small Cell Lung Cancer. *Cancers*. 2023;15.
147. Al-Sawaf O, Weiss J, Skrzypski M, et al. Body composition and lung cancer-associated cachexia in TRACERx. *Nat Med*. 2023;29:846-858.
148. Iyengar P, Gandhi AY, Granados J, et al. Tumor loss-of-function mutations in STK11/LKB1 induce cachexia. *JCI Insight*. 2023;8.
149. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646-674.
150. Ganguly D, Chandra R, Karalis J, et al. Cancer-Associated Fibroblasts: Versatile Players in the Tumor Microenvironment. *Cancers*. 2020;12:2652.
151. Cords L, Engler S, Haberecker M, et al. Cancer-associated fibroblast phenotypes are associated with patient outcome in non-small cell lung cancer. *Cancer cell*. 2024;42:396-412 e395.
152. Pellinen T, Paavolainen L, Martin-Bernabe A, et al. Fibroblast subsets in non-small cell lung cancer: Associations with survival, mutations, and immune features. *Journal of the National Cancer Institute*. 2023;115: 71-82.
153. Schliekelman MJ, Creighton CJ, Baird BN, et al. Thy-1(+) Cancer-associated Fibroblasts Adversely Impact Lung Cancer Prognosis. *Scientific reports*. 2017;7:6478.
154. Shien K, Papadimitrakopoulou VA, Ruder D, et al. JAK1/STAT3 Activation through a Proinflammatory Cytokine Pathway Leads to Resistance to Molecularly Targeted Therapy in Non-Small Cell Lung Cancer. *Molecular cancer therapeutics*. 2017;16:2234-2245.
155. Su S, Chen J, Yao H, et al. CD10(+) GPR77(+) Cancer-Associated Fibroblasts Promote Cancer Formation and Chemoresistance by Sustaining Cancer Stemness. *Cell*. 2018;172: 841-856 e816.
156. Irvine AF, Waise S, Green EW, et al. Characterising cancer-associated fibroblast heterogeneity in non-small cell lung cancer: a systematic review and meta-analysis. *Scientific reports*. 2021;11:3727.
157. Huang H, Wang Z, Zhang Y, et al. Mesothelial cell-derived antigen-presenting cancer-associated fibroblasts induce expansion of regulatory T cells in pancreatic cancer. *Cancer cell*. 2022;40:656-673 e657.
158. Wang L, Cao L, Wang H, et al. Cancer-associated fibroblasts enhance metastatic potential of lung cancer cells through IL-6/STAT3 signaling pathway. 2017;8:76116.
159. Zhang J, Qi J, Wei H, et al. TGFβ1 in Cancer-Associated Fibroblasts Is Associated With Progression and Radiosensitivity in Small-Cell Lung Cancer. *Frontiers in cell and developmental biology*. 2021;9.
160. Rachman-Tzemah C, Zaffryar-Eilot S, Grossman M, et al. Blocking Surgically Induced Lysyl Oxidase Activity Reduces the Risk of Lung Metastases. *Cell reports*. 2017;19:774-784.
161. Gao Y, Xiao Q, Ma H, et al. LKB1 inhibits lung cancer progression through lysyl oxidase and extracellular matrix remodeling. *Proceedings of the National Academy of Sciences of the United States of America*. 2010;107:18892-18897.
162. Guo J-Y, Chiu C-H, Wang M-J, et al. Proteoglycan serglycin promotes non-small cell lung cancer cell migration through the interaction of its glycosaminoglycans with CD44. *Journal of biomedical science*. 2020;27:1-18.
163. Yang YC, Pan KF, Lee WJ, et al. Circulating Proteoglycan Endocan Mediates EGFR-Driven Progression of Non-Small Cell Lung Cancer. *Cancer research*. 2020;80:3292-3304.
164. Li L, Wei JR, Dong J, et al. Laminin gamma2-mediating T cell exclusion attenuates response to anti-PD-1 therapy. *Science advances*. 2021;7: eabc8346.
165. Hodkinson PS, Mackinnon AC, Sethi T. Extracellular matrix regulation of drug resistance in small-cell lung cancer. *Int J Radiat Biol*. 2007;83:733-741.
166. Sethi T, Rintoul RC, Moore SM, et al. Extracellular matrix proteins protect small cell lung cancer cells against apoptosis: a mechanism for small cell lung cancer growth and drug resistance in vivo. *Nat Med*. 1999;5:662-668.
167. Hartmann TN, Burger JA, Glodek A, et al. CXCR4 chemokine receptor and integrin signaling co-operate in mediating adhesion and chemo-resistance in small cell lung cancer (SCLC) cells. *Oncogene*. 2005;24: 4462-4471.
168. Hall RD, Le TM, Haggstrom DE, Gentzler RD. Angiogenesis inhibition as a therapeutic strategy in non-small cell lung cancer (NSCLC). *Translational lung cancer research*. 2015;4:515.
169. Crino L, Metro G. Therapeutic options targeting angiogenesis in non-small cell lung cancer. *Eur Respir Rev*. 2014;23:79-91.
170. Ancel J, Perotin JM, Dewolf M, et al. Hypoxia in Lung Cancer Management: A Translational Approach. *Cancers*. 2021;13:3421.
171. Ogawa E, Takenaka K, Yanagihara K, et al. Clinical significance of VEGF-C status in tumour cells and stromal macrophages in non-small cell lung cancer patients. *British journal of cancer*. 2004;91:498-503.
172. Liu G, Xu S, Jiao F, et al. Vascular endothelial growth factor B coordinates metastasis of non-small cell lung cancer. *Tumour biology: the journal of the International Society for Oncodevelopmental Biology and Medicine*. 2015;36:2185-2191.
173. Lucchi M, Mussi A, Fontanini G, et al. Small cell lung carcinoma (SCLC): the angiogenic phenomenon. *Eur J Cardiothorac Surg*. 2002;21:1105-1110.
174. Xu F, Wei Y, Tang Z, et al. Tumor-associated macrophages in lung cancer: Friend or foe? (Review). *Mol Med Rep*. 2020;22:4107-4115.

175. Poh AR, Ernst M. Targeting Macrophages in Cancer: From Bench to Bedside. *Front Oncol*. 2018;8:49.
176. Fridlender ZG, Kapoor V, Buchlis G, et al. Monocyte chemoattractant protein-1 blockade inhibits lung cancer tumor growth by altering macrophage phenotype and activating CD8+ cells. *Am J Respir Cell Mol Biol*. 2011;44:230-237.
177. Jackute J, Zemaitis M, Pranys D, et al. Distribution of M1 and M2 macrophages in tumor islets and stroma in relation to prognosis of non-small cell lung cancer. *BMC Immunol*. 2018;19:3.
178. Ma J, Liu L, Che G, et al. The M1 form of tumor-associated macrophages in non-small cell lung cancer is positively associated with survival time. 2010;10:1-9.
179. Rakaee M, Busund LR, Jamaly S, et al. Prognostic Value of Macrophage Phenotypes in Resectable Non-Small Cell Lung Cancer Assessed by Multiplex Immunohistochemistry. *Neoplasia (New York, NY).* 2019;21:282-293.
180. Cao L, Che X, Qiu X, et al. M2 macrophage infiltration into tumor islets leads to poor prognosis in non-small-cell lung cancer. 2019;11:6125.
181. Poczobutt JM, De S, Yadav VK, et al. Expression Profiling of Macrophages Reveals Multiple Populations with Distinct Biological Roles in an Immunocompetent Orthotopic Model of Lung Cancer. *J Immunol.* 2016;196:2847-2859.
182. Ellis S, Lin EJ, Tartar D. Immunology of Wound Healing. *Curr Dermatol Rep.* 2018;7:350-358.
183. Teixido C, Rosell R. Neutrophils dominate the immune landscape of non-small cell lung cancer. *J Thorac Dis.* 2017;9:E468-E469.
184. Kargl J, Busch SE, Yang GH, et al. Neutrophils dominate the immune cell composition in non-small cell lung cancer. *Nature communications*. 2017;8:14381.
185. Kargl J, Zhu X, Zhang H, et al. Neutrophil content predicts lymphocyte depletion and anti-PD1 treatment failure in NSCLC. *JCI Insight*. 2019;4.
186. Mitchell KG, Diao L, Karpinets T, et al. Neutrophil expansion defines an immunoinhibitory peripheral and intratumoral inflammatory milieu in resected non-small cell lung cancer: a descriptive analysis of a prospectively immunoprofiled cohort. *J Immunother Cancer*. 2020;8.
187. Schernberg A, Mezquita L, Boros A, et al. Neutrophilia as prognostic biomarker in locally advanced stage III lung cancer. 2018;13:e0204490.
188. Huang C, Yue J, Li Z, et al. Usefulness of the neutrophil-to-lymphocyte ratio in predicting lymph node metastasis in patients with non-small cell lung cancer. *Tumour biology: the journal of the International Society for Oncodevelopmental Biology and Medicine.* 2015;36:7581-7589.
189. Huang W, Wang S, Zhang H, et al. Prognostic significance of combined fibrinogen concentration and neutrophil-to-lymphocyte ratio in patients with resectable non-small cell lung cancer. *Cancer Biol Med*. 2018;15:88-96.
190. Liu D, Huang Y, Li L, et al. High neutrophil-to-lymphocyte ratios confer poor prognoses in patients with small cell lung cancer. *BMC cancer*. 2017;17:882.
191. Lu Y, Xu W, Gu Y, et al. Non-small Cell Lung Cancer Cells Modulate the Development of Human CD1c(+) Conventional Dendritic Cell Subsets Mediated by CD103 and CD205. *Front Immunol*. 2019;10:2829.
192. Chandra R, Karalis JD, Liu C, et al. The Colorectal Cancer Tumor Microenvironment and Its Impact on Liver and Lung Metastasis. *Cancers*. 2021;13:6206.
193. Yang J, Liu X, Cheng Y, et al. Roles of Plasmacytoid Dendritic Cells in Gastric Cancer. *Front Oncol*. 2022;12:818314.
194. Wang JB, Huang X, Li FR. Impaired dendritic cell functions in lung cancer: a review of recent advances and future perspectives. *Cancer Commun (Lond).* 2019;39:43.
195. Kuo PL, Huang MS, Cheng DE, et al. Lung cancer-derived galectin-1 enhances tumorigenic potentiation of tumor-associated dendritic cells by expressing heparin-binding EGF-like growth factor. *J Biol Chem.* 2012;287:9753-9764.
196. Shi W, Li X, Porter JL, et al. Level of plasmacytoid dendritic cells is increased in non-small cell lung carcinoma. *Tumor Biology.* 2014;35:2247-2252.
197. Katsenelson NS, Shurin GV, Bykovskaia SN, et al. Human small cell lung carcinoma and carcinoid tumor regulate dendritic cell maturation and function. *Modern pathology: an official journal of the United States and CanadianAcademy of Pathology, Inc*. 2001;14:40-45.
198. Principe DR, Chiec L, Mohindra NA, Munshi HG. Regulatory T-Cells as an Emerging Barrier to Immune Checkpoint Inhibition in Lung Cancer. *Frontiers in Oncology*. 2021;11:2092.
199. Zhao S, Jiang T, Zhang L, et al. Clinicopathological and prognostic significance of regulatory T cells in patients with non-small cell lung cancer: A systematic review with meta-analysis. *Oncotarget*. 2016;7:36065-36073.
200. Hu X, Gu Y, Zhao S, et al. Elevated Circulating CD4(+)CD25(-)Foxp3(+) Regulatory T Cells in Patients with Nonsmall Cell Lung Cancer. *Cancer Biother Radiopharm*. 2019;34:325-333.
201. Shimizu K, Nakata M, Hirami Y, et al. Tumor-infiltrating Foxp3+ regulatory T cells are correlated with cyclooxygenase-2 expression and are associated with recurrence in resected non-small cell lung cancer. *Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer.* 2010;5:585-590.
202. Kagamu H, Kitano S, Yamaguchi O, et al. CD4(+) T-cell Immunity in the Peripheral Blood Correlates with Response to Anti-PD-1 Therapy. *Cancer Immunol Res.* 2020;8:334-344.
203. Jiang M, Wu C, Zhang L, et al. FOXP3-based immune risk model for recurrence prediction in small-cell lung cancer at stages I–III. *Journal for immunotherapy of cancer*. 2021;9.
204. Wang W, Hodkinson P, McLaren F, et al. Small cell lung cancer tumour cells induce regulatory T lymphocytes, and patient survival correlates negatively with FOXP3+ cells in tumour infiltrate. *International journal of cancer.* 2012;131:E928-937.
205. Tay RE, Richardson EK, Toh HC. Revisiting the role of CD4+ T cells in cancer immunotherapy—new insights into old paradigms. *Cancer Gene Therapy.* 2021;28:5-17.
206. Salazar Y, Zheng X, Brunn D, et al. Microenvironmental Th9 and Th17 lymphocytes induce metastatic spreading in lung cancer. *J Clin Invest.* 2020;130:3560-3575.
207. Chae YK, Chang S, Ko T, et al. Epithelial-mesenchymal transition (EMT) signature is inversely associated with T-cell infiltration in non-small cell lung cancer (NSCLC). 2018;8:1-8.
208. Kasahara N, Kaira K, Yamaguchi K, et al. Fluorodeoxyglucose uptake is associated with low tumor-infiltrating lymphocyte levels in patients with small cell lung cancer. *Lung cancer (Amsterdam, Netherlands)*. 2019;134:180-186.

209. Soo RA, Chen Z, Yan Teng RS, et al. Prognostic significance of immune cells in non-small cell lung cancer: meta-analysis. *Oncotarget*. 2018;9:24801-24820.
210. Niemeijer AN, Sahba S, Smit EF, et al. Association of tumour and stroma PD-1, PD-L1, CD3, CD4 and CD8 expression with DCB and OS to nivolumab treatment in NSCLC patients pre-treated with chemotherapy. British journal of cancer 2020;123:392-402.
211. Raskov H, Orhan A, Christensen JP, Gogenur I. Cytotoxic CD8(+) T cells in cancer and cancer immunotherapy. *British journal of cancer*. 2021;124:359-367.
212. Nan Z, Guoqing W, Xiaoxu Y, et al. The Predictive Efficacy of Tumor Mutation Burden (TMB) on Nonsmall Cell Lung Cancer Treated by Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis. *Biomed Res Int*. 2021;2021:1780860.
213. Zhou ZJ, Zhan P, Song Y. PD-L1 over-expression and survival in patients with non-small cell lung cancer: a meta-analysis. *Translational lung cancer research*. 2015;4:203-208.
214. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med.* 2015;373:1627-1639.
215. To KKW, Fong W, Cho WCS. Immunotherapy in Treating EGFR-Mutant Lung Cancer: Current Challenges and New Strategies. *Front Oncol*. 2021;11:635007.
216. An N, Wang H, Jia W, et al. The prognostic role of circulating CD8(+) T cell proliferation in patients with untreated extensive stage small cell lung cancer. *Journal of translational medicine*. 2019;17:402.
217. Zhu M, Huang Y, Bender ME, et al. Evasion of Innate Immunity Contributes to Small Cell Lung Cancer Progression and Metastasis. *Cancer research.* 2021;81:1813-1826.
218. Milovanovic IS, Stjepanovic M, Mitrovic D. Distribution patterns of the metastases of the lung carcinoma in relation to histological type of the primary tumor: An autopsy study. *Ann Thorac Med.* 2017;12:191-198.
219. Riihimaki M, Hemminki A, Fallah M, et al. Metastatic sites and survival in lung cancer. *Lung cancer (Amsterdam, Netherlands).* 2014;86:78-84.
220. Perlikos F, Harrington KJ, Syrigos KN. Key molecular mechanisms in lung cancer invasion and metastasis: a comprehensive review. *Crit Rev Oncol Hematol*. 2013;87:1-11.
221. Xiao D, He J. Epithelial mesenchymal transition and lung cancer. *J Thorac Dis.* 2010;2:154-159.
222. Xie S, Wu Z, Qi Y, et al. The metastasizing mechanisms of lung cancer: Recent advances and therapeutic challenges. *Biomed Pharmacother.* 2021;138:111450.
223. Larsen JE, Nathan V, Osborne JK, et al. ZEB1 drives epithelial-to-mesenchymal transition in lung cancer. *J Clin Invest.* 2016;126:3219-3235.
224. Drapkin BJ, George J, Christensen CL, et al. Genomic and Functional Fidelity of Small Cell Lung Cancer Patient-Derived Xenografts. *Cancer discovery.* 2018;8:600-615.
225. Hodgkinson CL, Morrow CJ, Li Y, et al. Tumorigenicity and genetic profiling of circulating tumor cells in small-cell lung cancer. *Nat Med.* 2014;20:897-903.
226. Ko J, Winslow MM, Sage J. Mechanisms of small cell lung cancer metastasis. *EMBO Mol Med.* 2021;13:e13122.
227. Qu F, Brough SC, Michno W, et al. Crosstalk between small-cell lung cancer cells and astrocytes mimics brain development to promote brain metastasis. *Nat Cell Biol.* 2023;25:1506-1519.
228. Stewart CA, Tong P, Cardnell RJ, et al. Dynamic variations in epithelial-to-mesenchymal transition (EMT), ATM, and SLFN11 govern response to PARP inhibitors and cisplatin in small cell lung cancer. 2017;8:28575.
229. Dhanyamraju PK. Drug resistance mechanisms in cancers: Execution of pro-survival strategies. *J Biomed Res.* 2024;38:95-121.
230. Sosa Iglesias V, Giuranno L, Dubois LJ, et al. Drug Resistance in Non-Small Cell Lung Cancer: A Potential for NOTCH Targeting? *Front Oncol.* 2018;8:267.
231. Del Re M, Rofi E, Restante G, et al. Implications of KRAS mutations in acquired resistance to treatment in NSCLC. *Oncotarget*. 2018;9:6630-6643.
232. Macerelli M, Caramella C, Faivre L, et al. Does KRAS mutational status predict chemoresistance in advanced non-small cell lung cancer (NSCLC)? *Lung cancer (Amsterdam, Netherlands).* 2014;83:383-388.
233. Tulpule A, Bivona TG. Acquired resistance in lung cancer. *Annual Review of Cancer Biology*. 2020;4:279-297.
234. Robichaux JP, Le X, Vijayan RSK, et al. Structure-based classification predicts drug response in EGFR-mutant NSCLC. *Nature*. 2021;597:732-737.
235. Yenerall P, Kittler R, Minna J. Structure-based classification of EGFR mutations informs inhibitor selection for lung cancer therapy. *Cancer cell*. 2021;39:1455-1457.
236. Yenerall P, Kollipara RK, Avila K, et al. Lentiviral-Driven Discovery of Cancer Drug Resistance Mutations. *Cancer research*. 2021;81:4685-4695.
237. Quintanal-Villalonga A, Chan JM, Yu HA, et al. Lineage plasticity in cancer: a shared pathway of therapeutic resistance. *Nat Rev Clin Oncol.* 2020;17:360-371.
238. Le Magnen C, Shen MM, Abate-Shen C. Lineage Plasticity in Cancer Progression and Treatment. *Annu Rev Cancer Biol.* 2018;2:271-289.
239. Boumahdi S, de Sauvage FJ. The great escape: tumour cell plasticity in resistance to targeted therapy. *Nat Rev Drug Discov.* 2020;19:39-56.
240. Blaquier JB, Ortiz-Cuaran S, Ricciuti B, et al. Tackling Osimertinib Resistance in EGFR-Mutant Non-Small Cell Lung Cancer. Clinical cancer research : an official journal of the American Association for Cancer Research 2023;29:3579-3591.
241. Le X, Puri S, Negrao MV, et al. Landscape of EGFR-Dependent and -Independent Resistance Mechanisms to Osimertinib and Continuation Therapy Beyond Progression in EGFR-Mutant NSCLC. *Clinical cancer research: an official journal of the American Association for Cancer Research*. 2018;24:6195-6203.
242. Leonetti A, Sharma S, Minari R, et al. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *British journal of cancer*. 2019;121:725-737.
243. Lim SM, Syn NL, Cho BC, Soo RA. Acquired resistance to EGFR targeted therapy in non-small cell lung cancer: Mechanisms and therapeutic strategies. *Cancer Treat Rev*. 2018;65:1-10.
244. LaFave LM, Kartha VK, Ma S, et al. Epigenomic State Transitions Characterize Tumor Progression in Mouse Lung Adenocarcinoma. *Cancer cell*. 2020;38:212-228 e213.
245. Marjanovic ND, Hofree M, Chan JE, et al. Emergence of a High-Plasticity Cell State during Lung Cancer Evolution. *Cancer cell*. 2020;38:229-246 e213.
246. Lv X, Mao Z, Sun X, Liu B. Intratumoral Heterogeneity in Lung Cancer. *Cancers.* 2023;15.

247. Wu HJ, Temko D, Maliga Z, et al. Spatial intra-tumor heterogeneity is associated with survival of lung adenocarcinoma patients. *Cell Genom*. 2022;2.
248. Zhou H, Hu Y, Luo R, et al. Multi-region exome sequencing reveals the intratumoral heterogeneity of surgically resected small cell lung cancer. *Nature communications*. 2021;12:5431.
249. Wu F, Fan J, He Y, et al. Single-cell profiling of tumor heterogeneity and the microenvironment in advanced non-small cell lung cancer. *Nature communications*. 2021;12:2540.
250. Gregorc V, Lazzari C, Mandala M, et al. Intratumoral Cellular Heterogeneity: Implications for Drug Resistance in Patients with Non-Small Cell Lung Cancer. *Cancers*. 2021;13.
251. Dentro SC, Leshchiner I, Haase K, et al. Characterizing genetic intra-tumor heterogeneity across 2,658 human cancer genomes. *Cell*. 2021;184:2239-2254 e2239.
252. Stewart CA, Gay CM, Xi Y, et al. Single-cell analyses reveal increased intratumoral heterogeneity after the onset of therapy resistance in small-cell lung cancer. *Nat Cancer*. 2020;1:423-436.
253. Hua X, Zhao W, Pesatori AC, et al. Genetic and epigenetic intratumor heterogeneity impacts prognosis of lung adenocarcinoma. *Nature communications*. 2020;11:2459.
254. Ghaderi N, Jung JH, Odde DJ, Peacock J. Clinically validated model predicts the effect of intratumoral heterogeneity on overall survival for non-small cell lung cancer (NSCLC) patients. *Comput Methods Programs Biomed*. 2021;212:106455.
255. Dzobo K, Ganz C, Thomford NE, Senthebane DA. Cancer Stem Cell Markers in Relation to Patient Survival Outcomes: Lessons for Integrative Diagnostics and Next-Generation Anticancer Drug Development. *OMICS.* 2021;25:81-92.
256. Firdous S, Ghosh A, Saha S. BCSCdb: a database of biomarkers of cancer stem cells. *Database (Oxford)*. 2022;2022.
257. Sullivan JP, Minna JD, Shay JW. Evidence for self-renewing lung cancer stem cells and their implications in tumor initiation, progression, and targeted therapy. *Cancer metastasis reviews*. 2010;29:61-72.
258. Madden EC, Gorman AM, Logue SE, Samali A. Tumour Cell Secretome in Chemoresistance and Tumour Recurrence. *Trends in cancer*. 2020;6:489-505.
259. Pan Z, Zhang M, Zhang F, et al. Single-Cell Transcriptomics Unveils the Dedifferentiation Mechanism of Lung Adenocarcinoma Stem Cells. *International journal of molecular sciences.* 2022;24.
260. Shao C, Sullivan JP, Girard L, et al. Essential role of aldehyde dehydrogenase 1A3 for the maintenance of non-small cell lung cancer stem cells is associated with the STAT3 pathway. *Clinical cancer research: an official journal of the American Association for Cancer Research.* 2014;20:4154-4166.
261. Sullivan JP, Spinola M, Dodge M, et al. Aldehyde dehydrogenase activity selects for lung adenocarcinoma stem cells dependent on notch signaling. *Cancer research*. 2010;70:9937-9948.
262. Cortes-Dericks L, Galetta D. Impact of Cancer Stem Cells and Cancer Stem Cell-Driven Drug Resiliency in Lung Tumor: Options in Sight. *Cancers*. 2022;14:267.
263. Kryczka J, Kryczka J, Czarnecka-Chrebelska KH, Brzezianska-Lasota E. Molecular Mechanisms of Chemoresistance Induced by Cisplatin in NSCLC Cancer Therapy. *International journal of molecular sciences*. 2021;22:8885.
264. Dhanyamraju PK, Schell TD, Amin S, Robertson GP. Drug-Tolerant Persister Cells in Cancer Therapy Resistance. *Cancer research*. 2022;82:2503-2514.
265. Mikubo M, Inoue Y, Liu G, Tsao MS. Mechanism of Drug Tolerant Persister Cancer Cells: The Landscape and Clinical Implication for Therapy. *Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer.* 2021;16:1798-1809.
266. Pu Y, Li L, Peng H, et al. Drug-tolerant persister cells in cancer: the cutting edges and future directions. *Nat Rev Clin Oncol.* 2023;20:799-813.
267. Mulshine JL, Ujhazy P, Antman M, et al. From clinical specimens to human cancer preclinical models-a journey the NCI-cell line database-25 years later. *J Cell Biochem.* 2020;121:3986-3999.
268. Arnal-Estape A, Foggetti G, Starrett JH, et al. Preclinical Models for the Study of Lung Cancer Pathogenesis and Therapy Development. *Cold Spring Harb Perspect Med.* 2021;11.
269. Hynds RE, Frese KK, Pearce DR, et al. Progress towards non-small-cell lung cancer models that represent clinical evolutionary trajectories. Open Biol 2021;11:200247.
270. Sun H, Cao S, Mashl RJ, et al. Comprehensive characterization of 536 patient-derived xenograft models prioritizes candidatesfor targeted treatment. *Nature communications*. 2021;12:5086.
271. Morgan KM, Riedlinger GM, Rosenfeld J, et al. Patient-derived xenograft models of non-small cell lung cancer and their potential utility in personalized medicine. *Frontiers in oncology.* 2017;7:2.
272. Drapkin BJ, George J, Christensen CL, et al. Genomic and Functional Fidelity of Small Cell Lung Cancer Patient-Derived XenograftsGenomic and Functional Fidelity of SCLC PDX Models. *Cancer discovery.* 2018;8:600-615.
273. Meraz IM, Majidi M, Meng F, et al. An Improved Patient-Derived Xenograft Humanized Mouse Model for Evaluation of Lung Cancer Immune ResponsesHumanized-PDX Mouse Model for Cancer Immunotherapy. *Cancer immunology research*. 2019;7:1267-1279.
274. Li H, Liu Z, Liu L, et al. AXL targeting restores PD-1 blockade sensitivity of STK11/LKB1 mutant NSCLC through expansion of TCF1(+) CD8 T cells. *Cell Rep Med*. 2022;3:100554.
275. Dijkstra KK, Monkhorst K, Schipper LJ, et al. Challenges in Establishing Pure Lung Cancer Organoids Limit Their Utility for Personalized Medicine. *Cell reports*. 2020;31:107588.
276. Hu Y, Sui X, Song F, et al. Lung cancer organoids analyzed on microwell arrays predict drug responses of patients within a week. *Nature communications*. 2021;12:2581.
277. Kim M, Mun H, Sung CO, et al. Patient-derived lung cancer organoids as in vitro cancer models for therapeutic screening. *Nature communications*. 2019;10:3991.
278. Larsen BM, Kannan M, Langer LF, et al. A pan-cancer organoid platform for precision medicine. *Cell reports*. 2021;36:109429.
279. Li Z, Qian Y, Li W, et al. Human Lung Adenocarcinoma-Derived Organoid Models for Drug Screening. *iScience.* 2020;23:101411.
280. Ma HC, Zhu YJ, Zhou R, et al. Lung cancer organoids, a promising model still with long way to go. *Crit Rev Oncol Hematol.* 2022;171:103610.
281. Rossi R, De Angelis ML, Xhelili E,

et al. Lung Cancer Organoids: The Rough Path to Personalized Medicine. *Cancers.* 2022;14.
282. Shi R, Radulovich N, Ng C, et al. Organoid Cultures as Preclinical Models of Non-Small Cell Lung Cancer. *Clinical cancer research: an official journal of the American Association for Cancer Research.* 2020;26:1162-1174.
283. Wang HM, Zhang CY, Peng KC, et al. Using patient-derived organoids to predict locally advanced or metastatic lung cancer tumor response: A real-world study. *Cell Rep Med.* 2023;4:100911.
284. Westcott PM, Halliwill KD, To MD, et al. The mutational landscapes of genetic and chemical models of Kras-driven lung cancer. *Nature.* 2015;517:489-492.
285. Oser MG, MacPherson D, Oliver TG, et al. Genetically-engineered mouse models of small cell lung cancer: the next generation. *Oncogene.* 2024;43:457-469.
286. Kwon MC, Berns A. Mouse models for lung cancer. *Molecular oncology.* 2013;7:165-177.
287. Yang D, Denny SK, Greenside PG, et al. Intertumoral Heterogeneity in SCLC Is Influenced by the Cell Type of Origin. *Cancer discovery*. 2018;8:1316-1331.
288. Ramirez RD, Sheridan S, Girard L, et al. Immortalization of human bronchial epithelial cells in the absence of viral oncoproteins. *Cancer research.* 2004;64:9027-9034.
289. Vaughan MB, Ramirez RD, Wright WE, et al. A three-dimensional model of differentiation of immortalized human bronchial epithelial cells. *Differentiation.* 2006;74:141-148.
290. Delgado O, Kaisani AA, Spinola M, et al. Multipotent capacity of immortalized human bronchial epithelial cells. *PloS one*. 2011;6:e22023.
291. Kaisani A, Delgado O, Fasciani G, et al. Branching morphogenesis of immortalized human bronchial epithelial cells in three-dimensional culture. *Differentiation.* 2014;87:119-126.
292. Gao B, Huang C, Kernstine K, et al. Non-malignant respiratory epithelial cells preferentially proliferate from resected non-small cell lung cancer specimens cultured under conditionally reprogrammed conditions. *Oncotarget*. 2017;8:11114-11126.
293. LaRanger R, Peters-Hall JR, Coquelin M, et al. Reconstituting Mouse Lungs with Conditionally Reprogrammed Human Bronchial Epithelial Cells. *Tissue Eng Part A.* 2018;24:559-568.
294. Peters-Hall JR, Min J, Tedone E, et al. Proliferation of adult human bronchial epithelial cells without a telomere maintenance mechanism for over 200 population doublings. *FASEB J.* 2020;34:386-398.
295. Sato M, Vaughan MB, Girard L, et al. Multiple oncogenic changes (K-RAS (V12), p53 knockdown, mutant EGFRs, p16 bypass, telomerase) are not sufficient to confer a full malignant phenotype on human bronchial epithelial cells. *Cancer research.* 2006;66:2116-2128.
296. Sato M, Larsen JE, Lee W, et al. Human lung epithelial cells progressed to malignancy through specific oncogenic manipulations. *Molecular cancer research: MCR.* 2013;11:638-650.
297. Zhou X, Updegraff BL, Guo Y, et al. PROTOCADHERIN 7 Acts through SET and PP2A to Potentiate MAPK Signaling by EGFR and KRAS during Lung Tumorigenesis. *Cancer research.* 2017;77:187-197.
298. Haley B, Roudnicky F. Functional Genomics for Cancer Drug Target Discovery. *Cancer cell.* 2020;38:31-43.
299. Johannessen CM, Boehm JS. Progress towards precision functional genomics in cancer. *Current Opinion in Systems Biology.* 2017;2:74-83.
300. Mahgoub EO, Cho WC, Sharifi M, et al. [Not Available]. *Heliyon.* 2024;10:e22095.
301. Nguyen LV, Caldas C. Functional genomics approaches to improve pre-clinical drug screening and biomarker discovery. *EMBO Mol Med.* 2021;13:e13189.
302. Hight SK, Mootz A, Kollipara RK, et al. An in vivo functional genomics screen of nuclear receptors and their co-regulators identifies FOXA1 as an essential gene in lung tumorigenesis. *Neoplasia (New York, NY).* 2020;22:294-310.
303. Lee MC, Cai H, Murray CW, et al. A multiplexed in vivo approach to identify driver genes in small cell lung cancer. *Cell reports.* 2023;42:111990.
304. Rogers ZN, McFarland CD, Winters IP, et al. A quantitative and multiplexed approach to uncover the fitness landscape of tumor suppression in vivo. *Nat Methods.* 2017;14:737-742.
305. Huang J, Chan SC, Pang WS, et al. Global Incidence, Risk Factors, and Temporal Trends of Mesothelioma: A Population-Based Study. *Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer.* 2023;18:792-802.
306. Walker-Bone K, Benke G, MacFarlane E, et al. Incidence and mortality from malignant mesothelioma 1982-2020 and relationship with asbestos exposure: the Australian Mesothelioma Registry. *Occup Environ Med.* 2023;80:186-191.
307. Carbone M, Yang H, Pass HI, Taioli E. Did the Ban on Asbestos Reduce the Incidence of Mesothelioma? *Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer.* 2023;18:694-697.
308. Sluis-Cremer GK, Liddell FD, Logan WP, Bezuidenhout BN. The mortality of amphibole miners in South Africa, 1946-80. *Br J Ind Med.* 1992;49:566-575.
309. Baumann F, Carbone M. Environmental risk of mesothelioma in the United States: An emerging concern-epidemiological issues. *Journal of toxicology and environmental health Part B, Critical reviews.* 2016;19:231-249.
310. Alpert N, van Gerwen M, Taioli E. Epidemiology of mesothelioma in the 21(st) century in Europe and the United States, 40 years after restricted/banned asbestos use. *Translational lung cancer research.* 2020;9:S28-S38.
311. Carbone M, Adusumilli PS, Alexander HR, Jr., et al. Mesothelioma: Scientific clues for prevention, diagnosis, and therapy. *CA Cancer J Clin*. 2019;69:402-429.
312. Carbone M, Harbour JW, Brugarolas J, et al. Biological Mechanisms and Clinical Significance of BAP1 Mutations in Human Cancer. *Cancer discovery.* 2020;10:1103-1120.
313. Farioli A, Ottone M, Morganti AG, et al. Radiation-induced mesothelioma among long-term solid cancer survivors: a longitudinal analysis of SEER database. *Cancer medicine.* 2016;5:950-959.
314. Guo Z, Carbone M, Zhang X, et al. Improving the Accuracy of Mesothelioma Diagnosis in China. *Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer.* 2017;12:714-723.
315. Zhai Y, Hui Z, Chen W, et al. The epidemic of malignant mesothelioma in China: a prediction of incidence during 2016-2030. *Translational lung cancer research.* 2022;11:2403-2411.

316. Dostert C, Petrilli V, Van Bruggen R, et al. Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. *Science (New York, NY)*. 2008;320:674-677.
317. Yang H, Rivera Z, Jube S, et al. programmed necrosis induced by asbestos in human mesothelial cells causes high-mobility group box 1 protein release and resultant inflammation. *Proceedings of the National Academy of Sciences of the United States of America.* 2010;107:12611-12616.
318. Chow MT, Tschopp J, Moller A, Smyth MJ. NLRP3 promotes inflammation-induced skin cancer but is dispensable for asbestos-induced mesothelioma. *Immunol Cell Biol*. 2012;90:983-986.
319. Suarez JS, Novelli F, Goto K, et al. HMGB1 released by mesothelial cells drives the development of asbestos-induced mesothelioma. *Proceedings of the National Academy of Sciences of the United States of America.* 2023;120:e2307999120.
320. Novelli F, Bononi A, Wang Q, et al. BAP1 forms a trimer with HMGB1 and HDAC1 that modulates gene x environment interaction with asbestos. *Proceedings of the National Academy of Sciences of the United States of America.* 2021;118.
321. Yang H, Pellegrini L, Napolitano A, et al. Aspirin delays mesothelioma growth by inhibiting HMGB1-mediated tumor progression. *Cell death & disease.* 2015;6:e1786.
322. Novelli F, Yoshikawa Y, Vitto V, et al. Germline BARD1 variants predispose to mesothelioma by impairing DNA repair and Calcium signaling. *Proceedings of the National Academy of Sciences of the United States of America In Press*. 2024;121:e2405231121.
323. Bononi A, Goto K, Ak G, et al. Heterozygous germline BLM mutations increase susceptibility to asbestos and mesothelioma. *Proceedings of the National Academy of Sciences of the United States of America.* 2020;117:33466-33473.
324. Pastorino S, Yoshikawa Y, Pass HI, et al. A Subset of Mesotheliomas With Improved Survival Occurring in Carriers of BAP1 and Other Germline Mutations. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology.* 2018;36:JCO2018790352.
325. Panou V, Gadiraju M, Wolin A, et al. Frequency of Germline Mutations in Cancer Susceptibility Genes in Malignant Mesothelioma. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology.* 2018;36:2863-2871.
326. Sculco M, La Vecchia M, Aspesi A, et al. Malignant pleural mesothelioma: Germline variants in DNA repair genes may steer tailored treatment. *Eur J Cancer.* 2022;163:44-54.
327. Mitchell OD, Gilliam K, Del Gaudio D, et al. Germline Variants Incidentally Detected via Tumor-Only Genomic Profiling of Patients With Mesothelioma. *JAMA Netw Open.* 2023;6:e2327351.
328. Carbone M, Pass HI, Ak G, et al. Medical and Surgical Care of Patients With Mesothelioma and Their Relatives Carrying Germline BAP1 Mutations. *Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer.* 2022;17:873-889.
329. Louw A, Panou V, Szejniuk WM, et al. BAP1 Loss by Immunohistochemistry Predicts Improved Survival to First-Line Platinum and Pemetrexed Chemotherapy for Patients With Pleural Mesothelioma: A Validation Study. *Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer.* 2022;17:921-930.
330. Yoshikawa Y, Emi M, Hashimoto-Tamaoki T, et al. High-density array-CGH with targeted NGS unmask multiple noncontiguous minute deletions on chromosome 3p21 in mesothelioma. *Proceedings of the National Academy of Sciences of the United States of America.* 2016;113:13432-13437.
331. McCambridge AJ, Napolitano A, Mansfield AS, et al. Progress in the Management of Malignant Pleural Mesothelioma in 2017. *Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer.* 2018;13:606-623.
332. Scherpereel A, Mazieres J, Greillier L, et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. *The Lancet Oncology*. 2019;20:239-253.
333. Fennell DA, Ewings S, Ottensmeier C, et al. Nivolumab versus placebo in patients with relapsed malignant mesothelioma (CONFIRM): a multicentre, double-blind, randomised, phase 3 trial. *The Lancet Oncology*. 2021;22:1530-1540.
334. Peters S, Scherpereel A, Cornelissen R, et al. First-line nivolumab plus ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma: 3-year outcomes from CheckMate 743. *Annals of oncology: official journal of the European Society for Medical Oncology.* 2022;33:488-499.
335. McNamee N, Harvey C, Gray L, et al. Brief Report: Real-World Toxicity and Survival of Combination Immunotherapy in Pleural Mesothelioma-RIOMeso. *Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer.* 2024;19:636-642.
336. Meirson T, Pentimalli F, Cerza F, et al. Comparison of 3 Randomized Clinical Trials of Frontline Therapies for Malignant Pleural Mesothelioma. *JAMA Netw Open.* 2022;5:e221490.
337. Smesseim I, Baas P. Immunotherapy Is a Good Standard Option for Patients With Malignant Pleural Mesothelioma, Despite the Real-World Results From Australia. *Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer.* 2024;19:547-550.
338. Gray SG, Meirson T, Mutti L. Based on the Real-World Results From Australia, Immunotherapy Is Not a Good Option for Patients With Mesothelioma. *Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer.* 2024;19:541-546.
339. Flores RM, Pass HI, Seshan VE, et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. *J Thorac Cardiovasc Surg.* 2008;135:620-626, 626 e621-623.
340. Lim E, Waller D, Lau K, et al. PL03.10 MARS 2: A Multicentre Randomised Trial Comparing (Extended) Pleurectomy Decortication versus No Radical Surgery for Mesothelioma. *Journal of Thoracic Oncology.* 2023;18:S36.
341. Woodard GA, Jablons DM. Surgery for pleural mesothelioma, when it is indicated and why: arguments against surgery for malignant pleural mesothelioma. *Translational lung cancer research.* 2020;9:S86-S91.
342. Garzon JC, Lai FM, Mok TS, et al. Clear cell carcinoma of the lung revisited.

J Thorac Cardiovasc Surg. 2005;130: 1198-1199.
343. Bahadur S, Pujani M, Jetley S, et al. Large cell lung carcinoma with rhabdoid phenotype: Report of a rare entity presenting with chest wall involvement. *J Cancer Res Ther.* 2015;11:657.
344. Hiroshima K, Mino-Kenudson M. Update on large cell neuroendocrine carcinoma. *Translational lung cancer research.* 2017;6:530-539.
345. Karlsson A, Brunnstrom H, Lindquist KE, et al. Mutational and gene fusion analyses of primary large cell and large cell neuroendocrine lung cancer. *Oncotarget*. 2015;6:22028-22037.
346. Yoshizawa A, Motoi N, Riely GJ, et al. Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. *Modern pathology*. 2011;24:653-664.
347. Moro-Sibilot D, Lantuejoul S, Diab S, et al. Lung carcinomas with a basaloid pattern: a study of 90 cases focusing on their poor prognosis. *European Respiratory Journal*. 2008;31:854-859.

14

PATHOLOGY AND BIOMARKERS

Ming Sound Tsao,[1] **Mary Beth Beasley,**[2] **Erik Thunnissen,**[3] **William D. Travis,**[4] **Jia-Tao Zhang,**[4] **Yasushi Yatabe,**[5] **and Fred R. Hirsch**[6] |
[1]Princess Margaret Cancer Centre/University Health Network, University of Toronto, Toronto, Canada; [2]Center for Thoracic Oncology/Tisch Cancer Institute, Mount Sinai Health System, New York, USA; [3]Amsterdam University Medical Center, Amsterdam, The Netherlands; [4]Memorial Sloan Kettering Cancer Center, New York, USA; [5]National Cancer Center, Tokyo, Japan; [6]Center for Thoracic Oncology/Tisch Cancer Institute, Mount Sinai Health System, New York, USA

Since pathology is the basis of disease diagnosis and classification, hence treatment, its role in IASLC history has also been foundational. In 1982, the IASLC Board of Directors and General Assembly approved the formation of the IASLC Pathology Panel, as proposed by Drs. Mary J. Matthews, Fred R. Hirsch, Adi Gazdar, Yukio Shimosato, and Raymond Yesner. This followed the publication of the 2nd edition of the World Health Organization's Histological Typing of Lung Tumours[1] (Figures 1 and 2). (Note: Additional information about WHO's pathology panel/committee can be found in Chapter 8.)

Dr. Mary Matthews was the inaugural Chair of the Pathology Panel/Committee from 1983 to 1991.[2] Consistent with the international nature of the IASLC, since its inception, the members of the committee are globally represented by pathologists with special interests in the pathological classification and pathobiology of lung tumors. Under the leaderships of Drs. William Travis and Fred Hirsch, the IASLC Pathology Panel was a co-participant in the publication of the 3rd WHO edition of Histological

Figure 1. World Health Organization Expert Committee on Lung Cancer, Geneva, Switzerland, October 24, 1977: standing (right to left): Raymond Yesner, Chairman (USA); Dr. Wong (WHO); Roger Seal (Wales); WHO Representative; Herbert Spencer, MD (England); Leslie Sobin (WHO), Leiv Kreyberg (Norway); Yukio Shimosato (Japan); P. Mirejovsky (Czechoslovakia); E. Chaves (Brazil); J. Chretien (France); and K. Shanmugaratnam (Singapore). Seated (right to left): Dr. Sobin's secretary; L. G. Olchovskaya (USSR); Mary Matthews (USA); L. Hochholzer (USA); and O. Campobasso (Italy). WHO, World Health Organization (reprinted from Tsao et al. J Thorac Oncol. 2014;9: 1740–1749)[2]

I. EPITHELIAL TUMOURS

A. BENIGN

1. Papillomas	8050/0 [3]
a) Squamous cell papilloma	8052/0
b) « Transitional » papilloma	8120/0
2. Adenomas	8140/0
a) Pleomorphic adenoma [« mixed » tumour]	8940/0
b) Monomorphic adenoma	8146/0
c) Others	
B. DYSPLASIA	74000
CARCINOMA IN SITU	8070/2 [4]
C. MALIGNANT	
1. Squamous cell carcinoma [epidermoid carcinoma]	8070/3
Variant: a) Spindle cell (squamous) carcinoma	8074/3
2. Small cell carcinoma	8041/3
a) Oat cell carcinoma	8042/3
b) Intermediate cell type	8043/3 [4]
c) Combined oat cell carcinoma	[4]
3. Adenocarcinoma	8140/3
a) Acinar adenocarcinoma	8550/3
b) Papillary adenocarcinoma	8260/3
c) Bronchiolo-alveolar carcinoma	8250/3
d) Solid carcinoma with mucus formation	8230/3 [5]
4. Large cell carcinoma	8012/3
Variants: a) Giant cell carcinoma	8031/3
b) Clear cell carcinoma	8310/3
5. Adenosquamous carcinoma	8560/3
6. Carcinoid tumour	8240/3
7. Bronchial gland carcinomas	
a) Adenoid cystic carcinoma	8200/3
b) Mucoepidermoid carcinoma	8430/3
c) Others	
8. Others	

II. SOFT TISSUE TUMOURS

III. MESOTHELIAL TUMOURS

A. BENIGN MESOTHELIOMA	9050/0
B. MALIGNANT MESOTHELIOMA	9050/3
1. Epithelial	9052/3
2. Fibrous [spindle-cell]	9051/3
3. Biphasic	9053/3

IV. MISCELLANEOUS TUMOURS

A. BENIGN	
B. MALIGNANT	
1. Carcinosarcoma	8980/3
2. Pulmonary blastoma	8981/3
3. Malignant melanoma	8720/3
4. Malignant lymphomas	9590/3
5. Others	
V. SECONDARY TUMOURS	----/6 [6]
VI. UNCLASSIFIED TUMOURS	8000/- [7]

VII. TUMOUR-LIKE LESIONS

A. HAMARTOMA	75500
B. LYMPHOPROLIFERATIVE LESIONS	[8]
C. TUMOURLET	8041/0 [9]
D. EOSINOPHILIC GRANULOMA	77860
E. « SCLEROSING HAEMANGIOMA »	8832/0
F. INFLAMMATORY PSEUDOTUMOUR	76820
G. OTHERS	

Figure 2. From World Health Organization's Histological Typing of Lung Tumours, 2nd edition.[1]

Typing of Lung and Pleural Tumours[3] (Figure 3). Since then, the IASLC Pathology Committee and its members have continued to be major contributors to the development and writing of editions 4 and 5. Additional information about the Pathology Panel/Committee can be found in Chapter 8.

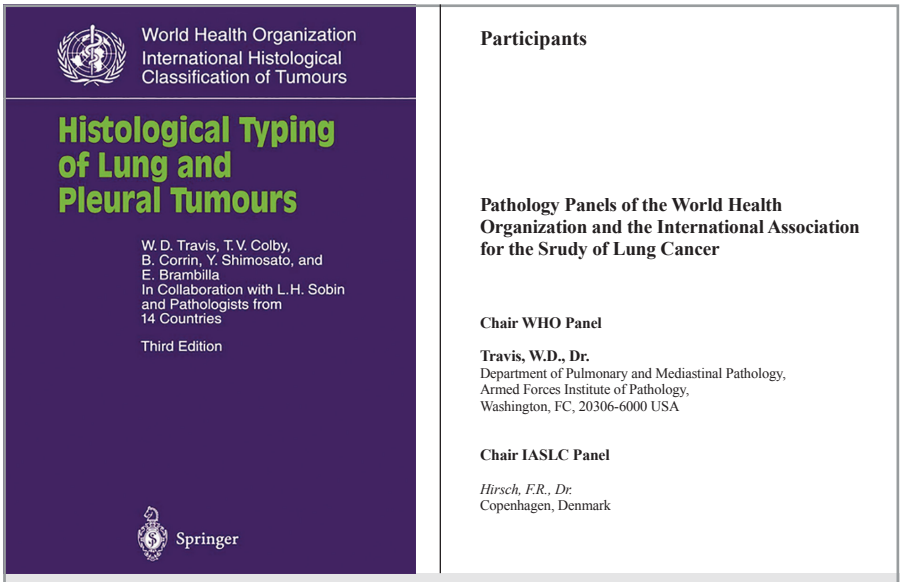


Figure 3. Cover of 3rd edition of World Health Organization: Histological Typing of Lung and Pleural Tumours, as well as monograph and page showing the IASLC's co-participation.[3]

PATHOLOGY OF LUNG CANCER

Two major conceptual transitions occurred between the 2nd (1982) and 3rd (1997) editions of the WHO classifications. The first witnessed the consolidation of small cell carcinoma (SCLC) variants (fusiform, polygonal, and lymphocyte-like, or "oat cell," cell types) into a single entity. The consolidation was in spite of morphological variations, and all SCLC demonstrated similar clinical behaviors and responses to therapy. The only variant recognized in the 3rd edition was the combined SCLC, which was defined as "a SCLC combined with an additional component that consists of any of the histological types of non-small cell carcinoma (NSCLC)."[3,4]

The second major change was in the definition of bronchioloalveolar carcinoma (BAC). Initially, in the 2nd edition, BAC was defined as an adenocarcinoma in which cylindrical tumor cells grow upon the walls of preexisting alveoli. BAC and papillary adenocarcinoma were then considered by some to be a single group,[5] with BAC showing less scarring and those with mucus-secreting cells lining air spaces tend to spread more rapidly than those tumors where air spaces are non-mucus-secreting cells. In the 3rd edition, the BAC definition was limited to an adenocarcinoma with a pure bronchioloalveolar growth pattern and no evidence of stromal, vascular, or pleural invasion. This definition implied that BAC is a non-invasive adenocarcinoma, and its diagnosis requires thorough histological sampling of a resected specimen.

The concept that BAC was an in-situ adenocarcinoma arose from the seminal paper by Drs. M. Noguchi and Y. Shimosato,[6] which reported that small lung adenocarcinoma (≤2 cm) showing alveolar surface replacement (lepidic) growth pattern, with or without focal stromal fibrosis (alveolar collapse), was associated with 100% survival. While pathologists were enhancing their understanding of BAC as a distinct pathological entity, clinicians were recognizing BAC features within invasive or metastatic adenocarcinomas, particularly those with EGFR mutations, which could guide treatment decisions toward targeted therapies.[7,8]

In November of 2004, this contradiction brought together a consensus workshop organized by the IASLC for a multidisciplinary discussion on the diagnosis and treatment of adenocarcinoma with BAC features, leading to multiple publications on the issues discussed during the workshop.[7,9-11] An important outcome of this workshop was the importance of a multidisciplinary approach involving pathologists, radiologists, and clinical oncologists, and their greater interaction in the management of lung cancer patients.

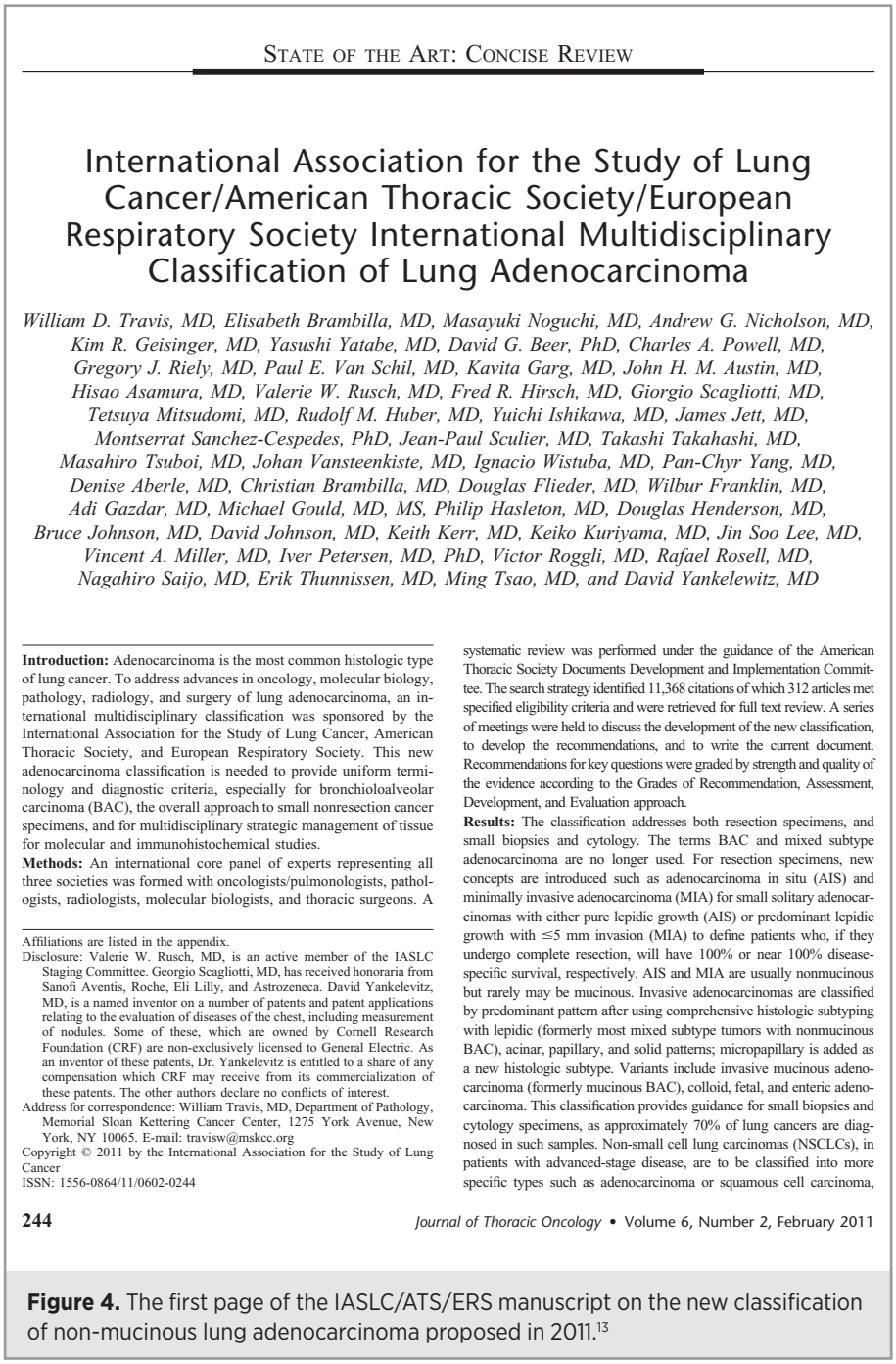
The confusion on the term bronchioloalveolar (BAC) directly led to a consensus decision to avoid this nomenclature from the IASLC, American Thoracic Society (ATS) and European Respiratory Society (ERS) international multidisciplinary classification of lung adenocarcinoma newly proposed in 2011 (Figure 4).[12]

This seminal work was the foundation of current classification system for non-mucinous adenocarcinoma of the lung, after its incorporation in the WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart (4th edition, 2015), and the WHO Classification of Tumours-Thoracic Tumours (5th edition, 2021).[13-14]

With the new classification system, the IASLC Pathology Committee also conducted several studies that led to recommendations for improving diagnostic reproducibility in SCLC, NSCLC, and lung adenocarcinoma subtypes, as well as a new clinically relevant grading system for the latter.[15-19]

Since the 2015 WHO classification of lung cancer, immunohistochemistry became an important tool to determine histological subtypes. Solid carcinomas, where differentiation is not morphologically evident, have been reclassified based on immunohistochemical results as either solid adenocarcinoma or non-keratinizing squamous cell carcinoma. Consequently, large cell carcinoma is limited to unclear or null phenotype when immunohistochemical analysis is applied. This change would provide a significant impact on epidemiologic data histological subtypes of lung cancer.

To improve the utility of IHC in pathology practice, the IASLC Pathology Committee published the recommendations on immunohistochemistry of lung cancer diagnoses, with further details provided in the *IASLC Atlas of Diagnostic Immunohistochemistry* (Figure 5).[20] The Atlas provides a comprehensive view of diagnostic IHC to help pathologists deliver best practices with IHC and to make more accurate diagnoses in thoracic malignancies.



STATE OF THE ART: CONCISE REVIEW

International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma

William D. Travis, MD, Elisabeth Brambilla, MD, Masayuki Noguchi, MD, Andrew G. Nicholson, MD, Kim R. Geisinger, MD, Yasushi Yatabe, MD, David G. Beer, PhD, Charles A. Powell, MD, Gregory J. Riely, MD, Paul E. Van Schil, MD, Kavita Garg, MD, John H. M. Austin, MD, Hisao Asamura, MD, Valerie W. Rusch, MD, Fred R. Hirsch, MD, Giorgio Scagliotti, MD, Tetsuya Mitsudomi, MD, Rudolf M. Huber, MD, Yuichi Ishikawa, MD, James Jett, MD, Montserrat Sanchez-Cespedes, PhD, Jean-Paul Sculier, MD, Takashi Takahashi, MD, Masahiro Tsuboi, MD, Johan Vansteenkiste, MD, Ignacio Wistuba, MD, Pan-Chyr Yang, MD, Denise Aberle, MD, Christian Brambilla, MD, Douglas Flieder, MD, Wilbur Franklin, MD, Adi Gazdar, MD, Michael Gould, MD, MS, Philip Hasleton, MD, Douglas Henderson, MD, Bruce Johnson, MD, David Johnson, MD, Keith Kerr, MD, Keiko Kuriyama, MD, Jin Soo Lee, MD, Vincent A. Miller, MD, Iver Petersen, MD, PhD, Victor Roggli, MD, Rafael Rosell, MD, Nagahiro Saijo, MD, Erik Thunnissen, MD, Ming Tsao, MD, and David Yankelewitz, MD

Introduction: Adenocarcinoma is the most common histologic type of lung cancer. To address advances in oncology, molecular biology, pathology, radiology, and surgery of lung adenocarcinoma, an international multidisciplinary classification was sponsored by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society. This new adenocarcinoma classification is needed to provide uniform terminology and diagnostic criteria, especially for bronchioloalveolar carcinoma (BAC), the overall approach to small nonresection cancer specimens, and for multidisciplinary strategic management of tissue for molecular and immunohistochemical studies.

Methods: An international core panel of experts representing all three societies was formed with oncologists/pulmonologists, pathologists, radiologists, molecular biologists, and thoracic surgeons. A systematic review was performed under the guidance of the American Thoracic Society Documents Development and Implementation Committee. The search strategy identified 11,368 citations of which 312 articles met specified eligibility criteria and were retrieved for full text review. A series of meetings were held to discuss the development of the new classification, to develop the recommendations, and to write the current document. Recommendations for key questions were graded by strength and quality of the evidence according to the Grades of Recommendation, Assessment, Development, and Evaluation approach.

Results: The classification addresses both resection specimens, and small biopsies and cytology. The terms BAC and mixed subtype adenocarcinoma are no longer used. For resection specimens, new concepts are introduced such as adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) for small solitary adenocarcinomas with either pure lepidic growth (AIS) or predominant lepidic growth with ≤5 mm invasion (MIA) to define patients who, if they undergo complete resection, will have 100% or near 100% disease-specific survival, respectively. AIS and MIA are usually nonmucinous but rarely may be mucinous. Invasive adenocarcinomas are classified by predominant pattern after using comprehensive histologic subtyping with lepidic (formerly most mixed subtype tumors with nonmucinous BAC), acinar, papillary, and solid patterns; micropapillary is added as a new histologic subtype. Variants include invasive mucinous adenocarcinoma (formerly mucinous BAC), colloid, fetal, and enteric adenocarcinoma. This classification provides guidance for small biopsies and cytology specimens, as approximately 70% of lung cancers are diagnosed in such samples. Non-small cell lung carcinomas (NSCLCs), in patients with advanced-stage disease, are to be classified into more specific types such as adenocarcinoma or squamous cell carcinoma,

Affiliations are listed in the appendix.

Disclosure: Valerie W. Rusch, MD, is an active member of the IASLC Staging Committee. Georgio Scagliotti, MD, has received honoraria from Sanofi Aventis, Roche, Eli Lilly, and Astrozeneca. David Yankelevitz, MD, is a named inventor on a number of patents and patent applications relating to the evaluation of diseases of the chest, including measurement of nodules. Some of these, which are owned by Cornell Research Foundation (CRF) are non-exclusively licensed to General Electric. As an inventor of these patents, Dr. Yankelevitz is entitled to a share of any compensation which CRF may receive from its commercialization of these patents. The other authors declare no conflicts of interest.

Address for correspondence: William Travis, MD, Department of Pathology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065. E-mail: travisw@mskcc.org

Copyright © 2011 by the International Association for the Study of Lung Cancer

ISSN: 1556-0864/11/0602-0244

Figure 4. The first page of the IASLC/ATS/ERS manuscript on the new classification of non-mucinous lung adenocarcinoma proposed in 2011.[13]

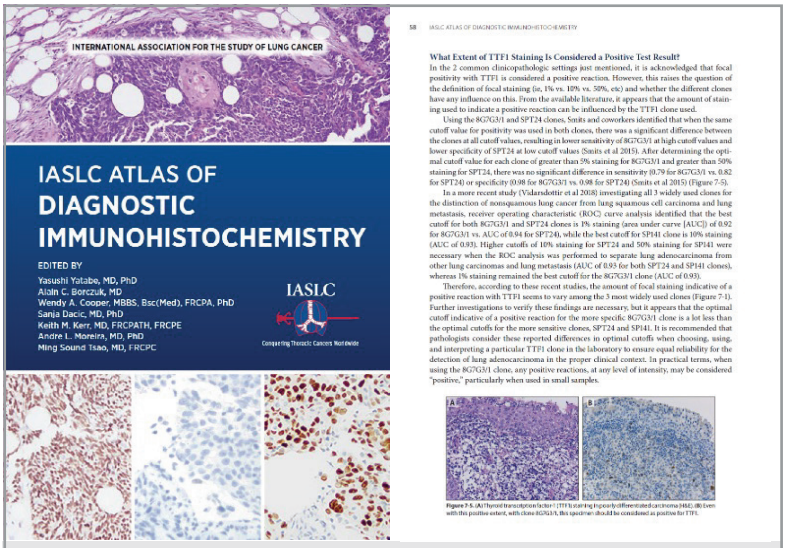


Figure 5. Cover and representative page of the *IASLC Atlas of Diagnostic Immunohistochemistry.*[21]

DEVELOPMENT OF BIOMARKERS

The contributions of the IASLC pathology committee are not limited to histological examinations in lung cancer, such as histologic changes in bronchial epithelia as biomarkers of cigarette-induced carcinogenesis in 1970, and multistep development of invasive adenocarcinoma from adenocarcinoma in-situ in 2004. With the development of molecular testing strategies, results are now reflected in clinical practice, also established is the concept of a biomarker to predict therapeutic efficacy, called predictive biomarkers.

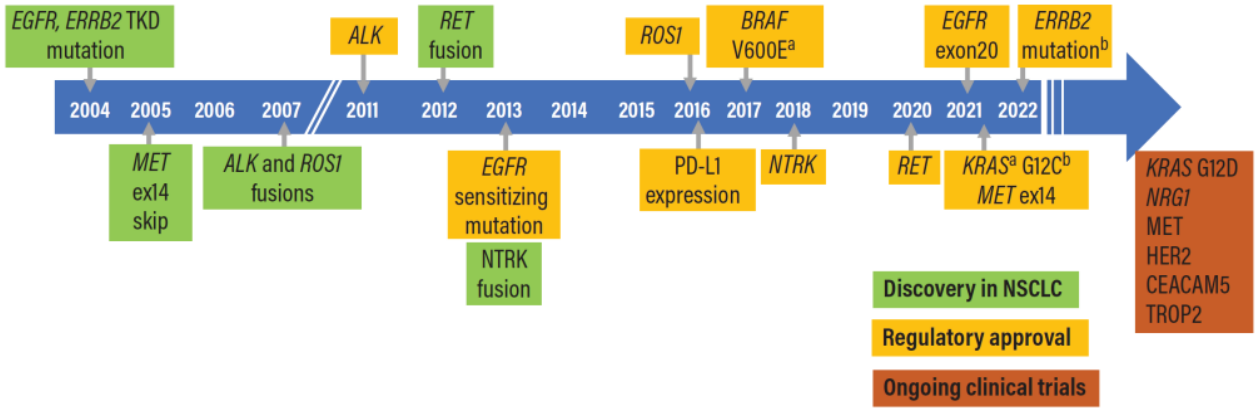
Between 1980 and 1990, the discovery of oncogenes and tumor suppressor genes stimulated numerous studies on the role of *TP53, KRAS*, and other cancer-associated genes as prognostic biomarkers in lung cancer. The role of EGFR expression in the lung carcinogenesis and perspectives for targeted therapies was studied in detail by the University of Colorado lung cancer group.[22-24] However, the concept of predictive biomarkers had to wait until the discovery of *EGFR* mutations.

The early clinical trials using gefitinib, IDEAL 1 and 2, were conducted without known biomarkers, thus tumor responses only observed in 20% or less of enrolled patients.[25,26] However, some patients showed dramatic responses within a short period of treatment, most frequently women and those who never smoked, as well as patients with adenocarcinomas or whose ethnicity was Japanese. In contrast, a high level of EGFR expression was more common in squamous cell carcinoma—tumors more prevalent among males and/or smokers. Because of this, the subset of the patients with gefitinib responses were very different from NSCLC with high EGFR expression, which was the putative target of gefitinib therapy.[27]

The mechanism for the response remained an enigma until 2004, when three groups identified somatic mutations at *EGFR* tyrosine kinase (TK) domain in NSCLC.[28-30] Subsequent clinical studies established the close association of *EGFR* TK mutations and therapeutic responses with EGFR-TKI treatment, introducing the novel concept of "oncogene addiction." Already in 2006, it was demonstrated that not all *EGFR* mutations were equal and subtypes of *EGFR* might play a clinical differential role.[31] Currently, EGFR-TKI is the standard first-line therapy for tumors with *EGFR* mutations in the kinase domain, but there have been twists and turns in establishing the concept of a predictive biomarker.

Through several EGFR focused consensus meetings, where clinical directions were made, the IASLC has been instrumental in the development of EGFR-inhibitors.[32-33] The next advance in targeted therapy came with the discovery of *ALK* fusion oncogenes. This was as a result of intrachromosomal translocation of the anaplastic lymphoma kinase ALK gene. These discoveries were revolutionary and led to general recognition that kinase-activating mutations, or fusions, are candidate therapeutic targets in cancers. The current list of such targets has expanded to include *ROS1, RET, NTRK, KRAS, BRAF, MET,* and *HER2* (Figure 6).

The development of immune checkpoint inhibitors, also called ICIs, further shifted the clinical paradigm as an additional therapeutic option for advanced



[a] Dates of discovery are not shown on the timeline; *KRAS* mutations first observed in NSCLC in 1984; *BRAF* mutations in 2002.
[b] Indicates approval in the second-line setting only.
For clinical trials supporting the first- (or second-) line regulatory approval, see references.[1-8]
Biomarker discovery reports are listed in the references.[9-17]

Figure 6. Timeline for the FDA approvals of targeted therapies and the discoveries of their therapeutic targets (reprinted with permission from the *IASLC Atlas of Molecular Testing for Targeted Therapies in Lung Cancer*, Chapter 1, Figure 1-1, the IASLC 2023)[34]

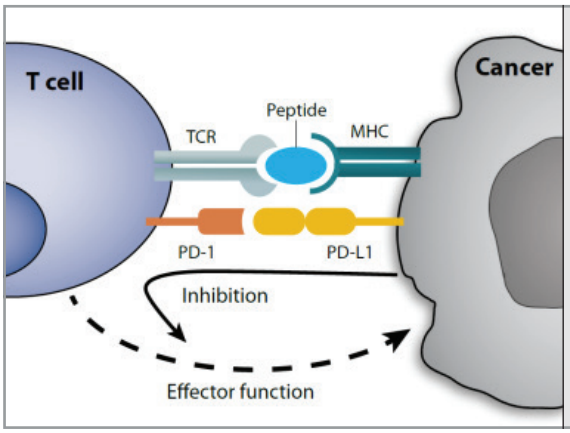


Figure 7. In normal situations, the T-lymphocytes that have been activated by exposure to tumor cell specific new "foreign" proteins can engage mechanisms (effector function) that kill the tumor cells. Cancer cells may be able to resist this T-cell function by expressing PD-L1, which blocks the effector function of the T-cell.[35]

NSCLCs. The first set of effective ICIs that were developed targeted the program death (PD)-1 and PD ligand (PD-L)-1 axis. With these ICIs, PD-L1 immunohistochemistry emerged as the most promising biomarker for selecting patients who are most likely to benefit from anti-PD1/PD-L1 therapies.

BIOMARKER TESTING FOR PRECISION LUNG CANCER THERAPY

Since *EGFR* mutations were identified after the clinical use of the drug, testing for *EGFR* was initially conducted using laboratory developed tests (LDTs) or assays developed by individual laboratories. Many of the LDTs resulted from research conducted in laboratories, leading to wide variation in their quality, including sensitivity, specificity, and reliability.

To address this variability and the time-consuming nature of test development, diagnostic companies often develop and commercialize testing as "kits," which include prepared reagents and protocols to facilitate testing. While individual labs still need to validate the quality of these kits, their performance typically did not include clinical endpoints, such as response rate to the therapy for which the biomarker (test) was used to select patients.

In contrast, in the case of *ALK*, diagnostics were developed simultaneously with the drug, introducing the concept of companion diagnostics in the field of lung cancer treatment. The US FDA defined a companion diagnostic as a medical device, often an in vitro device, which provides information essential for the safe and effective use of a corresponding drug or biological product. In 2011, FDA approved crizotinib for the treatment of late-stage NSCLC patients with *ALK* gene rearrangement. At the same time, the Vysis Break Apart *ALK* fluorescent in situ hybridization (FISH) assay (Abbott

Molecular) was also approved as the companion diagnostic assay for diagnosing patients with *ALK* rearranged tumors.

ALK activating mutations involve fusion of two separate genes resulting from genomic rearrangement involving the driver gene. This rearrangement can be detected by FISH break-apart assay, which was initially developed as a clinical method to detect *ALK* fusion and subsequently selected as a companion diagnostic assay. While FISH assays had also been used to detect copy number changes, or amplification of *HER2* gene in breast cancer, *ALK* FISH is more labor intensive, costly, and may be technically challenging in comparison. Furthermore, as *ALK* rearrangement are found in only 3% to 5% of lung adenocarcinomas, the development and recommendation of a screening test utilizing immunohistochemistry, or IHC, have been included in numerous molecular testing guidelines.

During this period, as ALK IHC was not commercially available, the *IASLC Atlas of ALK Testing in Lung Cancer* (Figure 8), which was published in 2013, contributed to explaining the technical challenges of FISH and provided methods to develop the ALK IHC LDT. This helped many laboratories establish ALK IHC, a test frequently used in routine pathology practice, to increase ALK testing in the lung cancer pathological community. ALK IHC assay was subsequently also added as a companion diagnostic to detect *ALK* rearranged tumors, based on its association with clinical outcomes derived from reports of IHC and FISH discordance.

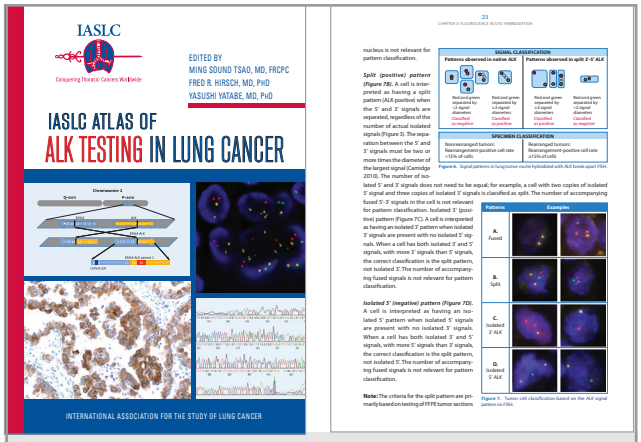


Figure 8. The first Atlas that the IASLC published to serve as a resource for methods that were available for testing ALK aberrations that result from the rearrangement of ALK gene and formation of ALK fusion protein.[36]

With the widespread approval of EGFR and ALK inhibitors worldwide, the importance of selecting individuals for molecular targeted drugs became increasingly recognized. In 2013, the IASLC, in collaboration with the College of American Pathologists (CAP) and the Association of Molecular Pathologists (AMP), published the first molecular testing guideline for advanced lung cancer patients (Figure 9).[37]

This groundbreaking guideline recommended that *EGFR* and *ALK* molecular testing should be used to select people for EGFR and ALK targeted TKI therapies, emphasizing that individuals with lung adenocarcinoma should not be excluded from testing based on clinical characteristics or risk factors. The American Society of Clinical Oncology (ASCO) endorsed this guideline, and it and it served as the foundation for similar guidelines published by other societies, such as the European Society of Medical Oncology, (ESMO).[38-40] The guidelines were updated in 2018 to include a recommendation of *ROS1* testing, and ASCO subsequently endorsed it with addition of *BRAF* testing for patients with advanced lung adenocarcinoma.[41,42] The guidelines were again updated

Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology

Neal I. Lindeman, MD, Philip T. Cagle, MD, Mary Beth Beasley, MD, Dhananjay Arun Chitale, MD, Sanja Dacic, MD, PhD, Giuseppe Giaccone, MD, PhD, Robert Brian Jenkins, MD, PhD, David J. Kwiatkowski, MD, PhD, Juan-Sebastian Saldivar, MD, Jeremy Squire, PhD, Erik Thunnissen, MD, PhD, and Marc Ladanyi, MD

Figure 9. Title of first guideline published by CAP, the IASLC, and AMP on molecular testing for lung cancer patients to receive EGFR and ALK inhibitor therapies.[37]

in 2023 to include additional molecular targets.

Between 2013 to 2015, multiple immune checkpoint inhibitors (anti-PD1/PD-L1) were in development. However, different companies developing these agents employed various clones of PD-L1 antibody as potential predictive biomarkers for these agents in individual clinical trials (Figure 10). Due to significant variability in the properties of the PD-L1 antibody clones, as well as the assays and scoring algorithms being developed, there were concerns among pathologists, clinicians, and the FDA on the cross-utilization and reproducibility of various PD-L1 IHC assays in clinical settings.

To investigate the comparability of the various commercially developed PD-L1 IHC assays, the IASLC Pathology Committee in collaboration with the FDA and industry partners conducted the Blueprint studies.

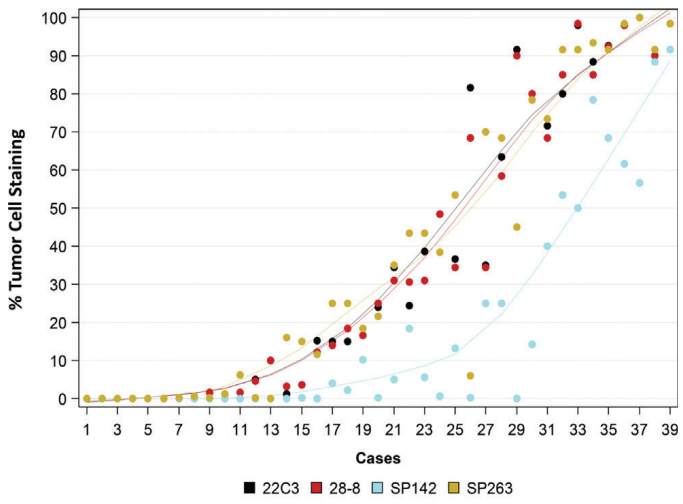
Blueprint phase 1 assessed the analytical performance of four PD-L1 clones and assays, as well as the concordance among the scoring algorithms used in clinical trials for the drugs.[43] Blueprint phase 2 study used real-world patient tumor samples to confirm the comparability of 3 out of 5 PD-L1 assays and demonstrated the high concordance of the PD-L1 scoring among a large number of expert lung cancer pathologists.[44] These results, which showed the interchangeability of the 22C3, 28-8, and SP263 assays provided, significantly boosted confidence in their clinical use within the community. In 2017, the *IASLC Atlas for PD-L1 Testing in Lung Cancer* was released, with major contributions by members of the pathology committee.

Over the past decade, alongside the development of molecular targeted and immunotherapy drugs, there has been a significant technological revolution in molecular testing. High throughput parallel massive next-generation sequencing (NGS) has established itself as the primary technique for biomarker testing in personalized and precision oncology. Rapid advancements in NGS technology led to significant decrease in the analytical cost, allowing for greater genetic detail to be obtained from tumor tissues in clinical practice.

While the FDA approved multiplex hot-spot gene panel testing

PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project

Fred R. Hirsch, MD, PhD, Abigail McElhinny, PhD, Dave Stanforth, MBA



PD-L1 Immunohistochemistry Comparability Study in Real-Life Clinical Samples: Results of Blueprint Phase 2 Project

Ming Sound Tsao, MD, Keith M. Kerr, MD, Mark Kockx, MD, PhD

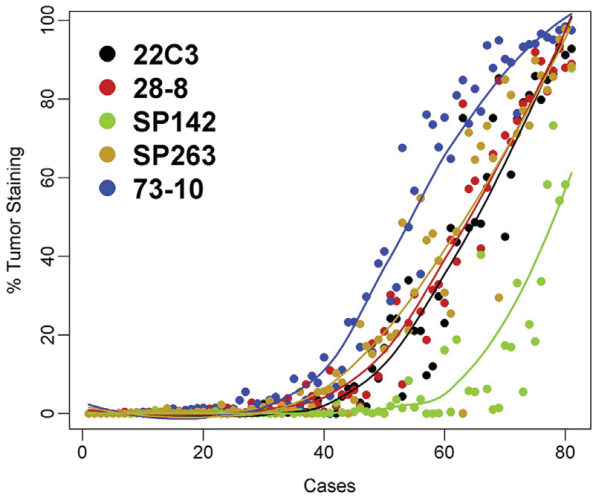


Figure 10. Blueprint phase 1 and 2 studies on comparability of PD-L1 immunohistochemistry assays developed in conjunction with the various immune checkpoint inhibitor drugs. (L) Reprinted from reference 43 with permission; (R) reprinted from reference 44 with permission.

using NGS as a companion diagnostic in 2017, comprehensive genome profiling tests, which analyze more than 200 genes, gained rapid and widespread use throughout the world. Major institutes have developed their own gene panel tests, some of which have been adopted as commercial assays under various labels. Examples include FoundationOne CDx and MSK-IMPACT, among many others available in clinical practice worldwide.

Precision medicine has renewed attention on pathology samples, particularly as most lung cancers are diagnosed with invasive biopsy procedures that yield limited tissue materials. Approximately 20% of such samples lack sufficient tissue for molecular testing. To address this challenge, the IASLC Pathology Committee, in its 2011 seminal paper on the new classification of lung adenocarcinoma, provided a detailed schema on how to prioritize diagnostic immunostaining in order to conserve tissue for molecular testing (Figure 11).[12] This recommendation remains a best practice approach in lung cancer pathology workflow.

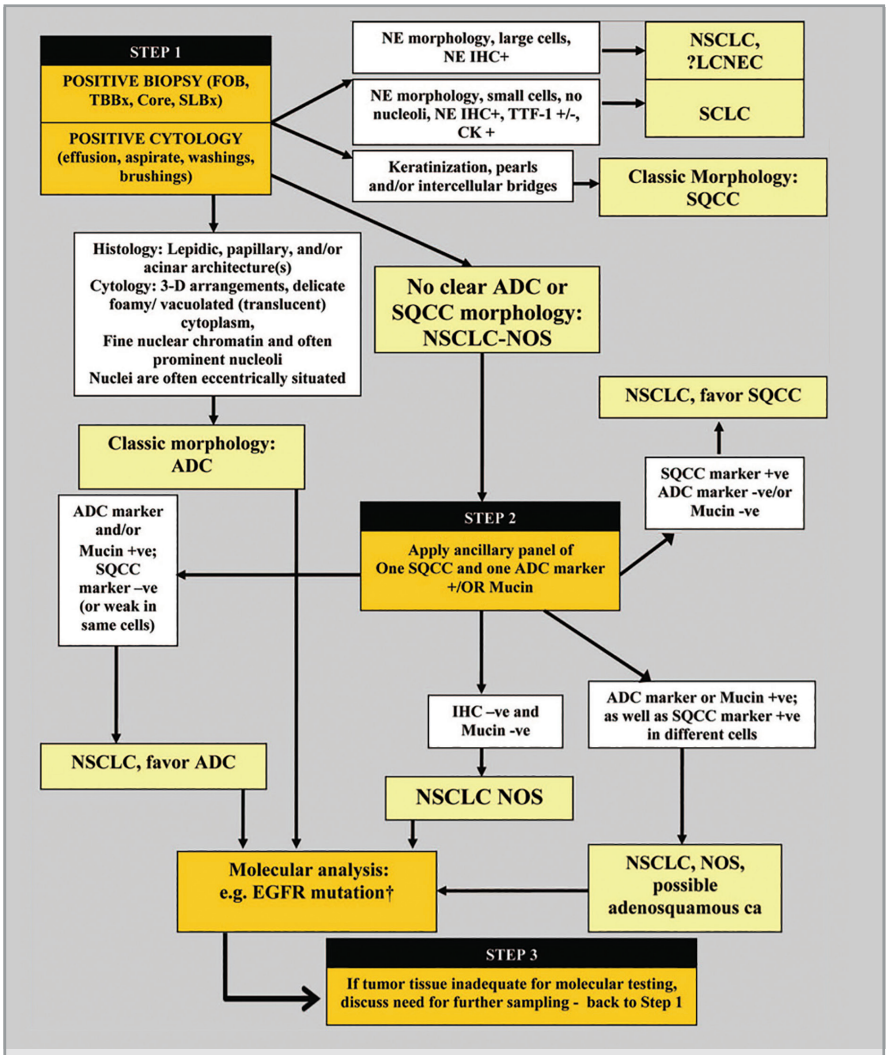


Figure 11. Recommendation on diagnostic workflow in pathology practice to minimize sample loss by unnecessary immunostaining and to improve success rates in molecular testing on these samples. Reprinted from reference 12 with permission.

Following the success of the previous IASLC Atlases on biomarker testing of specific targets in lung cancer, in 2023, the IASLC published an *Atlas for Molecular Testing*, covering comprehensive molecular testing of cancer-associated genes in lung cancer (Figure 12).[47]

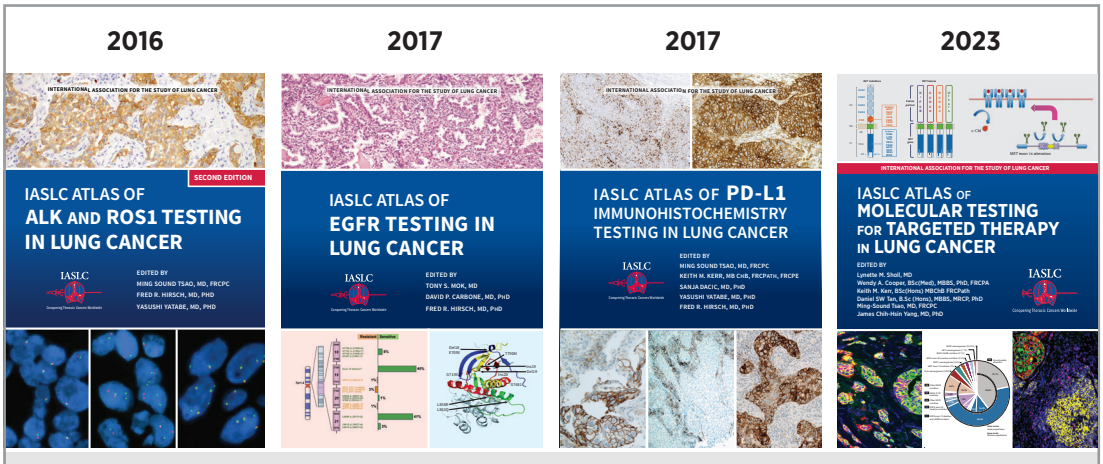


Figure 12. Covers of the IASLC Atlas series on molecular testing in lung cancer.[45]

MESOTHELIOMA

Diffuse pleural mesothelioma is a rare tumor with a poor prognosis, and its very existence was once debated. In 1767, mesothelioma was arguably first described by French anatomist and physician, Jacques-Bénigne Winslow, commonly referred to as Lieutaud. Lieutaud reported two cases of "pleural tumors" in a study of 3,000 autopsies. Another French physician, René-Théophile-Hyacinthe Laennec, also suggested the concept of primary pleural malignancy in 1819.[46] However, this concept was disputed in the 1840s by Carl Freiherr von Rokitansky, also known as Karl Freiherr von Rokitansky, an Austrian pathologist and politician. Von Rokitansky believed pleural cancers were always secondary to a primary focus elsewhere. This view persisted among many pathologists well into the 20th century, despite likely cases of mesothelioma being reported in the 19th century. Over time, there was gradual acceptance that some sarcomas could originate from the pleura, provided there was lack of evidence that there was a primary tumor elsewhere. It was thought that such tumors arose from the subpleural fibroblast, as opposed to the pleural tissue itself.

In 1931, two pathologists, Paul Klemperer and Carl B. Rabin, reported five cases with both epithelial and mesenchymal characteristics, which they felt should be called "mesothelioma," as they arose from the surface lining cells.[47] Subsequently, in 1942, researchers Alexander Perry Stout and Martin R. Murray reported data from tissue cultures that supported the contention that tumors arose from the mesothelial cells, and in 1944 AV Postoloff reported that mesothelium could transform into both epithelioid and sarcomatous malignancies.[48,49] Debate continued, but in the Atlas of Tumor Pathology published by the Armed Forces Institute of Pathology (AFIP) in 1956, it was stated that "the majority opinion" was that primary mesotheliomas were rare but existed.[50] A caveat at the time was the general belief that a mesothelioma diagnosis could not be made unless there was a complete autopsy excluding a potential primary tumor elsewhere which had metastasized to the pleura.

Since the 1981 WHO classification, mesothelioma has been histologically categorized into epithelioid, biphasic, and sarcomatoid (originally termed "fibrous") subtypes, with the epithelioid variety being the most prevalent.[5,51] The histologic and cytologic features can vary, resulting in overlap with various malignancies, although carcinoma, particularly of lung origin, is the most common entity in the differential diagnosis. Initially, histochemical stains were the primary ancillary method for diagnosis, with immunohistochemical stains currently being the most widely used diagnostic tool. Mesothelial cells produce hyaluronic acid, whereas adenocarcinomas produce neutral mucins. Initially, a combination of stains to detect neutral mucins and hyaluronic acid were utilized as diagnostic adjuncts. However, these had limitations and interpretation difficulties, as a negative stain was often inconclusive due to variability in mucin and hyaluronic acid production by tumors.

Immunohistochemistry became the primary method for supporting or refuting a mesothelioma diagnosis. In the absence of "positive" mesothelial markers initially, a series of negative stains, typically glycoprotein markers like CEA, CD15, BER-EP4, and B72.3 were used. However, these stains had varying sensitivity and specificity issues. In the late 1990s/early 2000s, stains such as calretinin and later CK5/6, WT-1, and D2-40, emerged as "positive" mesothelial markers. Nevertheless, these markers also have limitations and pitfalls, which have been documented in the mesothelioma guidelines paper authored by an international panel of experts, most recently updated in 2018.[52] This document recommended a panel consisting of a minimum of two "carcinoma" markers and two "mesothelial" markers to support a diagnosis, and a combination of immunohistochemical staining alongside appropriate radiographic findings has significantly enhanced diagnostic accuracy. Nonetheless, a percentage of cases remain challenging, particularly the sarcomatoid subtype, which less frequently stains with "mesothelial" markers.[52-54]

In recent decades, pathologic developments in mesothelioma have primarily focused on identifying histologic and/or molecular features to inform clinical management. Table 1 shows the current 2021 WHO classification of architectural, cytologic, and stromal features within the epithelioid mesothelioma category.[51]

Some of these features are prognostically significant, while others serve to prevent misdiagnosis. While some epithelioid growth patterns correlate with either favorable (e.g., tubulopapillary) or adverse (e.g., micropapillary) prognoses, overall, the epithelioid subtype carries a better prognosis than biphasic or sarcomatoid types.

Historically, mesotheliomas have not been graded due to their generally poor survival rates.[55] Nonetheless, a recent proposal introduced a two-tiered grading system for the epithelioid subtype, which considers nuclear atypia, mitotic count, and the presence or absence of necrosis to classify tumors into high and low grades.[56] As of yet, a grading system has not been proposed for biphasic or sarcomatoid subtypes. In resected specimens, the biphasic designation requires the second component to constitute at least 10% of the tumor mass; however, this criterion does not apply to biopsy specimens. The proportion of sarcomatoid component within a biphasic tumor seems to correlate with prognosis, especially in larger specimens, although further refinement is necessary.

Table 1. 2021 WHO Classification of Diffuse Pleural Mesothelioma[51]

Mesothelioma Subtype	Architectural Patterns	Cytologic Features	Stromal Features
Epithelioid	Tubulopapillary Trabecular Adenomatoid Solid Micropapillary	Rhabdoid Deciduoid Small cell Clear cell Signet ring Lymphohistiocytoid Pleomorphic	Myxoid
Sarcomatoid mesothelioma (includes desmoplastic pattern)		Lymphohistiocytoid Transitional Pleomorphic	Desmoplastic Heterologous differentiation
Biphasic			

Biphasic mesotheliomas have faced challenges in diagnostic reproducibility, due to difficulties in distinguishing the sarcomatoid component from exuberant stroma, though some progress has been made in this area.[57,58]

As with other malignancies, molecular analysis of mesothelioma has contributed significantly to our concept of the disease and has refined tumor classification, although a "targetable" mutation for therapy has yet to be identified. Mesotheliomas commonly exhibit mutations in *BAP-1, NF2, CDKN2A, TERT, TP53, SETD2*, and other mutations to a lesser extent. Molecular abnormalities typically cluster with the histologic subtype, aiding in the optimal classification of ambiguous categories.[59,60] Molecular analysis of the "transitional pattern," which has features in between epithelioid and sarcomatoid, demonstrated that this pattern clustered with the sarcomatoid group.[61] In addition, the pleomorphic subtype has been found to cluster with either epithelioid or sarcomatoid subtypes and is currently regarded as a cytologic feature which may be found in both.[62]

The identification of *BAP-1* and homozygous *CDKN2A* (p16) deletions has led to significant diagnostic advancements, notably improving the confidence of mesothelioma diagnosis on cytology specimens, or ambiguous small biopsies, and reintroducing the concept of mesothelioma in situ. The development of the BAP-1 immunostains and the ability to detect homozygous *CDKN2A* deletions by FISH, or the corresponding MTAP immunostain, represents a significant leap forward.

While invasion, a crucial feature in distinguishing malignant from a benign mesothelial proliferation, cannot be evaluated on cytology specimens and may be challenging in small tissue biopsies, immunostains aiding in this distinction have been sought, albeit without significant success.[52] Loss of BAP-1 and/or MTAP staining (or homozygous *CKND2A* deletion by FISH) currently supports malignancy in a mesothelial proliferation.[63-65]

Similarly, mesothelioma in situ was first introduced in 1992 by Diana M. Whitaker, a pathologist who made contributions to the field of cytopathology, but her work faced criticism due to concerns about excluding surface extension of invasive tumors.[66]

Andrew Churg, a pathologist, re-introduced the concept in 2018, describing two cases of mesothelioma in situ in patients with recurrent pleural effusions but lacking radiographic or gross evidence of disease at the time of surgery.[67] These cases exhibited an atypical surface proliferation of mesothelial cells, showing loss of BAP-1 staining and homozygous *CKND2A* deletion by FISH. Subsequent studies supported this concept, incorporating the loss of MTAP immunostaining as a surrogate for homozygous deletion of *CKND2A* detected by FISH.[68-70]

In 2018, a multidisciplinary group comprising pathologists, surgeons, radiologists, oncologists, and molecular biologists, sponsored by the IASLC and the European Network for Rare Adult Solid Cancers (EURACAN), convened in Lyon, France (Figure 13). The resulting proposals aimed at optimizing patient management were published in the *Journal of Thoracic Oncology* (JTO) in 2020.[71]

Several of these proposals in the pathology domain were integrated into the 2021 WHO tumor classification. It was acknowledged that there is a greater demand for tumor biomarkers.[75] Although primarily within the purview of clinicians, as the majority of patients are not candidates for surgery and pathologic staging is generally unfeasible outside of the setting of extra-pleural pneumonectomy, the IASLC has been actively engaged in assessing parameters for TNM staging in mesothelioma since its initial proposal in 1994.[72-76]

Moving forward, in addition to traditional genetic analysis, there has been an increased focus on the immune cell and stromal microenvironment. The application of deep learning algorithms also holds promise for identifying more optimal treatment modalities.[77,78]

CONCLUSION AND FUTURE PERSPECTIVES

Spanning the last five decades, through interdisciplinary collaborations, the IASLC Pathology Committee and its members (see Chapter 8) have played pivotal roles in establishing the reference standards for the diagnosis of lung and pleural malignancies. These standards encompass the World Health Organization (WHO) classification, tumor staging systems, and biomarker testing for precision diagnosis and therapies. The Committee has also formulated recommendations for grading lung adenocarcinomas and evaluating resected tumors following neoadjuvant therapy.

With rapid advancements in slide scanning and image analysis techniques, as well as in artificial intelligence, and the emergence of new therapy modalities, such as antibody drug conjugates (ADCs) and bi-specific antibodies,

Figure 13. Group picture of participants at the IASLC/EURACAN meeting that took place in Lyon, France in July 2018.

the roles of the IASLC Pathology Committee will become increasingly critical in leading their implementation to benefit all patients with thoracic malignancies.

References

1. Histological typing of lung tumours. *Tumori*. 1981;67:253–272. https://doi.org/10.1177/030089168106700401. PMID: 6274068
2. Tsao MS, Travis WD, Brambilla E, et al. Forty years of the International Association for Study of Lung Cancer Pathology Committee. *J Thorac Onco*l. 2014;9:1740–1749. PMID: 25393791.
3. Travis WD, Colby TV, Corrin B, Shimosato Y, Brambilla E. World Health Organization. Histological typing of lung and pleural tumours (3rd ed.). Springer, 1999.
4. Hirsch FR, Matthews MJ, Yesner R. Histopathologic classification of small cell carcinoma of the lung: Comments based on an interobserver examination. *Cancer.* 1982;50:1360–1366. PMID: 6286092.
5. The World Health Organization histological typing of lung tumours. Second edition. *Am J Clin Pathol*. 1982 Feb;77(2):123-36. doi: 10.1093/ajcp/77.2.123. PMID: 7064914
6. Noguchi M, Morikawa A, Kawasaki M, Matsuno Y, Yamada T, Hirohashi S, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. *Cancer*. 1995;75:2844–2852. https://doi.org/10.1002/1097-0142(19950615)75:12<2844:aid-cncr2820751209>3.0.co;2-#. PMID: 7773933.
7. Miller VA, Hirsch FR, Johnson DH. Systemic therapy of advanced bronchioloalveolar cell carcinoma: challenges and opportunities. *J Clin Oncol*. 2005;23:3288–3293. https://doi.org/10.1200/JCO.2005.19.240. PMID: 15886316
8. Miller VA, Riely GJ, Zakowski MF, Li AR, Patel JD, Heelan RT, et al. Molecular characteristics of bronchioloalveolar carcinoma and adenocarcinoma, bronchioloalveolar carcinoma subtype, predict response to erlotinib. *J Clin Oncol*. 2008;26:1472–1478. https://doi.org/10.1200/JCO.2007.13.0062 PMID: 18349398
9. Travis WD, Garg K, Franklin WA, Wistuba II, Sabloff B, Noguchi M, et al. Evolving concepts in the pathology and computed tomography imaging of lung adenocarcinoma and bronchioloalveolar carcinoma. *J Clin Oncol*. 2005;23:3279–3287. https://doi.org/10.1200/JCO.2005.15.776. PMID: 15886315
10. Travis WD, Garg K, Franklin WA, Wistuba II, Sabloff B, Noguchi M, et al. Bronchioloalveolar carcinoma and lung adenocarcinoma: the clinical importance and research relevance of the 2004 World Health Organization pathologic criteria. *J Thorac Oncol*. 2006;1-S19. PMID: 17409995.
11. Kris MG, Giaccone G, Davies A, Fukuoka M, Garfield DH, Jassem J, et al. Systemic therapy of bronchioloalveolar carcinoma: results of the first IASLC/ASCO consensus conference on bronchioloalveolar carcinoma. *J Thorac Oncol*. 2006;1–S36. PMID: 17409999.
12. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma. *J Thorac Oncol*. 2011;6:244–285. https://doi.org/10.1097/JTO.0b013e318206a221. PMID: 21252716.
13. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG, eds. WHO classification of tumours of lung, pleura, thymus and heart (4th ed.). International Agency for Research on Cancer, 2015. https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-The-Lung-Pleura-Thymus-And-Heart-2015
14. WHO Classification of Tumours Editorial Board. Thoracic Tumours. Lyon (France); International Agency for Research on Cancer;2021]. (WHO classification of tumours series, 5th ed.; vol.5.)] https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Thoracic-Tumours-2021
15. Thunnissen E, Borczuk AC, Flieder DB, Witte B, Beasley MB, Chung JH, et al. The use of immunohistochemistry improves the diagnosis of small cell lung cancer and its differential diagnosis. An international reproducibility study in a demanding set of cases. *J Thorac Oncol*. 2017;12:334–346. https://doi.org/10.1016/j.jtho.2016.12.004. PMID: 27998793.
16. Thunnissen E, Noguchi M, Aisner S, Beasley MB, Brambilla E, Chirieac LR, et al. Reproducibility of histopathological diagnosis in poorly differentiated NSCLC: an international multiobserver study. *J Thorac Oncol*. 2014;9:1354–1362. https://doi.org/10.1097/JTO.0000000000000264. PMID: 25122431.
17. Thunnissen E, Beasley MB, Borczuk AC, Brambilla E, Chirieac LR, Dacic S, et al. Reproducibility of histopathological subtypes and invasion in pulmonary adenocarcinoma. An international interobserver study. *Mod Pathol*. 2012;25:1574–1583. https://doi.org/10.1038/modpathol.2012.106. PMID: 22814311.
18. Thunnissen E, Beasley MB, Borczuk A, Dacic S, Kerr KM, Lissenberg-Witte B, et al. Defining morphologic features of invasion in pulmonary nonmucinous adenocarcinoma with lepidic growth: a proposal by the International Association for the Study of Lung Cancer Pathology Committee. *J Thorac Oncol*. 2023;18:447–462. https://doi.org/10.1016/j.jtho.2022.11.026. PMID: 36503176.
19. Moreira AL, Ocampo PSS, Xia Y, Zhong H, Russell PA, Minami Y, et al. A grading system for invasive pulmonary adenocarcinoma: a proposal from the International Association for the Study of Lung Cancer Pathology Committee. *J Thorac Oncol*. 2020;15:1599–1610. https://doi.org/10.1016/j.jtho.2020.06.001. PMID: 32562873.
20. Yatabe Y, Dacic S, Borczuk AC, Warth A, Russell PA, Lantuejoul S, et al. Best practices recommendations for diagnostic immunohistochemistry in lung cancer. *J Thorac Onco*l. 2019;14:377–407. https://doi.org/10.1016/j.jtho.2018.12.005. PMID: 30572031.
21. IASLC. IASLC Atlas of Diagnostic Immunohistochemistry. International Association for the Study of Lung Cancer, 2023.
22. Franklin WA, Veve R, Hirsch FR, Helfrich BA, Bunn PA Jr. Epidermal growth factor receptor family in lung cancer and premalignancy. *Semin Oncol*. 2002;29(1 Suppl 4):3–14. https://doi.org/10.1053/sonc.2002.31520. PMID: 11894009.
23. Hirsch FR, Varella-Garcia M, Bunn PA Jr, Di Maria MV, Veve R, Bremmes RM, et al. Epidermal growth factor receptor in non-small-cell lung carcinomas: correlation between gene copy number and protein expression and impact on prognosis. *J Clin Oncol.* 2003;21:3798–3807. https://doi.org/10.1200/JCO.2003.11.069l. PMID: 12953099.
24. Cappuzzo F, Hirsch FR, Rossi E, Bartolini S, Ceresoli GL, Bemis L, et al. Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. *J Natl Cancer Inst*. 2005;97:643–655. https://doi.org/10.1093/jnci/dji112. PMID: 15870435.

25. Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard JY, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected]. *J Clin Oncol*. 2003;21:2237–2246. https://doi.org/10.1200/JCO.2003.10.038. PMID: 12748244.
26. Kris MG, Natale RB, Herbst RS, Lynch TJ Jr, Prager D, Belani CP, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAMA*. 2003;290:2149–2158. https://doi.org/10.1001/jama.290.16.2149. PMID: 14570950.
27. Baselga J, Albanell J. Targeting epidermal growth factor receptor in lung cancer. *Curr Oncol Rep*. 2002;4:317–324. https://doi.org/10.1007/s11912-002-0007-1. PMID: 12044241.
28. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004;350:2129–2139. https://doi.org/10.1056/NEJMoa040938. PMID: 15118073.
29. Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004;304:1497–1500. https://doi.org/10.1126/science.1099314. PMID: 15118125.
30. Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci U S A*. 2004;101:13306–13311. https://doi.org/10.1073/pnas.0405220101. PMID: 15329413.
31. Hirsch FR, Varella-Garcia M, Bunn PA Jr, Franklin WA, Dziadziuszko R, Thatcher N, et al. Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. *J Clin Oncol*. 2006;24:7072-7080. https://doi.org/10.1200/JCO.2006.09.0654. PMID: 17075123.
32. Hirsch FR, Jänne PA, Eberhardt WE, Cappuzzo F, Thatcher N, Pirker R, et al. Epidermal growth factor receptor inhibition in lung cancer: status 2012. *J Thorac Oncol*. 2013;8:373–384. https://doi.org/10.1097/JTO.0b013e31827ed0ff. PMID: 23370315.
33. Tan DS, Yom SS, Tsao MS, Pass HI, Kelly K, Peled N, et al. The International Association for the Study of Lung Cancer Consensus Statement on Optimizing Management of EGFR Mutation-Positive Non-Small Cell Lung Cancer: Status in 2016. *J Thorac Oncol*. 2016;11:946–963. https://doi.org/10.1016/j.jtho.2016.05.008. PMID: 27229180.
34. IASLC. IASLC atlas of molecular testing for targeted therapies in lung cancer (Chapter 1, Figure 1-1). International Association for the Study of Lung Cancer, 2023.
35. IASLC. IASLC atlas of PD-L1 immunohistochemistry testing in lung cancer. IASLC, 2017. Retrieved from IASLC.
36. IASLC. IASLC atlas of ALK testing in lung cancer. International Association for the Study of Lung Cancer, 2016. Retrieved from IASLC.
37. Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol*. 2013;8:823–859. https://doi.org/10.1097/JTO.0b013e318290868f. PMID: 23552377.
38. Leighl NB, Rekhtman N, Biermann WA, Huang J, Mino-Kenudson M, Ramalingam SS, et al. Molecular testing for selection of patients with lung cancer for epidermal growth factor receptor and anaplastic lymphoma kinase tyrosine kinase inhibitors: American Society of Clinical Oncology endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology guideline. *J Clin Oncol*. 2014;32:3673–3679. https://doi.org/10.1200/JCO.2014.57.3055. PMID: 25311215.
39. Kerr KM, Bubendorf L, Edelman MJ, Marchetti A, Mok T, Novello S, et al. Second ESMO consensus conference on lung cancer: pathology and molecular biomarkers for non-small-cell lung cancer. *Ann Oncol.* 2014;25:1681–1690. https://doi.org/10.1093/annonc/mdu145. PMID: 24718890.
40. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(Suppl 4) iv237. https://doi.org/10.1093/annonc/mdy275. PMID: 30285222.
41. Lindeman NI, Cagle PT, Aisner DL, Arcila ME, Beasley MB, Bernicker EH, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. *J Thorac Oncol*. 2018;13:323–358. https://doi.org/10.1016/j.jtho.2017.12.001. PMID: 29396253.
42. Kalemkerian GP, Narula N, Kennedy EB, Biermann WA, Donington J, Leighl NB, et al. Molecular Testing Guideline for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice Guideline Update. *J Clin Oncol*. 2018;36:911–919. https://doi.org/10.1200/JCO.2017.76.7293. PMID: 29401004.
43. Hirsch FR, McElhinny A, Stanforth D, Ranger-Moore J, Jansson M, Kulangara K, et al. PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project. *J Thorac Oncol*. 2017;12:208–222. https://doi.org/10.1016/j.jtho.2016.11.2228 . PMID: 27913228.
44. Tsao MS, Kerr KM, Kockx M, Beasley MB, Borczuk AC, Botling J, et al. PD-L1 Immunohistochemistry Comparability Study in Real-Life Clinical Samples: Results of Blueprint Phase 2 Project. *J Thorac Oncol*. 2018;13:1302–1311. https://doi.org/10.1016/j.jtho.2018.05.013. PMID: 29800747.
45. IASLC. IASLC Atlas of Molecular Testing for Targeted Therapy in Lung Cancer. International Association for the Study of Lung Cancer, 2023. Retrieved from IASLC Atlas.
46. Smith D. The history of mesothelioma. In: Pass HI, Vogelzang J, Carbone M, eds. Malignant Mesothelioma: Advances in Pathogenesis, Diagnosis, and Translational Therapies. Springer; 2005:3–20.
47. Klemperer P, Rabin CB. Primary neoplasms of the pleura: A report of five cases. *Arch Pathol*. 1931;11:385.
48. Stout AP, Murray MR. Localized pleural mesothelioma. *Arch Pathol*. 1942;34:951–964.
49. Postoloff AV. Mesothelioma of the pleura. *Arch Pathol*. 1944;37:286–289.

50. Ackerman LV. Atlas of Tumor Pathology (Section 6, p. 100). Armed Forces Institute of Pathology, 1956.
51. Sauter JL, Dacic S, Galateau-Salle F, Attanoos RL, Butnor KJ, Churg A, et al. The 2021 WHO Classification of Tumors of the Pleura: Advances Since the 2015 Classification. *J Thorac Oncol*. 2022;17:608–622. doi:10.1016/j.jtho.2021.12.014. Epub 2022 Jan 10. PMID: 35026477.
52. Husain AN, Colby TV, Ordóñez NG, Allen TC, Attanoos RL, Beasley MB, et al. Guidelines for Pathologic Diagnosis of Malignant Mesothelioma 2017 Update of the Consensus Statement From the International Mesothelioma Interest Group. *Arch Pathol Lab Med*. 2018;142:89–108. doi:10.5858/arpa.2017-0124-RA. Epub 2017 Jul 7. PMID: 28686500.
53. Husain AN, Colby TV, Ordóñez NG, Krausz T, Borczuk A, Cagle PT, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: a consensus statement from the International Mesothelioma Interest Group. *Arch Pathol Lab Med*. 2009;133:1317–31. doi:10.5858/133.8.1317. PMID: 19653732.
54. Husain AN, Colby T, Ordonez N, Krausz T, Attanoos R, Beasley MB, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. *Arch Pathol Lab Med*. 2013;137:647–67. doi:10.5858/arpa.2012-0214-OA. Epub 2012 Aug 28. PMID: 22929121.
55. Kadota K, Suzuki K, Sima CS, Rusch VW, Adusumilli PS, Travis WD. Pleomorphic epithelioid diffuse malignant pleural mesothelioma: a clinicopathological review and conceptual proposal to reclassify as biphasic or sarcomatoid mesothelioma. *J Thorac Oncol*. 2011;6:896–904. doi:10.1097/JTO.0b013e318211127a. PMID: 21358344.
56. Rosen LE, Karrison T, Ananthanarayanan V, Gallan AJ, Adusumilli PS, Alchami FS, et al. Nuclear grade and necrosis predict prognosis in malignant epithelioid pleural mesothelioma: a multi-institutional study. *Mod Pathol.* 2018;31:598–606. doi:10.1038/modpathol.2017.170. Epub 2018 Jan 12. PMID: 29327706.
57. Dacic S, Le Stang N, Husain A, Weynand B, Beasley MB, Butnor K, et al. Interobserver variation in the assessment of the sarcomatoid and transitional components in biphasic mesotheliomas. *Mod Pathol*. 2020;33:255–262. doi:10.1038/s41379-019-0320-y. Epub 2019 Jul 4. PMID: 31273316.
58. Galateau-Salle F, Le Stang N, Nicholson AG, Pissaloux D, Churg A, Klebe S, et al. New insights on diagnostic reproducibility of biphasic mesotheliomas: a multi-institutional evaluation by the International Mesothelioma Panel from the MESOPATH reference center. *J Thorac Oncol.* 2018;13:1189–1203. doi:10.1016/j.jtho.2018.04.023. Epub 2018 Apr 30. PMID: 29723687; PMCID: PMC7558835.
59. Hmeljak J, Sanchez-Vega F, Hoadley KA, Shih J, Stewart C, Heiman D, et al. Integrative molecular characterization of malignant pleural mesothelioma. *Cancer Discov.* 2018;8:1548–1565. doi:10.1158/2159-8290.CD-18-0804. Epub 2018 Oct 15. PMID: 30322867; PMCID: PMC6310008.
60. Bueno R, Stawiski EW, Goldstein LD, Durinck S, De Rienzo A, Modrusan Z, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. *Nat Genet*. 2016;48:407–416. doi:10.1038/ng.3520. Epub 2016 Feb 29. PMID: 26928227.
61. Galateau-Salle F, Le Stang N, Tirode F, Courtiol P, Nicholson AG, Tsao MS, et al. Comprehensive molecular and pathologic evaluation of transitional mesothelioma assisted by deep learning approach: a multi-institutional study of the International Mesothelioma Panel from the MESOPATH reference center. *J Thorac Oncol*. 2020;15:1037–1053. doi:10.1016/j.jtho.2020.01.025. Epub 2020 Mar 9. PMID: 32165206; PMCID: PMC8864581.
62. Roy S, Galateau-Sallé F, Le Stang N, Churg A, Lyons MA, Attanoos R, et al. Molecular characterization of pleomorphic mesothelioma: a multi-institutional study. *Mod Pathol*. 2022;35:82–86. doi:10.1038/s41379-021-00900-z. Epub 2021 Sep 16. PMID: 34531524.
63. Monaco SE, Brcic L, Dacic S. State-of-the-art cytology of pleural fluid, focusing on the diagnosis of mesothelioma. *Cytopathology*. 2022;33:57–64. doi:10.1111/cyt.13055. Epub 2021 Sep 18. PMID: 34467576.
64. Chevrier M, Monaco SE, Jerome JA, Galateau-Salle F, Churg A, Dacic S. Testing for BAP1 loss and CDKN2A/p16 homozygous deletion improves the accurate diagnosis of mesothelial proliferations in effusion cytology. *Cancer Cytopathol*. 2020;128:939–947. doi:10.1002/cncy.22326. Epub 2020 Jul 17. PMID: 32678499.
65. Monaco S, Mehrad M, Dacic S. Recent advances in the diagnosis of malignant mesothelioma: focus on approach in challenging cases and in limited tissue and cytologic samples. *Adv Anat Pathol*. 2018;25:24–30. doi:10.1097/PAP.0000000000000180. PMID: 29227332.
66. Whitaker D, Henderson DW, Shilkin KB. The concept of mesothelioma in situ: implications for diagnosis and histogenesis. *Semin Diagn Pathol*. 1992;9:151–161. PMID: 1609157.
67. Churg A, Hwang H, Tan L, Qing G, Taher A, Tong A, et al. Malignant mesothelioma in situ. *Histopathology*. 2018;72:1033–1038. doi:10.1111/his.13468. Epub 2018 Feb 26. PMID: 29350783.
68. Churg A, Dacic S, Galateau-Salle F, Attanoos R, de Perrot M. Malignant mesothelioma in situ: Clinical and pathologic implications. *J Thorac Oncol*. 2020;15:899–901. doi:10.1016/j.jtho.2020.03.014. Epub 2020 Apr 16. PMID: 32307274.
69. Klebe S, Nakatani Y, Dobra K, Butnor KJ, Roden AC, Nicholson AG, et al. The concept of mesothelioma in situ, with consideration of its potential impact on cytology diagnosis. *Pathology*. 2021;53:446–453. doi:10.1016/j.pathol.2020.12.005. Epub 2021 Mar 26. PMID: 33775406.
70. Churg A, Galateau-Salle F, Roden AC, Attanoos R, von der Thusen JH, Tsao MS, et al. Malignant mesothelioma in situ: morphologic features and clinical outcome. *Mod Pathol*. 2020;33:297–302. doi:10.1038/s41379-019-0347-0. Epub 2019 Aug 2. PMID: 31375770.
71. Nicholson AG, Sauter JL, Nowak AK, Kindler HL, Gill RR, Remy-Jardin M, et al. EURACAN/IASLC Proposals for Updating the Histologic Classification of Pleural Mesothelioma: Towards a More Multidisciplinary Approach. *J Thorac Oncol*. 2020;15:29–49. doi:10.1016/j.jtho.2019.08.2506. Epub 2019 Sep 20. PMID: 31546041.
72. Pass H, Giroux D, Kennedy C, Ruffini E, Cangir AK, Rice D, et al. The IASLC Mesothelioma Staging Project: Improving Staging of a Rare Disease Through International Participation. *J Thorac Oncol*. 2016;11:2082–2088. doi:10.1016/j.jtho.2016.09.123. Epub 2016 Sep 23. PMID: 27670823.
73. Rice D, Chansky K, Nowak A, Pass H, Kindler H, Shemanski L, et al. The IASLC Mesothelioma Staging Project: Proposals for Revisions of the N Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Pleural Mesothelioma. *J Thorac Oncol*. 2016;11:2100–2111. doi:10.1016/j.

jtho.2016.09.121. Epub 2016 Sep 26. PMID: 27687964.
74. Nowak AK, Chansky K, Rice DC, et al; Staging and Prognostic Factors Committee, Advisory Boards and Participating Institutions. The IASLC Mesothelioma Staging Project: Proposals for Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Pleural Mesothelioma. *J Thorac Oncol*. 2016;11:2089–2099. doi:10.1016/j.jtho.2016.08.147. Epub 2016 Sep 26. PMID: 27687963.
75. Rusch VW, Chansky K, Kindler HL, et al; IASLC Staging and Prognostic Factors Committee, advisory boards, and participating institutions. The IASLC Mesothelioma Staging Project: Proposals for the M Descriptors and for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Mesothelioma. *J Thorac Oncol.* 2016;11:2112–2119. doi:10.1016/j.jtho.2016.09.124. Epub 2016 Sep 28. PMID: 27687962.
76. Rice D, Rusch V, Pass H, et al International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group. Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma: a consensus report of the international association for the study of lung cancer international staging committee and the international mesothelioma interest group. *J Thorac Oncol*. 2011;6:1304–1312. doi:10.1097/JTO.0b013e3182208e3f. PMID: 21847060.
77. Ujiie H, Kadota K, Nitadori JI, et al. The tumoral and stromal immune microenvironment in malignant pleural mesothelioma: A comprehensive analysis reveals prognostic immune markers. *Oncoimmunology*. 2015;4. doi:10.1080/2162402X.2015.1009285. PMID: 26155428; PMCID: PMC4485766.
78. Courtiol P, Maussion C, Moarii M, et al. Deep learning-based classification of mesothelioma improves prediction of patient outcome. *Nat Med*. 2019 Oct;25(10):1519-1525. doi: 10.1038/s41591-019-0583-3. PMID: 31591589.

15

SURGICAL ADVANCES AND SURGERY

Jack A. Roth,[1] **Harubumi Kato,**[2] **Hisashi Saji,**[3] **Yi-Long Wu,**[4] **Jia-Tao Zhang,**[4] **Valerie W. Rusch,**[5] **Lawek Berzenji,**[6] **and Paul E. Van Schil**[6] |
[1]W.M. Keck Center for Innovative Cancer Therapies, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Tokyo Medical University, Tokyo, Japan; [3]St. Marianna University School of Medicine, Kawasaki, Japan; [4]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China; [5]Memorial Sloan Kettering Cancer Center, New York, NY; [6]Antwerp University Hospital and University of Antwerp, Antwerp, Belgium

EVOLVING ROLE FOR SURGERY IN STAGE IIIA-N2 LUNG CANCER

When the IASLC was founded, treatment for stage IIIA non-small cell lung cancer (NSCLC) was primarily single modality (surgery or radiation therapy). Also, the staging system was less refined because each stage was very heterogeneous, and preoperative staging was inaccurate. In highly selected patients, surgery at best could obtain a 20% five-year survival. As of 2021, 2.21 million new cases of lung cancer are diagnosed yearly worldwide.[1] Among people with newly diagnosed NSCLC, approximately 20% present with stage IIIA disease.[2] Although 5-year survival has improved to 40% with multimodality treatment, outcomes remain unsatisfactory for most patients.

The recognition of poor outcomes from stage IIIA NSCLC and the heterogeneity of this group depended on developing an accurate clinical and pathologic staging system. In 1964, Dr. Clifton Mountain, a surgeon at the University of Texas MD Anderson Cancer Center, and Dr. David Carr, a medical oncologist at Mayo Clinic, realized the importance of a staging system for lung cancer. At that time, no such system existed for lung cancer, although the TNM system was already being used in Europe for other organs. Together, Dr. Mountain and Dr. Carr developed the first TNM staging system for lung cancer, supported by a large database of collected clinical material. This work was undertaken under the auspices of the Task Force on Lung Cancer of the American Joint Committee on Cancer (AJCC) Staging and End Results Reporting and was subsequently adopted by the AJCC. Dr. Mountain continued to refine this system throughout the rest of his career, and his staging system became the worldwide standard for managing lung cancer. Recognizing the need to coordinate international efforts in lung cancer research, Dr. Mountain was a founder of the IASLC in 1973. He carried the message of multidisciplinary care for lung cancer developed at MD Anderson to physicians and researchers worldwide. This effort seeded the framework for national guidelines to come and established the foundation for the IASLC Staging Committee.

Despite refining the staging system for NSCLC, now in its eighth edition, stage IIIA is one of the most heterogeneous stages with T-descriptors ranging from T1-T4 and nodal descriptions ranging from N0-N2, with single or multiple stations. Most clinical trials have focused on "classic" IIIA, which are primarily T1-T2 N2. However, this small group makes completing such trials difficult, and many of the subsequently discussed clinical trials failed to meet accrual goals.

Converging clinical advances in the 1980s set the stage for developing the multimodality treatment of stage IIIA NSCLC. Preoperative staging improved with wider use of more accurate CT scans and mediastinoscopy.

Clinical trials with cisplatin in NSCLC began in the 1970s with a 21% single-agent response rate.[3] This response rate was the highest achieved for a single agent in NSCLC up to that time. Also, other trials, many led by IASLC members, showed that responses to combination drug treatments (e.g., etoposide) were higher. These results stimulated the hypothesis that adding systemic drug treatment, either before (neoadjuvant) or after (adjuvant) surgical resection, could improve long-term survival. It was possible that more drug could be delivered before vs after surgery with deterioration of the patient's performance status. A second benefit of induction therapy would be a more accurate assessment of the tumor response to chemotherapy, which could influence postoperative treatment.

Based on this rationale, the first neoadjuvant chemotherapy clinical trial in NSCLC was started.[4] Patients with stage IIIA NSCLC were randomized to receive either (1) immediate surgery or (2) up to 3 cycles of cisplatin combination chemotherapy followed by surgery, followed by up to 3 cycles of chemotherapy if the tumor was initially stable or responded. The trial showed a significant difference in overall survival (OS), in favor of the induction chemotherapy group. The results were first presented at an IASLC Symposium in Brussels in 1993. A second clinical trial, also lead by IASLC members, began 3 years later and confirmed these findings.[5] Another large, randomized adjuvant chemotherapy trial for stages I-III, also lead by IASLC members, showed a modest survival benefit with adjuvant chemotherapy. This trial shifted interest away from induction trials.[6]

Adjuvant chemotherapy has its greatest survival benefit in patients with stage III NSCLC. The overall magnitude of the benefit is similar to that of induction chemotherapy vs adjuvant chemotherapy. However, it is more likely that full-dose chemotherapy will be given preoperatively instead of postoperatively. Brandt and colleagues showed that patients who received neoadjuvant chemotherapy vs adjuvant chemotherapy were more likely to receive the full dose (78% neoadjuvant vs 63% adjuvant) and full-cycle regimen (91% neoadjuvant vs 78% adjuvant).[7] Patients receiving adjuvant chemotherapy were more than twice as likely to have an adverse event than patients who had neoadjuvant therapy (15% neoadjuvant vs 38% adjuvant). These findings are similar to the NATCH trial, in which more patients began their planned course for neoadjuvant chemotherapy vs adjuvant therapy (97% neoadjuvant vs 66.2% adjuvant).[8]

During this period, developments in the treatment of lung cancer with radiation therapy combined with chemotherapy showed that concurrent chemoradiation was more effective than sequential administration.[9] This observation stimulated a large number of RCTs, many led by IASLC members, which attempted to define the benefits of surgery vs non-surgical chemoradiation in patients with stage III NSCLC. In the Intergroup 0139 trial, patients were treated with induction chemoradiation and subsequently randomized to surgery or further radiotherapy.[10] The OS did not differ between both arms, although progression-free survival (PFS) was better in the surgical resection group. Mortality after pneumonectomy was very high, emphasizing the high morbidity of induction chemoradiation in this group and likely neutralizing any survival advantage for surgery. An unplanned subset analysis matched patients having lobectomy after induction chemoradiation to patients treated by chemoradiation alone. There was a highly significant difference in survival, favoring the surgical group.

In the ESPATUE trial, patients with IIIA-N2 and selected patients with IIIB received induction chemotherapy, as well as concurrent chemoradiotherapy. Patients were then randomly assigned to receive a chemoradiotherapy boost or undergo surgery.[11] No difference in OS was observed between the 2 arms. In the European Organization for Research and Treatment of Cancer (EORTC) 08941 trial, only induction chemotherapy was given, followed by surgery or radiotherapy in case of response to chemotherapy, also randomizing patients with a minor response.[12] Once again, OS and PFS did not differ between the 2

randomized groups. These trials were completed when mediastinal staging by PET (positron emission tomography) and endobronchial ultrasound–guided biopsies were not routinely available. As of 2024, surgical mortality and morbidity have decreased dramatically due to more widespread use of minimally invasive techniques and enhanced recovery protocols.[13] Despite the number of trials and large numbers of patients, definitive answers to the optimal management of stage IIIA NSCLC are lacking, due to the heterogeneity of enrolled patients and continuing advances in radiation, surgical, and staging technology.

Other recent trials have attempted to fill the gaps. The Swiss Group for Clinical Cancer Research (SAKK) study compared induction chemotherapy and surgery vs induction chemoradiation and surgery for stage IIIA-N2 NSCLC.[14] No differences were found in OS or event-free survival, suggesting that in future clinical trials, the appropriate control group is induction chemotherapy and surgery. Before this study, only one completed randomized trial, the German Lung Cancer Cooperative Group, compared induction chemotherapy to induction chemoradiation.[15] Although this study was important, it had limitations. Many patients were included who would be considered unresectable (including those with T4 tumors), and 44% of patients did not have surgery. No survival difference was observed between the 2 arms.

A recent review of the surgical management of stage IIIA NSCLC, authored by IASLC members, summarized the results of 5 meta-analyses of stage IIIA clinical trials to date.[16] In none of the 5 studies was the surgical arm better than definitive chemoradiotherapy. The authors concluded that "after induction therapy for preoperative N2 involvement, best surgical results are obtained with proven mediastinal downstaging when a lobectomy is feasible to obtain a microscopic complete resection. However, no definite, universally accepted guidelines exist." These findings emphasize that all patients with stage IIIA NSCLC should undergo multidisciplinary management and treatment.

The emergence of targeted drug therapy and immunotherapy has greatly improved outcomes for patients with stage IV NSCLC. These therapies include osimertinib, which targets mutations in epidermal growth factor, and monoclonal antibodies (e.g., nivolumab, pembrolizumab), which block the immune-checkpoint protein programmed cell death-1 (PD-1). PD-1 is an inhibitory receptor expressed by all T cells during activation, and it stimulates T cells to kill neo-antigen-expressing tumor cells. In a recent randomized trial, durvalumab (an anti-PD-L1 monoclonal antibody that binds to the PD-1 ligand) was evaluated as an adjuvant therapy after definitive chemoradiotherapy. Patients with unresectable stage III NSCLC who had no evidence of disease progression after 2 or more cycles of platinum-based chemoradiotherapy received either durvalumab or placebo.[17] The PFS and OS were significantly longer for durvalumab than placebo.[18]

Many investigators are moving these agents into earlier disease settings, including neoadjuvant treatment, once again with IASLC members leading the way. In the CheckMate 816 clinical trial, neoadjuvant chemotherapy with nivolumab plus platinum-doublet chemotherapy significantly improved the pathologic complete response rate and event-free survival compared with chemotherapy alone in patients with resectable stage IB to IIIA NSCLC.[19] This regimen is now approved by the Federal Drug Administration based on the data in this clinical trial.

Cascone and co-workers reported the results of the phase II randomized NEOSTAR trial (NCT03158129) of neoadjuvant nivolumab or nivolumab + ipilimumab (a monoclonal antibody that blocks the CTLA4 checkpoint) followed by surgery. This trial included 44 patients with operable NSCLC and used the major pathologic response (MPR) as the primary endpoint.[20] The nivolumab + ipilimumab arm met the prespecified primary endpoint threshold of 6 MPRs in 21 patients, with a 38% (8/21) MPR rate. In the 37 patients resected in the trial, nivolumab + ipilimumab had an MPR rate of 50%. The authors concluded

that nivolumab + ipilimumab resulted in higher pathologic complete response rates (10% neoadjuvant nivolumab vs 38% nivolumab + ipilimumab), less viable tumor (median 50% neoadjuvant nivolumab vs 9% nivolumab + ipilimumab), and greater frequencies of effector, tissue-resident memory, and effector memory T cells. They evaluated the gut microbiome and found that greater abundance of gut *Ruminococcus* and *Akkermansia spp* was associated with MPR to dual therapy. They concluded that neoadjuvant nivolumab + ipilimumab–based therapy enhances pathologic responses, tumor immune infiltrates, and immunologic memory, and merits further study in operable NSCLC. Although no definitive conclusions can be made, the results are promising, and further randomized trials are in progress to evaluate the effects on OS. Members of the IASLC are fortunate to be associated with the IASLC and participate in its members' clinical trials over the past 35 years, from the first induction chemotherapy trial to the latest studies of the induction checkpoint blockade.

GROUND-GLASS NODULES: WHEN TO OPERATE?

With the growing implementation of CT (computed tomography) programs for screening lung cancer, early detection of small pulmonary ground-glass nodules (GGNs) has increased. If GGN is an incidental finding, it should be managed according to the relevant guidelines (Table 1). Although GGNs are nonspecific

Table 1. Guidelines for Managing Pure Ground-Glass and Part-Solid Nodules

Nodule Type	Work-Up	Japanese Society of CT screening (2012)	American College of Chest Physicians (2013)	British Thoracic Society (2015)	National Comprehensive Cancer Network (2021)	Fleischner Society (2017)
Pure GGN	F/U CT	<1.5 mm CT at 3 months. Without grow/ develop, F/U CT in 1, 2 years and thereafter.	>5 mm F/U CT examinations annually for 3 years.	>5 mm; F/U CT at 3 months, then: (1) Resolved: discharge (2) Stable: assess risk of malignancy: low-risk (F/U CT at 1, 2, 4 years), high-risk (F/U CT, nonsurgical and/or surgical resection) (3) Growth/altered morphology: resection	≥6 mm F/U CT examination at 6-12 months, and then every 2 years for 5 years.	≥6 mm F/U CT examination at 6-12 months, and then every 2 years for 5 years.
	Nonsurgical biopsy of surgical resection	≥15mm	(1)>5 mm and for nodule that solid component or growth develop on F/U CT (2) >10 mm and persistent at F/U CT		≥20 mm and for nodules that grow/ develop	≥6 mm and for nodules that have a solid component or grow/develop
Part-solid GGN	F/U CT	<15 mm CT at 3 months. If solid component ≤5 mm, F/U CT.	≤8 mm F/U CT examinations at 3, 12, and 24 months, and then annually for 1-3 years.		≥6 mm F/U CT examination at 3-6 months, and then annually for 5 years.	≥6 mm F/U CT examination at 3-6 months, and then annually for 5 years
	Nonsurgical biopsy of surgical resection	≥15 mm	>8 mm and persistent at F/U CT		≥6 mm and for nodules with a solid component ≥6 mm	For nodules with suspicious morphology (i.e., lobulated margins or cystic components), or growing solid component, or solid component >8 mm

Abbreviations: CT, computed tomography; F/U, follow-up.

radiologic findings that may represent benign conditions, some GGNs are adenocarcinomas or their precursors, so-called atypical adenomatous hyperplasia (AAH). Therefore, a multidisciplinary team discussion should be started if a new solid component develops or if the solid part appears to have grown on follow-up CT. Preoperative attempts to biopsy solid components in part-solid GGNs are not helpful and often not feasible. If malignant morphology is suspected, a surgical biopsy under the guidance of various localization methods is recommended.

Pulmonary adenocarcinomas can present as solid, pure, or part-solid GGNs. Among them, persistent part-solid GGNs have the highest probability of being pulmonary adenocarcinomas. Surgery is a curative treatment for early-stage IA lung cancers, and lobectomy with lymph node dissection has been the standard mode of surgery to date. However, the final results of the JCOG0804/WJOG4507L study led to anatomic segmentectomy being the standard treatment for radiologically noninvasive lung cancers with significant ground-glass opacity (GGO) in the periphery of the lung field.[21] When lesions are at the center of the lung field and sublobar resection is not possible, lobectomy is the preferred treatment. However, GGN with slow progress and favorable prognosis might be immediately resected or observed for a variable time. Thus, there is no consensus on the timing of the surgery.

Natural History of GGN

In terms of the natural course of GGN, Kakinuma et al prospectively studied nodules with a diameter less than or equal to 3 cm and solid component less than or equal to 0.5 cm, including pure GGNs (1,053 cases) and part-solid GGNs (104 cases).[22] Annual CT was performed with a mean follow-up time of 4.3 years. During an observation period of 5 years, 14% of pure GGNs and 48% of part-solid GGNs had an increase in nodule diameter less than or equal to 2 mm, whereas 22% of part-solid GGNs had an increase in the solid component greater than or equal to 2 mm. For part-solid GGNs, the proportion of cases in which the nodule diameter increased greater than or equal to 2 mm and the solid component increased greater than or equal to 2 mm in 10 years was about 50%. In addition to a large-scale randomized controlled trial (RCT) that examined the efficacy of CT screening for lung cancer (NELSON trial),[23] Scholten et al reported that 20 of 69 cases (29%) of pure GGNs progressed to part-solid GGNs.[24] Yankelevitz et al reported that 19 of 73 cases (26%) of pure GGNs diagnosed as adenocarcinoma on CT screening progressed to part-solid GGNs during the course of the disease.[25] Other retrospective studies on the natural course of GGNs reported that 10% to 25% of pure GGN cases and approximately 50% of part-solid GGN cases increased during observation.[26-29] All reports show a slow increase of around several millimeters per year.[30,31]

Surgical Strategy for Lung Cancer With GGN

The prognosis of peripheral small-sized lung cancers is closely related to the area of GGO on the chest thin-section CT. As a result, The JCOG Lung Cancer Surgical Study Group has consistently worked to establish a noninvasive surgical treatment for radiologically early-stage lung cancers with GGO (Figure 1). The JCOG0804/WJOG4507L "verification nonrandomized trial of cytoreductive resection on lung-field early-stage lung cancers based on chest thin-section CT findings" was conducted to verify the efficacy and safety of cytoreductive surgery for lung-field radiologically noninvasive lung cancers of less than or equal to 2 cm and a consolidation/tumor (C/T) ratio of less than or equal to 0.25 (12). The results showed that in 314 registered cases, the 5-year relapse-free survival rate (the primary endpoint) was 99.7% (95% CI, 97.7-100.0), which is extremely favorable. At this time, sublobar resection of nodules less than or equal to 2 cm with a C/T ratio of less than or equal to 0.25 would suffice. The final results of 3 studies have been presented, and all showed positive results in 2022.[21,32,33]

Is Surgery Necessary for GGN?

As mentioned earlier, studies

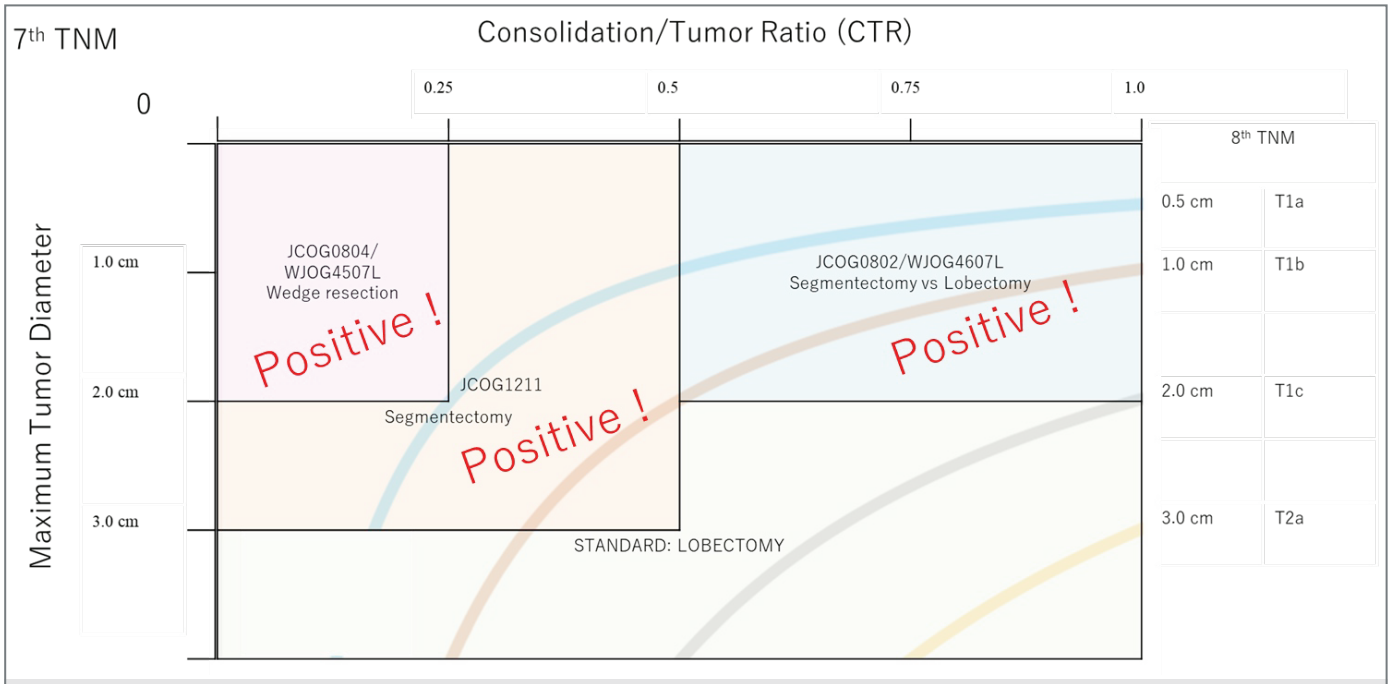


Figure 1. JCOG/WJOG Strategy for Stage I Non-Small Cell Lung Cancer.

on the natural course of GGNs reported that the proportion of GGNs that increased during the observation was 10% to 20% for pure GGNs, and approximately 50% for part-solid GGNs. The rate of increase was approximately several millimeters per year in all reports, which represents slow growth. In a subgroup of radiologically noninvasive lung cancers, surgical resection does not improve long-term prognosis, but we have yet to identify it. In routine exams, there is no clear standard or consensus on the appropriate time to operate. In an observational study of the natural course of GGNs by Kakinuma et al, approximately 7% of lesions were resected during the course of the disease.[22] However, as there was no clear recommendation for surgical intervention, the appropriate timing to operate was unknown.

JCOG1906

Based on the above, JCOG planned the EVERGREEN (Prospective Evaluation of Watchful Waiting for Early-Stage Lung Cancer with Ground-Glass Opacity: A Single-Arm Confirmatory Multicenter Study; JCOG1906, UMIN000040818) trial. This single-arm verification trial observed early-stage lung cancers based on chest thin-section CT findings and began registration in June, 2020 (Figure 2). The treatment was "resection after a course observation of radiologically noninvasive lung cancer until it reached a certain level." The primary endpoint was a 10-year survival rate. In the EVERGREEN trial, it was necessary to select a group with a favorable prognosis and a low risk of deterioration during follow-up while observing the course of radiologically early-stage lung cancers without resection. Because noninvasive cancers without vascular invasion or lymph node metastasis had to be selected, patients with diagnostic criteria for radiologically noninvasive lung cancers (lesion diameter ≤ 2 cm and C/T ratio ≤ 0.25) were enrolled. If the trial shows that prognosis for surgery performed after the course observation, in which GGO reached these criteria, is favorable and a large number of patients can avoid the surgery, the trial may establish surgery as the standard treatment after an observation period.

On imaging, GGNs are divided into pure GGN sand part-solid GGNs, and pathologic classification comprises AAH, adenocarcinoma in situ (AIS), and minimally invasive adenocarcinoma. The surgical cure rate of these lesions

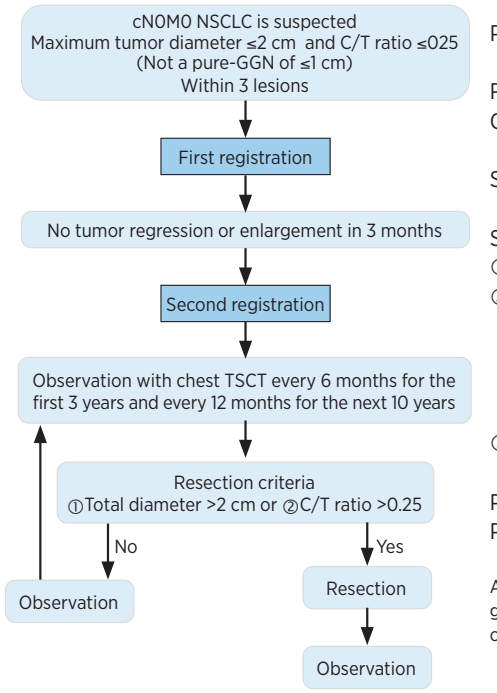


Figure 2. Schema of the EVERGREEN Trial. JCOG1906: Prospective Evaluation of Watchful Waiting for Early-Stage Lung Cancer With Ground-Glass Opacity: A Single-Arm Multicenter Study.

is nearly 100%. As previously stated, limited resection is indicated for these lesions. However, the resection area should be determined based on the patient's age, size of lesion, location, and solid area. According to a biologic proteomic analysis of early lung cancer, AAH, AIS, and minimally invasive adenocarcinoma had similar proteomic patterns that included some carcinogenetic proteins but differed significantly from invasive adenocarcinoma.[34,35] Furthermore, the normal pulmonary tissue adjacent to GGO showed some abnormal protein content, such as leukotriene A4 hydrolase and superoxide dismutase 2, characteristically recognized in AIS. Therefore, the normal tissue adjacent to GGO should also be removed. For a more accurate resection of GGO, a more intensive proteogenomic study of GGO is needed.

ROLE OF SURGERY IN OLIGOMETASTATIC LUNG CANCER

The Evolution of Concept of Oligometastatic Disease in Lung Cancer

In 1995, Hellman and Weichselbaum proposed a clinically significant state of metastasis, "oligometastasis," which refers to a restricted tumor metastatic capacity.[36] This clinical entity was initially considered an intermediate state of metastatic evolution, and local treatments were considered potentially curative in this setting.[37,38]

Over the years, the definition and nomenclature of oligometastatic lung cancer has been a controversial question. Broadly speaking, according to the interval between diagnosis of oligometastatic disease and primary cancer (typically less than 6 months), oligometastatic disease is usually categorized into synchronous and metachronous metastases. In a systematic review, Giaj-Levra and colleagues identified 21 eligible articles to query the definition of synchronous oligometastatic NSCLC.[39] However, large heterogeneity existed between the analysis of individual studies. The total number of metastases allowed in the definitions of these eligible studies ranged from 1 to 8, but in 38.1% of them, the maximum number was 5. Most of the publications did not define the number of involved organs or the maximum number of metastases per organ. Regarding mediastinal lymph node involvement, only a few studies counted this location as a metastatic site. Hence, no uniform definition of synchronous oligometastatic NSCLC could be retrieved by this systematic review. But a comprehensive radiological staging is needed to diagnose oligometastatic disease, including PET with fludeoxyglucose F18 integrated with CT and brain magnetic resonance imaging. In the same year, a consensus report on the definition of synchronous oligometastatic NSCLC was published.[40] A pan-European

multidisciplinary consensus group of 35 thoracic oncology experts was established. After a rigorous multi-step process, considering results of a systematic review, a European survey, and real case discussions, a multidisciplinary consensus statement was formulated. Synchronous oligometastatic NSCLC was proposed as a maximum of 5 metastases and 3 organs. Mediastinal lymph node involvement is not counted as a metastatic site. This definition has been receiving growing recognition in clinical trials.

With the relatively recent widespread concept of oligometastasis, a more detailed disease classification system has been proposed to suit a wide variety of clinical scenarios, including oligoprogression, oligopersistence, oligorecurrence, and so forth.[41] However, the prognostic value and compliance of the system in clinical practice needs to be further verified. Also, another consensus document mentioned that all metastatic sites of oligometastatic disease must be safely treatable.[42]

The most prominent effect of oligometastatic disease in NSCLC would be the M1b stage re-subclassification in the eighth edition of the AJCC Staging Manual.[43] The M1b subclassification was redefined to a solitary metastasis outside the chest cavity, and the new M1c stage was created to include all patients with more than 1 metastasis. As mentioned in the IASLC Lung Cancer Staging Project, this new division is a first step in providing rational definitions for an oligometastatic disease stage in NSCLC in the future. In this way, more patients with oligometastatic NSCLC would be effectively identified and cured.

Surgery for Oligometastatic Lung Cancer

Up to now, many studies have confirmed a specific role for local consolidative therapy (LCT) in oligometastatic NSCLC disease. The conclusions are broadly consistent: adding LCT to systemic therapy for oligometastatic NSCLC could significantly improve PFS, and even OS, for such patients.

In 2016, the first phase II randomized study by Gomez et al finally enrolled 49 patients with oligometastatic NSCLC who had received first-line therapy. These patients were randomly assigned (1:1) to (1) LCT either with or without subsequent maintenance treatment or (2) maintenance treatment alone.[44] Median PFS was 11.9 months (90% CI, 5.7 - 20.9 months) in the LCT arm vs 3.9 months (90% CI, 2.3 - 6.6 months) in the control arm. Long-term follow-up showed that median OS was 41.2 months (95% CI, 18.9 - not reached) in the LCT arm vs only 17.0 months (95% CI, 10.1 - 39.8 months) in the control arm.[45] Subsequently, 2 other phase II randomized trials confirmed the survival benefit of stereotactic ablative radiotherapy for patients with oligometastatic NSCLC and up to 5 metastatic sites.[46,47] Recently, a phase III study by Wang et al enrolled 133 lung adenocarcinomas with mutations in epidermal growth factor receptor (EGFR) and synchronous oligometastases (≤ 5 metastases; ≤ 2 lesions in any 1 organ, but no brain metastases).[48] All patients received a first-generation tyrosine kinase inhibitor (TKI) of EGFR, and randomization was between no radiotherapy vs radiotherapy (of all involved sites). The median PFS was 12.5 months for no radiotherapy vs 20.2 months for radiotherapy, and the median OS was 17.4 months for no radiotherapy vs 25.5 months for radiotherapy. Therefore, based on the growing evidence, multiple international guideline committees recommend LCT for select patients with oligometastatic NSCLC.

Importantly, the LCT procedure of these randomized trials was only or mainly radiotherapy. The role of surgery in oligometastatic disease seems to be limited by resectability (of all involved sites) and surgical trauma.[49] Published studies, including surgery in oligometastatic NSCLC, in the past 10 years are summarized in Table 2. Brain was the most common metastatic site. The proportion of surgery as an LCT strategy was highly diverse in different studies, ranging from 0% to 65% for primary tumors and 0% to 66% for metastatic tumors. Overall, evidence for surgery in patients with oligometastatic NSCLC is still limited to small, single-institution retrospective series. A randomized trial comparing surgical vs non-surgical LCT would be quite

challenging. The possible contributions of surgical resection for oligometastatic NSCLC include local control, tissue acquisition, and complete resection. For local control of a resectable primary or metastatic tumor, surgical resection might be a better choice. For tissue acquisition, precise staging and genomic analysis could be better provided by surgical resection of the whole specimen.[51,52] For complete resection, particularly in solitary brain metastasis, this strategy could effectively control intracranial symptoms.[53]

For oligoprogression, Yang et al proposed a clinical model for when TKIs targeting EGFR fail for EGFR-mutant NSCLC. One failure model is local progression (oligoprogression) that could be successfully treated with local therapy, including surgery.[54] Later, some retrospective reports confirmed the role of surgery in oncogene-driven NSCLC or after checkpoint blockade as treatments for advanced lung cancer.[55,56]

Future Direction of Oligometastatic Lung Cancer

Diagnosis of oligometastatic disease is based solely on imaging findings. Thus, an effective biomarker for identifying patients with true oligometastatic disease is urgently needed in the clinic. This issue could be addressed in 2 ways. First, the metastatic ability of tumors could be evaluated. In a recent large cohort study (MSK-MET), 25,000 patients with pan-cancer metastatic disease were included.[57] The association between genomic changes and patterns of metastatic dissemination were analyzed. Chromosomal instability positively correlated with metastatic burden. It remains to be seen whether any future studies using a low degree of chromosomal instability could identify patients with synchronous oligometastatic NSCLC with limited metastatic capacity. Second, analysis of circulating tumor DNA (ctDNA) has shown promise as a predictive biomarker for disease burden.[58-60] In a pilot study at the 2021 World Conference on Lung Cancer, Dong et al explored the feasibility of ctDNA-guided "drug holidays" for patients with TKI-treated oligopersistent NSCLC after LCT.[61] A total of 34 eligible patients with invisible tumor burden and undetectable ctDNA were enrolled and undertook a drug holiday. After a median follow-up of 6.9 months, 19 patients (56%) were still on the drug holiday with no evidence of disease progression. Therefore, using dynamic ctDNA changes to identify patients with true oligometastatic NSCLC will be a promising option in future studies.

MALIGNANT PLEURAL MESOTHELIOMA: CONTRIBUTIONS OF THE IASLC TO SURGICAL MANAGEMENT AND STAGING

Historically, establishing standards of care for malignant pleural mesothelioma (MPM) has been challenging because of the

Table 2. Summary of Clinical Studies of LCT for Synchronous Oligometastatic NSCLC From 2012 to 2022.

Author/Reference	Sample size	Proportion of surgery for primary lung tumor, %	Metastases, site, %	Proportion of surgery for metastases, %
De Ruysscher (62)	39	0	Brain, 43.9	23.1
Sheu (63)	90	9.0	Brain, 49.0	34.0
Pessina (64)	156	NA	Brain, 100	11.5
Kwint (65)	91	8.8	Brain, 39.6	12.1
Elamin (66)	8	12.5	Brain, 17	0
Frost (67)	180	47.2	Brain, 44.4	20
Loi (68)	51	27.0	Brain, 80.4	66.0
Jiang (69)	24	NA	Liver, 100	8.3
Arrieta (70)	37	21.6	Brain, 43.2	32.4
Galata (71)	31	65.0	Brain, 21.6	31.9
Mitchell (72)	88	28.4	Brain, 53.4	NA
Chen (73)	183	46.2	Brain, 100	44.4
Antonoff (49)	194	15.0	NA	NA

Abbreviations: LCT, local consolidative therapy; NA, not available; NSCLC, non-small cell lung cancer.

rarity of the disease, somewhat variable clinical behavior, and poorly understood tumor biology. Fifty years ago, surgical resection, performed via extrapleural pneumonectomy (EPP), was associated with high mortality and short OS.[74] Small phase II clinical trials of cytotoxic chemotherapy yielded disappointing results, and limited retrospective studies attempted to define the natural history of MPM and prognostic factors.[75-77] Most patients with MPM received only supportive care, and there was no widely accepted TNM-based staging system.

During the 1980s and 1990s, experience with surgical treatment of MPM grew,[78-80] and a landmark clinical trial established cisplatin and pemetrexed as a standard systemic therapy for MPM.[81] These efforts underscored the need for a universally accepted staging system to provide a framework for future studies. Through an effort partly funded by the IASLC at the seventh World Conference in 1994, members of the International Mesothelioma Interest Group (IMIG) reviewed available data and, by consensus, proposed a TNM-based staging system for MPM.[82] This "IMIG staging system" was accepted by the Union for International Cancer Control (UICC) and AJCC for the 6th edition of their staging manuals. The system was also gradually incorporated into analyses of surgical series and the design of prospective clinical trials.[83]

Development and Initial Analyses of the IASLC Malignant Pleural Mesothelioma Database

The IASLC Staging and Prognostic Factors Committee (SPFC) established the international database that informed revisions to the 7th edition of the UICC and AJCC lung-cancer staging system.[84] After that success, a decision was made to extend this effort to other thoracic malignancies, including MPM. Concerns existed about the 6th edition of the MPM staging system because it was mainly derived from analyses of small, retrospective surgical series; difficult to apply to clinical staging; and used the descriptors for lymph node involvement in lung cancer that were not necessarily appropriate for MPM. Therefore, in 2009, the IASLC SPFC developed the first international MPM database to study data-driven revisions for the 7th edition of the staging systems. Participation in the database was solicited from investigators active in IASLC and/or IMIG.

The initial analyses focused on patients who had surgery as part of their care simply because existing MPM databases worldwide were principally maintained by thoracic surgeons. Data were submitted on a total of 3,101 patients from 15 centers on 4 continents. Of these patients, 1,708 had surgical resection performed with curative intent (either EPP or pleurectomy/decortication). Notable findings included a high discrepancy between clinical and pathological staging, good discrimination in OS by IMIG stage, but lack of discrimination in OS for T1 vs T2 and N1 vs N2 categories. Significantly better OS was seen in patients who had epithelioid tumor histology and curative intent surgery. Patients with stage I cancer who underwent EPP experienced the best outcomes with a median OS of 40 months. However, patients who had a more advanced stage of disease had similar median OS whether or not they underwent EPP or pleurectomy/decortication (P/D). Based on these analyses, the original IMIG staging system was maintained for the 7th edition of the UICC/AJCC staging system. However, areas for potential future revisions in the T and N categories were identified, and the limited benefit of EPP in surgical treatment was highlighted.[85] The findings about nodal involvement and the effect of EPP vs P/D on OS corroborated previous, smaller institutional reports.[86-88]

Additional IASLC Studies Between the 7th and 8th Editions of the Staging Systems

During the early 2000s, the IASLC data and smaller institutional reports (noted above) led to a shift from EPP toward P/D as the most common approach to resection for MPM. Although operative mortality after EPP was reduced to 3% to 5% when this operation was performed at centers of excellence,[83,86,88-90] OS was poor for patients who had stage II or higher tumors, and subsequent disease progression

in metastatic sites was common. Controversy about the method of surgical resection was further fueled by the results of the controversial MARS 1 trial. Though designed only as a 50-patient, multicenter, feasibility trial, the study reported high morbidity and mortality and poor OS after EPP, which diminished enthusiasm for EPP.[91] This study set the stage for the recently completed, but not yet analyzed, landmark MARS 2 trial (NCT 02040272), in which patients with MPM and a potentially resectable tumor received chemotherapy and then were randomized to undergo either P/D or no surgery.[92]

However, there was significant variation in the nomenclature used to describe P/D, making it difficult to interpret outcomes. Based on a survey of 130 surgeons in 59 centers worldwide that frequently performed MPM resections, the IMIG and IASLC MPM subcommittee proposed a universal nomenclature for lung-sparing procedures. P/D was defined as resection of parietal and visceral pleura, whereas extended P/D (EPD) was defined as complete pleural resection plus resection of the diaphragm and/or pericardium. Both P/D and EPD were considered operations for macroscopic complete resection of tumor. Incomplete pleural resection done for symptom palliation was termed partial pleurectomy.[93] Subsequently, these definitions have been widely adopted in clinical practice and the design of prospective trials, including the MARS 2 trial. A decade later, the elements of MPM surgical resections were further defined in a detailed manuscript by a task force supported jointly by the National Cancer Institute, Mesothelioma Applied Research Foundation, and the IASLC.[94]

The IASLC MPM analyses for the 7th edition of the staging system also afforded an opportunity to explore supplementary prognostic variables. Based on data from 2,141 patients, 3 prognostic models were defined that depended on the number of parameters available. These models considered scenarios with maximal information, including pathologic stage vs others, in which only clinical information was available and thus useful across the spectrum of clinical care.[95]

During this same timeframe, small studies suggested that either systematic measurements of pleural thickness on CT or volumetric measurement of pleural tumor potentially provided more accurate clinical T staging than the T categories in the UICC/AJCC staging system, which qualitatively characterized tumor extent and invasion into the chest wall on CT.[96] To assess this further, members of the IASLC MPM subcommittee joined in a limited institution study of volumetric CT for staging MPM.[97] A network was established for image sharing and semi-automated volumetric assessment blinded to clinical data, and correlative clinical data were drawn from the IASLC database. Analyses showed that preoperative tumor volume correlated with OS and with pathologic T and N categories, suggesting that volumetric assessment might be a better approach to pretreatment clinical staging.[98]

Analyses for the 8th Edition of the MPM Staging System

To prepare for the 8th edition of the MPM staging system, the IASLC MPM subcommittee extensively revised the data elements in the MPM database to address questions raised by 7th edition analyses. These questions included the need for improved T, N, and M descriptors; and the potential role of pleural thickness measurements (a simple and practical alternative to volumetric assessment) in clinical T staging. An electronic data–capture system was started. Additional participation from non-surgical investigators was sought. The resulting eighth edition MPM database included 3,519 cases (2,460 eligible for analysis after data review) submitted by 29 centers spanning 4 continents.[99]

In this revised MPM database, analyses of primary tumor characteristics led to preservation of all T descriptors but collapse of T1a and T1b into a single T1 category. Pleural thickness measurements were available for 472 M0 cases. Both the sum of pleural thickness measurements at 3 prespecified levels and the maximal pleural thickness measurements were correlated with OS. This correlation suggested that such

measurements might ultimately provide more accurate clinical T staging and indicated the need to validate this approach further in data for the ninth edition.[100]

Analyses of lymph node data found no separation between clinical N0 and N(+) categories, emphasizing the difficulty in reliably obtaining clinical nodal staging with current imaging and pre-resection modalities. Pathologic staging indicated no difference in OS for hilar vs mediastinal nodal involvement. Thus, the N categories were substantially revised so that N1 described ipsilateral intrathoracic nodal disease, whereas N2 designated contralateral hilar or mediastinal and supraclavicular nodal disease. However, the combination of ipsilateral hilar and mediastinal nodal metastases was associated with worse OS than mediastinal alone, suggesting that the burden of nodal disease was an important prognostic factor. All these findings will be reassessed in data for the 9th edition of the staging system.[101]

Analyses of M descriptor data confirmed the adverse impact of distant metastases (M1) on OS and suggested a different outcome for patients with single-site vs multiple-site M1 disease. However, analyses of single-site vs multiple-site disease were based on data from only 84 patients. These data will need to be explored further in analyses for the 9th edition. Stage-grouping categories were extensively revised based on correlation of the new TNM categories with OS.[102]

Additional Studies After Analyses for the 8th Edition

Virtually all published MPM studies identified a significant difference in outcomes based on MPM histological subtype. For example, epithelioid tumors were associated with significantly better OS, sarcomatoid tumors were associated with the worst OS, and biphasic histology was associated with OS between epithelioid and sarcomatoid tumors. However, unlike the histological classification for lung adenocarcinoma, which was extensively refined a decade ago in ways that directly affected clinical care, the subtyping of MPM has been rudimentary. Recently, members of the IASLC SPFC, along with the European Network for Rare Adult Solid Cancers, proposed updating the histologic classification of MPM through a multidisciplinary approach. Proposals included classifying architectural patterns, as well as stromal and cytologic features to refine prognostication; adding MPM in situ as a separate category; routine grading of epithelioid MPM; reporting of favorable/unfavorable histologic characteristics; and incorporating clinically relevant molecular data.[103] The investigators have focused on establishing reproducible assessments of biphasic MPM and using a deep learning approach to the comprehensive molecular and pathologic evaluation of transitional MPM, a rare subtype that was previously difficult to classify.[104-105] It is expected that these refinements will support improved clinical care in MPM.

The Future

Staging, patient selection for optimal treatment, and prognostication in MPM have lagged behind similar efforts in more common thoracic malignancies, particularly NSCLC. Work by the IASLC SPFC mesothelioma subcommittee has led to substantial progress in these areas and helped inform current treatment guidelines, such as those from the American Society of Clinical Oncology.[106] However, much remains to be done. Analyses for the upcoming 9th edition of the staging system will hopefully address gaps in the current staging system, including the role of pleural thickness measurements in clinically assessing T category. They will also provide an initial multicenter evaluation of molecular features related to clinical characteristics.

TECHNICAL ADVANCES IN THORACIC SURGERY

History of Thoracic Surgery

For many centuries, the inside of the thoracic cavity was a black box for physicians and surgeons. Nevertheless, a number of chest diseases that are still very common were already known more than 2,000 years ago. Hippocrates (ca. 460-375 BC), to whom the famous Hippocratic Oath is attributed, was the first

physician to accurately describe pleural effusion and pneumonia. To treat thoracic empyema, he introduced a combined technique of tracheal intubation, using a thin tin tube through the larynx and a simultaneous drainage of the empyema with a metallic catheter through and between the ribs after a thoracotomy.[107] Another example is the ancient Greek Celsus, who, around the year 30 AD, described the complications of an open pneumothorax: "as soon as the knife really penetrates to the chest, by cutting through the transverse septum, a sort of membrane which divides the upper from the lower parts, the man loses his life at once."[108]

The first reported case of a successful lung resection dates back to 1499. At this time, a surgeon called Roland dei Capelluti, also known as Roland of Parma, resected a herniating and infected part of a lung in a patient who had a penetrating chest trauma.[109] However, major advances in the field of thoracic surgery were seen in the 19th century after William Morton introduced general anesthesia using ether in 1846 in Boston.[110] Anatomic lung resections were first performed in animals using en-masse ligation of the hilar structures. The first reported case of a lung resection for a lung tumor was performed by Jules Emil Pean, a French surgeon who removed a peripheral lung tumor by suturing the pleura to the lung and then removing the tumor using cautery. More and more cases of lung resections were reported in the following years, usually to treat advanced stages of tuberculosis.[111] The first successful pneumonectomy for tuberculosis was performed by Dr. William MacEwen in 1895.[112] In 1901, the first anatomic lobectomy was performed by Dr. Lothar Heidenhain in Germany for a patient with bronchiectasis. In 1912, the first lobectomy for cancer was performed in London by a Welsh thoracic surgeon, Hugh Morriston Davies. After Meltzer and Auer introduced intratracheal insufflation anesthesia in 1913, more and more surgeons started to perform major lung resections.[111] Initially, lobectomies were performed as 2-stage resections due to high mortality rates in patients undergoing 1-stage procedures. These 2-stage procedures involved an initial rib resection with removal of the affected lobe 10 days later using a tourniquet.[113] However, starting in the 1920s, 1-stage lung resections became more feasible. Then, in 1933, Dr. Evarts A. Graham performed the first successful 1-stage pneumonectomy for lung cancer.[114] With time, the field of thoracic surgery evolved, and techniques, such as sublobar resections, sleeve resections, and tracheal resections, became possible as well.[111]

Video-Assisted Thoracoscopic Surgery

The advent of minimally invasive surgery has unequivocally changed the landscape of surgery worldwide. By combining various technological advances, such as high-definition cameras and surgical micro-instruments, surgeons can now perform more and more complex procedures through small incisions.[115] Since the introduction of minimally invasive surgery, safe and feasible procedures using video-assisted thoracoscopic surgery (VATS) have been developed for many indications. For most of these procedures, the minimally invasive approach results in fewer complications, shortened hospital stays, and faster return to normal functions than their respective open approach.[115-117] In thoracic surgery, VATS lobectomy has, indeed, become the gold standard for operable lung cancers, especially in early stages.[118-121]

A significant amount of evidence supports that VATS provides many potential advantages over open thoracotomy for lung resections. Outcomes such as OS rates, complication rates, postoperative pain, hospital length of stay (LOS), chest-tube duration, and postoperative quality of life all seem similar or better with VATS lobectomy vs open thoracotomy.[122,123] In 2016, Bendixen et al studied differences in the postoperative pain rates and quality of life after lobectomy via VATS or anterolateral thoracotomy for early-stage lung cancer in a RCT.[124] A total of 206 patients who were scheduled for lobectomy for stage I NSCLC were enrolled in this RCT. The

trial results showed that clinically relevant pain (determined by a numeric rating scale ≥ 3) was significantly lower during the first 24 hours after VATS than anterolateral thoracotomy (38% VATS vs 63% anterolateral thoracotomy; P = .0012).[124] Even the extent of systematic lymph node dissections and oncologic efficacy of VATS seems similar to open surgery. Although several studies indicated that open thoracotomy results in higher lymph node upstaging rates and, possibly, more radical lymph node dissections, OS does not seem better after thoracotomy. Furthermore, in propensity-matched studies, differences in nodal upstaging seem diminished, possibly indicating a selection bias and that these differences are partly subject to the surgeon's experience with VATS lobectomy.[125-127]

More recently, the results of the VIOLET trial were published. This multicenter parallel-group, superiority RCT compared the outcomes of open vs VATS resection of early-stage NSCLC lesions.[128] A total of 503 patients were randomized to either VATS (247 patients) or open lobectomy (256 patients). The primary outcome was physical function at 5 weeks after surgery using the core health-related quality of life questionnaire established by the European Organization for Research and Treatment of Cancer (QLQ-C30). Scores for this questionnaire range from 0 to 100, with higher scores indicating better function. The researchers of the VIOLET trial used a 5-point difference as the clinical minimally important difference for improvement. At 5 weeks, median physical function was 73 in the VATS group and 67 in the open surgery group, with a mean difference of 4.65 points (95% CI, 1.69 - 7.61). Furthermore, serious adverse events were 30.7% in the VATS group and 37.8% in the open surgery group (risk ratio, 0.81; 95% CI, 0.66 - 1.00). At 52 weeks, no significant differences were found in cancer PFS (hazard ratio, 0.74; 95% CI, 0.43 - 1.27) or OS (hazard ratio, 0.67; 95% CI, 0.32 - 1.40). The authors concluded that, although the 5-unit improvement set a priori was not reached, patients had significantly better recovery of physical function at 5 weeks after VATS lobectomy vs open surgery (128). Unfortunately, this study could not uncover oncologic outcomes of VATS lobectomy vs open surgery, due to its relatively short follow-up period of 1 year.

In the past decade, new thoracoscopic techniques and approaches have been proposed with the aim of reducing surgical trauma after VATS. The introduction of surgical robotic systems has offered surgeons worldwide the possibility to perform complex minimally invasive surgery with 3-dimensional vision.[115] However, despite the benefits for the surgeon, these systems do not seem to reduce surgical access trauma as they still rely on 3 or 4 surgical ports. Alongside developing robotic surgery, VATS surgeons have aimed to improve VATS not with better technology, but with better techniques. These next-generation VATS surgeons mainly strive to improve VATS by reducing the size and/or number of surgical ports.[129] Examples are needlescopic VATS, 2-port VATS, and uniportal VATS.[119] Emerging clinical evidence shows that uniportal VATS may significantly reduce postoperative pain, even when compared to conventional VATS.[130,131] However, more data is needed to corroborate these findings.

Robotic-Assisted Thoracoscopic Surgery

In the past 2 decades, robotic-assisted surgery (RATS) has emerged as a new minimally invasive approach to surgery that integrates new technologic advances. The idea of robotic-assisted surgery is to enable the surgeon to control laparoscopic or thoracoscopic instruments through a robotic device that can be operated by a remote console. Robotic-assisted surgery supports 3-dimensional optics, an enhanced range of precise and intuitive instrument motions, and improved ergonomics for the surgeon.[115,117]

In recent years, robotic-assisted thoracoscopic surgery has been widely adopted among thoracic surgeons around the world, especially for lung cancer surgery. Emerging data has demonstrated a clear advantage of RATS lobectomy vs open surgery related to perioperative blood loss, postoperative need for analgesia,

postoperative recovery, hospital LOS, and 30-day mortality rates.[132] Results from studies comparing RATS and VATS are less conclusive. In a recent meta-analysis including 3,239 patients, 30-day mortality and conversion rates to thoracotomy were lower for RATS vs VATS.[133] Other studies also found better OS, fewer postoperative complications, and shorter hospital LOS for RATS vs VATS.[134] However, in a propensity-matched analysis by Oh et al, no difference in mortality rate was found between VATS and RATS.[135] Similarly, no significant difference in OS was reported in an analysis of the Society of Thoracic Surgeons database, which included 12,378 VATS and 1,220 RATS lobectomies.[136]

There is only limited data comparing oncologic outcomes of RATS to VATS and/or open surgery. Some studies suggested that RATS results in higher rates of nodal upstaging and greater numbers of sampled nodal stations. The single-center, open-labeled prospective RVlob Trial compared perioperative outcomes and long-term efficacy of RATS vs VATS.[137] A total of 320 patients were included (157 RATS vs 163 VATS). Perioperative outcomes were not significantly different, but RATS resulted in a significantly higher lymph node yield.[137] Similarly, the results of the multicenter ROMAN study showed improved lymph node dissection, despite not finding a significant difference in perioperative outcomes.[138] However, in a recent database analysis of 64,676 patients with NSCLC from the National Cancer Database in the United States, no significant difference in lymph node yield and nodal upstaging was found between RATS, VATS, or open surgery.[139]

Some authors suggested that RATS may be well-suited for more technically difficult, centrally located lesions. In a retrospective study from 2020, Qiu et al compared access and oncologic outcomes of RATS and VATS in patients undergoing open-sleeve lobectomy for centrally located NSCLC lesions. A total of 188 patients were included. For the oncologic prognosis, RATS was non-inferior to both VATS and open surgery. Furthermore, the RATS group had significantly less blood loss, reduced operative times, and shorter chest-tube drainage times than the VATS and open surgery groups. The authors concluded that RATS sleeve lobectomy is a safe, feasible, and effective procedure for centrally located NSCLC.[140] In a recent meta-analysis by Zhang et al that included 11,247 patients, RATS was similar to VATS in terms of both short-term and long-term outcomes after lobectomy or segmentectomy for NSCLC.[141] However, despite these promising studies, none of these findings have been supported by large prospective series or multicenter RCTs.

The Future of Thoracic Surgery

The past decade included an exponential growth in new technologies and advances across all surgical fields. Since its introduction in 2000, the da Vinci robotic surgery system (Intuitive Surgical Inc., Sunnyvale, CA, USA) has been used in more than 5 million operations, making Intuitive Surgical the largest player in the surgical robotic market (Figure 3).[142] However, with the origi-

Figure 3. The da Vinci Robotic System Consists of a Surgeon Console, Surgical Cart, and Vision Cart.

nal core patents for the da Vinci System now expiring, new medical startups are launching their own systems. New robotic systems in the future will likely improve the current models by integrating new technologies, such as single-port instrumental arms, haptic feedback, eye-movement tracking, and virtual reality.[143] Most probably, greater competition in the robotic surgery market will reduce costs and improve accessibility for these systems in the near future.

In addition to developments in these existing fields, new concepts are emerging as well. Ideas that were once considered science fiction are now entering the realm of modern surgery. One of these concepts is the surgical microrobot. Microrobotic surgery is fundamentally different from our current robotic systems as it is not physically connected to a console. Instead, these "microrobots" are propelled externally via electromagnetic fields or ultrasonographic energy, or internally using specific chemical reactions. A number of proof-of-concept efforts have demonstrated that these microrobots can perform various surgical maneuvers, such as dissecting, grasping, and ablation, at a microscale.[144-146] Without any doubt, the future of thoracic surgery will be exciting with new technologies that are emerging at an exponential pace. Many IASLC members contribute to this development and play a leading role in introducing these new techniques in our daily practice, evaluating them, and further refining them.

Disclosure statement:
Dr. Rusch has institutional clinical trial funding from Genentech. Dr. Van Schil P. received honoraria for advisory boards and/or fees for lectures from AstraZeneca, BMS, MSD, Roche and Janssen. Dr. Van Schil P. is also IASLC president 2023-2025.

Funding statement:
Dr. Rusch is supported, in part, by a Cancer Center Support Grant from that the National Institutes of Health/National Cancer Institute (P30 CA008748).

References

1. Organization WH. Cancer: WHO; 2021 [Available from: https://www.who.int/news-room/fact-sheets/detail/cancer.
2. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al. AJCC Cancer Staging Manual. 8th ed: Springer International Publishing: American Joint Commission on Cancer; 2017.
3. Wozniak AJ. Cisplatin Alone vs Cisplatin Plus Vinorelbine in Stage IV NSCLC. *Oncology*. 1997;11(10).
4. Roth JA, Fossella F, Komaki R, Ryan MB, Putnam JB, Jr., Lee JS, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *J Natl Cancer Inst*. 1994;86(9):673-80.
5. Rosell R, Gomez-Condina J, Camps C, Maestre J, Padilla J, Canto A, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med*. 1994;330(3):153-8.
6. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med*. 2004;350(4):351-60.
7. Brandt WS, Yan W, Zhou J, Tan KS, Montecalvo J, Park BJ, et al. Outcomes after neoadjuvant or adjuvant chemotherapy for cT2-4N0-1 non-small cell lung cancer: A propensity-matched analysis. *J Thorac Cardiovasc Surg*. 2019;157(2):743-53 e3.
8. Felip E, Rosell R, Maestre JA, Rodriguez-Paniagua JM, Moran T, Astudillo J, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. *J Clin Oncol*. 2010;28(19):3138-45.
9. Rabatic BM, Kong FM. Pros: concurrent chemo-radiotherapy remains the ideal treatment in fit patients with large volume unresectable stage III non-small cell lung cancer. *Transl Lung Cancer Res*. 2016;5(2):190-4.
10. Albain KS, Swann RS, Rusch VW, Turrisi AT, Shepherd FA, Smith C, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet*. 2009;374(9687):379-86.
11. Eberhardt WE, Pottgen C, Gauler TC, Friedel G, Veit S, Heinrich V, et al. Phase III Study of Surgery Versus Definitive Concurrent Chemoradiotherapy Boost in Patients With Resectable Stage IIIA(N2) and Selected IIIB Non-Small-Cell Lung Cancer After Induction Chemotherapy and Concurrent Chemoradiotherapy (ESPATUE). *J Clin Oncol*. 2015;33(35):4194-201.
12. van Meerbeeck JP, Kramer GW, Van Schil PE, Legrand C, Smit EF, Schramel F, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst*. 2007;99(6):442-50.
13. Shewale JB, Corsini EM, Correa AM, Brown EL, Leon-Novelo LG, Nyitray AG, et al. Time trends and predictors of survival in surgically resected early-stage non-small cell lung cancer patients. *J Surg Oncol*. 2020;122(3):495-505.
14. Pless M, Stupp R, Ris HB, Stahel RA, Weder W, Thierstein S, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. *Lancet*. 2015;386(9998):1049-56.
15. Thomas M, Rube C, Hoffknecht P, Macha HN, Freitag L, Linder A, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol*. 2008;9(7):636-48.
16. Van Schil PE, Berzenji L, Yogeswaran SK, Hendriks JM, Lauwers P. Surgical Management of Stage IIIA Non-Small Cell Lung Cancer. *Front Oncol*. 2017;7:249.

17. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *N Engl J Med*. 2017;377(20):1919-29.
18. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *N Engl J Med*. 2018;379(24):2342-50.
19. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Nivolumab (NIVO) plus platinum-doublet chemotherapy (chemo) vs chemo as neoadjuvant treatment (tx) for resectable (IB-IIIA) non-small cell lung cancer (NSCLC) in the phase 3 CheckMate 816 trial. *Cancer Res*. 2021;81(13).
20. Cascone T, William WN, Weissferdt A, Leung CH, Lin HY, Pataer A, et al. Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase 2 randomized NEOSTAR trial. *Nat Med*. 2021;27(3):504-+.
21. Suzuki K, Watanabe SI, Wakabayashi M, Saji H, Aokage K, Moriya Y, et al. A single-arm study of sublobar resection for ground-glass opacity dominant peripheral lung cancer. *J Thorac Cardiovasc Surg*. 2022;163(1):289-301 e2.
22. Kakinuma R, Noguchi M, Ashizawa K, Kuriyama K, Maeshima AM, Koizumi N, et al. Natural History of Pulmonary Subsolid Nodules: A Prospective Multicenter Study. *J Thorac Oncol*. 2016;11(7):1012-28.
23. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. *N Engl J Med*. 2020;382(6):503-13.
24. Scholten ET, de Jong PA, de Hoop B, van Klaveren R, van Amelsvoort-van de Vorst S, Oudkerk M, et al. Towards a close computed tomography monitoring approach for screen detected subsolid pulmonary nodules? *Eur Respir J*. 2015;45(3):765-73.
25. Yankelevitz DF, Yip R, Smith JP, Liang M, Liu Y, Xu DM, et al. CT Screening for Lung Cancer: Nonsolid Nodules in Baseline and Annual Repeat Rounds. *Radiology*. 2015;277(2):555-64.
26. Chang B, Hwang JH, Choi YH, Chung MP, Kim H, Kwon OJ, et al. Natural history of pure ground-glass opacity lung nodules detected by low-dose CT scan. *Chest*. 2013;143(1):172-8.
27. Kobayashi Y, Mitsudomi T. Management of ground-glass opacities: should all pulmonary lesions with ground-glass opacity be surgically resected? *Transl Lung Cancer Res*. 2013;2(5):354-63.
28. Kakinuma R, Muramatsu Y, Kusumoto M, Tsuchida T, Tsuta K, Maeshima AM, et al. Solitary Pure Ground-Glass Nodules 5 mm or Smaller: Frequency of Growth. *Radiology*. 2015;276(3):873-82.
29. Matsuguma H, Mori K, Nakahara R, Suzuki H, Kasai T, Kamiyama Y, et al. Characteristics of subsoil pulmonary nodules showing growth during follow-up with CT scanning. *Chest*. 2013;143(2):436-43.
30. Lee SW, Leem CS, Kim TJ, Lee KW, Chung JH, Jheon S, et al. The long-term course of ground-glass opacities detected on thin-section computed tomography. *Respir Med*. 2013;107(6):904-10.
31. Kobayashi Y, Sakao Y, Deshpande GA, Fukui T, Mizuno T, Kuroda H, et al. The association between baseline clinical-radiological characteristics and growth of pulmonary nodules with ground-glass opacity. *Lung Cancer*. 2014;83(1):61-6.
32. Saji H, Okada M, Tsuboi M, Nakajima R, Suzuki K, Aokage K, et al. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. *Lancet*. 2022;399(10335):1607-17.
33. Aokage K, Saji H, Suzuki K, Mizutani T, Katayama H, Shibata T, et al. A non-randomized confirmatory trial of segmentectomy for clinical T1N0 lung cancer with dominant ground glass opacity based on thin-section computed tomography (JCOG1211). *Gen Thorac Cardiovasc Surg*. 2017;65(5):267-72.
34. Nishimura T, Nakamura H, Tan KT, Zhuo DW, Fujii K, Koizumi H, et al. A proteogenomic profile of early lung adenocarcinomas by protein co-expression network and genomic alteration analysis. *Sci Rep*. 2020;10(1):13604.
35. Kato Y, Nakamura H, Tojo H, Nomura M, Nagao T, Kawamura T, et al. A proteomic profiling of laser-microdissected lung adenocarcinoma cells of early lepidic-types. *Clin Transl Med*. 2015;4(1):64.
36. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. 1995;13(1):8-10.
37. Weichselbaum RR HS. Oligometastases revisited. *Nature Reviews Clinical Oncology*. 2011;8:378-82.
38. Barton MK. Local consolidative therapy may be beneficial in patients with oligometastatic non-small cell lung cancer. *CA Cancer J Clin*. 2017;67(2):89-90.
39. Giaj-Levra N, Giaj-Levra M, Durieux V, Novello S, Besse B, Hasan B, et al. Defining Synchronous Oligometastatic Non-Small Cell Lung Cancer: A Systematic Review. *J Thorac Oncol*. 2019;14(12):2053-61.
40. Dingemans AC, Hendriks LEL, Berghmans T, Levy A, Hasan B, Faivre-Finn C, et al. Definition of Synchronous Oligometastatic Non-Small Cell Lung Cancer-A Consensus Report. *J Thorac Oncol*. 2019;14(12):2109-19.
41. Guckenberger M, Lievens Y, Bouma AB, Collette L, Dekker A, deSouza NM, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol*. 2020;21(1):e18-e28.
42. Lievens Y, Guckenberger M, Gomez D, Hoyer M, Iyengar P, Kindts I, et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. *Radiother Oncol*. 2020;148:157-66.
43. Eberhardt WE, Mitchell A, Crowley J, Kondo H, Kim YT, Turrisi A, 3rd, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revision of the M Descriptors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer. *J Thorac Oncol*. 2015;10(11):1515-22.
44. Gomez DR, Blumenschein GR, Jr., Lee JJ, Hernandez M, Ye R, Camidge DR, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol*. 2016;17(12):1672-82.
45. Gomez DR, Tang C, Zhang J, Blumenschein GR, Jr., Hernandez M, Lee JJ, et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. *J Clin Oncol*. 2019;37(18):1558-65.
46. Iyengar P, Wardak Z, Gerber DE, Tumati V, Ahn C, Hughes RS, et al. Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. *JAMA Oncol*. 2018;4(1):e173501.
47. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of

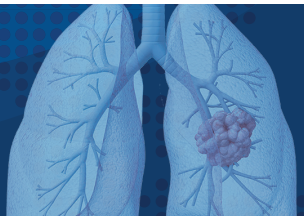
Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial. *J Clin Oncol*. 2020;38(25):2830-8.
48. Wang XS, Bai YF, Verma V, Yu RL, Tian W, Ao R, et al. Randomized Trial of First-Line Tyrosine Kinase Inhibitor With or Without Radiotherapy for Synchronous Oligometastatic EGFR-Mutated NSCLC. *J Natl Cancer Inst*. 2022.
49. Antonoff MB, Feldman HA, Mitchell KG, Farooqi A, Ludmir EB, Hofstetter WL, et al. Surgical Complexity of Pulmonary Resections Performed for Oligometastatic NSCLC. *JTO Clin Res Rep*. 2022;3(3):100288.
50. Isbell JM, Li BT, Gomez DR. The emerging role of local therapy in oligometastatic non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2022;163(3):819-25.
51. Donington JS. Commentary: Keeping surgery relevant in oligometastatic non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2019;157(4):1629-30.
52. Chenesseau J, Bourlard D, Cluzel A, Trousse D, D'Journo XB, Thomas PA. Intent-to-cure surgery for small-cell lung cancer in the era of contemporary screening and staging methods. *Interact Cardiovasc Thorac Surg*. 2020;30(4):541-5.
53. Cheufou DH, Welter S, Chalvatzoulis E, Christof D, Theegarten D, Stamatis G. Surgery of primary lung cancer with oligometastatic m1b synchronous single brain metastasis: analysis of 37 cases. *Thorac Cardiovasc Surg*. 2014;62(7):612-5.
54. Yang JJ, Chen HJ, Yan HH, Zhang XC, Zhou Q, Su J, et al. Clinical modes of EGFR tyrosine kinase inhibitor failure and subsequent management in advanced non-small cell lung cancer. *Lung Cancer*. 2013;79(1):33-9.
55. Joosten PJM, de Langen AJ, van der Noort V, Monkhorst K, Klomp HM, Veenhof A, et al. The role of surgery in the treatment of oligoprogression after systemic treatment for advanced non-small cell lung cancer. *Lung Cancer*. 2021;161:141-51.
56. Kim C, Hoang CD, Kesarwala AH, Schrump DS, Guha U, Rajan A. Role of Local Ablative Therapy in Patients with Oligometastatic and Oligoprogressive Non-Small Cell Lung Cancer. *J Thorac Oncol*. 2017;12(2):179-93.
57. Nguyen B, Fong C, Luthra A, Smith SA, DiNatale RG, Nandakumar S, et al. Genomic characterization of metastatic patterns from prospective clinical sequencing of 25,000 patients. *Cell*. 2022;185(3):563-75 e11.
58. Chae YK, Oh MS. Detection of Minimal Residual Disease Using ctDNA in Lung Cancer: Current Evidence and Future Directions. *J Thorac Oncol*. 2019;14(1):16-24.
59. Pantel K, Alix-Panabieres C. Liquid biopsy and minimal residual disease- latest advances and implications for cure. *Nat Rev Clin Oncol*. 2019;16(7):409-24.
60. Zhang JT, Liu SY, Gao W, Liu SM, Yan HH, Ji L, et al. Longitudinal Undetectable Molecular Residual Disease Defines Potentially Cured Population in Localized Non-Small Cell Lung Cancer. *Cancer Discov*. 2022:OF1-OF12.
61. Dong S WZ, Zhou Q et al. P49.01 Drug holiday based on minimal residual disease status after local theray following EGFR-TKI treatment for patients with advanced NSCLC. *J Thorac Oncol.* 2021;16:S1113-S4.
62. De Ruysscher D, Wanders R, van Baardwijk A, Dingemans AM, Reymen B, Houben R, et al. Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: long-term results of a prospective phase II trial (Nct01282450). *J Thorac Oncol*. 2012;7(10):1547-55.
63. Sheu T, Heymach JV, Swisher SG, Rao G, Weinberg JS, Mehran R, et al. Propensity score-matched analysis of comprehensive local therapy for oligometastatic non-small cell lung cancer that did not progress after front-line chemotherapy. *Int J Radiat Oncol Biol Phys*. 2014;90(4):850-7.
64. Pessina F, Navarria P, Cozzi L, Tomatis S, Ascolese AM, Franzese C, et al. Outcome appraisal of patients with limited brain metastases (BMs) from non small cell lung cancer (NSCLC) treated with different local therapeutic strategies: a single institute evaluation. *Br J Radiol*. 2017;90(1072):20170022.
65. Kwint M, Walraven I, Burgers S, Hartemink K, Klomp H, Knegjens J, et al. Outcome of radical local treatment of non-small cell lung cancer patients with synchronous oligometastases. *Lung Cancer*. 2017;112:134-9.
66. Elamin YY, Gomez DR, Antonoff MB, Robichaux JP, Tran H, Shorter MK, et al. Local Consolidation Therapy (LCT) After First Line Tyrosine Kinase Inhibitor (TKI) for Patients With EGFR Mutant Metastatic Non-small-cell Lung Cancer (NSCLC). *Clin Lung Cancer*. 2019;20(1):43-7.
67. Frost N, Tessmer A, Schmittel A, van Laak V, Raspe M, Ruwwe-Glosenkamp C, et al. Local ablative treatment for synchronous single organ oligometastatic lung cancer-A propensity score analysis of 180 patients. *Lung Cancer*. 2018;125:164-73.
68. Loi M, Mazzella A, Mansuet-Lupo A, Bobbio A, Canny E, Magdeleinat P, et al. Synchronous Oligometastatic Lung Cancer Deserves a Dedicated Management. *Ann Thorac Surg*. 2019;107(4):1053-9.
69. Jiang T, Chu Q, Wang H, Zhou F, Gao G, Chen X, et al. EGFR-TKIs plus local therapy demonstrated survival benefit than EGFR-TKIs alone in EGFR-mutant NSCLC patients with oligometastatic or oligoprogressive liver metastases. *Int J Cancer*. 2019;144(10):2605-12.
70. Arrieta O, Barron F, Maldonado F, Cabrera L, Corona-Cruz JF, Blake M, et al. Radical consolidative treatment provides a clinical benefit and long-term survival in patients with synchronous oligometastatic non-small cell lung cancer: A phase II study. *Lung Cancer*. 2019;130:67-75.
71. Galata C, Wimmer E, Kasper B, Wenz F, Reissfelder C, Jakob J. Multidisciplinary Tumor Board Recommendations for Oligometastatic Malignancies: A Prospective Single-Center Analysis. *Oncol Res Treat*. 2019;42(3):87-94.
72. Mitchell KG, Farooqi A, Ludmir EB, Corsini EM, Sepesi B, Gomez DR, et al. Pulmonary resection is associated with long-term survival and should remain a therapeutic option in oligometastatic lung cancer. *J Thorac Cardiovasc Surg*. 2021;161(4):1497-504 e2.
73. Chen XR, Hou X, Li DL, Sai K, Dinglin XX, Chen J, et al. Management of Non-Small-Cell Lung Cancer Patients Initially Diagnosed With 1 to 3 Synchronous Brain-Only Metastases: A Retrospective Study. *Clin Lung Cancer.* 2021;22(1):e25-e34.
74. Butchart EG, Ashcroft T, Barnsley WC, Holden MP. Pleuropneumonectomy in the management of diffuse malignant mesothelioma of the pleura. Experience with 29 patients. *Thorax*. 1976;31(1):15-24.
75. Law MR, Gregor A, Hodson ME, Bloom HJ, Turner-Warwick M. Malignant mesothelioma of the pleura: a study of 52 treated and 64 untreated patients. *Thorax*. 1984;39(4):255-9.
76. Antman K, Shemin R, Ryan L, Klegar K, Osteen R, Herman T, et al. Malignant mesothelioma: prognostic variables in a registry of 180 patients, the Dana-Farber Cancer Institute and Brigham and Women's Hospital experience over two decades, 1965-1985. *J Clin Oncol*. 1988;6(1):147-53.

77. Ruffie P, Feld R, Minkin S, Cormier Y, Boutan-Laroze A, Ginsberg R, et al. Diffuse malignant mesothelioma of the pleura in Ontario and Quebec: a retrospective study of 332 patients. *J Clin Oncol*. 1989;7(8):1157-68.
78. Rusch VW, Piantadosi S, Holmes EC. The role of extrapleural pneumonectomy in malignant pleural mesothelioma. A Lung Cancer Study Group trial. *J Thorac Cardiovasc Surg*. 1991;102(1):1-9.
79. Sugarbaker DJ, Heher EC, Lee TH, Couper G, Mentzer S, Corson JM, et al. Extrapleural pneumonectomy, chemotherapy, and radiotherapy in the treatment of diffuse malignant pleural mesothelioma. *J Thorac Cardiovasc Surg*. 1991;102(1):10-4; discussion 4-5.
80. Boutin C, Rey F. Thoracoscopy in pleural malignant mesothelioma: a prospective study of 188 consecutive patients. Part 1: Diagnosis. *Cancer*. 1993;72(2):389-93.
81. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol*. 2003;21(14):2636-44.
82. Rusch VW. A proposed new international TNM staging system for malignant pleural mesothelioma. From the International Mesothelioma Interest Group. *Chest*. 1995;108(4):1122-8.
83. Rusch VW, Venkatraman E. The importance of surgical staging in the treatment of malignant pleural mesothelioma. *J Thorac Cardiovasc Surg*. 1996;111(4):815-25; discussion 25-6.
84. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol*. 2007;2(8):706-14.
85. Rusch VW, Giroux D, Kennedy C, Ruffini E, Cangir AK, Rice D, et al. Initial analysis of the international association for the study of lung cancer mesothelioma database. *J Thorac Oncol*. 2012;7(11):1631-9.
86. Flores RM, Pass HI, Seshan VE, Dycoco J, Zakowski M, Carbone M, et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. *J Thorac Cardiovasc Surg*. 2008;135(3):620-6, 6 e1-3.
87. Flores RM, Routledge T, Seshan VE, Dycoco J, Zakowski M, Hirth Y, et al. The impact of lymph node station on survival in 348 patients with surgically resected malignant pleural mesothelioma: implications for revision of the American Joint Committee on Cancer staging system. *J Thorac Cardiovasc Surg*. 2008;136(3):605-10.
88. Sugarbaker DJ, Flores RM, Jaklitsch MT, Richards WG, Strauss GM, Corson JM, et al. Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. *J Thorac Cardiovasc Surg*. 1999;117(1):54-63; discussion -5.
89. Weder W, Kestenholz P, Taverna C, Bodis S, Lardinois D, Jerman M, et al. Neoadjuvant chemotherapy followed by extrapleural pneumonectomy in malignant pleural mesothelioma. *J Clin Oncol*. 2004;22(17):3451-7.
90. Krug LM, Pass HI, Rusch VW, Kindler HL, Sugarbaker DJ, Rosenzweig KE, et al. Multicenter phase II trial of neoadjuvant pemetrexed plus cisplatin followed by extrapleural pneumonectomy and radiation for malignant pleural mesothelioma. *J Clin Oncol*. 2009;27(18):3007-13.
91. Treasure T, Lang-Lazdunski L, Waller D, Bliss JM, Tan C, Entwisle J, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. *Lancet Oncol*. 2011;12(8):763-72.
92. Lim E, Darlison L, Edwards J, Elliott D, Fennell DA, Popat S, et al. Mesothelioma and Radical Surgery 2 (MARS 2): protocol for a multicentre randomised trial comparing (extended) pleurectomy decortication versus no (extended) pleurectomy decortication for patients with malignant pleural mesothelioma. *BMJ Open*. 2020;10(9):e038892.
93. Rice D, Rusch V, Pass H, Asamura H, Nakano T, Edwards J, et al. Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma: a consensus report of the international association for the study of lung cancer international staging committee and the international mesothelioma interest group. *J Thorac Oncol*. 2011;6(8):1304-12.
94. Friedberg JS, Culligan MJ, Tsao AS, Rusch V, Sepesi B, Pass HI, et al. A Proposed System Toward Standardizing Surgical-Based Treatments for Malignant Pleural Mesothelioma, From the Joint National Cancer Institute-International Association for the Study of Lung Cancer-Mesothelioma Applied Research Foundation Taskforce. *J Thorac Oncol*. 2019;14(8):1343-53.
95. Pass HI, Giroux D, Kennedy C, Ruffini E, Cangir AK, Rice D, et al. Supplementary prognostic variables for pleural mesothelioma: a report from the IASLC staging committee. *J Thorac Oncol*. 2014;9(6):856-64.
96. Pass HI, Temeck BK, Kranda K, Steinberg SM, Feuerstein IR. Preoperative tumor volume is associated with outcome in malignant pleural mesothelioma. *J Thorac Cardiovasc Surg*. 1998;115(2):310-7; discussion 7-8.
97. Gill RR, Naidich DP, Mitchell A, Ginsberg M, Erasmus J, Armato SG, 3rd, et al. North American Multicenter Volumetric CT Study for Clinical Staging of Malignant Pleural Mesothelioma: Feasibility and Logistics of Setting Up a Quantitative Imaging Study. *J Thorac Oncol*. 2016;11(8):1335-44.
98. Rusch VW, Gill R, Mitchell A, Naidich D, Rice DC, Pass HI, et al. A Multicenter Study of Volumetric Computed Tomography for Staging Malignant Pleural Mesothelioma. *Ann Thorac Surg*. 2016;102(4):1059-66.
99. Pass H, Giroux D, Kennedy C, Ruffini E, Cangir AK, Rice D, et al. The IASLC Mesothelioma Staging Project: Improving Staging of a Rare Disease Through International Participation. *J Thorac Oncol*. 2016;11(12):2082-8.
100. Nowak AK, Chansky K, Rice DC, Pass HI, Kindler HL, Shemanski L, et al. The IASLC Mesothelioma Staging Project: Proposals for Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Pleural Mesothelioma. *J Thorac Oncol*. 2016;11(12):2089-99.
101. Rice D, Chansky K, Nowak A, Pass H, Kindler H, Shemanski L, et al. The IASLC Mesothelioma Staging Project: Proposals for Revisions of the N Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Pleural Mesothelioma. *J Thorac Oncol*. 2016;11(12):2100-11.
102. Rusch VW, Chansky K, Kindler HL, Nowak AK, Pass HI, Rice DC, et al. The IASLC Mesothelioma Staging Project: Proposals for the M Descriptors and for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification

for Mesothelioma. *J Thorac Oncol*. 2016;11(12):2112-9.
103. Nicholson AG, Sauter JL, Nowak AK, Kindler HL, Gill RR, Remy-Jardin M, et al. EURACAN/IASLC Proposals for Updating the Histologic Classification of Pleural Mesothelioma: Towards a More Multidisciplinary Approach. *J Thorac Oncol*. 2020;15(1):29-49.
104. Galateau Salle F, Le Stang N, Nicholson AG, Pissaloux D, Churg A, Klebe S, et al. New Insights on Diagnostic Reproducibility of Biphasic Mesotheliomas: A Multi-Institutional Evaluation by the International Mesothelioma Panel From the MESOPATH Reference Center. *J Thorac Oncol*. 2018;13(8):1189-203.
105. Galateau Salle F, Le Stang N, Tirode F, Courtiol P, Nicholson AG, Tsao MS, et al. Comprehensive Molecular and Pathologic Evaluation of Transitional Mesothelioma Assisted by Deep Learning Approach: A Multi-Institutional Study of the International Mesothelioma Panel from the MESOPATH Reference Center. *J Thorac Oncol*. 2020;15(6):1037-53.
106. Kindler HL, Ismaila N, Armato SG, 3rd, Bueno R, Hesdorffer M, Jahan T, et al. Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018;36(13):1343-73.
107. Tsoucalas G, Sgantzos M. Hippocrates (ca 460-375 bc), Introducing Thoracotomy Combined With a Tracheal Intubation for the Parapneumonic Pleural Effusions and Empyema Thoracis. *Surg Innov*. 2016;23(6):642-3.
108. Celsus AC, Spencer WG. De medicina. With an English translation by WG Spencer: London; Harvard University Press: Cambridge, Mass.; 1935.
109. Paget S. The surgery of the chest: Wright; 1896.
110. Robinson DH, Toledo AH. Historical development of modern anesthesia. *J Invest Surg*. 2012;25(3):141-9.
111. Khaitan PG, D'Amico TA. Milestones in thoracic surgery. *J Thorac Cardiovasc Surg*. 2018;155(6):2779-89.
112. Macewen W. The Cavendish Lecture On Some Points in the Surgery of the Lung. *Br Med J*. 1906;2(2375):1-7.
113. Shenstone NS, Janes RM. Experiences in Pulmonary Lobectomy. *Can Med Assoc J*. 1932;27(2):138-45.
114. Brunn H. Surgical Principles Underlying One-Stage Lobectomy. *Archives of Surgery*. 1929;18(1_PART_II):490-515.
115. Diana M, Marescaux J. Robotic surgery. *Br J Surg*. 2015;102(2):e15-28.
116. Power AD, D'Souza DM, Moffatt-Bruce SD, Merritt RE, Kneuertz PJ. Defining the learning curve of robotic thoracic surgery: what does it take? *Surg Endosc*. 2019;33(12):3880-8.
117. Wright JD. Robotic-Assisted Surgery: Balancing Evidence and Implementation. *JAMA*. 2017;318(16):1545-7.
118. Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e278S-e313S.
119. Sihoe ADL. Video-assisted thoracoscopic surgery as the gold standard for lung cancer surgery. *Respirology* (Carlton, Vic). 2020;25(S2):49-60.
120. Levy MH, Back A, Benedetti C, Billings JA, Block S, Boston B, et al. NCCN clinical practice guidelines in oncology: palliative care. *Journal of the National Comprehensive Cancer Network: JNCCN*. 2009;7(4):436-73.
121. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]. *Annals of Oncology*. 2017;28:iv1-iv21.
122. Ikeda N. Updates on Minimally Invasive Surgery in Non-Small Cell Lung Cancer. *Curr Treat Options Oncol*. 2019;20(2):16.
123. Ujiie H, Gregor A, Yasufuku K. Minimally invasive surgical approaches for lung cancer. *Expert Rev Respir Med*. 2019;13(6):571-8.
124. Bendixen M, Jørgensen OD, Kronborg C, Andersen C, Licht PB. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. *Lancet Oncol*. 2016;17(6):836-44.
125. Boffa DJ, Kosinski AS, Paul S, Mitchell JD, Onaitis M. Lymph node evaluation by open or video-assisted approaches in 11,500 anatomic lung cancer resections. *Ann Thorac Surg*. 2012;94(2):347-53; discussion 53.
126. Licht PB, Jorgensen OD, Ladegaard L, Jakobsen E. A national study of nodal upstaging after thoracoscopic versus open lobectomy for clinical stage I lung cancer. *Ann Thorac Surg*. 2013;96(3):943-9; discussion 9-50.
127. Vannucci F, Gonzalez-Rivas D. Is VATS lobectomy standard of care for operable non-small cell lung cancer? *Lung Cancer*. 2016;100:114-9.
128. Lim E, Batchelor TJP, Dunning J, Shackcloth M, Anikin V, Naidu B, et al. Video-Assisted Thoracoscopic or Open Lobectomy in Early-Stage Lung Cancer. *NEJM Evidence*. 2022;1(3):EVIDoa2100016.
129. Sihoe AD. The evolution of minimally invasive thoracic surgery: implications for the practice of uniportal thoracoscopic surgery. *Journal of thoracic disease*. 2014;6(Suppl 6):S604.
130. Sihoe AD. Uniportal lung cancer surgery: state of the evidence. *The Annals of thoracic surgery*. 2019;107(3):962-72.
131. Chen J, Volpi S, Ali JM, Aresu G, Wu L, Chen Z, et al. Comparison of post-operative pain and quality of life between uniportal subxiphoid and intercostal video-assisted thoracoscopic lobectomy. *J Thorac Dis*. 2020;12(7):3582-90.
132. Zirafa CC, Romano G, Key TH, Davini F, Melfi F. The evolution of robotic thoracic surgery. *Annals of Cardiothoracic Surgery*. 2019;8(2):210-7.
133. Liang H, Liang W, Zhao L, Chen D, Zhang J, Zhang Y, et al. Robotic Versus Video-assisted Lobectomy/Segmentectomy for Lung Cancer: A Meta-analysis. *Ann Surg*. 2018;268(2):254-9.
134. Emmert A, Straube C, Buentzel J, Roever C. Robotic versus thoracoscopic lung resection: A systematic review and meta-analysis. *Medicine* (Baltimore). 2017;96(35):e7633.
135. Oh DS, Reddy RM, Gorrepati ML, Mehendale S, Reed MF. Robotic-Assisted, Video-Assisted Thoracoscopic and Open Lobectomy: Propensity-Matched Analysis of Recent Premier Data. *Ann Thorac Surg*. 2017;104(5):1733-40.
136. Louie BE, Wilson JL, Kim S, Cerfolio RJ, Park BJ, Farivar AS, et al. Comparison of Video-Assisted Thoracoscopic Surgery and Robotic Approaches for Clinical Stage I and Stage II Non-Small Cell Lung Cancer Using The Society of Thoracic Surgeons Database. *Ann Thorac Surg*. 2016;102(3):917-24.
137. Jin R, Zheng Y, Yuan Y, Han D, Cao Y, Zhang Y, et al. Robotic-assisted Versus Video-assisted Thoracoscopic Lobectomy: Short-term Results of a Randomized Clinical Trial (RVlob Trial). *Annals of Surgery*. 2022;275(2):295-302.
138. Veronesi G, Abbas AE, Muriana P, Lembo R, Bottoni E, Perroni G, et al. Perioperative Outcome of Robotic Approach Versus Manual

Videothora-coscopic Major Resection in Patients Affected by Early Lung Cancer: Results of a Randomized Multicentric Study (ROMAN Study). *Front Oncol*. 2021;11:726408.
139. Hennon MW, DeGraaff LH, Groman A, Demmy TL, Yendamuri S. The association of nodal upstaging with surgical approach and its impact on long-term survival after resection of non-small-cell lung cancer. *Eur J Cardiothorac Surg*. 2020;57(5):888-95.
140. Qiu T, Zhao Y, Xuan Y, Qin Y, Niu Z, Shen Y, et al. Robotic sleeve lobectomy for centrally located non-small cell lung cancer: A propensity score-weighted comparison with thoracoscopic and open surgery. *J Thorac Cardiovasc Surg*. 2020;160(3):838-46.e2.
141. Ma J, Li X, Zhao S, Wang J, Zhang W, Sun G. Robot-assisted thoracic surgery versus video-assisted thoracic surgery for lung lobectomy or segmentectomy in patients with non-small cell lung cancer: a meta-analysis. *BMC Cancer*. 2021;21(1):498.
142. Khandalavala K, Shimon T, Flores L, Armijo PR, Oleynikov D. Emerging surgical robotic technology: a progression toward microbots. *Annals of Laparoscopic and Endoscopic Surgery*. 2019;5.
143. Gosrisirikul C, Don Chang K, Raheem AA, Rha KH. New era of robotic surgical systems. *Asian J Endosc Surg*. 2018;11(4):291-9.
144. Ceylan H, Yasa IC, Kilic U, Hu W, Sitti M. Translational prospects of untethered medical microrobots. *Progress in Biomedical Engineering*. 2019;1(1):012002.
145. Li J, Esteban-Fernandez de Avila B, Gao W, Zhang L, Wang J. Micro/Nanorobots for Biomedicine: Delivery, Surgery, Sensing, and Detoxification. *Sci Robot*. 2017;2(4).
146. Sitti M, Ceylan H, Hu W, Giltinan J, Turan M, Yim S, et al. Biomedical Applications of Untethered Mobile Milli/Microrobots. *Proc IEEE Inst Electr Electron Eng*. 2015;103(2):205-24.

16



ADVANCES IN RADIATION ONCOLOGY

David Ball,[1] **Hak Choy,**[2] **Walter J. Curran, Jr,**[3] **Françoise Mornex,**[4] **and Suresh Senan,**[5] | [1]Peter MacCallum Cancer Centre, Melbourne, Australia; [2]UT Southwestern Medical Center, Dallas, USA; [3]Piedmont Oncology Institute, Atlanta, USA; [4]Université Claude Bernard, Lyon, France; [5]Amsterdam University Medical Centers, Amsterdam, The Netherlands

IN THE BEGINNING – THE 1970S

At the time of the foundation of the IASLC in the early 1970s, there was no international consensus on the role of radiation therapy in the curative treatment of patients with lung cancer. There was anecdotal evidence that radiation therapy could induce responses and relieve some symptoms of the disease, but not much more. In the United Kingdom, practice was strongly influenced by a randomized trial published in 1971. In this trial, radiation therapy was compared with chemotherapy or a "wait and see" policy in patients with inoperable "carcinoma of the bronchus." The primary endpoint was survival, and there was no difference seen between the study arms. In fact, no patient appeared to survive longer than 4 years, regardless of the treatment approach. In other words, if the lung cancer could not be removed surgically, it was incurable. The results of this trial ushered in 20 years of nihilism related to the potential impact of radiation therapy on survival, at least in the United Kingdom.[1]

In 1973, the Radiation Therapy Oncology Group (RTOG) in the United States embarked on a randomized trial (RTOG 73-01) comparing four dose and fractionation schedules of radiation therapy in patients with inoperable "non-oat-cell carcinoma of the lung." Some schedules were more intense than the 40 Gy prescribed in the British trial. For example, the highest dose was 60 Gy.[2] The results of RTOG 73-01 revealed that the highest dose of 60 Gy given as 30 doses (fractions) over six weeks was associated with the best control of locoregional disease, but this did not lead to a survival advantage. Analysis of patterns of failure revealed that up to 80% of patients had relapse at distant sites. This suggested that more aggressively treating the primary site and regional nodes would be futile in most patients in whom the disease was already widespread. Nevertheless, 60 Gy became the standard of care for locally advanced lung cancer in the United States (as opposed to "wait and see" in the United Kingdom). Interestingly, this dose is still the international benchmark for locally advanced disease.

During this period, obsolescent orthovoltage and cobalt-60 machines, which were used to deliver radiation therapy in the British trial, were widely superseded by more accurate megavoltage linear accelerators. These accelerators remain the workhorses of the modern radiation therapy department (although with many technical modifications and improvements).

Both the British and North American trials used radiation therapy techniques hampered by the limited staging available at the time (which explained the high extrathoracic failure rate). These trials were also limited by suboptimal tumor localization that was based on 2-dimensional (2D) radiography with a high likelihood of geographic miss.

THE DIGITAL REVOLUTION– THE 1980S

The introduction of computed tomography (CT) scanning in the late 1970s was a revolutionary development. CT scanning improved soft-tissue visualization, not only of the tumor and regional nodes, but also of the surrounding normal structures that were dose-limiting. The potential for CT to improve the accuracy of planning radiation therapy was quickly appreciated (Figure 1).[3] The soft-tissue anatomy lying in the path of the treatment beams, especially those angled to avoid critical organs, was now clearly visible in contrast to oblique radiographs in which it was hard to interpret the soft-tissue anatomy. CT provided what was called the "beam's eye view." The use of CT for planning treatment was the first of many practice-changing advances in radiation therapy for lung cancer that were made possible by the "Digital Revolution."

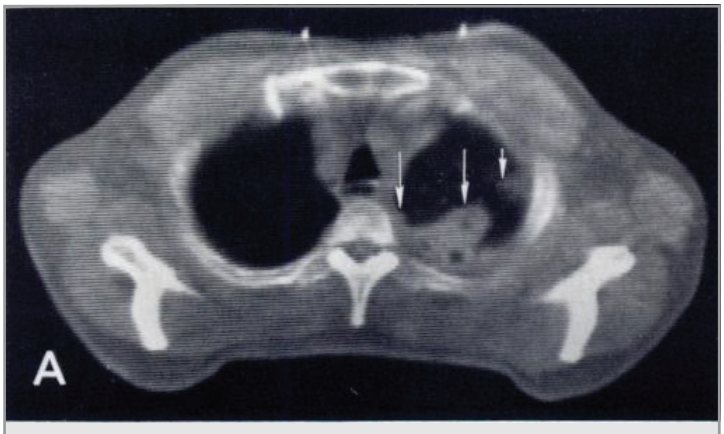


Figure 1. Computed Tomography of Tumor. The relationship of the tumor to the spinal canal, as well as a possible pleural metastasis, can be clearly seen. Reprinted with permission from Emami et al.[3]

The 3D anatomical information could be used to shape the multiple rectangular beams of the linear accelerator by shielding healthy structures on each beam's eye view. As a result, the prescribed high-dose region conformed more closely to irregularities in tumor target's shape (3D conformal therapy). Computerized treatment planning systems (TPS) developed to calculate tumor doses could also calculate the volumes of various organs at risk and their tissue density from the CT images. The CT images were obtained in the treatment position (CT simulation) and loaded directly into the TPS. This approach was particularly important in the thorax, where tissue heterogeneities result in differences in dose absorption between low-density lung and more dense solid organs.

Of the organs at risk in thoracic radiation therapy, the spinal cord and functioning lung are two of the most critical. In the spinal cord, higher dose is the most important determinant of risk of damage. However, in the lung, both dose and greater volumes of irradiated lung contribute to risk of injury. The TPS was able to generate dose-volume histograms from which metrics, such as the mean lung dose and the percentage of lung receiving 20 Gy (V20) or more, could be derived. Higher values of such metrics were associated with greater risk of radiation pneumonitis, a potentially fatal toxicity,[4] and these same metrics still provide an objective measure of toxicity risk in current practice. Surprisingly, it was not until 2011 that population-based evidence finally became available, revealing a survival advantage if patients with stage III non-small cell lung cancer (NSCLC) were planned using 3D CT-based simulation, almost two decades after this approach started replacing 2D simulation.[5]

Another major development at this time was the combination of chemotherapy with radiotherapy for treating locally advanced disease. That topic is discussed in Chapter 21.

STUDIES OF DOSE AND FRACTIONATION – THE 1990S

The importance of overall treatment time was highlighted by the results of a British randomized trial in NSCLC led by a pioneering female member of the IASLC, Dr. Michelle Saunders. The trial compared continuous hyperfractionated accelerated radiotherapy (CHART) given three times per day over 12 days with the standard-of-care treatment given over six weeks in patients with inoperable NSCLC.[6] Even though

the total dose was lower in the CHART arm (54 Gy) than the standard arm (60 Gy), survival was significantly longer in the CHART arm (Figure 2). The demands of the accelerated schedule has resulted in it being difficult to implement in daily practice. However, the importance of the CHART result is that it supports the hypothesis that the failure to control some lung cancers may be due to accelerated repopulation of remaining viable clonogens during treatment. This concept has implications for designing future treatment strategies in which prolongation of overall treatment time should be avoided. This finding also advanced British practice into a new era in which radiation therapy was accepted as a modality that could improve survival in inoperable NSCLC.

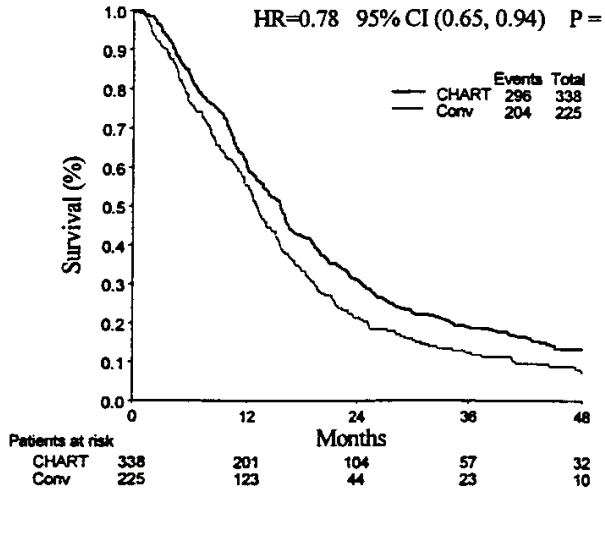


Figure 2. Overall Survival in the CHART Trial. Reprinted with permission from Saunders et al.[7]

FURTHER IMPROVEMENTS IN IMAGING: THE ARRIVAL OF POSITRON EMISSION TOMOGRAPHY/CT - THE 2000S

The introduction of whole-body scanning using positron emission tomography (PET) with the tracer ^{18}F-fluorodeoxyglucose combined with CT was a major advance in managing NSCLC with radiation therapy. More sensitive and specific for malignancy than CT alone, PET and PET/CT had an enormous impact on detecting distant metastases, especially in patients who were thought to have had locally advanced NSCLC confined to the primary site and regional lymph nodes based on CT alone. Futile local therapy was thus avoided in patients with presumed stage III disease and otherwise undetectable distant metastases.[8] Also, the PET/CT images could be loaded onto the TPS to more accurately delineate the gross primary and nodal tumor volumes (Figure 3).[9] PET also provided more accurate information about post-treatment responses.[10]

Two more technical developments at this time enabled greater treatment precision. The first was the ability to measure and track tumor motion due to breathing during delivery of radiation therapy using 4D CT.[11] This further reduced the risk of geographic miss of mobile tumors, especially those in the lower lobes. The extent to which a tumor can move as a result of ventilation is illustrated in Figure 4, which shows the same tumor imaged with 4D PET/CT and 3D PET/CT.

The second technical development was the invention of on-board imaging with cone beam CT attached to the linear

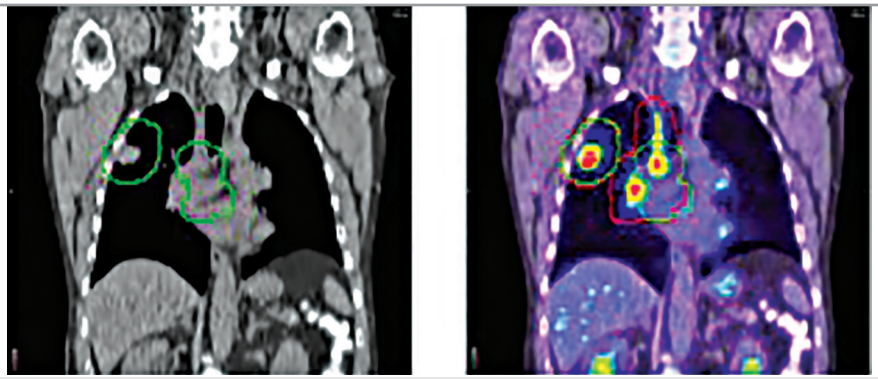


Figure 3. Coronal View of Outlines of Planning Target Volume. Outlines include primary and mediastinal nodes (green contours) on CT images (left panel). On the corresponding PET/CT image (right panel), the nodal planning target volume based on PET (red contour) is more extensive. If PET had not been used, there would have been a geographic miss.

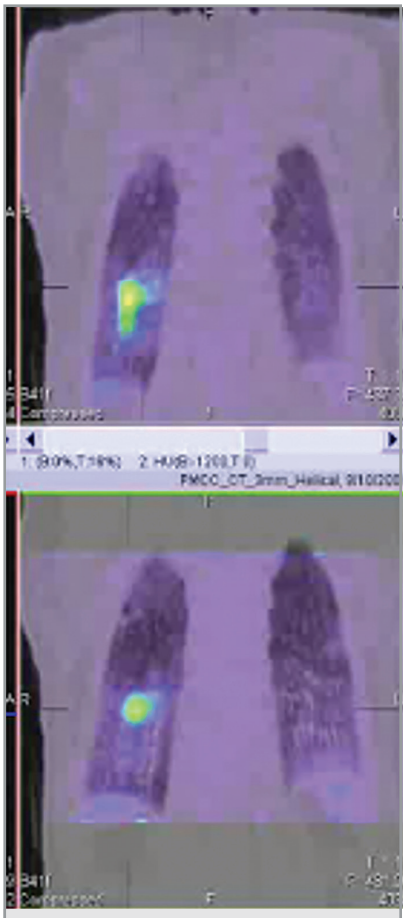


Figure 4. Imaging of an Early-Stage Lung Cancer during the Ventilatory Cycle. Coronal view of maximum intensity projection of 4D PET/CT representing cranio-caudal motion (upper panel). The corresponding 3D PET/CT image (lower panel) underestimates the anatomic extent of the tumor's location over time.

accelerator treatment gantry. This invention enabled the position of the target to be verified immediately before and during treatment with 3D CT images so that corrections could be made for any interfraction and intrafraction movement.[12] This concept is referred to as image-guided radiotherapy, which was an essential prerequisite for the next major development, stereotactic ablative body radiotherapy (SABR) for early-stage lung cancer. Figure 5 illustrates a cone beam CT taken after 40 Gy of a 60 Gy course of fractionated radiotherapy.

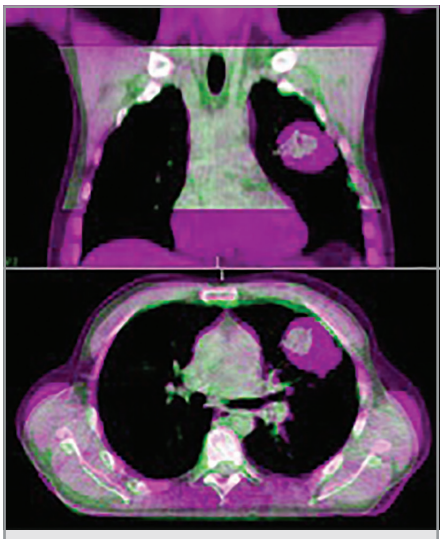


Figure 5. Cone Beam CT After 40 Gy of a 60 Gy Course of Fractionated Radiotherapy. Coronal and transverse images in which the pre-fraction cone beam CT (green) at 40 Gy is overlaid on the original planning scan (pink). The tumor has reduced in size to the gray-green mass that is still within the original contour of gross tumor volume (pink), so no position adjustment is needed.

STEREOTACTIC ABLATIVE BODY RADIOTHERAPY

SABR is a revolutionary technique in which a very high radiation dose (in terms of biologic efficacy) is given in a small number of fractions (typically 1-5) with submillimeter precision to a small target with very tight margins. Conceptually, SABR is quite different from classical fractionated radiation therapy given over a period of weeks. Classical fractionated radiation therapy relies less on precision and more on the radiobiological rationale to maximize the therapeutic ratio by exploiting differences in repair and repopulation between normal and tumor tissues. Stereotactic radiation therapy was originally used to treat intracranial tumors in which the required precision was achievable by immobilizing the skull and, consequently, the intracranial contents. Outside the skull, the technique was limited by less satisfactory patient fixation and greater target mobility or positional uncertainty. As mentioned, the development of image guidance with a cone beam CT and the ability to track tumor motion with 4D CT overcame these hurdles. Further enablers included the use of multiple (8 or more) intersecting fixed beams or dynamic arc therapy (Figure 6) to limit entry dose to normal lung, as well as more accurate algorithms for calculating and planning doses for treatment.

The first reports that used SABR for inoperable stage I NSCLC indicated that radiation therapy could be safely hypofractionated to small targets in the lung. These reports also indicated

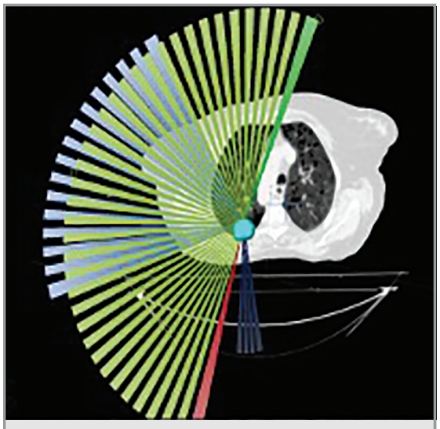


Figure 6. Dynamic Arc Therapy to treat a Stage I Non-Small Cell Lung Cancer.

that the very high biologically effective doses administered were associated with more than 90% local control.[13] A later phase I dose-escalation study showed that doses as high as 60 Gy given in three fractions were safe for peripherally located tumors.[14] Since then, SABR has been of intense research interest for treating not only primary lung cancers, but also distant metastases.

The randomized CHISEL study revealed that fractionated SABR delivery led to better local control and survival in patients with an inoperable stage I NSCLC vs those undergoing conventionally fractionated radiotherapy.[15] SABR has now replaced conventional radiotherapy for this indication. Population studies performed in Europe and North America revealed that access to SABR increased the proportion of patients who received some form of curative treatment after a diagnosis of of early stage NSCLC.[16,17] Randomized clinical trials have also established a role for single-fraction SABR in certain patients based on non-inferior outcomes seen in randomized trials that compared fractionated SABR for both NSCLC[18,19] and pulmonary metastases.[20]

ADVANCES IN RADIATION THERAPY FOR PATIENTS WITH BRAIN METASTASES

Brain metastases are a common and debilitating complication of NSCLC. The standard of care in the 1970s was palliative whole-brain radiotherapy (WBRT), although there was modest evidence for its benefit. Once anatomic localization became possible with the development of CT in the late 1970s, and later magnetic resonance imaging, metastases that were solitary or limited in size and number (1-4) could be treated more aggressively with surgical resection, stereotactic irradiation, or a combination of these approaches. The addition of a stereotactic radiotherapy boost in patients treated with WBRT for a single metastasis led to a survival benefit in a RTOG randomized trial published in 2004.[21] This trial established stereotactic radiotherapy as the first advance in radiation therapy for brain metastases since the IASLC began. Until recently, WBRT continued to be the standard of care for patients who did not qualify for surgery or stereotactic radiotherapy because of metastatic extent.

The routine use of WBRT was questioned after the finding that many patients lived for only a matter of weeks. In 2007, a randomized trial (QUARTZ) compared WBRT + dexamethasone vs dexamethasone alone in patients in whom clinicians were uncertain of the benefit of WBRT. This trial found no improvement in overall survival or quality-adjusted life years in this patient population with the addition of WBRT.[22] As a result, supportive care with dexamethasone became an acceptable option for patients with a poor prognosis. With advances in tumor classification, the selection and aggressiveness of treatment can be determined using prognostic models, such as the graded prognostic assessment for lung cancer using molecular markers (Lung-molGPA). This assessment includes performance status, age, presence of extracranial metastases, and molecular markers.[23]

The potential adverse effect of WBRT on cognitive function has encouraged efforts to protect normal brain where WBRT is indicated. These efforts include reducing the dose to the hippocampus using intensity-modulated radiotherapy (IMRT) and the drug memantine. This strategy was associated with lower cognitive decline and no survival detriment in patients with a variety of cancers (predominantly lung cancer) randomized to hippocampal avoidance.[24]

Technical advances have supported the delivery of stereotactic radiotherapy to multiple brain targets. One randomized trial compared stereotactic radiotherapy vs WBRT for patients with 4 to 15 brain metastases from a variety of cancers.[25] Survival was similar in both arms, but cognitive function scores were better in patients randomized to stereotactic radiotherapy alone.

As a result of these advances, the use of standard WBRT for treating brain metastases is declining and being replaced with stereotactic techniques. For example, WBRT is no longer recommended after resection of brain metastases, as several studies have confirmed WBRT does not improve survival.

RADIATION THERAPY TO PROLONG SURVIVAL IN PATIENTS WITH EXTRACRANIAL METASTATIC DISEASE

Long regarded as incurable, patients with metastatic NSCLC have generally been treated with systemic rather than local therapies, and the role of radiation therapy has been relegated to the palliation of troublesome symptoms. The landmark randomized trial conducted by Patchell and colleagues compared surgical resection of a solitary brain metastasis with brain irradiation vs brain radiotherapy alone. This trial found longer survival in patients randomized to surgical resection.[26] In this trial, most patients had a primary NSCLC. Based on these findings, some investigators thought it may be possible to achieve similar benefits with stereotactic radiation rather than surgical resection, not only in the brain, but also at extracranial sites. Hellman and Weichselbaum[27] posited that in some patients, there may exist an intermediate state between locoregional disease and widespread metastatic disease, which they termed oligometastases. If the limited but finite number of metastases could be ablated with surgery or other means, these patients might be cured. To ablate a cancer with standard techniques for radiation therapy would require high doses over a period of weeks. However, with SABR, this ablation might be done in 1 to 3 doses over a period of days, making it a practical approach that is acceptable to patients and busy radiation therapy departments. A randomized trial (SABR-COMET) compared SABR in up to 5 metastases with standard-of-care palliative treatment in a variety of cancers. Patients randomized to SABR had significantly longer survival, supporting the oligometastatic concept (Figure 7).[28,29]

A second category of patients who might benefit from SABR are those with NSCLC due to driver mutations susceptible to targeted therapies, but with oligoprogressive disease. Oligoprogressive disease occurs when the disease is progressing at a limited number of sites and responding to the targeted agent at other sites. SABR to the sites of progression allows patients to continue the targeted agent rather than switching to another systemic drug.[30]

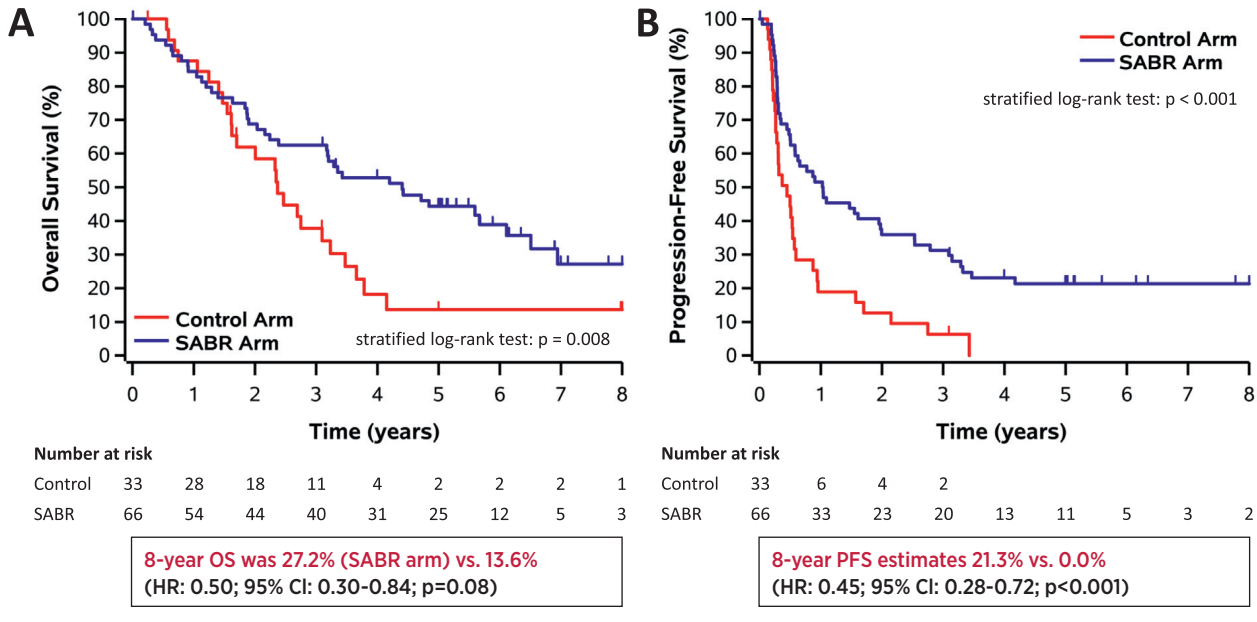


Figure 7. Long-Term Overall and Progression-Free Survival in the SABR-COMET study. These results indicate significantly longer survival in patients treated with SABR to sites of metastatic disease in addition to the standard of care. HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SABR, stereotactic ablative body radiotherapy. Reprinted with permission.[29]

INTENSITY-MODULATED RADIATION THERAPY AND VOLUMETRIC-MODULATED ARC THERAPY

During the 2D and early 3D eras, critical structures and normal tissues had to be shielded from unnecessary irradiation. For this process, lead blocks were used to shape the rectangular beam as much as possible to conform to the tumor target with a margin added for subclinical spread. This process was cumbersome and could only be applied to convex tumor contours. Structures within a concavity in the tumor (e.g., spinal cord) could not be protected without also shielding the tumor.

In the 1990s, the development of multileaf collimators (MLCs) housed in the treatment head of the linear accelerator allowed for the beam to be shaped without the need for lead shielding blocks. Computer-controlled MLCs can be programmed to execute complex, dynamic leaf sequences during treatment delivery. As a result, the intensity of the beam can be modulated to produce dose distributions that conform to irregular geometric shapes, including tumor concavities. An example of a plan to modulate the intensity of radiation therapy to reduce the dose to the spinal cord is shown in Figure 8.

An even more efficient form of intensity-modulated treatment delivery, known as volumetric-modulated arc therapy (VMAT), can be achieved by continuously rotating the treatment gantry at the same time as the MLCs go through their leaf sequence.

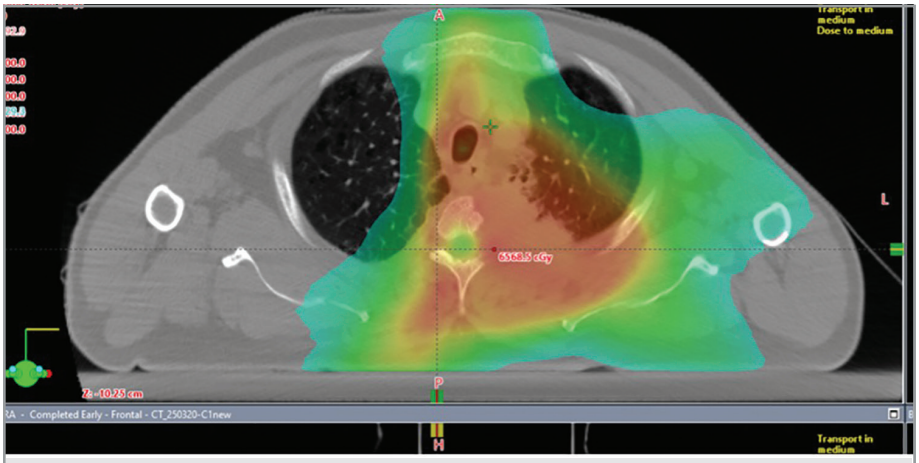


Figure 8. Intensity-Modulated Radiation Therapy Plan for an Apical Lung Tumor Adjacent to the Spinal Canal. The color wash represents regions of equivalent dose. The higher dose region (brown) covers the gross tumor, but the adjacent spinal cord receives a lower dose (green).

The improved conformality with sparing of dose-limiting normal tissues should theoretically make it possible to treat larger tumors using IMRT without increasing toxicity. A secondary analysis of the NRG Oncology RTOG 0617 randomized clinical trial suggested that compared with 3D conformal techniques, patients treated with IMRT had lower rates of severe pneumonitis and lower cardiac doses.[31] The RTOG 0617 trial had been designed to test the hypothesis (among others) that chemoradiation using a dose of 74 Gy resulted in better survival than a dose of 60 Gy in patients with locally advanced NSCLC. Surprisingly, survival was better in the 60 Gy arm. Furthermore, the survival times were the longest ever seen in an RTOG NSCLC trial up to that time, reflecting the incremental gains achieved in technical accuracy over time and the benefits of multimodality therapy.

CONCLUSIONS AND FUTURE DIRECTIONS

Over the 50 years of the IASLC's history, inoperable NSCLC has gone from being a disease incurable with radiation therapy, even in its early stages, to one in which most patients with stage I disease can be cured with non-invasive means with SABR. In most patients with locally advanced disease, and certain patients with distant metastases, radiation therapy now contributes to meaningful prolongation and quality of life, if not a cure.

The potential for future improvements in radiation therapy for patients with lung cancer can be divided into 2 categories: technical and biological. In the first two decades of the 21st century, technical progress, fueled by rapid advances in computer tech-

nology, has outstripped biological advances. Even so, further refinements in technology hold promise for greater precision (e.g., lower dose to normal tissues using protons), and trials are ongoing. The use of a very high dose rate for radiation therapy (FLASH) has the potential to reduce normal tissue toxicity in preclinical models, and early clinical trials are underway to confirm these findings. Because of the very short time of delivery, FLASH also has the advantage of minimizing the challenges of hitting a moving tumor target caused by physiologic motion.

The biological opportunities for improving the efficacy of radiation therapy are relatively unexplored relative to, for example, developing biomarker-directed oncology drugs. An attempt to personalize the radiotherapy prescription based on tumor genomics (genomic-adjusted radiation dose) described by Scott et al[32] is an example of an approach that could make up lost ground in this area. There may also be opportunities to target aspects of the tumor microenvironment, such as hypoxia, which can now be detected non-invasively with hypoxia-specific PET tracers.

Finally, as patients live longer due to more effective therapies, late toxicities that contribute significantly to mortality and morbidity are being identified. Refining the organ tolerances for previously underappreciated structures, such as the brain and heart, are examples of work in progress in this area.

References

1. Durrant KR, Berry RJ, Ellis F, Ridehalgh FR, Black JM, Hamilton WS. Comparison of treatment policies in inoperable bronchial carcinoma. *Lancet*. 1971;297:715-719.
2. Perez CA, Stanley K, Rubin P, et al. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung. Preliminary report by the Radiation Therapy Oncology Group. *Cancer*. 1980;45:2744-2753.
3. Emami B, Melo A, Carter BL, Munzenrider JE, Apiro AJ. Value of computed tomography in radiotherapy of lung cancer. *Am J Roentgenol*. 1978;131:63-67.
4. Martel MK, Ten Haken RK, Hazuka MB, Turrisi AT, Fraass BA, Lichter AS. Dose-volume histogram and 3-D treatment planning evaluation of patients with pneumonitis. *Int J Radiat Oncol Biol Phys*. 1994;28:575-581.
5. Chen AB Neville BA, She DJ, Chen K, Schrag D. Survival outcomes after radiation therapy for stage III non-small-cell lung cancer after adoption of computed tomography-based simulation. *J Clin Oncol*. 2011;29:2305-2311.
6. Saunders M, Dische S, Barrett A, Harvey A, Gibson D, Parmar M. Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: A randomised multicentre trial. CHART Steering Committee. *Lancet*. 1997;350:161-165.
7. Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Palmar M. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee. *Radiother Oncol*. 1999;52:137-148.
8. MacManus MP, Hicks RJ, Matthews JP, et al. High rate of detection of unsuspected distant metastases by pet in apparent stage III non-small-cell lung cancer: implications for radical radiation therapy. *Int J Radiat Oncol Biol Phys*. 50:287-293, 2001.
9. Bradley J, Thorstad WL, Mutic S, et al. Impact of FDG-PET on radiation therapy volume delineation in non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 59:78-86, 2004.
10. Mac Manus MP, Hicks RJ, Matthews JP, et al. Positron emission tomography is superior to computed tomography scanning for response-assessment after radical radiotherapy or chemoradiotherapy in patients with non-small-cell lung cancer. *J Clin Oncol*. 21:1285–1292, 2003.
11. Keall PJ, Starkschall G, Shukla HEE, et al. Acquiring 4D thoracic CT scans using a multislice helical method. *Physics Med Bio*. 2004;49:2053-2067.
12. Dawson LA, Jaffray DA. Advances in image-guided radiation therapy. *J Clin Oncol*. 2007;25:938-946.
13. Uematsu M, Shioda A, Suda A, et al. Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: A 5-year experience. *Int J Rad Oncol Biol Phys*. 2001;51:666-670.
14. Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: Results of a phase I study in medically inoperable stage I non-small cell lung cancer. *Chest*. 2003;124:1946-1955.
15. Ball D, Mai GT, Vinod S, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): A phase 3, open-label, randomised controlled trial. *Lancet Oncol*. 2019;20: 494-503.
16. Haasbeek CJA, Palma D, Visser O, Lagerwaard FJ, Slotman B, Senan S. Early-stage lung cancer in elderly patients: A population-based study of changes in treatment patterns and survival in the Netherlands. *Ann Oncol*. 2012;23:2743-2747.
17. Syed YA, Stokes W, Rupji M, et al. Surgical outcomes for early stage non-small cell lung cancer at facilities with stereotactic body radiation therapy. *Chest*. 2022;161:833-844.
18. Videtic GM, Paulus R, Singh AK, et al. Long-term Follow-up on NRG Oncology RTOG 0915 (NCCTG N0927): A randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage i peripheral non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2019;103:1077-1084.
19. Singh AK, Gomez-Suescun JA, Stephans KL, et al. One versus three fractions of stereotactic body radiation therapy for peripheral stage I to II non-small cell lung cancer: A randomized, multi-institution, phase 2 trial. *Int J*

Radiat Oncol Biol Phys. 2019;105: 752-759.
20. Siva S, Bressel M, Mai T, et al. Single-fraction vs multifraction stereotactic ablative body radiotherapy for pulmonary oligometastases (SAFRON II): The Trans Tasman Radiation Oncology Group 13.01 phase 2 randomized clinical trial. JAMA Oncol. 7:1476-1485, 2021.
21. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomised trial. *Lancet*. 2004;363:1665-1672.
22. Mulvenna P, Nankivell M, Barton R, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): Results from a phase 3, non-inferiority, randomised trial. *Lancet*. 2016;388:2004-2014.
23. Sperduto PW, Yang TJ, Beal K, et al. estimating survival in patients with lung cancer and brain metastases: An update of the graded prognostic assessment for lung cancer using molecular markers (Lung-molGPA). *JAMA Oncol*. 2017;3:827-831.
24. Brown PD, Gondi V, Pugh S, et al. Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC001. *J Clin Onco*l. 2020;38:1019-1029.
25. Jing Li. Stereotactic Radiosurgery Versus Whole-brain Radiation Therapy For Patients With 4-15 Brain Metastases: A Phase III Randomized Controlled Trial. ASTRO 2020 (abstract 41).
26. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *New Engl J Med*. 1990;322: 494-500.
27. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. 1995;13:8-10.
28. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): A randomised, phase 2, open-label trial. *Lancet*. 2019;393:2051-2058.
29. Harrow S, Palma DA, Olson R, et al. stereotactic radiation for the comprehensive treatment of oligometastases (SABR-COMET): extended long-term outcomes. *J Rad Oncol Biol Phys*. 2022;114:611-616.
30. Weickhardt AJ, Scheier B, Burke JM, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. *J Thorac Oncol*. 2012;7:1807-1814.
31. Chun SG, Hu C, Choy H, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: A Secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial. *J Clin Oncol*. 2017;35:56-62.
32. Scott JG, Sedor G, Ellsworth P, et al. Pan-cancer prediction of radiotherapy benefit using genomic-adjusted radiation dose (GARD): A cohort-based pooled analysis. *Lancet Oncol*. 2021;22:1221-1229.

17

CHEMOTHERAPY FOR METASTATIC NON-SMALL CELL LUNG CANCER

Joan H. Schiller,[1] **Myung-Ju Ahn,**[2] **Keunchil Park,**[2] **and Suresh Ramalingam**[3] | [1]Inova Schar Cancer Institute, Falls Church, USA; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, South Korea; [3]Winship Cancer Institute, Emory University, Atlanta, USA

The history of chemotherapy for advanced, unresectable non-small cell lung cancer (NSCLC) has been a tortuous one. With the advent of systemic chemotherapy for successfully treating leukemia, Hodgkin's disease, and testicular cancer, researchers started examining the role of chemotherapy for treating metastatic lung cancer. SCLC turned out to be a subtype of lung cancer that is exquisitely sensitive to systemic chemotherapy. whereas NSCLC is not as responsive.

FIRST-LINE CHEMOTHERAPY

Chemotherapy vs No Chemotherapy

In the 1970s and early 1980s, available chemotherapy included alkylating agents (e.g., mitomycin, cyclophosphamide, carmustine), vinca alkaloids (e.g., vinblastine, vincristine), and antimetabolites (e.g., fluorouracil, methotrexate). Early researchers conducted randomized trials of supportive care vs alkylating agents[1,2] or vs. vinca alkaloids + etoposide.[3] Primary end points generally included response rates, overall survival (OS), and survival of responders. All these studies had different eligibility criteria, small sample sizes, and different end points. Most of these studies, however, were disappointingly negative. In fact, these results even raised the question of whether patients with advanced NSCLC should be offered chemotherapy at all.[4,5]

Because of its use of drugs which were active in other malignancies (cisplatin), perhaps the trial that is the most widely accepted to support the use of chemotherapy was a phase III Canadian trial. Two hundred and fifty-one patients were randomized to best supportive care (BSC) or 1 of 2 chemotherapy regimens: vindesine + cisplatin (VP) or cyclophosphamide + doxorubicin + and cisplatin (CAP).[6] Patients had a median survival of 32.6 weeks when treated with VP, 24.7 weeks with CAP, and 17 weeks with BSC (Figure 1). All the comparisons were statistically significant (chemotherapy vs BSC, $P = .02$; VP vs. BSC, $P = .01$; CAP vs BSC, $P = .05$). As expected, toxicity

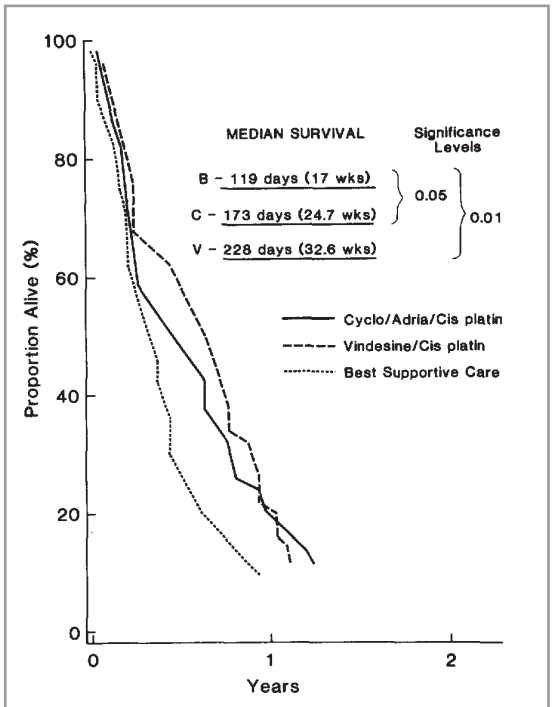


Figure 1. Phase III Canadian trial: Best Supportive Care for Either VP or CAP therapy. BSC, best supportive care; CAP, cyclophosphamide + doxorubicin + cisplatin; VP, vindesine + cisplatin. Reprinted with permission from Rapp E, et al.[6]

on the chemotherapy arms was significant, with leukopenia of a severe or greater degree, occurring in 37.8% (CAP) and 40.0% (VP), and severe vomiting in 12.2% (CAP). Despite the adverse side effects seen with chemotherapy, a cost-benefit analysis supported the use of chemotherapy in this trial.[7]

Two meta-analyses involving different methodologies found a benefit to chemotherapy over BSC, despite the heterogeneity between the trials. This heterogeneity included different eligibility criteria (stage IIIB vs IV; presence of brain metastases, previous chest radiotherapy) and different chemotherapy regimens. One meta-analysis involving 7 studies with more than 700 patients showed lower mortality during the first 6 months of chemotherapy.[8] Another meta-analysis looked at 8 randomized trials involving 712 patients randomized to chemotherapy vs BSC and found a greater median survival from 3.9 months for BSC to 6.7 for chemotherapy.[9]

In 1995, the Non-small Cell Lung Cancer Collaborative Group published a meta-analysis on individual patients from 52 randomized clinical trials involving chemotherapy and supportive care, radiation, or surgery.[10] Data were available from 11 trials (1,190 patients), which compared supportive care vs supportive care plus chemotherapy in patients with advanced disease (Figure 2). Two of the 11 trials used long-term alkylating agents, and 1 used etoposide as a single agent. The remaining 8 trials (778 patients) used cisplatin-based chemotherapy, and 7 of these trials used a combination of cisplatin and vinca alkaloids or etoposide. The cisplatin-based trials showed a benefit of chemotherapy with a reduced risk of death of 27%, with a hazard ratio of 0.73 ($P < .0001$), and an absolute improvement in survival of 10% (5% to 15%) at 1 year. The median survival, however, improved by only 1.5 months. Because the number of trials involving alkylating agents or etopside or "other" regimens was relatively small, no conclusion could be made in this meta-analysis about which drugs provided the most benefit, although there was a non-significant trend showing a detriment with alkylating agents.

First-Generation Chemotherapy Regimens vs First-Generation and Second-Generation Chemotherapy Regimens

Having established that chemotherapy could improve survival, the race was on to determine which regimens were best. Some studies compared different alkylating agents with each other. For example, a study by the Eastern Oncology Cooperative Group (ECOG) randomized 486 patients with metastatic NSCLC to 1 of the 4 most-active chemotherapy regimens at the time: cyclophosphamide + doxorubicin + methotrexate+procarbazine (CAMP); mitomycin + vinblastine+cisplatin (MVP); etoposide + cisplatin (VP-P); or vindesine + cisplatin (VDA-P). Although the response rate for

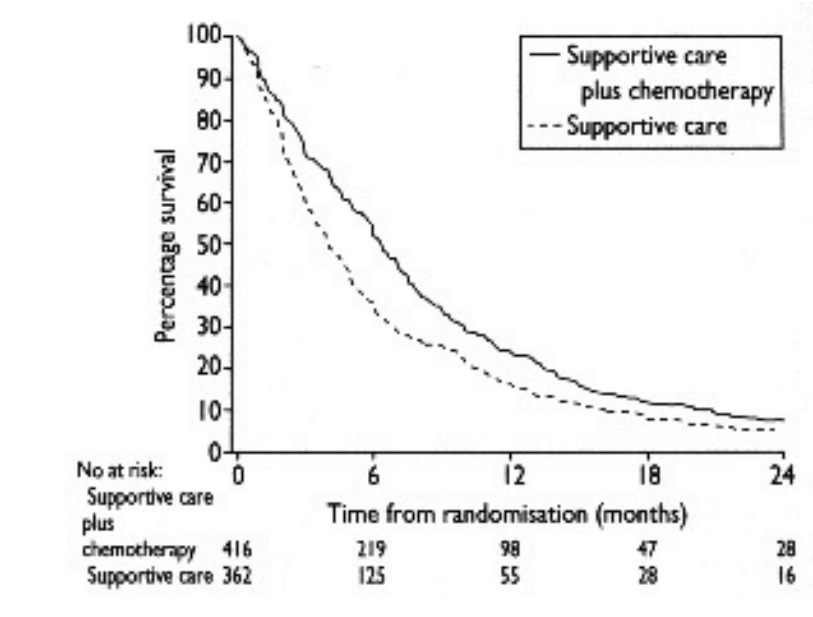


Figure 2. Meta-analysis by the Non-small Cell Lung Cancer Collaborative Group. Data from 11 trials comparing supportive care vs supportive care plus chemotherapy in patients with advanced disease. Reprinted with permission from the Non-small Cell Lung Cancer Collaborative Group.[10]

MVP was significantly higher (31%) than CAMP (17%), VP-P (20%), or VDA-P (25%), there was no impact on median OS (24.5 weeks). In addition, toxicity was significant with 20 treatment-related deaths.[11]

A number of newer drugs became available in the late 1980s and 1990s, including vinorelbine, ifosfamide, interferon, gallium nitrate, amonafide, teniposide, echinomycin, and trimetrexate.[12] In 1986, ECOG reviewed the results of 893 patients with NSCLC who were treated with 7 different phase-III combination chemotherapies between December 1979 and June 1983.[13] The overall median survival was 23.5 weeks, with no significant differences between treatments. Because the etoposide-platinum combination had the highest proportion of 1-year survivors (25%), it was chosen as ECOG's standard regimen for future trials.

Cisplatin

Because cisplatin looked like an active drug—albeit with unique, potentially severe toxicities—a number of randomized studies compared cisplatin-based regimens to supportive care or to regimens containing alkylating agents. These studies included cisplatin + vindesine,[14] cisplatin + vinblastine,[15] cisplatin + etoposide,[14] or cisplatin + mitomycin with or without other alkylating agents.[11,16] Cisplatin regimens alternating with alkylating agent-based regimens[17] or high-dose cisplatin regimens (120 mg/m2)[18] yielded slightly greater response rates and survival, but at the cost of significantly more toxicity. However, because of the small sample sizes, the results of most of the studies were not statistically significant.[2,7,15,17,18]

Cisplatin vs Carboplatin

With increasing evidence that platinum-based chemotherapy regimens provided only modest survival benefit for patients with advanced NSCLC, efforts to improve the safety profile by introducing carboplatin instead of cisplatin were undertaken. Carboplatin-based regimens were associated with a lower incidence of non-hematologic toxicities relative to cisplatin. In addition, the duration of infusion was also shorter for carboplatin, which eased administration in the outpatient setting.

Third-Generation Drugs

Other cytotoxic drugs were forthcoming, including gemcitabine, paclitaxel, and docetaxel, sometimes known as "third-generation" drugs. Initially, concerns about hypersensitivity reactions to the taxanes prompted studies looking at the duration of infusion and appropriate prophylaxis. These studies concluded that survival was comparable whether paclitaxel is given by short or prolonged infusion, although the toxicity profiles differ. Greater myelosuppression was seen after a 24-hour infusion of paclitaxel, whereas a higher incidence of neurotoxicity and arthralgia/myalgia was seen with the 1-hour infusion.[19]

Multiple randomized studies compared the efficacy of cisplatin-based regimens to carboplatin-based regimens. A study by the European Organization for Research and Treatment of Cancer compared the regimen of cisplatin + etoposide to carboplatin + etoposide[20] for patients with advanced NSCLC. Although the response rate was higher with cisplatin-based therapy (27% vs 16%, $P = .07$), the toxicity profile was less favorable. There was no difference in OS. Another study compared the combination of cisplatin + paclitaxel with the combination of carboplatin + paclitaxel.[21] This study enrolled 618 patients with advanced-stage NSCLC. The response rate was 25% for the carboplatin arm and 28% for the cisplatin arm ($P = .45$), and the median survival was 8.5 months for the carboplatin arm and 9.8 months for the cisplatin arm. There was a modest numerical advantage in the 1-year survival rate favoring cisplatin (38% vs 33%), though the difference was not statistically significant. Nausea, vomiting, and nephrotoxicity were more common with cisplatin-based chemotherapy. This study concluded that cisplatin-based chemotherapy may be associated with a modest increment in efficacy over carboplatin-based therapy.

However, other contemporary studies done during this period

failed to support a clear superiority for cisplatin-based therapy.[22,23] In 2004, Hotta and colleagues published a meta-analysis of randomized trials that compared cisplatin to carboplatin in patients with advanced NSCLC.[24] This analysis included 8 trials with a combined 2948 patients (Figure 3). Despite a higher response rate with cisplatin-based chemotherapy, there was no improvement in OS. There was a trend toward a slight improvement in survival when cisplatin was combined with a third-generation chemotherapy agent, and there was no difference in treatment-related mortality.

In 2007, Ardizzoni and colleagues reported a meta-analysis addressing the same issue using individual patient data.[25] This analysis included 9 clinical trials with a combined 2,968 patients. Similar to prior reports, the response rate was higher with cisplatin (30% vs 24%). However, there was no statistically significant difference in OS between the 2 regimens. Cisplatin-based regimens were associated with a higher incidence of nausea, vomiting, and nephrotoxicity, whereas carboplatin-based regimens were associated with higher thrombocytopenia.

The relatively modest improvement in response rate associated with cisplatin-based chemotherapy over carboplatin-based regimens was affirmed by multiple reports. However, there was no clear improvement in OS. Because the goal of therapy for advanced

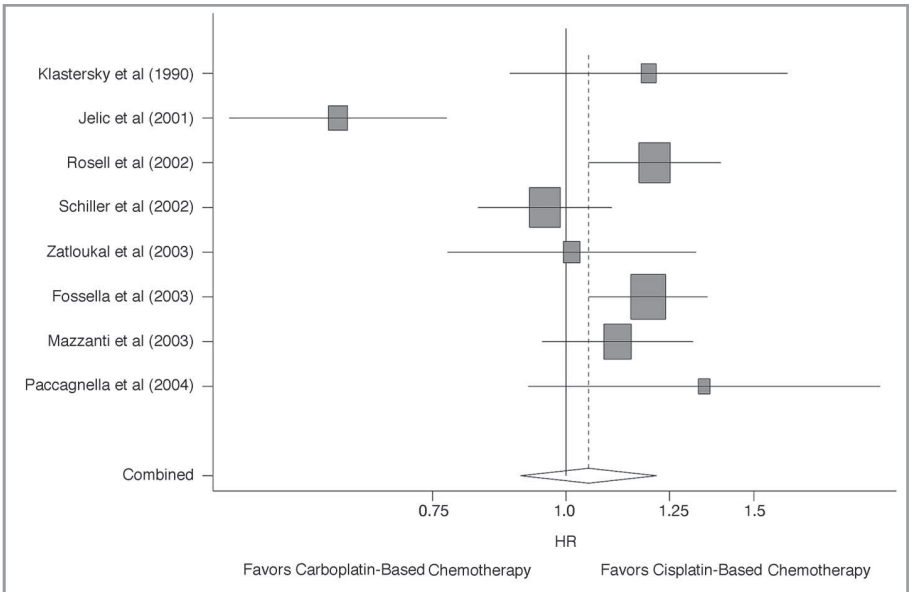


Figure 3. Meta-analysis of Cisplatin-Based vs Carboplatin-Based Chemotherapy for Advanced NSCLC. HR, hazard ratio. Reprinted with permission from Hotta K, et al.[24]

NSCLC is to provide palliation, the favorable therapeutic index and the ease of administration made carboplatin-based regimens the common choice in the United States. In Europe, cisplatin-based regimens were used preferentially by oncologists in the pre-immunotherapy era. Now, it is appropriate to consider cisplatin-based therapy for younger patients with good renal function, as well as the use of appropriate prophylactic antiemetic therapy.

Platinum-Containing Third-Generation Regimens vs Other Platinum-Containing Third-Generation Regimens

In 2002, ECOG reported the results of a randomized study that evaluated whether 1 of 3 chemotherapy regimens containing third-generation drugs was better than cisplatin + paclitaxel in advanced NSCLC (Figure 4).[21] The 4-arm study involved more than 1,200 patients who were randomized to receive 1 of 3 platinum-based combination regimens containing third-generation drugs (gemcitabine + cisplatin, docetaxel + cisplatin, and paclitaxel + carboplatin). The reference arm was cisplatin + paclitaxel. For this arm, the median survival was 7.8 months, the 1-year survival

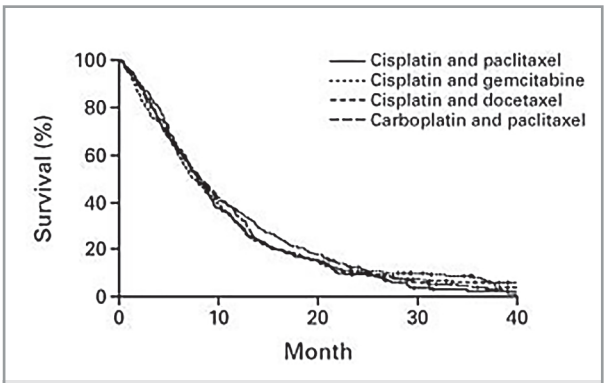


Figure 4. OS for 4 Cisplatin or Carboplatin Treatment Arms. Reprinted with permission from Schiller JH, et al.[23]

was 31%, and the 2-year survival was 10%. There were no statistically significant differences in the response rate and survival of patients between cisplatin + paclitaxel and any of the 3 experimental arms. Patients with a performance status of 2 (PS2) had a significantly lower rate of survival than those with a PS0 or PS1. Carboplatin + paclitaxel had a lower rate of toxic effects than the other regimens and cisplatin + gemcitabine had the highest. Based on these data, ECOG chose carboplatin + paclitaxel as its reference arm for future studies.

Pemetrexed, an inhibitor of thymidylate synthase and other folate-dependent enzymes, was approved in the United States for non-squamous cell NSCLC based on a phase III non-inferiority trial of more than 1,700 patients who were chemotherapy-naïve. This trial compared pemetrexed + cisplatin and gemcitabine + cisplatin (Figure 5).[26] The median OS for cisplatin + pemetrexed was noninferior to cisplatin + gemcitabine (both 10.3 months) with an improved toxicity profile in the pemetrexed arm. However, in a prespecified subset analysis, the OS was statistically better for cisplatin + pemetrexed (12.6 months) than cisplatin + gemcitabine (10.9 months) for patients with adenocarcinoma. The OS was also better for cisplatin + pemetrexed (10.4 months) than cisplatin + gemcitabine (6.7 months) for patients with large-cell carcinoma histology. Conversely, patients with squamous cell histology

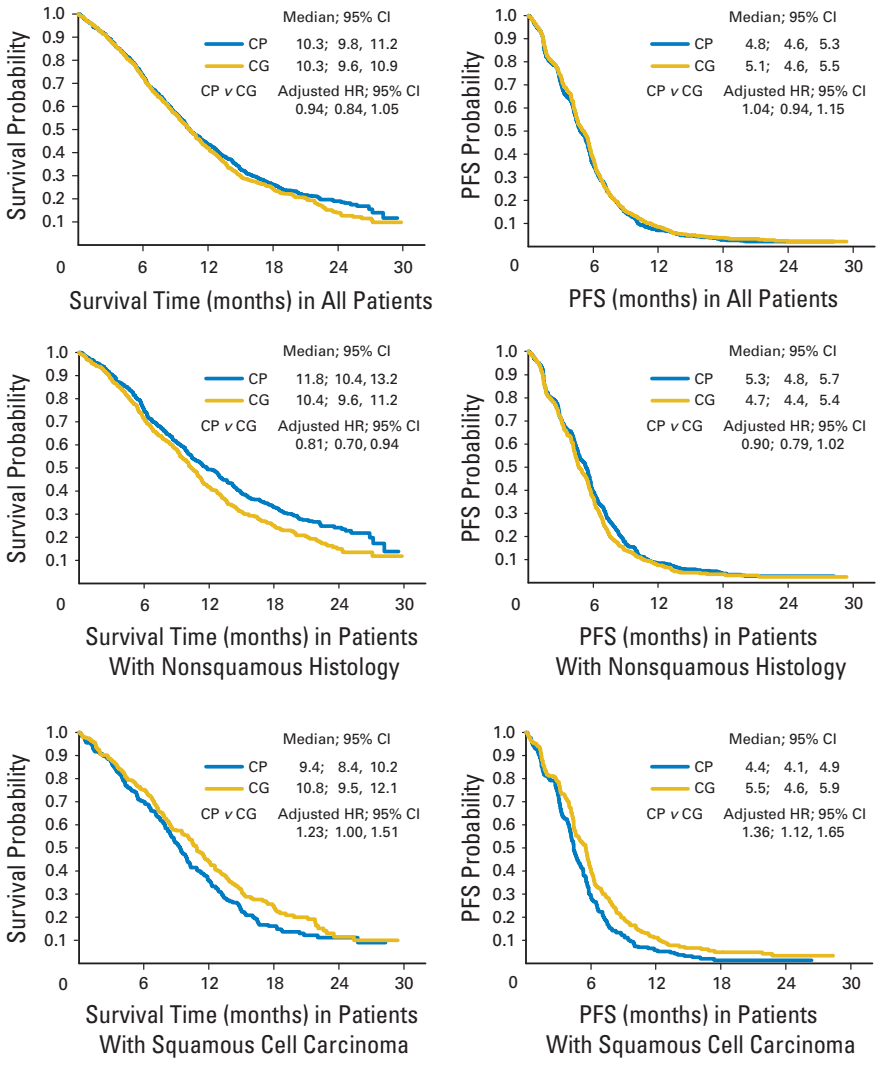


Figure 5. Kaplan-Meier Overall Survival and PFS Curves for the Entire Population, Patients with Non-squamous Histology (Adenocarcinoma Plus Large Cell), and Patients with Squamous Histology. CG, cisplatin + gemcitabine; CP, cisplatin + pemetrexed; HR, hazard ratio; PFS, progression-free survival. Reprinted with permission from Scagliotti GV, et al.[26]

experienced significantly better survival with cisplatin + gemcitabine (10.8 months) than cisplatin + pemetrexed (9.4 months).[26]

Platinum vs Non-Platinum Regimens

The availability of third-generation chemotherapy agents that had a more favorable tolerability profile relative to older cytotoxic drugs prompted the evaluation of non-platinum combination regimens for advanced NSCLC. A large multicenter trial led by Georgoulias and colleagues compared the combination of docetaxel with either cisplatin or gemcitabine for advanced NSCLC.[27] For the 441 patients enrolled in the study, there was no difference in the response rate

(32% platinum and 31% non-platinum). There were also no differences in the time to progression, OS, or 1-year survival between the 2 regimens. In the United States, Treat and colleagues conducted a randomized 3-arm trial to compare gemcitabine + carboplatin, gemcitabine + paclitaxel, and carboplatin + paclitaxel.[28] The study enrolled 1,135 patients with advanced-stage NSCLC. Among the patients, median survival was 7.9 months with gemcitabine + carboplatin vs 8.5 months for gemcitabine + paclitaxel. The response rate for the 2 regimens were 25% for gemcitabine + carboplatin and 32% for gemcitabine + paclitaxel. In addition, the efficacy of the carboplatin + paclitaxel regimen was similar to the gemcitabine-based regimens. There was no difference in OS between the 3 regimens.

Another definitive trial to address this question randomized patients with advanced NSCLC to either carboplatin + paclitaxel or gemcitabine + paclitaxel.[29] Among these patients, the median survival was 10.4 months with carboplatin + paclitaxel vs 9.8 months with gemcitabine + paclitaxel ($P = .32$). The 1-year survival rates were 41% for both regimens. The response rate was better at 35% with gemcitabine + paclitaxel and 28% with carboplatin + paclitaxel, but this difference did not reach statistical significance. Notably, the mean total cost was not different between the 2 regimens.

The active interest in this clinical question is supported by more than 35 trials that aimed to identify the optimal role of non-platinum doublets in advanced NSCLC. A meta-analysis by D'Addario and colleagues analyzed phase II and III studies that compared platinum-based chemotherapy with the same regimen without platinum or with platinum replaced by a non-platinum agent (Figure 6).[30] Nearly 7,600 patients enrolled to 37 trials were included. In this meta-analysis, there was a higher odds ratio (OR) for tumor response with platinum-based chemotherapy. In addition, the 1-year survival was 34% with the platinum-based regimen vs 29% with non-platinum regimens, and there was no difference in OS. The toxicity profile was predictable with more hematologic toxicity, nephrotoxicity, nausea, and emesis with platinum-based regimens. Overall, the study concluded that there was no advantage to using non-platinum regimens in advanced NSCLC.

These data support the use of non-platinum combinations for patients who are not candidates for platinum-based chemotherapy. However, in the era of chemotherapy-immunotherapy combination regimens, all the key studies have used platinum-based chemotherapy as the backbone. Hence, the

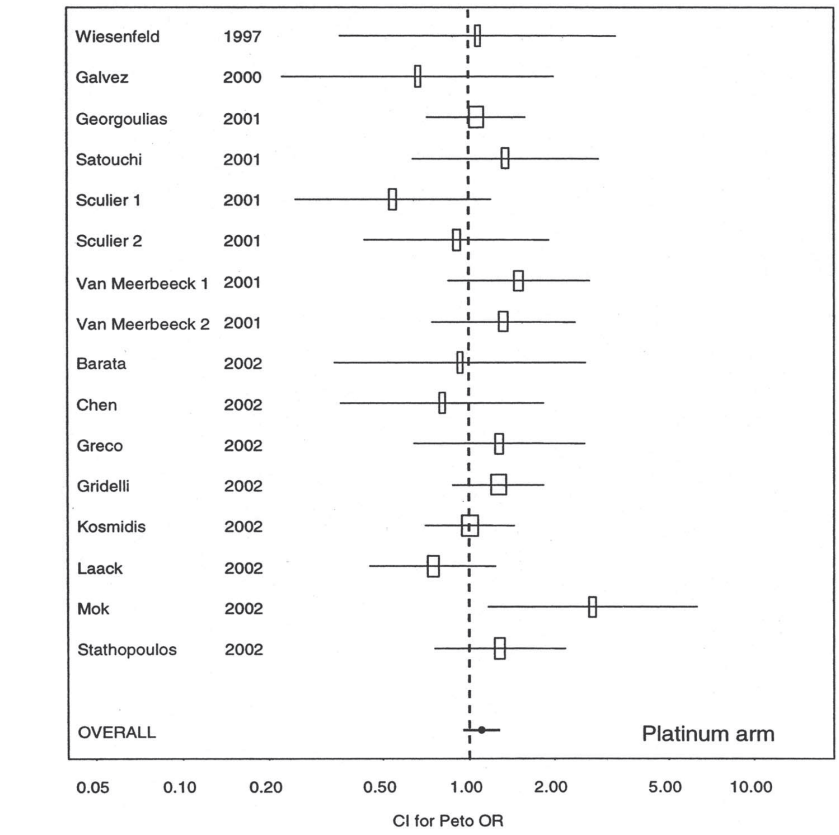


Figure 6. Comparison of the 1-Year Survival Rate Between Platinum Combinations vs Non-Platinum Regimens in Trials Using Combinations Containing Third-Generation Agents in the Non-Platinum Arm (N = 3307 patients). OR, odds ratio. Reprinted with permission from D'Addario G et al.[30]

role of non-platinum regimens in NSCLC is still relatively limited.

Two-Drug vs Triplet Combination Regimens

As noted above, comparison of several 2-drug combination regimens for advanced NSCLC yielded similar results. To extend the benefit of 2-drug regimens, several trials were conducted to study the potential use of adding a third cytotoxic agent to various regimens. A 3-arm Italian study by Comella and colleagues randomized patients to cisplatin + vinorelbine + gemcitabine, cisplatin + vinorelbine, or cisplatin + gemcitabine.[31] The median survival for the 3 groups were 51 weeks (cisplatin + vinorelbine + gemcitabine), 42 weeks (cisplatin + vinorelbine), and 35 weeks (cisplatin + gemcitabine). The response rates were 47% (cisplatin + vinorelbine + gemcitabine), 30% (cisplatin + vinorelbine), and 25% (cisplatin + gemcitabine). The authors concluded that the triplet regimen was associated with improved survival. However, conflicting results were noted in another study reported by Alberola and colleagues.[32] In their study, patients were randomized to cisplatin + gemcitabine, cisplatin + gemcitabine + vinorelbine, or gemcitabine + vinorelbine for 3 cycles followed by vinorelbine + ifosfamide for 3 cycles. The response rate was similar between the triplet (41%) and the cisplatin + gemcitabine (42%) regimens. There was no difference in median survival or time to progression. The incidence of grades 3/4 neutropenia was 57% with the 3-drug regimen vs 32% with gemcitabine + cisplatin. The incidence of fever with neutropenia was almost 4-fold higher for the 3-drug combination. Based on these results, the authors concluded that 2-drug regimens should continue as the standard of care for advanced NSCLC.

These observations were affirmed in a meta-analysis reported by Delbado and colleagues (Figure 7).[33] The meta-analysis included randomized clinical trials that added a chemotherapy to either a single-agent or 2-drug regimen for advanced NSCLC. Sixty-five trials were eligible for this analysis. Although 2-drug regimens were better than single-agent therapy with a survival hazard ratio of 0.83, triplet regimens were not better than 2-drug regimens. The response rate was more favorable with the triplet regimen with an absolute improvement of 8%. Also, the 1-year survival rate (OR 1.01, $P = .88$) and OS were not improved by the addition of a third drug. Grade 3/4 toxicity was more frequent with triplet regimens with an OR of 1.4 to 2.9, with the exception of neurologic, renal, auditory, and gastrointestinal toxic effects. The authors also noted that triplet regimens frequently lowered doses to improve tolerability, which appeared to adversely impact the response rate, but not OS.

From these results, it can be concluded that triplet combinations of cytotoxic agents are not recommended for treating advanced NSCLC. Two-drug combinations are better suited as a backbone for adding other novel agents to improve the efficacy of systemic chemotherapy for advanced NSCLC.

Optimal Number of Cycles of Chemotherapy

Patients with stage IV NSCLC are not curable, and accompanying adverse effects after cytotoxic chemotherapy are inevitable and significantly impact quality of life (QOL). Thus, it is of utmost importance to keep the favorable risk-benefit ratio with systemic chemotherapy.

The 1997 American Society of Clinical Oncology (ASCO) clinical practice guideline[34] states that, without compelling data, chemotherapy should be administered for no more than 8 cycles in patients with stage IV NSCLC. Despite this ASCO recommendation, up until the early 2000s, there was a general consensus that first-line palliative chemotherapy should continue for at least 6 courses, throughout disease progression, or until significant toxicities prohibit further therapy. Since then, there have been several randomized phase III trials[35-37] to address the question of optimal duration of chemotherapy. In the first randomized trial,[35] patients with stage IIIB or IV NSCLC were randomized to receive either 3 or 6 courses of MVP every 21 days. The study did not meet the primary end point

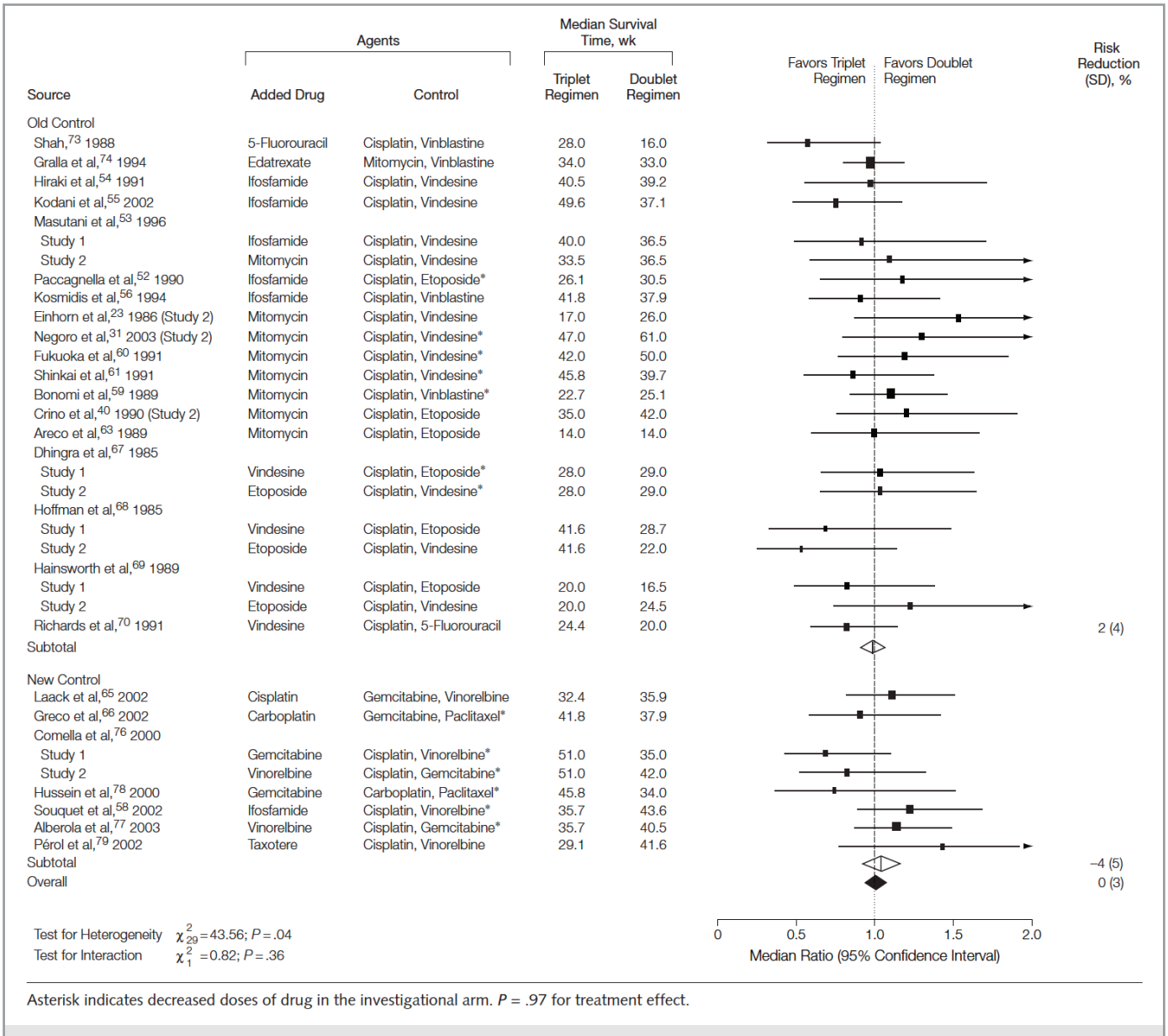


Figure 7. Median Ratio for Survival with Triplet vs 2-Drug Regimens. Reprinted with permission from Delbaldo C et al.[33]

of median OS; 6 vs 7 months, respectively, and 1-year survival 22% vs 25% ($P = .2$) showing no evidence for additional clinical benefit by continuing chemotherapy beyond 3 courses, challenging the orthodoxy of 6 courses or more. In another randomized trial,[36] patients with stage IIIB/IV NSCLC were randomized to 4 cycles of carboplatin + paclitaxel or continuous treatment with carboplatin + paclitaxel until progression. The median survival time and 1-year survival rates were 6.6 months and 28%, and 8.5 months and 34%, respectively (log-rank $P = .63$) showing no overall benefit in survival, response rates, or QOL to continuing treatment with carboplatin + paclitaxel beyond 4 cycles in advanced NSCLC.

Another phase III trial[37] involved Asian patients with stages IIIB to IV NSCLC who had not progressed after 2 cycles of chemotherapy. These patients were randomly assigned to receive either 4 more (6 total) or 2 more (4 total) cycles of a third-generation, platinum-doublet treatment. In this study, the 1-year survival rates were 59.0% for 6 cycles

and 62.4% for 4 cycles. Also, the study confirmed the noninferiority in OS with 4 cycles vs 6 cycles of the first-line chemotherapy for advanced NSCLC. There was also a favorable QoL in shorter-treatment group with reduced risk of any cumulative toxicity that may negatively affect an individual patient's QOL and outcome.

Unfortunately, most of the studies were underpowered and inconclusive. A subsequent meta-analysis of all randomized trials compared 6 vs fewer planned cycles of first-line platinum-based chemotherapy for patients with advanced NSCLC. This meta-analysis showed that the longer duration of first-line platinum-based chemotherapy improved progression-free survival (PFS) but not OS with increased hematologic toxicity compared to shorter duration (Figure 8).[38]

The 2015 ASCO guideline[39] states that first-line cytotoxic chemotherapy should be stopped at disease progression or after 4 cycles in patients with nonresponsive stable disease. However, if a patient is tolerating therapy well, consideration can be given to continue to 6 cycles.

Recently, the first-line treatment paradigm of advanced NSCLC shifted with the introduction of targeted agents and immune checkpoint inhibitors.[40 (40NCCN 2022)] When the patient harbors a driver alteration, the appropriate target therapy is recommended as a single agent and usually continued until disease progression or toxicity without a predefined period of first-line therapy. When the patient does not have any driver alterations, a checkpoint inhibitor with or without chemotherapy is recommended, depending on the programmed death-ligand 1 expression, unless there is a contraindication to immunotherapy. (See Chapters 19 and 20, respectively.)

Maintenance Chemotherapy

With first-line platinum-based chemotherapy, the median PFS is only 4 to 5 months, and the disease comes back, eventually leading to death. One strategy to improve this prognosis includes the so-called "maintenance" therapy. Maintenance therapy is defined as the systemic therapy administered to patients who have a tumor response or stable disease without progression after 4 to 6 cycles of first-line chemotherapy (usually platinum-based) to prolong the time-to-disease progression with minimal toxicities. Because of the risk of cumulative toxicities, combination chemotherapy is not generally

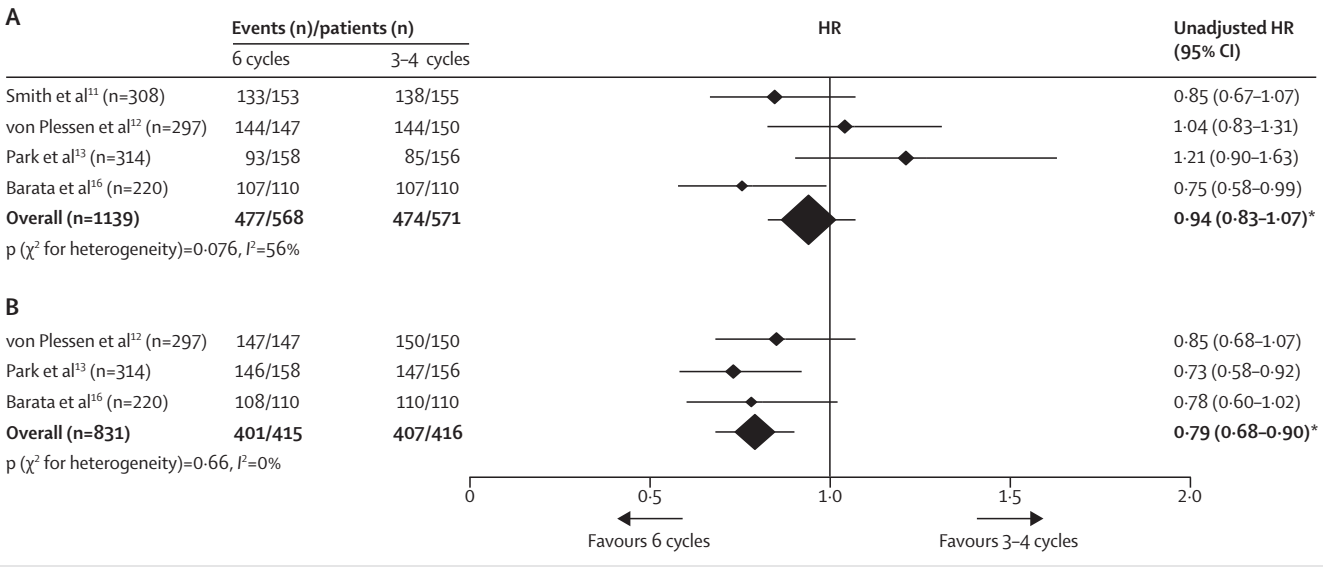


Figure 8. 6 cycles vs 3-4 cycles of chemotherapy: OS (A) and PFS (B) by Trial. HR, hazard ratio; OS, overall survival; PFS, progression-free survival. Reprinted with permission from A Rossi P.[38]

used, and using a single agent as maintenance has been widely investigated. The introduction of new agents with better tolerability (e.g., pemetrexed, targeted agents, immune checkpoint inhibitors) provided an excellent opportunity to develop this strategy. This strategy replaced the traditional approach of first-line chemotherapy followed by treatment holidays until progression, at which time second-line chemotherapy is offered. There are 2 types of maintenance therapy: "continuation" maintenance therapy involves the same agent(s) administered as in the first-line regimen, and "switch" maintenance therapy involves 1 or more alternative non-cross-resistant agents that were not contained in the first-line regimen.

For patients who do not experience disease progression after first-line chemotherapy, optimal timing and duration of second-line therapy remain unclear. A phase III randomized trial included patients with advanced/metastatic NSCLC who completed four 21-day cycles of gemcitabine + carboplatin without disease progression. These patients were randomly assigned to either an immediate docetaxel group (every 21 days with a maximum of 6 cycles) or a delayed docetaxel group at disease progression. The study showed a significantly greater PFS (5.7 months immediate vs 2.7 months delayed; $P = .0001$) and a non-statistically significant increase in OS (12.3 months immediate vs 9.7 months delayed; $P = .0853$) when docetaxel was administered immediately after first-line GC, without increasing toxicity or decreasing QOL. However, a closer look revealed that there was a major difference in the number of patients actually receiving docetaxel in each arm. In the immediate arm, most patients (145/153; 94.8%) received docetaxel, whereas in the delayed arm, a large number of patients (58/156; 37.2%) never received docetaxel. Notably, the median OS for patients in the delayed arm who actually received docetaxel (n = 98) was 12.5 months (95% CI, 9.6-14.6 months), which was similar to the OS for the safety populations in the immediate docetaxel arm (12.5 months; 95% CI, 10.6-15.8 months). These data support the role of maintenance therapy using non-cross-resistant agents following first-line chemotherapy.[41] Many trials of maintenance therapy with cytotoxic agents have been conducted. They have consistently shown improved PFS with mixed results for OS. Randomized maintenance trials with a single cytotoxic agent are summarized in Table 1.[42]

Cytotoxic agents studied as either switch or continuation maintenance therapy include gemcitabine, docetaxel, and vinorelbine. These therapies yielded mixed results of efficacy and are not routinely recommended as a maintenance.[43] The JMEN trial was a randomized phase III trial for patients with advanced NSCLC and

Table 1. Maintenance Trials with Single Chemotherapeutic Agents

Trial	Number randomized	First line agents	Maintenance	Survival in months (Hazard ratio; P-value)
Westeel et al.	181	MIC	Vinorelbine	OS 12.3 vs 12.3 (HR=1.08; P=0.48)
Brodowitz et al.	206	GC	Gemcitabine	OS 13 vs 11 (HR=n.r.; P=0.195)
Perol et al.	464	GC	Gemcitabine	PFS 3.7 vs 2.1 (HR=0.51; P<0.001)
Belani et al.	255	GCb	Gemcitabine	OS 8 vs 9.3 (HR=0.97; P=0.84)
Fidias et al.	307	GCb	Docetaxel	OS 12.3 vs 9.7 (HR=n.r.; P=0.0853)
Ciuleanu et al.	663	Cb/C G/Pac/D	Pemetrexed	OS 13.4 vs 10.6 (HR=0.79; P=0.012)
Paz-Ares et al.	539	PemC	Pemetrexed	PFS 3.9 vs 2.6 (HR=0.64; P=0.002)

Abbreviations: C, cisplatin; Cb, carboplatin; D, docetaxel; G, gemcitabine; HR, hazard ratio; I, ifosfamide; M, mitomycin; OS, overall survival; Pac, paclitaxel; Pem, pemetrexed; PFS, progression-free survival, V, vinorelbin; n.r., not reported. Reprinted with permission from Schmid-Bindert G.[42]

non-squamous pathology who had not progressed on 4 cycles of a platinum-based, non-pemetrexed-containing chemotherapy.[44] Patients were randomized to immediately start taking pemetrexed vs placebo until disease progression or unacceptable toxicity. Compared to placebo, switch maintenance therapy with pemetrexed was well tolerated and improved PFS [4.3 months switch (95% CI, 4.1-4.7) vs 2.6 months placebo (95% CI, 1.7-2.8); hazard ratio (HR), 0.50; 95% CI, 0.42-0.61; $P < .0001$] and OS [13.4 months switch (95% CI, 11.9-15.9) vs 10.6 months placebo (8.7-12.0); HR 0.79, 0.65-0.95; $P = .012$]. In the double-blind randomized phase III PARAMOUNT trial, patients with advanced non-squamous NSCLC who did not progress after completing 4 cycles of induction pemetrexed + cisplatin were randomly assigned (2:1 ratio) to receive either placebo or maintenance therapy with pemetrexed plus BSC until disease progression.[45] The study demonstrated that pemetrexed continuation maintenance therapy reduced the risk of disease progression when compared to placebo (median PFS, 4.1 months pemetrexed vs 2.8 months placebo; HR, 0.62; $P < .001$) and also the risk of death (median OS, 13.9 months pemetrexed vs 11.0 months placebo; HR, 0.78; $P = .0195$). Based on these results, the ASCO 2015 guidelines recommended pemetrexed continuation maintenance for patients with stable disease or response after 4 cycles of a first-line pemetrexed-containing regimen.[39] If the initial regimen does not contain pemetrexed, an alternative chemotherapy (switch) may be used, or a break from chemotherapy may be recommended until disease progression.

Several meta-analyses have suggested that OS improvement was more marked with switch rather than with continuation maintenance. However, the interaction test suggested the magnitude of benefit from the 2 maintenance strategies was similar. In general, toxicity was greater with maintenance therapy.[46]

Certainly, not all patients need or benefit from maintenance therapy. There is a controversy on patient selection. Also, some factors predicting benefit from maintenance chemotherapy include the degree of response to first-line therapy, performance status, the likelihood of receiving further therapy at the time of progression, and tumor histology and molecular characteristics.[47]

In summary, maintenance chemotherapy has shown PFS benefit without QOL deterioration and sometimes OS benefit as well. Nevertheless, given the cost, toxicity, socioeconomic burden, and patient preference, the decision about maintenance therapy must be individualized. Some patients may be safely observed after the initial 4 to 6 cycles of induction chemotherapy. However, some patients recur with devastating complications and may miss their window for further therapy. The entire practice of maintenance therapy may change greatly in the near future if combination chemotherapy with immunotherapy in the first-line setting is shown to be better than chemotherapy alone.[48,49]

The combination maintenance trials of AVAPERL, PointBreak, PRONOUNCE, and ECOG5508 did not show improved OS by combining pemetrexed + bevacizumab as maintenance (Table 2).[43]

SECOND-LINE CHEMOTHERAPY AND BEYOND

Patients treated with first-line chemotherapy for advanced NSCLC eventually experience progression. Despite many small phase II trials testing various agents, such as the vinca alkaloid, taxanes, and gemcitabine, the role of second-line chemotherapy was uncertain until 2 randomized phase III trials were published in 2000 (Table 3).[50,51] The first trial compared 100 mg/m^2 or 75 mg/m^2 docetaxel to BSC for patients with advanced NSCLC who were previously treated with platinum-based chemotherapy.[50] The primary end point was OS. The median OS was significantly improved for patients in the docetaxel arm (7.0 months docetaxel vs 4.6 months BSC; log-rank test, $P = .047$). The difference was more significant for the docetaxel 75 mg/m^2 group (7.5 months) vs the 100 mg/m2 group (4.6 months) (log-rank test, $P = .010$). The 1-year survival rate was also significantly different for the 75 mg/m^2 group (37%) vs the 100 mg/m^2 group (11%; $P = .003$).

Table 2. Combination Maintenance Trials

Trial	Patients, No.	Induction	Maintenance	PFS, months	HR	P value	OS, months	HR	P value
AVAPERL	253	Cis + Pem + Bev	Bev + Pem	7.4	0.57	<.001	17.1	0.87	.29
			Bev	3.7			13.2		
PointBreak	939	Carb + Pem + Bev	Pem + Bev	6.0	0.83	.012	12.6	1.00	.949
		Carb + Pac + Bev	Bev	5.6			13.4		
PRONOUNCE	361	Carb + Pem	Pem	4.4	1.06	.610	10.5	1.07	.616
		Carb + Pac + Bev	Bev	5.5			11.7		
ECOG 55088	1561	Carb + Pac + Bev	Pem	4.2	0.85	.06	15.9	0.86	.12
			Bev	5.1			14.4		
			Bev + Pem	7.5	0.67	<.001	16.4	0.90	.28

Abbrevations: Bev, bevacizumab; Carb, carboplatin; HR, hazard ratio; OS, overall survival; Pem, pemetrexed; PFS, progression-free survival. Modified from Gentzler RD et al,[43] reprinted with permission.

Table 3. Randomized Phase III Trials of Second-Line Chemotherapy in NSCLC

	Docetaxel vs BSC	Docetaxel vs vinorelbine or ifosfamide	Pemetrexed vs Docetaxel	Ramucirumab + docetaxel vs placebo + docetaxel
	D (75) D (100) BSC	D (75) D (100) V/I	Pem D	R + D P + D
Patients, No.	55 49 100	125 125 123	283 288	628 625
Age, median	61 61 61	59 60 60	59 57	62 61
Stage IIIA/B IV	 27.3% 18.4% 19.0% 72.7% 81.6% 81.0%	 10% 14% 9% 90% 86% 91%	 74.9% 74.7%	 NA NA
Performance status 0 or 1 2	 74.56% 77.6% 75.0% 25.5% 22.4% 25.0%	 18% 17% 15%	 88.6% 87.6% 11.4% 12.4%	 67% 68% 33% 32%
Response PR SD PD NE	 7.1% 7.1% – 47.3% 37.5% – 32.7% 33.3% – 14.5% 22.9% –	 6.7% 10.8% 0.8%	 9.1% 8.8% 45.8% 46.4% 45.1% 44.8%	 22.9% 13.6% 41.1% 39% 20.4% 33% 15.6% 14.4%
Duration of response	26.1 23.9 – (wks)	9.1 7.5 5.9 (wks)	4.6 5.3 (months)	NA NA
Survival, months Median 1-year, %	 7.5 5.9 4.6 37% 19% 19%	 5.7 5.5 5.6 32% 21% 19%	 8.3 7.9 29.7% 29.7%	 10.5 9.1
Grade 3/4 hematologic toxicity Anemia Neutropenia Thrombocytopenia Febrile neutropenia Septic deaths	 5.5% 16.3% – 67.3% 58.7% – – 2.0% – 1.8% 22.4% – – 6.1% –	Grade 4 toxicities 0% 1% 2% 54% 77% 31% 2% 1% 0% 8% 12% 1%	Grade 3/4 4.2% 4.3% 5.3% 40.2% 1.9% 0.4% 1.9% 12.7%	Grade 3/4 3% 6% 49% 39% 3% 1% 16% 10%

Abbreviations: BSC, best supportive care; D, docetaxel; I, ifosfamide; NA, not applicable; NE, XX; P, placebo; PD, XX; Pem, pemetrexed; PR, XX; R, ramucirumab; SD, XX; V, vinorelbine. Modified from *Hematol Oncol Clin North Am* 2017;31(1):71-81, reprinted with permission.

Time to progression was also longer for patients treated with docetaxel (10.6 weeks) vs BSC (6.7 weeks; $P < .001$). However, 3 patients treated with docetaxel at 100 mg/m^2 dose died from toxicity-related deaths. When the docetaxel dose was reduced to 75 mg/m^2, the median cycle of chemotherapy increased from 2 to 4, and the rate of febrile neutropenia decreased from 22% to 2%.

The second trial conducted a 3-arm multicenter, open-label randomized phase III trial of docetaxel 100 mg/m^2 vs docetaxel 75 mg/m^2 vs the control arm of either vinorelbine 30 mg/m^2 or ifosfamide 2 g/m^2 in patients with stage IIIB or IV NSCLC who had progressed on platinum-based chemotherapy.[51] The overall response rates were 10.8% for docetaxel 100 mg/m^2, 6.7% for docetaxel 75 mg/m2, and 0.8% for vinorelbine/ifosfamide. Although the OS was not significantly different among the 3 arms, the 1-year survival rate was significantly prolonged for the docetaxel 75 mg/m^2 arm (32%) vs the control arm (19%; $P = .025$). The time to progression ($P = .046$) and PFS ($P = .05$) were also improved in the docetaxel arms. Although grade 4 neutropenia and febrile neutropenia were higher in the 2 docetaxel arms than the control arm, other treatment-related adverse events were similar among the 3 arms. Based on these 2 studies that showed improved OS, docetaxel was registered with the Federal Drug Administration and European Medicines Agency as a second-line treatment for advanced NSCLC.

A phase III multinational study compared docetaxel with pemetrexed as a second-line therapy for NSCLC.[52] The primary end point was non-inferiority of OS. A total of 571 patients were randomized to receive either pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2. The overall response rate was 9.1% for pemetrexed vs 8.8% for docetaxel ($P = .105$). The median survival was 8.3 months for pemetrexed vs 7.9 months for docetaxel, and the 1-year survival rate was 29.7% for pemetrexed vs 29.7% for docetaxel. These findings met the primary end point. In contrast, the docetaxel arm was associated with more grade 3 or 4 neutropenia ($P < .001$), febrile neutropenia ($P < .001$), and neutropenia with infection ($P = .0004$). Also, the use of granulocyte colony-stimulating factor was higher (13.4% for docetaxel vs 1.5% for pemetrexed; $P < .001$) and hospitalization for neutropenic fever was more frequent in the docetaxel arm (19.2% for docetaxel vs 2.6% for pemetrexed; $P = .001$). Given the lack of benefit of pemetrexed for patients with squamous histology,[53] pemetrexed was approved for patients with non-squamous histology as a second-line therapy. However, pemetrexed eventually moved forward to the first-line setting when it was combined with platinum.[54]

In 2 phase II trials, weekly docetaxel was compared to docetaxel every 3 weeks. The study found no difference in the OS or QOL between these 2 regimens.[55]

Other randomized trials looked at single-agent vs doublet therapy in the second-line setting.[56,57] Several meta-analyses reported that doublet therapy does not appear to improve survival compared to single-agent therapy.[58-61] In the REVEL trial, ramucirumab, a monoclonal antibody to vascular endothelial growth factor receptor 2 (VEGFR-2), improved OS when combined with docetaxel vs docetaxel alone in the second-line setting of NSCLC.[62] A modest but statistically significant survival benefit of 1.4 months with ramucirumab combination was observed. However, a post-hoc exploratory subgroup analysis measured OS in patients with rapidly progressing disease, defined as time to progression within 12 weeks after starting initial platinum-based treatment. This analysis showed a median OS of 9.1 months in the combination arm vs 5.8 months in the docetaxel arm, suggesting that docetaxel + ramucirumab can be used when a rapid response is needed.[63] Because the REVEL trial was not adequately powered for this subgroup analysis, the treatment differences cannot be regarded as statistically significant.

Docetaxel + ramucirumab for all histologic types has been approved by the Federal Drug Administration, and docetaxel + nintedanib for non-squamous NSCLC has been approved by European Medicines

Agency.[64] However, docetaxel still remains a standard of care as a second-line therapy.

Recently, the treatment landscape of second-line chemotherapy for NSCLC has been evolving with the introduction of immune checkpoint inhibitors. Several phase III clinical trials showed improved OS with these agents over docetaxel in the second-line setting, thus replacing docetaxel ± ramucirumab with immune checkpoint inhibitors as a second-line therapy. However, as immune checkpoint–inhibitor monotherapy or with a platinum-based doublet have moved into the front-line setting, docetaxel ± ramucirumab has once again been repositioned as a second-line or third-line therapy. Data on the efficacy of docetaxel after failure of prior immune checkpoint inhibitors are limited and should be investigated further. Excluding molecular targeted agents or immune check–point inhibitors, the role of third or more lines of therapy is very limited and needs to be explored further.

SPECIAL POPULATIONS

Chemotherapy in Older Populations

Lung cancer is predominantly a disease in older people (>65 years old). About 30% to 40% of patients with lung cancer are aged 70 years or older.[65] Although chronologic age itself is not a poor prognostic factor, higher prevalence of comorbid disease, including of the kidney, liver, heart, and bone-marrow, interferes with patient PS and is associated with greater risk of morbidity and mortality in older people.[66] Furthermore, both older patients and patients with a PS2 are underrepresented in clinical trials.[67]

Early studies of older populations looked at single-agent chemotherapy vs BSC or another single agent (Table 4). The Elderly Lung cancer Vinorelbine Italian Study (ELVIS) trial was the first randomized phase III trial that specifically focused on older patients (>70 years) to compare vinorelbine as a single-agent therapy with BSC. The trial showed significantly improved OS with chemotherapy.[68] Kudoh et al conducted a phase III trial of vinorelbine vs docetaxel as a first-line therapy, which improved PFS but not OS and was associated with higher grade 3/4 hematologic toxicities in patients treated with docetaxel.[69] In the phase III MILES trial, single-agent vinorelbine, single-agent gemcitabine, or gemcitabine + vinorelbine was compared in patients aged 70 years and older. This study did not show any significant difference in the response rate, PFS, or OS among the 3 arms.[70]

Platinum-based doublet treatments have also been compared to single agents in several

Table 4. Randomized Phase III Trials of Chemotherapy in Elderly Patients with Advanced NSCLC

Trial	Regimen	Patients, No.	OS, months	PFS, months
ELVIS	BSC Vinorelbine	78 76	21 weeks 28 weeks HR, 0.65	NR NR
WJTOG 9904	Vinorelbine Docetaxel	91 89	9.9 14.3 HR, 0.78; *P*=.065	3.1 5.4 *P*<.001
MILES	Vinorelbine Gemcitabine Gemcitabine + Vinorelbine	233 233 222	36 28 30 HR, 1.17 (VNR) HR, 1.06 (Gem)	18 17 19
IFCT-0501	Vinorelbine or Gemcitabine Paclitaxel+carboplatin	226 225	6.2 10.3 HR, 0.64	2.8 6.0 HR, 0.51
MILES-3/MILES-4	Gem or pemetrexed Cisplatin+gemcitabine or Pemetrexed	268 263	7.5 9.6 HR, 0.86	3.0 4.6 HR, 0.76
Sosinski et al	Nab-paclitaxel Solvent-based paclitaxel	521 531	12.1 11.2 HR, 0.922	6.3 5.8 HR, 0.902

Abbreviations: BSC, best supportive care; HR, hazard ratio; OS, overall survival; PFS, progression-free survival. Modified from *Curr Opin Oncol* 2012;24(2):130-136, reprinted with permission.

trials (Table 4). In IFCT-0501, patients older than 70 years were randomized to receive either weekly paclitaxel + carboplatin or single-agent vinorelbine or gemcitabine. This study showed significantly improved PFS and OS in patients treated with doublet chemotherapy vs the control arm. However, patients in the combination arm were associated with a higher incidence of grade 3 neutropenia (48% combination vs 12.4% control), asthenia (10.3% combination vs 5.8% control), and toxic death (4.4% combination vs 1.3% control).[71] The MILES-3 and MILES-4 trials were phase III studies in which patients who were previously untreated, had good PS, and were ages 70 years and older were randomized to doublet chemotherapy or monotherapy with gemcitabine in MILES-3, or gemcitabine or pemetrexed in MILES-4. MILES-3 was open to all histologies, and MILES-4 was open to only non-squamous histologies. Both studies were closed early due to slow accrual. However, a combined analysis of MILES-3 and MILES-4 showed that the combination regimen improved PFS but did not prolong OS and was associated with a higher hematologic toxicity and fatigue.[72] A subgroup analysis of a weekly nab-paclitaxel + carboplatin trial compared solvent-based paclitaxel + carboplatin. This study found that older people (≥ 70 years) had significantly improved OS.[73] Based on these data, a randomized trial was conducted in which patients 70 years and older with treatment-naïve, locally advanced/metastatic NSCLC were randomized to receive either (1) nab-paclitaxel 100 mg/m^2 on days 1, 8, and 15 plus carboplatin or (2) the same nab-paclitaxel + carboplatin dose every 3 weeks followed by a 1-week break. The primary end point was the incidence of grade 2 peripheral neuropathy or greater than grade 3 myelosuppression. Although this trial met its primary end point, nab-paclitaxel did not show improved OS.[74]

Chemotherapy in Patients With PS2

Patients with an ECOG PS2 account for 30% to 40% of patients with NSCLC.[75] PS2 is considered a prognostic factor and also predictive of more toxicities. Similar to older patients, patients with PS2 are usually excluded from clinical trials. Nevertheless, several studies were conducted to address the issue of PS2 in advanced NSCLC (Table 5). The ECOG1599 study was the first randomized trial designed for patients with PS2 that compared dose-attenuated, platinum-based doublets.[76] Two different platinum doublets had similar PFS and OS. Of note, after dose attenuation, toxicities in patients with PS2 were similar to those previously observed in patients with PS0-1. Reynolds et al reported that gemcitabine + carboplatin doublets improved the response rate but not the PFS or OS. They also reported that patients' tumoral amounts of ribonucleotide reductase catalytic subunit M1 and excision repair cross-complementation 1 protein were not predictive of response to therapy.[77] In contrast, a small phase III trial showed significantly improved PFS and OS with gem-

Table 5. Randomized Trials for Patients with PS2 Advanced NSCLC

Trial	Regimen	Patients, No.	OS, months	PFS, months	1-year OS,%
ECOG 1599	Paclitaxel + carboplatin Gemcitabine + cisplatin	49 54	6.2 6.9	3.5 3.0	19 25
Reynolds et al	Gemcitabine Gemcitabine + carboplatin	85 85	5.1 6.7 *P*=.242	2.7 3.8 *P*=.143	21.2 31.3
CAPPA-2	Gemcitabine Gemcitabine + cisplatin	28 28	3.0 5.9 *P*=.039	1.7 3.3 *P*=.017	NR NR
Langer et al	Nab-paclitaxel + carboplatin Paclitaxel + carboplatin	199 201	7.9 8.0	3.9 4.6	31 31
O'Brien et al	Nab-paclitaxel Gemcitabine or vinorelbine	191 190	7.3 6.6	2.9 3.6	26 36
Zukin et al	Pemetrexed Pemetrexed + carboplatin	102 103	5.3 9.3 HR, 0.46	2.8 5.8 HR, 0.62	21.9 40.1

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
Modified from *Eur J Cancer* 2017;83:266-278, reprinted with permission.

citabine + cisplatin.[78] However, given the small sample size, caution should be emphasized when interpreting the data.

A first-line study with nab-paclitaxel in patients with PS0-2 did not show any survival benefit over solvent-based paclitaxel + carboplatin. However, this study did meet its primary end point of a statistically significant improvement in response rate.[79] Grades greater than or equal to 3 neuropathy, neutropenia, arthralgia, and myalgia occurred significantly less often in the nab-paclitaxel + carboplatin arm, and less thrombocytopenia and anemia occurred in the solvent-based paclitaxel + carboplatin arm.

Another study randomized patients with chemotherapy-naïve PS2 and advanced NSCLC to receive single-agent nab-paclitaxel (175 mg/m^2) or single-agent vinorelbine or gemcitabine. The median survival was 7.3 months for nab-paclitaxel vs 6.6 months for the control arm, and the 1-year survival was 26% for nab-paclitaxel vs 26% for the control arm. Although lower rates of hematologic ($P < .001$) and gastrointestinal ($P = .004$) adverse events were observed in the nab-paclitaxel arm, neuropathy occurred more frequently in the paclitaxel arm (30%) than the control arm (5%; $P < .001$).[80]

A landmark phase III trial studied carboplatin + pemetrexed vs pemetrexed alone in patients with PS2 advanced NSCLC.[81] The study showed a nearly double improvement in the response rate (23.8% with vs 10.3% without carboplatin, $P = .032$), median PFS (5.8 months with vs 2.8 months without carboplatin; HR, 0.46; $P < .001$), median OS (9.3 months with vs 5.3 months without carboplatin; HR, 0.62; $P = .001$), and 1-year OS rate (40.1% with vs 21.9% without carboplatin). Further, in terms of adverse events, grade 3/4 anemia (11.7% with vs 3.9% without carboplatin), neutropenia (6.8% with vs 1.0% without carboplatin), and thrombocytopenia (1.0% with vs 0% without carboplatin) were non-significantly higher in the combination arm. Because the patients in this trial did not represent a broad range of patients with PS2 globally, the results of this study limit the generalizability of combination chemotherapy in patients with PS2.

According to the ASCO and European Society for Medical Oncology, all patients without driver mutations with PS0-2 and adequate function should receive receive immunotherapy +/- platinum-based doublet treatment as a first-line treatment rather than non-platinum doublets, regardless of their age.[82,83] For patients who are not eligible for doublet chemotherapy, single agents, such as vinorelbine, gemcitabine, or docetaxel, are considered standard of care, although they have not been explored as single agents with immunotherapy. For older patients who do not meet these criteria or have poor health, BSC or single agent immunotherapy is recommended (see Chapter 20).

CHEMOTHERAPY PLUS ANTI-ANGIOGENIC DRUGS

VEGF is a growth factor that prevents the development of new blood vessels and promotes the formation of a disorganized and leaky vasculature within tumors, increasing the interstitial pressure and decreasing delivery of chemotherapy. Inhibition of VEGF has been shown to have in-vivo anti-tumor effects.

Bevacizumab has been approved in the United States for managing non-squamous cell carcinoma based on results from the ECOG E4599 trial. This phase III trial randomly assigned 878 patients to chemotherapy (paclitaxel + carboplatin) or to chemotherapy plus bevacizumab (Figure 9).[84] The median PFS was 6.2 months for chemotherapy alone and 4.5 months for chemotherapy plus bevacizumab, and OS was 12.3 months for chemotherapy alone and 10.3 months for chemotherapy plus bevacizumab. These data indicate significantly higher survival for patients who received chemotherapy plus bevacizumab vs chemotherapy alone. However, because of the grades III through V bleeding episodes observed in the phase II study that preceded this one, it should be noted that eligibility for this study was restricted to patients with non-squamous cell carcinoma (due to higher levels of severe hemoptysis observed in squamous tumors), no brain metastases, as well as no hemoptysis,

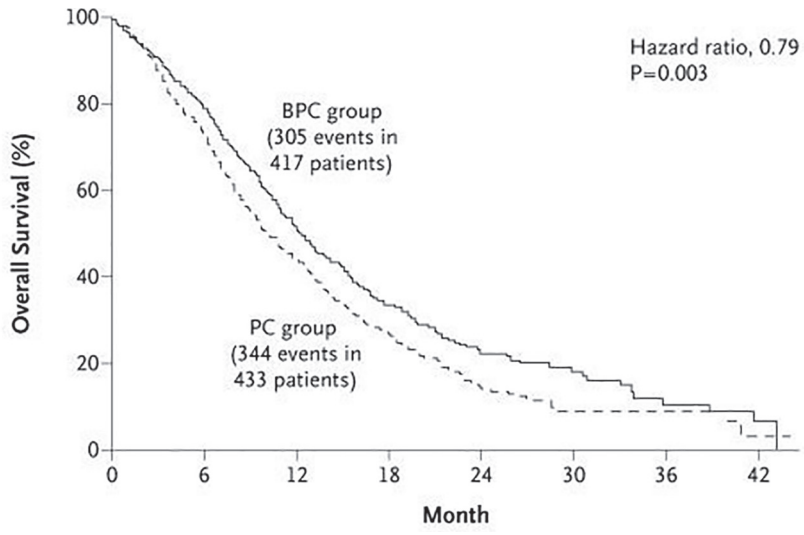


Figure 9. Results from the ECOG E4599. This phase III trial randomly assigned 878 patients to chemotherapy (paclitaxel + carboplatin) or chemotherapy plus bevacizumab. BPC, bevacizumab + paclitaxel + carboplatin; PC, paclitaxel + carboplatin. Reprinted with permission from Sandler A et al.[84]

bleeding disorders, or anticoagulation requirement. Despite these restrictions, significant bleeding was more frequent for patients who received chemotherapy plus bevacizumab (4.4%) vs chemotherapy alone (0.9%; *P* = .001). There were 15 treatment-related deaths in the group of patients who received chemotherapy plus bevacizumab, including 5 as a result of pulmonary hemorrhage.

A second phase III study, called AVAiL, involved more than 1,000 patients who were randomly assigned to chemotherapy (gemcitabine + cisplatin) plus placebo, or chemotherapy with 1 of 2 different doses of bevacizumab.[85] The study met its primary end point of PFS, with HRs of 0.75 for the low-dose bevacizumab arm and 0.82 for the high-dose bevacizumab arm. However, the absolute benefit was modest (6.7 and 6.5 months median PFS vs 6.1 months), with no improvement in survival. It is unclear whether the lack of survival benefit is a result of differences in the chemotherapy doublets between the ECOG study and AVAiL trial, bevacizumab dose, or study design.

Ramucirumab is a monoclonal antibody that binds directly to the ligand-binding pocket of VEGFR-2 to block binding of VEGF-A, VEGF-C, and VEGF-D. A phase III trial evaluated more than 1,200 patients in which a platinum-based therapy failed. This trial found a median OS of 10.5 months in patients randomized to docetaxel + ramucirumab vs 9.1 months in patients randomized to docetaxel + BSC (HR, 0.86; 95% CI, 0.75-0.98; P = .024), leading to approval of docetaxel + ramucirumab in the second-line setting.[86]

References

1. Laing AH, Berry RJ, Newman CR, et al. Treatment of inoperable carcinoma of bronchus. *Lancet*. 1975;2:1161-1164.
2. Cormier Y, Bergeron D, La Forge J, et al. Benefits of polychemotherapy in advanced non-small-cell bronchogenic carcinoma. *Cancer*. 1982;50:845-849.
3. Anderson G, Payne H. Response rate and toxicity of etoposide (VP-16) in squamous carcinoma of the lung: report from the Lung Cancer Treatment Study Group. *Semin Oncol*. 1985;12:21-22.
4. Buccheri G. Chemotherapy and survival in non-small cell lung cancer. The old vexata questio. *Chest*. 1991;99:1328-1329.
5. Haskell CM. Chemotherapy and survival of patients with non-small cell lung cancer. A contrary view. *Chest*. 1991;99:1325-1326.
6. Rapp E, Pater JL, Willan A, et al. Chemotherapy can prolong survival in patients with advanced non-small-cell lung cancer—report of a Canadian multicenter randomized trial. *J Clin Oncol*. 1988;6:633-641.
7. Jaakkimainen L, Goodwin PJ, Pater J, et al. Counting the costs of chemotherapy in a National Cancer Institute of Canada randomized trial in nonsmall-cell lung cancer. *J Clin Oncol*. 1990;8:1301-1309.
8. Souquet PJ, Chauvin F, Boissel JP, et al. Polychemotherapy in advanced non small cell lung cancer: a meta-analysis. *Lancet*. 1993;342:19-21.
9. Marino P, Pampallona S, Preatoni A, et al. Chemotherapy vs supportive care in advanced non-small-cell lung cancer. Results of a meta-analysis of the literature. *Chest*. 1994;106:861-865.
10. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. *BMJ*. 1995;311:899-909.
11. Ruckdeschel JC, Finkelstein DM, Ettinger DS, et al. A randomized trial of the four most active regimens for metastatic non-small-cell lung cancer. *J Clin Oncol*. 1986;4:14-22.
12. Chang AY, Tu ZN, Smith JL, et al. Phase II trial of gallium nitrate, amonafide and teniposide in metastatic non-small cell lung cancer. An Eastern Cooperative Oncology Group study (E2588). *Invest New Drugs*. 1995;13:137-141.
13. Finkelstein DM, Ettinger DS, Ruckdeschel JC. Long-term survivors in metastatic non-small-cell lung cancer: an Eastern Cooperative Oncology Group Study. *J Clin Oncol*. 1986;4:702-709.

14. Kaasa S, Lund E, Thorud E, et al. Symptomatic treatment versus combination chemotherapy for patients with extensive non-small cell lung cancer. *Cancer*. 1991;67:2443-2447.
15. Ganz PA, Figlin RA, Haskell CM, et al. Supportive care versus supportive care and combination chemotherapy in metastatic non-small cell lung cancer. Does chemotherapy make a difference? *Cancer*. 1989;63:1271-1278.
16. Tummarello D, Graziano F, Isidori P, et al. Symptomatic, stage IV, non-small-cell lung cancer (NSCLC): response, toxicity, performance status change and symptom relief in patients treated with cisplatin, vinblastine and mitomycin-C. *Cancer* Chemother Pharmacol. 1995;35:249-253.
17. Cellerino R, Tummarello D, Guidi F, et al. A randomized trial of alternating chemotherapy versus best supportive care in advanced non-small-cell lung cancer. *J Clin Oncol*. 1991;9:1453-1461.
18. Woods RL, Williams CJ, Levi J, et al. A randomised trial of cisplatin and vindesine versus supportive care only in advanced non-small cell lung cancer. B*r J Cancer*. 1990;61:608-611.
19. DeVore RF, 3rd, Jagasia M, Johnson DH. Paclitaxel by either 1-hour or 24-hour infusion in combination with carboplatin in advanced non-small cell lung cancer: preliminary results comparing sequential phase II trials. *Semin Oncol*. 1997;24:S12-29.
20. Klastersky J, Sculier JP, Lacroix H, et al. A randomized study comparing cisplatin or carboplatin with etoposide in patients with advanced non-small-cell lung cancer: European Organization for Research and Treatment of Cancer Protocol 07861. *J Clin Oncol*. 1990;8:1556-1562.
21. Rosell R, Gatzemeier U, Betticher DC, et al. Phase III randomised trial comparing paclitaxel/carboplatin with paclitaxel/cisplatin in patients with advanced non-small-cell lung cancer: a cooperative multinational trial. *Ann Oncol*. 2002;13:1539-1549.
22. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol*. 2003;21:3016-3024.
23. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*. 2002;346:92-98.
24. Hotta K, Matsuo K, Ueoka H, et al. Meta-analysis of randomized clinical trials comparing Cisplatin to Carboplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol*. 2004;22:3852-3859.
25. Ardizzoni A, Boni L, Tiseo M, et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. *J Natl Cancer Inst*. 2007;99:847-857.
26. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*. 2008;26:3543-3551.
27. Georgoulias V, Papadakis E, Alexopoulos A, et al. Platinum-based and non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a randomised multicentre trial. *Lancet*. 2001;357:1478-1484.
28. Treat JA, Gonin R, Socinski MA, et al. A randomized, phase III multicenter trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin in patients with advanced or metastatic non-small-cell lung cancer. *Ann Oncol*. 2010;21:540-547.
29. Kosmidis P, Mylonakis N, Nicolaides C, et al. Paclitaxel plus carboplatin versus gemcitabine plus paclitaxel in advanced non-small-cell lung cancer: a phase III randomized trial. *J Clin Oncol*. 2002;20:3578-3585.
30. D'Addario G, Pintilie M, Leighl NB, et al. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. *J Clin Oncol*. 2005;23:2926-2936.
31. Comella P, Frasci G, Panza N, et al. Randomized trial comparing cisplatin, gemcitabine, and vinorelbine with either cisplatin and gemcitabine or cisplatin and vinorelbine in advanced non-small-cell lung cancer: interim analysis of a phase III trial of the Southern Italy Cooperative Oncology Group. *J Clin Oncol.* 2000;18:1451-1457.
32. Alberola V, Camps C, Provencio M, et al. Cisplatin plus gemcitabine versus a cisplatin-based triplet versus nonplatinum sequential doublets in advanced non-small-cell lung cancer: a Spanish Lung Cancer Group phase III randomized trial. *J Clin Oncol*. 2003;21:3207-3213.
33. Delbado C, Michiels S, Syz N, et al. Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen in advanced non-small-cell lung cancer: a meta-analysis. *JAMA*. 2004 Jul 28;292(4):470-84.
34. Clinical practice guidelines for the treatment of unresectable non-small-cell lung cancer. Adopted on May 16, 1997 by the American Society of Clinical Oncology. *J Clin Oncol*. 1997;15:2996-3018.
35. IE Smith, MER O'Brien, DC Talbot, et al. Duration of chemotherapy in advanced non small cell lung cancer: A randomized trial of three versus six courses of mitomycin, vinblastine, and cisplatin. *J Clin Oncol*. 2001;19:1336–1343.
36. MA Socinski, MJ Schell, A Peterman, et al. Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second line therapy in advanced stage IIIB/IV non small cell lung cancer. *J Clin Oncol*. 2002;20:1335–1343.
37. JO Park, SW Kim, JS Ahn, et al. Phase III trial of two versus four additional cycles in patients who are non progressive after two cycles of platinum based chemotherapy in non-small cell lung cancer. *J Clin Oncol*. 2007;25: 5233–5239.
38. A Rossi, P. Chiodini, J-M Sun, et al. Six versus fewer planned cycles of first-line platinum-based chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data. *Lancet Oncol*. 2014;15:1254–1262.
39. Masters GA, Temin S, Azzoli CG, et al. Systemic therapy for stage IV non–small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2015;33:3488-3515.
40. NCCN Clinical Practice Guidelines in Oncology; Non-Small Cell Lung Cancer V2.2022, Mar 7, 2022.
41. Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after frontline therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. *J Clin Oncol*. 2009;27:591-598.
42. Schmid-Bindert G. Maintenance therapy in non-small-cell lung cancer. *Transl Lung Cancer Res*. 2012;1(2):105-110.
43. Gentzler RD, Johnson ML. Complex Decisions for First-Line and Maintenance Treatment of Advanced Wild-Type Non-Small Cell Lung Cancer. *The Oncologist*. 2015;20:299–306.
44. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet*. 2009;374(9699):1432–1440.

45. Paz-Ares L, de Marinis F, Dediu M,et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol*. 2012 Mar;13(3):247-55.
46. Wakelee H, Paz-Ares L. Maintenance Chemotherapy for Non Small Cell Lung Cancer. In: Pass HI, Ball D, Scagliotti GV (eds). The IASLC Multidisciplinary Approach to Thoracic Oncology. Aurora, CO 2014;625-646.
47. Gerber DE, Schiller JH. Maintenance Chemotherapy for Advanced Non–Small-Cell Lung Cancer: New Life for an Old Idea. *J Clin Oncol*. 2013;31:1009-1020.
48. Chiang A, Detterbeck FC, Stewart T, et al. Non-small cell lung cancer. In: DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology, 11th Ed. Lippincott Williams & Wilkins 2019; 618-670.
49. Ramalingam SS, Dahlberg SE, Belani CP, et al. Pemetrexed, Bevacizumab, or the Combination As Maintenance Therapy for Advanced Nonsquamous Non–Small-Cell Lung Cancer: ECOG-ACRIN 5508. *J Clin Oncol*. 2019;37:2360-2367.
50. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol*. 2000;18:2095-2103.
51. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol*. 2000;18:2354-2362.
52. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol*. 2004;22:1589-1597.
53. Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. *Oncologist*. 2009;14:253-263.
54. Scagliotti G, Brodowicz T, Shepherd FA, et al. Treatment-by-histology interaction analyses in three phase III trials show superiority of pemetrexed in nonsquamous non-small cell lung cancer. *J Thorac Oncol*. 2011;6:64-70.
55. Gridelli C, Gallo C, Di Maio M, et al. A randomised clinical trial of two docetaxel regimens (weekly vs 3 week) in the second-line treatment of non-small-cell lung cancer. The DISTAL 01 study. *Br J Cancer.* 2004;91:1996-2004.
56. Schuette W, Nagel S, Blankenburg T, et al. Phase III study of second-line chemotherapy for advanced non-small-cell lung cancer with weekly compared with 3-weekly docetaxel. *J Clin Oncol*. 2005;23:8389-8395.
57. Tassinari D, Scarpi E, Sartori S, et al. Second-line treatments in non-small cell lung cancer. A systematic review of literature and metaanalysis of randomized clinical trials. *Chest*. 2009;135:1596-1609.
58. Qi WX, Shen Z, Yao Y. Meta-analysis of docetaxel-based doublet versus docetaxel alone as second-line treatment for advanced non-small-cell lung cancer. *Cancer Chemother Pharmacol*. 2012;69:99-106.
59. Qi WX, Tang LN, He AN, et al. Effectiveness and safety of pemetrexed-based doublet versus pemetrexed alone as second-line treatment for advanced non-small-cell lung cancer: a systematic review and meta-analysis. *J Cancer Res Clin Oncol*. 2012;138:745-751.
60. Di Maio M, Chiodini P, Georgoulias V, et al. Meta-analysis of single-agent chemotherapy compared with combination chemotherapy as second-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol*. 2009;27:1836-1843.
61. Stinchcombe TE, Socinski MA. Considerations for second-line therapy of non-small cell lung cancer. *Oncologist*. 2008;13 Suppl 1:28-36.
62. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384:665-673.
63. Reck M, Shepherd F, Pérol M, et al. Effects of second-line ramucirumab after rapid time to progression on first-line therapy: subgroup analysis of REVEL in advanced non-small cell lung cancer. *J Thorac Oncol.* 2017;12:S1808-S1809.
64. Reck M, Kaiser R, Mellemgaard A, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. *Lancet Oncol*. 2014;15:143-155.
65. Gridelli C, Balducci L, Ciardiello F, et al. Treatment of Elderly Patients With Non-Small-Cell Lung Cancer: Results of an International Expert Panel Meeting of the Italian Association of Thoracic Oncology. *Clin Lung Cancer*. 2015;16:325-333.
66. Balducci L, Extermann M. Management of cancer in the older person: a practical approach. *Oncologist*. 2000;5:224-237.
67. Sacher AG, Le LW, Leighl NB, et al. Elderly patients with advanced NSCLC in phase III clinical trials: are the elderly excluded from practice-changing trials in advanced NSCLC? *J Thorac Oncol*. 2013;8:366-368.
68. Gridelli C. The ELVIS trial: a phase III study of single-agent vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer. Elderly Lung Cancer Vinorelbine Italian Study. *Oncologist*. 2001;6 Suppl 1:4-7.
69. Kudoh S, Takeda K, Nakagawa K, et al. Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). *J Clin Oncol*. 2006;24:3657-3663.
70. Gridelli C, Perrone F, Gallo C, et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. *J Natl Cancer Inst*. 2003;95:362-372.
71. Quoix E, Zalcman G, Oster JP, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. *Lancet*. 2011;378:1079-1088.
72. Gridelli C, Morabito A, Cavanna L, et al. Cisplatin-Based First-Line Treatment of Elderly Patients With Advanced Non-Small-Cell Lung Cancer: Joint Analysis of MILES-3 and MILES-4 Phase III Trials. *J Clin Oncol*. 2018;36:2585-2592.
73. Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. *J Clin Oncol.* 2012;30:2055-2062.
74. Langer CJ, Anderson EC, Jotte RM, et al. ABOUND.70+: Safety and efficacy of

nab-paclitaxel/carboplatin (nab-P/C) in elderly patients (pts) with advanced non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2017;35:9059-9059.
75. Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. *Eur J Cancer*. 1996;32A:1135-1141.
76. Langer C, Li S, Schiller J, et al. Randomized phase II trial of paclitaxel plus carboplatin or gemcitabine plus cisplatin in Eastern Cooperative Oncology Group performance status 2 non-small-cell lung cancer patients: ECOG 1599. *J Clin Oncol*. 2007;25:418-423.
77. Reynolds C, Obasaju C, Schell MJ, et al. Randomized phase III trial of gemcitabine-based chemotherapy with in situ RRM1 and ERCC1 protein levels for response prediction in non-small-cell lung cancer. *J Clin Oncol.* 2009;27:5808-5815.
78. Morabito A, Gebbia V, Di Maio M, et al. Randomized phase III trial of gemcitabine and cisplatin vs. gemcitabine alone in patients with advanced non-small cell lung cancer and a performance status of 2: the CAPPA-2 study. *Lung Cancer.* 2013;81:77-83.
79. Langer CJ, O'Byrne KJ, Socinski MA, et al. Phase III trial comparing paclitaxel poliglumex (CT-2103, PPX) in combination with carboplatin versus standard paclitaxel and carboplatin in the treatment of PS 2 patients with chemotherapy-naive advanced non-small cell lung cancer. *J Thorac Oncol*. 2008;3:623-630.
80. O'Brien ME, Socinski MA, Popovich AY, et al. Randomized phase III trial comparing single-agent paclitaxel Poliglumex (CT-2103, PPX) with single-agent gemcitabine or vinorelbine for the treatment of PS 2 patients with chemotherapy-naive advanced non-small cell lung cancer. *J Thorac Oncol*. 2008;3:728-734.
81. Zukin M, Barrios CH, Pereira JR, et al. Randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non-small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2. *J Clin Oncol.* 2013;31:2849-2853.
82. Hanna N, Johnson D, Temin S, et al. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2017;35:3484-3515.
83. Novello S, Barlesi F, Califano R, et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2016;27:v1-v27.
84. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355:2542-2550.
85. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. *J Clin Oncol*. 2009;27:1227-1234.
86. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384:665-673.

18

PROGRESS IN SMALL CELL LUNG CANCER: CELEBRATING 50 YEARS

Natasha B. Leighl,[1] **Fred R. Hirsch,**[2] **and Paul A. Bunn, Jr.**[3] | [1] Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada; [2] Center for Thoracic Oncology/Tisch Cancer Institute, Mount Sinai Health System, New York, USA; [3] University of Colorado School of Medicine, Aurora, USA

Despite its history as a "recalcitrant" cancer, scientific advances have led to important progress in the diagnosis, treatment and molecular understanding of small-cell lung cancer (SCLC) over the past 5 decades (Figures 1,2).[1] SCLC has historically been considered a phenotypically uniform disease with multiple co-existing genomic abnormalities, including alterations in *TP53*, *RB1,* and *MYC*.[2-4] A key challenge has been the inability to identify specific oncogene or signaling pathway "addiction" in SCLC, in contrast to NSCLC. With the rapid evolution of targeted therapy in non–small-cell lung cancer (NSCLC), the pace of therapeutic progress in small-cell lung cancer (SCLC) has been disappointing but is now moving forward.

The 5-year survival for SCLC remains low and less than 5% in extensive stage disease. This is in contrast to an estimated 30% for NSCLC.[5] Falling tobacco use in Western nations has led to a declining incidence in SCLC since the 1970s. For example, in North America, the incidence has dropped from 17% to approximately 13%.[6] However, among women, in parallel with the prevalence of tobacco use, the incidence of SCLC has increased. Currently, more than 98% of cases of SCLC are deemed smoking-

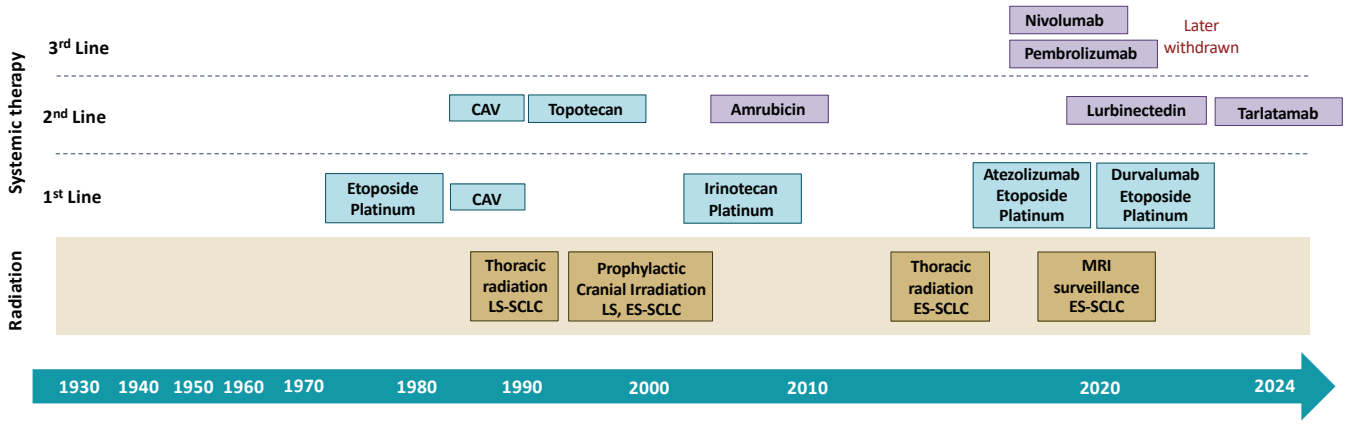


Figure 1. Advances in SCLC Treatment.
CAV/CEV: cyclophosamide, doxorubicin/epirubicin, vincristine; PCI: prophylactic cranial irradiation; RTR: thoracic radiotherapy; *US Food and Drug Administration approved. Gazdar et al, Nat Rev Cancer, 2017; Haddadin & Perry, Clin Lung Cancer, 2011; Leighl, J Clin Oncol, 2015; Roth et al, J Clin Oncol, 1992; Arriagada et al, J Natl Cancer Inst, 1995; Slotman et al, NEJM, 2007; Seto et al, J Clin Oncol; Noda et al, NEJM, 2002; Hanna et al, J Clin Oncol, 2006; Lara et al, J Clin Oncol, 2009; Slotman et al, Lancet, 2015; Van Pawel et al, J Clin Oncol, 1999; O'Brien et al, J Clin Oncol, 2006; Van Pawel et al, J Clin Oncol, 2014; Antonio et al, Lancet Oncol, 2016; Sabari et al, Nat Rev Clin Oncol, 2017; Horn et al, New Engl J Med, 2018; Ahn et al, New Engl J Med, 2023; www.fda.gov (accessed July 2024).

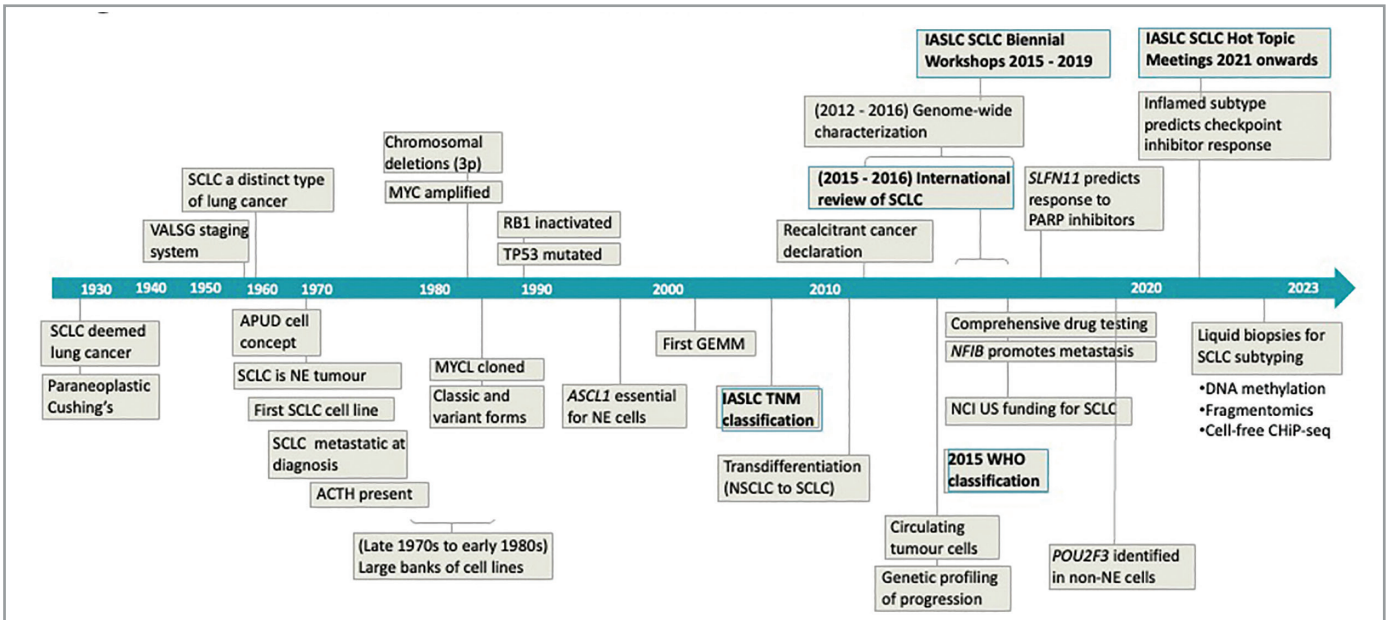


Figure 2. Selected Scientific Advances in SCLC.
SCLC: small cell lung cancer; VALSG: Veterans Association Lung Study Group; APUD: amine precursor uptake decarboxylase; NE: neuroendocrine; ACTH: adrenocorticotropic hormone; NFIB: nuclear factor I/B; WHO: World Health Organization; CHiP-seq: chromatin modifications followed by sequencing. Bold text highlights selected key IASLC initiatives. Adapted from Gazdar et al Nat Rev Cancer, 2017.[1]

related. Other causes include radon exposure, for example in miners.[7] More recently, small cell or neuroendocrine transformation has been described in oncogene addicted cancers, such as *EGFR* mutant lung cancer.[8] Pre-existing alterations in *TP53, RB1*, 3p chromosomal arm deletions, signaling via NOTCH, and PI3K/AKT may be associated with small cell transformation.[9] Although uncommon, this diagnosis of transformed SCLC or neuroendocrine cancer should be considered in light or never-smokers with a diagnosis of SCLC.

SCLC still exacts a significant toll, with more than 250,000 new cases estimated per year globally, and up to 90% dying within 1 to 2 years from diagnosis.[10]

1970S

Biology

In the 1970s, a key research focus was to understand the biology of SCLC. Cell lines from human SCLC tumors were derived, enabling further discovery. In 1974, Yalow described ectopic adrenocorticotropin (ACTH) production in patients with bronchogenic carcinoma.[11] The ACTH derived from SCLC tumors differed from the pituitary-produced ACTH, with a different amino acid composition. This led to intensive discovery efforts on different hormones secreted by SCLC tumors. SCLC became characterized as an ectopic hormone-producing tumor with several hallmark paraneoplastic syndromes. These included diabetes insipidus and Cushing's Syndrome related to ectopic ACTH production, and hyponatremia due to the syndrome of inappropriate ADH production (SIADH). Several hormones were identified in patients with SCLC, including calcitonin, ACTH, and melanin-stimulating hormones and estrogen.[12,13] To facilitate further research, a source of tumor cells was critical. Thus, several permanent cell lines were established at the US National Cancer Institute by Gazdar, Minna, and others,[14] and also at other institutions.[15,16] Further investigations through SCLC cell lines confirmed that the ectopic hormone production seen in SCLC patients was also identified in cell lines, including ACTH and others.[17] The IASLC arranged in that period of time many workshops in Europe and in the US, where progress in SCLC-research were discussed, summarized, and future strategies formulated.

Treatment

Prior to the use of chemotherapy, SCLC outcomes with surgical resection or radiotherapy alone were poor, with 1 year survival rates less than 10%.[18] A 10-year update of the randomized trial from the British Medical Research Council of radical radiation versus surgery confirmed that radical radiotherapy was superior to resection, although long term survival was 4% with radiation, and 0% with surgery.[19] The use of single agent chemotherapy led to response rates of 20% or higher, with multiple active agents identified. Combinations yielded even better results.

1980S

Biology

More than 100 SCLC cell lines were established during this decade. Autocrine growth factors from these cell lines were identified and key factors for sustained cell line growth in serum-free conditioned medium, including hydrocortisone, insulin and estrogen, were established.[20] Additional efforts to develop xenograft models of SCLC were also undertaken.[21] Further characterization of SCLC cell lines included neuroendocrine features, and the production of several growth factors, including gastrin-releasing peptide (GRP) and bombesin.[22]

While most SCLC cell lines and tumors retained classic SCLC morphology, approximately 10% to 15% were termed "variant SCLC." These corresponded to mixed small cell/large cell morphology or collision tumors.[23] These variant cell lines behaved differently in vitro, and had common MYC amplification and protein overexpression.[24-27] SCLC cell lines revealed a consistent deletion in chromosomal region 3p (14-23), seen in all major types of lung cancer.[28] Allelic loss and inactivation of tumor suppressor genes was commonly identified, including the retinoblastoma (Rb) gene and inactivation of TP53.[29,30] Minna and colleagues proposed that loss of tumor suppressor function was a key event in lung carcinogenesis, coupled with oncogene activation.[31]

Pathology

In 1981, the IASLC Pathology Committee proposed a revision to the WHO classification of small cell carcinoma by combining "oat cell" and "intermediate" variants into a single entity of "small cell," and the recognition of "mixed small cell/large cell" and "combined small cell carcinoma" as new variants in the classification with prognostic and even therapeutic implications.[23,32] This pioneering work established the recognition of heterogeneity in lung cancer tumors, supported by in vitro studies. This proposed histopathologic classification was later adopted in the 1997 and 2004 WHO classifications.

Another key finding was the changing incidence of lung cancer pathologic subtypes. In particular, an increase in adenocarcinoma was seen during the 1970s, a trend which continues today.[33,34]

Chemotherapy

In limited-stage SCLC, the results of the first randomized trials comparing combined chemotherapy and radiotherapy were reported and showed superior survival for the combined approach.[35] Studies examining the role of maintenance chemotherapy or longer duration of therapy were undertaken. Results were fairly consistent across trials, with either no benefit seen, or only minor benefit with incremental toxicity.[36-38] The use of 4 cycles of combination chemotherapy emerged as a standard in both limited and extensive stage. After both clinical and preclinical research focused on etoposide as a potential active drug in SCLC, randomized studies were conducted and verified the effect of etoposide in combination with platinum, which became standard of care therapy of SCLC (Hirsch FR J Clin Oncol 1987).[39]

While there were no available therapies for relapsed SCLC, re-treatment with etoposide/ platinum (EP) or other non-cross resistant regimens like cyclophosphamide/ doxorubicin/vincristine (CAV) were shown to induce responses. Rechallenge with EP is still an important second-line option today.[40]

Surgery and Adjuvant Therapy

Despite historically poor outcomes with surgical resection alone for patients with SCLC, a

subgroup of patients with very limited disease has been further studied by investigators in Japan, Toronto, and other areas. Patients with T1 or even T2N0 tumors, without effusions, may benefit from aggressive local therapy like resection, followed by adjuvant chemotherapy with EP. Patients receiving adjuvant chemotherapy after surgical resection have similar outcomes to those receiving radical chemoradiation, with a projected 5-year survival of approximately 31%.[41] Otherwise, surgical resection remains relevant for patients with combined SCLC and NSCLC tumors in limited stage or selected cases for surgical salvage after primary chemoradiation.

Staging

The IASLC published a consensus report in 1989, recommending changes to the previous staging system established by the Veterans' Administration Lung Study Group (VALSG), which classified patients as having limited or extensive disease.[42,43] In the VALSG system, limited disease was defined as having tumor confined to one hemithorax, including local extension and ipsilateral mediastinal and supraclavicular nodal disease, so long as the disease could be encompassed in a single radiation field. Contralateral, more extensive disease or the presence of extrathoracic metastases were classified as extensive disease. In the IASLC consensus, it was recommended that limited disease should be expanded to include contralateral mediastinal and supraclavicular nodes. It was also recommended that ipsilateral pleural effusion, even with positive cytology, be included in the definition of limited disease if no extrathoracic spread was identified.

1990S

Biology

With advancing technology, multiple regions of allelic loss on the short arm of chromosome 3, harboring several crucial tumor suppressor genes, including FHIT and RASSF1A, were described in SCLC and NSCLC.[44,45] Amplification of the MYC family of oncogenes was well defined in SCLC, and later found to be over-expressed in NSCLC. The important role of RB inactivation in SCLC was further established by Shimizu et al.[46] While almost uniformly present in SCLC, it was rarely seen in NSCLC.

Radiation

A meta-analysis of 13 randomized trials including 2,140 patients confirmed improved survival when thoracic radiotherapy was added to chemotherapy in patients with limited disease, confirming thoracic radiation as a key component of curative therapy in SCLC. Three-year survival was increased by 5%, from 8.9% to 14.3% (HR, 0.86, $P = .001$).[47] Radiation improved local control, decreasing the local failure rate at 2 years from 48% with chemotherapy alone versus 23% with chest radiation ($P = .0001$). Trade-offs included higher rates of esophagitis, pneumonitis, and a small increase in treatment-related mortality, at approximately 1%.

With respect to radiotherapy timing, a Canadian randomized trial led by the National Cancer Institute of Canada demonstrated that in patients with limited stage SCLC, early thoracic radiotherapy resulted in longer survival if given with the second cycle of chemotherapy, rather than later with the last cycle.[48] The median survival of 21 months and 5-year survival rate of 20% in the early thoracic radiation arm set a new benchmark for the standard of care in SCLC and outcomes. Subsequent trials and meta-analyses further confirmed these results.

By 1999, a randomized trial demonstrated that twice-daily radiation totaling 45 Gy in 3 weeks, starting with cycle one of chemotherapy, was associated with better survival ($P = .04$) compared to once-daily radiation of 45 Gy over 5 weeks.[49] This was practice-changing in some areas, but some considered the standard arm inferior to standard radiotherapy treatment at the time and further trials were initiated.

In addition to advances in thoracic radiation, prophylactic cranial irradiation was also established as a new standard for patients with both limited and extensive stage SCLC. The Prophylactic Cranial Irradiation Overview Collaborative Group demonstrated that in patients with SCLC who had achieved complete remission with initial therapy, prophylactic cranial

irradiation (PCI) significantly reduced the risk of central nervous system (CNS) metastasis by approximately 30% and led to an improvement in survival.[50]

Chemotherapy

As combination therapy had superior activity to single agent treatment, multiple combinations were pursued. Several studies established that three- and even four-drug combinations were not superior to two-drug combinations, and led to greater toxicity. Trials compared SCLC patient outcomes with the two-drug etoposide/cisplatin (EP) combination to outcomes with three- and four-drug combinations including CAV, CAP, CODE, or alternating combinations.[39,51-53] Outcomes were largely similar, with treatment responses occurring in 80-90% of patients for a median duration of 9 to 12 months. While median survival times ranged from 11 to 18 months, depending on stage of disease, long term survival remained low with 5-year survival less than 5%.[54]

Second-line Therapy

In the setting of relapse, non-cross resistant regimens were commonly offered. For example, patients that failed EP could be offered CAV and vice-versa. Topotecan was compared to CAV in a randomized trial in patients with that had relapsed SCLC at least 60 days after initial therapy.[55] Outcomes were similar in both arms, with response rates between 18% and 24%, and median survival times from the start of second-line therapy of approximately 6 months. Greater symptom improvement was seen in patients receiving topotecan, although they had more myelosuppression. This was the first second-line therapy approved by the US FDA and remains a standard option today.

2000s

Staging

The IASLC established a database of thoracic malignancy patients, including disease stage and survival. This included over 12,000 SCLC patients diagnosed between 1990 and 2000. The IASLC Staging Committee analysed the relevance of TNM staging in SCLC, and demonstrated a clear association between survival and T and N category, even within limited disease.[56,57] Patients with pleural effusions and extensive N3 disease had intermediate outcomes between limited and extensive disease patients. The Staging Committee recommended that TNM staging be used in clinical trials of limited disease going forward and that the impact of pleural effusions and extent of N3 disease on prognosis be further studied.

Radiation

The optimal dose, fractionation and timing for radiation in SCLC has been extensively studied. A Cochrane Collaboration meta-analysis demonstrated a survival benefit at 5 years with early thoracic radiation treatment, consistent with earlier randomized trials.[58] This was defined as radiation starting within 30 days of the first day of chemotherapy and included 1,706 patients in 7 trials. The hazard ratio for survival with early radiation was 0.64, (P = .02), with a significant reduction in 2- and 5-year mortality and improved 5-year survival. Toxicity rates, specifically esophagitis and pulmonary toxicity, were higher with early concurrent radiation and chemotherapy than with delayed radiation. In another analysis, patients that completed radiation within 30 days of the start of treatment had better survival (HR, 0.62, P = .0003), although again this was associated with greater esophageal toxicity.[59] This has become the standard of care for patients with limited or stage I-III disease.

With respect to radiotherapy dose and delivery schedules concurrent with systemic therapy, there are variations in practice patterns around the world, according to the radiotherapy dose delivered as part of concurrent chemoradiation. Historical regimens include 40 Gy in 15 daily fractions over 3 weeks.[53] Others have escalated doses as high as 70 Gy, although the benefit of dose escalation was unclear.[60]

Chemotherapy

In the pre-immunotherapy era, irinotecan/cisplatin (IP) was compared with EP in patients with extensive or stage IV disease in three randomized trials.

The first study from the Japanese Clinical Oncology Group (JCOG) demonstrated significantly better response and survival with IP, including 2-year survival of 19.5% with IP and only 5.2% with EP.[61] Two subsequent trials conducted in North America reported similar outcomes with the two regimens, but with differing toxicity profiles.[62,63] In the North American study that used the same IP doses as the JCOG trial, increased toxicity was seen including diarrhea and myelosuppression.[63] Pharmacogenomic analyses confirmed an association between polymorphisms in ABCB1, (involved in cellular membrane transport) and irinotecan-related diarrhea. Polymorphisms in UGT1A1 (involved in drug metabolism) were associated with IP related neutropenia.[63] Prior to the introduction of immunotherapy, IP remained the preferred option in Japan for extensive or stage IV disease, while EP remained standard elsewhere.

Investigators also explored the role of chemotherapy dose intensification with growth factor support, leading to toxicity without significant incremental benefit.[64,65] Studies of novel chemotherapy agents as maintenance therapy showed similar results, with no resulting change to the standard of care of doublet chemotherapy.

Second-line Therapy

A study of topotecan compared to best supportive care in patients with relapsed SCLC defined the survival impact of second-line chemotherapy. Patients receiving topotecan had a median survival of approximately 6 months, compared to 3.2 months for patients receiving supportive care alone.[66]

In Japan, amrubicin was approved in 2002 as a treatment option in patients with relapsed SCLC based on randomized phase II and single arm trials demonstrating promising efficacy.[67] A phase III study conducted outside Japan, comparing amrubicin with topotecan in relapsed SCLC, did not show a difference in survival, although amrubicin had a higher response rate.[68]

2010S

In 2012, the National Cancer Institute US was tasked to develop research strategies for recalcitrant cancers. SCLC was identified as one of these cancers, and international experts, including those from the IASLC, were convened to advise the NCI on strategy. The NCI SCLC Consortium was established in 2017 and advanced research in the US as well as supporting momentum in SCLC research globally. Initiatives to expand SCLC research included a focus on comprehensive genomic profiling of SCLC, novel diagnostic and therapeutic approaches, and greater discovery efforts to understand chemo- and radio-resistance. In the US, a four-fold increase was seen in the number of grants awarded to SCLC research, and a six-fold increase in SCLC publications since 2017.[69]

In 2015, the IASLC hosted its first Small Cell Lung Cancer Workshop, gathering basic scientists and clinical investigators from around the world to focus on advancing the treatment and eradication of SCLC. The SCLC Workshop was hosted every other year and has now transformed into an IASLC "Hot Topic" meeting. At these meetings, the IASLC brings together the global lung cancer community to review the latest advances in SCLC research, novel therapeutics, and prevention.

Pathology

In 2015, the WHO revised the histopathological classification of lung cancer in order to incorporate advances in lung cancer molecular pathology.[70] This included recommendations previously made by the IASLC and other groups. A new category of "neuroendocrine tumors" was established, comprising SCLC, large cell neuroendocrine carcinoma (LCNEC), and carcinoid tumors (typical and atypical).

Biology

Molecular characterization of SCLC has advanced both at a genetic and transcriptional level. As previously described, SCLC tumors are aneuploid, with frequent chromosomal deletions in 3p (almost universal), 4, 5q, 10q, 13q, and 17p, and copy number gains in 3q, 5p, 6p, 8q, 17q, 19, and 20q.

In 2012, Rudin et al. and Peifer et al. reported comprehensive

genomic analyses of SCLC.[2,3] In 2015, George et al. reported further data from comprehensive genomic profiling of 110 SCLC tumors.[4] Bi-allelic inactivation of *TP53* and *RB1* are seen almost universally, along with common amplification or overexpression of *MYC* genes. Carcinoid tumors, by contrast, are less likely to harbor *TP53* mutations. Recurrent mutations in *CREBBP, EP300* and *MLL* related to histone modification were reported. Other recurrent alterations were identified in *PTEN, SLIT2, EPHA7, NOTCH, TP73,* and amplification of *FGFR1* and *SOX2*. Multiple fusion transcripts have been identified by RNA sequencing, including a novel, recurrent *RLF-MYCL1* fusion which may be associated with proliferation.[2] However, further work is needed to understand the functional significance of these alterations.

In 2019, Rudin, Gazdar, and colleagues proposed that up to four subtypes of SCLC could be defined by four key transcriptional regulators: achaete-scute homologue 1 (ASCL1; SCLC-A), neurogenic differentiation factor (NeuroD1; SCLC-N), yes-associated protein 1 (YAP1; SCLC-Y) and POU class 2 homeobox 3 (POU2F3; SCLC-P).[71] ASCL1 expression correlated with expression of neuroendocrine markers, while a subset of ASCL1/NEUROD1 double negative cells, or "non-neuroendocrine" SCLC, appeared dependent on POU2F3 (normally expressed on chemosensory tuft cells). YAP1, a regulator of transcription in the HIPPO pathway, was initially hypothesized to identify another subset of non-NE SCLC, but it has been subsequently suggested that YAP1 is predominantly expressed in the non-small cell component of mixed tumors.[72]

Radiation

The CONVERT trial established once-daily as well as twice-daily radiation as standard radiotherapy treatment options in patients with limited disease.[73] Radiation delivery of 45 Gy in 30 twice-daily fractions over 3 weeks was compared to 66 Gy in 33 once-daily fractions over 6.5 weeks, along with 4 to 6 cycles of standard EP therapy. Survival was similar for both arms of the trial, with just over 50% of patients alive at 2 years and median survival times of 25 to 30 months. Toxicity was also similar in both groups, allowing greater flexibility in radiotherapy delivery options.

Another area of controversy is the potential benefit of consolidative chest radiotherapy in extensive SCLC. In the pre-immunotherapy era, investigators compared consolidation chest radiation with 30Gy in 10 fractions to observation in patients with extensive disease that completed initial chemotherapy and had persistent intrathoracic disease.[74] While 1-year survival, the primary endpoint of the trial, was similar in both arms, two-year survival appeared longer in the thoracic radiation consolidation arm in an unplanned analysis (13% versus 3%, 95% CI 2–8; p=0.004). In addition, the utility of thoracic radiation after chemo-immunotherapy for extensive or advanced SCLC is unknown, leaving this as an open question for further study.

Although PCI was considered in patients with excellent response to first-line therapy, even in the setting of extensive disease, the benefit in advanced SCLC was unclear. In one randomized trial, PCI versus observation after chemotherapy response for extensive disease was associated with a clear reduction in the risk of symptomatic CNS metastasis (14.6% versus 40.4% control; HR 0.27; 95% CI 0.16-0.44; P<0.001).[75] One-year survival survival was also improved (27.1% versus 13.3%). Trade-offs included neurocognitive effects, alopecia and fatigue, although these did not have a major effect on patient-reported global health.[76] However, this study was criticized for not including MRI staging of the brain at baseline. A second randomized trial led by investigators in Japan compared PCI to observation in patients with extensive disease and no evidence of CNS metastasis on MRI imaging.[77] Patients receiving PCI had inferior survival (11.6 versus 13.7 months, HR 1.27; 95% CI 0.96-1.68; p = 0.094), and the study was closed for futility. This has changed practice in many countries, with MRI surveillance being used in this patient population instead.

Systemic Therapy

Over the past decade, key advances have been made in systemic therapy, including the introduction of immune checkpoint inhibitors, as part of standard of care, and active investigation of targeting VEGF, aurora kinase, poly (ADP-ribose) polymerase (PARP) inhibitors, and delta-like ligand 3 (DLL3) signaling pathways.

Immunotherapy

It was anticipated that patients with SCLC would be even more likely to benefit from PD-(L)1 checkpoint inhibitors than their counterparts with NSCLC. This is due to the high mutation burden of SCLC, a median of 7.37 mutations/megabase, plus the prevalence of tobacco use.[4] PD-L1 tumor expression is reported in approximately 10% of SCLC tumors and up to 40% of immune cells.[74,75] However, many SCLC tumors tend to have an immune-excluded phenotype, and defects in MHC antigen presentation may impair the potential for checkpoint inhibitor activity. Single agent activity of PD-(L)1 inhibitors was reported in pretreated SCLC patients, with response rates from 6% to 33% in selected patients and median durations of response ranging from 7 to 19 months.[78] The safety profile of these agents is similar to that seen in NSCLC patients, although there are uncommon reports of emergent neurologic paraneoplastic syndromes or myasthenia in trials. Nivolumab (2018) and pembrolizumab (2019) were granted conditional approval in pre-treated patients by the United States Food and Drug Administration, based on single agent activity.[79-82] These were later withdrawn when subsequent randomized trials were non-confirmatory.

At the 2018 World Conference on Lung Cancer Presidential Plenary, the practice-changing results of IMpower133 were presented, demonstrating improved survival with the addition of atezolizumab to first-line EP in patients with extensive disease, with median survival times improved to 12.3 months from 10.3 months with EP alone.[83] One year later, at the 2019 World Conference on Lung Cancer Presidential Plenary, similar results from the CASPIAN study were presented, demonstrating improved survival with durvalumab plus EP versus EP alone as first-line therapy.[84] These trials have established a new standard of care for extensive disease patients in the first-line setting.

SLFN11 as a Potential Marker for Response to PARP Inhibition

SLFN11 is a DNA/RNA leicase inhibitor has been shown preclinically to predict SCLC sensitivity to PARP inhibitors.[85] In a study of pre-treated SCLC patients that received veliparib plus temozolomide, those with SLFN11-positive tumors (by immunohistochemistry) had longer survival than patients with SLFN11-negative tumors.[86]

2020s

The IASLC held the first "SCLC–Hot Topic" meeting in 2021, which is to be held every two years. These meetings continue to bring together scientists and clinical investigators to share the latest developments in SCLC research and treatment, and they promote further advances to improve patient outcomes and eradicate the burden of SCLC.

At the 2023 IASLC Targeted Therapies in Lung Cancer meeting, the opening keynote address was delivered by Dr. Lauren Byers on advances in the biology and treatment of targeted therapies in SCLC.[87]

Pathobiology

Based on unsupervised mRNA analysis, Byers, Gay, and colleagues identified a novel SCLC "inflamed" subtype (SCLC-I), in addition to the previously described transcriptional subtypes SCLC-N (NEUROD1), SCLC-A (ASCL1), and SCLC-P (POU2F3).[88] The SCLC-I subtype has been characterized as having low expression of NEUROD1, ASCL1 and POU2F3, higher expression of non-neuroendocrine transcription factors, and higher expression of interferon gamma signatures, PD-L1 and other checkpoints.

Retrospective exploration of the first-line IMpower133 and CASPIAN studies suggest that patients with the SCLC-I phenotype may derive greater survival benefit from anti-PD-L1 inhibitors plus EP for extensive SCLC. In

the IMpower133 trial, Gay et al. found that survival with atezolizumab plus EP was significantly longer in the patients with the SCLC-I subtype, 18.2 months, compared to 10.4 months with EP alone.[88] Similar findings were reported in the CASPIAN trial, in which patients with the SCLC inflamed subtype that received durvalumab plus EP had a median survival of 17.6 months compared to 11.3 months in those receiving EP alone.[89]

Preclinical data suggest that each SCLC subtype may have different susceptibilities, such as DLL-3 and BCL2 for SCLC-A tumors. Targeting aurora kinase or somatostatin receptor 2 may be relevant for SCLC-N, while PARP inhibition may be important for SCLC-P or POU2F-3 driven tumors, and checkpoint inhibitors for SCLC-I, among other agents (Figure 3).[88,90] Byers and colleagues are leading efforts to bring this into clinical practice with ongoing development of validated immunohistochemistry assays to define these different SCLC subtypes.[87]

Recent advances in blood-based markers also hold promise. Circulating tumor cells can be isolated in the blood of SCLC patients and have been shown to be prognostic.[91] In the research setting, they have been used for further molecular characterization of SCLC and the development of xenograft models.[92] In a recent study of genome-wide DNA methylation profiling, Chemi, Dive et al. demonstrated that SCLC-specific methylation patterns could be detected in patient cell free DNA samples and were prognostic.[93] Methylation could also help discriminate between SCLC-A, -N and -P subtypes, with the potential for future subtyping of SCLC using liquid biopsies, in addition to tissue-based methods.

Systemic Therapy

Multiple novel therapies and targets are being explored, with nearly 200 trials actively recruiting patients. Targets of interest for systemic therapy approaches include DLL3, SEZ6, and novel agents in clinical development for SCLC patients, such as multiple antibody drug conjugates, bispecific T-cell engagers, and CAR-T cell therapy, are ongoing.[87]

Immunotherapy

After the initial success of PD-L1 inhibitors atezolizumab and durvalumab plus EP in the first line treatment of extensive disease, similar results have been demonstrated with PD-1 inhibitors, including pembrolizumab (though not statistically significant) and serplulimab.[94,95]

In limited stage disease, initial studies have not yet demonstrated benefit in the maintenance setting with combined PD-1 and CTLA-4 inhibition, although studies are ongoing of adding PD-(L)1 inhibitors to initial chemoradiation for limited disease and of other targeted agents, such as PARP inhibitors.[96.97]

Studies of additional checkpoint inhibitors are also ongoing or recently reported, including

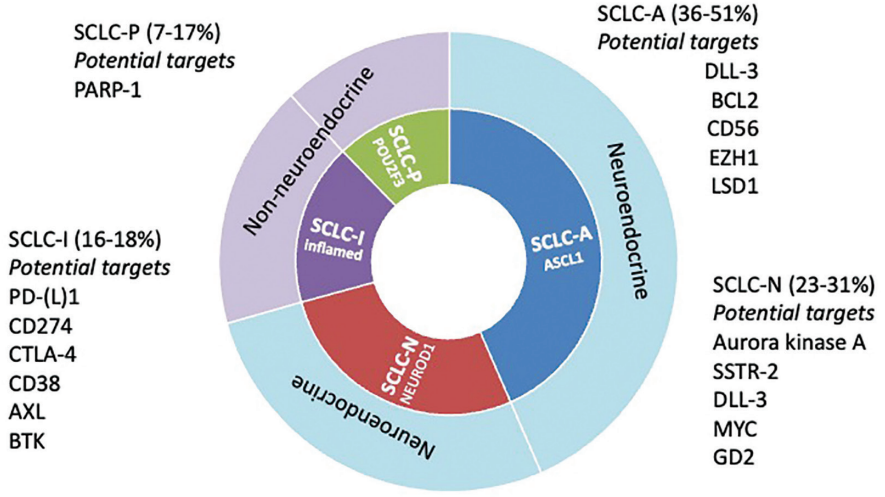


Figure 3. Potential Future Targets in SCLC.[4,87,88]
POU2F3: POU class 2 homeobox 3; ASCL1: achaete-scute homolog 1; NEUROD1: neuronal differentiation 1; PARP1: poly(ADP-ribose) polymerase-1;DLL3: delta-like ligand 3; BCL2: B-cell lymphoma 2; CD56: neural cell adhesion molecule; EZH1: enhancer of zeste 1 polycomb repressive complex 2 subunit; LSD1: lysine-specific demethylase 1; PD-(L)1: programmed cell death protein 1 (ligand); CTLA-4: cytotoxic T-lymphocyte associated protein 4; CD274: cluster of differentiation 274; CD38: cluster of differentiation 38; BTK: Bruton's tyrosine kinase; SSTR-2: somatostatin receptor type 2; GD2:disialoganglioside

targeting TIGIT, LAG-3, TIM3, ICOS and others. Combinations of checkpoint inhibitors with PARP inhibitors and VEGF inhibitors are under study and some have shown initial promise.

Exciting initial results have been seen with DLL3-targeting immunotherapy agents. These include demonstration of durable responses to tarlatamab, a bispecific T-cell engager targeting DLL3, and CD3.[98] Early data with an engineered CAR-T cell, AMG119, has also demonstrated activity.[99] Multiple trials are ongoing, targeting DLL3 and other targets in patients with SCLC.

Second-line therapy

In 2020, the US Food and Drug Administration granted accelerated approval for lurbinectedin in patients with extensive SCLC that failed initial therapy. Lurbinectedin is an alkylating agent that demonstrated a response rate of 35% in patients with recurrent or progressive SCLC.[100] While a phase III study of lurbinectedin plus doxorubin did not improve survival compared to topotecan, other studies are ongoing. Preclinical data suggest that markers such as SLFN-11 may be associated with greater lurbinectedin efficacy as a single agent or in combination with ATR inhibition.[101]

The Groupe Français de Pneumo-Cancérologie demonstrated that etoposide/platinum rechallenge in patients relapsing at least 90 days after initial therapy led to improved progression-free survival compared to topotecan (median 4·7 vs 2·7 months, stratified hazard ratio 0·57, 90% CI 0·41-0·73; p=0·0041).[40] This reinforces rechallenge etoposide/platinum as an important second-line therapy in this patient population.

CONCLUSIONS

Over the past 50 years, the International Association for the Study of Lung Cancer has been part of major advances in the scientific discovery and treatment of SCLC. With promotion of tobacco cessation and control policies, the incidence of SCLC has decreased in several countries, although more work needs to be done to prevent SCLC. Greater genomic and transcriptomic understanding of SCLC has led to the recognition of distinct SCLC subtypes, with the potential for unique therapeutic strategies tailored to each.

Progress in patient treatment has led to cure in approximately 20% of patients who present with limited disease with early concurrent chemoradiation and PCI. Immunotherapy has improved outcomes when added to combination chemotherapy in patients with extensive disease, and better imaging surveillance with MRI has led to a marked decrease in the use of PCI in advanced SCLC patients. Second-line therapy has been shown to improve survival compared to supportive care alone, with several agents approved in the second-line setting.

The future holds great promise with greater tobacco control, the potential use of liquid biopsy for SCLC diagnosis and subtyping, and an unprecedented number of clinical trials ongoing in SCLC with innovative new therapies. The IASLC continues to advance the scientific understanding and treatment of SCLC, and continues to move closer to the goal of eradicating the burden of SCLC worldwide.

References

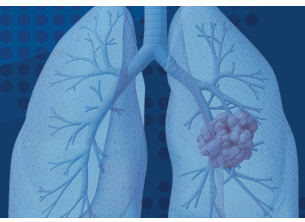
1. Gazdar AF, Bunn PA, Minna JD. Small-cell lung cancer: what we know, what we need to know and the path forward. *Nat Rev Cancer*. 2017;17:725-737.
2. Rudin CM, Durinck S, Stawiski EW, et al. Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer. *Nat Genet*. 2012;44:1111-1116.
3. Peifer M, Fernández-Cuesta L, Sos ML, et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. *Nat Genet*. 2012; 44:1104-1110.
4. George J, Lim JS, Jang SJ, et al. Comprehensive genomic profiles of small cell lung cancer. *Nature*. 2015; 524:47-53
5. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73:17-48.
6. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: Analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol*. 2006; 24:4539-4544.
7. Saccomanno G, Huth GC, Auerbach O, Kuschner M. Relationship of radioactive radon daughters and cigarette smoking in the genesis of lung cancer in uranium miners. *Cancer*. 1988;62:1402-1408.
8. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med*. 2011;3:75ra26.
9. Quintanal-Villalonga A, Taniguchi H, Zhan YA, et al. Multiomic analysis of lung tumors defines pathways activated in neuroendocrine transformation. *Cancer Discov*. 2021; 11:3028-3047.

10. Forman D, Bray F, Brewster DH, Gombe Mbalawa C, Kohler B, Piñeros M, Steliarova- Foucher E, Swaminathan R, Ferlay J, editors (2014). Cancer Incidence in Five Continents, Vol. X. IARC Scientific Publication no. 164. Lyon: International Agency for Research on Cancer.
11. Gewirtz G, Yalow RS. Ectopic ACTH production in carcinoma of the lung. *J Clin Invest*. 1974;53:1022-1032.
12. Abe K, Adachi I, Miyakawa S, et al. Production of calcitonin, adrenocorticotropic hormone, and beta-melanocyte-stimulating hormone in tumors derived from amine precursor uptake and decarboxylation cells. *Cancer Res*. 1977; 37:4190-4194.
13. Munck A, Brinck-Johnsen T. Is cortisol metabolized as it dissociates from glucocorticoid receptors in thymus cells? *J Steroid Biochem*. 1974;5:203-205.
14. Gazdar AF, Carney DN, Russell EK, et al. Establishment of continuous, clonable cultures of small-cell carcinoma of lung which have amine precursor uptake and decarboxylation cell properties. *Cancer Res*. 1980;40:3502-3507
15. Pettengill OS, Sorenson GD, Wurster-Hill DH, et al. Isolation and growth characteristics of continuous cell lines from small-cell carcinoma of the lung. *Cancer*. 1980;45:906-918.
16. McCann FV, Pettengill OS, Cole JJ, Russell JA, Sorenson GD. Calcium spike electrogenesis and other electrical activity in continuously cultured small cell carcinoma of the lung. *Science*. 1981; 212:1155-1157.
17. Bertagna XY, Nicholson WE, Pettengill OS, Sorenson GD, Mount CD, Orth DN. Ectopic production of high molecular weight calcitonin and corticotropin by human small cell carcinoma cells in tissue culture: evidence for separate precursors. *J Clin Endocrinol Metab*. 1978;47:1390-1393.
18. Miller AB, Fox W, Tall R. Five-year follow-up of the Medical Research Council comparative trial of surgery and radiotherapy for the primary treatment of small-celled or oat-celled carcinoma of the bronchus. *Lancet*. 1969;2:501-505.
19. Fox W, Scadding JG. Medical Research Council comparative trial of surgery and radiotherapy for primary treatment of small-celled or oat-celled carcinoma of bronchus. Ten-year follow-up. *Lancet*. 1973;2:63-65.
20. Carney DN, Bunn PA Jr, Gazdar AF, Pagan JA, Minna JD. Selective growth in serum-free hormone-supplemented medium of tumor cells obtained by biopsy from patients with small cell carcinoma of the lung. *Proc Natl Acad Sci U S A*. 1981;78:3185-3189.
21. Gazdar AF, Carney DN, Sims HL, Simmons A. Heterotransplantation of small-cell carcinoma of the lung into nude mice: comparison of intracranial and subcutaneous routes. *Int J Cancer*. 1981;28:777-783.
22. Carney DN, Cuttitta F, Moody TW, Minna JD. Selective stimulation of small cell lung cancer clonal growth by bombesin and gastrin-releasing peptide. *Cancer Res*. 1987;47:821-825.
23. Hirsch FR, Matthews MJ, Aisner S, et al. Histopathologic classification of small cell lung cancer. Changing concepts and terminology. *Cancer*. 1988;62:973-977.
24. Bunn PA Jr, Carney DN, Gazdar AF, Whang-Peng J, Matthews MJ. Diagnostic and biological implications of flow cytometric DNA content analysis in lung cancer. *Cancer Res*. 1983;43:5026-5032.
25. Kok K, Osinga J, Schotanus DC, Berendsen HH, de Leij LF, Buys CH. Amplification and expression of different myc-family genes in a tumor specimen and 3 cell lines derived from one small-cell lung cancer patient during longitudinal follow-up. *Int J Cancer*. 1989;44:75-78.
26. Gazdar AF, Carney DN, Nau MM, Minna JD. Characterization of variant subclasses of cell lines derived from small cell lung cancer having distinctive biochemical, morphological, and growth properties. *Cancer Res*. 1985;45:2924-2930.
27. Carney DN, Gazdar AF, Bepler G,et al. Establishment and identification of small cell lung cancer cell lines having classic and variant features. *Cancer Res*. 1985;45:2913-2923.
28. Whang-Peng J, Bunn PA Jr, Kao-Shan CS, et al. A nonrandom chromosomal abnormality, del 3p(14-23), in human small cell lung cancer (SCLC). *Cancer Genet Cytogenet*. 1982;6:119-134.
29. Harbour JW, Lai SL, Whang-Peng J, Gazdar AF, Minna JD, Kaye FJ. Abnormalities in structure and expression of the human retinoblastoma gene in SCLC. *Science*. 1988;241:353-357.
30. Watanabe H, Takahashi T, Ueda R, et al. Antigenic phenotype and biological characteristics of two distinct sublines derived from a small cell lung carcinoma cell line. *Cancer Res*. 1988;48:2544-2549.
31. Minna JD, Battey JF, Brooks BJ, et al. Molecular genetic analysis reveals chromosomal deletion, gene amplification, and autocrine growth factor production in the pathogenesis of human lung cancer. *Cold Spring Harb Symp Quant Biol*. 1986;51 Pt 2:843-853.
32. Yesner R. Classification of lung-cancer histology. *N Engl J Med*. 1985;312:652-653.
33. Wu AH, Henderson BE, Thomas DC, Mack TM. Secular trends in histologic types of lung cancer. *J Natl Cancer Inst*. 1986;77:53-56.
34. Dodds L, Davis S, Polissar L. A population-based study of lung cancer incidence trends by histologic type, 1974-81. *J Natl Cancer Inst*. 1986;76:21-29.
35. Bunn PA Jr, Lichter AS, Makuch RW, et al. Chemotherapy alone or chemotherapy with chest radiation therapy in limited stage small cell lung cancer. A prospective, randomized trial. *Ann Intern Med*. 1987;106:655-662.
36. Cullen M, Morgan D, Gregory W, et al. Maintenance chemotherapy for anaplastic small cell carcinoma of the bronchus: A randomised, controlled trial. *Cancer Chemother Pharmacol*. 1986;17:157-160.
37. Controlled trial of twelve versus six courses of chemotherapy in the treatment of small-cell lung cancer. Report to the Medical Research Council by its Lung Cancer Working Party. *Br J Cancer*. 1989;59:584-590.
38. Giaccone G, Dalesio O, McVie GJ, et al. Maintenance chemotherapy in small-cell lung cancer: Long-term results of a randomized trial. European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. *J Clin Oncol*. 1993;11:1230-1240.
39. Hirsch FR, Hansen HH, Hansen M, et al.: The superiority of combination chemotherapy including etoposide based on in vivo cell cycle analysis in thebtreatment of extensive small-cell lung cancer: A randomized trial of 288 consecutive patients. *J Clin Oncol*. 1987;5:585-591.
40. Baize N, Monnet I, Greillier L, et al; Groupe Français de Pneumo-Cancérologie 01–13 investigators. Carboplatin plus etoposide versus topotecan as second-line treatment for patients with sensitive relapsed small-cell lung cancer: an open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol*. 2020;21:1224-1233.

41. Shepherd FA, Evans WK, Feld R, et al. Adjuvant chemotherapy following surgical resection for small-cell carcinoma of the lung. *J Clin Oncol*. 1988;6:832-838.
42. Zelen M. Keynote address on biostatistics and data retrieval. *Cancer Chemother Rep 3*. 1973;4:31-42.
43. Stahel RA, Ginsberg R, Havemann K, et al. Staging and prognostic factors in small cell lung cancer: A consensus report. *Lung Cancer*. 1989;5:119-126.
44. Sozzi G, Veronese ML, Negrini M, et al. The FHIT gene 3p14.2 is abnormal in lung cancer. *Cell*. 1996;85:17-26.
45. Dammann R, Li C, Yoon JH, Chin PL, Bates S, Pfeifer GP. Epigenetic inactivation of a RAS association domain family protein from the lung tumour suppressor locus 3p21.3. *Nat Genet*. 2000;25:315-319.
46. Shimizu E, Coxon A, Otterson GA, Steinberg SM, Kratzke RA, Kim YW, Fedorko J, Oie H, Johnson BE, Mulshine JL, et al. RB protein status and clinical correlation from 171 cell lines representing lung cancer, extrapulmonary small cell carcinoma, and mesothelioma. *Oncogene*. 1994;9:2441-2448.
47. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med*. 1992;327:1618-1624.
48. Murray N, Coy P, Pater JL, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 1993;11:336-344.
49. Turrisi AT 3rd, Kim K, Blum R, Sause WT, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med*. 1999;340:265-271.
50. Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med*. 1999;341:476-484.
51. Roth BJ, Johnson DH, Einhorn LH, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. *J Clin Oncol*. 1992; 10:282-291.
52. Fukuoka M, Furuse K, Saijo N, et al. Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. *J Natl Cancer Inst*. 1991;83:855-861
53. Murray N, Livingston RB, Shepherd FA, et al. Randomized study of CODE versus alternating CAV/EP for extensive-stage small-cell lung cancer: an Intergroup Study of the National Cancer Institute of Canada Clinical Trials Group and the Southwest Oncology Group. *J Clin Oncol*. 1999; 17:2300-2308.
54. Hansen HH, Rørth M. Lung cancer. *Cancer Chemother Biol Response Modif*. 1997; 17:444-463.
55. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol*. 1999;17:658-667.
56. Shepherd FA, Crowley J, Van Houtte P, et al; International Association for the Study of Lung Cancer International Staging Committee and Participating Institutions. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. *J Thorac Oncol*. 2007;2: 1067-1077.
57. Vallières E, Shepherd FA, Crowley J, et al; International Association for the Study of Lung Cancer International Staging Committee and Participating Institutions. The IASLC Lung Cancer Staging Project: Proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2009;4:1049-1059.
58. Pijls-Johannesma MC, De Ruysscher D, Lambin P, Rutten I, Vansteenkiste JF. Early versus late chest radiotherapy for limited stage small cell lung cancer. *Cochrane Database Syst Rev*. 2004; CD004700, 2005.
59. De Ruysscher D, Pijls-Johannesma M, Bentzen SM, et al. Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer. *J Clin Oncol*. 2006;24:1057-1063.
60. Bogart JA, Herndon JE 2nd, Lyss AP, et al; Cancer and Leukemia Group B study 39808. 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: Analysis of Cancer and Leukemia Group B study 39808. *Int J Radiat Oncol Biol Phys*. 2004; 59:460-468.
61. Noda K, Nishiwaki Y, Kawahara M, et al; Japan Clinical Oncology Group. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med*. 2002;346:85-91.
62. Hanna N, Bunn PA Jr, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol*. 2006;24:2038-2043.
63. Lara PN Jr, Natale R, Crowley J, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. *J Clin Oncol*. 2009; 27:2530-2535.
64. Ardizzoni A, Tjan-Heijnen VC, Postmus PE, et al; European Organization for Research and Treatment of Cancer-Lung Cancer Group. Standard versus intensified chemotherapy with granulocyte colony-stimulating factor support in small-cell lung cancer: A prospective European Organization for Research and Treatment of Cancer-Lung Cancer Group Phase III Trial-08923. *J Clin Oncol*. 2002;20:3947-3955.
65. Niell HB, Herndon JE 2nd, Miller AA, et al; Cancer and Leukemia Group. Randomized phase III intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B Trial 9732. *J Clin Oncol*. 2005;23:3752-3759.
66. O'Brien ME, Ciuleanu TE, Tsekov H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. *J Clin Oncol*. 2006;24:5441-5447.
67. Inoue A, Sugawara S, Yamazaki K, et al. Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0402. *J Clin Oncol*. 2008;26:5401-5406.
68. von Pawel J, Jotte R, Spigel DR, et al. Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. *J Clin Oncol*. 2014;32:4012-4019.
69. Ujhazy P, Lindwasser OW. Small cell lung cancer: Updates and new concepts. *Transl Lung Cancer Res*. 2018;7:1-3.
70. Travis WD, Brambilla E, Nicholson AG, et al; WHO Panel. The 2015 World Health Organization Classification of Lung Tumors: Impact of genetic, clinical and

radiologic advances since the 2004 classification. *J Thorac Oncol*. 2015;10:1243-1260.
71. Rudin CM, Poirier JT, Byers LA, et al. Molecular subtypes of small cell lung cancer: A synthesis of human and mouse model data. *Nat Rev Cancer*. 2019;19:289-297.
72. Baine MK, Hsieh MS, Lai WV, et al. SCLC subtypes defined by ASCL1, NEUROD1, POU2F3, and YAP1: A comprehensive immunohistochemical and histopathologic Characterization. *J Thorac Oncol*. 2020;15:1823-1835.
73. Faivre-Finn C, Snee M, Ashcroft L, et al; CONVERT Study Team. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. *Lancet Oncol*. 2017;18:1116-1125.
74. Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: A phase 3 randomised controlled trial. *Lancet*. 2015;385:36-42.
75. Slotman B, Faivre-Finn C, Kramer G, et al; EORTC Radiation Oncology Group and Lung Cancer Group. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med*. 2007;357:664-672
76. Slotman BJ, Mauer ME, Bottomley A, et al. Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. *J Clin Oncol.* 2009;27:78-84.
77. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18:663-671.
78. Schultheis AM, Scheel AH, Ozretić L, et al. PD-L1 expression in small cell neuroendocrine carcinomas. *Eur J Cancer*. 2015;51:421-426.
79. Gadgeel SM, Pennell NA, Fidler MJ, et al. Phase II study of maintenance pembrolizumab in patients with extensive-stage small cell lung cancer (SCLC). *J Thorac Oncol*. 2018;13:1393-1399.
80. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): A multicentre, open-label, phase 1/2 trial. *Lancet Oncol*. 2016;17:883-895.
81. Ott PA, Elez E, Hiret S, et al. Pembrolizumab in patients with extensive-stage small-cell lung cancer: Results from the phase Ib KEYNOTE-028 study. *J Clin Oncol*. 2017;35:3823-3829.
82. Chung HC, Piha-Paul SA, Lopez-Martin J, et al. Pembrolizumab after two or more lines of previous therapy in patients with recurrent or metastatic SCLC: Results from the KEYNOTE-028 and KEYNOTE-158 Studies. *J Thorac Oncol*. 2020;15:618-627.
83. Horn L, Mansfield AS, Szczęsna A, et al; IMpower133 Study Group. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. *N Engl J Med*. 2018;379:2220-2229.
84. Paz-Ares L, Dvorkin M, Chen Y, et al; CASPIAN investigators. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2019;394:1929-1939.
85. Lok BH, Gardner EE, Schneeberger VE, et al. PARP inhibitor activity Correlates with SLFN11 expression and demonstrates synergy with temozolomide in small cell lung cancer. *Clin Cancer Res*. 2017;23:523-535.
86. Pietanza MC, Waqar SN, Krug LM, et al. Randomized, double-blind, phase ii study of temozolomide in combination with either veliparib or placebo in patients with relapsed-sensitive or refractory small-cell lung cancer. *J Clin Oncol*. 2018;36:2386-2394.
87. Byers L. Progress and Promise in Small Cell Lung Cancer. Presented at: 2023 IASLC Targeted Therapies in Lung Cancer Meeting: February 22-25, 2023; Santa Monica, CA. abstract OK.01.
88. Gay CM, Stewart CA, Park EM, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. *Cancer Cell*. 2021;39:346-360.
89. Xie M, Chugh P, Braodhurst H, Lai Z, Whitston D, Paz-Ares L, Gay C, Byers L, Rudin CM, Stewart R, Barrett JC, Shrestha Y. Durvalumab + platinum-etoposide in first-line extensive-stage small cell lung cancer: exploratory analysis of SCLC molecular subtypes in CASPIAN. Presented at: 2022 AACR Annual Meeting: April 8-13, 2022; New Orleans, LA. abstract CT024.
90. Frese KK, Simpson KL, Dive C. Small cell lung cancer enters the era of precision medicine. *Cancer Cell*. 2021;39:297-299.
91. Hou JM, Krebs MG, Lancashire L, et al. Clinical significance and molecular characteristics of circulating tumor cells and circulating tumor microemboli in patients with small-cell lung cancer. *J Clin Oncol*. 2012;30:525-532.
92. Foy V, Fernandez-Gutierrez F, Faivre-Finn C, Dive C, Blackhall F. The clinical utility of circulating tumour cells in patients with small cell lung cancer. Transl Lung Cancer Res. 2017; 6:409-417.
93. Chemi F, Pearce SP, Clipson A, et al. cfDNA methylome profiling for detection and subtyping of small cell lung cancers. *Nat Cancer*. 2020;3:1260-1270.
94. Rudin CM, Awad MM, Navarro A, et al; KEYNOTE-604 Investigators. Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: Randomized, double-blind, phase III KEYNOTE-604 study. *J Clin Oncol*. 2020;38:2369-2379.
95. Cheng Y, Han L, Wu L, et al; ASTRUM-005 Study Group. Effect of first-line serplulimab vs placebo added to chemotherapy on survival in patients with extensive-stage small cell lung cancer: The ASTRUM-005 randomized clinical trial. *JAMA*. 2022;328:1223-1232.
96. Owonikoko TK, Park K, Govindan R, et al. Nivolumab and ipilimumab as maintenance therapy in extensive-disease small-cell lung cancer: CheckMate 451. *J Clin Oncol*. 2021;39:1349-1359.
97. Peters S, Pujol JL, Dafni U, et al; ETOP/IFCT 4-12 STIMULI Collaborators. Consolidation nivolumab and ipilimumab versus observation in limited-disease small-cell lung cancer after chemo-radiotherapy - Results from the randomised phase II ETOP/IFCT 4-12 STIMULI trial. *Ann Oncol*. 2022;33:67-79.
98. Ahn MJ, Cho BC, Felip E, et al. Tarlatamab for patients with previously treated small-cell lung cancer. *N Engl J Med*. 2023; 389:2063-2075. [PMID: 37861218]
99. Byers L, Heymach J, Gibbons D, et al. A phase 1 study of AMG 119, a DLL3-targeting, chimeric antigen receptor (CAR) T cell therapy, in relapsed/refractory small cell lung cancer (SCLC). Presented at: SITC 37th Annual Meeting: November 8-12, 2022; Boston, MA. abstract 697.
100. Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. *Lancet Oncol.* 2020;21:645-654.
101. Kundu K, Cardnell RJ, Zhang B, et al. SLFN11 biomarker status predicts response to lurbinectedin as a single agent and in combination with ATR inhibition in small cell lung cancer. *Transl Lung Cancer Res*. 2021;10:4095-4105.

19



ADVANCES IN MOLECULAR THERAPY

Molly Li,[*1] **Claudia Parisi,**[*2] **Pasi A Jänne,**[3] **Benjamin Solomon,**[4] **Fabrice Barlesi,**[+2] **and Tony Mok**[+1] | [1]Chinese University of Hong Kong, Hong Kong, China; [2]Gustave Roussy, Paris, France; [3]Dana-Farber Cancer Institute, Boston, USA; [4]Peter MacCallum Cancer Centre, Melbourne, Australia. **Both authors contributed equally. [+]Senior authors.*

Over the past two decades, the discovery of multiple driver oncogenic alterations and their relevant targeted therapies have transformed the treatment landscape of non-small cell lung cancer (NSCLC). Globally, many patients attribute their dramatic tumor responses and prolonged survival to molecular targeted therapies. This has led to an era of precision oncology, also called personalized therapy. This comprehensive approach has not only impacted treatment strategies, but also molecular diagnostics, clinical trial designs, and regulatory standards, to name a few.[1,2]

In 2020, the United States first reported an accelerated decline in lung cancer mortality (incidence based mortality among men reduced annually by 6.3% from 2013 to 2016, compared to 3.2% from 2006 to 2013; similar trend was observed among women), which was attributed to the adoption of targeted therapies.[3] Multiple retrospective analyses have consistently demonstrated improved survival outcomes in patients who received genome-matched targeted therapies, compared to those who did not.[4-6] Additionally, molecular therapies are associated with favorable toxicity profiles that support quality of life. Even patients with poor performance status may still benefit from molecular therapies.[7]

Based on these developments, NSCLC treatment is now based on both histologic subtype and molecular profile.[8-10] All international management guidelines recommend mandatory testing for oncogenic drivers in newly diagnosed metastatic lung adenocarcinoma (LUAD). Despite good initial responses to molecular therapy in most patients, primary and acquired resistance remains a major challenge and extensive research has been dedicated to the topic. Molecular therapies tailored to overcome resistance mechanisms have emerged for patients who fail first-line treatment. Table 1 and Figure 1 summarize the landmark trials and the list of FDA-approved molecular therapies in NSCLC, respectively.

The IASLC has played an instrumental role in facilitating scientific developments regarding molecular targeted therapies. This has been achieved through several mechanisms. Notably, the transition to an annual World Conference on Lung Cancer was clearly a requested need to disseminate new scientific findings in a timely manner. Annual Targeted Therapies of Lung Cancer meetings started in Aspen, Colorado, in 2000 and have continued annually in Santa Monica. These meetings provide a vital platform for discussing the rapid developments in targeted therapy while fostering collaboration with industry partners. Moreover, the establishment of regional lung cancer meetings in Latin America, Asia, Europe, and North America has significantly contributed to educational initiatives, thus spreading new results to communities worldwide. In addition, the IASLC also developed "Diagnostic Atlases" in order to reach out to communities and give guidance in navigating the rapidly changing diagnostic and therapeutic

Table 1. Landmark Trials in Molecular Therapies in NSCLC

Randomized Clinical Trials							
	Study Drug	**Comparator**	**Median BIRC-assessed PFS, months**	**PFS, HR**	**Median OS, months**	**OS, HR**	**Ref**
EGFR							
IPASS (EGFR mutation positive)	Gefitinib	Chemotherapy	9.5 vs 6.3	0.48	21.6 vs 21.9	1.0	44, 45
AURA3	Osimertinib	Chemotherapy	11.0 vs 4.2	0.28	26.8 vs 22.5	0.87	60, 61
FLAURA	Osimertinib	1st generation EGFR TKI	17.7 vs 9.7	0.45	38.6 vs 31.8	0.80	59, 62
FLAURA2	Osimertinib Pemetrexed Platinum	Osimertinib	29.4 vs 19.9	0.62	N/A	N/A	63
MARIPOSA	Amivantamab Lazertinib	Osimertinib	23.7 vs 16.6	0.70	N/A	N/A	64
ADAURA (stage IB to III)	Osimertinib	Placebo	DFS per investigator: 65.8 vs 28.1	0.27	5-year OS: 88% vs 78%	0.49	22, 90
LAURA	Osimertinib	Placebo	39.1 vs 5.6	0.16	N/A	N/A	91
PAPILLON	Amivantamab Pemetrexed Platinum	Chemotherapy	11.4 vs 6.7	0.40	N/A	N/A	86
ALK							
PROFILE-1014	Crizotinib	Chemotherapy	10.9 vs 7.0	0.45	4-year OS: 57% vs 49%	0.76	95, 96
ALEX	Alectinib	Crizotinib	25.7 vs 10.4	0.50	5-year OS: 63% vs 46%	0.67	103, 109
CROWN	Lorlatinib	Crizotinib	NR vs 9.3	0.28	N/A	N/A	107
ALINA (stage IB to III)	Alectinib	Chemotherapy	DFS per investigator: NR vs 41.3	0.24	N/A	N/A	21
KRAS G12C							
CODEBREAK-200	Sotorasib	Docetaxel	5.6 vs 4.5	0.66	10.6 vs 11.3	1.01	132
RET							
LIBRETTO-431	Selpercatinib	Chemotherapy with or without Pembrolizumab	24.8 vs 11.2	0.46	N/A	N/A	163

Single-arm Clinical Trials						
	Study Drug	**Sample Size**	**ORR, %**	**Median PFS, months**	**Median OS, months**	**Ref**
ROS1						
PROFILE-1001	Crizotinib	53	72	19.3	51.4	120
TRIDENT-1	Repotrectinib (ROS1 TKI naïve)	71	79	35.7	N/A	125
BRAF V600E						
	Dabrafenib + Trametinib (1st line)	36	64	10.8	17.3	143
HER2						
DESTINY-LUNG 02	Trastuzumab deruxtecan 5.4mg/kg (2nd line)	102	49	9.9	19.5	151
MET ex14 skipping						
GEOMETRY	Capmatinib (1st line)	28	68	12.4	20.8	171
VISION	Tepotinib (any line)	152	46	8.5	17.6	172
NTRK						
	Larotrectinib	20	73	35.4	40.7	180
	Entrectinib	51	63	28.0	41.5	184

Abbreviations: BIRC, blinded independent review committee; HR, hazard ratio; PFS, progression-free survival; ORR, objective response rate; OS, overall survival.

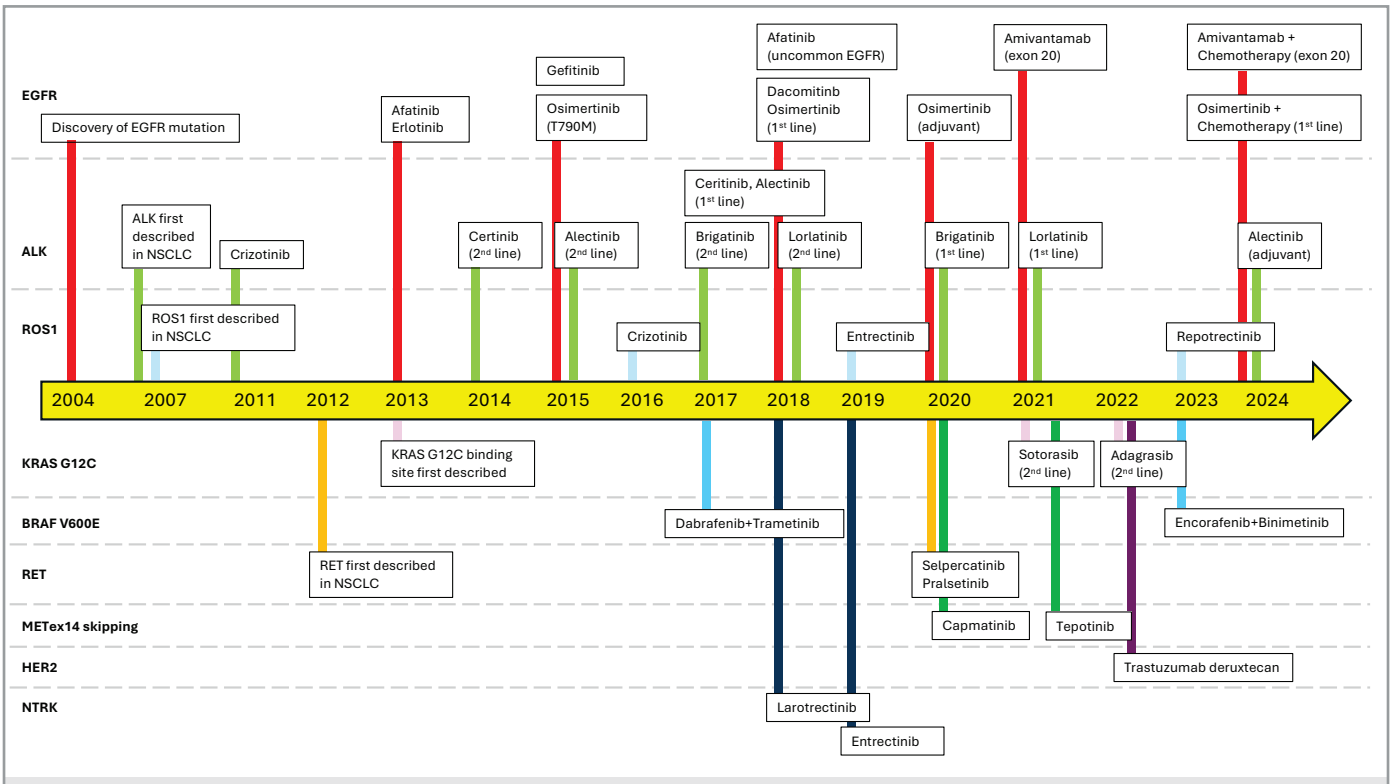


Figure 1. Timeline of FDA approval for molecular therapies in NSCLC.

landscapes, including Atlases for epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), and immunohistochemistry. Furthermore, the IASLC collaborates with organizations such as the College of American Pathologists (CAP) and the American Society for Molecular Pathology (AMP) on guidance for molecular testing in personalized medicine.[11]

OVERVIEW OF ADVANCES IN MOLECULAR THERAPIES IN NSCLC

Oncogene Addiction in NSCLC

About 40% to 60% of NSCLCs harbor a driver oncogenic alteration.[12] The phenomenon of "oncogene addiction" implies that the driver oncogene is often clonal and plays a central part in oncogenesis. As a result, inhibition of the driver oncogene with molecular therapy leads to cancer cell death.[13] Due to inhibition of a selective biological pathway, molecular therapies are typically associated with fewer toxicities, unlike cytotoxic chemotherapy that affects both normal growing and malignant cells.

Conventionally, two major classes of molecular targeting therapies are available for NSCLC treatment: small molecule inhibitors (SMIs) and monoclonal antibodies (MoAbs). SMIs generally act intracellularly by inhibition of gene-specific tyrosine kinases, whereas MoAbs act extracellularly by binding to transcellular receptors and plasma proteins. Most SMIs, such as those targeting *EGFR* mutation or *ALK* translocation, function as receptor tyrosine kinase inhibitors (TKIs), potentially disrupting their downstream signalling pathways directly. MoAbs, on the other hand, operate by either blocking ligand-receptor binding or by promoting immune-mediated destruction of tumor cells.

The past decade has witnessed significant advances in molecular therapy development in multiple ways. This includes improvement and innovations in drug design, clinical application, and relevant diagnostic strategies (Figure 2).

Refinements in Drug Design

Clinical challenges of molecular therapy include therapeutic

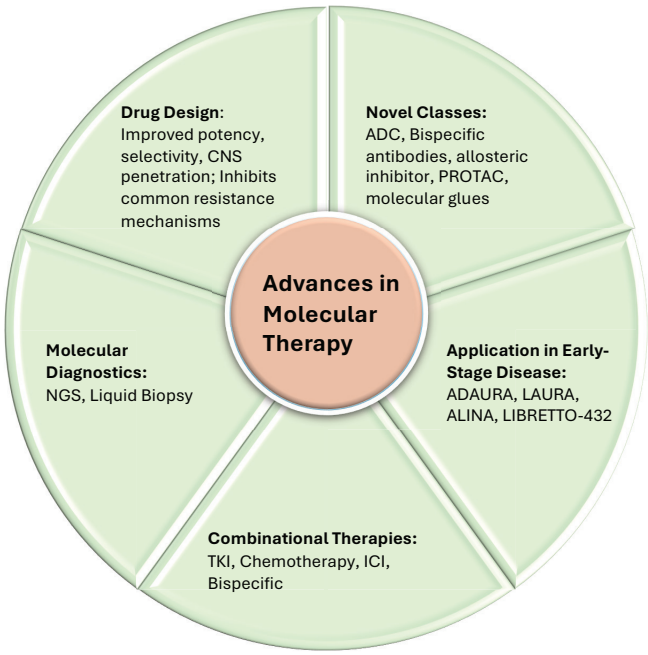


Figure 2. The multifaceted development in molecular therapy.

resistance, either systemic or intracranial, and treatment-related toxicities. Newer generations of targeted therapies are designed to overcome these challenges with increased potency and selectivity in oncogene inhibition and better CNS penetration. It is also important for next-generation targeted therapies to be able to overcome common, recurrent resistance mechanisms. The progress in molecular therapy development in NSCLC, using *EGFR* as an example, is summarized in Table 2.

Novel Drug Classes

Advances in bioinformatics and structural modelling techniques have led to development of novel classes of molecular therapies apart from TKIs and MoAbs.[14] New classes of MoAb, namely antibody-drug conjugates (ADCs) and bispecific antibodies, have been introduced into clinic for lung cancer treatment. ADCs connect MoAbs to cytotoxic payloads via linkers. ADCs are stable within circulation, but upon antibody-tumor binding, the complex is internalized into the cytoplasm where the linker is degraded, releasing the cytotoxic payload.[15] This process ensures selective delivery of cytotoxic agent into cancer cells and a wider therapeutic index can be achieved. Instead, bispecific antibodies can be harnessed to reduce drug resistance or activate antitumor immunity by simultaneously targeting two antigens.[16]

Other novel classes showing promising data include allosteric inhibitors, tri-complex inhibitors, and targeted protein degraders. Allosteric inhibitors bind to target proteins outside their kinase ATP/GTP-binding sites. As a result, kinase inhibition can still be achieved in proteins without drug-binding pockets and those with acquired resistance mutations preventing drug binding at the kinase domain.[17,18] As its name suggests, tri-complex inhibitors bind to the target protein and cyclophilin A, forming a tri-complex that sterically blocks target protein activation. These compounds are now actively tested in tumors harboring *KRAS* mutations.[19] Targeted protein degraders, such as PROTACs (proteolysis-targeting chimera) and molecular glues, facilitates degradation of oncogenic proteins by linking up the targeted protein with an E3 ubiquitin ligase. Targeted protein degraders targeting *EGFR, ALK*, and *KRAS* mutant proteins are under development.[20]

Application in Early-Stage Disease

Adjuvant chemotherapy offer modest survival benefit in patients with lung cancer after surgical resection. Targeted therapies such as osimertinib and alectinib display favorable toxicity profiles and high CNS efficacy thus are ideal agents to be adopted in adjuvant setting. Both adjuvant osimertinib and alectinib dramatically reduced recurrence in patients with early-stage disease after tumor resection.[20,22,23] Drug discontinuation rates were low and patients had preserved

Table 2. Progress in TKI Development Using *EGFR* as an Example

	1st Generation	2nd Generation	3rd Generation	Combination Strategies	
Example	Erlotinib, Gefitinib	Afinitib, Dacomitinab	Osimertinib	Osimertinib + Chemotherapy	Lazertinib + Amivantamab
Drug Characteristics					
Potency	+	++	++	N/A	N/A
Mutant to wild-type selectivity	+	–	++	N/A	N/A
Resistance inhibition	–	–	Inhibits T790M	N/A	Enhanced EGFR and MET inhibition
CNS efficacy	+	+	++	+++	Unpublished
Clinical Data					
mPFS (1st line)	9-13 months	11-14 months	19 months	25 months	24 months
Toxicity	+	++ (skin, GI)	+	++ (cytopenia)	++ (skin, VTE)
Common Resistance Profile	~50-60% develop T790M mutation		EGFR C797S MET amplification	Similar to osimertinib	Unpublished

quality-of-life despite years of treatment.[24,25] As a result, molecular testing for *EGFR* and *ALK* is now mandated in early-stage NSCLC. While similar trials in other rare oncogenic drivers are ongoing (e.g., NAUTIKA2, NCT04302025; LIBRETTO-432, NCT03157128), whether these results can be directly extrapolated to these rare genetic alterations is under active debate.

Achieving Synergism With Combinational Therapies

Various molecular therapy drug combinations have been investigated to explore potential synergistic effect. Combining a targeted therapy with another targeted therapy may enable inhibition of feedback pathways or acquired resistance mechanisms, while combining a targeted therapy with chemotherapy may delay therapeutic resistance through elimination of residual resistant clones.

There is also interest in combining TKI with immune checkpoint inhibitors (ICI). However, some of these combinations are not feasible due to excessive toxicities. For instance, the combination of osimertinib and ICI results in high rates of pneumonitis, and the combination of sotorasib and ICI results in high rates of hepatotoxicity.[26,27] This underscores the importance of toxicity monitoring when combinational strategies are included in the drug development roadmap.

Biomarker Testing

Accurate and efficient biomarker testing is essential for precision oncology. The diagnostic paradigm of NSCLC has dramatically evolved along with emerging treatment options and advancing molecular testing technologies. Conventionally, single biomarker testing was performed sequentially, considering the mutually exclusive nature of driver mutations. Standard testing methods include polymerase chain reaction (PCR), immunohistochemistry (IHC), and fluorescence in situ hybridization (FISH). These tests are characterized by low costs, short turnaround times, and high accessibility in local community facilities.

As the list of actionable genomic alterations continues to expand, multiplexed genomic assays via next-generation sequencing (NGS) have become more important. NGS allows for the simultaneous analysis of

multiple genes, providing a comprehensive genomic profile from a single test. Multiple studies have demonstrated that NGS identified more actionable oncogenes compared to sequential biomarker testing.[28,29] The IASLC, in collaboration with the CAP, has provided guidelines to standardized molecular testing for these biomarkers, ensuring that patients receive the most effective treatments based on their genetic profiles.[8]

The major barrier to molecular testing is inadequate tumor sample, especially when only small tumor biopsy or cytology samples are available. Liquid biopsy via circulating tumor DNA (ctDNA) is an alternative for molecular testing when tumor DNA is insufficient.[30] Multiple prospective clinical studies have validated the predictive ability of plasma genotyping.[31-33] However, the sensitivity of plasma genotyping ranges from 60% to 85%, depending on the testing platform, tumor burden, and whether the tumor sheds DNA into circulation.[34-36] For patients who fail *EGFR* and *ALK*-targeted therapy, ctDNA testing is considered standard of care for evaluating drug resistance mechanism. Compared with tumor re-biopsy, liquid biopsy is more efficient, repeatable, and may better capture tumor heterogeneity.[30] In 2018, the IASLC published the first statement article on liquid biopsy for advanced NSCLC[37]; this was followed by an update in 2021 in view of the rapidly evolving diagnostic landscape in NSCLC.[30]

SPECIFIC DRIVER ONCOGENES

Epidermal Growth Factor Receptor

The discovery of sensitizing *EGFR* mutations marked the beginning of the molecular era in lung cancer treatment. Initially investigated without knowledge of *EGFR* mutations, the first-generation EGFR TKIs, erlotinib and gefitinib, were approved as salvage therapies for all lung cancer patients following chemotherapy failure.[30,39] However, tumor response rate with EGFR TKI was less than 10% in an unselected population.[40] In 2004, two research groups sequenced the *EGFR* gene from tumor samples of patients with dramatic responses to either gefitinib or erlotinib, identifying two specific mutations in the kinase domain of *EGFR* that led to sustained activation of cellular signalling and cancer development.[41,42] These mutations, namely *EGFR* exon 19 deletion and exon 21 L858R point mutation, constitute 90% of activating *EGFR* mutations. There is significant geographical heterogeneity, with *EGFR* mutation present in 40% of Asians but only 15% of Caucasians with NSCLC.[43] *EGFR* mutation is also enriched among females and non-smokers.

The IPASS study was the milestone in defining personalized medicine for lung cancer. This trial verified that patients with *EGFR* mutation benefited more from gefitinib than standard chemotherapy (tumor response rate 71% versus 47%), while patients without the *EGFR* mutation did not benefit from gefitinib (tumor response rate 1%).[44,45] This interaction test definitively established the role of *EGFR* mutation as a predictive biomarker. Subsequent randomized studies exclusively enrolled patients with proven *EGFR* mutation, and all of them demonstrated superiority of EGFR TKI over chemotherapy in terms of tumor response rate and progression-free survival (PFS).[46-50] Patient treated with EGFR TKI also experienced less treatment-related adverse events and reported better quality of life.[44] These studies have established a new paradigm of molecular testing in advanced lung cancer and the selection of therapy based on mutation status.

Second generation EGFR TKIs, namely afatinib and dacomitinib, are irreversible pan-HER inhibitors with increased potency of EGFR inhibition compared to first generation TKI. Randomized studies comparing second generation EGFR TKIs with gefitinib as first-line treatment demonstrated improved PFS.[51,52] However, treatment-related toxicity remains a major limitation for second-generation EGFR TKIs. Due to potent inhibition of wild-type EGFR, a significant portion of patients may experience grade 2 to 3 skin rash and diarrhea, with more than 50% requiring dose reduction.

Acquired resistance to first- and second-generation EGFR TKIs invariably develops after a median of 9 to 14 months, with the *EGFR* exon 20 Thr790M (T790M) point

mutation constituting approximately 50% of cases.[53,54] Third-generation EGFR TKIs such as osimertinib were designed to target both sensitizing *EGFR* mutations and the acquired exon 20 T790M mutations by using a pyrimidine-based molecule that binds in proximity to the exon 20 C797 site.[55] Comparing to first- and second-generation EGFR TKIs, osimertinib also demonstrated improved CNS penetration and increased selectivity of mutant-to-wild type EGFR inhibition, with less skin toxicities.[56-59] AURA3 was a randomized phase III study that demonstrated improvements in tumor response rates and PFS with osimertinib over platinum-based chemotherapy in T790M mutation-positive patients.[60,61] This led to a new paradigm of testing for T790M mutation from either plasma cell-free DNA (cfDNA) or tumor re-biopsy in all patients who had failed first- or second-generation EGFR TKIs. The FLAURA study investigated first-line osimertinib against first-generation EGFR TKIs and reported improvements in both PFS and OS.[59,62] Based on the FLAURA study, osimertinib is now adopted as the current standard of care in multiple countries.

Attempts to delay third-generation EGFR TKI resistance include combining third-generation EGFR TKI with platinum-based chemotherapy or bispecific antibody such as amivantamab. FLAURA2 compared osimertinib plus platinum-based chemotherapy against osimertinib and MARIPOSA compared amivantamab with lazertinib (a third-generation EGFR TKI) against osimertinib in the first-line setting.[63,64] Both studies met the primary endpoint with significant PFS improvement thus establishing these regimens as viable first-line treatment options. However, these regimens are associated with increased toxicities and require regular infusions. Selection of the optimal first-line regimen requires an individualized approach, taking tumor factor, treatment factor, patient preference, and drug accessibility into consideration.[65]

Acquired resistance to osimertinib involves multiple mechanisms of action.[66] The most significant on-target (EGFR-dependent) resistance mechanism is the development of C797S mutation at exon 20. Bypass signalling pathway activation, such as mesenchymal-to-epithelial transition (*MET*) and human epidermal growth factor receptor 2 (*HER2*) amplification, may account for approximately 20% of the resistance, while other targetable alterations such as *ALK* and *RET* fusion, *BRAF* V600E mutation, may account for 1-2% of cases. About 10% of cases may develop mesenchymal transformation to small-cell lung cancer histology.[66,67]

Multiple treatment strategies have emerged for management of osimertinib resistance, which can be broadly classified into chemotherapy-based or genotype-guided approach. For years, platinum-based doublet chemotherapy has remained the standard treatment for patients following TKI resistance. MARIPOSA-2 was a phase III trial that showed adding amivantamab on top of chemotherapy improved tumor response and PFS albeit with increased toxicities.[68] Several phase III trials compared the combination of anti-PD-(L)1 plus anti-VEGF plus chemotherapy versus chemotherapy alone but yielded conflicting results.[69-72]

Genotyping-guided approach involves combining EGFR TKI with another molecular therapy tailored to the identified resistance mechanism, with early data showing encouraging results. For example, the combination of EGFR TKI and MET inhibitor, such as tepotinib or savolitinib, in patients with *MET* amplification reported objective response rates (ORR) of 30% to 60% in the INSIGHT-2 and SAVANNAH studies.[73,74] However, definition of *MET* amplification remains to be defined. Randomized comparative trials, such as SAFFRON (NCT05261399), comparing osimertinib- savolitinib combination with standard platinum-based chemotherapy in patients with MET amplification as defined by protein expression, are ongoing. Clinical efficacy of combining EGFR TKI with other targeted therapies tailored to specific resistance mechanisms has been supported by case series.[75-77]

Antibody-drug conjugates (ADC) have demonstrated promising efficacy against *EGFR*-mutant NSCLC. Patritumab-

deruxtecan, an ADC targeting HER3, achieved an ORR of 30% and median PFS of 5.5 months in a phase II study involving 225 patients who were previously treated with EGFR TKI and platinum-based chemotherapy.[78] Datopotamab deruxtecan, a TROP-directed ADC, demonstrated ORR of 44% among 77 patients with heavily-pretreated disease.[79] Clinical efficacy was observed independent of specific resistance mechanisms to prior EGFR TKI, while biomarkers for ADCs are still under investigation.

Uncommon *EGFR* mutations constitute approximately 10% of all *EGFR* mutations. A combined post-hoc analysis of LUX-Lung 2, 3, and 6 studies showed that afatinib to be efficacious, with a pooled ORR of 71% against *EGFR* G719X, L861Q, and S768I mutation-positive NSCLC.[80] Two phase II studies investigating the use of osimertinib in patients with uncommon mutations also reported similar response rate.[81,82] A recent study on the combination of amivantimab and lazertinib also reported high ORR of 55% and prolonged PFS of 19.5 months among 49 patients without prior EGFR TKI treatment.[83]

Contrarily, *EGFR* exon 20 insertions were traditionally considered "non-targetable" as they are resistant to conventional EGFR TKIs due to their unique steric configurations.[84] Amivantamab, an anti-EGFR-MET bispecific antibody, and novel EGFR exon 20 targeting TKIs have demonstrated promising treatment efficacy. Amivantamab exhibited tumor response rate of 36% following chemotherapy failure.[85] The phase III PAPILLON study investigated the combination of amivantamab plus chemotherapy and demonstrated superior efficacy over chemotherapy alone as first-line treatment in patients with NSCLC harboring *EGFR* exon 20 insertions.[86] *EGFR* exon 20 targeting TKIs, such as sunvozertinib and zipalertinib, exhibited tumor response rates of 38-61% in single arm studies.[87-89] First-line clinical trials investigating *EGFR* exon 20 targeting TKIs are ongoing (NCT05668988, NCT05973773, NCT05607550).

The role of EGFR-TKI in early-stage NSCLC was explored, given the huge success in treating metastatic disease. The ADAURA study enrolled patients with resected stage IB-IIIA (AJCC 7th edition) NSCLC harboring *EGFR* mutation and randomized them to three years of osimertinib versus placebo. A significant improvement in DFS and OS was observed with osimertinib, with a hazard ratio of 0.20 and 0.50, respectively.[22,23] Patients in the osimertinib arm also had significantly less CNS recurrence.[90] This study established the role of adjuvant osimertinib in *EGFR* mutation positive NSCLC after surgical resection and the need for molecular testing in early-stage disease. The LAURA study investigated osimertinib in patients with unresectable stage III NSCLC after radical chemoradiotherapy. Patients achieved significantly longer PFS with osimertinib (39.1 months) compared to placebo (5.6 months, HR 0.16), establishing osimertinib as a new standard of care in this population.[91] Outstanding questions regarding adjuvant EGFR TKI include patient selection, optimal treatment duration, management of disease recurrence after adjuvant TKI, and whether these data can be extrapolated to other rarer driver mutations.

Year 2024 marked the 20th anniversary since the discovery of *EGFR* mutation. Now we have multiple treatment options approved for patients with *EGFR* mutation-positive NSCLC, in both early and advanced stage.

ANAPLASTIC LYMPHOMA KINASE

ALK rearrangement was first discovered in anaplastic large-cell lymphoma, which led to its naming.[92] *ALK* rearrangements are present in 3% to 8% of NSCLCs, with a higher occurrence among young individuals who have never smoked or are light smokers.[93] The most prevalent *ALK* abnormalities involve the fusion of EML4 with *ALK* in NSCLC. NSCLC with *ALK* fusions is commonly associated with CNS metastasis, reaching 30% to 40% at the time of presentation.[94]

Crizotinib was the first ALK TKI that demonstrated superiority over platinum-based chemotherapy for treatment-naïve *ALK*-positive NSCLC in the randomized phase III PROFILE 1014 trial.[95,96] Second-generation ALK TKIs offer higher

potency, increased specificity, and better CNS penetration.[97] Four second-generation ALK TKIs, namely, ceritinib, alectinib, brigatinib, and ensartinib, reported ORR ranging from 38% to 69% after crizotinib failure.[98-101] Ceritinib was initially compared with chemotherapy in treatment-naïve patients and reported a median PFS of 16.6 months versus 8.1 months.[102] However, due to significant gastrointestinal toxicities, this drug has not been widely adopted in clinical practice. Three major randomized studies compared second-generation ALK TKIs with crizotinib.[103-105] Median PFS with first-line second-generation ALK TKIs could exceed 34 months, compared to about 10 months with crizotinib.

Lorlatinib, classified as a third-generation ALK TKI, is a macrocyclic compound with high CNS penetration and the ability to inhibit selective resistant mutations.[106] The CROWN study, a randomized phase III trial, compared first-line lorlatinib with crizotinib. Median PFS was not reached with lorlatinib, versus 9.3 months with crizotinib (HR 0.28).[107] The 3-year progression free rate with lorlatinib was 63%.[108] When cross-trial comparisons were made with alectinib and brigatinib, the 3-year progression-free rates in ALEX and ALTA-1 were 45% and 43%, respectively.[109,110] Recently, a post-hoc analysis of 5-year follow-up results of CROWN was presented, and median PFS was not reached in the lorlatinib arm.[111] This was the longest PFS ever reported with targeted therapy across all metastatic solid tumors.

CNS control is an important endpoint in clinical trials involving ALK TKIs. Crizotinib has poor CNS penetration, thus intracranial failure is common. Second-generation TKIs demonstrated lower rates of CNS relapse compared to crizotinib.[103-105] Among patients with baseline CNS metastases in the CROWN study, complete intracranial RR with lorlatinib reached 60%. Median time to intracranial failure was NR compared to 7.2 months in crizotinib (HR 0.03) after 5 years.[111] Among patients without CNS metastases at baseline, lorlatinib offered significantly superior CNS protection (HR 0.05).[111] The role of upfront radiotherapy to brain metastasis is debatable, given the high CNS efficacy with systemic therapy. While lorlatinib demonstrated superior efficacy, ongoing debate persists regarding its toxicity profile compared to second-generation ALK TKIs, raising questions about which agent should be prioritized as first-line treatment.

Resistance mechanisms to ALK TKIs encompass both on-target and off-target mechanisms. On-target resistance commonly involves *ALK* kinase domain mutations that interfere with drug-binding constitute a major aspect of on-target resistance, occurring more frequently after exposure to second-generation TKIs compared to crizotinib. Among these mutations, the G1202R solvent-front mutation is the most common, occurring in 20% to 40% of patients after second-generation TKI failure.[112] Lorlatinib is the preferred drug for patients harboring this resistance mutation.[106]

Analyses of post-progression tumor and plasma samples suggest that sequential ALK-inhibitor treatment may predispose to the emergence of compound *ALK*-resistant mutations, potentially conferring resistance to lorlatinib.[113,114] The development of fourth-generation ALK TKIs, such as NVL-655, is underway to overcome double- or triple-mutant-resistant kinase mutations.[115] Contrarily, preliminary data from CROWN showed that no ALK resistance mutations were detected among patients after first-line lorlatinib failure.[111] Further understanding of resistance mechanisms to first-line lorlatinib is needed.

The ALINA trial studied the role of adjuvant alectinib in early-stage setting. Patients with completely resected stage IB (≥4cm)-III *ALK* positive NSCLC were randomized to two years of adjuvant alectinib versus four cycles of platinum-based chemotherapy. In ALINA, two-year PFS was 94% in the alectinib arm versus 64% in the chemotherapy arm, corresponding to a HR of 0.24. CNS recurrence was significantly reduced in the alectinib arm (HR 0.22). Based on ALINA, adjuvant alectinib is now the standard of care for patients with resected stage IB (≥4cm)-III NSCLC harboring *ALK* rearrangement.[21]

ROS1

ROS1 rearrangements account for 1% to 2% of lung adenocarcinoma cases.[116] To date, more than 20 *ROS1* fusion partners have been identified in *ROS1* rearranged NSCLCs, with CD74 being the most common.[117] The kinase domain of *ROS1* shares 70% homology with ALK, although not all ALK TKIs may be effective against *ROS1*-driven NSCLC.[118]

Crizotinib, the first approved ROS1 inhibitor, demonstrated an ORR of 72% and a median PFS of 19.3 months in 53 subjects enrolled to the single-arm PROFILE 1001 study.[119,120] Ceritinib showed similar activity in treatment-naïve *ROS1*-positive NSCLC patients but was ineffective against crizotinib-resistant tumors.[121] Entrectinib was approved based on data from three large multicenter, single-arm studies.[122] Its response rates and median PFS of entrectinib (ORR 77%, median PFS 19.0 moths) were similar to those of crizotinib. However, unlike crizotinib, entrectinib demonstrated superior intracranial activity (intracranial ORR 55%), making it the preferred treatment for patients with brain metastases.[122]

The G2032R mutation in the *ROS1* kinase domain prevents drug binding and is the most common resistance mechanism post-crizotinib treatment.[123] While lorlatinib has shown promise with a 35% ORR and 50% intracranial ORR in resistant populations, its activity against the G2032R mutation remains uncertain.[124] Second-generation ROS1 TKIs, such as repotrectinib and taletrectinib, may overcome ROS1 G2032R resistance and demonstrate potent intracranial activity.[125,126] In the TRIDENT-1 study, repotrectinib achieved ORR of 38% and median PFS of 9.0 months among 56 patients who had previously received one ROS1 TKI. In patients who had not previously received ROS1 TKI, ORR was 79% and median PFS was 35.7 months.[125] Repotrectinib received FDA approval for treatment of *ROS1* positive NSCLC in both TKI-naïve or TKI-resistant setting in November 2023.

KRAS

The human homologue of the Kirsten rat sarcoma viral oncogene (*KRAS*) was first discovered in 1982.[127] *KRAS* encodes a membrane-bound G-protein with intrinsic guanosine triphosphatase (GTPase) activity. Mutations in KRAS occur in about 20% to 30% of LUADs in Western population and less frequently in Asians.[128] In contrast to other oncogenic drivers, KRAS mutations occur mostly in smokers. Amino acid substitution of glycine by cysteine at codon 12 (*KRAS* G12C) accounts for about 40% of KRAS mutations in NSCLC.[128] Co-mutations, including *TP53, STK11*, and *KEAP1*, may have potential impact on clinical outcomes of KRAS G12C inhibitors.[129,130]

Historically, *KRAS* mutations were considered undruggable due to their lack of drug-binding pocket and high affinity to guanosine triphosphate (GTP). In 2013, the discovery of covalent irreversible allosteric inhibitors binding to the KRAS G12C S-IIP sub-pocket in its inactive GDP-bound form represented a breakthrough in direct anticancer targeting.[17,131] Sotorasib became the first FDA-approved KRAS G12C inhibitor based on an ORR of 37% and a median PFS of 6.8 months in the open-label phase II CodeBreak 100 trial.[130] Subsequently, two phase III randomized trials comparing sotorasib (CodeBreak200) and adagrasib (KRYSTAL-12) to docetaxel, respectively, in the second-line setting, were reported. Both studies confirmed superiority of KRAS G12C inhibitor over docetaxel (sotorasib - median 5.6 months versus 4.3 months, HR 0.66; adagrasib - median PFS 5.5 months versus 3.8 months, HR 0.58), establishing KRAS G12C inhibitor as the preferred treatment option after immunochemotherapy failure.[132,133]

Newer KRAS G12C inhibitors with higher potency and selectivity have demonstrated numerically higher response rates and longer PFS in single-arm studies compared to sotorasib and adagrasib. In a single arm phase I study including 58 patients with NSCLC, tumor response rate was 53% and median PFS was 13.1 months with divarasib.[134] Another KRAS G12C inhibitor, D3S-001, achieved tumor response in 14 out of 20 (70%) patients with NSCLC.[135]

A heterogenous spectrum of resistance mechanisms to

KRAS G12C inhibitors has been reported, including mutations at the binding pocket, *KRAS* amplification, activation of *RAS*-dependent and independent bypass signaling pathways, and phenotypic switching.[136] Preclinical and early clinical data revealed that combining a KRAS G12C inhibitor with chemotherapy, immunotherapy, and other novel small molecule inhibitors (e.g., SHP2 inhibitors, SOS1 inhibitors, MEK inhibitors) may yield synergistic effects and overcome adaptive feedback mechanisms.[137] Understanding the multifaceted nature of resistance and investigating appropriate combinational strategies is required to overcome these challenges in treating *KRAS*-mutant cancers.

Aside G12C, novel small molecular inhibitors targeting KRAS non-G12C mutants have shown early promising signals. RMC-6236 is a RAS(ON) multi-selective tri-complex inhibitor that targets any *KRAS* glycine 12 mutant. It forms a tri-complex with the activated RAS-GTP (RAS[ON]) protein and cyclophilin A blocking the interaction between RAS and its effector, disrupting the downstream signaling pathway.[138] RMC-6236 exhibited an ORR of 38% in 40 patients with NSCLC harboring various *KRAS* G12X mutations in a phase I study.[139] Additionally, targeted protein degraders and KRAS peptide vaccines are also actively investigated in treatment for *KRAS*-mutant NSCLC.[137]

BRAF

V-Raf murine sarcoma viral oncogene homolog (*BRAF*) mutations occur in 1% to 5% of NSCLCs, with the class I *BRAF* V600E mutation accounting for the majority of cases (50% to 60%).[140] The incidence of *BRAF* V600E-mutation in NSCLC is similar between smokers and non-smokers.[141]

Combining BRAF inhibitor and MEK inhibitor was found to be superior to BRAF inhibition alone.[142] Significant clinical benefit was noted in patients treated with the combination of dabrafenib and trametinib, with an ORR at 64%, median PFS of 10.8 months, and median OS of 17.3 months. Pyrexia is a common toxicity but manageable by dose modification.[143] The combination of encorafenib, a highly selective BRAF inhibitor, and binimetinib, a potent, selective allosteric MEK1/2 inhibitor, was recently FDA approved based on the phase II PHAROS study.[144] ORR in treatment naïve (n=59) and previously treated (n=39) patients harboring *BRAF* V600E mutation was 75% and 46%, respectively, with durable responses in the two groups. Intracranial antitumor responses were observed with this combination.[144]

Resistance mechanisms largely involve signaling pathways related to *RAS*, including the RTK-Ras-MAPK pathway and the PI3K-AKT-mTOR pathway with up to 30% of patients harboring baseline concurrent mutations (e.g., *TP53, SET2, PIK3CA E545K, PTEN* R14K), which may be cause of primary resistance.[145,146]

Optimal approach against non-V600E mutant NSCLC warrants further investigation.[147] Candidate therapeutic strategies include pan-RAF inhibitors, paradox breakers, downstream *ERK* inhibitors, as well as combinations with standard therapy (e.g., chemo-immunotherapy) or SHP2 and CDK4/6 inhibitors combination.

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (ERBB-2)

The human epidermal growth factor receptor 2 (*HER2*) gene can be deregulated in NSCLC due to mutation (1% to 4%), amplification (2% to 5%), and protein overexpression (2% to 30%).[148] The most common *HER2* mutation occurs in the exon 20 kinase domain (*HER2* ex20ins). *HER2* mutations are more common in Asian patients and those with no history of smoking or light smoking.[149]

Available data on novel, promising treatments against *HER2* mutation in NSCLC refer to two class of agents: ADCs and TKIs. Trastuzumab deruxtecan (T-DXd), a HER2-targeted ADC with topoisomerase I inhibitor, was established as a new treatment option in this rare, oncogene addicted disease.[150] The DESTINY-Lung02 trial randomized 152 patients with previously treated *HER2*-mutant NSCLC to receive T-DXd 5.4mg/kg or 6.4mg/kg. Similar antitumor response was observed between two arms (ORR 49% and 56% in 5.4mg/kg and 6.4mg/kg arm respectively),

but the incidence of drug-related interstitial lung disease in the 5.4mg/kg arm was lower (13% versus 28%), establishing 5.4mg/kg T-DXd as the new treatment paradigm for patients with previously treated *HER2*-mutant NSCLC.[151] T-DXd also showed promising activity in a single arm cohort of 49 HER2-overexpressing NSCLC with ORR of up to 34%.[152] The phase III DESTINY-Lung04 trial (NCT05048797) is ongoing to evaluate its role as first-line treatment.

Several pan-HER TKIs, such as pyrotinib and poziotinib, were explored in *HER2*-mutant NSCLC. However, clinical application of pan-HER TKI was limited by the high incidence of EGFR-related adverse events, such as diarrhea.[153,154] Zongertinib (BI1810631) is a novel TKI specifically and covalently binding to the HER2 tyrosine kinase domain without interacting with wild-type EGFR, hence limiting EGFR-associated side-effects. In the BEAMION-Lung-1 phase 1b study (NCT04886804), zongertinib achieved an ORR of 74% and DCR of 91% in *HER2*-mutant NSCLC patients (n=23) with acceptable tolerability.[155] Promising signals of activity were observed among T-DXd-pretreated patients. BAY 2927088, an EGFR and HER2 exon 20 insertion specific TKI, showed early evidence of efficacy (ORR=60%) among patients harboring *HER2* ex20ins in a phase I trial (NCT05099172), with no major safety issues.[156] The field of HER2 selective TKIs is evolving rapidly with several investigational compounds currently under early phase trials.[157-159]

RET

Rearranged during transfection (*RET*) gene fusions are reported in around 2% of NSCLC cases.[160] This genomic anomaly is more common in younger never-smokers with adenocarcinoma.[161,162] Common fusion partners include KIF5B and CCDC6.[162]

Two novel RET-specific TKIs (RETi), selpercatinib (LOXO-292) and pralsetinib (BLU-667), were approved by the FDA in 2020. With 13 months advantage in PFS, the phase III trial LIBRETTO-431 demonstrated superiority with selpercatinib compared to immunochemotherapy among *RET*-rearranged NSCLC patients.[163] OS data is not yet mature. Pralsetinib was tested in *RET*-fusion positive NSCLC in the phase II ARROW study, with an ORR of 70% in treatment-naïve and 61% in platinum-pretreated populations.[164] Both drugs exhibited high intracranial ORR.[164,165] The phase III AcceleRET study is currently underway, comparing first-line pralsetinib to the standard of care (NCT04222972).

Acquired resistance to RET inhibitors may include secondary *RET* mutations, such as G810S/R/C solvent-front mutations, observed in 8% to 10 % of cases, as well as activation of bypass tracks involving RAS and MET signaling, present in more than 40% of cases.[166,167] Newer molecules targeting solvent front-mediated resistance, with significant nanomolar level potent antitumor activity, are currently in clinical trials (HM06, NCT04683250; APS03118, NCT05653869).

MESENCHYMAL-TO-EPITHELIAL TRANSITION EXON 14 SKIPPING

MET alterations are reported in 4% of LUADs and up to 30% of pulmonary sarcomatoid carcinoma (PSCs).[168,169] Genomic alterations, such as *MET* exon 14 skipping (*MET*ex14) and high-level *MET* amplification (e.g., gene copy number ≥ 10), serve as potential predictive biomarkers for *MET*-directed therapy.[170] *MET*ex14 is associated with poor prognosis and older age (≥70 years), with no clear relationship to smoking history. De novo *MET* amplification (*MET*amp) is identified in 1% to 5% of cases and in 15% to 20% of cases as a bypass mechanism to EGFR TKIs.[170]

Two highly selective type Ib MET inhibitors, capmatinib and tepotinib, have shown rapid and durable responses in NSCLC with *MET* exon 14 skipping alterations. In 2020, the FDA granted capmatinib accelerated approval based on positive results from the GEOMETRY mono-1 phase II trial, which showed an ORR of 65.6% in treatment-naïve patients and 41% in pretreated patients, and mOS of 20.8 months and 13.6 months, respectively.[171] The phase II VISION trial demonstrated similar efficacy for tepotinib in both pretreated and untreated patients, with ORRs of 48.5% for liquid biopsy

and 50% for tissue biopsy.[172] Favorable outcomes were also observed in patients with CNS involvement.[172,173] Savolitinib is a selective MET inhibitor approved in China based on robust antitumor activity demonstrated in the first-line (ORR=60%) as well as platinum-refractory setting (ORR 49%).[174,175]

The bispecific EGFR-MET antibody amivantamab demonstrated antitumor activity and durable benefit in both treatment-naïve and pretreated patients with primary *MET*ex14 NSCLC according to update results from the phase 1 CHRYSALIS trial.[176] A clinical trial (NCT05488314) of amivantamab plus capmatinib is now underway.

MET-dependent resistance mechanisms include kinase domain mutations at residues H1094, G1163, L1195, D1228, and Y1230, as well as high level *MET* amplifications. Genomic bypass mechanisms are sustained by amplifications in *EGFR, KRAS, BRAF, HER2, HER3*, and mutations in *KRAS*.[177] Novel treatment strategies, including MET-based antibody-drug conjugates (e.g., telisotuzumab vedotin) and human bispecific antibody (e.g., REGN5093), are currently under investigation.

NTRK

Tropomyosin receptor kinase (TRK) proteins (Trk A, B, and C) are encoded by the genes *NTRK1-3* and activated by neurotrophins. Rearrangements of *NTRK* genes result in constitutive activation of fusion proteins, with more than 80 gene partners identified.[178] *NTRK* fusions are oncogenic drivers in 0.1% to 1% of NSCLC cases and mutually exclusive with other known oncogenic drivers.[179] Clinical features of NTRK fusion-positive NSCLCs are similar to other oncogene driven lung cancers, such as adenocarcinoma histology, younger age, and minimal or absent history of smoking.[180]

In 2018, the FDA granted accelerated approval for the first-in-class larotrectinib as a tumor-agnostic therapy in patients with *NTRK* fusion-positive tumors followed by the approval of entrectinib for the same indication. Larotrectinib demonstrated good efficacy with ORR of 79% among 159 patients with TRK fusion-positive solid tumor of multiple types.[181] ORR was 73% among 15 patients with lung cancer and intracranial ORR was 63% among 8 patients with brain metastases.[182]

Entrectinib is a multi-kinase inhibitor active against ROS1, ALK, and TRK. In the integrated analysis of *NTRK* fusion-positive NSCLC patients enrolled in STARTRK-2, STARTRK-1, and ALKA 372–001, entrectinib achieved an ORR of 69% and a clinically meaningful intracranial RR of 67%.[183,184] TRK inhibitors are associated with unique on-target side effects, including cognitive impairment, dizziness, weight gain, TRK inhibitor withdrawal pain, and sleep disturbance. However, the rate of grade* 3 to 4 adverse events in NSCLC patients was less than 15%.[185]

Multiple mechanisms of resistance are known, including acquired amino acid substitutions in the solvent front (G595R, G639R, G623R), gatekeeper residues (F589L, F633L, F617L), and xDFG motif mutations in the activation loop (G667C, G667S, and G696A). Off-target resistance via *KRAS* and *BRAF* mutations, *MET* amplification and *IGF1E* activation may also occur.[186] Second-generation TRK inhibitors (selitrectinib, repotrectinib, and taletrectinib) were designed to address on-target resistance mediated by mutations in kinase domain but were inactive against xDFG motif substitution or bypass resistance mechanisms.[187,188]

NRG1

Neuregulin 1 (*NRG1*) fusion is a rare oncogenic driver in NSCLC, occurring in about 0.2% of cases, with CD74 being the most common fusion partner.[189] The CD74-NRG1 fusion leads to the activation of PI3K-AKT pathway through the induction of ErbB2-ErbB3 heterodimerization.[190] Pre-clinical evidence and small case series suggest that pan-ErbB inhibitors, such as afatinib, may be active in *NRG1*-fusion-positive (NRG1+) NSCLC.[191]

The eNRGy1 registry has provided valuable real-world data on the efficacy of systemic therapies in *NRG1* fusion-positive NSCLCs, representing a global collaborative effort to better understand of rare oncogenic alterations.[192] *NRG1* fusion is more often observed in females with

no smoking history, more often detected by RNA sequencing, and enriched in invasive mucinous adenocarcinomas (IMAs). Afatinib has shown a RR of 25% and a median PFS of 2.8 months, while single-agent immunotherapy yielded an RR of 20% and a median PFS of 3.6 months.[192]

There has been a rapid evolution in the development of novel treatment options for *NRG1*-rearranged NSCLC over the past three years. The bispecific HER2/HER3 antibody zenocutuzumab (MCLA-128) provided robust and durable efficacy in pretreated NRG1+ NSCLC with an ORR of 34% and a median DOR of 12.9 months in the phase 2 eNRGY study.[193] Initial data support the use of another novel anti-HER3 monoclonal antibody, seribantumab (MM-121), in pretreated NSCLC patients harboring *NRG1* fusions.[194] Seribantumab is now under investigation in the ongoing phase 2 CRESTONE trial (NCT04383210).

MOLECULAR THERAPY IN SQUAMOUS CELL CARCINOMA OF THE LUNG

Genomic sequencing of lung squamous cell carcinoma (SCC) reveals molecular profiles distinct from LUADs.[195] Targetable mutations commonly found in LUADs are mostly absent in SCCs, especially among smokers. However, potentially targetable mutations in lung SCCs include *PIK3CA* mutations (11%) and *FGFR* alterations (20%).[196] *EGFR* mutations may be enriched in patients who are non-smokers and has been reported in up to 5% of lung SCC cases.[197] Retrospective data suggest that EGFR TKI are active in *EGFR*-mutation-positive SCC, but might be less efficacious compared to LUADs.[198]

Adenosquamous carcinoma (ASC) is a rare subtype of NSCLC, defined by coexistence of LUAD and lung SCC within one tumor specimen. It accounts for 2% to 4% of all NSCLCs.[199] Genomic profiling of the LUAD and SCC components of lung ASC reveals that both components share a common clonal origin, with their genomic profiles resembling adenocarcinoma and a high incidence of *EGFR* mutations.[200,201] As a result, current guidelines recommend *EGFR* testing for SCC patients who are light or never-smokers.

Necitumumab, an anti-EGFR MoAb, was approved in combination with chemotherapy for treatment-naïve metastatic SCC of lung. A phase III study showed minor improvement in OS compared to chemotherapy alone. However, its clinical application is limited globally.[202] Afatinib was approved as a second-line treatment for advanced SCC after failure of platinum-based chemo-therapy, as demonstrated in the positive LUX-Lung 8 study. However, the comparator arm in this study was erlotinib, an agent with minimal activity against lung SCC. The PFS and ORR of afatinib were 2.6 months and 6%, respectively.[203]

These treatment options have largely fallen out of favor since immunotherapy became available. At present, immunotherapy and chemotherapy are the mainstay treatments for advanced lung SCCs.

TRIAL DESIGN IN THE ERA OF PRECISION MEDICINE IN NSCLC

Availability of genomic sequencing in clinic has transformed treatment of solid tumors. This paradigm shift is exemplified by the management of advanced NSCLC, where extended molecular characterization is essential to navigate tailored treatments.[204] An increasing number of targeted agents have been developed to address actionable genomic alterations, despite their rarity. The same genome sequencing technologies have opened the door to management of resistance mutations.[205] Based on advances in cancer genomics, novel clinical trial designs are now implicated for NSCLC.[206]

Clinical trial design based on "Master Protocols" allows the allocation of participants into different treatment arms based on molecular biomarker-driven selection, testing multiple regimens in parallel. Master protocols design may include basket trials, umbrella trials, and platform trials.[207] Umbrella and platform trial designs have the advantage of using the same control arm across multiple experimental treatments being tested in parallel. The Lung Master Protocol (Lung-MAP, S1400) is a reference model of innovative clinical trials

aimed at expediting the development of targeted therapies for SCC.[208,209]

In basket trials, participants receive the same experimental regimen irrespective of tumor type, based on a common molecular biomarker.[210] This design has allowed the enrollment of rare molecular subgroups and led to the tumor-agnostic approval of larotrectinib and entrectinib for *TRK*-fusion positive tumors, selpercatinib for *RET*-fusion positive tumors, and the combination of dabrafenib plus trametinib for tumors harboring *BRAF* V600E mutation. The ongoing phase II NCI-MATCH (Molecular Analysis for Therapy Choice) Trial is a landmark precision medicine study aiming to evaluate >100 mutations in a basket study design.[211] The novel adaptive design allows for prospectively planned modifications, according to newly accumulated data from enrolled subjects.

CONCLUSION

The unprecedented growth of new knowledge in molecular biology over the past two decades has transformed the therapeutic landscape and survival outcomes for lung cancer patients. We have witnessed an expanding list of targetable driver mutations and relevant approved targeted therapies with improved potency, CNS efficacy, and toxicity profiles. Global and regional collaborative efforts, such as those led by the IASLC, have been instrumental in collecting prospective and real-world clinical evidence for patients with rare mutations and subpopulations with specific resistance mechanisms. The treatment approach of early-stage lung cancer has also become increasingly personalized with the adoption of perioperative targeted therapy.

Management of treatment resistance remains the key challenge for patients who fail targeted therapy. New therapeutic approaches are being developed based on better understanding of resistance mechanisms. Identification of persister cells may offer the opportunity to eradicate the resistant clones and potentially achieve cure.

Lastly, the uptake of biomarker testing and novel drugs remains suboptimal in low-income countries due to limited access and financial constraints.[212,213] Joint efforts are required to reduce health disparities and ensure that patients from diverse backgrounds benefit from personalized management of lung cancer. The IASLC continues to play a pivotal role in advancing these research efforts and improving patient outcomes.

References

1. Mansfield EA. FDA perspective on companion diagnostics: an evolving paradigm. *AACR*. 2014;1453-1457.
2. Kurzrock R, Kantarjian HM, Kesselheim AS, Sigal EV. New drug approvals in oncology. *Nature Reviews Clinical Oncology*. 2020;17(3):140-146.
3. Howlader N, Forjaz G, Mooradian MJ, Meza R, Kong CY, Cronin KA, et al. The Effect of Advances in Lung-Cancer Treatment on Population Mortality. *N Engl J Med*. 2020;383(7):640-649.
4. Zhao S, Zhang Z, Zhan J, Zhao X, Chen X, Xiao L, et al. Utility of comprehensive genomic profiling in directing treatment and improving patient outcomes in advanced non-small cell lung cancer. *BMC Medicine*. 2021;19(1):223.
5. Kris MG, Johnson BE, Berry LD, Kwiatkowski DJ, Iafrate AJ, Wistuba, II, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA*. 2014;311(19):1998-2006.
6. Tsimberidou A-M, Hong DS, Wheler JJ, Falchook GS, Janku F, Naing A, et al. Long-term overall survival and prognostic score predicting survival: the IMPACT study in precision medicine. *Journal of Hematology & Oncology*. 2019;12(1):145.
7. Carmichael JA, Wing-San Mak D, O'Brien M. A Review of Recent Advances in the Treatment of Elderly and Poor Performance NSCLC. *Cancers (Basel)*. 2018;10(7):236.
8. Lindeman NI, Cagle PT, Aisner DL, Arcila ME, Beasley MB, Bernicker EH, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. *J Thorac Oncol*. 2018;13(3):323-358.
9. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(Suppl 4):iv192-iv237.
10. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, et al. Non-Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2022;20(5):497-530.
11. Cancer IAftSoL. IASLC ATLAS of MOLECULAR TESTING for TARGETED THERAPY in LUNG CANCER2023.
12. Tan AC, Tan DSW. Targeted Therapies for Lung Cancer Patients With Oncogenic Driver Molecular Alterations. *J Clin Oncol*. 2022;40(6):611-625.
13. Lee YT, Tan YJ, Oon CE. Molecular targeted therapy: treating cancer with specificity. *European Journal of Pharmacology*. 2018;834:188-196.
14. Lounnas V, Ritschel T, Kelder J, McGuire R, Bywater RP, Foloppe N. Current progress in Structure-Based Rational Drug Design marks a new mindset in drug discovery. *Comput Struct Biotechnol J*. 2013;5:e201302011.

15. Khongorzul P, Ling CJ, Khan FU, Ihsan AU, Zhang J. Antibody–drug conjugates: a comprehensive review. *Molecular Cancer Research*. 2020;18(1):3-19.
16. Klein C, Brinkmann U, Reichert JM, Kontermann RE. The present and future of bispecific antibodies for cancer therapy. *Nat Rev Drug Discov*. 2024;23(4):301-319.
17. Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. K-Ras (G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature*. 2013;503(7477):548-551.
18. To C, Beyett TS, Jang J, Feng WW, Bahcall M, Haikala HM, et al. An allosteric inhibitor against the therapy-resistant mutant forms of EGFR in non-small cell lung cancer. *Nat Cancer*. 2022;3(4):402-417.
19. Holderfield M, Lee BJ, Jiang J, Tomlinson A, Seamon KJ, Mira A, et al. Concurrent inhibition of oncogenic and wild-type RAS-GTP for cancer therapy. *Nature*. 2024;629(8013):919-926.
20. Hagopian G, Grant C, Nagasaka M. Proteolysis targeting chimeras in non-small cell lung cancer. *Cancer Treat Rev*. 2023;117:102561.
21. Wu YL, Dziadziuszko R, Ahn JS, Barlesi F, Nishio M, Lee DH, et al. Alectinib in Resected ALK-Positive Non-Small-Cell Lung Cancer. *N Engl J Med*. 2024;390(14):1265-1276.
22. Tsuboi M, Herbst RS, John T, Kato T, Majem M, Grohé C, et al. Overall Survival with Osimertinib in Resected EGFR-Mutated NSCLC. *N Engl J Med*. 2023;389(2):137-147.
23. Wu YL, Tsuboi M, He J, John T, Grohe C, Majem M, et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. *N Engl J Med*. 2020;383(18):1711-1723.
24. John T, Grohé C, Goldman JW, Shepherd FA, de Marinis F, Kato T, et al. Three-Year Safety, Tolerability, and Health-Related Quality of Life Outcomes of Adjuvant Osimertinib in Patients With Resected Stage IB to IIIA EGFR-Mutated NSCLC: Updated Analysis From the Phase 3 ADAURA Trial. *J Thorac Oncol*. 2023;18(9):1209-21.
25. Nishio M, Wu Y-L, Barlesi F, Ahn JS, Lee DH, Lee J-S, et al. Health-related quality of life (HRQoL) results for adjuvant alectinib vs chemotherapy in patients with resected ALK+ non-small cell lung cancer (NSCLC): Data from ALINA. *J Clin Oncol*. 2024;42(16_suppl):8006-.
26. Ahn MJ, Cho BC, Ou X, Walding A, Dymond AW, Ren S, et al. Osimertinib Plus Durvalumab in Patients With EGFR-Mutated, Advanced NSCLC: A Phase 1b, Open-Label, Multicenter Trial. *J Thorac Oncol*. 2022;17(5):718-723.
27. Chour A, Denis J, Mascaux C, Zysman M, Bigay-Game L, Swalduz A, et al. Brief Report: Severe Sotorasib-Related Hepatotoxicity and Non-Liver Adverse Events Associated With Sequential Anti-Programmed Cell Death (Ligand)1 and Sotorasib Therapy in KRAS(G12C)-Mutant Lung Cancer. *J Thorac Oncol*. 2023;18(10):1408-1415.
28. Park E, Shim HS. Detection of Targetable Genetic Alterations in Korean Lung Cancer Patients: A Comparison Study of Single-Gene Assays and Targeted Next-Generation Sequencing. *Cancer Res Treat*. 2020;52(2):543-551.
29. Drilon A, Wang L, Arcila ME, Balasubramanian S, Greenbowe JR, Ross JS, et al. Broad, Hybrid Capture-Based Next-Generation Sequencing Identifies Actionable Genomic Alterations in Lung Adenocarcinomas Otherwise Negative for Such Alterations by Other Genomic Testing Approaches. *Clin Cancer Res*. 2015;21(16):3631-3639.
30. Rolfo C, Mack P, Scagliotti GV, Aggarwal C, Arcila ME, Barlesi F, et al. Liquid Biopsy for Advanced NSCLC: A Consensus Statement From the International Association for the Study of Lung Cancer. *J Thorac Oncol*. 2021;16(10):1647-1662.
31. Wang Z, Cheng Y, An T, Gao H, Wang K, Zhou Q, et al. Detection of EGFR mutations in plasma circulating tumour DNA as a selection criterion for first-line gefitinib treatment in patients with advanced lung adenocarcinoma (BENEFIT): a phase 2, single-arm, multicentre clinical trial. *The Lancet Respiratory Medicine*. 2018;6(9):681-690.
32. Dziadziuszko R, Mok T, Peters S, Han JY, Alatorre-Alexander J, Leighl N, et al. Blood First Assay Screening Trial (BFAST) in Treatment-Naive Advanced or Metastatic NSCLC: Initial Results of the Phase 2 ALK-Positive Cohort. *J Thorac Oncol*. 2021;16(12):2040-2050.
33. Aggarwal C, Thompson JC, Black TA, Katz SI, Fan R, Yee SS, et al. Clinical Implications of Plasma-Based Genotyping With the Delivery of Personalized Therapy in Metastatic Non–Small Cell Lung Cancer. *JAMA Oncology*. 2019;5(2):173-180.
34. Wu Y-L, Sequist LV, Hu C-P, Feng J, Lu S, Huang Y, et al. EGFR mutation detection in circulating cell-free DNA of lung adenocarcinoma patients: analysis of LUX-Lung 3 and 6. *Br J Cancer*. 2017;116(2):175-185.
35. Sacher AG, Paweletz C, Dahlberg SE, Alden RS, O'Connell A, Feeney N, et al. Prospective Validation of Rapid Plasma Genotyping for the Detection of EGFR and KRAS Mutations in Advanced Lung Cancer. *JAMA Oncol*. 2016;2(8):1014-1022.
36. Sacher AG, Komatsubara KM, Oxnard GR. Application of Plasma Genotyping Technologies in Non-Small Cell Lung Cancer: A Practical Review. *J Thorac Oncol*. 2017;12(9):1344-1356.
37. Rolfo C, Mack PC, Scagliotti GV, Baas P, Barlesi F, Bivona TG, et al. Liquid Biopsy for Advanced Non-Small Cell Lung Cancer (NSCLC): A Statement Paper from the IASLC. *J Thorac Oncol*. 2018;13(9):1248-1268.
38. Cohen MH, Johnson JR, Chen YF, Sridhara R, Pazdur R. FDA drug approval summary: erlotinib (Tarceva) tablets. *Oncologist*. 2005;10(7):461-466.
39. Cohen MH, Williams GA, Sridhara R, Chen G, Pazdur R. FDA Drug Approval Summary: Gefitinib (ZD1839) (Iressa®) Tablets. *The Oncologist*. 2003;8(4):303-306.
40. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005;353(2):123-132.
41. Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004;304(5676):1497-1500.
42. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004;350(21):2129-2139.
43. Zhang Y-L, Yuan J-Q, Wang K-F, Fu X-H, Han X-R, Threapleton D, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. *Oncotarget*. 2016;7(48):78985-78993.
44. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361(10):947-957.
45. Fukuoka M, Wu YL, Thongprasert S, Sunpaweravong P, Leong SS, Sriuranpong V, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label,

first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol*. 2011;29(21):2866-2874.
46. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol*. 2010;11(2):121-128.
47. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non–small-cell lung cancer with mutated EGFR. *N Engl J Med*.2010;362(25):2380-2388.
48. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2011;12(8):735-742.
49. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13(3):239-246.
50. Wu Y-L, Zhou C, Liam C-K, Wu G, Liu X, Zhong Z, et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. *Annals of Oncology*. 2015;26(9):1883-1889.
51. Park K, Tan EH, O'Byrne K, Zhang L, Boyer M, Mok T, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. *Lancet Oncol*. 2016;17(5):577-589.
52. Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(11):1454-1466.
53. Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res*. 2013;19(8):2240-2247.
54. Kuiper JL, Heideman DA, Thunnissen E, Paul MA, van Wijk AW, Postmus PE, et al. Incidence of T790M mutation in (sequential) rebiopsies in EGFR-mutated NSCLC-patients. *Lung Cancer*. 2014;85(1):19-24.
55. Jänne PA, Yang JC, Kim DW, Planchard D, Ohe Y, Ramalingam SS, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med*. 2015;372(18):1689-1699.
56. Finlay MR, Anderton M, Ashton S, Ballard P, Bethel PA, Box MR, et al. Discovery of a potent and selective EGFR inhibitor (AZD9291) of both sensitizing and T790M resistance mutations that spares the wild type form of the receptor. *J Med Chem*. 2014;57(20):8249-8267.
57. Colclough N, Chen K, Johnström P, Strittmatter N, Yan Y, Wrigley GL, et al. Preclinical Comparison of the Blood-brain barrier Permeability of Osimertinib with Other EGFR TKIs. *Clin Cancer Res*. 2021;27(1):189-201.
58. Reungwetwattana T, Nakagawa K, Cho BC, Cobo M, Cho EK, Bertolini A, et al. CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer. *J Clin Oncol*. 2018;36(33):3290-3297.
59. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018;378(2):113-125.
60. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. *N Engl J Med*. 2017;376(7):629-640.
61. Papadimitrakopoulou VA, Mok TS, Han JY, Ahn MJ, Delmonte A, Ramalingam SS, et al. Osimertinib versus platinum-pemetrexed for patients with EGFR T790M advanced NSCLC and progression on a prior EGFR-tyrosine kinase inhibitor: AURA3 overall survival analysis. *Ann Oncol*. 2020;31(11):1536-1544.
62. Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. *N Engl J Med*. 2020;382(1):41-50.
63. Planchard D, Jänne PA, Cheng Y, Yang JC, Yanagitani N, Kim SW, et al. Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. *N Engl J Med*. 2023;389(21):1935-1948.
64. Cho BC, Felip E, Spira AI, Girard N, Lee JS, Lee SH, et al. LBA14 Amivantamab plus lazertinib vs osimertinib as first-line treatment in patients with EGFR-mutated, advanced non-small cell lung cancer (NSCLC): Primary results from MARIPOSA, a phase III, global, randomized, controlled trial. *Annals of Oncology*. 2023;34:S1306.
65. Saw SPL, Le X, Hendriks LEL, Remon J. New Treatment Options for Patients With Oncogene-Addicted Non-Small Cell Lung Cancer Focusing on EGFR-Mutant Tumors. *Am Soc Clin Oncol Educ Book*. 2024;44(3):e432516.
66. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E, Tiseo M. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br J Cancer*. 2019;121(9):725-737.
67. Marcoux N, Gettinger SN, O'Kane G, Arbour KC, Neal JW, Husain H, et al. EGFR-Mutant Adenocarcinomas That Transform to Small-Cell Lung Cancer and Other Neuroendocrine Carcinomas: Clinical Outcomes. *J Clin Oncol*. 2019;37(4):278-285.
68. Passaro A, Wang J, Wang Y, Lee SH, Melosky B, Shih JY, et al. Amivantamab plus chemotherapy with and without lazertinib in EGFR-mutant advanced NSCLC after disease progression on osimertinib: primary results from the phase III MARIPOSA-2 study. *Ann Oncol*. 2024;35(1):77-90.
69. Lu S, Wu L, Jian H, Chen Y, Wang Q, Fang J, et al. Sintilimab plus bevacizumab biosimilar IBI305 and chemotherapy for patients with EGFR-mutated non-squamous non-small-cell lung cancer who progressed on EGFR tyrosine-kinase inhibitor therapy (ORIENT-31): first interim results from a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol*. 2022;23(9):1167-1179.
70. Park S, Kim TM, Han JY, Lee GW, Shim BY, Lee YG, et al. Phase III, Randomized Study of Atezolizumab Plus Bevacizumab and Chemotherapy in Patients With EGFR- or ALK-Mutated Non-Small-Cell Lung Cancer (ATTLAS, KCSG-LU19-04). *J Clin Oncol*. 2024;42(11):1241-1251.
71. Zhou C, Dong X, Chen G, Wang Z, Wu X, Yao Y, et al. OA09.06 IMpower151:

Phase III Study of Atezolizumab + Bevacizumab + Chemotherapy in 1L Metastatic Nonsquamous NSCLC. Journal of Thoracic Oncology. 2023;18(11, Supplement):S64-S5.
72. Zhang L, Fang W, Zhao Y, Luo Y, Yang R, Huang Y, et al. Ivonescimab combined with chemotherapy in patients with EGFR-mutant non-squamous non-small cell lung cancer who progressed on EGFR tyrosine-kinase inhibitor treatment (HARMONi-A): A randomized, double-blind, multi-center, phase 3 trial. *J Thorac Oncol*. 2024;42(16_suppl):8508-.
73. Ahn Mj, De Marinis F, Bonanno L, Cho BC, Kim TM, Cheng S, et al. EP08.02-140 MET Biomarker-based Preliminary Efficacy Analysis in SAVANNAH: savolitinib+osimertinib in EGFRm NSCLC Post-Osimertinib. *J Thorac Oncol*. 2022;17(9, Supplement):S469-S470.
74. Tan DS-W, Kim TM, Guarneri V, Voon PJ, Lim BK, Wislez M, et al. Tepotinib + osimertinib for EGFR mutant (EGFRm) NSCLC with MET amplification (METamp) after first-line (1L) osimertinib. *J Clin Oncol*. 2023;41(16_suppl):9021-.
75. Rotow J, Patel JD, Hanley MP, Yu H, Awad M, Goldman JW, et al. Osimertinib and Selpercatinib Efficacy, Safety, and Resistance in a Multicenter, Prospectively Treated Cohort of EGFR-Mutant and RET Fusion-Positive Lung Cancers. *Clin Cancer Res*. 2023;29(16):2979-2987.
76. Batra U, Sharma M, Amrith BP, Mehta A, Jain P. EML4-ALK Fusion as a Resistance Mechanism to Osimertinib and Its Successful Management With Osimertinib and Alectinib: Case Report and Review of the Literature. *Clin Lung Cancer*. 2020;21(6):e597-e600.
77. Meng P, Koopman B, Kok K, Ter Elst A, Schuuring E, van Kempen LC, et al. Combined osimertinib, dabrafenib and trametinib treatment for advanced non-small-cell lung cancer patients with an osimertinib-induced BRAF V600E mutation. *Lung Cancer.* 2020;146:358-361.
78. Yu HA, Goto Y, Hayashi H, Felip E, Chih-Hsin Yang J, Reck M, et al. HERTHENA-Lung01, a Phase II Trial of Patritumab Deruxtecan (HER3-DXd) in Epidermal Growth Factor Receptor-Mutated Non-Small-Cell Lung Cancer After Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and Platinum-Based Chemotherapy. *J Clin Oncol*. 2023;41(35):5363-5375.
79. Paz-Ares L, Ahn MJ, Lisberg AE, Kitazono S, Cho BC, Blumenschein G, et al. 1314MO TROPION-Lung05: Datopotamab deruxtecan (Dato-DXd) in previously treated non-small cell lung cancer (NSCLC) with actionable genomic alterations (AGAs). *Annals of Oncology*. 2023;34:S755-S6.
80. Yang JC, Sequist LV, Geater SL, Tsai CM, Mok TS, Schuler M, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol*. 2015;16(7):830-838.
81. Cho JH, Lim SH, An HJ, Kim KH, Park KU, Kang EJ, et al. Osimertinib for Patients With Non-Small-Cell Lung Cancer Harboring Uncommon EGFR Mutations: A Multicenter, Open-Label, Phase II Trial (KCSG-LU15-09). *J Clin Oncol*. 2020;38(5):488-495.
82. Okuma Y, Kubota K, Shimokawa M, Hashimoto K, Kawashima Y, Sakamoto T, et al. First-Line Osimertinib for Previously Untreated Patients With NSCLC and Uncommon EGFR Mutations: The UNICORN Phase 2 Nonrandomized Clinical Trial. *JAMA Oncol*. 2024;10(1):43-51.
83. Cho BC, Wang Y, Felip E, Cui J, Spira AI, Neal JW, et al. Amivantamab plus lazertinib in atypical EGFR-mutated advanced non-small cell lung cancer (NSCLC): Results from CHRYSALIS-2. *J Clin Oncol*. 2024;42(16_suppl):8516-.
84. Friedlaender A, Subbiah V, Russo A, Banna GL, Malapelle U, Rolfo C, et al. EGFR and HER2 exon 20 insertions in solid tumours: from biology to treatment. *Nature Reviews Clinical Oncology*. 2022;19(1):51-69.
85. Park K, Haura EB, Leighl NB, Mitchell P, Shu CA, Girard N, et al. Amivantamab in EGFR Exon 20 Insertion-Mutated Non-Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study. *J Clin Oncol*. 2021;39(30):3391-3402.
86. Zhou C, Tang KJ, Cho BC, Liu B, Paz-Ares L, Cheng S, et al. Amivantamab plus Chemotherapy in NSCLC with EGFR Exon 20 Insertions. *N Engl J Med*. 2023;389(22):2039-2051.
87. Piotrowska Z, Tan DS, Smit EF, Spira AI, Soo RA, Nguyen D, et al. Safety, Tolerability, and Antitumor Activity of Zipalertinib Among Patients With Non-Small-Cell Lung Cancer Harboring Epidermal Growth Factor Receptor Exon 20 Insertions. *J Clin Oncol*. 2023;41(26):4218-4225.
88. Yang JC-H, Doucet L, Wang M, Fan Y, Sun M, Greillier L, et al. A multinational pivotal study of sunvozertinib in platinum pretreated non-small cell lung cancer with EGFR exon 20 insertion mutations: Primary analysis of WU-KONG1 study. *J Clin Oncol*. 2024;42(16_suppl):8513-.
89. Wang M, Fan Y, Sun M, Wang Y, Zhao Y, Jin B, et al. Sunvozertinib for patients in China with platinum-pretreated locally advanced or metastatic non-small-cell lung cancer and EGFR exon 20 insertion mutation (WU-KONG6): single-arm, open-label, multicentre, phase 2 trial. *Lancet Respir Med.* 2024;12(3):217-224.
90. Herbst RS, Wu YL, John T, Grohe C, Majem M, Wang J, et al. Adjuvant Osimertinib for Resected EGFR-Mutated Stage IB-IIIA Non-Small-Cell Lung Cancer: Updated Results From the Phase III Randomized ADAURA Trial. *J Clin Oncol*. 2023;41(10):1830-1840.
91. Lu S, Kato T, Dong X, Ahn MJ, Quang LV, Soparattanapaisarn N, et al. Osimertinib after Chemoradiotherapy in Stage III EGFR-Mutated NSCLC. *N Engl J Med*. 2024.
92. Morris SW, Kirstein MN, Valentine MB, Dittmer KG, Shapiro DN, Saltman DL, et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. *Science*. 1994;263(5151):1281-1284.
93. Zhou W, Christiani DC. East meets West: ethnic differences in epidemiology and clinical behaviors of lung cancer between East Asians and Caucasians. *Chin J Cancer*. 2011;30(5):287-292.
94. Rangachari D, Yamaguchi N, VanderLaan PA, Folch E, Mahadevan A, Floyd SR, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. *Lung Cancer*. 2015;88(1):108-111.
95. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371(23):2167-2177.
96. Solomon BJ, Kim D-W, Wu Y-L, Nakagawa K, Mekhail T, Felip E, et al. Final Overall Survival Analysis From a Study Comparing First-Line Crizotinib Versus Chemotherapy in ALK-Mutation-Positive Non–Small-Cell Lung Cancer. *J Clin Oncol*. 2018;36(22):2251-2258.
97. Wu J, Savooji J, Liu D. Second- and third-generation ALK inhibitors for non-small cell lung cancer. *J Hematol Oncol*. 2016;9:19.
98. Shaw AT, Kim TM, Crinò L, Gridelli C, Kiura K, Liu G, et al. Ceritinib versus

chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(7):874-886.
99. Kim DW, Tiseo M, Ahn MJ, Reckamp KL, Hansen KH, Kim SW, et al. Brigatinib in Patients With Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial. *J Clin Oncol*. 2017;35(22):2490-2498.
100. Novello S, Mazières J, Oh IJ, de Castro J, Migliorino MR, Helland Å, et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study. *Annals of Oncology : official journal of the European Society for Medical Oncology*. 2018;29(6):1409-1416.
101. Horn L, Infante JR, Reckamp KL, Blumenschein GR, Leal TA, Waqar SN, et al. Ensartinib (X-396) in ALK-positive non–small cell lung cancer: results from a first-in-human phase I/II, multicenter study. *Clinical Cancer Research*. 2018;24(12):2771-2779.
102. Soria JC, Tan DSW, Chiari R, Wu YL, Paz-Ares L, Wolf J, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet.* 2017;389(10072): 917-929.
103. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. *N Engl J Med*. 2017;377(9):829-838.
104. Camidge DR, Kim HR, Ahn MJ, Yang JCH, Han JY, Hochmair MJ, et al. Brigatinib Versus Crizotinib in Advanced ALK Inhibitor-Naive ALK-Positive Non-Small Cell Lung Cancer: Second Interim Analysis of the Phase III ALTA-1L Trial. *J Clin Oncol*. 2020;38(31):3592-3603.
105. Horn L, Wang Z, Wu G, Poddubskaya E, Mok T, Reck M, et al. Ensartinib vs Crizotinib for Patients With Anaplastic Lymphoma Kinase–Positive Non–Small Cell Lung Cancer: A Randomized Clinical Trial. *JAMA Oncology*. 2021;7(11):1617-1625.
106. Shaw AT, Felip E, Bauer TM, Besse B, Navarro A, Postel-Vinay S, et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. *Lancet Oncol*. 2017;18(12):1590-1599.
107. Shaw AT, Bauer TM, de Marinis F, Felip E, Goto Y, Liu G, et al. First-Line Lorlatinib or Crizotinib in Advanced ALK-Positive Lung Cancer. *N Engl J Med*. 2020;383(21):2018-2029.
108. Solomon BJ, Bauer TM, Mok TSK, Liu G, Mazieres J, de Marinis F, et al. Efficacy and safety of first-line lorlatinib versus crizotinib in patients with advanced, ALK-positive non-small-cell lung cancer: updated analysis of data from the phase 3, randomised, open-label CROWN study. *Lancet Respir Med*. 2023;11(4):354-366.
109. Mok T, Camidge DR, Gadgeel SM, Rosell R, Dziadziuszko R, Kim DW, et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. *Ann Oncol*. 2020;31(8):1056-1064.
110. Camidge DR, Kim HR, Ahn MJ, Yang JCH, Han JY, Hochmair MJ, et al. Brigatinib Versus Crizotinib in ALK Inhibitor-Naive Advanced ALK-Positive NSCLC: Final Results of Phase 3 ALTA-1L Trial. *J Thorac Oncol*. 2021;16(12):2091-2108.
111. Solomon BJ, Liu G, Felip E, Mok TSK, Soo RA, Mazieres J, et al. Lorlatinib Versus Crizotinib in Patients With Advanced ALK-Positive Non-Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study. *J Clin Oncol*. 2024:Jco2400581.
112. Gainor JF, Dardaei L, Yoda S, Friboulet L, Leshchiner I, Katayama R, et al. Molecular Mechanisms of Resistance to First- and Second-Generation ALK Inhibitors in ALK-Rearranged Lung Cancer. *Cancer Discov*. 2016;6(10): 1118-1133.
113. Dagogo-Jack I, Rooney M, Lin JJ, Nagy RJ, Yeap BY, Hubbeling H, et al. Treatment with Next-Generation ALK Inhibitors Fuels Plasma ALK Mutation Diversity. *Clin Cancer Res*. 2019;25(22):6662-6670.
114. Yoda S, Lin JJ, Lawrence MS, Burke BJ, Friboulet L, Langenbucher A, et al. Sequential ALK Inhibitors Can Select for Lorlatinib-Resistant Compound ALK Mutations in ALK-Positive Lung Cancer. *Cancer Discov*. 2018;8(6): 714-729.
115. Lin JJ, Johnson M, Felip E, Ou S-HI, Besse B, Baik C, et al. Abstract B154: Safety and preliminary activity of the selective ALK inhibitor NVL-655 in patients with ALK fusion-positive solid tumors. *Molecular Cancer Therapeutics*. 2023;22(12_ Supplement):B154-B.
116. Bergethon K, Shaw AT, Ou S-HI, Katayama R, Lovly CM, McDonald NT, et al. ROS1 rearrangements define a unique molecular class of lung cancers. *J Clin Oncol*. 2012;30(8):863.
117. Ou S-HI, Nagasaka M. A Catalog of 5' Fusion Partners in ROS1-Positive NSCLC Circa 2020. *JTO Clinical and Research Reports*. 2020;1(3):100048.
118. Chin LP, Soo RA, Soong R, Ou S-HI. Targeting ROS1 with Anaplastic Lymphoma Kinase Inhibitors: A Promising Therapeutic Strategy for a Newly Defined Molecular Subset of Non–Small-Cell Lung Cancer. *J Thorac Oncol*. 2012;7(11):1625-1630.
119. Shaw AT, Ou S-HI, Bang Y-J, Camidge DR, Solomon BJ, Salgia R, et al. Crizotinib in ROS1-rearranged non–small-cell lung cancer. *N Engl J Med*. 2014;371(21):1963-71.
120. Shaw AT, Riely GJ, Bang YJ, Kim DW, Camidge DR, Solomon BJ, et al. Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001. *Ann Oncol.* 2019;30(7):1121-6.
121. Lim SM, Kim HR, Lee JS, Lee KH, Lee YG, Min YJ, et al. Open-Label, Multicenter, Phase II Study of Ceritinib in Patients With Non-Small-Cell Lung Cancer Harboring ROS1 Rearrangement. *J Clin Oncol*. 2017;35(23):2613-2618.
122. Drilon A, Siena S, Dziadziuszko R, Barlesi F, Krebs MG, Shaw AT, et al. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1–2 trials. *The Lancet Oncology*. 2020;21(2):261-270.
123. Gainor JF, Tseng D, Yoda S, Dagogo-Jack I, Friboulet L, Lin JJ, et al. Patterns of Metastatic Spread and Mechanisms of Resistance to Crizotinib in ROS1-Positive Non-Small-Cell Lung Cancer. *JCO Precis Oncol*. 2017;2017.
124. Shaw AT, Solomon BJ, Chiari R, Riely GJ, Besse B, Soo RA, et al. Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1-2 trial. Lancet Oncol. 2019;20(12):1691-701.
125. Drilon A, Camidge DR, Lin JJ, Kim SW, Solomon BJ, Dziadziuszko R, et al. Repotrectinib in ROS1 Fusion-Positive

Non-Small-Cell Lung Cancer. *N Engl J Med*. 2024;390(2):118-131.
126. Li W, Xiong A, Yang N, Fan H, Yu Q, Zhao Y, et al. Efficacy and Safety of Taletrectinib in Chinese Patients With ROS1+ Non–Small Cell Lung Cancer: The Phase II TRUST-I Study. Journal of Clinical Oncology.0(0):JCO.24.00731.
127. Parada LF, Tabin CJ, Shih C, Weinberg RA. Human EJ bladder carcinoma oncogene is homologue of Harvey sarcoma virus ras gene. *Nature*. 1982;297(5866):474-478.
128. Dearden S, Stevens J, Wu Y-L, Blowers D. Mutation incidence and coincidence in non small-cell lung cancer: meta-analyses by ethnicity and histology (mutMap). *Ann Oncol*. 2013;24(9):2371-2376.
129. Arbour KC, Jordan E, Kim HR, Dienstag J, Yu HA, Sanchez-Vega F, et al. Effects of Co-occurring Genomic Alterations on Outcomes in Patients with KRAS-Mutant Non-Small Cell Lung Cancer. *Clin Cancer Res*. 2018;24(2):334-340.
130. Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J, et al. Sotorasib for lung cancers with KRAS p. G12C mutation. *N Engl J Med*. 2021;384(25):2371-2381.
131. Canon J, Rex K, Saiki AY, Mohr C, Cooke K, Bagal D, et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature*. 2019;575(7781):217-223.
132. de Langen AJ, Johnson ML, Mazieres J, Dingemans AC, Mountzios G, Pless M, et al. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRAS(G12C) mutation: a randomised, open-label, phase 3 trial. *Lancet*. 2023;401(10378):733-746.
133. Mok TSK, Yao W, Duruisseaux M, Doucet L, Martínez AA, Gregorc V, et al. KRYSTAL-12: Phase 3 study of adagrasib versus docetaxel in patients with previously treated advanced/metastatic non-small cell lung cancer (NSCLC) harboring a KRASG12C mutation. *J Clin Oncol*. 2024;42(17_suppl): LBA8509-LBA.
134. Sacher A, LoRusso P, Patel MR, Miller WH, Jr., Garralda E, Forster MD, et al. Single-Agent Divarasib (GDC-6036) in Solid Tumors with a KRAS G12C Mutation. *N Engl J Med*. 2023;389(8):710-721.
135. Cho BC, Lu S, Lee MA, Song Z, Park J, Lim SM, et al. Abstract CT117: A phase 1 study of D3S-001, a second-generation GDP-bound KRAS G12C inhibitor, as monotherapy in patients with KRAS G12C-mutated solid tumors. *Cancer Research*. 2024;84(7_Supplement):CT117-CT.
136. Awad MM, Liu S, Rybkin, II, Arbour KC, Dilly J, Zhu VW, et al. Acquired Resistance to KRAS(G12C) Inhibition in Cancer. *N Engl J Med*. 2021;384(25): 2382-2393.
137. Singhal A, Li BT, O'Reilly EM. Targeting KRAS in cancer. *Nat Med*. 2024;30(4):969-983.
138. Jiang J, Jiang L, Maldonato BJ, Wang Y, Holderfield M, Aronchik I, et al. Translational and Therapeutic Evaluation of RAS-GTP Inhibition by RMC-6236 in RAS-Driven Cancers. *Cancer Discov.* 2024;14(6):994-1017.
139. Arbour KC, Punekar S, Garrido-Laguna I, Hong DS, Wolpin B, Pelster MS, et al. 652O Preliminary clinical activity of RMC-6236, a first-in-class, RAS-selective, tri-complex RAS-MULTI(ON) inhibitor in patients with KRAS mutant pancreatic ductal adenocarcinoma (PDAC) and non-small cell lung cancer (NSCLC). *Ann Oncol*. 2023;34:S458.
140. O'Leary CG, Andelkovic V, Ladwa R, Pavlakis N, Zhou C, Hirsch F, et al. Targeting BRAF mutations in non-small cell lung cancer. *Transl Lung Cancer Res*. 2019;8(6):1119-1124.
141. Marchetti A, Felicioni L, Malatesta S, Grazia Sciarrotta M, Guetti L, Chella A, et al. Clinical features and outcome of patients with non-small-cell lung cancer harboring BRAF mutations. *J Clin Oncol*. 2011;29(26):3574-3579.
142. Planchard D, Besse B, Groen HJM, Souquet PJ, Quoix E, Baik CS, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. *Lancet Oncol*. 2016;17(7):984-993.
143. Planchard D, Besse B, Groen HJM, Hashemi SMS, Mazieres J, Kim TM, et al. Phase 2 Study of Dabrafenib Plus Trametinib in Patients With BRAF V600E-Mutant Metastatic NSCLC: Updated 5-Year Survival Rates and Genomic Analysis. *J Thorac Oncol*. 2022;17(1):103-115.
144. Riely GJ, Smit EF, Ahn MJ, Felip E, Ramalingam SS, Tsao A, et al. Phase II, Open-Label Study of Encorafenib Plus Binimetinib in Patients With BRAF(V600)-Mutant Metastatic Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2023;41(21):3700-3711.
145. Facchinetti F, Lacroix L, Mezquita L, Scoazec JY, Loriot Y, Tselikas L, et al. Molecular mechanisms of resistance to BRAF and MEK inhibitors in BRAF(V600E) non-small cell lung cancer. *Eur J Cancer*. 2020;132:211-223.
146. Planchard D, Sanborn RE, Negrao MV, Vaishnavi A, Smit EF. BRAF(V600E)-mutant metastatic NSCLC: disease overview and treatment landscape. *NPJ Precis Oncol*. 2024;8(1):90.
147. Dankner M, Maxwell J, Rose AAN. The evolving treatment landscape for BRAF-mutated non-small cell lung cancer. *Transl Lung Cancer Res*. 2024;13(4):930-935.
148. Zhao J, Xia Y. Targeting HER2 Alterations in Non-Small-Cell Lung Cancer: A Comprehensive Review. *JCO Precis Oncol*. 2020;4:411-425.
149. Kim EK, Kim KA, Lee CY, Shim HS. The frequency and clinical impact of HER2 alterations in lung adenocarcinoma. *PLoS One*. 2017;12(2):e0171280.
150. Li BT, Smit EF, Goto Y, Nakagawa K, Udagawa H, Mazières J, et al. Trastuzumab Deruxtecan in HER2-Mutant Non-Small-Cell Lung Cancer. *N Engl J Med*. 2022;386(3):241-251.
151. Goto K, Goto Y, Kubo T, Ninomiya K, Kim SW, Planchard D, et al. Trastuzumab Deruxtecan in Patients With HER2-Mutant Metastatic Non-Small-Cell Lung Cancer: Primary Results From the Randomized, Phase II DESTINY-Lung02 Trial. *J Clin Oncol*. 2023;41(31):4852-4863.
152. Smit EF, Felip E, Uprety D, Nagasaka M, Nakagawa K, Paz-Ares Rodríguez L, et al. Trastuzumab deruxtecan in patients with metastatic non-small-cell lung cancer (DESTINY-Lung01): primary results of the HER2-overexpressing cohorts from a single-arm, phase 2 trial. *Lancet Oncol*. 2024;25(4):439-454.
153. Zhou C, Li X, Wang Q, Gao G, Zhang Y, Chen J, et al. Pyrotinib in HER2-Mutant Advanced Lung Adenocarcinoma After Platinum-Based Chemotherapy: A Multicenter, Open-Label, Single-Arm, Phase II Study. *J Clin Oncol*. 2020;38(24):2753-2761.
154. Le X, Cornelissen R, Garassino M, Clarke JM, Tchekmedyian N, Goldman JW, et al. Poziotinib in Non-Small-Cell Lung Cancer Harboring HER2 Exon 20 Insertion Mutations After Prior Therapies: ZENITH20-2 Trial. *J Clin Oncol*. 2022;40(7):710-718.
155. Heymach J, Opdam F, Barve MA, Tu H-Y, Wu Y-L, Berz D, et al. Phase Ia/Ib trial of zongertinib (BI 1810631), a HER2-specific tyrosine kinase inhibitor

(TKI), in patients (pts) with HER2 aberration-positive solid tumors: Updated Phase Ia data from Beamion LUNG-1, including progression-free survival (PFS) data. *J Clin Oncol*. 2024;42(16_suppl):8514-.
156. Loong HHF, Daniele G, Yang TY, Leal TA, Goto K, Shinno Y, et al. 1320MO Early evidence of efficacy in patients (pts) with non-small cell lung cancer (NSCLC) with HER2 exon20 insertion (ex20ins) mutations treated in a phase I study with BAY 2927088. *Ann Oncol*. 2023;34:S761-S2.
157. Andrews KL, Sun Y, Gerard B, Tangpeerachaikul A, Mente S, Kemper RA, et al. 212 (PB092) - NVL-330 is a selective, brain-penetrant inhibitor of oncogenic HER2 exon 20 insertion mutations in preclinical models. *European Journal of Cancer*. 2022;174:S76-S7.
158. Aujay M, Broad AJ, Gross SD, Ren L, Lyssikatos JP, Kintz S, et al. Abstract 4019: Preclinical activity of ELVN-002: A potent, selective, and irreversible HER2 and pan-HER2 mutant small molecule inhibitor for the treatment of HER2 driven malignancies. *Cancer Research*. 2023;83(7_Supplement):4019-.
159. Yu MR, Yun MR, Lee JB, Lee JY, Aum SW, Choi SJ, et al. Abstract 4029: JIN-A04, highly effective tyrosine kinase inhibitor targeting HER2 exon 20 insertion mutations in NSCLC. *Cancer Research*. 2023;83(7_Supplement):4029-.
160. Adashek JJ, Desai AP, Andreev-Drakhlin AY, Roszik J, Cote GJ, Subbiah V. Hallmarks of RET and Co-occuring Genomic Alterations in RET-aberrant Cancers. *Mol Cancer Ther*. 2021;20(10):1769-1776.
161. Drilon A, Lin JJ, Filleron T, Ni A, Milia J, Bergagnini I, et al. Frequency of Brain Metastases and Multikinase Inhibitor Outcomes in Patients With RET-Rearranged Lung Cancers. *J Thorac Oncol*. 2018;13(10):1595-1601.
162. Ferrara R, Auger N, Auclin E, Besse B. Clinical and Translational Implications of RET Rearrangements in Non-Small Cell Lung Cancer. *J Thorac Oncol*. 2018;13(1):27-45.
163. Zhou C, Solomon B, Loong HH, Park K, Pérol M, Arriola E, et al. First-Line Selpercatinib or Chemotherapy and Pembrolizumab in RET Fusion-Positive NSCLC. *N Engl J Med*. 2023;389(20):1839-1850.
164. Gainor JF, Curigliano G, Kim DW, Lee DH, Besse B, Baik CS, et al. Pralsetinib for RET fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study. *Lancet Oncol*. 2021;22(7):959-969.
165. Subbiah V, Gainor JF, Oxnard GR, Tan DSW, Owen DH, Cho BC, et al. Intracranial Efficacy of Selpercatinib in RET Fusion-Positive Non-Small Cell Lung Cancers on the LIBRETTO-001 Trial. *Clin Cancer Res*. 2021;27(15):4160-4167.
166. Lin JJ, Liu SV, McCoach CE, Zhu VW, Tan AC, Yoda S, et al. Mechanisms of resistance to selective RET tyrosine kinase inhibitors in RET fusion-positive non-small-cell lung cancer. *Ann Oncol*. 2020;31(12):1725-33.
167. Subbiah V, Shen T, Terzyan SS, Liu X, Hu X, Patel KP, et al. Structural basis of acquired resistance to selpercatinib and pralsetinib mediated by non-gatekeeper RET mutations. *Ann Oncol*. 2021;32(2):261-268.
168. Tong JH, Yeung SF, Chan AW, Chung LY, Chau SL, Lung RWM, et al. MET amplification and exon 14 splice site mutation define unique molecular subgroups of non–small cell lung carcinoma with poor prognosis. *Clin Cancer Res*. 2016;22(12):3048-3056.
169. Lee JK, Madison R, Classon A, Gjoerup O, Rosenzweig M, Frampton GM, et al. Characterization of Non-Small-Cell Lung Cancers With MET Exon 14 Skipping Alterations Detected in Tissue or Liquid: Clinicogenomics and Real-World Treatment Patterns. *JCO Precis Oncol*. 2021;5.
170. Recondo G, Che J, Jänne PA, Awad MM. Targeting MET Dysregulation in Cancer. *Cancer Discov*. 2020;10(7):922-934.
171. Wolf J, Seto T, Han JY, Reguart N, Garon EB, Groen HJM, et al. Capmatinib in MET Exon 14-Mutated or MET-Amplified Non-Small-Cell Lung Cancer. *N Engl J Med*. 2020;383(10):944-957.
172. Paik PK, Felip E, Veillon R, Sakai H, Cortot AB, Garassino MC, et al. Tepotinib in non–small-cell lung cancer with MET exon 14 skipping mutations. *N Engl J Med*. 2020;383(10):931-943.
173. Le X, Sakai H, Felip E, Veillon R, Garassino MC, Raskin J, et al. Tepotinib Efficacy and Safety in Patients with MET Exon 14 Skipping NSCLC: Outcomes in Patient Subgroups from the VISION Study with Relevance for Clinical Practice. *Clin Cancer Res*. 2022;28(6):1117-1126.
174. Lu S, Fang J, Li X, Cao L, Zhou J, Guo Q, et al. Once-daily savolitinib in Chinese patients with pulmonary sarcomatoid carcinomas and other non-small-cell lung cancers harbouring MET exon 14 skipping alterations: a multicentre, single-arm, open-label, phase 2 study. *Lancet Respir Med*. 2021;9(10):1154-1164.
175. Lu S, Yu Y, Guo Q, Li Y, Zhong D, Gu L, et al. OA21.03 A Phase 3b Study of 1L Savolitinib in Patients with Locally Advanced or Metastatic NSCLC Harboring MET Exon 14 Mutation. *J Thorac Oncol*. 2023;18(11, Supplement):S92-S3.
176. Leighl N, Cho BC, Hiret S, Han JY, Lee KH, Llacer Perez C, et al. OA21.04 Amivantamab in Patients with Advanced NSCLC and MET Exon 14 Skipping Mutation: Results from the CHRYSALIS Study. *J Thorac Oncol*. 2023;18(11, Supplement):S93-S4.
177. Fujino T, Kobayashi Y, Suda K, Koga T, Nishino M, Ohara S, et al. Sensitivity and Resistance of MET Exon 14 Mutations in Lung Cancer to Eight MET Tyrosine Kinase Inhibitors In Vitro. *J Thorac Oncol*. 2019;14(10):1753-1765.
178. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol*. 2018;15(12):731-747.
179. Vaishnavi A, Capelletti M, Le AT, Kako S, Butaney M, Ercan D, et al. Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer. *Nat Med*. 2013;19(11):1469-1472.
180. Farago AF, Taylor MS, Doebele RC, Zhu VW, Kummar S, Spira AI, et al. Clinicopathologic Features of Non-Small-Cell Lung Cancer Harboring an NTRK Gene Fusion. *JCO Precis Oncol*. 2018;2018.
181. Hong DS, DuBois SG, Kummar S, Farago AF, Albert CM, Rohrberg KS, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol*. 2020;21(4):531-540.
182. Drilon A, Tan DSW, Lassen UN, Leyvraz S, Liu Y, Patel JD, et al. Efficacy and Safety of Larotrectinib in Patients With Tropomyosin Receptor Kinase Fusion-Positive Lung Cancers. *JCO Precis Oncol*. 2022;6:e2100418.
183. Doebele RC, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AF, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol*. 2020;21(2):271-282.
184. Cho BC, Chiu CH, Massarelli E, Buchschacher GL, Goto K, Overbeck TR, et al. Updated efficacy and safety of entrectinib in NTRK fusion-positive non-small cell lung cancer. *Lung Cancer*. 2024;188:107442.

185. Liu D, Flory J, Lin A, Offin M, Falcon CJ, Murciano-Goroff YR, et al. Characterization of on-target adverse events caused by TRK inhibitor therapy. *Ann Oncol*. 2020;31(9):1207-1215.
186. Cocco E, Schram AM, Kulick A, Misale S, Won HH, Yaeger R, et al. Resistance to TRK inhibition mediated by convergent MAPK pathway activation. *Nat Med*. 2019;25(9):1422-1427.
187. Drilon A, Nagasubramanian R, Blake JF, Ku N, Tuch BB, Ebata K, et al. A Next-Generation TRK Kinase Inhibitor Overcomes Acquired Resistance to Prior TRK Kinase Inhibition in Patients with TRK Fusion-Positive Solid Tumors. *Cancer Discov*. 2017;7(9):963-972.
188. Besse B, Baik C, Springfeld C, Hervieu A, Moreno V, Bazhenova L, et al. Abstract P02-01: Repotrectinib in patients with NTRK fusion-positive advanced solid tumors: update from the registrational phase 2 TRIDENT-1 trial. *Molecular Cancer Therapeutics*. 2021;20(12_Supplement):P02-1-P-1.
189. Fernandez-Cuesta L, Plenker D, Osada H, Sun R, Menon R, Leenders F, et al. CD74-NRG1 fusions in lung adenocarcinoma. *Cancer Discov*. 2014;4(4): 415-422.
190. Drilon A, Somwar R, Mangatt BP, Edgren H, Desmeules P, Ruusulehto A, et al. Response to ERBB3-Directed Targeted Therapy in NRG1-Rearranged Cancers. *Cancer Discov*. 2018;8(6):686-695.
191. Laskin J, Liu S, Tolba K, Heining C, Schlenk R, Cheema P, et al. NRG1 fusion-driven tumors: biology, detection, and the therapeutic role of afatinib and other ErbB-targeting agents. *Ann Oncol*. 2020;31(12):1693-1703.
192. Drilon A, Duruisseaux M, Han JY, Ito M, Falcon C, Yang SR, et al. Clinicopathologic Features and Response to Therapy of NRG1 Fusion-Driven Lung Cancers: The eNRGy1 Global Multicenter Registry. *J Clin Oncol*. 2021;39(25):2791-2802.
193. Schram A, Goto K, Kim DW, Hollebecque A, Rha SY, Nishino K, et al. 1315MO Durable efficacy of zenocutuzumab, a HER2 x HER3 bispecific antibody, in advanced NRG1 fusion-positive (NRG1+) non-small cell lung cancer (NSCLC). *Ann Oncol*. 2023;34:S756-S7.
194. Patil T, Carrizosa DR, Burkard ME, Reckamp KL, Desai J, Chae YK, et al. Abstract CT229: CRESTONE: A Phase 2 study of seribantumab in adult patients with neuregulin-1 (NRG1) fusion positive locally advanced or metastatic solid tumors. *Cancer Research*. 2023;83(8_Supplement):CT229-CT.
195. Hammerman PS, Lawrence MS, Voet D, Jing R, Cibulskis K, Sivachenko A, et al. Comprehensive genomic characterization of squamous cell lung cancers. *Nature*. 2012;489(7417):519-525.
196. Sands JM, Nguyen T, Shivdasani P, Sacher AG, Cheng ML, Alden RS, et al. Next-generation sequencing informs diagnosis and identifies unexpected therapeutic targets in lung squamous cell carcinomas. *Lung Cancer*. 2020;140:35-41.
197. Meng H, Guo X, Sun D, Liang Y, Lang J, Han Y, et al. Genomic Profiling of Driver Gene Mutations in Chinese Patients With Non-Small Cell Lung Cancer. *Front Genet*. 2019;10:1008-.
198. Zhuang J, Yu Y, Li Z, Lu S. Efficacy of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) in targeted therapy of lung squamous cell carcinoma patients with EGFR mutation: a pooled analysis. *Oncotarget*. 2017;8(32):53675-53683.
199. Vassella E, Langsch S, Dettmer MS, Schlup C, Neuenschwander M, Frattini M, et al. Molecular profiling of lung adenosquamous carcinoma: hybrid or genuine type? *Oncotarget*. 2015;6(27):23905-23916.
200. Lin G, Li C, Li PS, Fang WZ, Xu HP, Gong YH, et al. Genomic origin and EGFR-TKI treatments of pulmonary adenosquamous carcinoma. *Ann Oncol*. 2020;31(4):517-524.
201. Wang R, Pan Y, Li C, Zhang H, Garfield D, Li Y, et al. Analysis of major known driver mutations and prognosis in resected adenosquamous lung carcinomas. *J Thorac Oncol.* 2014;9(6): 760-768.
202. Thatcher N, Hirsch FR, Luft AV, Szczesna A, Ciuleanu TE, Dediu M, et al. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. *Lancet Oncol*. 2015;16(7):763-774.
203. Soria JC, Felip E, Cobo M, Lu S, Syrigos K, Lee KH, et al. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. *Lancet Oncol*. 2015;16(8):897-907.
204. Hyman DM, Solit DB, Arcila ME, Cheng DT, Sabbatini P, Baselga J, et al. Precision medicine at Memorial Sloan Kettering Cancer Center: clinical next-generation sequencing enabling next-generation targeted therapy trials. *Drug Discov Today*. 2015;20(12):1422-1428.
205. Thompson JC, Yee SS, Troxel AB, Savitch SL, Fan R, Balli D, et al. Detection of Therapeutically Targetable Driver and Resistance Mutations in Lung Cancer Patients by Next-Generation Sequencing of Cell-Free Circulating Tumor DNA. *Clin Cancer Res*. 2016;22(23):5772-5782.
206. Tan DS, Thomas GV, Garrett MD, Banerji U, de Bono JS, Kaye SB, et al. Biomarker-driven early clinical trials in oncology: a paradigm shift in drug development. *Cancer J*. 2009;15(5):406-420.
207. Park JJH, Siden E, Zoratti MJ, Dron L, Harari O, Singer J, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. *Trials*. 2019;20(1):572.
208. Herbst RS, Gandara DR, Hirsch FR, Redman MW, LeBlanc M, Mack PC, et al. Lung Master Protocol (Lung-MAP)-A Biomarker-Driven Protocol for Accelerating Development of Therapies for Squamous Cell Lung Cancer: SWOG S1400. *Clin Cancer Res*. 2015;21(7):1514-1524.
209. Redman MW, Papadimitrakopoulou VA, Minichiello K, Hirsch FR, Mack PC, Schwartz LH, et al. Biomarker-driven therapies for previously treated squamous non-small-cell lung cancer (Lung-MAP SWOG S1400): a biomarker-driven master protocol. *Lancet Oncol*. 2020;21(12):1589-1601.
210. Redig AJ, Jänne PA. Basket trials and the evolution of clinical trial design in an era of genomic medicine. *J Clin Oncol*. 2015;33(9):975-977.
211. Flaherty KT, Gray RJ, Chen AP, Li S, McShane LM, Patton D, et al. Molecular Landscape and Actionable Alterations in a Genomically Guided Cancer Clinical Trial: National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH). *J Clin Oncol*. 2020;38(33):3883-3894.
212. Kurtovic-Kozaric A, Vranic S, Kurtovic S, Hasic A, Kozaric M, Granov N, et al. Lack of Access to Targeted Cancer Treatment Modalities in the Developing World in the Era of Precision Medicine: Real-Life Lessons From Bosnia. *J Glob Oncol*. 2018;4:1-5.
213. Raez LE, Cardona AF, Santos ES, Catoe H, Rolfo C, Lopes G, et al. The burden of lung cancer in Latin-America and challenges in the access to genomic profiling, immunotherapy and targeted treatments. *Lung Cancer*. 2018;119:7-13.

20

LUNG CANCER - ADVANCES IN IMMUNOTHERAPY

Meina Wang,[1] **Anne Chiang,**[1] **Jhanelle E. Gray,**[2] **Luis Paz-Ares,**[3] **Aakash Desai,**[4] **Solange Peters,**[5] **Fei Zhou,**[6] **Caicun Zhou,**[6] **and Roy S. Herbst**[1] | [1]Yale Comprehensive Cancer Center, Yale University School of Medicine, New Haven, USA; [2]H. Lee Moffitt Cancer Center and Research Institute, Tampa, USA; [3]Hospital Universitario 12 de Octubre, National Cancer Research Center (CNIO), Complutense University, Madrid, Spain; [4]The University of Alabama at Birmingham, Birmingham, USA; [5]University Hospital of Lausanne, Lausanne, Switzerland; [6]Shanghai Pulmonary Hospital, Thoracic Cancer Institute, Tongji University School of Medicine, Shanghai, China.

Since the first marketed immunotherapy drug to treat hairy cell leukemia was approved by the United States Food and Drug Administration (FDA) in 1986,[1] immunotherapy drugs such as cytokines [interferon (IFN)α2a/IFNα2b, tumor necrosis factor (TNF), interleukin (IL)-2 and IFNγ], oncolytic viruses [genetically-modified Herpes simplex virus (HSV) type 1], vaccines (Sipuleucel-T, Bacillus Calmette–Guérin), bispecific antibodies (CD19 and CD3), engineered T-cell therapies -[CD19-specific chimeric antigen receptor (CAR) T cells], and checkpoint blockers [cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1)] have been approved by the FDA for various cancer treatments.[2] Today, immunotherapy has become a powerful tool in the fight against cancer, and is the standard of care (SOC) for various cancer types.[3]

In 2015 and 2017, the immune check-point blockers (ICBs) nivolumab and pembrolizumab (anti-PD-1) heralded the age of immunochemotherapy in lung cancer as an addition to platinum-based frontline chemotherapy.[4-6] Immunotherapy has since been established as standard treatment for patients with advanced non-small cell lung cancer (NSCLC) whose tumors progress on first-line cytotoxic therapy, and as a first-line treatment for advanced or metastatic NSCLC for those presenting with advanced or metastatic NSCLC not harboring driver mutations in the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) tyrosine kinase receptor, or other genes/proteins. In the latter setting, immunotherapy can be utilized in combination with chemotherapy or as a single agent for patients whose tumors express high PD-L1. The current FDA-approved immunotherapy drugs for NSCLC all target the immunosuppressive tumor microenvironment (TME) by blocking the PD-1/PD-L1 inhibitory axis: both nivolumab and pembrolizumab are monoclonal anti-PD-1 antibodies; atezolizumab, durvalumab, and avelumab are anti-PD-L1 monoclonal antibodies.

Immunotherapy has shown significant benefit in a broad population of patients with NSCLC (Table 1). In the second-line NSCLC setting, treatment with nivolumab was first revealed to provide significantly longer median overall survival (mOS) compared to cytotoxic therapy in patients with previously treated advanced-stage NSCLC.[6,7] Subsequently, other immunotherapies, including pembrolizumab and atezolizumab showed OS improvement compared to treatment with docetaxel.[8,9] In the first-line NSCLC setting, pembrolizumab treatment for patients with advanced or metastatic NSCLC (mNSCLC) with tumor PD-L1 expression levels of 50% or more indicated a significant improvement in overall response rates (ORRs), progression-free survival (PFS) and OS compared to platinum-based cytotoxic therapy.[10]

This established the new SOC for patients with PD-L1 expression levels ≥ 50%. Combining immunotherapy with cytotoxic therapy may promote cancer cell death by elevating the T cell-to-tumor ratio and restoring metabolic restrictions that were formerly causing T cell hyporesponsiveness in cancer. Combining cytotoxic therapy with immunotherapy may also reduce the release of immunosuppressive factors by tumors or promote the release of antigens for presentation, enhancing T cell response.

Immunotherapy in NSCLC is successful predominately due to the introduction of ICBs such as monoclonal antibodies against PD-1 or PD-L1 for lung cancer care. Binding of PD-1 to its ligand PD-L1 inhibits T cell activation and thus functions to restrain hyperactivation of the immune system and prevent autoimmune diseases. However, during tumorigenesis, PD-1 signaling is primarily driven by adaptive expression of PD-L1 within the tumor. This leads to inactivation of T cells that recognize tumor-specific antigens and allow for tumor progression and metastasis. Blocking the PD-1/PD-L1 axis with antibodies offers a therapeutic approach to restoring T cell-mediated antitumor immunity.[11-13]

Even though immunotherapy in lung cancer has transformed the SOC, the vast majority of advanced NSCLC will eventually progress due to treatment resistance. The resistance can be classified as primary or secondary (acquired) based on clinical outcomes, or innate and adaptive based on biological mechanisms.[14,15] The immune resistance mechanisms are highly diverse.

Primary immune escape occurs when tumors are resistant to immunotherapy from the time of first treatment. The drivers of primary immune resistance are likely to have evolved over years and are the product of the endogenous host immune response. Well-described factors associated with sensitivity or resistance to immunotherapy include the number of non-synonymous somatic mutations or predicted neoantigens, specific genetic mutations, the nature of the tumor immune infiltrate, expression of PD-L1 on tumor and immune cells, local immune dysfunction through expression of immune inhibitory molecules, and developmental fate of T cells. Emerging mechanisms of resistance to immunotherapy include activity of the gut microbiota, epigenetics, and alterations in metabolism. However, there is insufficient patient data to confirm the roles of metabolism, epigenetics, and the microbiota in resistance to immunotherapy. Multi-omics analyses on immune cell regulation, the TME, and tumors exposed to immunotherapy will continue to elucidate a more comprehensive understanding of the factors that contribute to primary immune escape. Multi-omics analyses will require large data sets and artificial intelligence (AI) tools, necessitating collaboration between industry and academia.

Secondary immune escape indicates an initial tumor response, but eventual progression. Compared to primary immune escape, secondary immune escape arises over far shorter time periods. The question of how to define secondary resistance, especially when many patients are receiving various immunochemotherapy combinations, is a moving target. Although the mechanisms involved in primary and secondary immune escape overlap to some degree, they do not overlap temporally. Understanding both intrinsic and extrinsic factors resulting in resistance to immunotherapies is crucial for developing approaches to delay resistance, or for re-sensitizing tumors to immunotherapy treatment. Major mechanisms of secondary immune escape to immunotherapy can be defined in three subtypes. One mechanism involves genetic alterations that induce an immunosuppressive TME. During treatment with ICBs, tumor cells acquire or select for genetic alterations such as the loss of *PTEN, KEAP1*, or *STK11*, that eventually result in the induction of an immunosuppressive TME.[16,17] A second mechanism of resistance is caused by defective antigen processing and presentation. In this case, tumor cells may be unable to present neoantigens due to loss of MHC I or β2 microglobulin (B2M) expression, or other mechanisms of interference with antigen presentation, thereby allowing for tumor

immune escape.[18] The third mechanism is due to T cell exhaustion, for instance, by an upregulation of the T cell immunoreceptor with Ig and ITIM domains (TIGIT), T cell immunoglobulin and mucin-domain containing-3 (TIM-3), lymphocyte-activation gene-3 (LAG-3) or PD-1 expression.[19,20]

To overcome lung cancer immunotherapy resistance in practice, we need a better understanding of tumor biology and the mechanisms of immune resistance to enable both the development of effective ICBs and optimize personalized treatment for patients. Better predictors of response to immunotherapy are critical for its optimal use. Currently, PD-L1 and tumor mutational burden (TMB) are widely used for selecting patients for therapy.[21] However, the majority of patients will not fit the ideal profile using just these two biomarkers. Developing new biomarkers will be indispensable to determine the most appropriate immunotherapy to be used independently or in combination with other therapies. Combination therapy is another approach to overcome resistance by boosting antitumor responses via combined treatment. Since there are other key regulators involved in TME during immune escape, normalization cancer immunotherapy – the approach of targeting the local dysfunctional immune response within the TME – should be developed to identify and target these other key regulators and mechanisms involved.[22] In addition, cross-referencing or combining cancer genomic data with the cellular component of the TME could inform rationally designed combination therapies. The application of liquid biopsies measuring circulating tumor DNA (ctDNA) that provides invaluable information on the dynamic and evolving status of the patient's cancer, should also be expanded to detect both oncogenic drivers and track resistance factors. Systematic collection of patient tissue samples at the time of diagnosis and serially at the times of relapse also enables the evaluation of the dynamic clonal evolution that occurs over time, and possibly at different metastatic sites, and provides insights for new therapeutic approaches. Recent advances in next-generation histology, digital spatial profiling, and spatial transcriptomics will also assist in the identification of resistance mechanisms at various levels. Nevertheless, the current SOC has provided patients with the unprecedented benefits of immunotherapy and continued hope to cure cancer.

Immunotherapy drugs have revolutionized the treatment of NSCLC, offering significant improvements in PFS and OS. However, these treatments can be associated with immune-related adverse events (irAEs) such as pneumonitis, colitis, hepatitis, endocrinopathies, and skin reactions. Management of these toxicities involves early identification, graded intervention with corticosteroids and immunosuppressants for severe cases, and multidisciplinary care to address complex side effects. Despite these challenges, the overall benefits of immunotherapy in NSCLC are substantial. Clinical trials in Table 1 have demonstrated notable survival advantages, even with the occurrence of irAEs. Effective management strategies allow patients to continue benefiting from these therapies, underscoring the importance of immunotherapy in improving NSCLC outcomes.

IMMUNE CHECKPOINT INHIBITION IN NSCLC-LOCALLY ADVANCED (STAGE III) NSCLC

Among patients with NSCLC, one-third present with stage III disease.[33] Surgical interventions have offered limited survival benefits to patients with multilevel N2 disease; however, concurrent chemotherapy plus radiotherapy (CCRT) has since become the SOC for patients with unresectable disease and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0/1.[34] The concurrent approach allows local regional control with radiotherapy (RT) and reduced risks of metastatic disease through chemotherapy.[35] Per National Comprehensive Cancer Network (NCCN) guidelines, patients with unresectable stage IIIA/IIIB disease have superior benefits with CCRT versus RT alone.

Current Progress

CCRT and consolidation ICB. Despite success with CCRT, patients are likely to progress. Investigations of combined

Table 1. Recent or Practice-changing Immunotherapy Trials for NSCLC

Drug	Treatment	Study	Outcome	Ref
Nivolumab vs Chemo	Stage IIIB or IV or recurrent non-squamous NSCLC post radiotherapy or surgical resection Randomization stratified by prior treatment and line of therapy Biomarker: PD-L1 ≥1%, or ≥5% or ≥10%	Phase 3 CheckMate 057	Median OS: 12.2 (nivolumab) vs 9.4 (docetaxel) months (HR: 0.73; 96% CI: 0.59 to 0.89; P=0.002) OS at 18 months: 39% (nivolumab) (95% CI: 34-45) vs 23% (docetaxel) (95% CI: 19-28)	Borghaei et al., 2015[5]
Pembrolizumab vs Chemo	No prior treatment Stage IV NSCLC Squamous or non-squamous No sensitizing EGFR mutation or No ALK translocation PD-L1 ≥ 50%	Phase 3, KEYNOTE-024	PFS: 10.3 (pembrolizumab) vs 6.0 months (chemo) (HR, 0.50; 0.37-0.68, P<0.001) OS at 6 months: 80.2% (pembrolizumab) vs 72.4% (chemo) (HR, 0.60, 0.41-0.89, P=0.005)	Reck et al., 2016[10]
Pembrolizumab vs. Chemo	No prior treatment Locally advanced or metastatic NSCLC Squamous or non-squamous PD-L1 ≥ 1%	Phase 3, KEYNOTE-042	OS: PD-L1≥50%, 20.0 (pembrolizumab) vs 12.2 months (chemo) (HR 0.69; P=0.0003) PD-L1≥20%, 17.7 (pembrolizumab) vs 13·0 months (chemo) (HR 0.77; P=0.002) PD-L1≥1%, 16.7 (pembrolizumab) vs 12.1 months (chemo) (HR, 0.81; P=0.0018)	Mok et al., 2019[23]
Pembrolizumab +Chemo	No prior metastatic disease treatment Metastatic NSCLC Nonsquamous No sensitizing EGFR or ALK mutations Randomization stratified by PD-L1 ≥1% vs <1%	Phase 3, KEYNOTE-189	OS at 12 months: 69.2% (pembrolizumab combo) vs 49.4% (placebo combo) (HR, 0.49; 0.38-0.64; P<0.001) PFS: 8.8 (pembrolizumab combo) vs 4.9 months (placebo combo) (HR, 0.52; 0.43-0.64; P<0.001)	Gandhi et al., 2018[24]
Pembrolizumab	No prior treatment for metastatic disease Stage IV squamous NSCLC Randomization stratified by PD-L1 ≥1% vs <1%	Phase 3, KEYNOTE-407	OS: 15.9 (pembrolizumab combo) vs 11.3 months (placebo combo) (HR, 0.64; 0.49-0.85; P<0.001) PFS: 6.4 (pembrolizumab combo) vs 4.8 months (placebo combo) (HR, 0.56; 0.45-0.70; P<0.001)	Paz-Ares et al., 2018[5]
Nivolumab + Ipilimumab	No prior chemotherapy Stage IV or recurrent and PD-L1³1% NSCLC: Squamous or non-squamous Randomization stratified by PD-L1 ≥1% vs <1%	Phase 3, CheckMate 227	PD-L1³1%, OS: 17.1 (nivolumab + ipilimumab) vs 14.9 months (chemo) PD-L1<1%, OS: 17.2 (nivolumab + ipilimumab) vs 12.2 months (chemo) (HR, 0.79; P=0.007)	Hellmann et al., 2019[26]
Nivolumab + Ipilimumab + Chemo	Treatment-naive, stage IV or recurrent Squamous or nonsquamous NSCLC Randomization stratified by PD-L1 ≥1% vs <1%	Phase 3, CheckMate 9LA	OS: 14.1 (nivolumab + ipilimumab + chemo) vs 10.7 months (chemo alone) (HR, 0.69; P=0.00065)	Paz-Ares et al., 2021[27]
Durvalumab	Stage III, locally advanced, unresectable NSCLC Prior chemoradiotherapy No prior anti-PD-1 or PD-L1 exposure Enrollment not restricted to PD-L1 expression	Phase 3, PACIFIC	PFS: 16.8 (durvalumab) vs 5.6 months (placebo) (HR, 0.52; P<0.001)	Antonia et al., 2017[28]

Table 1. cont.

Drug	Treatment	Study	Outcome	Ref
Atezolizumab + +bevacizumab +carboplatin +paclitaxel	Stage IV or recurrent Metastatic non-squamous NSCLC No prior chemotherapy Randomization stratified by PD-L1 ≥1% vs <1%	Phase 3, IMpower150	PFS: 8.3 (atezolizumab +bevacizumab +carboplatin +paclitaxel) vs 6.8 months (bevacizumab +carboplatin +paclitaxel) (HR, 0.62; 0.52-0.74; P<0.001) OS in WT patients: 19.2 (atezolizumab +bevacizumab +carboplatin +paclitaxel) vs 14.7 months (bevacizumab +carbo-platin +paclitaxel) (HR, 0.78; 0.64-0.96; P=0.02)	Socinski et al., 2018[29]
Atezolizumab + carboplatin + nab-paclitaxel	Stage IV NSCLC Non-squamous No prior chemotherapy With sensitising *EGFR* or *ALK* mutations Must have had disease progression Randomization stratified by PD-L1 expression	Phase 3, IMpower130	OS: 18.6 (atezolizumab + chemo) vs 13.9 months (chemo) (HR, 0.79, 0.64-0.98, P=0·033) PFS: 7.0 (atezolizumab + chemo) vs 5.5 months (chemo) (HR, 0.64, 0.54-0.77, P<0.0001)	West et al., 2019[30]
Atezolizumab + Chemo vs. Chemo	First-line treatment of PD-L1-selected Stage IV NSCLC Squamous or non-squamous No prior chemotherapy PD-L1 ≥1%	Phase 3, IMpower110	OS: 20.2 (atezolizumab) vs 13.1 months (chemo) (HR, 0.59; P=0.01).	Herbst et al., 2020[31]
Cemiplimab	First line locally advanced or metastatic NSCLC Squamous or non-squamous Advanced NSCLC with PD-L1≥50%	Phase 3, EMPOWER-Lung 1	36 months follow-up for PD-L1≥50%: OS: 26.1 months (cemiplimab) vs 13.3 months (chemo) (HR 0.57; 95% CI 0.46–0,71; p<0.0001) PFS: 8.1 months (cemiplimab) vs 5.3 months (chemo) (HR 0.51, 95% CI 0.42–0.62; p<0.0001)	Özgüroğlu et al., 2023[172]
Durvalumab	Treatment naive Resectable NSCLC (stage II to IIIB) Squamous or non-squamous Randomization stratified by PD-L1 ≥1% vs <1%	phase 3, AEGEAN	At 12-month: EFS: 73.4% (durvalumab) (95% CI, 67.9-78.1) vs 64.5% (placebo) (95% CI, 58.8 to 69.6) PCR: 17.2% (durvalumab) vs 4.3% (placebo) (difference, 13.0 percentage points; 95% CI, 8.7-17.6; P<0.001)	Heymach et al., 2023[173]
Nivolumab + Chemo	No prior treatment Stage IB to IIIA resectable NSCLC Squamous or non-squamous *ALK* translocations or *EGFR* mutations excluded Randomization stratified by PD-L1 ≥1% vs <1%	phase 3, CheckMate 816	EFS: 31.6 months (nivolumab + chemo) (95% CI, 30.2 to not reached) vs 20.8 months (chemo) (95% CI, 14.0 to 26.7) (HR, 0.63; 97.38% CI, 0.43 to 0.91; P=0.005) PCR: 24.0% (nivolumab + chemo) (95% CI, 18.0 to 31.0) and 2.2% (chemo) (95% CI, 0.6 to 5.6) (odds ratio, 13.94; 99% CI, 3.49-55.75; P<0.001)	Forde et al., 2022[140]
Pembrolizumab	Neoadjuvant Resectable stage II, IIIA, or IIIB NSCLC Squamous or non-squamous Randomization stratified by disease stage (II vs. III) and PD-L1 (<50% vs. ≥50%)	Phase 3 KEYNOTE-671	24-month EFS: 62.4% (pembrolizumab) vs 40.6% (placebo) (HR, 0.58; 95% [CI], 0.46 to 0.72; P<0.001). 24-month OS: 80.9% (pembrolizumab) and 77.6% (placebo) (P=0.02)	Wakelee et al, 2023[174]

Table 1. cont.

Drug	Treatment	Study	Outcome	Ref
Nivolumab	Neoadjuvant Resectable stage IIA to IIIB NSCLC Randomization stratified by disease stage (II or III), tumor histology (squamous or nonsquamous), and PD-L1 (<1%, ≥1%, or not evaluable or indeterminate)	Phase 3 CheckMate 77T	18-month EFS: 70.2% (nivolumab) vs 50.0% (chemotherapy) (HR, 0.58; 97.36% [CI], 0.42 to 0.81; P<0.001)	Cascone et al., 2024[175]

PFS: progression-free survival; OS: overall survival; EFS: Event-free survival; PCR: pathological complete response; TPS: tumor proportion score; DFS: disease-free survival; HR: hazard ratio; DCR: disease control rate (including stable disease); DOR: duration of response; ORR: objective response rate; RR: response rate (complete or partial response); Chemo: chemotherapy; CNS: central nervous system.[5,6,10,23-33,140,172,173]

immunotherapy-CCRT started with durvalumab, an ICB, in the phase 3 PACIFIC study (NCT02125461).[28] Between 2014 and 2016, 709 patients with stage III, locally advanced, unresectable NSCLC and without progression post-CCRT received ≥1 dose of study drug as consolidation therapy every 2 weeks for 12 months. The durvalumab group (n=473) had significantly longer median progression-free survival (mPFS) versus the placebo group (n=236) of 16.8 versus 5.6 months [hazard ratio (HR) 0.52; 95% confidence interval (CI), 0.42–0.65]. Durvalumab improved 5-year OS (42.9% vs. 33.4% with placebo), with approximately one-third of the durvalumab group free of disease progression.[36] The PACIFIC study (Figure 1)[28] demonstrated improved outcomes for consolidation durvalumab as part of SOC, supported an FDA approval and NCCN listing, and helped pave the way for combined immunotherapy-CCRT studies.

However, the PACIFIC study also highlighted the need for personalized approaches based on genetic drivers and PD-L1 expression. In the study, EGFR mutations were present in 6.0% of patients,

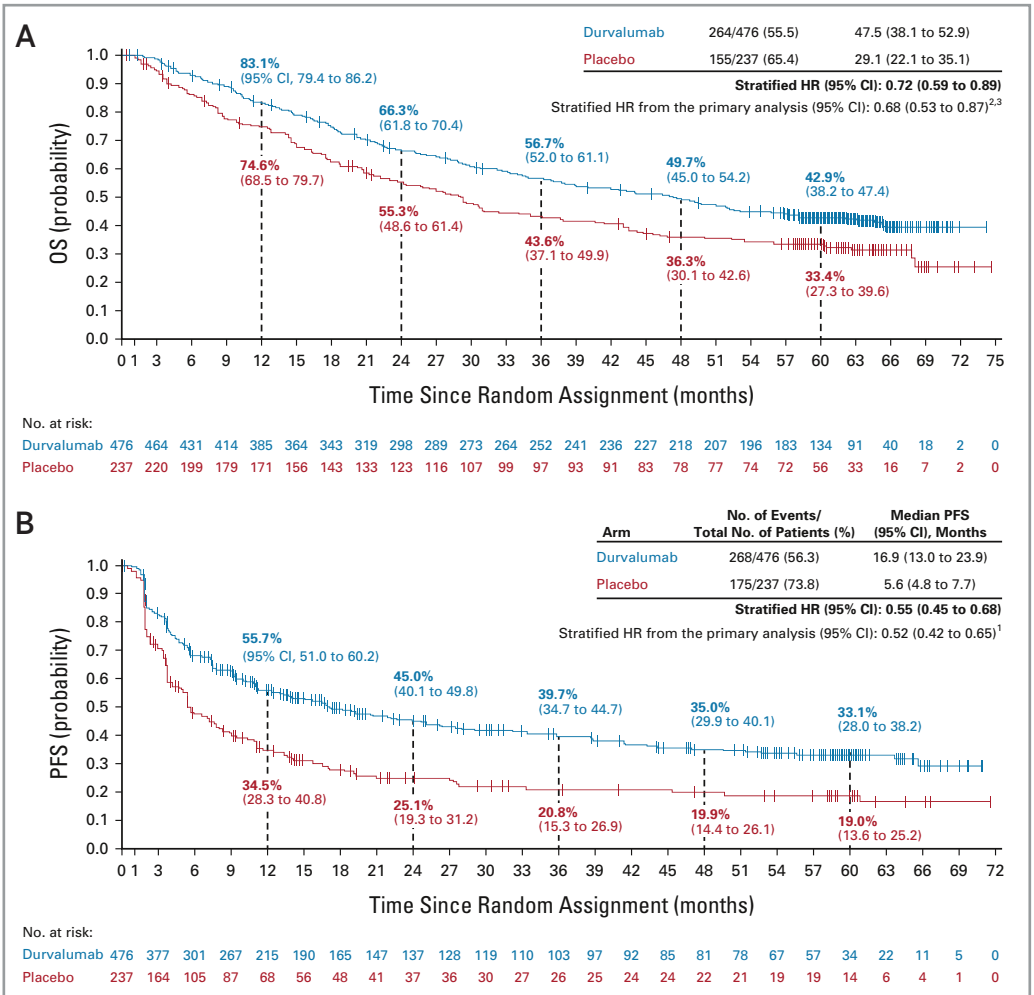


Figure 1. Five-year survival outcomes from the PACIFIC trial. **A)** OS and **B)** PFS (blinded independent central review) in the intent-to-treat population. Vertical dashed lines indicate yearly OS and PFS rates. HR, hazard ratio; OS, overall survival; PFS, progression-free survival. From reference 36, reprinted with permission.

with similar distribution in both the durvalumab (6.1%) and placebo (5.9%) groups. Most patients (67.3%) had EGFR-negative or wild-type tumors, with no significant differences between the groups in terms of EGFR mutation status or PD-L1 expression levels (<25% or ≥25%). This underscores the complexity of treating NSCLC and the necessity for more refined strategies. Further studies are required to explore the optimal immunotherapy treatment for EGFR-mutated NSCLC, as these patients typically have a lower response rate to immune checkpoint inhibitors. Additionally, continued research into additional biomarkers beyond EGFR and PD-L1 will help tailor personalized treatments for NSCLC patients.

To model real-world outcomes of consolidation durvalumab, PACIFIC-R (NCT03798535), an international observational study initiated in 2017, evaluated investigator-assessed PFS and OS. From 290 sites, 1399 patients without progression have so far completed platinum-based CCRT and started durvalumab. mPFS was slightly longer for PACIFIC-R than for PACIFIC (21.7 vs. 16.8 months), although PFS events were similar (52.7% vs. 56.3%).[37]

In 2015/2016, LUN 14-179 (NCT02343952), a single-arm phase 2 trial, investigated consolidation pembrolizumab in 93 patients (92 eligible for the efficacy analysis). Eligible patients had previous platinum-based CCRT; those without progressive disease post-CCRT received consolidation pembrolizumab. Of 93 patients, only 4 received consolidation chemotherapy. Median time to death or disease metastasis (TTDM; primary endpoint) was 30.7 months, and HRs for 12-, 18-, 24-, and 36-month TTDM were 77.6%, 61.8%, 55.3%, and 49.9%, respectively. Median OS was 35.8 months, and estimated 1-, 2-, and 3-year OS rates were 81.2%, 62.0%, and 48.5%, respectively. Stratification by PD-L1 status revealed no significant differences in OS between patients with PD-L1 modified proportion scores of <1% and ≥1% (HR 0.79; 95% CI, 0.27–2.31). mPFS was 18.7 months (95% CI, 12.4–33.8), and estimated HRs at 12, 18, 24, and 36 months were 61.2%, 50.3%, 46.3%, and 37.4%, respectively. Sixteen patients experienced pneumonitis with median time to occurrence of 8.4 weeks. Consolidation pembrolizumab improved TTDM, PFS, and OS compared with historical controls. The improved outcomes in the pembrolizumab (LUN 14-179) and durvalumab (PACIFIC) studies supported consolidation PD-1/PD-L1 inhibitors following CCRT.[38] Although most studies evaluate patient outcomes for ICI treatment following CCRT, which is the SOC, some patients receive sequential CCRT instead. Whether sequential CCRT followed by ICI can improve outcomes remains unknown.

The single-arm phase 2 NICOLAS (NCT02434081) trial evaluated concurrent nivolumab plus 3 cycles of platinum-based CCRT followed by consolidation nivolumab in 74 patients with stage IIIA/B, unresectable, treatment-naïve NSCLC. Before inclusion, patients received homogenized treatment of first induction cycle of platinum-based chemotherapy. Consolidation nivolumab was then continued for up to 1 year. Once safety of treatment was proven, 37 of 74 patients (50%) reached PFS at 1 year (primary endpoint), with mPFS of 27.4 and 12.1 months for stage IIIA and IIIB patients, respectively. Median, 1-year, and 2-year OS results were 38.8 months, 75.7%, and 63.7%, respectively. ORR was 73.4%, and median duration of response (mDoR) was 11.0 months in 58 patients with overall response. Five patients had complete response (6.3%). Nine patients (11.7%) experienced grade ≥3 pneumonitis.[39] Although toxicity of nivolumab with CCRT was demonstrated to be within limits, continued investigations are needed.

GEMSTONE-301 (NCT03728556), a randomized, double-blind, multicenter, phase 3 trial conducted in China, evaluated the safety and efficacy of the PD-L1 inhibitor sugemalimab versus placebo as consolidation therapy. Participants had locally advanced, unresectable stage III NSCLC with no disease progression following concurrent or sequential CRT and ECOG PS of 0/1. From 2018 to 2020, 564 patients were randomized 2:1 to sugemalimab (n=255) or placebo (n=126) and followed for median of 14.3 and 13.7 months, respectively. PFS (primary objective) was significantly longer with

sugemalimab versus with placebo following CCRT or sequential CRT. OS with sugemalimab initially demonstrated a HR of 0.4. Six patients (5/255 sugemalimab, 1/126 placebo) experienced grade 3 pneumonitis or immune-mediated pneumonitis. Despite improved PFS with sugemalimab versus placebo, longer follow-up studies are needed for sugemalimab plus CCRT.[40]

CCRT plus ICB with consolidation ICB

Although consolidation durvalumab following CCRT became SOC for patients with locally advanced NSCLC, other combined immunotherapy-CCRT regimens have been investigated. The phase 2 two-part DETERRED trial (NCT02525757) investigated atezolizumab-CCRT, with primary endpoints of safety and tolerability. In part 1, patients first received fractionated CCRT (carboplatin/paclitaxel/RT); if no extent-of-disease (EOD) progression occurred, patients received consolidation CCRT plus atezolizumab followed by maintenance atezolizumab for 1 year (n=10). If safety with atezolizumab was shown during the consolidation phase, patients were then enrolled into part 2; patients received CCRT plus atezolizumab followed by the same regimen for consolidation and maintenance for up to 1 year (n=30). Primary and secondary endpoints included safety/tolerability of atezolizumab-CCRT and consolidation chemotherapy (primary) and PFS, OS, and PD-L1 immunohistochemistry (IHC) staining (secondary). No additive toxicities were shown compared with historical rates. Overall, 80% of patients experienced at least one grade ≥3 adverse event, and 10% of part 1 and 16% of part 2 patients experienced grade ≥1 pneumonitis. Although not significant, 1-year PFS in tumor PD-L1 IHC staining score of ≥1% versus <1% or ≥50% versus <50% trended to improve. This study demonstrated the feasibility of concurrent atezolizumab with CCRT.[41]

The phase 2 nonrandomized, open-label KEYNOTE-799 (NCT03631784) study explored consolidation pembrolizumab-CCRT in two cohorts of stage III NSCLC patients with similar median age (66.0/64.0 years). From 2018 to 2020, cohort A patients (n=112 with squamous and non-squamous NSCLC; 67.9% men) received carboplatin/paclitaxel/pembrolizumab on day 1 followed by carboplatin/paclitaxel weekly, daily RT for 6 weeks, and 2 cycles of pembrolizumab. Cohort B patients (n=102 with nonsquamous; 60.8% men) received 3 cycles of cisplatin/pemetrexed/pembrolizumab every 3 weeks and daily RT concurrently in cycles 2 and 3. All patients received 14 additional cycles of pembrolizumab. In cohort A and B, 58.9% and 39.2% of patients, respectively, had PD-L1 tumor proportion score ≥1. ORR (primary endpoint) was comparable between cohorts (70.5%/70.6%). Neither cohort reached mDoR, but 79.7% (cohort A) and 75.6% (cohort B) had response duration of ≥12 months, with 67% and 65.7% achieving partial response. Grade ≥3 pneumonitis was observed in 8.0% and 6.9% of cohort A and B, respectively.[42]

Further trials of ICB-CRT include PACIFIC-2 (NCT03519971), a randomized, placebo-controlled, double-blind, multicenter, international phase 3 study investigating durvalumab plus platinum-based CRT in 328 patients with stage III, unresectable NSCLC. Outcome measures include PFS (primary) and OS, ORR, TTDM, and DoR among secondary outcomes. This study has completed accrual, and results are eagerly awaited.

ECOG-ACRIN 5181 (NCT04092283), a phase 3 prospective, randomized trial, will test whether durvalumab plus CCRT improves OS (primary endpoint) and PFS (secondary endpoint) in patients with unresectable stage III NSCLC. Patients will receive either concomitant durvalumab plus platinum-doublet CCRT (Arm A) or CCRT alone (Arm B) followed by consolidation durvalumab for 1 year (Arm C). Patients with grade ≤2 toxicities or no progression after the first posttreatment computed tomography (CT) are eligible for Arm C. Other secondary endpoints include best ORR and toxicity.[43] Results are pending for this ongoing study, which may have the potential to change SOC.

CheckMate 73L (NCT04026412), a three-arm, multicenter, randomized, open-label phase 3 study initiated in 2019, is evaluating the

safety and efficacy of nivolumab plus CCRT followed by nivolumab with ipilimumab (Arm A) or without ipilimumab (Arm B) as maintenance therapy versus CCRT followed by durvalumab (Arm C).[44] By October 2022, 888 patients with treatment-naïve locally advanced-stage III NSCLC are projected to be randomized 1:1:1 to each treatment group (~1400 screened). Primary endpoints are PFS and OS comparing Arms A and C; secondary endpoints include additional PFS and OS analyses comparing Arm A versus B and Arm B versus C as well as other response measures and safety/tolerability. With the study still ongoing, results are pending on its impact on SOC for NSCLC patients.

Table 2 lists the ongoing ICB-CRT trials in locally advanced NSCLC.

Future Directions of Combination Therapies

The safety and efficacy of combination treatments for patients with unresectable, stage III NSCLC continue to be investigated. With preclinical models showing increased antitumor activity of RT/anti-CD73/NKG2A with or without anti-PD-L1/PD-1, the phase 2, open-label COAST trial is comparing investigator-assessed ORR in patients randomized to control (durvalumab), durvalumab/oleclumab (Arm A), or durvalumab/monalizumab (Arm B) treatment. As of May 2021, 189 randomized patients have been followed-up for median 11.5 months. ORR was 30.0% and 35.5% in Arms A and B, respectively, versus 17.9% in control, with comparable rates of pneumonitis across all three groups (18.0%–20.3%).[43] SKYSCRAPER-03 (NCT04513925), an open-label, randomized, combination therapy phase 3 trial initiated in August 2020, is evaluating PFS, safety, and tolerability of atezolizumab/tiragolumab (an anti-TIGIT anti-

Table 2. Ongoing ICB-CRT Trials in Locally Advanced (Stage III) Unresectable NSCLC

Study and Phase	Cancer Type and Stage	Design and Official Title	# of pts (enrolled)	Status
DETERRED trial NCT02525757 Phase II	Unresectable NSCLC (local)	Chemotherapy + Radiation vs MPDL3280A (anti-PD-L1) + Chemotherapy + Radiation	52 (enrolled)	Active, not recruiting
PACIFIC-2 NCT03519971 Phase III	Locally Advanced, Unresectable, Stage III NSCLC	Durvalumab + platinum-based chemotherapy and radiation vs Placebo + platinum-based chemotherapy and radiation	328 (enrolled)	Active, not recruiting Results: missed PFS end point
ECOG-ACRIN 5181 NCT04092283 Phase III	Unresectable, Stage III NSCLC	Durvalumab, chemotherapy, durvalumab vs chemotherapy, durvalumab	660 (enrolled)	Active, not recruiting
CheckMate 73L NCT04026412 Phase III	Treatment naïve, locally advanced NSCLC	Nivolumab + concurrent CCRT followed by Nivolumab + Ipilimumab or Nivolumab + CCRT followed by Nivolumab vs CCRT followed by Durvalumab	888 (enrolled)	Active, not recruiting
SKYSCRAPER-03 NCT04513925 Phase III	Locally advanced, unresectable, Stage III NSCLC Previously received ≥ 2 cycles of CRT, and no radiographic disease progression	Atezolizumab + Tiragolumab vs Durvalumab	829 (enrolled)	Active, not recruiting
PACIFIC-9 NCT05221840	Phase III Locally advanced (Stage III), unresectable NSCLC	Durvalumab with oleclumab or durvalumab with monalizumab following concurrent chemoradiation	999 (estimate)	Recruiting

body) versus durvalumab alone. Patients (n=800) with locally advanced, unresectable stage III NSCLC, prior treatment with platinum-based CCRT, and no disease progression will be included.[46] These studies demonstrate the future of the field, where ICBs beyond anti-PD-L1 therapy will also be interrogated.

NSCLC – STAGE IV

Over the last few decades, we have acquired significant knowledge about the genomic aberrations and signaling disturbances underlying lung cancer that are responsible for its initiation, progression, and the development of metastasis. Some of the molecular alterations lead to oncogene addiction in certain subtypes of NSCLC, particularly adenocarcinomas, that may be exploited therapeutically.[47] As a result, patients with advanced NSCLC typically have their tumors (and/or ctDNA) screened for those biomarkers that would guide treatment with targeted therapy. However, many tumors lack actionable targets [most of squamous cell carcinoma (SCC), some 30-50% of adenocarcinomas], and those patients that are candidates for specific molecular inhibitors universally develop resistance at some stage requiring alternative treatment approaches. Fortunately, the discovery of immune evasion mechanisms that enable tumor progression has led to the development of a new generation of immunotherapeutics, including monoclonal antibodies directed against critical immune checkpoint signals such as the PD-1 receptor and its ligand PD-L1, and the CTLA-4 receptor that have had a remarkable impact on many patients with solid tumors including those with lung cancer.[48,49] PD-1/PD-L1 blockers were first used as monotherapies in previously treated patients with advanced NSCLC. Now, they are also used in the front-line setting as single agents or in combination with chemotherapy regimens, CTLA-4 inhibitors, or both.[6-8,50] Today, immunotherapy with ICBs is the cornerstone of the treatment of advanced NSCLC and their use has impacted the natural history of the disease and outcomes, including long term survival of patients.[51]

Pretreated Patients

The development of ICBs in NSCLC was initially restricted to single agent PD-1/PD-L1 inhibitors on previously treated, no prior ICB exposed patients, as no relevant activity had been reported with CTLA-4 blockade. Early trials in this context have shown rapid and durable responses in some 15–20% of patients. Of note, even though PFS rates were not overwhelming (median 2–4 months; PFS at 1 year 20%), survival rates were encouraging. The 5-year OS on the phase I NSCLC cohorts treated with pembrolizumab (n=449) and nivolumab (n=129) reached 15-16%.[11,52-54] Antitumor activity was independent of histology but related to PD-L1 expression in tumor cells and to smoking history. The safety profile of this class of agents was favorable, with about 10% of patients developing severe (grades III-IV) events. The most frequent adverse effects observed were asthenia, fatigue, loss of appetite, nausea, and diarrhea. Less than 15% of patients developed immune related side-effects including rash, colitis, transaminitis, pneumonitis, and endocrinopathies.

The clinical efficacy and safety of anti–PD-1/PD-L1 agents in previously treated, ICB-naive patients with advanced disease have been confirmed in several randomized studies. Two trials have compared nivolumab to docetaxel in patients who progressed on platinum-based chemotherapy, both in SCC (CheckMate 017 trial) and non-SCC NSCLC (CheckMate 057 trial).[6,7] In SCC patients, nivolumab treatment resulted in improved OS (HR 0.59, P<0.001; median 9.2 vs 6.0 months), PFS (HR 0.62, P<0.001; median 3.5 vs 2.8 months) and response rate (20% vs 9%, P<0.008) over docetaxel.[7] Nivolumab benefits were largely independent of clinical and tumor characteristics, including PD-L1 expression. In the non-SCC trial, nivolumab improved OS (median 12.2 vs 9.4 months, HR 0.73) and ORR (P<0.02) but not PFS in the overall population.[6] Treatment effect was seen in all patient subgroups except for never-smokers and those with wild-type EGFR tumors. In addition, in non-SCC, PD-L1 expression emerged as a significant determinant of nivolumab benefit. Atezolizumab

has also showed superiority over docetaxel in a randomized phase III trial including all NSCLC histologies, and the benefit from the PD-L1 blocker was mostly restricted to the PD-L1 positive tumor population.[9] A randomized phase III trial of pembrolizumab versus docetaxel in patients harbouring PD-L1–positive tumours (>1% of cells) favoured the anti–PD-1 treatment, and the magnitude of the survival benefit was related to PD-L1 expression (HR of 0.53 if PD-L1>50%; HR of 0.76 if PD-L1 expression 1–49%).[8] Long term follow-up of these trials reported survival rates at 5 years in the range of 12.3-16.6% for patients treated with PD-1/PD-L1 inhibitors as compared to 2.1-8.8% in the docetaxel treated groups.[54-56]

Initially, trials were conducted in ICB naive patients in the refractory setting. But then in the second iteration of the Lung-MAP study, all patients had received IO inhibitors with chemotherapy (e.g., Keynote-189), IO inhibitors alone (e.g., Keynote-024), or atezolizumab alone. Consequently, these patients were IO-refractory, representing a more challenging population to treat. The current Lung-MAP 1400 and pragmatic trials also focus on IO-refractory patients, specifically those who have been on immunotherapy for at least 12 weeks or 84 days.

Treatment-Naïve Patients

Single-agent ICB

Following the results in pretreated patients, the development of ICBs in the front-line setting concentrated mostly in PD-L1-expressing tumors. Treatment-naïve patients included in the pembrolizumab phase I advanced NSCLC expansion cohort (n=101) demonstrated responses in some 23% (50% if PD-L1>50%), and median OS of 22.3 months.[11,54] Overall 5-year OS was 23.2%, and was 29.6% for patients whose tumors expressed PD-L1 in more than 50% of cells.[11] Subsequently four out of five trials including 3137 patients with SCC and non-SCC and a PD-L1>1% (KEYNOTE 042 and Impower 110), >5% (CheckMate 026) or >50% (KEYNOTE 024, Empower Lung1) showed consistent improved outcomes for patients treated with PD-1/PD-L1 inhibitors as compared to histology-driven platinum-based chemotherapy.[10,23,31,32,58-62] The benefit was evident in terms of increased responses and prolonged PFS and OS, and mostly restricted to patients whose tumors expressed PD-L1 in >50% that reached survival rates at 5 years of 22-32% (as compared to 10-16% with chemotherapy alone).[59,60] Indeed, even in the latter group the higher the expression the more pronounced magnitude of benefit.[32] IMpower110 (Figure 2) reported on the superior efficacy and better safety profile of atezolizumab over chemotherapy in patients with mNSCLC who had not previously received chemotherapy and whose tumors expressed high PD-L1.[31] This led to FDA approval of atezolizumab as a first-line treatment for adult patients with mNSCLC with high PD-L1 expression ([TC ≥ 50%] or [IC ≥ 10%]) with no EGFR or ALK genomic tumor aberrations.

Chemotherapy plus ICB

The fact that ~70% of patients did not derive relevant benefit from ICBs as monotherapy promoted the search for combination strategies.[63] The potential of chemotherapy inducing immunogenic cell death and facilitating antigen presentation led to combine a number of platinum-based regimens, with or without an antiangiogenic, with PD-1/PD-L1 blockers in treatment-naïve patients.

For SCC in previously untreated metastatic squamous NSCLC patients, the KEYNOTE-407 trial showed that adding pembrolizumab to chemotherapy significantly improved OS and PFS. Median OS was 15.9 months with the pembrolizumab combination versus 11.3 months with the placebo combination (HR 0.64; P<0.001), and median PFS was 6.4 months versus 4.8 months (HR 0.56; P<0.001) (Figure 3). The IMpower131 trial, involving first-line squamous NSCLC, found that adding atezolizumab to carboplatin and nabpaclitaxel significantly improved PFS (6.3 vs. 5.6 months; HR 0.71; P=0.0001) but not OS (14.2 vs. 13.5 months; HR 0.88; P=0.16). In the PD-L1-high subgroup, OS improvement was observed (HR 0.48). Treatment-related grade 3 and 4 adverse events were higher in the atezolizumab group (68.0% vs. 57.5%).

For non-SCC, the KEYNOTE-189 trial indicated that in metastatic

non-SCC without EGFR/ALK alterations, pembrolizumab plus pemetrexed and platinum significantly improved OS (HR 0.60) and PFS (HR 0.50) over placebo with chemotherapy (Figure 4). The 5-year OS rate was 19.4% for pembrolizumab versus 11.3% for placebo. Pembrolizumab was well tolerated, with manageable toxicity. The IMpower130 trial showed that atezolizumab combined with chemotherapy in stage IV non-squamous NSCLC significantly improved OS (18.6 vs. 13.9 months; HR 0.79, P=0.033) and PFS (7.0 vs. 5.5 months; HR 0.64, P<0.0001) compared to chemotherapy alone. Grade 3 or worse adverse events were higher with atezolizumab (32% vs. 28%).

Overall, the initial trials with pembrolizumab showed significantly improvements in OS (HR 0.60-0.71), RR (48-63% vs 20-39%) and PFS (HR 0.50-0.59), in SCC and non-SCC, regardless of the level of PD-L1 expression, although the likelihood of long-term survival was greater the higher the PD-L1 level.[5,64-66] With mature follow-up survival at 5 years were observed in 18.4-19.4% of patients, half of them being progression-free at that time.[65,66] The tested regimens have proven to be safe with an adverse event profile that includes the expected side effects of chemotherapy. To date, 13 phase 3 trials of chemotherapy with/without other PD-1/PD-L1 inhibitors including more than 7000 patients with advanced NSCLC have been reported.[5,10,64-77] Overall, consistent results were observed in non-SCC (RR:47-64% vs 20-48%; PFS HR: 0.48-0.82; OS HR:0.60-0.86) and SCC (RR:45-75% vs 37-50%; PFS HR: 0.33-0.71; OS HR: 0.52-0.88), but not always meeting the statistical requirements for significancy in OS (e.g. atezolizumab in Impower 132 and 131 studies in non-SCC and SCC).[69,75]

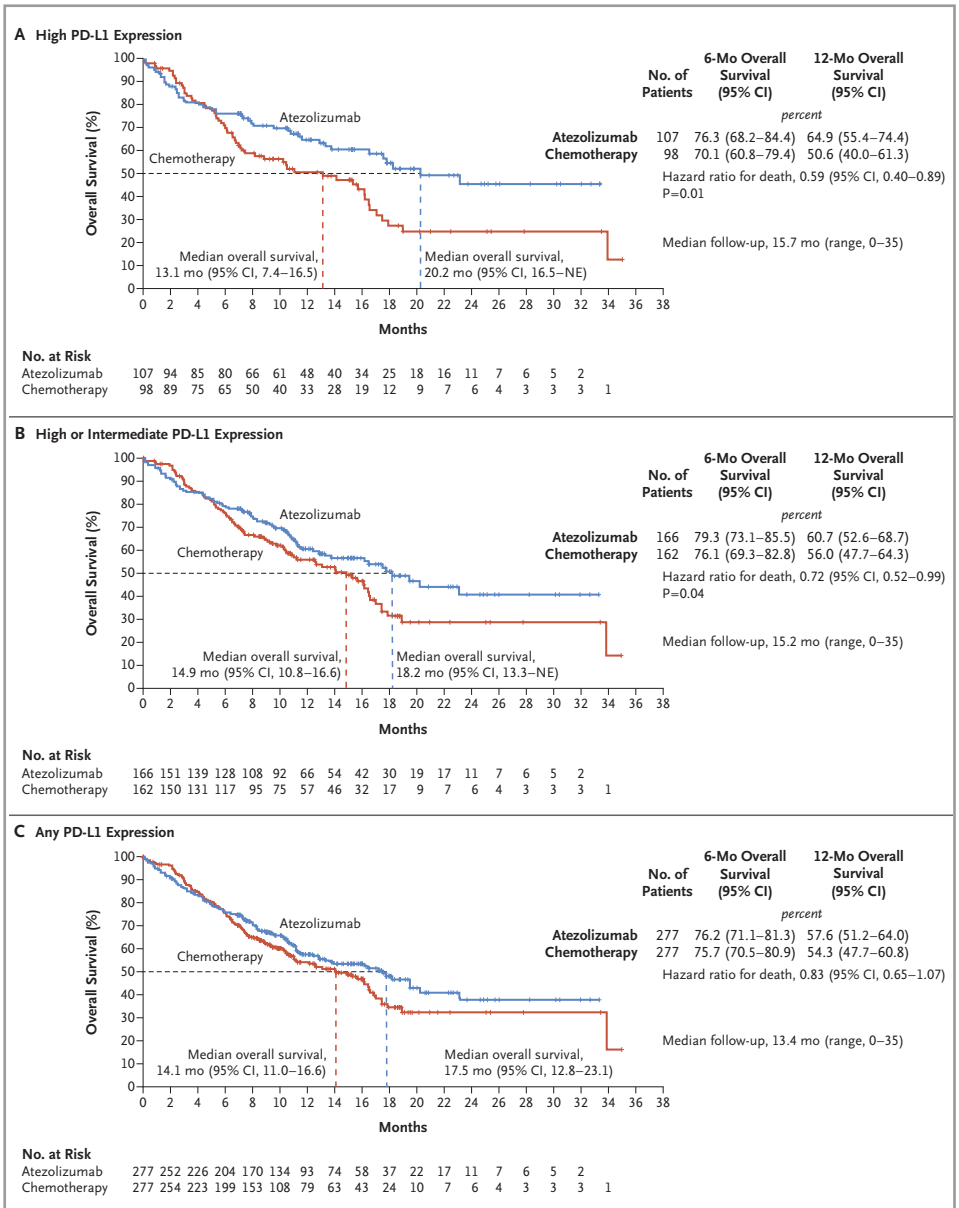


Figure 2. IMpower110: Atezolizumab for first-line treatment of PD-L1–selected patients with NSCLC. Overall Survival in the Atezolizumab Group and the Chemotherapy Group. Kaplan–Meier estimates of overall survival for patients with wild-type EGFR/ALK tumors. High PD-L1 (≥50% tumor cells or ≥10% immune cells, Panel A), high/intermediate PD-L1 (≥5%, Panel B), and any PD-L1 (≥1%). Stratified hazard ratios for PD-L1 levels and treatments (atezolizumab vs. chemo) based on stratified log-rank test. Medians by Kaplan–Meier, hazard ratios with 95% CIs by stratified Cox regression and Brookmeyer–Crowley method. High/intermediate PD-L1 results did not cross alpha boundary, so any PD-L1 not tested. Tick marks = censored data; NE = not estimable. From reference 31, reprinted with permission.

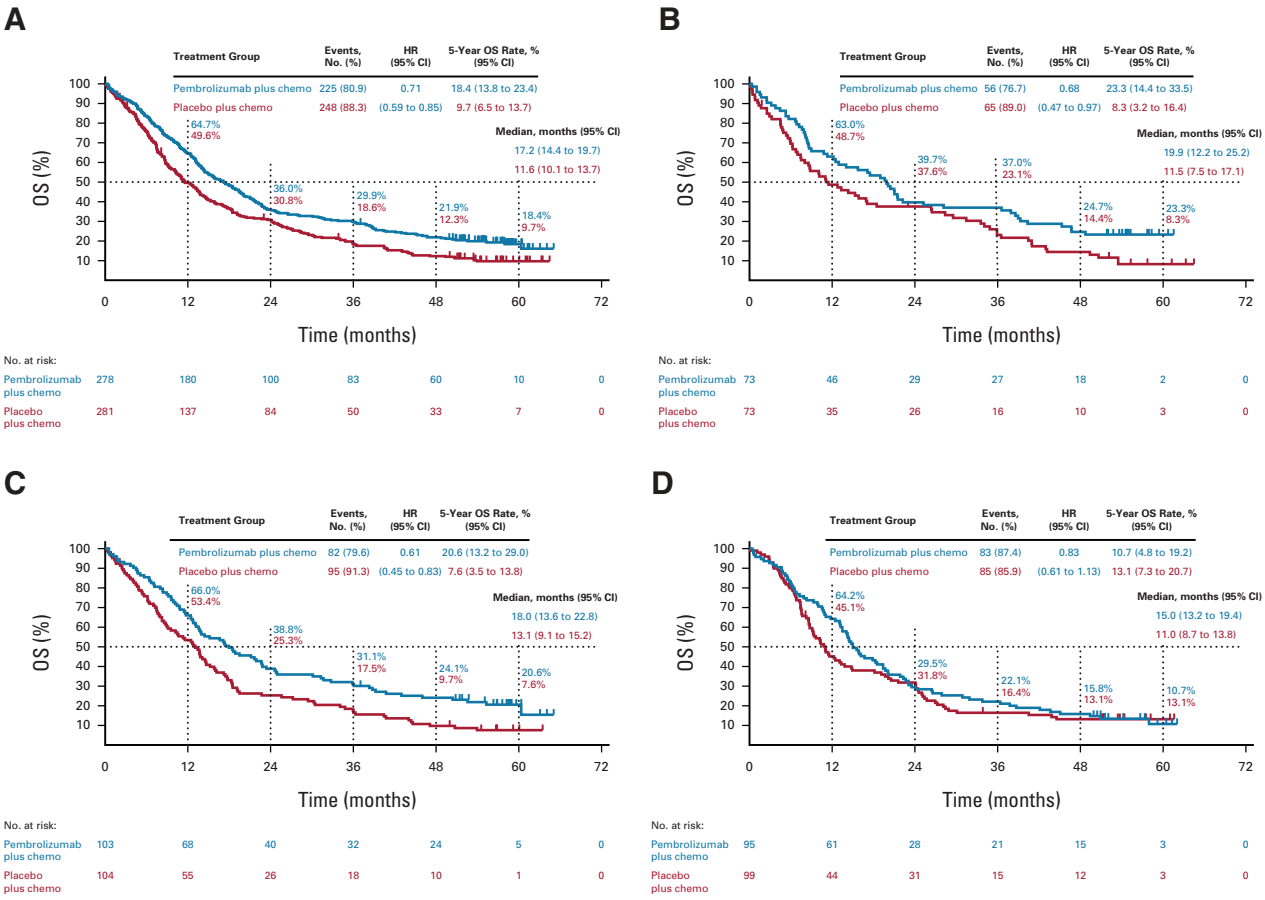


Figure 3. KEYNOTE-407: Pembrolizumab plus chemotherapy in squamous NSCLC: 5-year update. Kaplan-Meier estimates of OS in the **A)** ITT population, **B)** patients with PD-L1 TPS ≥ 50%, **C)** patients with PD-L1 TPS 1%-49%, and **D)** patients with PD-L1 TPS < 1%. chemo, chemotherapy; HR, hazard ratio; ITT, intention to treat; NR, not reached; OS, overall survival; PFS, progression-free survival; TPS, tumor proportion score. From reference 66, reprinted with permission.

Dual ICBs combinations

Dual blockade of CTLA-4 and PD-1 inhibitory signals have also been tested given their complementary mechanisms of action and clinical relevance in other settings such as renal cell carcinoma and melanoma.[78] Ipilimumab plus nivolumab (CheckMate 227 trial) was shown to improve survival over chemotherapy in both PD-L1>1% patients (primary endpoint population; HR: 0.77 [0.66-0.91]) and PD-L1<1% patients (HR: 0.65 [0.52-0.81]).[26] Remarkably the curves tended to plateau over time and survival rates at 5 years reached 24% in PD-L1>1% patients and 20% in PD-L1<1% patients, as compared to 14% and 7% with chemotherapy, respectively.[79] Half of patients treated with the dual immunotherapy arm remained progression free at this stage, compared with only 2% in the chemotherapy group. In contrast the combination of tremelimumab plus durvalumab did not meet its primary OS endpoint in the Mystic trial.[78] Ipilimumab plus pembrolizumab regimen showed superiority over pembrolizumab alone in patients with PD-L1>50%.[79] There was an increase in immune-related adverse events (irAEs) and discontinuation rates (20%) were appreciable with immunotherapy combination schemes.

In the aforementioned studies with dual ICBs, responses were long lasting but an augmented number of early progressions and reduced survival rates were observed within the initial months. This served as the basis to add two initial chemotherapy courses along with ipilimumab plus nivolumab in the 9LA trial compared to 4 chemotherapy cycles.[27] Among the 719 randomized patients, a survival benefit was observed for those

randomized to the chemo-immunotherapy schedule (HR 0.72 [0.61-0.86]). Remarkably there was decreased number of early progressions and deaths with the experimental treatment. A trial of similar design, POSEIDON, randomly assigned 1013 patients to two experimental treatments of four cycles of chemotherapy plus durvalumab plus tremelimumab or durvalumab alone versus a chemotherapy alone control arm. PFS (HR, 0.72 [0.60 to 0.86]) and OS (HR 0.77 [0.65 to 0.92]) were significantly improved with the dual immunotherapy combination.[82]

Given the existing evidence, most patients with advanced NSCLC, unless they have medical contraindications or bear tumors with targetable oncogenic drivers or access issues, are candidates for PD-1/PD-L1 blockade alone or in combination with chemotherapy and/or CTLA-4 inhibitors. Monotherapy with ICBs is the preferred option for patients with PD-L1>50%, given the, efficacy, favorable safety profile, and convenience.[83] Some 25-30% of patients may be better served with chemo-immunotherapy schedules if they present with adverse clinical (need for fast symptomatic response, clinical aggressiveness, never-smokers, females) or biological features (immunosuppressive genomic aberrations such as KEAP1, LKB1, EGFR and others, or low tumor burden).[10,32,68,84,85] Histology oriented carboplatin regimens plus PD-1/PD-L1 blockade is frequently used for low or negative PD-L1-expressors, unless chemotherapy is not feasible. Dual immunotherapy with ipilimumab plus nivolumab, with or without two cycles of chemotherapy, is more frequently used on

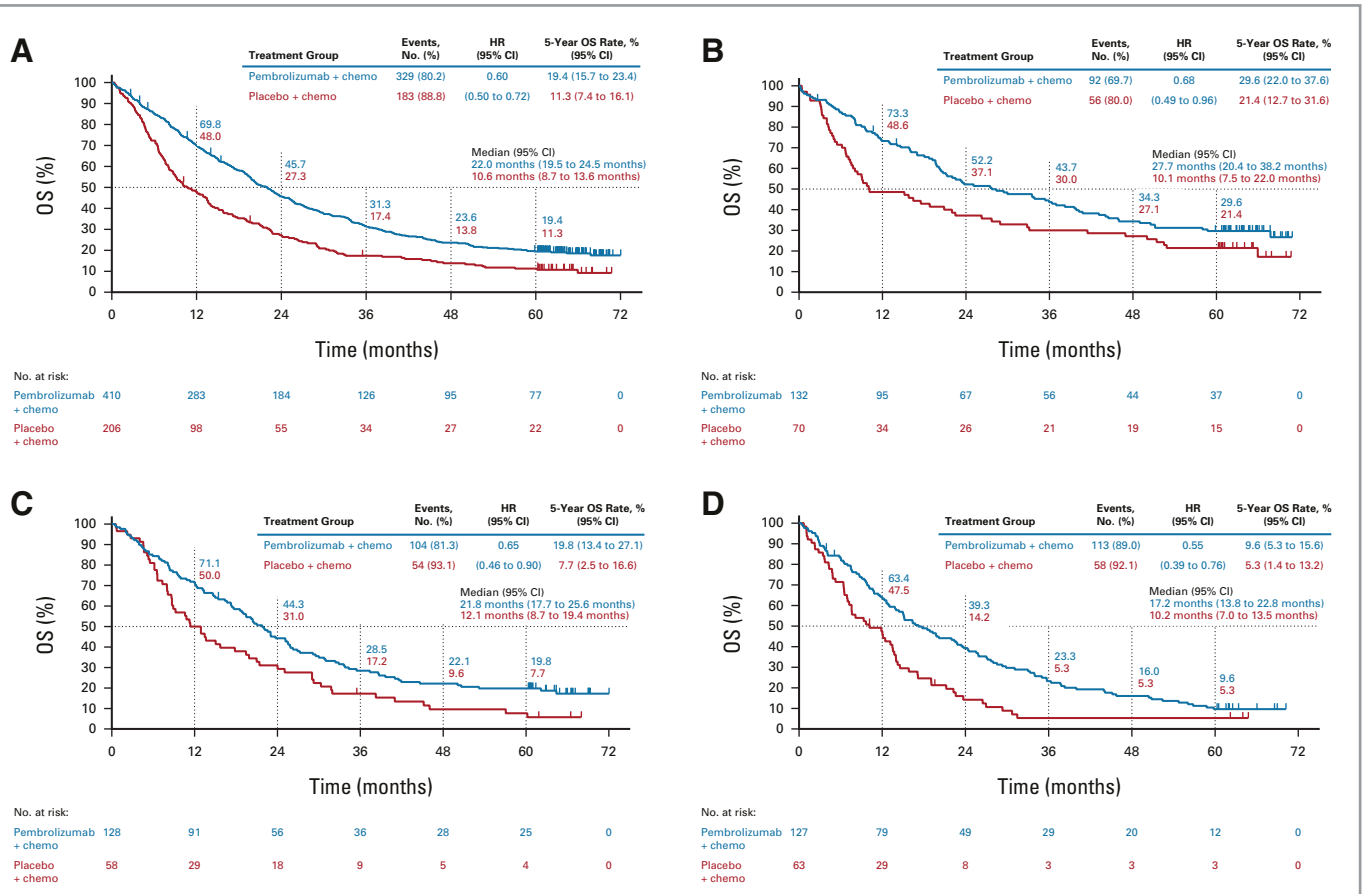


Figure 4. KEYNOTE 189: Pembrolizumab plus pemetrexed and platinum in nonsquamous NSCLC: 5-year outcomes. Kaplan-Meier estimates of OS in the **A)** ITT, **B)** PD-L1 TPS ≥ 50%, **C)** PD-L1 TPS 1%-49%, and **D)** PD-L1 TPS < 1% populations. Chemo, chemotherapy; ITT, intention-to-treat; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; TPS, tumor proportion score. From reference 65, reprinted with permission.

PD-L1<1% cases, where it may offer an increased chance of long-term benefit, and/or in patients bearing SCCs, or in poor candidates for prolonged chemotherapy.[26,27]

In the second line treatment setting, the Lung-MAP S1400I phase 3 trial[86] investigated the addition of ipilimumab to nivolumab in chemotherapy-pretreated, immunotherapy-naive squamous cell lung cancer patients. The study found no significant difference in overall survival between the groups (HR 0.87; P = 0.34), with median survival of 10 months for nivolumab/ipilimumab and 11 months for nivolumab. The IA-PFS HR was 0.80 (P = 0.09), with median IA-PFS of 3.8 months for nivolumab/ipilimumab and 2.9 months for nivolumab. Response rates were similar at 18% and 17%, respectively. However, grade 3 or higher adverse events were higher in the combination group (39.5% vs. 33.3%). Overall, adding ipilimumab to nivolumab did not improve outcomes in patients with advanced, pretreated, immune checkpoint inhibitor-naive SCC NSCLC.

IMMUNOTHERAPY COMBINATIONS IN NSCLC: THE PATH FORWARD

Since the first approval in 2015 by the U.S. FDA, the advent of immunotherapy has changed the treatment paradigm of mNSCLC.[8] With increased lung cancer screening efforts, and immunotherapy now approved in the perioperative setting, the use of immunotherapy will continue to increase in the coming decade.[87,88] Despite advances with immunotherapy, the outcomes for patients with mNSCLC are suboptimal with 5-year survival of 30% with the use of single agent immunotherapy in biomarker-selected (high PD-L1 expression) patients, and 10-15% in unselected patients receiving immunotherapy frontline or later.[55,59,65] Additionally, treatment options after immunotherapy resistance represent a strict unmet need and represents an opportunity for potential innovative immunotherapy combinations, which remain undefined as yet. Thus, identifying rational combinations of immunotherapy is a priority to improve clinical outcomes for patients with mNSCLC.[89]

Although the initial clinical development of immunotherapy focused on anti-PD-1 and anti-PD-L1 monotherapy in the second line, there has been recent progress in harnessing immunotherapy in combination with chemotherapy in the first-line setting. Chemotherapy seems to have a synergistic effect by increasing the neoantigen load for recognition by T cells, with immunotherapy inhibiting the T-cell checkpoint to harness antitumor immunity.[90,91] Currently, there are several approvals for chemo-immunotherapy both for patients with squamous and non-squamous histology, and PD-1/PD-L1 high and low tumors in patients with advanced NSCLC.[92] However, most patients on immunotherapy experience resistance over the course of treatment. Identifying rational combinations with anti-PD-1/PD-L1 ICBs with other novel checkpoints, tyrosine kinase inhibitors (TKIs), cytokines and radiation are strategies currently under investigation and show promise to further improve outcomes for our patients with mNSCLC.

#1: Combined immune checkpoint blockade

Since the discovery of CTLA-4 as a critical switch controlling T-cell responses, CTLA-4 blockade has been utilized to increase antitumor immunity.[93] With 3 different combinations currently FDA approved, nivolumab plus ipilimumab (in CheckMate-227), nivolumab plus ipilimumab and platinum doublet chemotherapy (in CheckMate-9LA), durvalumab plus tremelimumab and platinum doublet chemotherapy (in POSEIDON), anti-PD-1/PD-L1 and anti CTLA-4 combination checkpoint blockade strategies have been well studied.[27,79,82] While activity is seen in unselected NSCLC, a specific improvement of the magnitude of clinical benefit is consistently observed in the subgroup of patients with a poorly immunogenic NSCLC characterized by PD-L1 negative biomarker.

Novel checkpoints such as LAG3, TIGIT, TIM3, and NKG2A are of increasing interest with multiple trials reported or currently ongoing. The TACTI-002 phase 2 study investigating eftilagimod alpha in first-line mNSCLC in combination with pembrolizumab showed an ORR of 37.7% (n=114), with patients having PD-L1≥50% having the most benefit (52.6%, n=20).[94]

Two anti-TIGIT molecules have been studied in combination with anti-PD-1/PD-L1 immunotherapy: tiragolumab and vibostolimab. CITYSCAPE, a phase 2 placebo-controlled trial studied tiragolumab plus atezolizumab versus placebo plus atezolizumab in patients with chemotherapy-naive, PD-L1-positive (≥1%) mNSCLC.[93] The combination demonstrated clinically meaningful improvement in ORR (31.3% vs. 16.2%, P=0.031) and mPFS (5.4 vs. 3.6 months, P=0.015) compared to the placebo arm. Again, the outcomes for PD-L1>50% were better, even restricted to, those patients with PD-L1 TPS 1-49% (12-month PFS: 51% versus 24.9%). Based on these encouraging results, the FDA has granted a breakthrough therapy designation to tiragolumab. Furthermore, a confirmatory phase 3 study SKYSCRAPER-01 is currently underway evaluating tiragolumab plus atezolizumab versus atezolizumab alone in first-line PD-L1-high mNSCLC. Meanwhile, KEYVIBE-001 phase 1 study of vibostolimab monotherapy or in combination with pembrolizumab demonstrated ORR of 26% in patients who had not received prior anti-PD-1/PD-L1 therapy while responses were suboptimal among the cohort of anti-PD-1/PD-L1-refractory patients in both the monotherapy (3%) and combination arms (3%).[96]

To date, the data on anti-TIM3 antibody, MBG543 has only demonstrated ORR of 11.8% in the 17 patients with NSCLC treated with MBG543 in combination with spartalizumab.[97] Finally, targeting NKG2A has led to exciting results in resectable and locally advanced NSCLC. Monalizumab is a humanized IgG4 antibody blocking the interaction of human NKG2A with HLA-E.[98] The NeoCOAST platform study evaluated neoadjuvant durvalumab in combination with novel immunotherapy agents including monalizumab with the primary objective of evaluating major pathologic response (MPR) rate.[99] The study showed that novel immunotherapy combinations with anti-CD73 monoclonal antibody oleclumab (19%), monalizumab (30%), and anti-STAT-3 monoclonal antibody danvatirsen (31%) increased MPR rates compared to durvalumab alone (11%). These encouraging results have resulted in the launch of a randomized study of neoadjuvant and adjuvant treatment with novel immunotherapies in the NeoCOAST-2 trial (NCT05061550). The COAST trial evaluated durvalumab alone or combined with the oleclumab or monalizumab as consolidation therapy in unresectable stage III NSCLC, building upon the standard of durvalumab consolidation from the PACIFIC trial.[100] This phase 2 study demonstrated improved ORR (35.5% vs. 17.9%) and PFS with durvalumab in combination with monalizumab compared to durvalumab alone (15.1 vs. 6.3 months, HR: 0.42; 95% CI, 0.24 to 0.72).

#2: Immunotherapy and angiogenesis/tyrosine kinase inhibition for TME modification

There has been an increased recognition of the immunosuppressive effect of tumor angiogenesis on TME and its role in immune checkpoint inhibitor resistance. Vascular endothelial growth factor (VEGF) released by tumor cells inhibits T-cell responses and proliferation of regulatory T cells (Tregs) and myeloid derived suppressor cells (MDSCs).[101] Since efficacy of immunotherapy depends on the accumulation and activity of tumor-infiltrating lymphocytes, combining it with antiangiogenic therapy could improve local perfusion, relieve TME hypoxia, and reverse the immunosuppressive state.[102]

Another important component of TME is the TAM family of receptor tyrosine kinases (RTKs) which includes Tyro3, AXL, and MER RTKs.101 AXL, MER, and Tyro3 inhibit proinflammatory cytokines and stimulate immunosuppressive cytokines while MER also inhibits polarization of macrophages from M1 (immune stimulating) to M2 (immunosuppressive) subtype.[104] Given the strong pre-clinical rationale of augmentation of immune checkpoint inhibitor response, successful combinations in other tumor types, and approval of anti-VEGF monoclonal antibodies in the treatment of EGFR wild type, and EGFR-mutated NSCLC, the combination of immunotherapy and TKIs/anti-angiogenesis agents are currently under study.[105-109]

Ramucirumab, an intravenous monoclonal antibody against VEGFR-2, currently approved in the second-line setting, was evaluated in combination with pembrolizumab.[108] The phase 2 Lung Master Protocol (MAP) S1800A trial evaluated the combination of ramucirumab and pembrolizumab in patients previously treated with platinum-based chemotherapy and immunotherapy (with progressive disease at least 84 days after initiation of immunotherapy) and demonstrated an improvement in OS compared to SOC chemotherapy (14.5 versus 11.6 months, HR:0.69 [0.51 to 0.92]; P=0.05). Grade ≥3 treatment-related adverse events occurred in 42% in the ramucirumab/pembrolizumab arm compared to 60% on SOC.[110] This is being tested in SWOG S2302 Pragmatica-Lung trial.

Several multi TKI targeted oral therapies are also currently under investigation in combination with immunotherapy such as: cabozantinib with atezolizumab (COSMIC-021), sitravatinib and nivolumab (MRTX-500), and pembrolizumab with lenvatinib (LEAP 007).[111-113]

COSMIC-201, a multicenter phase 1b study, reported outcomes in NSCLC showing ORR 19% in the overall population with mDoR of 5.8 months (4.2, 6.9). The mPFS and OS were 4.5 and 13.8 months, respectively. The treatment discontinuation rate was 16%, with 26% of patients experiencing grade 3-4 toxicity.[111] The CONTACT-01 phase 3 study did not meet its primary endpoint of OS at the final analysis for cabozantinib with atezolizumab versus docetaxel in patients with mNSCLC).[114] MRTX-500 studied sitravatinib and nivolumab and demonstrated similar ORR of 18%, with mDoR of 12.8 months, mPFS 5.7 months, and median OS of 14.9 months respectively.[112] Another such combination is pembrolizumab and lenvatinib which demonstrated superior ORR of 33% within the NSCLC cohort of the phase 1b/ 2 trial.[115] However, it remains to be seen how these immunotherapy and TKI combinations will perform in controlled randomized phase 3 studies before incorporating them into standard management algorithms.

Despite the failure of the anti-IL-1b monoclonal antibody canakinumab in combination with pembrolizumab, there are other cytokine based therapies in development which may have the potential to be used in combination with anti PD-1/PD-L1 immunotherapy.[116,117] Synergism of radiation therapy with ICBs and the role of abscopal effect is under investigation, especially for those with oligometastatic disease given initial positive signals in studies.[118]

In conclusion, several immuno-oncology targets and combinations will be studied in the coming decades truly emphasizing the role of immunotherapy as one of the pillars of cancer care.[119] However, in order to truly advance and improve outcomes for patients with mNSCLC, we need better biomarker-driven studies which can harness our understanding of immunobiology and etiology of deficits in antitumor response at an individual level.[89] Ongoing efforts of implementation and design of multi-arm platform trials will provide deeper understanding of resistance to current ICBs, identification of biomarkers to evaluate novel therapies (PIONeeR), and provide biomarker matched treatment for patients resistant to both chemotherapy and immunotherapy treatments (HUDSON).[120,121]

The most recent report of the KEYNOTE-495/KeyImPaCT study demonstrates the feasibility of such an approach, where patients are divided into different subgroups based on biomarkers and randomized to different treatment arms based on our understanding of the immune biology of anti-tumor repsonses.[122] Successful combinations and smartly designed studies would require improved patient selection for a much needed a "precision immunotherapy" approach to identify the right dose of the right immunotherapy combination, for the right patient, at the right time.

NSCLC ADJUVANT THERAPY

Surgical resection with curative intent is recommended for patients with stage I/II and select stage IIIA NSCLC.[123] However, even after complete surgical resection, patients still have a high risk of recurrence, possibly due to occult micrometastases at

the time of surgical resection.[124] Adjuvant platinum-based chemotherapy has long been the SOC for patients with completely resected stage IB (tumor ≥ 4cm) to IIIA NSCLC, though the magnitude of benefit is modest, with a 5.4% absolute benefit at 5-year OS rate.[125] Subsequently, efforts including the addition of bevacizumab to chemotherapy, tailored adjuvant chemotherapy, or introducing postoperative adjuvant radiotherapy to completely resected N2 NSCLC, all failed to improve the survival outcomes compared with standard adjuvant chemotherapy.[126-128] Until recently, advances of ICBs, targeting PD-1 and its ligand (PD-L1), in patients with mNSCLC without oncogenic drivers have propelled this revolutionary paradigm into the treatment course of early-stage NSCLC.[129]

Impower 010 was the first trial to assess the efficacy of adjuvant ICB in patients with resected early-stage NSCLC.[130] In Impower 010, patients with resected stage IB-IIIA NSCLC were randomized to receive adjuvant atezolizumab or best supportive care (BSC) after adjuvant chemotherapy.[130] After a median follow-up of 32.2 months, adjuvant atezolizumab significantly extended disease-free survival (DFS) compared with BSC in patients with PD-L1 ≥1% stage II-IIIA NSCLC (HR, 0.66; 95% CI, 0.50–0.88) and in all stage II–IIIA patients (HR, 0.79; 95% CI, 0.64-0.96).[130] Inspiringly, in the recent interim analysis of OS, a trend towards better OS was observed in patients with PD-L1≥1% stage II-IIIA NSCLC with adjuvant atezolizumab (HR, 0.71; 95% CI, 0.49-1.03; 5-year OS rate: 76.8% vs. 67.5%).[131] Impower 010 was a practice-changing trial and represented a breakthrough in the adjuvant setting, leading to the approval of adjuvant atezolizuamb by the US FDA and the China National Medical Products Administration (NMPA) for resected stage II to IIIA NSCLC patients whose tumors express PD-L1≥1%. Recently, the results of adjuvant pembrolizumab in patients with resected IB to IIIA NSCLC from the KEYNOTE-091 trial was reported.[132] Consistent with the findings of Impower 010, adjuvant pembrolizumab also resulted in a significant improvement in DFS compared with placebo in the entire population (HR, 0.76; 95% CI, 0.63–0.91) (Figure 5).[132] Collectively, these two important trials established the fundamental role of adjuvant ICB in patients with early-stage NSCLC following completely surgical resection and adjuvant chemotherapy, but also raising several crucial questions including predictive biomarkers, optimal perioperative strategies.

Despite the Impower 010 trial meeting its primary endpoints demonstrating DFS advantages in stage II-IIIA patients with PD-L1≥1%, the benefit was most pronounced in patients with PD-L1≥50% (HR, 0.43; 95% CI, 0.27-0.68).[131] Further post-hoc analysis demonstrated that the HR was 0.87 (95% CI, 0.60-1.26) for DFS in stage II-IIIA patients with PD-L1 expression on 1-49% of tumor cells. Therefore, the European Medicines Agency (EMA) only approves adjuvant atezolizumab for patients with tumors expressing PD-L1 ≥50%. The interim analysis of OS also revealed that patients with PD-L1≥ 50% stage II-IIIA were the most beneficial population (HR, 0.43; 95% CI, 0.24-0.78).[131] In line with the predictive role of PD-L1 for ICB in mNSCLC, PD-L1 expression seems to predict the survival benefit of adjuvant atezolizumab in the Impower 010 trial.[23,31] However, in the KEYNOTE-091 trial, the dual primary endpoint of DFS in stage IB–IIIA patients with PD-L1 tumor proportion scores (TPS) ≥ 50% was not met (HR, 0.82; 95% CI 0.57-1.18).[132] Surprisingly, subgroup analysis revealed that DFS benefit was most pronounced in stage IB–IIIA patients with PD-L1 TPS 1-49% (HR, 0.67; 95% CI, 0.48-0.92), patients with stage II disease (HR, 0.70; 95% CI, 0.55-0.91), and with *EGFR* mutations (HR, 0.44; 95% CI, 0.23-0.84) though the post-hoc analysis results should be interpreted with caution.[132] Notably, retrospective analysis of the Impower 010 trial showed high assay concordance and a similar predictive value of the SP263 and 22C3 PD-L1 assays in demonstrating the benefit of adjuvant atezolizumab (unpublished data). Therefore, different PD-L1 assays may not fully explain the discrepant findings of the two trials. In the near future, analysis of

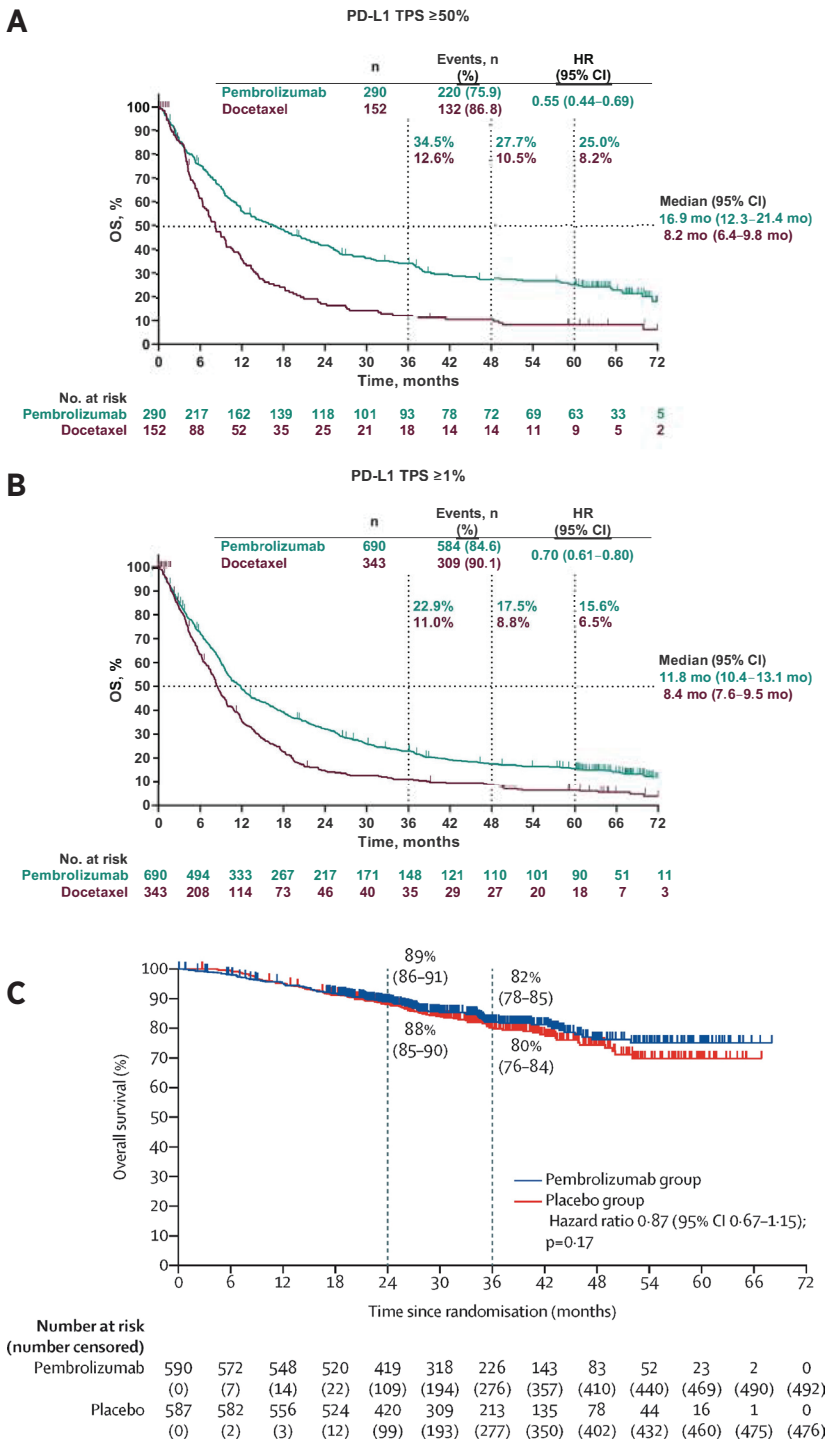


Figure 5. KEYNOTE-010 and KEYNOTE-091 overall survival. **A-B)** Five year survival opdate from KEYNOTE-010: Pembrolizumab versus docetaxel for previously treated, programmed death-ligand 1–positive advanced NSCLCKaplan-Meier analysis of OS in patients with **A)** PD-L1 TPS ≥50% and **B)** PD-L1 TPS ≥1%. **C)** PEARLS/KEYNOTE-091: Pembrolizumab vs placebo as adjuvant therapy for completely resected stage IB–IIIA NSCLC. Kaplan-Meier estimate of overall survival in the intention-to-treat population. Tick marks indicate censored data. Fig 5A/5B from reference 56, published under Creative Commons Attribution, no reprint permission required; 5C from reference 132, reprinted with permission.

the large numbers of resected tumors will allow a deeper understanding of the TME to illustrate predictive biomarkers to identify patients who may be most likely to benefit from adjuvant ICB.

Another promising direction to select patients for adjuvant therapy is on the basis of postoperative minimal residual disease (MRD). Previous studies have demonstrated that detectable MRD was associated with a high risk of recurrence in patients with early-stage NSCLC after surgical resection and patients with detectable MRD may be a population to benefit from adjuvant therapy.[133-135] Nonetheless, biomarker analyses of Impower 010 suggested that postoperative ctDNA appeared to be a prognostic factor rather than a predictive factor for DFS and adjuvant atezolizumab showed DFS advantages over BSC in stage II-IIIA patients with tumors expressing PD-L1≥1% regardless of ctDNA status.[136] Currently, several phase III, randomized trials are ongoing to evaluate the efficacy of adjuvant ICB in patients with resected early-stage NSCLC who have detectable MRD after surgery (NCT04385368, NCT04642469). These prospective trials will help define the role of MRD for guiding adjuvant ICB in patients with resected early-stage NSCLC.

Integrating ICB into the preoperative setting of patients with early-stage NSCLC is also an appealing strategy. Compared with adjuvant ICB, neoadjuvant ICB has several advantages, including greater ability to induce diverse T cell expansion and reinvigorate T cell function at earlier stages of cancer, radiographic

downstaging to improve surgical resectability, and quickly assessing patients' response to ICB (pathological response), though disadvantages also exist, including potential surgical delay, tumor progression, and irAEs.[137] In a pilot study, neoadjuvant nivolumab led to a MPR in 45% of resected early-stage NSCLC without surgical delay.[138] The larger LCMC3 trial further demonstrated that neoadjuvant atezolizumab induced a MPR rate of 20% and a pathological complete response (pCR) rate of 7% in resectable stage IB-IIIB NSCLC.[139] Recently, the landmark CheckMate 816 trial revealed that neoadjuvant nivolumab plus chemotherapy resulted in a higher pCR rate than chemotherapy alone (24.0% versus 2.2%) and a significant improvement in event-free survival (31.6 versus 20.8 months; HR, 0.63; 95% CI, 0.43-0.91) in patients with stage IB to IIIA resectable NSCLC (Figure 6).[140] Notably, the clinical benefit was most pronounced in patients whose tumors had PD-L1≥50%.[140] Although the percentages of patients who had pCR were similar between stage IB/II diseases versus stage IIIA diseases, the DFS benefit was more pronounced in patients with stage IIIA diseases. Furthermore, neoadjuvant nivolumab plus chemotherapy did not impede the feasibility of surgery. Although the OS data were not mature, the findings of Impower 010 and CheckMate 816 raised a critical question: which represents the optimal intervention time to derive the maximal clinical benefit from ICB, the adjuvant setting or neoadjuvant setting? Intriguingly, the NADIM trial demonstrated that neoadjuvant nivolumab plus chemotherapy followed by adjuvant nivolumab resulted in a 3-year OS rate of 81.9% in resectable stage IIIA NSCLC and the mOS was still not reached, suggesting it is a wise strategy to utilize ICB during the whole perioperative period of treatment.[141] The NADIM II trial, that evaluated 3 cycles of neoadjuvant nivolumab plus chemotherapy followed by 6-month adjuvant nivolumab versus neoadjuvant chemotherapy alone in potentially resectable IIIA-IIIB NSCLC, has demonstrated that neoadjuvant nivolumab plus chemotherapy improves the rate of patients with definitive surgery (93.0% versus 69.0%) and pCR rate (36.2% versus 6.8%) (Figure 6).[142] The 2-year PFS rate (67.3% versus 52.6%) and 2-year OS rate (85.3% versus 64.8%) were also improved.[142] Furthermore, in most of the ongoing phase III neoadjuvant ICB trials in patients with resectable early-stage NSCLC, ICB is now given in both the preoperative setting and postoperative setting (NCT03456063 [Impower 030], NCT04025879 [CheckMate 77T], NCT03425643

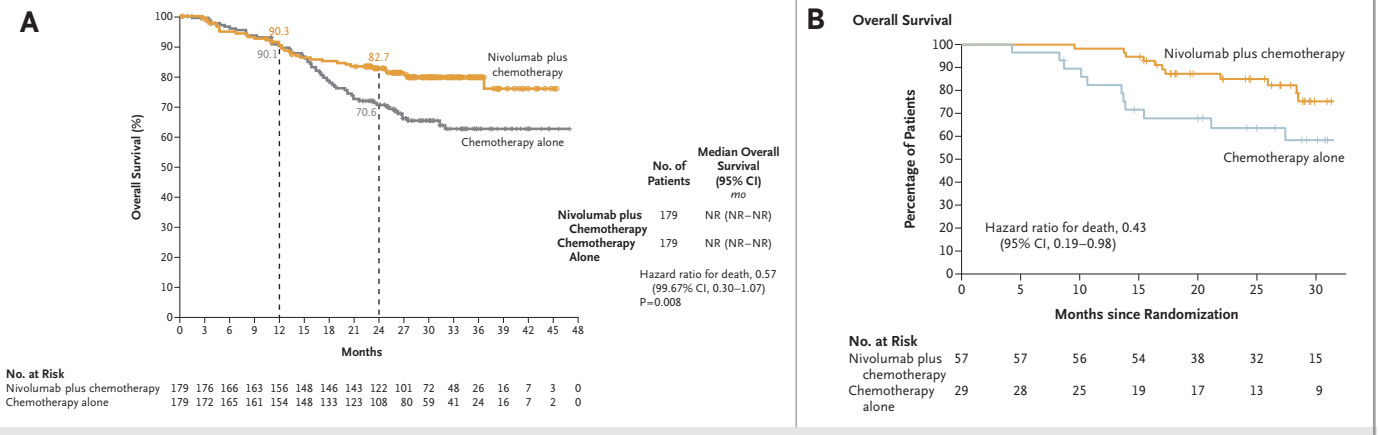


Figure 6. Checkmate 816 and NADIM II overall survival. **A)** Checkmate 816: Neoadjuvant mivolumab plus chemotherapy in resectable lung cancer.The 95% confidence interval of the hazard ratio was 0.38 to 0.87. At this first prespecified interim analysis, the P value for overall survival did not cross the boundary for statistical significance (0.0033). From reference 140, reprinted with permission. **B)** NADIM II trial: Perioperative nivolumab and chemotherapy in stage III NSCL. Kaplan–Meier curves for overall survival (intention-to-treat population). *N Engl J Med* 2023;389:504-13, reprinted with permission.

[KEYNOTE-671], NCT03800134 [AEGEAN], NCT04158440 [NEOTORCH].

In current practice, both adjuvant atezolizumab (for stage II–IIIA NSCLC whose tumors express PD-L1≥1%) and neoadjuvant nivolumab plus chemotherapy (for stage IB–IIIA NSCLC regardless of PD-L1 expression) have been advocated as the new SOC for patients with resected/resectable NSCLC. Especially, both of these strategies were more effective in patients with stage IIIA diseases, a potentially lethal disease with a high risk of recurrence. Despite these advances, more work is needed to optimize these therapeutic strategies, including longer follow-up to confirm OS benefit, pursuing predictive biomarkers to identify beneficial populations, exploring the optimal intervention time point, duration of treatment, and personalized management according to patients' disease stage (stage IB versus II versus IIIA) and pathological response.

UNRAVELLING KEY MYTHS ABOUT SMALL CELL LUNG CANCER (SCLC)

As paradigms shift in cancer therapy, myths are being shattered. For example, KRAS G12C inhibitors are now used to treat the previously "undruggable" *KRAS* gene in lung cancer, and the use of neoadjuvant chemoimmunotherapy regimen can now achieve 25% pCR at surgery for selected patients.[140,143] Indeed, the diagnosis of stage IV disease for NSCLC patients is now viewed as a chronic, treatable condition for some, with some patients still enjoying remission 5 years after diagnosis and beyond.

SCLC is an aggressive disease that represents about 15% of lung cancer.[144] An estimated 1.8 million people died from lung cancer worldwide in 2020, and 130,180 deaths are estimated to occur this year.[145,146] Seventy-five percent of SCLC patients present with metastatic or "extensive-stage" disease at diagnosis and the mOS despite dozens of clinical trials is still little over a year for these patients.[8] Patients with locally advanced or "limited-stage" disease who receive definitive chemoradiation have a 5-year OS of 30% and mOS of 25-30 months.[147] Nevertheless, more recent advancements have generated a renewed sense of optimism for SCLC; these include four FDA approvals for systemic agents—atezolizumab and durvalumab in the frontline, and lurbinectedin and tarlatamab in the relapsed setting—as well as new insights into the molecular characterization of disease.[148-151] For example, in the phase III CASPIAN study, first-line durvalumab combined with etoposide and either cisplatin or carboplatin (EP) significantly improved OS versus EP alone in ES-SCLC. Durvalumab plus tremelimumab with EP showed a numerical improvement in OS but was not statistically significant. After a median follow-up of over 3 years, durvalumab plus EP continued to demonstrate a median OS of 12.9 months compared to 10.5 months with EP alone, with a 36-month OS rate of 17.6% versus 5.8%. This establishes durvalumab plus EP as a first-line standard of care for ES-SCLC. The IMpower133 study, a randomized, double-blind, phase I/III trial, showed that adding atezolizumab to carboplatin and etoposide (CP/ET) for first-line treatment of ES-SCLC significantly improved OS and PFS compared to placebo plus CP/ET. Updated results with a median follow-up of 22.9 months showed a median OS of 12.3 months for the atezolizumab group versus 10.3 months for the placebo group (HR 0.76; P=0.0154). The 18-month OS rate was 34.0% with atezolizumab versus 21.0% with placebo. The benefits were consistent regardless of PD-L1 or bTMB status, confirming the regimen as a new standard of care.

Of the ongoing trials in limited stage SCLC, the first one to report out is the ADRIATIC trial, a phase 3, randomized, double-blind, multicenter study with over 700 patients having inoperable Stage I-III LS-SCLC. After chemoradiation, patients were randomized 1:1:1 to receive durvalumab + placebo, durvalumab + tremelimumab, or dual placebo for two years, with primary objectives of PFS and OS for D ± T vs placebo. An interim analysis reported significant improvement in median OS of 55.9 months for the durvalumab arm compared to 33.4 months for the placebo arm.[152] The PFS in the durvalumab

arm is 16.6 months compared to 9.2 months in the placebo arm, also significantly improved. life, safety, and tolerability.

Meanwhile, the phase III SKYSCRAPER-02 study investigated the addition of tiragolumab (anti-TIGIT) to atezolizumab plus chemotherapy in untreated ES-SCLC. Final analyses showed no significant improvement in progression-free survival (PFS) or overall survival (OS) with the tiragolumab combination. Tiragolumab did not enhance the benefits of the treatment and was well tolerated with no new safety concerns.

These studies highlight the ongoing efforts and challenges in improving treatment outcomes for SCLC. While the SKYSCRAPER-02 results underscore the complexity of enhancing immunotherapy efficacy, the ADRIATIC trial is likely to become a new standard of care improving outcomes in limited-stage disease, emphasizing the importance of continued research and innovation in this field.

In the relapsed setting, the May 2024 approval of tarlatamab, a bispecific antibody targeting DLL3 and CD3, is a major breakthrough. The 10 mg dose of Tarlatamab demonstrated an ORR of 40% and disease control rate of 70% in heavily pretreated relapsed SCLC patients, with 58% patients exhibiting a duration of response >6 months.[151]

What then are the myths surrounding SCLC, a unique disease that that can "melt away" with initial systemic treatment, allowing some patients to regain normality and hope for an extended survival? Even patients on the edge of clinical disaster with superior vena cava (SVC) syndrome, cord compression, or lung collapse, can feel better within days after initiating treatment with systemic therapy. One case report describes a SCLC patient presenting with a paraneoplastic opsoclonus-myoclonus syndrome who was unresponsive with respiratory failure but recovered fully with systemic treatment with only mild gait instability at 30 months.[153] Despite such dramatic ability to subdue cancer initially, it is humbling to know that standard treatments cannot prevent the disease from returning in almost all patients.

Myth #1: It is Difficult to Obtain Tissue from SCLC Patients

A National Cancer Institute (NCI)-developed Scientific Framework for SCLC in 2014 recognized the "paucity of available biospecimens" as a major barrier to progress in SCLC research and optimization of tissue collection as a priority.[154] In fact, SCLC patients often have bulky disease, including central lung lesions or mediastinal lymph nodes accessible by endobronchial ultrasound (EBUS) or metastatic liver or adrenal lesions accessible by CT-guided biopsy. Resected tissue is also available for early-stage SCLC patients that undergo resection. Although the diagnosis is often made by fine needle aspiration and repeat biopsies are uncommon, it is not usually due to lack of available sites for tissue biopsy.

Core needle biopsies that allow sufficient tissue for tumor profiling are routinely done for lung tumors by interventional radiologists and pulmonologists. In NSCLC, these are required for specific biomarker tests to direct treatment, e.g. PD-L1 and tumor profiling, but there is no reason that we should not ask for core biopsies for SCLC as well. As we learn more about the therapeutic vulnerabilities of the molecular subtypes of SCLC, adequate tissue biopsies will be increasingly important. Perhaps such a metric for SCLC cancer will be incorporated as a standard quality metric in the future, as is the case for the American Society of Clinical Oncology (ASCO) Quality Oncology Practice Initiative® (QOPI) metric of obtaining an adequate number of lymph nodes at time of colorectal surgery. As the overall burden of disseminated SCLC metastatic disease seems to be very high, research validating the use of liquid biopsies may also show benefit in determining response or early detection of relapse.[155,156]

Myth #2: "One Size Fits All" SCLC Approach

Clinicians still use the extensive/limited stage Veterans' Administration Lung Study Group (VALSG) SCLC staging system that was established decades ago, despite studies that show TNM information is prognostic.[157] We still think of the uniformity

of "small blue cells", but now are starting to appreciate that there is also heterogeneity beyond the "classic" and "variant" morphologic descriptions of cell growth in culture. Exciting research developments focus on molecular subtypes, e.g. subtypes A, N, P, characterized by overexpression of certain transcription factors, that may have therapeutic vulnerabilities.[158] Patients with the "inflammatory" subtype "I" fare better when treated with a platinum doublet regimen with atezolizumab than those who receive placebo.[159] Isolating and studying single cells also demonstrates heterogeneity in different populations of cells in the same tumor.[160]

Clinically, not all SCLC patients' disease acts the same, with some exhibiting primary refractory behavior during initial induction therapy or within 3-6 months (e.g. platinum resistant).[161] Some patients have predominantly central nervous system (CNS) disease or nodal disease, or may exhibit paraneoplastic syndromes.[162] Others can develop SCLC as a mechanism of EGFR TKI acquired resistance.[163] A few SCLC patients who respond to immunotherapy demonstrate longer-term survival.[164] We must do better in dissecting these subtypes and designing biomarker trials that exploit unique vulnerabilities of disease subtypes, such as the S2409 SCLC biomarker trial that will activate in 2025. Over 900 extensive stage SCLC patients will be screened for subtype and SLFN11 status and then randomized to immunotherapy +/- an agent targeted to their biomarker status.

Myth #3: SCLC Patients are Not Ideal Clinical Trial Candidates

SCLC patients often can present with signs and symptoms of advanced disease requiring timely and/or emergent systemic treatment; one study reports almost 25% patients initiating treatment during hospital admission.[165] As such, they are typically not eligible for clinical trials. Yet, S1929 is a SWOG maintenance trial employing an innovative approach, permitting patients to register on study despite having already received the first cycle of treatment, for example, as an inpatient.[166] This loosening of eligibility led to a brisk pace of accrual and completion. Overall, the number of underrepresented minorities who participate in clinical trials is low, for example, Black patients represent less than 1% of study population in the large phase 3 trials leading to FDA approvals.[167] We need to employ creative strategies to focus on outreach and education to enroll SCLC patients in clinical trials and increase diversity and inclusion.

Finally, SCLC patients are often willing to consider clinical trial participation to gain access to novel agents, especially as SOC options are limited. These patients often have bulky, widespread disease and are willing to donate tissue for translational research. We have found that 67% (n=16/22) patients are indeed amenable to paired biopsies pre- and on treatment at week 4 in a small clinical trial.[168] Thus, processes such as immune response and resistance, metastasis, and epigenetic regulation, to name a few, can be studied. Indeed, there is an active scientific community of translational researchers who have developed multiple approaches and resources including mouse models, patient-derived xenografts, and a single cell "atlas" and continue to collaborate with clinicians to advance the study of SCLC.[169-171]

Breaking down myths is crucial to moving the field forward to advance precision treatments designed for SCLC through innovative clinical-translational trials that include more diverse populations. One final area that clinicians need to be honest about is the natural history of the disease—patients may present with advanced disease in the hospital and enjoy extremely high responses to first line therapy, often with resolution of symptoms, regain of function, even returning to work. We clinicians need to use this opportunity to have crucial conversations that will prepare them for the inevitable recurrence of disease that is much less responsive. It takes a special courage and skillset to have this conversation in a way that doesn't scare and alienate and paralyze your patient. Developing psychosocial tools and skillsets for clinicians and patients will allow them to see past their constructed myths for better communication, coping, and living through the natural history of this fatal disease.

SUMMARY

Progress in the past decade has been remarkable in utilizing immunotherapy to target lung tumors, including both NSCLC and SCLC. This paradigm shift has led to potential cures in advanced metastatic settings, particularly for NSCLC. However, this benefit is observed in only about 20% of patients. Identifying the specific subset of patients who benefit most from immunotherapy is crucial to optimize treatment strategies. This includes directing other patients towards alternative or combination therapies early on and understanding mechanisms of resistance. Moreover, implementing these new therapies at earlier stages of the disease is even more beneficial. Neoadjuvant and adjuvant studies present significant opportunities to cure more patients with lung cancer. Although SCLC may not be as sensitive to immunotherapy as NSCLC, it has also shown significant benefits. This review demonstrates how translational science, moving from the lab to the clinic, can significantly impact patient outcomes across all stages of lung cancer.

References

1. Thomas B, Coates D, Tzeng V, Baehner L & Boxer. A Treatment of hairy cell leukemia with recombinant alpha-interferon. *Blood*. 1986;68:493–497.
2. Wang M, Herbst RS, Boshoff C. Toward personalized treatment approaches for non-small-cell lung cancer. *Nat Med*. 2021;27:1345–1356.
3. Quesada JR, Hersh EM, Manning J, et al. Treatment of hairy cell leukemia with recombinant alpha-interferon. *Blood*. 1986;68(2):493-497.
4. Gadgeel S, Rodríguez-Abreu D, Speranza G, et al. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2020;38(14): 1505-1517. doi:10.1200/JCO.19.03136
5. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018;379(21):2040-2051. doi:10.1056/NEJMoa1810865
6. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med*. 2015;373(17):1627-1639. doi:10.1056/NEJMoa1507643
7. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med*. 2015;373(2):123-135. doi:10.1056/NEJMoa1504627
8. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387(10027):1540-1550. doi:10.1016/S0140-6736(15)01281-7
9. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial [published correction appears in Lancet. 2017 Apr 8;389(10077):e5]. *Lancet*. 2017;389(10066):255-265. doi:10.1016/S0140-6736(16)32517-X
10. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med*. 2016;375(19):1823-1833. doi:10.1056/NEJMoa1606774
11. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372 (21):2018-2028. doi:10.1056/NEJMoa1501824
12. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature*. 2014;515(7528): 563-567. doi:10.1038/nature14011
13. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443-2454. doi:10.1056/NEJMoa1200690
14. Kim TK, Herbst RS, Chen L. Defining and Understanding Adaptive Resistance in Cancer Immunotherapy. *Trends Immunol*. 2018;39(8):624-631. doi:10.1016/j.it.2018.05.001
15. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. *Cell*. 2017;168(4):707-723. doi:10.1016/j.cell.2017.01.017
16. Cristescu R, Mogg R, Ayers M, et al. Pan-tumor genomic biomarkers for PD-1 checkpoint blockade-based immunotherapy [published correction appears in Science. 2019 Mar 1;363(6430):]. *Science*. 2018;362(6411):eaar3593. doi:10.1126/science.aar3593
17. Dongre A, Rashidian M, Reinhardt F, et al. Epithelial-to-Mesenchymal Transition Contributes to Immunosuppression in Breast Carcinomas. *Cancer Res*. 2017; 77(15):3982-3989. doi:10.1158/0008-5472.CAN-16-3292
18. Gettinger S, Choi J, Hastings K, et al. Impaired HLA Class I Antigen Processing and Presentation as a Mechanism of Acquired Resistance to Immune Checkpoint Inhibitors in Lung Cancer. *Cancer Discov*. 2017;7(12):1420-1435. doi:10.1158/2159-8290.CD-17-0593
19. Sade-Feldman M, Yizhak K, Bjorgaard SL, et al. Defining T Cell States Associated with Response to Checkpoint Immunotherapy in Melanoma [published correction appears in Cell. 2019 Jan 10;176(1-2):404]. *Cell*. 2018;175(4):998-1013.e20. doi:10.1016/j.cell.2018.10.038
20. Thommen DS, Koelzer VH, Herzig P, et al. A transcriptionally and functionally distinct PD-1+ CD8+ T cell pool with predictive potential in non-small-cell lung cancer treated with PD-1 blockade. *Nat Med*. 2018;24(7):994-1004. doi:10.1038/s41591-018-0057-z
21. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science*. 2015;348(6230):124-128. doi:10.1126/science.aaa1348
22. Vesely MD, Zhang T, Chen L. Resistance Mechanisms to Anti-PD Cancer Immunotherapy. *Annu Rev Immunol*. 2022;40:45-74. doi:10.1146/annurev-immunol-070621-030155
23. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393(10183):1819-1830. doi:10.1016/S0140-6736(18)32409-7

24. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018;378(22):2078-2092. doi:10.1056/NEJMoa1801005
25. Goldberg SB, Schalper KA, Gettinger SN, et al. Pembrolizumab for management of patients with NSCLC and brain metastases: long-term results and biomarker analysis from a non-randomised, open-label, phase 2 trial. *Lancet Oncol*. 2020;21(5):655-663. doi:10.1016/S1470-2045(20)30111-X
26. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. *N Engl J Med*. 2019;381(21):2020-2031. doi:10.1056/NEJMoa1910231
27. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial [published correction appears in Lancet Oncol. 2021 Mar;22(3):e92]. *Lancet Oncol*. 2021;22(2):198-211. doi:10.1016/S1470-2045(20)30641-0
28. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *N Engl J Med*. 2017;377(20):1919-1929. doi:10.1056/NEJMoa1709937
29. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *N Engl J Med*. 2018;378(24):2288-2301. doi:10.1056/NEJMoa1716948
30. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20(7):924-937. doi:10.1016/S1470-2045(19)30167-6
31. Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC. *N Engl J Med*. 2020;383(14):1328-1339. doi:10.1056/NEJMoa1917346
32. Sezer A, Kilickap S, Gümüş M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. *Lancet*. 2021;397(10274):592-604. doi:10.1016/S0140-6736(21)00228-2
33. Ahn MJ. Consolidation of immunotherapy becomes new standard of care in unresectable stage III non-small cell lung cancer. *J Thorac Dis*. 2018;10(3):1205-1206. doi:10.21037/jtd.2018.03.55
34. Martini N, Flehinger BJ. The role of surgery in N2 lung cancer. *Surg Clin North Am*. 1987;67(5):1037-1049. doi:10.1016/s0039-6109(16)44341-0
35. O'Rourke N, Roqué I Figuls M, Farré Bernadó N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database Syst Rev*. 2010;(6):CD002140. Published 2010 Jun 16. doi:10.1002/14651858.CD002140.pub3
36. Spigel DR, Faivre-Finn C, Gray JE, et al. Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer [published correction appears in J Clin Oncol. 2022 Jun 10;40(17):1965]. *J Clin Oncol*. 2022;40(12):1301-1311. doi:10.1200/JCO.21.01308
37. McDonald F, M.F., Garassino MC et al. . 79MO-PACIFIC-R: real-world characteristics of unresectable stage III NSCLC patients treated with durvalumab after chemoradiotherapy. European Lung Cancer Virtual Congress, 2021.
38. Durm GA, Jabbour SK, Althouse SK, et al. A phase 2 trial of consolidation pembrolizumab following concurrent chemoradiation for patients with unresectable stage III non-small cell lung cancer: Hoosier Cancer Research Network LUN 14-179. *Cancer*. 2020;126(19):4353-4361. doi:10.1002/cncr.33083
39. Peters S, Felip E, Dafni U, et al. Progression-Free and Overall Survival for Concurrent Nivolumab With Standard Concurrent Chemoradiotherapy in Locally Advanced Stage IIIA-B NSCLC: Results From the European Thoracic Oncology Platform NICOLAS Phase II Trial (European Thoracic Oncology Platform 6-14) [published correction appears in J Thorac Oncol. 2021 May 26;:]. *J Thorac Oncol*. 2021;16(2):278-288. doi:10.1016/j.jtho.2020.10.129
40. Zhou Q, Chen M, Jiang O, et al. Sugemalimab versus placebo after concurrent or sequential chemoradiotherapy in patients with locally advanced, unresectable, stage III non-small-cell lung cancer in China (GEMSTONE-301): interim results of a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol*. 2022;23(2):209-219. doi:10.1016/S1470-2045(21)00630-6
41. Lin SH, Lin Y, Yao L, et al. Phase II Trial of Concurrent Atezolizumab With Chemoradiation for Unresectable NSCLC. *J Thorac Oncol*. 2020;15(2):248-257. doi:10.1016/j.jtho.2019.10.024
42. Jabbour SK, Lee KH, Frost N, et al. Pembrolizumab Plus Concurrent Chemoradiation Therapy in Patients With Unresectable, Locally Advanced, Stage III Non-Small Cell Lung Cancer: The Phase 2 KEYNOTE-799 Nonrandomized Trial [published online ahead of print, 2021 Jun 4]. *JAMA Oncol*. 2021;7(9):1-9. doi:10.1001/jamaoncol.2021.2301
43. Varlotto JM, Sun Z, Ky B, et al. A Review of Immunotherapy for Stage III and Metastatic Non-Small Cell Lung Cancer and the Rationale for the ECOG-ACRIN EA5181 Study. *Oncologist*. 2021;26(6):523-532. doi:10.1002/onco.13725
44. De Ruysscher D, Ramalingam S, Urbanic J, et al. CheckMate 73L: A Phase 3 Study Comparing Nivolumab Plus Concurrent Chemoradiotherapy Followed by Nivolumab With or Without Ipilimumab Versus Concurrent Chemoradiotherapy Followed by Durvalumab for Previously Untreated, Locally Advanced Stage III Non-Small-Cell Lung Cancer. *Clin Lung Cancer*. 2022;23(3):e264-e268. doi:10.1016/j.cllc.2021.07.005
45. Herbst RS, Majem M, Barlesi F, et al. COAST: An Open-Label, Phase II, Multidrug Platform Study of Durvalumab Alone or in Combination With Oleclumab or Monalizumab in Patients With Unresectable, Stage III Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2022;40(29):3383-3393. doi:10.1200/JCO.22.00227
46. Dziadziuszko, R.A., M.J., Kelly, K. et al. . SKYSCRAPER-03: A Phase III, Open-Label, Randomized Study of Atezolizumab Plus Tiragolumab Compared with Durvalumab in Patients with Locally Advanced, Unresectable, Stage III NSCLC Who Have Not Progressed After Platinum-Based Concurrent Chemoradiation. ASTRO 63rd Annual Meeting. 2021.
47. Hirsch FR, Scagliotti GV, Mulshine JL, et al. Lung cancer: current therapies and new targeted treatments. *Lancet*. 2017;389(10066):299-311. doi:10.1016/S0140-6736(16)30958-8
48. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12(4):252-264. Published 2012 Mar 22. doi:10.1038/nrc3239
49. Sharma P, Allison JP. The future of immune checkpoint therapy. *Science*. 2015;348(6230):56-61. doi:10.1126/science.aaa8172
50. Reck M, Remon J, Hellmann MD. First-Line Immunotherapy for Non-Small-Cell Lung Cancer [published correction appears in J Clin Oncol.

2022 Apr 10;40(11):1265]. *J Clin Oncol*. 2022;40(6):586-597. doi:10.1200/JCO.21.01497
51. Howlader N, Forjaz G, Mooradian MJ, et al. The Effect of Advances in Lung-Cancer Treatment on Population Mortality. *N Engl J Med*. 2020;383(7):640-649. doi:10.1056/NEJMoa1916623
52. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med*. 2012;366(26):2455-2465. doi:10.1056/NEJMoa1200694
53. Garon EB, Hellmann MD, Rizvi NA, et al. Five-Year Overall Survival for Patients With Advanced Non-Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. *J Clin Oncol*. 2019;37(28):2518-2527. doi:10.1200/JCO.19.00934
54. Gettinger S, Horn L, Jackman D, et al. Five-Year Follow-Up of Nivolumab in Previously Treated Advanced Non-Small-Cell Lung Cancer: Results From the CA209-003 Study. *J Clin Oncol*. 2018;36(17):1675-1684. doi:10.1200/JCO.2017.77.0412
55. Borghaei H, Gettinger S, Vokes EE, et al. Five-Year Outcomes From the Randomized, Phase III Trials CheckMate 017 and 057: Nivolumab Versus Docetaxel in Previously Treated Non-Small-Cell Lung Cancer [published correction appears in J Clin Oncol. 2021 Apr 1;39(10):1190]. *J Clin Oncol*. 2021;39(7):723-733. doi:10.1200/JCO.20.01605
56. Herbst RS, Garon EB, Kim DW, et al. Five Year Survival Update From KEYNOTE-010: Pembrolizumab Versus Docetaxel for Previously Treated, Programmed Death-Ligand 1-Positive Advanced NSCLC. *J Thorac Oncol*. 2021;16(10):1718-1732. doi:10.1016/j.jtho.2021.05.001
57. Mazieres J, Rittmeyer A, Gadgeel S, et al. Atezolizumab Versus Docetaxel in Pretreated Patients With NSCLC: Final Results From the Randomized Phase 2 POPLAR and Phase 3 OAK Clinical Trials. *J Thorac Oncol*. 2021;16(1):140-150. doi:10.1016/j.jtho.2020.09.022
58. Carbone DP, Reck M, Paz-Ares L, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. *N Engl J Med*. 2017;376(25):2415-2426. doi:10.1056/NEJMoa1613493
59. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50. *J Clin Oncol*. 2021;39(21):2339-2349. doi:10.1200/JCO.21.00174
60. de Castro G Jr, Kudaba I, Wu YL, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy as First-Line Therapy in Patients With Non-Small-Cell Lung Cancer and Programmed Death Ligand-1 Tumor Proportion Score ≥ 1% in the KEYNOTE-042 Study [published online ahead of print, 2022 Oct 28]. *J Clin Oncol*. 2022;JCO2102885. doi:10.1200/JCO.21.02885
61. Jassem J, de Marinis F, Giaccone G, et al. Updated Overall Survival Analysis From IMpower110: Atezolizumab Versus Platinum-Based Chemotherapy in Treatment-Naive Programmed Death-Ligand 1-Selected NSCLC. *J Thorac Oncol*. 2021;16(11):1872-1882. doi:10.1016/j.jtho.2021.06.019
62. Lee SM, Schulz C, Prabhash K, et al. IPSOS: Results from a phase III study of first-line (1L) atezolizumab (atezo) vs single-agent chemotherapy (chemo) in patients (pts) with NSCLC not eligible for a platinum-containing regimen. *Annals of Oncology.* 2022;33 (suppl_7): S808-S869.
63. Rapoport BL, Anderson R. Realizing the Clinical Potential of Immunogenic Cell Death in Cancer Chemotherapy and Radiotherapy. *Int J Mol Sc*i. 2019;20(4):959. Published 2019 Feb 22. doi:10.3390/ijms20040959
64. Garassino MC, Gadgeel S, Esteban E, et al. Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020;21(3):387-397. doi:10.1016/S1470-2045(19)30801-0
65. Garassino MC, Gadgeel S, Speranza G, et al. Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study [published online ahead of print, 2023 Feb 21]. *J Clin Oncol*. 2023;JCO2201989. doi:10.1200/JCO.22.01989
66. Novello S, Kowalski DM, Luft A, et al. Pembrolizumab Plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study [published online ahead of print, 2023 Feb 3]. *J Clin Oncol*. 2023;JCO2201990. doi:10.1200/JCO.22.01990
67. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20(7):924-937. doi:10.1016/S1470-2045(19)30167-6
68. Nogami N, Barlesi F, Socinski MA, et al. IMpower150 Final Exploratory Analyses for Atezolizumab Plus Bevacizumab and Chemotherapy in Key NSCLC Patient Subgroups With EGFR Mutations or Metastases in the Liver or Brain. *J Thorac Oncol*. 2022;17(2):309-323. doi:10.1016/j.jtho.2021.09.014
69. Nishio M, Barlesi F, West H, et al. Atezolizumab Plus Chemotherapy for First-Line Treatment of Nonsquamous NSCLC: Results From the Randomized Phase 3 IMpower132 Trial. *J Thorac Oncol*. 2021;16(4):653-664. doi:10.1016/j.jtho.2020.11.025
70. Reck M, Mok TSK, Nishio M, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. *Lancet Respir Med*. 2019;7(5):387-401. doi:10.1016/S2213-2600(19)30084-0
71. Yang Y, Wang Z, Fang J, et al. Efficacy and Safety of Sintilimab Plus Pemetrexed and Platinum as First-Line Treatment for Locally Advanced or Metastatic Nonsquamous NSCLC: a Randomized, Double-Blind, Phase 3 Study (Oncology pRogram by InnovENT anti-PD-1-11). *J Thorac Oncol*. 2020;15(10):1636-1646. doi:10.1016/j.jtho.2020.07.014
72. Lu S, Wang J, Yu Y, et al. Tislelizumab Plus Chemotherapy as First-Line Treatment for Locally Advanced or Metastatic Nonsquamous NSCLC (RATIONALE 304): A Randomized Phase 3 Trial. *J Thorac Oncol*. 2021;16(9):1512-1522. doi:10.1016/j.jtho.2021.05.005
73. Zhou C, Chen G, Huang Y, et al. Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naive patients with advanced non-squamous non-small-cell lung cancer (CameL): a randomised, open-label, multicentre, phase 3 trial. *Lancet Respir Med*. 2021;9(3):305-314. doi:10.1016/S2213-2600(20)30365-9
74. Zhou C, Wang Z, Sun Y, et al.

Sugemalimab versus placebo, in combination with platinum-based chemotherapy, as first-line treatment of metastatic non-small-cell lung cancer (GEMSTONE-302): interim and final analyses of a double-blind, randomised, phase 3 clinical trial. *Lancet Oncol*. 2022;23(2):220-233. doi:10.1016/S1470-2045(21)00650-1
75. Jotte R, Cappuzzo F, Vynnychenko I, et al. Atezolizumab in Combination With Carboplatin and Nab-Paclitaxel in Advanced Squamous NSCLC (IMpower131): Results From a Randomized Phase III Trial. *J Thorac Oncol*. 2020;15(8):1351-1360. doi:10.1016/j.jtho.2020.03.028
76. Ren S, Chen J, Xu X, et al. Camrelizumab Plus Carboplatin and Paclitaxel as First-Line Treatment for Advanced Squamous NSCLC (CameL-Sq): A Phase 3 Trial. *J Thorac Oncol*. 2022;17(4):544-557. doi:10.1016/j.jtho.2021.11.018
77. Wang J, Lu S, Yu X, et al. Tislelizumab Plus Chemotherapy vs Chemotherapy Alone as First-line Treatment for Advanced Squamous Non-Small-Cell Lung Cancer: A Phase 3 Randomized Clinical Trial. *JAMA Oncol*. 2021;7(5):709-717. doi:10.1001/jamaoncol.2021.0366
78. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. *J Clin Oncol*. 2022;40(2):127-137. doi:10.1200/JCO.21.02229
79. Brahmer JR, Lee JS, Ciuleanu TE, et al. Five-Year Survival Outcomes With Nivolumab Plus Ipilimumab Versus Chemotherapy as First-Line Treatment for Metastatic Non-Small-Cell Lung Cancer in CheckMate 227. *J Clin Oncol*. 2023;41(6):1200-1212. doi:10.1200/JCO.22.01503
80. Rizvi NA, Cho BC, Reinmuth N, et al. Durvalumab With or Without Tremelimumab vs Standard Chemotherapy in First-line Treatment of Metastatic Non-Small Cell Lung Cancer: The MYSTIC Phase 3 Randomized Clinical Trial [published correction appears in JAMA Oncol. 2020 Nov 1;6(11):1815]. *JAMA Oncol*. 2020;6(5):661-674. doi:10.1001/jamaoncol.2020.0237
81. Boyer M, Şendur MAN, Rodríguez-Abreu D, et al. Pembrolizumab Plus Ipilimumab or Placebo for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50%: Randomized, Double-Blind Phase III KEYNOTE-598 Study. *J Clin Oncol*. 2021;39(21):2327-2338. doi:10.1200/JCO.20.03579
82. Johnson ML, Cho BC, Luft A, et al. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: The Phase III POSEIDON Study. *J Clin Oncol*. 2023;41(6):1213-1227. doi:10.1200/JCO.22.00975
83. Akinboro A, Jonathon JV, Nakajima EC, et al. Outcomes of anti–PD-(L)1 therapy with or without chemotherapy (chemo) for first-line (1L) treatment of advanced non–small cell lung cancer (NSCLC) with PD-L1 score ≥ 50%: FDA pooled analysis. *J Clin Oncol.* 2022;40 (16 suppl): 9000-9000.
84. Lu S, Wu L, Jian H, et al. Sintilimab plus bevacizumab biosimilar IBI305 and chemotherapy for patients with EGFR-mutated non-squamous non-small-cell lung cancer who progressed on EGFR tyrosine-kinase inhibitor therapy (ORIENT-31): first interim results from a randomised, double-blind, multicentre, phase 3 trial [published correction appears in Lancet Oncol. 2022 Sep;23(9):e404]. *Lancet Oncol*. 2022;23(9):1167-1179. doi:10.1016/S1470-2045(22)00382-5.
85. Skoulidis F, Heymach JV. Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy. *Nat Rev Cancer*. 2019;19(9):495-509. doi:10.1038/s41568-019-0179-8.
86. Gettinger SN, Redman MW, Bazhenova L, et al. Nivolumab plus ipilimumab vs nivolumab for previously treated patients with stage IV squamous cell lung cancer: The Lung-MAP S1400I phase 3 randomized clinical trial. *JAMA Oncol*. 2021 Sep; 7(9): 1368–1377.
87. Desai A, Prasad V. Low-Dose Computed Tomographic Screening for Lung Cancer: Time to Implement or Unresolved Questions?. *J Gen Intern Med*. 2021;36(10):3202-3204. doi:10.1007/s11606-021-06806-5
88. Desai AP, Adashek JJ, Reuss JE, West HJ, Mansfield AS. Perioperative Immune Checkpoint Inhibition in Early-Stage Non-Small Cell Lung Cancer: A Review [published correction appears in JAMA Oncol. 2023 Jan 1;9(1):151]. *JAMA Oncol*. 2023;9(1):135-142. doi:10.1001/jamaoncol.2022.5389
89. Desai A, Subbiah V. Rationalizing rules for immunotherapy combination trials: About time for precision immunotherapy. *Cancer*. 2023;129(1):11-14. doi:10.1002/cncr.34514
90. Dalgleish AG. Rationale for combining immunotherapy with chemotherapy. Immunotherapy. 2015;7(3):309-316. doi:10.2217/imt.14.111
91. Reck M, Remon J, Hellmann MD. First-Line Immunotherapy for Non-Small-Cell Lung Cancer [published correction appears in J Clin Oncol. 2022 Apr 10;40 (11):1265]. *J Clin Oncol*. 2022;40(6):586-597. doi:10.1200/JCO.21.01497
92. Dagogo-Jack I, Piotrowska Z. There Is No Unmet Need for Another Programmed Cell Death Protein-1 or Programmed Death-Ligand 1 Inhibitor for Metastatic NSCLC. *J Thorac Oncol*. 2022;17(10):1171-1174. doi:10.1016/j.jtho.2022.08.003
93. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. *Science*. 1996;271(5256):1734-1736. doi:10.1126/science.271.5256.1734
94. Felip E, Majem M, Doger B, et al. A phase II study (TACTI-002) in first-line metastatic non–small cell lung carcinoma investigating eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab: Updated results from a PD-L1 unselected population. *J Clin Oncol*. 2022;40: 9003-9003. DOI: 10.1200/jco.2022.40.16_suppl.9003.
95. Cho BC, Abreu DR, Hussein M, et al. Tiragolumab plus atezolizumab versus placebo plus atezolizumab as a first-line treatment for PD-L1-selected non-small-cell lung cancer (CITYSCAPE): primary and follow-up analyses of a randomised, double-blind, phase 2 study. *Lancet Oncol*. 2022;23(6):781-792. doi:10.1016/S1470-2045(22)00226-1
96. Niu J, Maurice-Dror C, Lee DH, et al. First-in-human phase 1 study of the anti-TIGIT antibody vibostolimab as monotherapy or with pembrolizumab for advanced solid tumors, including non-small-cell lung cancer. *Ann Oncol*. 2022;33(2):169-180. doi:10.1016/j.annonc.2021.11.002
97. Mach N, Curigliano G, Santoro A, et al. Phase (Ph) II study of MBG453+ spartalizumab in patients (pts) with non-small cell lung cancer (NSCLC) and melanoma pretreated with anti–PD-1/L1 therapy. *Ann Oncol*. 2019;30: v491-v492.
98. Tinker AV, Hirte HW, Provencher D, et al. Dose-Ranging and Cohort-Expansion Study of Monalizumab (IPH2201) in Patients with Advanced Gynecologic Malignancies: A Trial of the Canadian Cancer Trials Group (CCTG): IND221. *Clin Cancer Res*. 2019;25(20):6052-6060. doi:10.1158/1078-0432.CCR-19-0298

99. Cascone T, García-Campelo R, Spicer J, et al. Abstract CT011: NeoCOAST: open-label, randomized, phase 2, multidrug platform study of neoadjuvant durvalumab alone or combined with novel agents in patients (pts) with resectable, early-stage non-small-cell lung cancer (NSCLC). *Cancer Research.* 2022;82:CT011-CT011. DOI: 10.1158/1538-7445.am2022-ct011.
100. Herbst RS, Majem M, Barlesi F, et al. COAST: An Open-Label, Phase II, Multidrug Platform Study of Durvalumab Alone or in Combination With Oleclumab or Monalizumab in Patients With Unresectable, Stage III Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2022;40(29):3383-3393. doi:10.1200/JCO.22.00227
101. Patel SA, Nilsson MB, Le X, Cascone T, Jain RK, Heymach JV. Molecular Mechanisms and Future Implications of VEGF/VEGFR in Cancer Therapy. *Clin Cancer Res*. 2023;29(1):30-39. doi:10.1158/1078-0432.CCR-22-1366
102. Chen W, Shen L, Jiang J, et al. Antiangiogenic therapy reverses the immunosuppressive breast cancer microenvironment. *Biomark Res*. 2021;9(1):59. Published 2021 Jul 22. doi:10.1186/s40364-021-00312-w
103. Peters S, Paz-Ares L, Herbst RS, Reck M. Addressing CPI resistance in NSCLC: targeting TAM receptors to modulate the tumor microenvironment and future prospects. *J Immunother Cancer*. 2022;10(7):e004863. doi:10.1136/jitc-2022-004863
104. Bergerot P, Lamb P, Wang E, Pal SK. Cabozantinib in Combination with Immunotherapy for Advanced Renal Cell Carcinoma and Urothelial Carcinoma: Rationale and Clinical Evidence. *Mol Cancer Ther*. 2019;18(12):2185-2193. doi:10.1158/1535-7163. MCT-18-1399
105. Kimura T, Kato Y, Ozawa Y, et al. Immunomodulatory activity of lenvatinib contributes to antitumor activity in the Hepa1-6 hepatocellular carcinoma model. *Cancer Sci*. 2018;109(12):3993-4002. doi:10.1111/cas.13806
106. Bosma NA, Warkentin MT, Gan CL, et al. Efficacy and Safety of First-line Systemic Therapy for Metastatic Renal Cell Carcinoma: A Systematic Review and Network Meta-analysis. *Eur Urol Open Sci*. 2022;37:14-26. Published 2022 Jan 22. doi:10.1016/j.euros.2021.12.007
107. Socinski MA, Nishio M, Jotte RM, et al. IMpower150 Final Overall Survival Analyses for Atezolizumab Plus Bevacizumab and Chemotherapy in First-Line Metastatic Nonsquamous NSCLC. *J Thorac Oncol*. 2021;16(11):1909-1924. doi:10.1016/j.jtho.2021.07.009
108. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384(9944):665-673. doi:10.1016/S0140-6736(14)60845-X
109. Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20(12):1655-1669. doi:10.1016/S1470-2045(19)30634-5
110. Reckamp KL, Redman MW, Dragnev KH, et al. Phase II Randomized Study of Ramucirumab and Pembrolizumab Versus Standard of Care in Advanced Non-Small-Cell Lung Cancer Previously Treated With Immunotherapy-Lung-MAP S1800A [published correction appears in J Clin Oncol. 2022 Sep 1;40(25):3002]. *J Clin Oncol*. 2022;40(21):2295-2306. doi:10.1200/JCO.22.00912
111. Neal JW, Lim FL, Felip E, et al. Cabozantinib in combination with atezolizumab in non-small cell lung cancer (NSCLC) patients previously treated with an immune checkpoint inhibitor: Results from cohort 7 of the COSMIC-021 study. *J Clin Oncol*. 2020;38:9610-9610. DOI: 10.1200/jco.2020.38.15_suppl.9610.
112. Leal TA, Berz D, Rybkin I, et al. 43P MRTX-500: Phase II trial of sitravatinib (sitra) + nivolumab (nivo) in patients (pts) with non-squamous (NSQ) non-small cell lung cancer (NSCLC) progressing on or after prior checkpoint inhibitor (CPI) therapy. *Ann Oncol*. 2022;33:S19-S20. DOI: 10.1016/j.annonc.2022.01.052.
113. Csoszi T, Yang JC, Luft A, et al. Pembrolizumab (Pembro) With or Without Lenvatinib (Lenva) in First-Line Metastatic NSCLC With PD-L1 TPS ≥1% (LEAP-007): A Phase 3, Randomized, Doub... | OncologyPRO.
114. BusinessWire. Exelixis Provides Update on Phase 3 CONTACT-01 Trial Evaluating Cabozantinib in Combination with Atezolizumab in Patients with Metastatic Non-Small Cell Lung Cancer Previously Treated with Immunotherapy and Chemotherapy, https://www.businesswire.com/news/home/20221208005867/en/Exelixis-Provides-Update-on-Phase-3-CONTACT-01-Trial-Evaluating-Cabozantinib-in-Combination-with-Atezolizumab-in-Patients-with-Metastatic-Non-Small-Cell-Lung-Cancer-Previously-Treated-with-Immunotherapy-and-Chemotherapy (2022).
115. Taylor MH, Lee C-H, Makker V, et al. Phase IB/II Trial of Lenvatinib Plus Pembrolizumab in Patients With Advanced Renal Cell Carcinoma, Endometrial Cancer, and Other Selected Advanced Solid Tumors. *J Clin Oncol*. 2020;38:1154-1163. DOI: 10.1200/jco.19.01598
116. Tan DS, Felip E, Castro G, et al. Abstract CT037: Canakinumab in combination with first-line (1L) pembrolizumab plus chemotherapy for advanced non-small cell lung cancer (aNSCLC): Results from the CANOPY-1 phase 3 trial. *Cancer Research.* 2022;82:CT037-CT037.
117. Shi X, Yang J, Deng S, et al. TGF-β signaling in the tumor metabolic microenvironment and targeted therapies. *J Hematol Oncol*. 2022;15(1):135. Published 2022 Sep 17. doi:10.1186/s13045-022-01349-6
118. Theelen WSME, Peulen HMU, Lalezari F, et al. Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial. *JAMA Oncol*. 2019;5(9):1276-1282. doi:10.1001/jamancol.2019.1478
119. Sengupta R, Honey K. AACR Cancer ProgressReport 2020: Turning Science into Lifesaving Care. *Clin Cancer Res*. 2020;26(19):5055. doi:10.1158/1078-0432.CCR-20-3187
120. Barlesi F, Greillier L, Monville F, et al. Precision immuno-oncology for advanced non-small cell lung cancer (NSCLC) patients (pts) treated with PD1/L1 immune checkpoint inhibitors (ICIs): A first analysis of the PIONeeR study. *Ann Oncol*. 2020;31:S1183. DOI: 10.1016/j.annonc.2020.08.2286.
121. Besse B, Awad M, Forde P, et al. OA07.08 HUDSON: An Open-Label, Multi-Drug, Biomarker-Directed, Phase II Platform Study in Patients with NSCLC, who Progressed on Anti-PD(L)1 Therapy. *J Thorac Oncol*. 2021;16:S118-S119. DOI: 10.1016/j.jtho.2021.01.299.

122. Herbst R, Lam W-S, Hellmann M, et al. 635 KEYNOTE-495/KeyImPaCT: updated analysis of a biomarker-directed, randomized, phase 2 trial of pembrolizumab-based combination therapy for non-small cell lung cancer. Regul Young Investigator Award Abstr 2022: A665-A665. DOI: 10.1136/jitc-2022-sitc2022.0635.
123. Chaft JE, Rimner A, Weder W, et al. Evolution of systemic therapy for stages I-III non-metastatic non-small-cell lung cancer. *Nat Rev Clin Oncol.* 2021;18:547-557.
124. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol*. 2016;11(1):39-51. doi:10.1016/j.jtho.2015.09.009
125. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol*. 2008;26(21):3552-3559. doi:10.1200/JCO.2007.13.9030
126. Wakelee HA, Dahlberg SE, Keller SM, et al. Adjuvant chemotherapy with or without bevacizumab in patients with resected non-small-cell lung cancer (E1505): an open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol*. 2017;18(12):1610-1623. doi:10.1016/S1470-2045(17)30691-5
127. Novello S, Torri V, Grohe C, et al. International Tailored Chemotherapy Adjuvant (ITACA) trial, a phase III multicenter randomized trial comparing adjuvant pharmacogenomic-driven chemotherapy versus standard adjuvant chemotherapy in completely resected stage II-IIIA non-small-cell lung cancer [published correction appears in Ann Oncol. 2022 Jan24;:]. *Ann Oncol.* 2022;33(1):57-66. doi:10.1016/j.annonc.2021.09.017
128. Le Pechoux C, Pourel N, Barlesi F, et al. Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART): an open-label, randomised, phase 3 trial [published correction appears in Lancet Oncol. 2022 Jul;23(7):e319]. *Lancet Oncol*. 2022;23(1):104-114. doi:10.1016/S1470-2045(21)00606-9
129. Zhou F, Qiao M, Zhou C. The cutting-edge progress of immune-checkpoint blockade in lung cancer. *Cell Mol Immunol*. 2021;18(2):279-293. doi:10.1038/s41423-020-00577-5
130. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial [published correction appears in Lancet. 2021 Sep 23;:]. *Lancet*. 2021;398(10308):1344-1357. doi:10.1016/S0140-6736(21)02098-5
131. Wakelee H, Altorki N, Felip E, et al. PL03.09 IMpower010:Overall Survival Interim Analysis of a Phase III Study of Atezolizumab vs Best Supportive Care in Resected NSCLC. *J Thorac Oncol*. 2022;17:S2.
132. O'Brien M, Paz-Ares L, Marreaud S, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol.* 2022;23(10):1274-1286. doi:10.1016/S1470-2045(22)00518-6
133. Gale D, Heider K, Ruiz-Valdepenas A, et al. Residual ctDNA after treatment predicts early relapse in patients with early-stage non-small cell lung cancer. *Ann Oncol*. 2022;33(5):500-510. doi:10.1016/j.annonc.2022.02.007
134. Xia L, Mei J, Kang R, et al. Perioperative ctDNA-Based Molecular Residual Disease Detection for Non-Small Cell Lung Cancer: A Prospective Multicenter Cohort Study (LUNGCA-1). *Clin Cancer Res*. 2022;28(15):3308-3317. doi:10.1158/1078-0432.CCR-21-3044
135. Zhang JT, Liu SY, Gao W, et al. Longitudinal Undetectable Molecular Residual Disease Defines Potentially Cured Population in Localized Non-Small Cell Lung Cancer. *Cancer Discov*. 2022;12(7):1690-1701. doi:10.1158/2159-8290.CD-21-1486
136. Zhou C, Thakur M, Srivastava MK, et al. 2O IMpower010: Biomarkers of disease-free survival (DFS) in a phase III study of atezolizumab (atezo) vs best supportive care (BSC) after adjuvant chemotherapy in stage IB-IIIA NSCLC. *Ann Oncol.* 2021;32:S1374.
137. Versluis JM, Long GV, Blank CU. Learning from clinical trials of neoadjuvant checkpoint blockade. *Nat Med*. 2020;26(4):475-484. doi:10.1038/s41591-020-0829-0
138. Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer [published correction appears in N Engl J Med. 2018 Nov 29;379(22):2185]. *N Engl J Med*. 2018;378(21):1976-1986. doi:10.1056/NEJMoa1716078
139. Lee J, Chaft J, Nicholas A, et al. Surgical and Clinical Outcomes With Neoadjuvant Atezolizumab in Resectable Stage IB-IIIB NSCLC: LCMC3 Trial Primary Analysis. *J Thorac Oncol*. 2021;16:S59-S61. doi:10.1016/j.jtho.2021.01.320
140. Forde PM, Spicer J, Lu S,et al. CheckMate 816 Investigators. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. *N Engl J Med*. 2022 May 26;386(21):1973-1985. doi: 10.1056/NEJMoa2202170.
141. Provencio M, Serna-Blasco R, Nadal E, et al. Overall Survival and Biomarker Analysis of Neoadjuvant Nivolumab Plus Chemotherapy in Operable Stage IIIA Non-Small-Cell Lung Cancer (NADIM phase II trial) [published correction appears in J Clin Oncol. 2022 Nov 10;40(32):3785]. *J Clin Oncol.* 2022;40(25):2924-2933. doi:10.1200/JCO.21.02660
142. Provencio M, Serna R, Nadal E, et al. PL03.12 Progression Free Survival and Overall Survival in NADIM II Study. *J Thorac Oncol*. 2022;17:S2-S3. doi: 10.1016/j.jtho.2022.07.014
143. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for Lung Cancers with KRAS p.G12C Mutation. *N Engl J Med.* 2021 Jun 24;384(25):2371-2381. doi: 10.1056/NEJMoa2103695.
144. Miller KD, Nogueira L, Devasia T, et al. Cancer treatment and survivorship statistics, 2022. *CA Cancer J Clin*. 2022 Sep;72(5):409-436. doi: 10.3322/caac.21731.
145. https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf
146. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022 Jan;72(1):7-33. doi: 10.3322/caac.21708.
147. Byers LA, Rudin CM. Small cell lung cancer: where do we go from here? *Cancer*. 2015 Mar 1;121(5):664-72. doi: 10.1002/cncr.29098.
148. Liu SV, Reck M, Mansfield AS, et al. Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133). *J Clin Oncol*. 2021;39(6):619-630. doi:10.1200/JCO.20.01055

149. Goldman JW, Dvorkin M, Chen Y, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(1):51-65. doi:10.1016/S1470-2045(20)30539-8
150. Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial [published correction appears in Lancet Oncol. 2020 Dec;21(12):e553]. *Lancet Oncol*. 2020;21(5):645-654. doi:10.1016/S1470-2045(20)30068-1
151. Ahn, MJ, Cho, BC, Felip, E, et al. Tarlatamab for patients with previously treated small-cell lung cancer. *NEJM*. 2023;389:2063-2075.
152. Spigel DR, Cheng Y, Cho BC, et al. ADRIATIC: Durvalumab (D) as consolidation treatment (tx) for patients (pts) with limited-stage small-cell lung cancer (LS-SCLC). *J Clin Oncol*. 2024;42; 17_suppl (abstr). https://doi.org/10.1200/JCO.2024.42.17_suppl.LBA5.
153. Hassan KA, Kalemkerian GP, Trobe JD. Long-term survival in paraneoplastic opsoclonus-myoclonus syndrome associated with small cell lung cancer. *J Neuroophthalmol*. 2008 Mar;28(1):27-30. doi: 10.1097/WNO.0b013e318167550a.
154. National Cancer Institute. Scientific Framework for Small Cell Lung Cancer (SCLC). June 2014. Available online: http://deainfo.nci.nih.gov/advisory/ctac/workgroup/SCLC/SCLC%20Congressional%20Response.pdf.
155. Iams WT, Kopparapu PR, Yan Y, et al. Blood-Based Surveillance Monitoring of Circulating Tumor DNA From Patients With SCLC Detects Disease Relapse and Predicts Death in Patients With Limited-Stage Disease. *JTO Clin Res Rep*. 2020 Mar 12;1(2):100024. doi: 10.1016/j.jtocrr.2020.100024.
156. Almodovar K, Iams WT, Meador CB, et al. Longitudinal Cell-Free DNA Analysis in Patients with Small Cell Lung Cancer Reveals Dynamic Insights into Treatment Efficacy and Disease Relapse. *J Thorac Oncol*. 2018 Jan;13(1):112-123. doi: 10.1016/j.jtho.2017.09.1951.
157. Vallieres, E. et al. The IASLC Lung Cancer Staging Project: proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2009;4: 1049–1059.
158. Rudin CM, Poirier JT, Byers LA, et al. Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data [published correction appears in Nat Rev Cancer. 2019 Jun 7;:]. *Nat Rev Cancer*. 2019;19(5):289-297. doi:10.1038/s41568-019-0133-9
159. Gay CM, Stewart CA, Park EM, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. *Cancer Cell*. 2021 Mar 8;39(3):346-360.e7. doi: 10.1016/j.ccell.2020.12.014.
160. Chan JM, Quintanal-Villalonga Á, Gao VR, et al. Signatures of plasticity, metastasis, and immunosuppression in an atlas of human small cell lung cancer. *Cancer Cell*. 2021;39(11):1479-1496.e18. doi:10.1016/j.ccell.2021.09.008
161. Ganti AKP, Loo BW, Bassetti M, et al. Small Cell Lung Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2021;19(12):1441-1464. doi:10.6004/jnccn.2021.0058
162. Soomro Z, Youssef M, Yust-Katz S, Jalali A, Patel AJ, Mandel J. Paraneoplastic syndromes in small cell lung cancer. *J Thorac Dis*. 2020 Oct;12(10):6253-6263. doi: 10.21037/jtd.2020.03.88
163. Quintanal-Villalonga Á, Chan JM, Yu HA, et al. Lineage plasticity in cancer: a shared pathway of therapeutic resistance [published correction appears in *Nat Rev Clin Oncol*. 2020 Mar 17;:]. Nat Rev Clin Oncol. 2020;17(6):360-371. doi:10.1038/s41571-020-0340-z
164. Ready NE, Ott PA, Hellmann MD, et al. Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent Small Cell Lung Cancer: Results From the CheckMate 032 Randomized Cohort. *J Thorac Oncol*. 2020;15(3):426-435. doi:10.1016/j.jtho.2019.10.004
165. Dawe D, Pond GR, Ellis PM. Do patients with small cell lung cancer (SCLC) who have chemotherapy initiated during a hospital admission benefit from therapy? *J Clinical Oncol*. 2014;32(15). doi: 10.1200/jco.2014.32.15_suppl.e17661.
166. ClinicalTrials.gov Identifier: NCT04334941
167. Thomas PL, Madubata CJ, Aldrich MC, et al. A Call to Action: Dismantling Racial Injustices in Preclinical Research and Clinical Care of Black Patients Living with Small Cell Lung Cancer. *Cancer Discov*. 2021 Feb;11(2):240-244. doi: 10.1158/2159-8290.CD-20-1592
168. Chiang AC, Austin M, Stewart TF, et al. A pilot study of ipilimumab and nivolumab in recurrent extensive-stage small cell lung cancer after platinum-based chemotherapy, *J Clin Oncol*. 2022 June;40(16): 8583-8583. doi: 10.1200/JCO.2022.40.16_suppl.8583
169. Nguyen EM, Taniguchi H, Chan JM, et al. Targeting Lysine-Specific Demethylase 1 Rescues Major Histocompatibility Complex Class I Antigen Presentation and Overcomes Programmed Death-Ligand 1 Blockade Resistance in SCLC. *J Thorac Oncol*. 2022 Aug;17(8):1014-1031. doi: 10.1016/j.jtho.2022.05.014.
170. Poirier JT, George J, Owonikoko TK, et al. New Approaches to SCLC Therapy: From the Laboratory to the Clinic. *J Thorac Oncol*. 2020 Apr;15(4):520-540. doi: 10.1016/j.jtho.2020.01.016.
171. Ou SH, Ziogas A, Zell JA. Prognostic factors for survival in extensive stage small cell lung cancer (ED-SCLC): the importance of smoking history, socioeconomic and marital statuses, and ethnicity. *J Thorac Oncol*. 2009;4(1):37-43. doi:10.1097/JTO.0b013e31819140fb
172. Özgüroğlu M, Kilickap S, Sezer A, et al. First-line cemiplimab monotherapy and continued cemiplimab beyond progression plus chemotherapy for advanced non-small-cell lung cancer with PD-L1 50% or more (EMPOWER-Lung 1): 35-month follow-up from a mutlicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2023;24:989-1001. doi: 10.1016/S1470-2045(23)00329-7.
173. Heymach JV, Harpole D, Mitsudomi T, et al. Perioperative durvalumab for resectable non–small-cell lung cancer. *N Engl J Med*. 2023;389:1672-1684. DOI: 10.1056/NEJMoa230487
174. Wakelee H, Liberman M, Kato T, et al. Perioperative pembrolizumab for early-stage non–small-cell lung cancer. *N Engl J Med*. 2023; 389:491-503. DOI: 10.1056/NEJMoa2302983.
175. Cascone T, Awad MM, Spicer JD, et al. Perioperative nivolumab in resectable lung cancer. *N Engl J Med*. 2024; 390:1756-1769. DOI: 10.1056/NEJMoa2311926.

21

ADVANCES IN COMBINED MODALITY THERAPY FOR NON-SMALL CELL LUNG CANCER

Paul Van Houtte,[1] **Jacek Jassem,**[2] **Rodrigo Arriagada,**[3] **Thierry LeChevalier,**[3] **and Everett E. Vokes**[4] | [1]Université Libre Bruxelles, Hopital Universitaire Bruxelles (HUB) Institut Jules Bordet, Belgium; [2]Medical University of Gdańsk, Gdańsk, Poland; [3]Institut Gustave Roussy, Villejuif, France; [4]University of Chicago, Chicago, USA

Lung cancer is the leading cause of cancer death, and stage III disease that is locoregionally advanced accounts for approximately one-third of all non-small cell lung cancer (NSCLC). A very heterogeneous group of tumors are included in this stage classification (which has undergone revisions over the past 50 years) due to the variety of clinical presentations and treatment possibilities for both resectable and unresectable cases. However, most stage III disease can be treated with curative intent, and significant progress has been made over the past several decades. This stage favors combined modalities, such as a local treatment, surgery, or radiotherapy combined with a systemic approach that includes chemotherapy, targeted drugs, or immunotherapy. Many patients with less advanced disease (stage I and II) were often included in those randomized trials and secondary analysis were carried out according to the stage, but few trials were only designed for those specific stages.

STAGE III DISEASE AND RADIOTHERAPY

For patients who are not candidates for surgery, due to either comorbidity or a tumor or nodal extension, thoracic chemoradiation is the current standard of treatment. This standard is due to the poor results achieved with a single modality. However, in the 1970s, the curative potential of radiotherapy was extremely poor and often was considered palliative. Indeed, 5-year survival rates were far below 10%. Even randomized trials that compared radiotherapy to a placebo or the chemotherapy available at that time (procarbazine, doxorubicin, vinblastine, and cytoxan) did not show any substantial differences between the 3 arms, with a mean survival less than 9 months.[1,2] This finding led to a very nihilistic approach for lung cancer within the medical community.

This approach only changed in the late 1980s, after evidence emerged that chemotherapy could extend survival. Indeed, a 3-arm trial conducted in Canada showed a higher response rate and better survival with vindesine + cisplatin or cyclophosphamide + doxorubicin + cisplatin compared with the best supportive care for locally advanced NSCLC.[3] At the end of the 1970s, computed tomography (CT) and cisplatin became available, and radiation equipment started to use 2-dimensional (2D) dosimetry and linear accelerators. The Radiation Therapy Oncology Group (RTOG) established a reference dose of 60 Gy for 6 weeks, but the results were still disappointing, with less than a 10% 5-year survival and poor local control.[4]

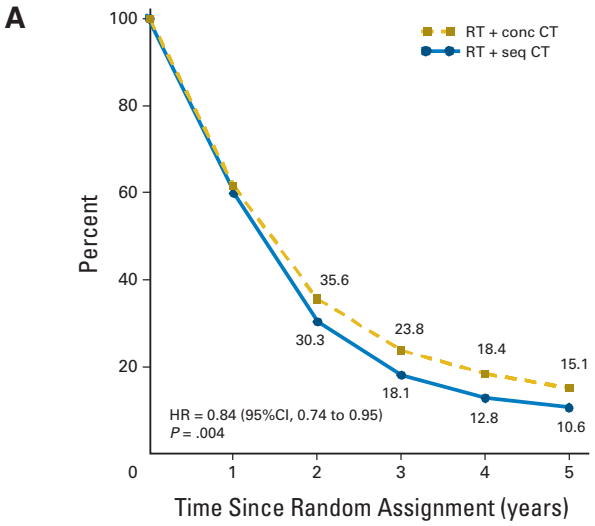
People have attempted to combine drugs with radiation therapy in lung cancer since the 1950s, when Roswit and Kaplan used nitrogen mustard. Those first approaches were very disappointing, which reflects the drugs available at that time. The response rate for patients with stage IV disease was very low, and preclinical and clinical trials were only beginning to study drug-radiation interactions.

Later, combining chemotherapy with radiation offered many theoretical and practical advantages for the local and distant control of disease. Also, several properties were identified, such as spatial cooperation, the radio-sensitizing effect, or possibly protection from radiation-induced damage to normal tissue. This advance in lung cancer led to 2 classical strategies: induction chemotherapy followed by definitive radiotherapy or a concurrent approach. At the end of the 1970s, doublet-chemotherapy options with cisplatin showed better survival and quality of life than placebo or best supportive care, which opened the door for combined chemoradiotherapy. Furthermore, experimental data revealed a possible radio-sensitizing effect. Two approaches were tested in several phase III trials during the 1980s. In this period, induction chemotherapy was considered the best way to combine drugs and radiation. One theoretical advantage was to be able to use a full dose of chemotherapy. Then, in the case of a response, better oxygenation may improve radiation efficacy, and tumor shrinkage may protect normal tissues.[5] This approach was also an easy way to combine both modalities with fewer logistic problems. The first positive results were reported by Dillman, who found that 2 cycles of cisplatin and vinblastine given before 60 Gy doubled the 2-year survival rate from 13% to 26%.[6] Randomized trials in the United States and Europe, as well as later meta-analyses, confirmed a clear survival benefit.[7,8] In the CEBI 138 French trial, an interesting observation was made: the survival benefit was due to lower distant failure. Meanwhile, the concurrent approach was evaluated in a series of trials. The EORTC trial used cisplatin at a dosage of 6 mg/m^2/day and found significantly better survival due to better local control.[9] Once again, the schedule of radiation therapy was not optimal due to the split-course schedule.

A next generation of trials compared the 2 approaches. The first published trial was from the West Japan Lung Cancer Group. This trial showed that concurrent chemoradiotherapy was better than a sequential approach with cisplatin + mitomycine C + vindesine, followed by radiation using a split-course schedule.[10] The 2-year survival rate increased from 27% (sequential approach) to 35% (concurrent approach). The RTOG trial compared the sequential approach (cisplatin + vindesine with 63 Gy delivered once daily) to the concurrent approach (the same drugs at the same time as 63 Gy). The concurrent approach yielded a better 5-year survival.[11] In 2010, a meta-analysis showed a significant benefit in favor of the concurrent chemoradiotherapy, which defined this approach as the standard care that is still used today. The absolute benefit in overall survival (OS) at 3 years was 5.7%, due to significantly less locoregional progression, but at the price of greater acute esophageal toxicity (grade 3-4), from 4% to 18% (Figure 1).[12]

Different approaches were then evaluated to improve those results. The approaches included induction chemotherapy, adjuvant or maintenance chemotherapy by docetaxel, targeted agents and third-generation cytotoxic drugs, or modifying the radiation schedule (e.g., increasing the total dose, hyperfractionation, hypofractionation). These approaches led to a clear breakthrough.[13] For example, a Cancer and Leukemia Group B trial compared immediate concurrent chemoradiotherapy with carboplatin + paclitaxel and 66 Gy of chest radiotherapy (treatment 1) to induction chemotherapy with 2 cycles of carboplatin + paclitaxel and identical chemoradiotherapy (treatment 2). The authors found that the 2-year survival rates were 29% for treatment 1 and 31% for treatment 2.[14]

One problem that arose was the difficulty to translate the benefit of newer agents in patients with stage IV disease to patients with less-advanced stages. Pemetrexed yields better results than gemcitabine for non-squamous cell cancers, and targeted agents erlotinib (in a properly selected patient population) also showed efficacy. In the PROCLAIM trial that compared pemetrexed + cisplatin with etoposide + cisplatin, both with concurrent chest radiation, in patients with stage III non-squamous cell cancer, no difference in survival was observed.[15] Although



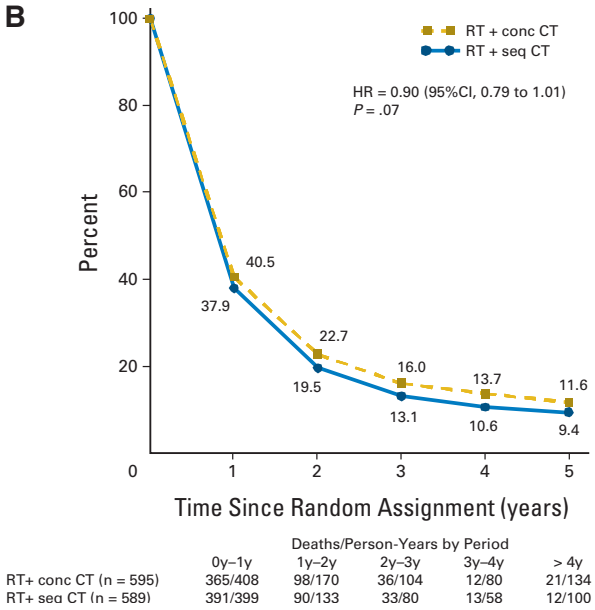


Figure 1. Meta-analysis of concurrent vs sequential chemotherapy for NSCLC. Abbreviations: conc, concurrent; CT, computed tomography; HR, hazard ratio; RT, radiation therapy; seq, sequential. Reprinted with permission: *J Clin Oncol*. 2010;28:2181-90.

not designed as a non-inferiority trial, both regimens were adopted as standard chemotherapy backbones (in addition to weekly administration of carboplatin and paclitaxel). In a systematic review and a Japanese phase III trial with a 10-year follow-up, no difference was observed between second-generation and third-generation chemotherapy.[16,17]

Patients who are older or have poor performance status are another concern. These patients are often not included in randomized trials due to the fear of greater toxicity. However, they represent a great number of patients. In the randomized trial of Atagi et al, patients older than 70 years with a good performance status were randomized to 60 Gy with concurrent low-dose carboplatin (30 mg/m^2/day) for 5 days per week for 20 days or radiation therapy alone. The combined approach led to a survival benefit, with 2-year survival rates of 46% (combined) vs 35% (alone).[18] Acute toxicity was a concern, especially before adapting the protocol, but late toxicities and treatment-related deaths were similar. In a pooled analysis of patients enrolled in 16 phase II or III trials in the United States, patients who were older and younger had similar progression-free survival (PFS). However, patients who were older had a higher rate of severe side effects and even grade 5 toxicity, outlining the need to adapt the chemoradiotherapy as seen in the Atagi trial.[19] Patients with poor performance status is another concern. In a subgroup analysis of a phase III trial, no difference was found in treatment adherence and toxicities between patients with ECOG 2 and ECOG 0-1 cancer, with interesting OS.[20]

For advanced-stage disease, tyrosine kinase inhibitors (TKIs) showed activity that led to better survival in patients with specific mutation-driven tumors, but also a possible synergistic effect with radiotherapy. In lung cancer, trials failed to show any benefit to adding cetuximab to chemo-

radiotherapy, but the mutation status of epidermal growth factor receptor (EGFR) was not evaluated systematically to select the patients.[21,22] EGFR TKIs were also tested as an adjuvant treatment. Erlotinib and gefinitib failed to show any benefit, likely due to the non-selection of patients who did or did not have an EGFR mutation.[23] Preclinical and clinical data suggest that anti-angiogenesis therapy and radiation therapy would be additive. In a phase III trial that included patients with advanced disease, platinum-based therapy combined with bevacizumab vs platinum-based therapy alone had a higher response rate, longer PFS interval, and longer OS time.[24] One problem with bevacizumab was the risk of severe local adverse effects. In phase II trials, tracheoesophageal fistulae occurred, so this drug is excluded from concurrent chemoradiotherapy.[25]

Another question directly concerns the radiation schedule: is 60 Gy in 6 weeks still the gold standard with the modern tools now available in our daily radiation practice? In 2010, the RTOG conducted a large phase III trial that tested a greater total radiation dose (from 60 Gy to 74 Gy) with concurrent carboplatin and paclitaxel.[21] Patients were also randomized to receive or not receive cetuximab. The radiation technique used intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy for half of the population. These techniques failed to show any benefit with the higher radiotherapy dose: more locoregional relapses were observed after 74 Gy (49.7%) than 60 Gy (55.4%). On the other hand, the lower radiation dose had an impressive 5-year survival rate: 32% after 60 Gy. An interesting observation was that IMRT had no detrimental effect on lung toxicity, even if more-advanced tumors were treated.[26]

Currently, new radiation techniques [stereotactic body radiotherapy (SBRT) and protons] have opened new doors and are being actively studied. SBRT is a technique that delivers ablative doses of radiation in a few fractions to tumors or even to metastatic disease. The technique is directly derived from our practice of radiosurgery for brain disease. This approach has opened doors to explore an aggressive approach for oligometastatic disease. Protons allow for obtaining a better dose distribution due to the Bragg peak, and allow for reducing the dose to the heart compared with 3D or IMRT techniques.[27] A first, small phase III trial compared IMRT with protons and failed to show any substantial benefit, partly due to the lack of onboard imaging in the proton facility. Also, larger margins were needed, leading to similar dose distribution to the organs at risk.[28] Ongoing trials are comparing the 2 modalities using concurrent cisplatin-based chemotherapy.

In the past, immunotherapy was not very successful in NSCLC. However, drugs that target programmed cell death protein 1 and programmed death-ligand 1 have completely changed the pattern of care for stage IV disease and markedly improved survival. Also, several preclinical studies reported greater tumor-antigen release, improved antigen presentation, T-cell infiltration in irradiated tumors, and also actions against tumor cells outside the radiation field (i.e., abscopal effect). Radiation may also increase programmed death-ligand 1 expression at the surface of tumoral cells, leading to improved survival in in vivo models.[29] In a phase II trial, patients treated with pembrolizumab given after SBRT to a single metastatic site had a higher response rate and better disease control at 12 weeks than pembrolizumab alone.[30] In a phase I trial, patients treated with radiotherapy before pembrolizumab had better survival, regardless of the site irradiated (31). The PACIFIC trial, a large-scale phase III trial, randomized patients with good performance status and without tumor progression after chemoradiotherapy to durvalumab for 1 year or a placebo. The absolute 2-year survival after durvalumab was above 10%. This trial also showed a persistent survival benefit up to 5 years, with the estimated 5-year survival rate at 42.9 % for durvalumab vs 33.4% for placebo (Figure 2).[32] One concern when combining immunotherapy and radiotherapy is a possible increase in lung toxicity, which was not seen in

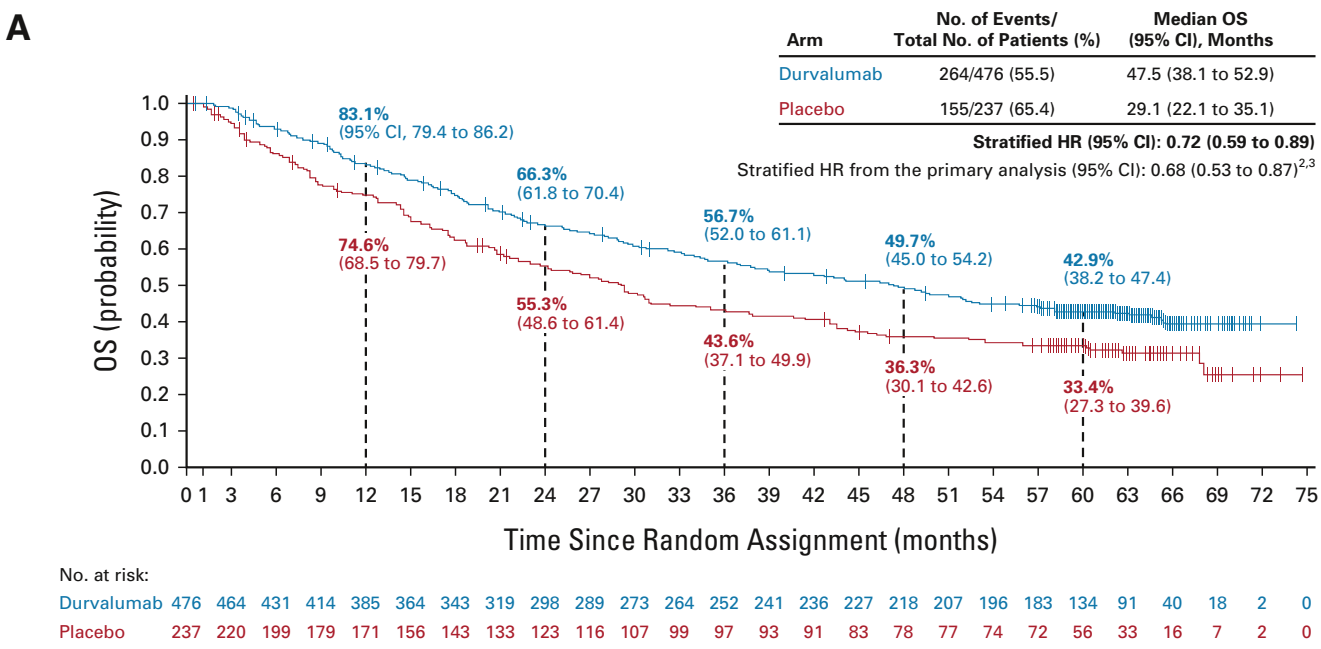


Figure 2. Adjuvant durvalumab from the PACIFIC trial. (A) OS and (B) PFS. Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival. Reprinted with permission: *J Clin Oncol*. 2022:40:1301-11.

a phase II trial.[33] Many ongoing trials are trying to optimize the combination of radiotherapy, chemotherapy, and immunotherapy.

To see the road of improvements, look at the evolution of median survival: 47 weeks with radiation alone in the old RTOG trial, 13.8 months in the induction arm of the RTOG-ECOG trial, 26.8 in the PROCLAIM trial, and 28.7 months in the RTOG trial (Figure 3). More interestingly, the 5-year survival is now approximately 25%. This result was due to technologic improvements, including the combined approach, the initial imaging procedure, and the introduction of positron emission tomography (PET)-CT not only as part of staging, but also for radiation planning.

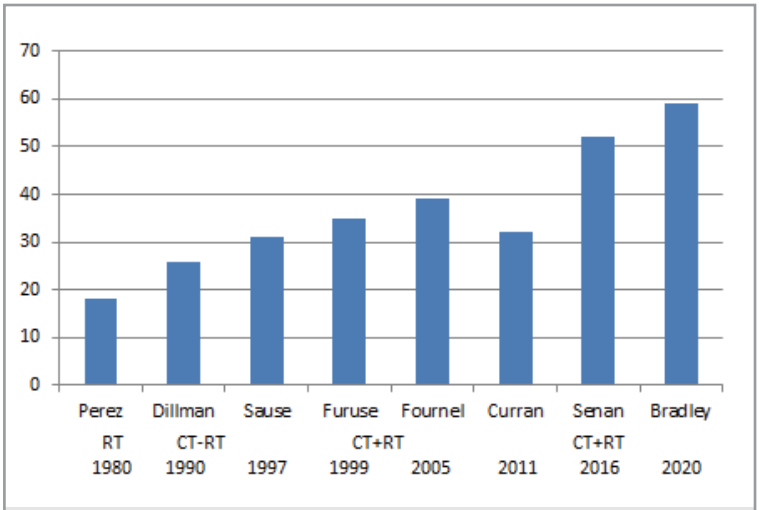


Figure 3. The 2-year survival rates from selected phase III trials. Abbreviations: CT, computed tomography; RT, radiation therapy; Y, year.

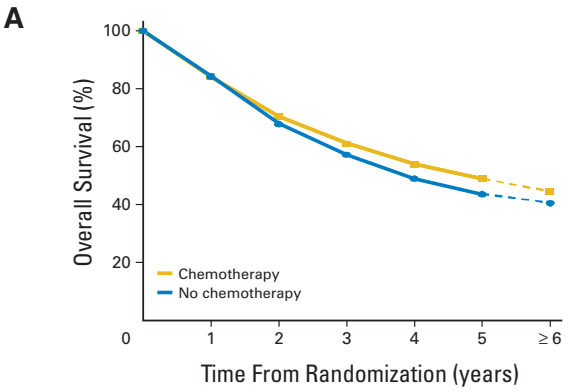
PATIENTS WITH STAGE III AND OPERABLE DISEASE

Many trials conducted over the past have included patients with stage I to III disease. However, few are designed to include a specific tumor stage, which is particularly the case for chemotherapy trials.

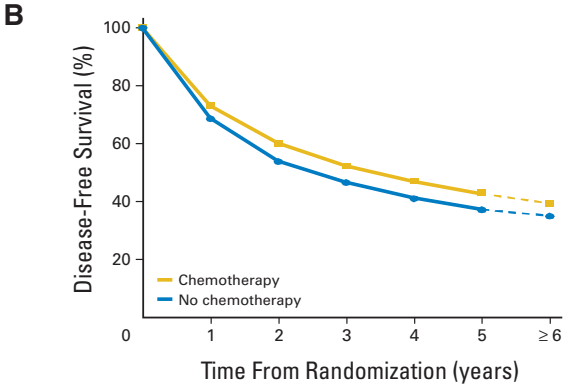
From Chemotherapy to Immunotherapy

Chemotherapy was also used and tested first as an adjuvant treatment after surgery and later as induction treatment. In 1980, a meta-analysis showed a small gain in survival with an absolute benefit of 5% at 5 years for regimens containing cisplatin. Later, trials tested adjuvant paclitaxel and carboplatin. During this period, many randomized trials and meta-analyses showed a significant survival advantage for neoadjuvant chemotherapy. However, in the 2000s, a publication of a new meta-analysis showed a statistically significant benefit with adjuvant chemotherapy for stage II and III NSCLC (Figure 4).[34] After that time, induction chemotherapy became less popular, especially for early-stage disease.[34-36]

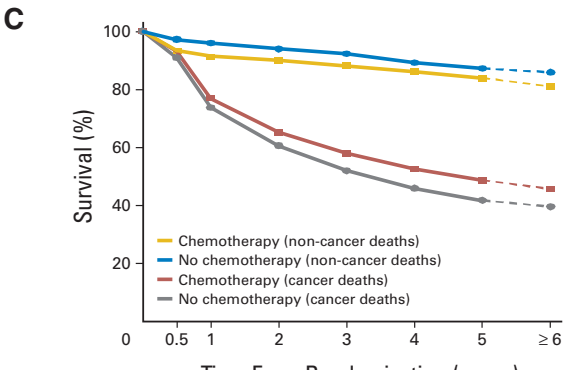
TKIs have also be tested in the adjuvant setting. However, 2 randomized trials conducted in China and Japan failed to confirm the small benefit found in retrospective studies. In a phase III trial of resected EGFR-mutated NSCLC at stages Ib to IIIa, osimertinib was given as adjuvant treatment. However, 60% of the patients had also received chemotherapy before randomization. Although this trial uncovered a better disease-free survival, we are waiting to see if it also uncovers a survival benefit.[37]



Deaths / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	966 / 5,155	239 / 1,668	49 / 720
Chemotherapy	857 / 5,181	203 / 1,817	76 / 790

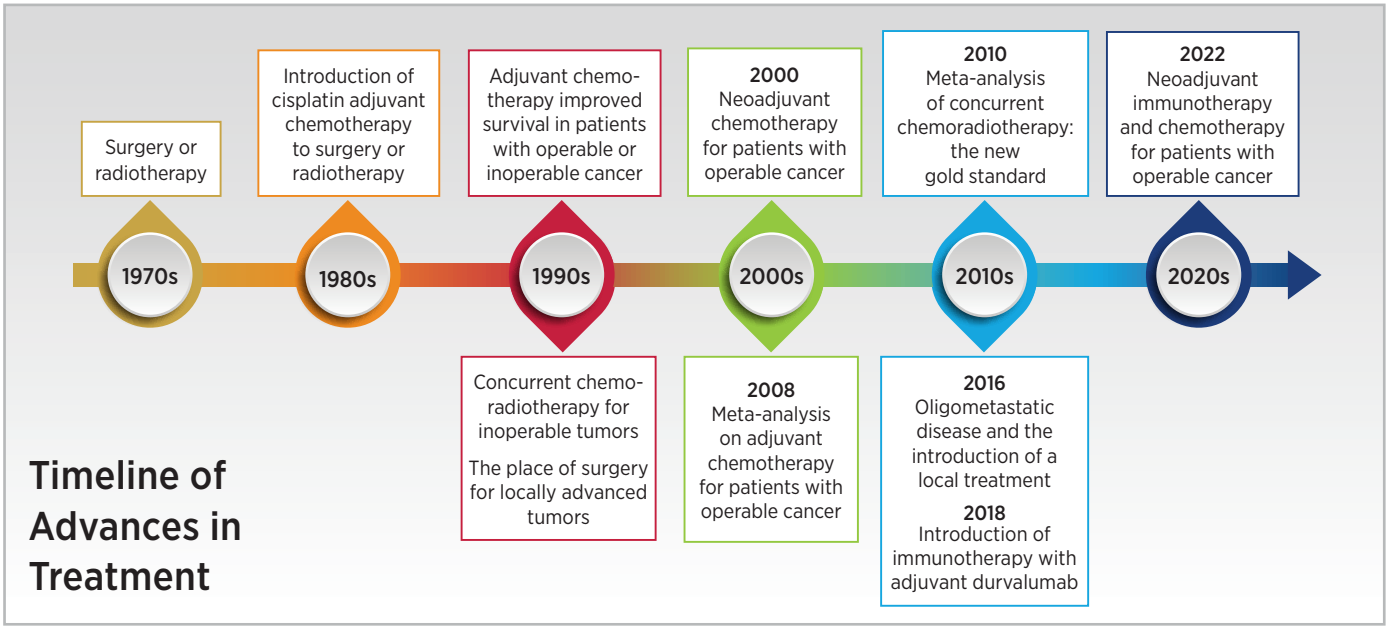


Events / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	1,222 / 4,341	163 / 1,396	35 / 610
Chemotherapy	1,047 / 4,627	159 / 1,606	59 / 708



Non-cancer deaths / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	88 / 4,353	42 / 1,399	9 / 611
Chemotherapy	141 / 4,635	38 / 1,611	24 / 708
Cancer deaths by period			
Control	878	197	40
Chemotherapy	716	165	52

Figure 4. Meta-analysis of adjuvant chemotherapy for NSCLC. Reprinted with permission: *J Clin Oncol*. 2008; 26:3552-3559.



Nowadays, immunotherapy is actively studied, and many ongoing trials are studying surgery. Several groups have reported single-arm phase II trials consisting of a short course of immunotherapy before surgery with or without chemotherapy or adjuvant immunotherapy. This approach was safe, with no significant delays to surgery or unexpected surgical complications. In a recent publication of a phase III trial, patients with stage Ib to IIIa disease were randomized between nivolumab and platinum-based chemotherapy or platinum-based chemotherapy alone. The combined immunotherapy chemotherapy led to a higher complete pathological response (24% combined vs 2.2% alone), significantly longer event-free survival, and similar toxicity. A longer follow-up study is needed to see the survival benefit.[38]

The Trimodality

A trimodality combine a systemic treatment with local modalities, surgery, and radiotherapy. Induction chemoradiotherapy achieved a higher response rate, more downstaging, and a pathologic complete response, but also more postoperative complications than chemotherapy alone. In an analysis of data from the US National Cancer database, the trimodality yielded a better 5-year survival of approximately 32%.[39] A German phase III trial included patients with stage IIIa or IIIb NSCLC who were randomized to either induction chemotherapy followed by surgery and postoperative radiotherapy, or to induction chemotherapy followed by an accelerated course of chemoradiotherapy and later surgery.[40] No difference was seen in R0 resection, but less than 60% of randomized patients underwent surgery. Chemoradiotherapy yielded a higher rate of complete pathological response, but without a survival benefit. Recently, a Swiss trial did not find any difference between induction chemotherapy and chemoradiotherapy for N2 disease.[41] An R0 resection was seen in 91% of the arm with radiotherapy and 81% in the arm without radiotherapy. The pathologic complete responses were very similar between the arms (16% with radiotherapy vs 12% without radiotherapy). However, the schedule was a sequential approach, leaving trimodality an open question. The key factors with the trimodality approach are local expertise and patient selection. All trials conducted had a less than optimal design.

The Place of Surgery

In the 1990s, in view of the results obtained with chemoradiotherapy, the question of the role of surgery was put forward in 2 trials. The EORTC trial randomized patients presenting with

inoperable N2 disease after induction chemotherapy to surgery or radiation. This trial found no difference in long-term survival between groups.[42] The US Intergroup Trial compared induction chemoradiotherapy with an exclusive chemoradiotherapy for N2 disease without a clear-cut benefit. However, a subsequent analysis looked at the difference between patients who possibly underwent a lobectomy and pneumonectomy. Only lobectomy led to a survival advantage.[43] The second trial published in 2015 and performed in Germany did not find any difference between the 2 approaches (Figure 5).[44] The latter 2 trials used concurrent chemoradiotherapy, and the EORTC trial used a sequential approach. The difference in long-term survival rates (5-years for approximately 15% of people in the EORTC trial and more than 40% for people in the last German trial) outlined the difference in patient selection, a clear issue for a trimodality program.

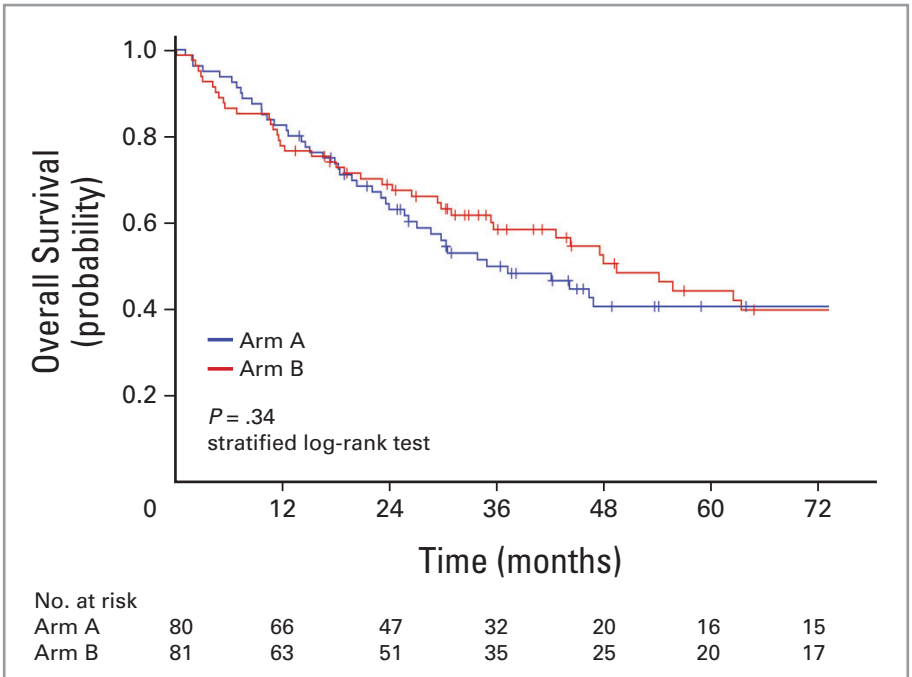


Figure 5. Overall survival from the ESPATUE trial. After induction chemoradiotherapy, patients were randomized to either additional chest radiotherapy (Arm A) or surgery (Arm B). Reprinted with permission: *J Clin Oncol*. 2015;33:4194-201.

Postoperative Radiotherapy

Postoperative radiotherapy was quite popular in the 1980s. However, a meta-analysis suggested a compromised outcome, especially for stage I and II disease, but remained controversial for stage IIIa disease.[45] The quality of postoperative radiotherapy was questioned, leading to many discussions and publications of individual series or large national databases. Then, results from 2 postoperative radiotherapy trials included only patients with N2 disease after induction or adjuvant chemotherapy. No survival benefit was observed in those 2 trials, which included 501 and 394 patients.[46-47]

Stage IV Disease

In the past, the role of radiotherapy for stage IV disease was mainly considered for its possible role as a palliative treatment to relieve symptoms related to the primary disease or metastatic sites. Early efforts focused mainly on radically treating resectable lesions, such as brain or adrenal metastases. The improvement in diagnostic imaging, the introduction of immunotherapy, and the new technique of radiotherapy (including radiosurgery and SBRT) have opened a new area of active research and treatment possibilities aimed at a cure. Radiosurgery and SBRT are ablative approaches to locally control the disease.

In addition, the concept of oligometastatic disease has regained a major interest. This interest includes different clinical scenarios with a limited number of metastatic lesions, from an oligometastatic lesion at presentation to oligorecurrent, oligoprogessive, or oligoresistant disease. There is a lack of consensus on the definition of oligometastatic disease, the number of lesions, and the staging procedure. However, a panel of experts reached a consensus statement on the definition and staging of synchronous oligometastatic NSCLC, including PET-CT.[48]

This aggressive approach is only relevant when a radical treatment is technically feasible, the toxicity is acceptable, and all sites are amenable to a local treatment modality aimed to achieve long-term disease control.

In the past, most studies focused on resectable lesions, like brain and adrenal metastases. Patients with a solitary site of metastasis who are undergoing surgery on the primary tumor and metastatic sites can have a long-term survival of approximately 12% at 4 years (based on a meta-analysis including 227 patients from 7 retrospective studies).[49] The recent technologic developments and advances in imaging procedures have changed the landscape for an aggressive approach for both the primary lesion and metastases.

Three randomized trials outlined the benefit of this aggressive approach. The first trial included only patients with lung cancer and 1 to 3 metastases treated with chemotherapy. In the case of stable disease, patients were randomized to a local surgery and radiotherapy or to chemotherapy. The PFS increased from a median of 4.4 months (chemotherapy) to 14.2 months (local surgery and radiotherapy). However, more interestingly, adding a local treatment increased OS from 17 months to 41.2 months.[50] A similar trend was seen in 2 other trials.[51,52]

Although immune checkpoint inhibitors have revolutionized the treatment of stage IV NSCLC, radiation therapy may increase the immune response both locally or systemically. In the phase I trial, patients treated with radiotherapy then then pembrolizumab had better survival regardless of the site irradiated.[31] Radiation-induced lymphopenia has also been associated with worse survival, so radiotherapy may be changed to enhance the immune response. For example, hypofractionation with a higher dose than the classical 2 Gy may have less immunosuppressive effects, and the planning target volume may be reduced to preserve the host immune response. A large series of ongoing trials are studying the best sequence of treatment.

A similar approach is also being studied for TKI. In a phase III trial, patients with EGFR-mutated adenocarcinoma and 5 or less metastases were randomized to receive upfront TKI with or without radiation therapy to all sites (primary or distant metastases). Adding radiation therapy to TKI improved OS from 17 months to 25 months. Another avenue of active research is adding a local treatment to an area escaping TKIs.[53]

PERSPECTIVES

The future will be to optimize the integration of immunotherapy into the multimodal approach for treating lung cancer. It will also include better personalizing treatments for each patient based on biomarkers. Laboratory research to identify these biomarkers will influence our treatments and our daily practice. Also, an important step will be to offer those treatments to all patients worldwide. Furthermore, the future will include improving classical local treatment, surgery, and radiotherapy to use technologic advances and an adaptative approach.

CONCLUSIONS

During the past 50 years, major progress has been made in managing NSCLC, partly due to the introduction of a combined treatment approach in our daily practice. The IASLC has contributed largely to sharing those improvements with the community through meetings, workshops, and publications. The IASLC actively sponsored and promoted several workshops on combined modalities in Europe (e.g., Bruges, Fontainebleau, Annecy, Cambridge), Asia, and the United States. It has also organized regional meetings and joint meetings with other societies (e.g., European Society for Medical Oncology, American Society for Radiation Oncology, European Society for Radiotherapy and Oncology). These meetings have led to several publications of the proceedings and consensus reports.[54-58] Many advances were largely discussed during those meetings, leading to new areas to be explored.

References

1. Durrant K, Berry RJ, Ellis F, et al. Comparison of treatment policies in inoperable bronchial carcinoma. *Lancet*. 1971;1:715-19
2. Roswit B, Patno ME, Rapp R, et al. The survival of patients with inoperable lung

cancer. A large scale randomized study of radiation therapy versus placebo. *Radiology*. 1968;90:688-697.
3. Rapp E, Pater JL, Willan A, et al. Chemotherapy can prolong survival in patients with advanced non-small-cell lung cancer—report of a Canadian multicenter randomized trial. *J Clin Oncol*. 1988;6:633-41.
4. Perez CA, Stanley K, Rubin P, et al. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of non-oat-cell carcinoma of the lung. Preliminary report by the Radiation Oncology Group. *Cancer*. 1980;45:2744-2753.
5. Muggia FM, Blum RH, Foreman JD. Role of chemotherapy in the treatment of lung cancers : evolving strategies for non-small cell histologies. I*nt J Radiat Oncol Biol Phys*. 1984;10:137-145.
6. Dillman RO, Seagren SL, Propert KJ, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. *N Engl J Med*. 1990;323:940-945.
7. Sause WT, Scott C, Taylor S, et al. Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. *J Natl Cancer Inst*. 1995;87:198-205.
8. Le Chevalier T, Arriagada R, Baldeyrou P, et al. Combined Chemotherapy and Radiotherapy in Nonresectable Non-Small-Cell Lung Cancer: First Analysis of a Randomized Trial in 353 Patients. *JNCI*. 1991;83,6: 417-423.
9. Schaake-Koning C, van den Bogaert W, Dalesio O, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med*. 1992;326:524-530.
10. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine and cisplatine in unresectble stage III non-small-cell lung cancer. *J Clin Oncol*. 1999;17:2692-2699.
11. Curran WJ, Paulus R, Langer CJ, et al. Sequential vs concurrent chemoradiation for stage III non-small cell lung cancer randomized phase III trial RTOG 9410. *J Natl Cancer Inst*. 2011;103:1452-60.
12. Auperin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol*. 2010;28:2181-90.
13. Hanna N, Neubauer M, Yannoutsos C, McGarry R, Arseneau J, Ansari R, et al. Phase III study of of cisplatin, etoposide and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. *J Clin Oncol*. 2008;26:5755-60.
14. Vokes EE, Herndon JE, 2nd, Kelley MJ, Cicchetti MG, Ramnath N, Neill H, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. *J Clin Oncol*. 2007;25:1698-704.
15. Senan S, Brade A, Wang LH, et al. PROCLAIM:Randomized phase III trial of Pemetrexed-Cisplatin or Etoposide-Cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. *J Clin Onco*l. 2016;34:953-62.
16. Steuer CE, Behera M, Ernani V, et al. Comparison of Concurrent Use of Thoracic Radiation With Either Carboplatin-Paclitaxel or Cisplatin-Etoposide for Patients With Stage III Non-Small-Cell Lung Cancer: A Systematic Review. *JAMA Onco*l. 2017;3:1120-1129.
17. Zenke Y, Tsuboi M, Chiba Y, et al. Effect of Second-generation vs Third-generation Chemotherapy Regimens With Thoracic Radiotherapy on Unresectable Stage III Non-Small-Cell Lung Cancer: 10-Year Follow-up of a WJTOG0105 Phase 3 Randomized Clinical Trial. *JAMA Oncol*. 2021;7:904-909.
18. Atagi S, Kawahara M, Yokoyama A, et al. Thoracic radiotherapy with or without daily low-dose carboplatin in elderly patients with non-small-cell lung cancer: a randomised, controlled, phase 3 trial by the Japan Clinical Oncology Group (JCOG0301). *Lancet Oncol*. 2012;13; 671-678.
19. Stinchcombe TE, Zhang Y, Vokes EE, Schiller JH, Bradley JD, Karen Kelly K, et al. Pooled Analysis of Individual Patient Data on Concurrent Chemoradiotherapy for Stage III Non-Small-Cell Lung Cancer in Elderly Patients Compared With Younger Patients Who Participated in US National Cancer Institute Cooperative Group Studies. *J Clin Oncol*. 2017;35:2885-2892.
20. Bi N, Liu L, Liang J, Wu S, Chen M, Lv C, et al. Efficacy and safety of concurrent chemoradiotherapy in ECOG 2 patients with locally advanced non-small-cell lung cancer: a subgroup analysis of a randomized phase III trial. *BMC Cancer*. 2020;20:278. doi:10.1186/s12885-020-06780-x.
21. Bradley JD, Hu C, Komaki R, et al. Long-term results of NRG Oncology RTOG 0617: standard-versus high-dose chemoradiotherapy with or without Cetuximab for unresectable stage III Non-Small-Cell lung cancer. *J Clin Oncol*. 2020;38:706-14.
22. van den Heuvel M, Uyterlinde W, Vincent AD, de Jong J, Aerts J, Koppe F, et al. Additional weekly Cetuximab to concurrent chemoradiotherapy in locally advanced non-small cell lung carcinoma: efficacy and safety outcomes of a randomized, multi-center phase II study investigating. *Radiother Oncol*. 2014;110:126-31.
23. Kelly K, Chansky K, Gaspar LE, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. *J Clin Oncol*. 2008;26:2450-6.
24. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355: 2542–2550.
25. Socinski MA, Stinchcombe TE, T Moore DT, et al. Incorporating bevacizumab and erlotinib in the combined-modality treatment of stage III non-small-cell lung cancer: results of a phase I/II trial. *J Clin Oncol*. 2012;30:3953-9.
26. Chun SG, Hu C, Choy H, Komaki RU, Timmerman RD, Schild SE, et al. Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non-Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial. *J Clin Oncol*. 2017;35:56-62.
27. Teoh S, Fiorini F, George B, Vallis KA, Van den Heuvel F. Proton vs photon: A model-based approach to patient selection for reduction of cardiac toxicity in locally advanced lung cancer. *Radiother Oncol*. 2020;152:151-162.
28. Liao Z, Lee JJ, Komaki R, Gomez DR, O'Reilly MS, Fossella FV, et al. Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non-Small-Cell Lung Cancer Randomized Controlled Trial. *J Clin Oncol*. 2018;36:1813-1822.
29. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, McKenna C, Jones S, Cheadle EJ. et al. Acquired resistance to fractionated radiotherapy can be overcome by

concurrent PD-L1 blockade. *Cancer Res*. 2014;74:5458-5468.
30. Theelen WS, Peulen H, Lalezari F, et al. Effect of Pembroluzimab after steretactic body radiotherapy vs pembroluzimab alone on tumor response in patients with non-small cell lung cancer/results of the PEMBRO-RT phase 2 randomized clinical trial. *JAMA Oncol*. 2019;5:1276-82.
31. Shaverdian N, Lisberg AE, Bornazyan K, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. *Lancet Oncol*. 2017;18:895-903.
32. Spigel DR, Faivre-Finn C, GrayJE, et al. Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2022:40:1301-11.
33. Peters S, Felip E, Dafni U, Belka C, Guckenberger M, Irigoyen A, et al. Safety evaluation of nivolumab added concurrently to radiotherapy in a standard first line chemo-radiotherapy regimen in stage III non-small cell lung cancer-The ETOP NICOLAS trial. *Lung Cancer*. 2019;133:83-87.
34. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatine evaluation: a pooled analysis by the L ACE Collaborative Group. *J Clin Oncol*. 2008; 26:3552-3559.
35. Song WA, Zhou NK, Wang W, et al. Survival benefit of neoadjuvant chemotherapy in non-small cell lung cancer : an updated meta-analysis of 13 randomized trials. *J Thorac.Oncol*. 2010;5:510-516.
36. Felip E, Rosll R, Maestre JA, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early stage non-small-cell lung cancer. *J ClinOncol*. 2010;28:3138-3145.
37. Wu YL, John T, Grohe C, Majem M, Goldman JW, Kim SW, et al. Postoperative Chemotherapy Use and Outcomes From ADAURA: Osimertinib as Adjuvant Therapy for Resected EGFR-Mutated NSCLC. *J Thorac Oncol*. 2022;17:423-433.
38. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. *N Engl J Med*. 2022;386: 1973-1985.
39. Koshy M, Fedewa SA, Malik R, Ferguson MK, Vigneswaran WT, Feldman L, et al. Improved survival associated with neoadjuvant chemoradiation in patients with clinical stage IIIA(N2) non-small-cell lung cancer. *J Thorac Oncol*. 2013;8:915-22.
40. Thomas M, Rübe C, Hoffinecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol*. 2008;9:636-48.
41. Pless M, Stupp R, Ris HB, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. *Lancet*. 2015;386:1049-56.
42. Van Meerbeeck JP, Kramer E., Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst*. 2007;99:442-50.
43. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. 2009;374:379-86.
44. Eberhardt WE, Pöttgen C, Gauler TC, et al. Phase III Study of Surgery Versus Definitive Concurrent Chemoradiotherapy Boost in Patients With Resectable Stage IIIA(N2) and Selected IIIB Non-Small-Cell Lung Cancer After Induction Chemotherapy and Concurrent Chemoradiotherapy (ESPATUE). *J Clin Oncol*. 2015;33: 4194-201.
45. PORT Meta-analysis Trialists Group Postoperative radiotherapy in non-small cell lung cancer: systematic review and meta-analysis of individual data from nine randomized controlled trials. *Lancet*. 1998;352:257-63.
46. Le Pechoux C, Pourel N, Barlesi F, et al. An international randomized trial, comparing post-operative conformal radiotherapy (PORT) to no PORT in patients with completely resected non-small cell lung cancer (NSCLC) and mediastinal N2 involvement: Primary end-point analysis of LungART (IFCT-0503, UK NCRI, SAKK, NCT00410683). *Ann Oncol*. 2020; 31 (suppl-4): S1142-1215.10.106/annonc/annonc325.
47. Hui Z, Men Y, Hu C, Kang J, Sun X, Bi N, et al. Effect of Postoperative Radiotherapy for Patients With pIIIA-N2 Non-Small Cell Lung Cancer After Complete Resection and Adjuvant Chemotherapy: The Phase 3 PORT-C Randomized Clinical Trial. *JAMA Oncol*. 2021;7:1178-1185.
48. Dingemans A, Hendriks L, Berghmans T, Levy A, Hasan B, Faivre-Finn C, et al. Definition of synchronous oligometastatic non-small cell lung cancer–a consensus report. *J Thorac Oncol*. 2019;14:2109-19. doi:10.1016/j. jtho.2019.07.02.
49. Li D, Zhu X, Wang H, Qiu M, Li N. Should aggressive thoracic therapy be performed in patients with synchronous oligometastatic non-small cell lung cancer? A meta-analysis. *J Thorac Dis*. 2017;9:310–317.
50. Gomez DR, Blumenschein GR, Jr, Lee JJ, Hernandez M, Ye R, Camidge D., et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol*. 2016;17: 1672-1682.
51. Iyengar P, Wardak Z, Gerber DE, Tumati V, Ahn C, Hughes RS, et al. Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. *JAMA Oncol*. 2018;11;4(1):e173501. doi: 10.1001/ jamaoncol.2017.3501. Epub 2018 Jan 11.
52. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET Phase II randomized trial. *J Clin Oncol*. 2020;38:2830-2838.
53. Wang XS, Bai YF, Verma V, Yu RL, Tian W, Ao R, et al. Randomized Trial of First-Line Tyrosine Kinase Inhibitor With or Without Radiotherapy for Synchronous Oligometastatic EGFR-Mutated NSCLC. *J Natl Cancer Inst*. 2022;30:djac015. doi: 10.1093/jnci/djac015. Online ahead of print. PMID: 35094066.
54. Van Houtte P. Guest editor Controversies in Staging and Treatment of Locally Advanced Non small Cell Lung Cancer Second IASLC workshop on Therapy of Non-Small Cell Lung Cancer. *Lung Cancer*. 1991;7:1-132.
55. Van Houtte P. Guest editor Controversies in Staging and treatment of Locally Advanced Non-Small Cell Lung Cancers Third IASLC Workshop on therapy of Non-Small Cell Lung Cancer. *Lung Cancer*. 1994; 11 Suppl 3: S91-111.
56. Van Houtte P. Guest editor Proceedings of the Fourth IASLC Workshop on Controversies in staging and combined treatment modalities in lung cancer. *Lung Cancer*. 1997;l 17 Suppl 1:1-179.
57. Van Houtte P. Guest editor IASLC Workshop Progress and guidelines in the management of non–small cell lung cancer 2003; 42 Suppl 1:S1-92.
58. Mornex F, Van Houtte P. Guest editors Treatment optimization for lung cancer from classical to innovative procedures. Edited by Elsevier, Paris 1998.

22

LUNG CANCER - ADVANCES IN SUPPORTIVE CARE

Richard J. Gralla,[1] **Jennifer Temel,**[2] **Silvia Novello,**[3] **Michael Boyer,**[4] **and Jean A. Klastersky**[5] | [1]Albert Einstein College of Medicine, Bronx New York, USA; [2]Massachusetts General Hospital, Boston, USA; [3]University of Turin, Turin, Italy; [4]Chris O'Brien Lifehouse, New South Wales, Australia; [5]Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

Supportive care is integral in thoracic oncology and has been emphasized by the IASLC since its inception. Thoracic oncologists in all disciplines have been leaders in supportive care research and have helped establish many of the approaches that are vital in caring for patients with all malignancies. Several definitions of this term 'supportive care' exist, including that used by the Multinational Association for Supportive Care in Cancer (MASCC): "the prevention and management of the adverse effects of cancer and its treatment. This includes management of physical and psychological symptoms and side effects across the continuum of the cancer experience."[1] Entire professional organizations and numerous publications are dedicated to supportive and palliative care. This makes it difficult to select only a few topics to include in this chapter. To narrow the focus, Table 1 illustrates how 660 patients with lung cancer ranked a set of 20 issues.[2] Notably, the top four issues identified in the survey are not symptoms of cancer but are more global concerns. The authors of this chapter endeavored to address many issues frequently found in patients with lung cancer and in its treatment.

Table 1. Patient Rated Issues of Importance.[a]

Supportive Care and Quality of Life Issues as Rated by Importance by 660 Patients with Lung Cancer	Percent of Patients Ranking Issues as Either "Very Important" or "Important"[b]
Quality of life	96%
Maintaining independence	95%
Being able to perform normal activities	94%
Being able to sleep	93%
Not being fatigued	91%
Not being a burden to others	89%
Not having shortness of breath	85%
Not having pain	83%
Not being depressed	81%
Symptom distress	78%
Appetite	78%
Financial concerns	76%
Anxiety	76%
Hemoptysis	75%
Spiritual concerns	64%
Cough	63%
Hoarseness	63%
Problems with urination	62%
Meaning of life	61%
Sexual difficulties	47%

[a]See reference 2
[b]Using a 5-point scale ,in which "Very Important" is the highest rank and "Important" is the second highest rank

IMPACT OF SUPPORTIVE CARE ON QUALITY OF LIFE AND SURVIVAL

Recently, there has been increased recognition from the cancer care community about the importance of focusing on supportive care for patients with lung cancer.[3,4] While data describing the challenging physical symptoms and poor quality of life experienced by patients with lung cancer has been available for several decades, we now have evidence-based interventions that improve the experience and outcomes of these patients.[5,6] Despite the growing scholarly literature demonstrating that symptom monitoring and palliative care interventions can improve patients' quality of life and survival, access to and uptake of these interventions remain low.[7] Thus, our research efforts must now focus on developing and testing scalable and disseminable interventions that can reach larger numbers of patients with lung cancer.

The major scientific discoveries in supportive care for lung cancer have focused on the integration of symptom monitoring and palliative care interventions, both of which have been shown to impact quality of life and survival. Quality of life and survival are correlated in patients with cancer, including those with lung cancer, so it is not surprising that interventions that enhance symptoms and quality of life lead to improved cancer outcomes.[8,9]

In 2017, Denis and colleagues published the results of a randomized trial of a web-based symptom monitoring intervention versus usual care among patients with low symptom burden and non-progressing small cell lung cancer (SCLC) and stage II through IV non-small cell lung cancer (NSCLC).[10] Patients assigned to the intervention reported their symptoms weekly through a web-based tool, which was then reviewed by the clinical team. The study demonstrated that those assigned to the intervention group had significantly longer survival than those receiving usual care.[11]

More recently, Dai and colleagues conducted a randomized trial of a symptom management intervention based on patient-reported outcomes in the post-operative setting or for patients undergoing curative lung cancer surgery.[12] Participants self-reported their symptoms daily during their hospitalization and twice-weekly after discharge for up to four weeks. Alerts were sent to surgeons for patients with significant symptoms in the intervention group. Those assigned to the intervention experienced lower symptom burden and fewer complications compared to the control group.

Based upon these and other trials in patients with other cancer types, symptom monitoring interventions hold promise for improving symptoms, quality of life, and survival for patients with lung cancer.

Early palliative care for patients with advanced lung and other cancers has been shown to improve a wide range of outcomes, including quality of life, care delivery at the end of life, coping, and possibly survival.[13-16] In 2010, Temel and colleagues demonstrated that early involvement of specialty trained palliative care clinicians, soon after a diagnosis of metastatic non-small-cell lung cancer, improved patients' quality of life at 12 months.[14] An unplanned analysis this study also showed prolonged survival for those receiving early palliative care compared to usual care.[13]

Follow-up trials in patients with advanced lung cancer and other advanced cancers have confirmed the benefits of early palliative care for improving symptoms and quality of life. However, the availability of and access to palliative care remains limited.[15,17-20]

PREVENTING EMESIS ASSOCIATED WITH CANCER TREATMENT

Marked improvements in preventing emesis have occurred over the history of the IASLC. This resulted from an increased understanding of the problem of emesis and the physiologic pathways involved. Antiemetic approaches reflect targeted therapy in supportive care. The American Society of Clinical Oncology (ASCO) recently noted in its 50th anniversary that progress in preventing emesis was among the top ten achievements

in oncology over that period. Thoracic oncologists incorporated antiemetic studies into anticancer research and have contributed greatly to this improvement in patient care.

In the late 1970s and early 1980s, studies demonstrated improved methodology for studying this problem and guided research in appropriate agents. As cisplatin became increasingly used in advanced lung cancer and in adjuvant therapy, it became clear that this agent caused emesis in 100% of patients.[21-23] Thus, a target population was easily identified for clinical trials, as cisplatin became part of first-line regimens in both NSCLC and SCLC.[22,24,25]

While dopamine type-2 receptor antagonists (RAs) had some antiemetic value, little activity was found against cancer chemotherapy with phenothiazines and butyrophenones.[26] Unlike these agents, the dopamine RA metoclopramide does not produce the hypotension, and its dose can be escalated. Phase I, II and III studies with metoclopramide showed safety at much higher doses (2 mg/kg/dose); these doses resulted in a marked reduction in cisplatin-induced emesis, with 40% of patients having no emesis.[26,27] This complete control rate increased to about 60% when dexamethasone was added to high-dose metoclopramide.[28] An unexpected finding was delayed emesis, occurring a day or more after chemotherapy in some patients.[29]

These improvements were appreciated; however, the regimens were cumbersome, and it was not understood why high doses of metoclopramide were required. Basic research demonstrated that when given in higher doses, the antiemetic effect of metoclopramide was primarily mediated via serotonin type-3 receptors ($5HT_3$), rather than via dopamine pathways.[30] This led to the development of highly specific $5HT_3$ receptor antagonists, such as ondansetron, granisetron, and palonosetron, which eliminated dopaminergic side effects while preserving antiemetic efficacy.[31,32]

Table 2. An Antiemetic Guidance for Systemic Treatment in Thoracic Oncology.

Risk Category*	Example Treatment Regimens in Thoracic Oncology**	Example Antiemetic Regimens***
High (Risk > 90%)	Cisplatin + Pemetrexed Cisplatin + Etoposide Cisplatin + Irinotecan Cisplatin + Gemcitabine Cisplatin + Vinorelbine	$5HT_3$-RA + NK_1-RA + Dexamethasone[a] ± Olanzapine[b]
Moderately High[c] (Risk 60 – 90%)	Carboplatin + Paclitaxel	$5HT_3$-RA + NK_1-RA + Dexamethasone[a]
Moderate (Risk 30 – 60%)	Docetaxel (single agent)	$5HT_3$-RA + Dexamethasone[a]
Low (Risk 10 – 30%)	Vinorelbine (single agent) Gemcitabine (single agent) Etoposide (single agent)	Single antiemetic agent, generally a corticosteroid (such as dexamethasone[a]) ***or*** a $5HT_3$-RA
Minimal (Risk <10%)	Pembrolizumab (single agent) Nivolumab (single agent)	No antiemetic agent typically needed

* Estimated risk without effective antiemetics

** All treatment regimens are with or without checkpoint inhibitors. If a checkpoint inhibitor is added, the antiemetic regimen does not change

*** Several studies indicate that just a single dosing of an antiemetic regimen, immediately before chemotherapy can result in similar efficacy to multiple days (see reference 37 as an example). Importantly, studies indicate that planned follow-on treatment with 5HT3-RAs (such as ondansetron) is not necessary and can be expensive. It is not clear that 5HT3-RA agents are more effective for as needed or breakthrough use than older generally less expensive agents such as metoclopramide or olanzapine.

[a]Dexamethasone is the most frequently used corticosteroid as an antiemetic. Other corticosteroids in equivalent doses, either oral or IV, can be used. Dexamethasone doses vary from 8 mg to 12 to 20 mg (the latter range with cisplatin). While multiple days can be used for delayed emesis, several studies indicate that just a single corticosteroid dose in a combination regimen gives similar efficacy. Delayed emesis is primarily an issue for high or moderate risk categories only. If a corticosteroid is already being used for other purposes (as with taxanes) either that corticosteroid, or the antiemetic dexamethasone dosing should suffice, and it is not necessary to use both.

[b]Dosing of olanzapine (it is only used orally as an antiemetic) is not completely defined. Ten mg is the most commonly used dose, but some trials indicate that 5 mg can be effective. Four-day regimens are effective, but other regimens have been tried, including as low dosing as one day. Little data is available for use with carboplatin.

[c]This category would also include older regimens, such as cyclophosphamide + doxorubicin + vincristine (CAV). The addition of olanzapine can be considered.

Abbreviations: RA = receptor antagonist; $5HT_3$ = serotonin type 3 (RA agents such as granisetron, ondansetron, palonosetron and others); NK_1 = neurokinin type 1 (RA agents such as aprepitant, fos-aprepitant, and netupitant).

Studies demonstrated that just one prechemotherapy administration of a combination of a $5HT_3$-RA with dexamethasone enhanced emetic control over either agent used alone.[32] This combination remained the standard until the introduction of neurokinin type-1 RAs (NK_1-RA), such as aprepitant. When added to $5HT_3$-RAs plus dexamethasone, the prevention of acute (first 24 hours) and delayed emesis (24 to 120 hours) reached 80% to 90% and 60% to 70%, respectively.[33] Recently, the addition of oral olanzapine contributed to further improvement in preventing vomiting and nausea.[34]

These same agents are useful in preventing emesis due to radiation therapy (RT). Their use is guided by the size of the RT portal and the dose administered.[35] While $5HT_3$-RAs and NK_1-RAs are useful in preventing postoperative emesis, a recent prospective trial demonstrated that a single intraoperative dexamethasone dose was effective and had no negative side effects.[36]

Current antiemetic research focuses on making the control of emesis practical and acceptable. Studies show that a single dose of a $5HT_3$-RA + NK_1-RA + dexamethasone is equivalent in the control of both acute and delayed emesis to multiple days of treatment.[37] Thus, other than the addition of olanzapine, all antiemetics can be given immediately prior to chemotherapy. Intravenous and oral dosing give similar results, and dosage formats combining NK_1-RAs with $5HT_3$-RAs enhance convenience.[38,39]

Table 2 outlines current antiemetic prevention strategies, using examples from thoracic oncology treatment regimens, and reflects suggestions listed in several guidelines.[40-42] Work on antiemetic guidance in all economic regions continues.[43]

FEBRILE NEUTROPENIA – A NARRATIVE EVALUATION OVER HALF A CENTURY

Febrile neutropenia (FN), which refers to a high fever in a patient with low levels of neutrophils, has been a significant challenge for oncologists for decades (Table 3). It is also one of the first examples of structured supportive care (e.g., an approach to improve the quality of life of patients receiving cancer treatment).

Table 3. Definition of Febrile Neutropenia

Febrile neutropenia (FN) is defined as an oral temperature of >38.3°C or two consecutive readings of >38.0°C for 2 hours and an absolute neutrophil count (ANC) of <0.5 x 10^9/l, or expected to fall below 0.5 x 10^9/l.

In the 1960s, aggressive chemotherapy used to be prescribed almost exclusively to patients with acute leukemia. The resulting thrombocytopenia and granulocytopenia was associated with major complications and frequent death. At that time, the mortality of Gram-negative bacteremia in such patients was over 90%.[44]

In 1966, Bodey et al. established the close relationship between the severity and duration of granulocytopenia and the risk of serious infection.[45] That observation led to a major effort to protect vulnerable neutropenic patients through strict isolation and the administration of non-absorbable antibiotics. However, these procedures were cumbersome and demanding for both patients and medical staff; moreover, they led to the emergence of resistant bacteria.[46] As a result, the "isolation-decontamination" approach did not become popular.

A major advance in the management of FN came from the concept of empiric antimicrobial therapy introduced by Schimpff et al.[47] Their study, although limited in terms of numbers of patients, clearly showed the benefits of not waiting for microbiological documentation of infection in severely neutropenic patients before starting therapy, as well as the effectiveness of using a combination of potentially synergic antibiotics.

While the concept of early empirical therapy was never formally validated in a controlled investigation, its efficacy is overwhelmingly obvious. The value of synergistic antibiotic combinations has been confirmed in many studies and was widely used until the advent of broad spectrum, super-potent agents, which made monotherapy acceptable for empiric treatment of FN.

Early in the 1980s, an increasing number of patients with solid

tumors—including patients with bronchial carcinomas—receiving chemotherapy and it became clear that the approach to FN in those patients might be different from that inspired from patients with acute leukemia. The concept of early empiric antimicrobial therapy was not being challenged, but clinicians started to question whether all these patients with solid tumors and relatively shorter and less pronounced neutropenia required high doses of intravenous antibiotics and prolonged hospitalization.

In 2000, MASCC published a scoring system to predict severe complications in patients with FN (Table 4), identifying those with less than 5% risk of such outcomes, and not surprisingly many whom are actually treated for solid tumors.[48] Following this, many studies evaluated the potential efficacy of orally administered antibiotics, namely broad-spectrum quinolone, in managing FN in low-risk patients, often with encouraging results. Subsequently, investigations explored whether those patients might be discharged early or even treated as outpatients. Of course, this simplified approach implies that a patient with FN is not only adequately evaluated throughout their condition as being at low risk of complications but also has good compliance, adequate surveillance, and easy access to specialized care throughout the duration of FN. Despite these limitations, the simplified approach of orally administered antibiotics and early discharge can be considered standard practice.[49]

A major achievement in preventing FN has been the introduction of the granulopoietic colony-stimulating factors (G-CSF). These agents stimulate granulopoiesis and reduce the severity and duration of neutropenia following chemotherapy. Numerous studies have clearly established the efficacy of G-CSF in reducing the incidence by at least 50% after chemotherapy, with some meta-analyses confirm a reduction in mortality.[50] There are no major short-term complications associated with the use of G-CSF.

Unfortunately, indications for the use of G-CSF has been restricted by cost-benefit considerations; nonetheless, it is accepted that G-CSF should be given after each course of chemotherapy to all patients with a FN risk greater than 10%, especially when at least one significant co-morbidity is present, which is typically the case, namely in patients with lung cancer.

Therefore, it took over 50 years of intense and dedicated clinical research to overcome a highly lethal complication associated with chemotherapy. Eventually, we succeeded in changing it into a preventable and treatable condition, with its management codified in many international consensuses. As a result, it no longer poses a major threat, at least for most patients with solid tumors.[51]

Today, several practical lessons emerge from the management of FN:

1. FN is preventable, and the liberal use of G-CSF can significantly reduce its incidence.
2. Prompt treatment is essential. When FN is occurs, it should be treated as a medical emergency. Early administration

Table 4. MASCC Febrile Neutropenia Risk Index.

Characteristics	Score
Burden of illness: no or mild symptoms	5
Burden of illness: moderate symptoms	3
Burden of illness: severe symptoms	0
No hypotension (systolic BP > 90 mmHg	5
No chronic obstructive pulmonary disease	4
Solid tumour/lymphoma with no previous fungal infection	4
No dehydration	3
Outpatient status (at onset of fever)	3
Age < 60 years	2

Patients with scores ≥21 are at low risk of complications. Points attributed to the variable "burden of illness" are not cumulative. The maximum theoretical score is therefore 26. The serious medical complication rate in low-risk cases is estimated to be 6% and the mortality rate to be below 1%.
BP = blood pressure.

of effective antimicrobial therapy is crucial to prevent complications.

3. A tailored approach is imperative for personalized care. Furthermore, this approach can be adjusted according to the risk of complications. Decisions regarding the use of oral vs intravenous antibiotics and in-hospital vs outpatient management require clinical judgement about a patient's overall status, compliance with medical instructions, and the quality of their psycho-social environment.

Finally, while international recommendations provide valuable guidance, seeking an expert opinion is advisable in cases of uncertainty.

PAIN MANAGEMENT, INCLUDING POST-OPERATIVE AND OPIOID CONSIDERATIONS

Recent evidence suggests that pain affects around 50% of cancer patients, regardless of tumor type or disease stage, with lung cancer patients experiencing the highest prevalence.[52] This pain is often heterogeneous, originating from neuropathic and inflammatory components, and inevitably leads to a diminished quality of life (QoL). Nevertheless, more than 40% of cancer patients currently do not receive adequate analgesic therapy.[53]

Comprehensive cancer pain management includes the use of pharmacological, non-pharmacological, integrative, and interventional therapies.[54] Opioids, available in both immediate and slow-release preparations, are typically the first choice in pharmacological management, particularly in advanced disease stages. Conversely, opioids alone are often ineffective in the treatment of neuropathic cancer pain (NCP), necessitating the addition of adjuvant analgesics.[55] These may include antidepressants, calcium channel ligands (gabapentin and pregabalin), and topical lidocaine. Nonetheless, questions remain about the safety and effectiveness of opioids in long-term survivors of cancer. Increasing evidence supports the potential role of cannabinoids in managing chronic pain, including neuropathy.[56]

Pain management is generally guided by a patient's perception of intensity level, often measured by self-reported scales. These scales include numerical rating scales (NRS), face pain scales (FPS), and visual analogue scales (VAS). However, due to inherent limitations, there is a growing need for reliable indicators of pain intensity. Among these, polymorphisms of inflammatory cytokines, such as IL6, TNF-α, IL8, and nuclear factor kB inhibitor α, have been significantly associated with pain intensity in lung cancer patients.[57-59] Additionally, emerging biomarkers, including neuroimaging and pharmacogenetic parameters, have shown promise in predicting clinical response to opioids. Further investigation in prospective studies is warranted to validate these methods.[60]

In addition to the cancer itself, pain may be induced by diagnostic procedures or anti-tumor treatments. Lung cancer patients undergoing thoracic surgical procedures are at high risk of postoperative pain, with reports indicating its occurrence in up to 39% of cases after curative intent surgery. Post-thoracotomy pain syndrome (PTPS) affects between 25% and 60% of lung cancer patients undergoing thoracic surgery and is probably related to a combination of both neuropathic and myofascial insidious pain, although specific pathogenic mechanisms underlying PTPS remain unclear.[62,63] The National Comprehensive Cancer Network (NCCN) guideline (Version 8. 2017) recommends video-assisted thoracoscopic surgery (VATS) lobectomy as the preferred approach for the surgical treatment of early-stage NSCLC.[64] This recommendation is based on improvements in objective perioperative surgical and quality of life (QoL) outcomes, including a reduction in perioperative pain.[65-69] However, to date, there is no universally recommended standard treatment for post-operative pain following either VATS or thoracotomy.

While, opioid-based postoperative analgesia can provide adequate pain control, it may also be associated with several adverse effects and the potential exacerbation of immunosuppression.[70,71]

Alternative analgesic approaches aimed at reducing the use of opioids in the post-surgical setting include intercostal catheter administration of ropivacaine, enhanced recovery protocols, and novel combinations of analgesics and non-steroidal anti-inflammatory drugs.[72-74]

Recently, a novel mixed agonist-antagonist opioid analgesic, dezocine, has exhibited unique properties by acting as a stimulating factor on the immune system, which may support its future application in postoperative pain management for lung cancer patients.[75] The ideal future scenario would involve achieving adequate postoperative pain control while minimizing immunosuppression and associated side effects.

PLEURAL EFFUSION

Pleural effusion is a common complication of lung cancer and other intrathoracic malignancies. It is the source of substantial morbidity and may indicate a poor prognosis.[76,77] The 7th edition of the TNM classification of lung cancer acknowledge this by classifying pleural effusions as M1 disease for the first time.[78] Over the past 20 to 30 years, the management of pleural effusions has evolved significantly, although most available data relate to the management of pleural effusions in general rather than specifically for primary intrathoracic malignancy.

Initially, thoracentesis was the major approach to managing pleural effusion, often performed as both a diagnostic and therapeutic procedure. Unfortunately, thoracentesis alone is associated with a high rate of recurrence of effusion and is only suitable as a definitive management strategy for patients with an extremely poor prognosis.

Consequently, the use of chemical pleurodesis has become an important part of longer-term management. This procedure creates pleural inflammation, leading to the obliteration of the pleural space. Pleurodesis can be performed surgically via thoracoscopy or medically via an intercostal catheter. Irrespective of the approach, the key consideration is the ability of the underlying lung to re-expand and allow the visceral and parietal pleura to come in contact with each other. Thus, assessing the lung's ability to expand is recognized as a first step in this procedure.

Over the past 45 years, a wide range of sclerosants has been evaluated. A network meta-analysis of randomized controlled trials (RCTs) suggests that talc is the most effective sclerosant, with little difference between the use of talc slurry or talc poudrage in terms of recurrence of effusion or patient-reported control of dyspnea.[79]

Indwelling pleural catheters (IPC) were introduced in the early 1990s as an alternative to chemical pleurodesis.[80,81] They are designed to remain in situ long-term, allowing for repeated drainage of effusions and long-term outpatient management.[82] IPCs are preferred when lung re-expansion is not expected to occur.[77] In a proportion of patients, IPCs induce spontaneous pleurodesis, and recent studies suggest that this may be related to the frequency of drainage, with daily drainage associated with higher rates pleurodasis.[83]

IPCs can also facilitate outpatient pleurodesis and the instillation of a talc slurry. When compared to placebo, this approach increased the rate of pleurodesis from 23% to 43% at 5 weeks.[84] The major disadvantage of IPCs is a higher rate of infection compared to pleurodesis, often necessitating the removal of the catheter.

Recent published guidelines can help direct management approaches.[85,86]

BONE METASTASES

Bone metastases occur in 30% to 40% of patients with advanced lung cancer and may result in pain and other skeletal-related events (SREs).[87] The approach to managing bony metastatic disease focuses on pain treatment and the prevention of SREs. Similar to other areas of supportive care, much of the data relates to the management of various malignancies rather than specifically lung cancer.

Optimal management of bony metastatic disease requires a multidisciplinary team. This approach has become increasingly important as treatment options have expanded. In addition to radiation and medical oncologists, radiologists and orthopaedic surgeons play

crucial roles.

When there is an impending fracture, prophylactic surgery is preferred over repairing fractured bones. Imaging to assess fracture risk and orthopaedic consultation are essential components of management.

Radiation therapy has long been a mainstay in the local treatment of bony metastases. There has been considerable interest in the dose and fractionation schedule, with meta-analyses showing no relationship between palliation and the number of fractions.[88,89] However, the need for retreatment was higher with single fractions, which is a consideration in an era when survival may be increasing due to improvements in systemic therapy.

Another approach to treat bone involves radioisotopes, such as samarium, strontium, or rhenium.[90] In lung cancer, these agents reduced pain in approximately 65% of patients, though there is limited information on the duration of pain control.

Bisphosphonates were developed to reduce bone turnover, impacting hypercalcemia, and osteolysis caused by metastatic cancer. Despite many trials involving agents like clodronate, ibandronate, and zoledronate, relatively few included lung cancer patients.[90] In a subgroup analysis of the largest of these trials, zoledronate was shown to reduce the risk of a first SRE in patients with NSCLC by 32%, although there was no impact on survival.[91]

The RANK ligand antagonist denosumab has been compared to zoledronate for the prevention of SREs in a limited number of patients with NSCLC.[92] Denosumab was found to be non-inferior to zoledronate in time to the first SRE and the cumulative number of SREs and is widely used as an alternative to bisphosphonates. Despite the relatively scant data, the use of bisphosphonates or denosumab is recommended in guidelines.[4,93]

CANCER CACHEXIA, SARCOPENIA, AND ANOREXIA

These issues are often clinically expressed as wasting or frailty and are common in advanced thoracic malignancies. Studies have indicated that cancer cachexia can affect up to 60% of patients with lung cancer and is associated with diminished quality of life and markedly poorer survival.[94,95] Similar negative findings have also been reported in breast cancer.[96]

Cancer cachexia has been characterized by the late Kenneth Fearon as a "multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment."[97]

Therapeutic approaches are now based on an enhanced molecular metabolic understanding and recognize that in advanced lung cancer, nutritional support is not sufficient.[98,99] Newer approaches focus on interfering with atrophy signaling (myostatin/activin inhibitors, anti-TNFα, anti-IL6) and stimulating hypertrophy, including ghrelin-analogs and androgenic-receptor modulators.[100, 101]

International groups have enumerated objective aspects of cancer cachexia that help with identifying such patients (Table 5).[93] Neither low BMI nor weight loss alone is sufficient. While DEXA and MRI can accurately measure skeletal muscle mass, there are strong correlations that can readily be estimated from already obtained computed tomography (CT) scans, measured at the L3 level, and even at L1 on essentially all chest CTs.[102,103] Such assessment can be useful in patient management and in

Table 5. Internationally Accepted Minimum Thresholds For Diagnosing of Cancer Cachexia.

1. BMI <20 and weight loss of >10%*
2. Unintended weight loss of >5% to >15% in the past 6 months
3. Serum albumin of <30g/l (3.0 g/dL)
4. A diagnosis of sarcopenia by dual energy X-ray absorptiometry **

*While BMI is a useful and simple screening tool, patients with high BMI can have sarcopenia.
** Gold standards, such as MRI and DEXA, can be highly accurate for measuring skeletal muscle mass, but measurements using CT can be practical and useful as well.[94,103]
Reference: See reference 97.

clinical trials.[96]

Recent large randomized trials in patients with lung cancer have utilized methods of stimulate hypertrophy, using either the ghrelin-analog, such as anamorelin, or the selective androgen-receptor modulator, such as enobosarm.[100] Both agents were associated with gains in weight, appetite, and lean body mass when compared with placebo. Findings were inconsistent when evaluating functional measures such as handgrip strength or stair-climbing speed, although the applicability of these as valued or sensitive measures of patient functioning in this population is unclear. As of this writing, anamorelin has recently been approved in Japan. These mechanistically-based agents represent important early steps which should encourage targeted approaches for improving these key issues.

EXERCISE

Physical activity has been associated with health benefits in several conditions characterized by chronic inflammation, including lung cancer. The World Health Organization recommends 150 to 300 minutes of moderate-intensity aerobic physical activity per week and resistance training of major muscle groups twice a week for adults.[104] In cancer patients, the main physical exercise schedules investigated involved 2 to 3 sessions per week of 30 to 90 minutes of either aerobic or resistance training. However, there are currently no standard physical activity programs recommended for cancer patients. Drawing evidence-based conclusions is challenging because randomized clinical trials have investigated different interventions in varying disease settings with diverse endpoints.

Despite such limitations, several potential advantages have been reported in the literature:

- **Prevention:** Higher weekly physical activity reduced the incidence of lung cancer, regardless of a patients' body max index (BMI) and smoking status.[105]
- **Non-metastatic setting:** Higher levels of physical exercise were associated with lower cancer-related mortality.[106]
- **Post-surgical setting:** Some physical activity programs appeared to decrease the incidence of pulmonary complications.[107]
- **Adjuvant setting:** A supervised exercise program improved both fatigue and emotional well-being, although it did not affect patients' quality of life.[108]
- **General benefits:** Some trials showed that physical exercise may reduce inflammation status, BMI, percentage of visceral fat, sarcopenia, and risk of cachexia, suggesting both IL-6 and IFN-γ may be useful as inflammatory surrogate biomarkers during physical exercise programs.[109-112] The reduction of systemic chronic inflammation mediated by physical exercise may also translate into an enhanced immune-system response.[113]

Prospective studies are imperative to define the efficacy, type, and duration of physical exercise interventions for specific treatment settings, including those involving lung cancer survivors.

PSYCHOLOGICAL CONSIDERATIONS OF LUNG CANCER CARE

The psychological burden of a serious cancer diagnosis, including depression with a risk of suicide and anxiety, has been well established. However, few interventions have been developed to improve the psychological well-being of patients with lung cancer.[114] Patients living with advanced lung cancer experience significant psychological distress, and those treated with curative intent or in the survivorship phase of their illness also face anxiety, including fear of cancer recurrence and depression.[115] Despite an extensive body of literature demonstrating the efficacy of behavioral strategies to improve psychological well-being for cancer survivors, patients with lung cancer have generally not been included in these trials.[116,117] Some interventions have specifically focused on addressing psychological distress or included measures of depression and anxiety as outcomes, showing positive results in patients with advanced lung cancer.

Many trials of psychological

interventions for patients with advanced cancer have included patients with multiple types of cancers, including lung cancer. Psychological interventions at the time of diagnosis, for those living with advanced disease, and for patients at the end of life have demonstrated a range of positive outcomes, such as improvements in depression, anxiety, distress, and self-efficacy.[118] Several clinical trials in patients with advanced lung cancer have studied dyadic interventions for patients and their caregivers, resulting in improved psychological well-being for both groups.[119,120]

In 2014, Walker and colleagues adapted their successful collaborative care model, which integrates depression management into cancer care for patients with good prognoses, to patients with lung cancer. They conducted a randomized trial of the collaborative care model for patients with lung cancer and major depression.[212,122] The study demonstrated that patients assigned to the collaborative care model had significantly lower depression and anxiety and improved quality of life compared to those receiving usual care. Similar to interventions focused on quality of life, access to mental health clinicians with experience delivering psychological care to patients with cancer is limited. Therefore, both collaborative care models and interventions using mobile health technology may be promising strategies to promote the psychological well-being of patients with lung cancer.

Several palliative care interventions for patients with advanced lung cancer have demonstrated improvements in depression with early palliative care.[13-15] Coping is another important psychological outcome in patients with advanced cancer.[123,124] The early palliative care model studied by Temel and colleagues has been shown to increase the use of approach-oriented coping strategies, such as positive reframing, and to decrease the use of avoiding coping, such as denial.[125] Additionally, the use of approach-orientated coping was associated with better quality of life and lower depression symptoms.[126] Thus, it is important that palliative care clinicians integrate strategies to assess and promote coping, including cognitive, behavioral, emotional, and existential coping, into their practice when caring for patients with lung cancer.[127]

QUALITY OF LIFE ASSESSMENT

Can quality of life (QL) be defined sufficiently for clinical trials and practice? While defining QL can be controversial, most can agree on its components or dimensions as a multidimensional concept. Common dimensions include physical, functional, psychological, social, and spiritual aspects. Capturing information from all of these differentiates QL from a unidimensional aspect, such as performance status. Performance status (KPS, ECOG scales) captures only the functional domain.[128-130] While measuring side effects and PS is helpful and often included as part of QL analysis, neither is a surrogate for QL.

Focusing on the reason for evaluating QL in a trial can help in selecting the instrument used. Different instruments may capture each dimension in detail or may concentrate specific areas while assessing others more globally. QL questionnaires are typically disease- and cancer-specific. QL measures require psychometric testing, which evaluates feasibility, acceptability, reliability, and validity using predetermined criteria.[131] Validated instruments have been available for years, including EORTC, FACT, and LCSS measures.[132] Appropriately, these measures were designed for evaluating patients with active lung cancer; however, it is not clear if they are valid for patients with very early lung cancer or with asymptomatic diseases.[133] Research in this area is needed.

Analysis of QL presents several problems. As most studies incorporate QL into clinical trials in which the primary endpoint is survival, the study may not be powered sufficiently powered to address QL considerations. QL assessments are troubled by missing data for two reasons. First, data may not be collected. Statisticians have labored over models to correct for such missing data. Rather than making adjustments, it is better to empha-

size prospectively with investigators the need to ensure these data are collected with the same vigor as imaging and blood tests.

The second source of missing information occurs when a patient goes off study or dies. Patients with lower QL at the outset of a trial have decreased survival with poorer prognostic parameters and drop out of studies earlier. Trials need to follow all patients on comparative treatment arms for the same length of time and not just for the duration of treatment, which differs among patients. Even after treatment ends, the prior intervention may continue to affect QL, such as delayed effects of RT or neuropathy from chemotherapy. It is important to continue assessment over a pre-specified time of interest or for the life of the patient.[134]

How should QL data be presented? In patients with advanced disease in comparative trials, improvement may not be the best parameter; maintaining a reasonable level of QL may be desirable. Overall, testing the degree of QL maintained for all patients in each comparison group can demonstrate differences among treatment groups. Presentations of results need to be clear and focus on aspects with which oncologists are familiar.

Incorporating QL into daily oncology practice enhances our treatment of thoracic malignancies. With only a small amount of additional study, accurate evaluation of QL can become an integral part of cancer trials and cancer care.

CONCLUSION

The last few years have seen remarkable progress in the approach to thoracic malignancies. This progress includes a much wider application of supportive care measures to maintain or improve quality of life and to prevent the side effects of treatment. As illustrated in this chapter, significant challenges remain in many areas, including attention to aspects of patient and family mental health issues. Preventing side effects of chemotherapy, such as neutropenia and emesis, helps reduce suffering for many individuals in ways that were not possible in the past. With the development of newer targeted and immune-oncology therapies, side effects are now seen that are mediated by mechanisms that were not previously an issue. Specific approaches to these issues can be found in chapters in this book that address those treatment modalities.

While new treatments present newer challenges in supportive care, the symptoms of lung cancer on presentation and many of the quality of life, meaning of life, and psychological concerns of patients and families endure. Continued attention to expertise and research in supportive care will benefit all individuals with thoracic malignancies.

References

1. MASCC. (n.d.). Retrieved from https://www.MASCC.org
2. Gralla RJ, Hollen PJ, Msaouel P, et al. (2014). An evidence-based determination of issues affecting quality of life and patient-reported outcomes in lung cancer: Results of a survey of 660 patients. *J Thorac Oncol*. 9, 1243-1248. PMID: 25122420.
3. Temel JS, & Jacobsen PB (2020). Palliative care in oncology: Continuing to build the evidence base and disseminate effective care models. *J Clin Oncol*. 38(9), 849-851. https://doi.org/10.1200/JCO.19.01069
4. Temel JS, Petrillo LA, & Greer JA (2022). Patient-centered palliative care for patients with advanced lung cancer. *J Clin Oncol.* 40(6), 626-634. https://doi.org/10.1200/JCO.21.01710
5. Lutz S, Norrell R, Bertucio C, et al. (2001). Symptom frequency and severity in patients with metastatic or locally recurrent lung cancer: A prospective study using the lung cancer symptom scale in a community hospital. *J Palliat Med*. 4(2), 157-165.
6. Tishelman C, Petersson LM, Degner LF, & Sprangers MA (2007). Symptom prevalence intensity and distress in patients with inoperable lung cancer in relation to time of death. *J Clin Oncol.* 25(34), 5381-5389. https://doi.org/10.1200/JCO.2006.08.7874
7. Sullivan DR, Chan B, Lapidus JA, et al. (2019). Association of early palliative care use with survival and place of death among patients with advanced lung cancer receiving care in the Veterans Health Administration. *JAMA Oncol*. https://doi.org/10.1001/jamaoncol.2019.3105
8. Montazeri A, Milroy R, Hole D, McEwen J, & Gillis CR (2001). Quality of life in lung cancer patients: As an important prognostic factor. *Lung Cancer*. 31(2-3), 233-240. https://doi.org/10.1016/s0169-5002(00)00179-3
9. Maione P, Perrone F, Gallo C, et al. (2005). Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: A prognostic analysis of the multicenter Italian lung cancer in the elderly study. *J Clin Oncol*. 23(28), 6865-6872.
10. Denis F, Lethrosne C, Pourel N, et al. (2017). Randomized trial comparing a web-mediated follow-up with routine surveillance in lung cancer patients.

J Natl Cancer Inst. 109(9). https://doi.org/10.1093/jnci/djx029
11. Denis F, Basch E, Septans AL, et al. (2019). Two-year survival comparing web-based symptom monitoring vs routine surveillance following treatment for lung cancer. *JAMA*. 321(3), 306-307. https://doi.org/10.1001/jama.2018.18085
12. Dai W, Feng W, Zhang Y, et al. Patient-reported outcome-based symptom management versus usual care after lung cancer surgery: A multicenter randomized controlled trial. *J Clin Oncol.* 2022;40(9):988-996. doi:10.1200/JCO.21.01344.
13. Bakitas M, Lyons KD, Hegel MT, et al. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: The Project ENABLE II randomized controlled trial. *JAMA*. 2009;302(7):741-749. doi:10.1001/jama.2009.1198.
14. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med*. 2010;363(8):733-742. doi:10.1056/NEJMoa1000678.
15. Temel JS, Greer JA, El-Jawahri A, et al. Effects of early integrated palliative care in patients with lung and GI cancer: A randomized clinical trial. *J Clin Oncol*. 2017;35(8):834-841. doi:10.1200/JCO.2016.70.5046.
16. Zimmermann C, Swami N, Krzyzanowska M, et al. Early palliative care for patients with advanced cancer: A cluster-randomised controlled trial. *Lancet*. 2014;383(9930):1721-1730. doi:10.1016/S0140-6736(13)62416-2.
17. Bakitas MA, Tosteson TD, Li Z, et al. Early versus delayed initiation of concurrent palliative oncology care: patient outcomes in the ENABLE III randomized controlled trial. *J Clin Oncol*. 2015;33(13):1438-1445. doi:10.1200/JCO.2014.58.6362.
18. Grudzen CR, Richardson LD, Johnson PN, et al. Emergency department-initiated palliative care in advanced cancer: A randomized clinical trial. *JAMA Oncol*. 2016. doi:10.1001/jamaoncol.2015.5252.
19. Ferrell BR, Temel JS, Temin S, et al. Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2017;35(1):96-112. doi:10.1200/JCO.2016.70.1474.
20. Kavalieratos D, Corbelli J, Zhang D, et al. Association between palliative care and patient and caregiver outcomes: A systematic review and meta-analysis. *JAMA*. 2016;316(20):2104-2114. doi:10.1001/jama.2016.16840.
21. Eagan RT, Carr DT, Lee RE, Frytak S, Rubin J, Coles DT. Phase II studies of polychemotherapy regimens in small cell lung cancer. *Cancer Treat Rep*. 1977;61:93-95.
22. Gralla RJ, Casper ES, Kelsen DP, et al. Cisplatin and vindesine combination chemotherapy for advanced carcinoma of the lung: A randomized trial investigating two dosage schedules. *Ann Intern Med*. 1981;95:414-420.
23. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med*. 2004;350:351-360.
24. Longeval E, Klastersky J. Combination chemotherapy with cisplatin and etoposide in bronchogenic squamous cell carcinoma and adenocarcinoma: A study by the EORTC lung cancer working party (Belgium). *Cancer*. 1982;50(12):2751-2756. doi:10.1002/1097-0142(19821215)50:12<2751::aid-cncr2820501210>3.0.co;2-3.
25. Sierocki JS, Hilaris B, Hopfan S, et al. Cis-Dichlorodiammineplatinum(II) and VP-16-213: An active induction regimen for small cell carcinoma of the lung. *Cancer Treat Rep*. 1979:639-641.
26. Gralla RJ, Itri LM, Pisko SE, et al. Antiemetic efficacy of high-dose metoclopramide: Randomized trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. *N Engl J Med*. 1981;305:905-909.
27. Roila F, Tonato M, Del Favero A, et al. Antiemetic effect of high-dose metoclopramide. *J Clin Oncol*. 1986;4(3):440-441. doi:10.1200/JCO.1986.4.3.440.
28. Kris MG, Gralla RJ, Tyson LB, et al. Improved control of cisplatin-induced emesis with high-dose metoclopramide and with combinations of metoclopramide, dexamethasone, and diphenhydramine: Results of consecutive trials in 255 patients. *Cancer.* 1985;55:527-534.
29. Kris MG, Gralla RJ, Clark RA, et al. Incidence, course, and severity of delayed nausea and vomiting following the administration of high-dose cisplatin. *J Clin Oncol*. 1985;3:1379-1384.
30. Ireland SJ, Straughan DW, Tyers MB. Influence of 5-hydroxytryptamine uptake on the apparent 5-hydroxytryptamine antagonist potency of metoclopramide in the rat isolated superior cervical ganglion. *Br J Pharmacol.* 1987;90(1):151-160. doi:10.1111/j.1476-5381.1987.tb16835.x.
31. Kris MG, Gralla RJ, Clark RA, Tyson LB. Dose-ranging evaluation of the serotonin antagonist GR C507/75 (GR38032F) when used as an antiemetic in patients receiving anticancer chemotherapy. *J Clin Oncol*. 1988;6:659-662.
32. The Italian Group for Antiemetic Research. Dexamethasone, granisetron, or both for the prevention of nausea and vomiting during chemotherapy for cancer. *N Engl J Med*. 1995;332:1-5. doi:10.1056/NEJM199501053320101.
33. Hesketh PJ, Grunberg SM, Gralla RJ, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: A multinational randomized double-blind placebo-controlled trial in patients receiving high-dose cisplatin--The Aprepitant Protocol 052 Study Group. *J Clin Oncol*. 2003;21:4112-4119.
34. Navari RM, Qin R, Ruddy KJ, et al. Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. *N Engl J Med*. 2016;375:134-142. doi:10.1056/NEJMoa1515725.
35. Ruhlmann CH, Jahn F, Jordan K, et al. 2016 updated MASCC/ESMO consensus recommendations: Prevention of radiotherapy-induced nausea and vomiting. *Support Care Cancer.* 2017;25:309-316. doi:10.1007/s00520-016-3407-8.
36. Corcoran TB, Myles PS, Forbes AB, et al. Dexamethasone and surgical-site infection. *N Engl J Med*. 2021;384:1731-1741. doi:10.1056/NEJMoa2028982.
37. Ito Y, Tsuda T, Minatogawa H, et al. Placebo-controlled double-blinded phase iii study comparing dexamethasone on day 1 with dexamethasone on days 1 to 3 with combined neurokinin-1 receptor antagonist and palonosetron in high-emetogenic chemotherapy. J *Clin Oncol*. 2018;36(10):1000-1006. doi:10.1200/JCO.2017.74.4375.
38. Hesketh PJ, Rossi G, Rizzi G, et al. Efficacy and safety of NEPA, an oral combination of netupitant and palonosetron for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy: A randomized dose-ranging pivotal study. *Ann Oncol*.

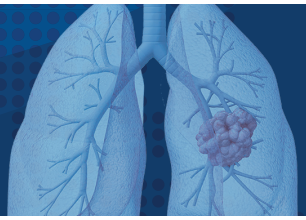
2014;25:1340-1346. doi:10.1093/annonc/mdu095.
39. Gralla RJ, Bosnjak SM, Honsta A, et al. A Phase 3 study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting (CINV) over repeated cycles of chemotherapy. *Ann Oncol*. 2014;25:1333-1339. doi:10.1093/annonc/mdu098.
40. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO Guideline Update. *J Clin Oncol*. 2020;38(24):2782-2797. doi:10.1200/JCO.20.01705.
41. Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. *Ann Oncol*. 2016;27:119-133. PMID: 27664248.
42. NCCN clinical practice guidelines in Oncology. Version 1 2019. Available at https://www.NCCN.org.
43. Galeas JN, Gralla RJ, Azimi-Nekoo E, et al. Guidelines for the prevention of chemotherapy induced nausea and vomiting (cinv) do not address economic variation and affordability in different populations and drug availability. *Support Care Cancer*. 2018;26(Suppl 2).
44. McCabe W, Jackson G. Gram-negative bacteremia. II. Clinical laboratory and therapeutic observations. *Arch Intern Med*. 1962;110:856-864.
45. Bodey GP, Buckley M, Sathe Y, et al. Quantitative relationship between circulating leucocytes and infection in patients with acute leukemia. *Ann Intern Med*. 1966;64:328-340.
46. Klastersky J, Debusscher L, Weerts D, et al. Use of oral antibiotics in protected units environment: clinical effectiveness and role in the emergence of antibiotic-resistant strains. *Pathol Biol (Paris)*. 1974;22:5-12.
47. Schimpff S, Satterlee W, Young VM, et al. Empiric therapy with carbenicillin and gemcitabine for febrile patients with cancer and granulocytopenia. *N Engl J Med*. 1971;284:1061-1065.
48. Klastersky J, Paesmans M, Rubenstein EB, et al. The Multinational Association for Supportive Care in Cancer Risk Index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol*. 2000;18:3038-3051.
49. Klastersky J, Paesmans M, Georgala A, et al. Outpatient oral antibiotics for febrile neutropenic cancer patients using a score predictive for complications. *J Clin Oncol.* 2006;24:4129-4134.
50. Kuderer NM, Dale DC, Crawford J, et al. Impact of primary prophylaxis with granulocyte colony-stimulating factors on febrile neutropenia and mortality in adult cancer patients. *J Clin Oncol.* 2007;25:3158-3167.
51. Klastersky J, de Naurois J, Rolston K, et al. Management of febrile neutropenia: ESMO clinical practice guidelines. *Ann Oncol*. 2016;27.
52. Van den Beuken-van Everdingen MH, Hochstenbach LM, et al. Update on prevalence of pain in patients with cancer: Systematic review and meta-analysis. *J Pain Symptom Manage*. 2016;51:1070-1090.
53. Greco MT, Roberto A, Corli O, et al. Quality of cancer pain management: An update of a systematic review of undertreatment of patients with cancer. *J Clin Oncol*. 2014;32(36): 4149-4154.
54. Van den Beuken-van, Everdingen MH, Hochstenbach, LM, et al. (2016). Update on prevalence of pain in patients with cancer: Systematic review and meta-analysis. *Journal of Pain and Symptom Management*, 51, 1070–1090.
55. National Comprehensive Cancer Network. Adult Cancer Pain: NCCN Clinical Practice Guidelines in Oncology Version 2.2016. Available at https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf. Accessed March 9, 2017.
56. Oldenmenger WH, Sillevis Smitt PA, van Dooren S, et al. A systematic review on barriers hindering adequate cancer pain management and interventions to reduce them: A critical appraisal. *Eur J Cancer*. 2009;45:1370-1380.
57. Penny F, Whiting RF, Wolff S, Deshpande S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA*. 2015;313(24):2456-2473.
58. Reyes-Gibby CC, Spitz M, Wu X, et al. Cytokine genes and pain severity in lung cancer: Exploring the influence of TNF-alpha-308 G/A, IL6-174G/C, and IL8-251T/A. *Cancer Epidemiol Biomarkers Prev.* 2007;16(12): 2745-2751.
59. Reyes-Gibby CC, Spitz MR, Yennurajalingam S, et al. Role of inflammation gene polymorphisms on pain severity in lung cancer patients. *Cancer Epidemiol Biomarkers Prev*. 2009;18(10):2636-2642.
60. Edantam A, Hou P, Chi TL, et al. Use of spinal cord diffusion tensor imaging to quantify neural ablation and evaluate outcome after percutaneous cordotomy for intractable cancer pain. *Stereotact Funct Neurosurg*. 2017;95(1):34-39.
61. Borys M, Zyzak K, Hanych A, et al. Survey of postoperative pain control in different types of hospitals: a multicenter observational study. *BMC Anesthesiol*. 2018;18:83.
62. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: Risk factors and prevention. *Lancet*. 2006;367:1618–1625.
63. Hamada H, Moriwaki K, Shiroyama K, et al. Myofascial pain in patients with postthoracotomy pain syndrome. *Reg Anesth Pain Med*. 2000;25:302–305.
64. National Comprehensive Cancer Network. (2019). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Available at https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
65. Cao C, D'Amico T, Demmy T, et al. Less is more: A shift in the surgical approach to non-small-cell lung cancer. *Lancet Respir Med*. 2016;4.
66. Singer ES, Kneuertz PJ, Nishimura J, et al. Effect of operative approach on quality of life following anatomic lung cancer resection. *J Thorac Dis*. 2020;12(11):6913-6919.
67. Wei B, D'Amico TA. Thoracoscopic versus robotic approaches: Advantages and disadvantages. *Thorac Surg Clin*. 2014;24(2):177–188. doi:10.1016/j.thorsurg.2014.02.001.
68. Kent M, Wang T, Whyte R, et al. Open video-assisted thoracic surgery and robotic lobectomy: Review of a national database. *Ann Thorac Surg*. 2014;97(1):236–244.
69. Bendixen M, Jørgensen OD, Kronborg C, et al. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: A randomised controlled trial. *Lancet Oncol*. 2016;17:836–844.
70. Cata JP, Keerty V, Keerty D, et al. A retrospective analysis of the effect of intraoperative opioid dose on cancer recurrence after non-small cell lung cancer resection. *Cancer Med*. 2014;3:900-908.

71. Vallejo R, Hord ED, Barna SA, et al. Perioperative immunosuppression in cancer patients. *J Environ Pathol Toxicol Oncol*. 2003;22:139-146.
72. Ponholzer F, Ng C, Maier H, et al. Intercostal catheters for postoperative pain management in VATS reduce opioid consumption. *J Clin Med*. 2021;10(2):372.
73. Rice D, Rodriguez-Restrepo A, Mena G, et al. Matched pairs comparison of an enhanced recovery pathway versus conventional management on opioid exposure and pain control in patients undergoing lung surgery. *Ann Surg*. 2021;274(6):1099-1106.
74. Miao Z, Wu P, Wang J, et al. Whole-course application of dexmedetomidine combined with ketorolac in nonnarcotic postoperative analgesia for patients with lung cancer undergoing thoraco-scopic surgery: A randomized control trial. *Pain Physician*. 2020;23(2).
75. Feng M, Jiang Y, Liu D, et al. RNA-seq analysis of peripheral blood dendritic cells maturated by dezocine in patients with lung cancer. *Mol Immunol*. 2022; 143:85-93.
76. Morgensztern D, Waqar S, Subramanian J, et al. Prognostic impact of malignant pleural effusion at presentation in patients with metastatic non–small-cell lung cancer. *J Thorac Oncol*. 2012;7(10):1485-1489. doi:10.1097/jto.0b013e318267223a.
77. Feller-Kopman D, Light R. Pleural disease. *N Engl J Med*. 2018;378(8):740-751. doi:10.1056/nejmra1403503.
78. Rami-Porta R, Crowley JJ, Goldstraw P. The revised TNM staging system for lung cancer. *Ann Thorac Cardiovasc Surg*. 2009;15(1):4-9.
79. Dipper A, Jones HE, Bhatnagar R, et al. Interventions for the management of malignant pleural effusions: A network meta-analysis. *Cochrane Database Syst Rev*. 2020;4(4) doi:10.1002/14651858.cd010529.pub3.
80. Putnam JB, Light RW, Rodriguez RM, et al. A randomized comparison of indwelling pleural catheter and doxy-cycline pleurodesis in the management of malignant pleural effusions. *Cancer.* 1999;86(10):1992-1999. doi:10.1002/(sici)1097-0142(19991115)86:10<1992::aid-cncr16>3.3.co;2-d.
81. Putnam JB, Walsh GL, Swisher SG, et al. Outpatient management of malignant pleural effusion by a chronic indwell-ing pleural catheter. *Ann Thorac Surg*. 2000;69(2):369-375. doi:10.1016/s0003-4975(99)01482-4.
82. Fysh ETH, Waterer GW, Kendall PA, et al. Indwelling pleural catheters reduce inpatient days over pleurodesis for malignant pleural effusion. *Chest*. 2012;142(2):394-400. doi:10.1378/chest.11-2657.
83. Wahidi MM, Reddy C, Yarmus L, et al. Randomized trial of pleural fluid drainage frequency in patients with malignant pleural effusions. The ASAP Trial. *Am J Respir Crit Care Med*. 2017;195(8):1050-1057. doi:10.1164/rccm.201607-1404oc.
84. Bhatnagar R, Keenan EK, Morley AJ, et al. Outpatient talc administration by indwelling pleural catheter for malignant effusion. *N Engl J Med*. 2018;378(14):1313-1322. doi:10.1056/nejmoa1716883.
85. Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ, Group BPDG. Management of a malignant pleural effusion: British Thoracic Society pleural disease guideline 2010. *Thorax*. 2010;65(Suppl 2) doi:10.1136/thx.2010.136994.
86. Feller-Kopman DJ, Reddy CB, DeCamp MM, et al. Management of malignant pleural effusions. An Official ATS/STS/STR Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2018;198(7):839-849. doi:10.1164/rccm.201807-1415st.
87. Coleman RE. Skeletal complications of malignancy. *Cancer*. 1997;80(S8): 1588-1594. doi:10.1002/(sici)1097-0142(19971015)80:8+<1588::aid-cncr9>3.0.co;2-g
88. Chow E, Harris K, Fan G, Tsao M, Sze WM, Wu J. Meta-analysis of palliative radiotherapy trials for bone metastases. *Clin Oncol (R Coll Radiol)*. 2007;19(3) doi:10.1016/j.clon.2007.01.346.
89. Wu JSY, Wong R, Johnston M, Bezjak A, Whelan T, Group CCOPGISC. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. I*nt J Radiat Oncol Biol Phys*. 2003;55(3):594-605. doi:10.1016/s0360-3016(02)04147-0.
90. Hendriks LEL, Hermans BCM, Everdingen MHJ van den B, et al. Effect of bisphosphonates, denosumab, and radioisotopes on bone pain and quality of life in patients with non-small cell lung cancer and bone metastases: A systematic review. *J Thorac Oncol*. 2015;11(2):155-173. doi:10.1016/j.jtho.2015.10.001.
91. Hirsh V, Major PP, Lipton A, et al. Zoledronic acid and survival in patients with metastatic bone disease from lung cancer and elevated markers of osteoclast activity. *J Thorac Oncol*. 2008;3(3):228-236. doi:10.1097/jto.0b013e3181651c0e.
92. Henry DH, Costa L, Goldwasser F, et al. Randomized double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol*. 2011;29(9):1125-1132. doi:10.1200/jco.2010.31.3304.
93. Coleman R, Hadji P, Body JJ, et al. Bone health in cancer: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2020;31(12):1650-1663. doi:10.1016/j.annonc.2020.07.019.
94. Baracos VE, Reiman T, Mourtzakis M, et al. Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. *Am J Clin Nutr*. 2010;91(4):1133S-1137S. doi:10.3945/ajcn.2010.28608C.
95. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. *Nat Rev Clin Oncol*. 2013;10:90-99. doi:10.1038/nrclinonc.2012.209.
96. Amitani M, Oba T, Kiyosawa N, et al. Skeletal muscle loss during neo-adjuvant chemotherapy predicts poor prognosis in patients with breast cancer. *BMC Cancer*. 2022;22:327. doi:10.1186/s12885-022-09443-1.
97. Fearon, K, Strasser, F, Anker, SD, et al. Definition and classification of cancer cachexia: An international consensus. *Lancet Oncol*. 2011:12(5), 489-495. https://doi.org/10.1016/S1470-2045(10)70218-7.
98. Fearon KC, Glass DJ, Guttridge DC. Cancer cachexia: Mediators, signaling, and metabolic pathways. *Cell Metab*. 2011: 16(2), 153-166. doi:10.1016/j.cmet.2012.06.011.
99. Evans WK, Nixon DW, Daly JM, et al. A randomized study of oral nutritional support versus ad lib nutritional intake during chemotherapy for advanced col-orectal and non-small-cell lung cancer. *J Clin Oncol*. 1987:5(1), 113-124.
100. Crawford J, Prado CM, Johnston MA, et al. Study design and rationale for the phase 3 clinical development program of Enobosarm, a selective androgen receptor modulator, for the prevention and treatment of muscle wasting in cancer patients (POWER Trials). *Current Oncology Reports*. 2016:18(6), 37. doi:10.1007/s11912-016-0522-0.

101. Temel JS, Abernethy AP, Currow DC, et al. Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): Results from two randomised, double-blind, phase 3 trials. *The Lancet Oncology*. 2016:17(4), 519-531. https://doi.org/10.1016/S1470-2045(15)00558-6.
102. Shen W, Punyanitya M, Wang Z, et al. Total body skeletal muscle and adipose tissue volumes: Estimation from a single abdominal cross-sectional image. *Journal of Applied Physiology*. 2004:97(6), 2333-2338. doi:10.1152/japplphysiol.00744.2004.
103. Recio-Boiles A, Galeas JN, Goldwasser, B, et al. Enhancing evaluation of sarcopenia in patients with non-small cell lung cancer (NSCLC) by assessing skeletal muscle index (SMI) at the first lumbar (L1) level on routine chest computed tomography (CT). *Support Care Cancer*. 2018:26,2353-2359. doi:10.1007/s00520-018-4051-2.
104. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med*. 2020: 54, 1451-1462.
105. Moore SC, Lee IM, Weiderpass E, et al. Leisure-time physical activity and risk of 26 types of cancer in 1.44 million adults. *JAMA Intern Med*. 2016:176, 816-825.
106. Friedenreich CM, Neilson HK, Farris MS, et al. Physical activity and cancer outcomes: A precision medicine approach. *Clin Cancer Re*s. 2016:22, 4766-4775.
107. Licker M, Karenovics W, Diaper J, et al. Short-term preoperative high-intensity interval training in patients awaiting lung cancer surgery: A randomized controlled trial. *J Thorac Oncol*. 2017:12, 323-333.
108. Adamsen L, Quist M, Andersen C, et al. Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy:randomised controlled trial. *BMJ*. 2009:339, b3410.
109. Fedewa MV, Hathaway ED, Ward-Ritacco CL. Effect of exercise training on C-reactive protein: a systematic review and meta-analysis of randomised and non-randomised controlled trials. *Br J Sports Med*. 2017:51, 670-676.
110. Schmidt ME, Meynköhn A, Habermann, N, et al. Resistance exercise and inflammation in breast cancer patients undergoing adjuvant radiation therapy: mediation analysis from a randomized, controlled intervention trial. *Int J Radiat Oncol Biol Phys*. 2016:94, 329-337.
111. Brooks SV, Vasilaki A, Larkin LM, et al. Repeated bouts of aerobic exercise lead to reductions in skeletal muscle free radical generation and nuclear factor κB activation. *J Physiol*. 2008:586, 3979-3990.
112. Kleckner IR, Kamen C, Cole C, et al. Effects of exercise on inflammation in patients receiving chemotherapy: a nationwide NCORP randomized clinical trial. *Support Care Cancer*. 2019:27, 4615-4625.
113. Pedersen L, Idorn M, Olofsson GH, et al. Voluntary running suppresses tumor growth through epinephrine- and IL-6-dependent NK cell mobilization and redistribution. *Cell Metab*. 2016:23, 554-562.
114. Lo C, Zimmermann C, Rydall A, et al. Longitudinal study of depressive symptoms in patients with metastatic gastrointestinal and lung cancer. *J Clin Oncol*. 2010:28(18), 3084-3089. doi:10.1200/JCO.2009.26.9712.
115. Vijayvergia N, Shah PC, Denlinger CS. Survivorship in Non-Small Cell Lung Cancer: Challenges Faced and Steps Forward. *J Natl Compr Canc Netw*. 2015:13(9), 1151-1161. doi:10.6004/jnccn.2015.0140.
116. Park CL, Pustejovsky JE, Trevino K, et al. Effects of psychosocial interventions on meaning and purpose in adults with cancer: A systematic review and meta-analysis. *Cancer*. 2019:125(14), 2383-2393. doi:10.1002/cncr.32078.
117. Salsman JM, Pustejovsky JE, Schueller SM, et al. Psychosocial interventions for cancer survivors: A meta-analysis of effects on positive affect. *J Cancer Surviv*. 2019:13(6), 943-955. doi:10.1007/s11764-019-00811-8.
118. Rodin G, An E, Shnall J, Malfitano C. Psychological Interventions for Patients With Advanced Disease: Implications for Oncology and Palliative Care. *J Clin Oncol*. 2020:38(9),885-904. doi:10.1200/JCO.19.00058.
119. Badr H, Smith CB, Goldstein NE, Gomez JE, Redd WH. Dyadic psychosocial intervention for advanced lung cancer patients and their family caregivers: Results of a randomized pilot trial. *Cancer*. 2015:121(1), 150-158. doi:10.1002/cncr.29009.
120. Schellekens MPJ, van den Hurk DGM, Prins JB, et al. Mindfulness-based stress reduction added to care as usual for lung cancer patients and/or their partners: A multicentre randomized controlled trial. *Psycho-Oncology*, 2017:26(12), 2118-2126. doi:10.1002/pon.4430.
121. Sharpe M, Walker J, Holm Hansen C, et al. Integrated collaborative care for comorbid major depression in patients with cancer (SMaRT Oncology-2): a multicentre randomised controlled effectiveness trial. *Lancet*. 2014:384(9948), 1099-1108. doi:10.1016/S0140-6736(14)61231-9.
122. Walker J, Hansen CH, Martin P, et al. Integrated collaborative care for major depression comorbid with a poor prognosis cancer (SMaRT Oncology-3): A multicentre randomised controlled trial in patients with lung cancer. *Lancet Oncol*. 2014:15(10), 1168-1176. doi:10.1016/S1470-2045(14)70343-2.
123. Nipp RD, El-Jawahri A, Fishbein JN, et al. The relationship between coping strategies, quality of life, and mood in patients with incurable cancer. *Cancer*. 2016:122(13), 2110-2116. doi:10.1002/cncr.30025.
124. Nipp RD, Greer JA, El-Jawahri A, et al. Coping and prognostic awareness in patients with advanced cancer. *J Clin Oncol*. 2017:35(18), 2060-2066. doi:10.1200/JCO.2016.71.3404.
125. Greer JA, Jacobs JM, El-Jawahri A, et al. Role of patient coping strategies in understanding the effects of early palliative care on quality of life and mood. *J Clin Oncol*. 2018:36(1), 53-60. doi:10.1200/JCO.2017.73.7221.
126. Hoerger M, Greer JA, Jackson VA, et al. Defining the elements of early palliative care that are associated with patient-reported outcomes and the delivery of end-of-life care. *J Clin Oncol*. 2018:36(11), 1096-1102. doi:10.1200/JCO.2017.75.6676.
127. Greer JA, Applebaum AJ, Jacobsen JC, Temel JS, Jackson VA. Understanding and Addressing the Role of Coping in Palliative Care for Patients With Advanced Cancer. *J Clin Oncol*. 2020:38(9), 915-925. doi:10.1200/JCO.19.00013.
128. Karnofsky DA, Burchenal JH. (1949). The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, ed. *Evaluation of Chemotherapeutic Agents*. New York: Columbia University Press. 191-205.
129. Zubrod CG, Schneiderman M, Frei E, et al. Appraisal of methods for the study of chemotherapy of cancer in man: Comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoramide. *J Chronic Di*s. 1960:11, 7-33.

130. Eastern Cooperative Oncology Group. (1983). Functional assessment scale. In: Rubin P, ed. *Clinical Oncology: A Functional Approach*. New York: American Cancer Society, 91.
131. Nunnally JC (1967). *Psychometric Theory*. New York: McGraw-Hill.
132. Hollen PJ, Gralla RJ Comparison of Instruments for Measuring Quality of Life in Patients with Lung Cancer. *Semin Oncol*. 1996:23, 31-40.
133. Reck M, Brahmer J, Bennett B, et al. Evaluation of health-related quality of life and symptoms in patients with advanced non-squamous non-small cell lung cancer treated with nivolumab or docetaxel in CheckMate 057. *Eur J Cancer*. 2018:102, 23-30. doi:10.1016/j.ejca.2018.05.005. PMID: 30103096.
134. Hollen PJ, Gralla RJ, Cox C, et al. A dilemma in analysis: issues in the serial measurement of quality of life in patients with advanced lung cancer. *Lung Cancer*. 1997:18, 119-136.

23



MESOTHELIOMA

Anna Nowak,[1,2] **Michele Carbone,**[3] **Harvey I. Pass,**[4] **Raja M. Flores,**[5] **and Paul Baas**[6] | [1]University of Western Australia Perth, WA, Australia; [2]Sir Charles Gairdner Hospital, Perth, WA, Australia, [3]University of Hawaii Cancer Center, Honolulu, USA; [4]NYU Langone Medical Center, New York, USA; [5]The Icahn School of Medicine at Mount Sinai, New York, USA; and [6]The Netherlands Cancer Institute and Leiden University Medical Center, Amsterdam, Netherland

For over 3 decades, the IASLC has focused on malignant pleural mesothelioma (MPM) and witnessed major developments in this field.

The mesothelioma group itself was assembled late in the last century and chaired by H. Pass, M. Carbone, P. Baas and now A. Mansfield. The international representatives in the field of mesothelioma focused on different aspects of epidemiology, diagnosis, predictive/prognostic factors, treatment, and translational research. The IASLC has supported several mesothelioma meetings, and in 2019, a meeting was held in New York.

EPIDEMIOLOGY

Although the World Health Organization (WHO) has classified MPM as a relatively rare malignancy, to date, the disease is a diagnostic and therapeutic challenge for clinicians. The legal regulations in the Western World on asbestos banning seem to have some effect, but mining of asbestos and export to developing countries will keep the disease a part of our focus. The incidence of the disease is highest in the elderly > 65 years, due to the latency period between asbestos exposure and development.[1] In the U.S., over 20 million people are at risk of developing mesothelioma due to asbestos exposure, and more due to exposure to other mineral fibers. Mortality rates for mesothelioma are estimated to increase by 5% to 10% per year in most industrialized countries until about 2020, due to past exposure.[1]

DIAGNOSIS AND MOLECULAR PATHOLOGY

Asbestos and Other Carcinogenic Fibers

Asbestos is a name that has been used to identify 6 different mineral fibers that were used commercially.[2]

The mechanism of asbestos carcinogenesis had remained enigmatic for decades, because when mesothelial cells were cultured with asbestos they invariably died.[3,4] A significant amount of work in the recent past has linked the mechanism of asbestos carcinogenesis to the chronic inflammatory process that is caused by the extracellular release of HMGB1 by mesothelial cells and macrophages nearby asbestos deposits.[5-9] The extracellular release of HMGB1 induces autophagy—a process that reduces asbestos-induced cell death—and that also causes the release of TNF-alpha and of other cytokines by nearby inflammatory cells, which in turn induce the activation of the NFkB pathway, which also protects cells from death and favors their proliferation.[10,11] In parallel, HMGB1-induced release of TNF-alpha and of other cytokines causes the release of mutagenic oxygen radicals, which favor malignant transformation. This inflammatory environment promotes the growth of malignant cells, often of multiple premalignant clones resulting in a polyclonal malignancy.[12,13] Accordingly, mesothelioma growth in mice can be delayed by drugs that inhibit HMGB1, including aspirin.[14,15]

In addition to work-related exposure, exposure to asbestos,

erionite, and to other carcinogenic fibers present in the environment has recently been linked to mesothelioma. This type of exposure is increasing because of the development of rural areas that naturally may contain carcinogenic mineral fibers in the terrain. When roads and homes are built in these areas, workers first, and later residents, are exposed and may develop mesothelioma.[16-18]

GENETICS AND MESOTHELIOMA

The recent advances in genetics have revolutionized our understanding of mesothelioma. It is hoped that these discoveries will soon result in effective preventive and therapeutic approaches. A study of an epidemic of mesothelioma in Cappadocia revealed that the risk of developing mesothelioma was transmitted in a Mendelian fashion in certain families.[18,19] Subsequent studies from these investigators in US families with a high incidence of mesothelioma revealed that all carriers of heterozygous germline BAP1 mutations developed one or more malignancies during their lifetime: one third of them developed mesothelioma.[20-23] Mesotheliomas developing in carriers of germline BAP1 mutations have a significantly improved median survival of 5-7 years—compared to [6-18] months survival for patients with sporadic, asbestos-related mesotheliomas—with ~ 20% of them surviving 10-20 or more years.[24-27] It has been suggested that the improved survival may be related to increased sensitivity of these patients to platinum therapy.[27] BAP1 is a deubiquitylase that regulates multiple cellular pathways. When the intracellular levels of BAP1 are reduced, cells show reduced ability to repair the DNA by homologous recombination, reduced ability to execute apoptosis because of impaired Ca^{2+} cytoplasmic transport, and they shift to aerobic glycolysis.[23,28-31] Therefore, cells with BAP1 mutations, accumulate DNA damage, do not die and they have a metabolism that facilitates tumor growth, resulting in the high incidence of cancer, mesothelioma in particular, in BAP1 mutant carriers. More recently, germline mutations of additional genes that regulate DNA repair and other critical cellular activities have been linked to mesothelioma development.[25,26,32-34]

Genetic mutations can cause cancer alone or interact with other genetic mutations (gene X gene interaction) or with environmental carcinogens (gene X environment interaction) to cause cancer.[22] BAP1 mutations, for example, have been shown to interact with asbestos and with gamma-radiation to cause malignant transformation of human cells in vitro,[28] and with asbestos in mice to cause mesothelioma.[28,30,35] Asbestos interacts with SV40, a DNA tumor virus, to cause malignant transformation of human mesothelial cells in vitro and mesothelioma in rodents.[36]

Genomic analyses to investigate the progression of genomic lesions that give rise to human mesothelioma[37] revealed that recurrent mutations are rare, with most tumors carrying anywhere between 2-50 genetic mutations.[38] The most commonly mutated genes in mesothelioma are the tumor suppressors BAP1, CDKN2A, and NF2.[38-41] Moreover, the study of Bueno R et al. identified four distinct molecular subtypes: epithelioid, sarcomatoid, biphasic epithelioid, and biphasic sarcomatoid, based on their genomic profiles.[41] Genomic targets have not been identified, as most mutations occur in tumor suppressor genes and are not gain of function. Studies in mice, however, revealed that down-regulation of the IGF1 receptor or of NFkB inhibits mesothelioma growth,[42-44] and several other potential targets are being investigated.[45]

DIAGNOSIS

In recent years significant improvements in immunohistochemistry provided pathologists with better tools to diagnose mesothelioma: however, overall these improvements did not result in an improved diagnostic accuracy because A) pathologists may not be aware of these improvements or do not know how to correctly interpret new stains B) In some countries, such as the USA, most insurances reimburse a maximum of 4 immunostains making the use of larger panels impractical for small pathology laboratories.[31,46-49] A difficult, critical and relatively frequent diag-

nostic problem is distinguishing benign reactive atypical mesothelial proliferations, such as chronic pleuritis and other chronic inflammatory processes accompanied by florid mesothelial proliferations, from malignant mesothelioma.[50,51] The recent discovery that BAP1 nuclear staining is lost in over 60% of mesotheliomas and that BAP1 is always expressed in the nucleus by normal nonmalignant cells has led to the current consensus that a negative BAP1 staining identify malignant cells.[39,51,52] However, while BAP1 negative staining is evidence of malignancy, since up to 40% of mesotheliomas contain wild-type BAP1, a positive staining is not helpful to decide if the lesion is benign or malignant. In these cases, fluorescence in situ hybridization (FISH) to detect homozygous deletions of CDKN2A, which encodes P16, or the use of MTAP immunohistochemistry—MTAP is a gene that is almost always co-deleted with CDKN2A—is the next (to BAP1) best diagnostic test to distinguish benign from malignant mesothelioma cells.[51]

As for distinguishing mesothelioma from other malignancies metastatic to the pleura or peritoneum, depending on the clinical presentation, the following antibodies should be used: WT1 and calretinin to identify malignant mesothelioma cells, Claudin-4 and TTF1 to identify metastatic adenocarcinomas of the lung, P63 or P40 to identify metastatic squamous cell carcinomas, ER and PR to identify metastatic breast and ovarian carcinomas, PAX8 with parallel negative staining for WT1, and calretinin to identify metastatic clear cell renal cell carcinoma. Moreover, diffuse positive pankeratin (CAM5.2 or other) staining and negative desmin staining, helps differentiate sarcomatoid mesotheliomas from primary sarcomas, and a positive calretinin or WT1 staining of the spindle cells further differentiates them from carcinosarcomas. Vimentin, D2-40, and mesothelin are positive in ~100% of mesotheliomas, but they are not specific, as they stain several other malignancies.[51,53-56]

SURVEILLANCE OF BAP1-MUTANT CARRIERS' COST/BENEFITS CONSIDERATIONS

Once a family or a patient is identified as a germline mutation-carrier, early detection of any of the associated malignancies could potentially lead to earlier local and systemic therapies. However, to date, surveillance trials require careful physical examinations and expensive imaging studies. It may be time to consider whether recently described blood-based pan cancer panels* should be added to surveillance trials in an exploratory fashion. These panels use a technique entitled "DNA evaluation of fragments for early interception" to detect a large number of abnormalities in cell-free DNA by genome-wide analysis of DNA fragmentation patterns. Cell-free DNA fragmentation profiles are expected to reflect both epigenomic and genomic alterations. Using low instead of high coverage of the cell-free DNA, mapped sequences are analyzed in non-overlapping 5 megabase windows that cover the genome. These windows evaluate cell-free DNA fragmentation patterns with >20,000 reads per window. Differences between cancer patients and non-cancer patients in the coverage and the size of the DNA fragmentation patterns are then analyzed by artificial intelligence to stratify for the presence of cancer and to distinguish differences in cancer histology. These DNA fragmentation patterns appear to be more sensitive in detecting chromosomal aberrances than the usual tumor copy number changes. A machine-learning model that incorporated genome-wide fragmentation features had sensitivities of detection, ranging from 57% to more than 99% among colorectal, lung, ovarian, pancreatic, and gastric or bile duct cancer at 98% specificity, with an overall area under the curve value of 0.94.

In 75% of cases, the fragmentation profiles could be used to identify the tissue of origin of the cancers to a limited number of sites. When this approach was combined with mutation-based cell-free DNA, 91% of patients with cancer were detected.[57] A different approach for early cancer detection has been described by Creatv MicroTech. Their early work with circulating tumor cells led to the development of the LifeTracDxTM blood test,[58] which enumerates

*Delfi Diagnostics® and Creative MicroTech Diagnostics®

the size and number of a particular subtype of circulating stromal cell, named Cancer Associated Macrophage-Like cells (CAMLs). These CAMLs, as reported by the company, may identify patients with cancer, since they appear to be absent in healthy persons. In a series of presentations at the American Society for Clinical Oncology, the blood test was 87% accurate in identifying cancer patients compared to healthy controls or patients with non-malignant conditions.

Further pan-cancer diagnostic tests that are potentially applicable to BAP1 include evaluation of DNA methylation. An example is Methylscape, a cfDNA whole epigenome scanning nanotechnology based on differential methylcytosine cluster patterns in cfDNA, which causes differences in solvation and DNA-gold affinity between cancer and healthy volunteer samples. This approach has proven effective in distinguishing cancer of the breast and colon from healthy volunteers in blood samples, and the test has a same day turnaround time.[59]

SURGERY IN MESOTHELIOMA

There has been a refocusing of the goals in the surgical treatment of mesothelioma, a lethal cancer of the membranes lining the outer surface of the lung and the inside of the chest wall. A shift favoring pleurectomy decortication (P/D) to extrapleural pneumonectomy (EPP) aims to improve survival and health related quality of life. Optimal goals should include removal of as much tumor as possible while avoiding pneumonectomy, lung re-expansion, prevention of fluid re-accumulation, while minimizing morbidity and mortality.[60] Surgery alone is incomplete because we cannot eradicate residual microscopic disease.[61] Surgical treatment is paired with preoperative or postoperative chemotherapy or radiation.

For mesothelioma treatment, a risk-benefit equation should take into account: Gain in survival time= (time gained by cytoreduction + time gained by lung reexpansion)—(time lost by operative mortality—time lost by long-term mortality of surgical procedure—time lost from accelerated death after recurrence).[60]

There have been two MARS (Mesothelioma and Radical Surgery) randomized controlled surgical trials. The first trial (ISRCTN95583524) investigated EPP, en bloc resection of the parietal and visceral pleura with the ipsilateral lung, pericardium, and diaphragm, but it did not successfully randomize patients.[62] The second trial (ISRCTN44351742) was exploring the effectiveness of surgery-extended pleurectomy decortication; parietal and visceral pleurectomy to remove all gross tumour without diaphragm or pericardial resection, extended includes resection of the diaphragm and/or pericardium.[63] The study indicated that after chemotherapy courses the survival and QoL was inferior to chemotherapy alone. These data from the UK have led to extensive discussions of the representativity and selection of patients for such an approach in different countries. In the MesoVATS (NCT00821860) trial it was concluded that partial pleurectomy (partial removal of parietal and/or visceral pleura) was not the optimal procedure for high-risk patients but may benefit those with a trapped lung and leads to better quality of life in low-risk patients.[64] While determining survival differences between the three procedures, P/D offers best overall survival, health-related quality of life, and options for mesothelioma recurrence.

A comprehensive meta-analysis conducted on published data that compared the two procedures found that P/D was more beneficial to MPM patient's outcomes.[65] Patients experienced more postoperative outcomes with EPP.

There is greater attention to diagnostic tools to assess patient cardiopulmonary reserve and level of disease: Pulmonary function tests, imaging (Standardized Uptake Values, PET Computed Tomography, Chest CT, Magnetic Resonance Imaging), mediastinoscopy, and fine needle biopsy. Also, more intraoperative (appropriate reconstruction) and postoperative care. Cardiopulmonary reserve can indicate complications and level of risk.

CHEMOTHERAPY AND IMMUNO-ONCOLOGY IN MPM

Chemotherapy has a longstanding

historical role in the management of malignant pleural mesothelioma. However, with the approval of ipilimumab and nivolumab as first-line therapy in this disease, the role of chemotherapy will change.

Until the late 1990s, mesothelioma was thought to be relatively chemoresistant. In the era of rapid development of chemotherapy agents and their use—1980's to 2000—numerous single-arm clinical trials in this disease failed to meet their primary endpoints.[66] Clinicians were challenged by the concept of 'response rate' and how to measure this in a tumor, which grew circumferentially, rather than as a spherical mass. Agents including anthracyclines, topoisomerase inhibitors, alkylating agents, and taxanes showed variable but low response rates.[66]

In 1999, a phase II clinical trial was published using the combination of cisplatin and gemcitabine. This was the first trial to use unidimensional tumour measurements for assessment of tumour response. It reported a promising partial response rate of nearly 48%.[67] With this result, a renewed interest in the possibilities of chemotherapy for mesothelioma started, as well as work codifying and validating the measurement of mesothelioma in unidimensional measurements of pleural thickness.[68] The trial was rapidly followed by an expanded multicenter phase II trial of the same combination,[69] and by two important randomized clinical trials,[70,71] all using combinations of cisplatin with an antimetabolite. With these randomized trials demonstrating survival benefits, the era of chemotherapy in mesothelioma had arrived.

The EMPHACIS trial has had the most penetration to clinical practice, and cisplatin and pemetrexed forms the control arm of many recent and ongoing clinical trials. Chemotherapy naïve patients were treated with either cisplatin 75mg/m^2 with pemetrexed 500mg/m^2 on day 1 of a 21 day cycle (n=226), or with cisplatin alone (n=222). The median overall survival was 12.1 months for those receiving the combination, and 9.3 months in those receiving cisplatin alone with a hazard ratio of 0.77 (p=0.02).[70] Other outcomes were similarly positive, including time to progression and objective tumour response rates. The response rate of approximately 41% became the standard against which other regimens, often adding to cisplatin and pemetrexed in the first line setting, were assessed in phase II studies. Patients required vitamin supplementation with vitamin B12 and folate to reduce hematological toxicities.

Results from the EMPHACIS study were extended by substituting carboplatin for cisplatin.[65-68,72,73] There are a number of contraindications to the use of cisplatin, including some comorbidities, which are common in the older age group, which comprises many people with mesothelioma. Hearing loss, renal dysfunction, and cardiac dysfunction are relative contraindications to the use of cisplatin or to the large fluid load required with this drug. The best evidence for this practice comes from the pemetrexed Expanded Access Program in which pemetrexed was combined with either cisplatin or carboplatin.[74]

Other important questions included the role of maintenance chemotherapy[75,76] and of triplet chemotherapy.[77-79] The first regimen to challenge cisplatin and pemetrexed as a first line standard of care was the combination of cisplatin, pemetrexed and bevacizumab from the MAPS study.[80] Patients received standard cisplatin and pemetrexed with or without bevacizumab on a 21-day cycle, with bevacizumab continuing after cessation of chemotherapy. 448 patients participated, with the hazard ratio for overall survival of 0.77 (p=0.17) and a median overall survival of 18.8 months in the triplet arm and 16.1 months in the control arm. This combination has been variably used internationally, with variation usually due to the regulatory approval and reimbursement status of bevacizumab in each jurisdiction. Overall, cisplatin and pemetrexed has remained an acceptable first-line therapy and clinical trial control arm through to 2021.

Chemotherapy has also been used and studied in the second and subsequent line settings. Agents have included vinorelbine, gemcitabine, ramucirumab, oxaliplatin, epirubicin, pemetrexed, docetaxel, raltitrexed, irinotecan,

mitomycin, and others. The agents most commonly supported in clinical practice guidelines have been vinorelbine, pemetrexed or gemcitabine.[81] In 2021, the first randomized clinical trial demonstrating efficacy of second line chemotherapy was reported. The VIM trial reported an improved progression free survival (HR 0.6, p=0.002) for oral vinorelbine 60mg/m^2 on days 1/8/15 of a 21 day cycle over active supportive care. Unfortunately, no difference was seen for overall survival (HR 0.79, p=0.24) in this randomized phase II trial in 120 participants.[82]

In 2021, with the advent of immunotherapy, chemotherapy will continue to have a role as a therapeutic option, with cisplatin/carboplatin and pemetrexed (with or without bevacizumab) and subsequent vinorelbine as the drugs with the most supporting data for their use.

IMMUNOTHERAPY IN MPM

In the late eighties of the last century, some research groups had already focused on interaction between immune cells and mesothelioma.[83] Despite these observations, suitable immune oncology (IO) drugs were not available at that time.

The promising results obtained in lung cancer and melanoma patients and the renewed clinical interest in mesothelioma were the reason to start studies with IO drugs.

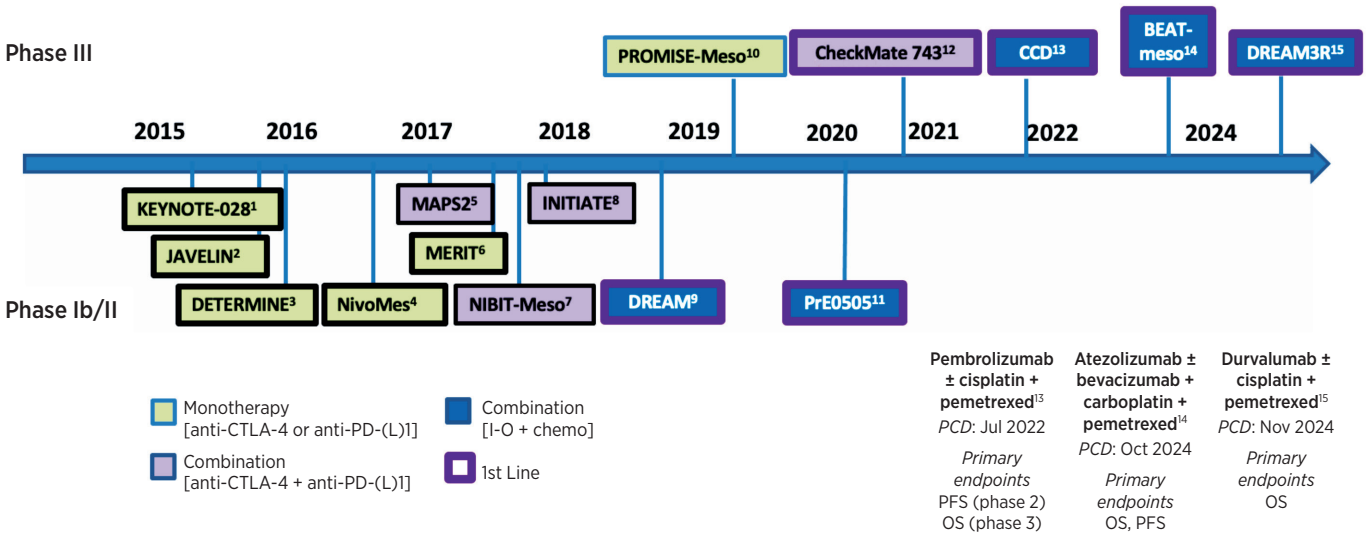
There have been discussions why IO therapy would work in MPM. The tumor microenvironment consists of a complex structure of immune cells, the vasculature and supporting stromal tissue. All of these components result in different mesothelioma phenotypes, making this disease difficult to treat.

It is known that the PD-L1 expression varies patients with MPM and one study reports a 36% positive staining of >1% in 214 patients.[84] Although PD-L1 has been identified as a bad prognostic marker in lung cancer, studies in MPM have reported contradictory findings. Besides PD-L1, Tumor Mutational Burden (TMB) is known to be a possible predictive factor for IO success. However, the TMB in mesothelioma is not high and does not exceed 1 Mut/Mega Base. It is therefore not considered to be a useful tool in MPM. Recently, new developments on this field are the processes chromotripsis and chromoplexy in MPM. Here, large parts of chromosomes are scattered or rearranged during cell division and can function as neo-antigens. Preliminary work has been presented by Dr Mansfield and research group from the Mayo Clinics.[85] Validation of this work is currently underway and may be a new marker to select the best candidates for IO therapy.

For the clinical studies in MPM, the timelines of IO treatment are presented in Figure 1.

Several studies were initiated in 2015 and 2016 in patients with recurrent MPM to find proof of efficacy. Initially, only single agents were tested, shortly followed by combination of IO agents. The phase III Confirm study in the UK showed that nivolumab was superior to Best Supportive Care.[86] Both response rate and progression-free survival were superior. Another randomized phase III study was reported in the second-line setting in Europe.[87] The study compared pembrolizumab to single agent gemcitabine or vinorelbine as by local preference. Besides an improved overall response rate (24 vs 6%), there was no difference in the primary endpoint of progression-free survival observed.[88]

In the same time, a large randomized phase III study in first-line therapy compared chemotherapy (platin + pemetrexed) to combination IO therapy with nivolumab and ipilimumab. This study randomized 605 patients and for all histologies, a HR of 0.74 was observed with a 4 months overall survival gain. The interesting observation in this study was that the IO combination performed similarly good in the epithelioid and non-epithelioid subgroups (18.7 and 18.1 month respectively). As expected, the chemotherapy performed badly in the non-epithelioid arm (8.8 vs 18.1 months respectively). This observation is a welcome improvement in a subgroup that has always had a bad prognosis.[87] The combination of chemotherapy plus pembrolizumab versus chemotherapy alone was tested



1. Alley et al. Lancet Oncol 2015;18;623-630. CT103. **2.** Hassan er al. Jama Onc 2019;5;351-357. **3.** Maio et al. Lancet Oncol 2017;18;1261-1273. 4. Quispel-Janssen et al. J Thor Oncol 2018;13;1569-1576. **5.** Scherpereel et al. Lancet Oncol 2019;20;239-253. **6.** Okada et al. Clin Cancer Res 2019;25;24585-25492. **7.** Calabro et al. Lancet Resp Med 2018;6;451-460. **8.** Disselhorst et al. Lancet Resp Med 2019;3;260-270. **9.** Nowak et al. Lancet Oncol 2020;21;1213-1223. **10.** Popat et al. Ann Oncol 31;1734-1745. **11.** Fordr P et al. Oral presentation at ASCO 2020. 9003. **12.** Baas et al. Lancet 2021;397;375-386. **13.** Clinicaltrials.gov NCT02784171. Accessed August 14, 2020. **14.** Clinicaltrials.gov NCT03762018. Accessed August 14, 2020. **15.** Nowack A. Oral presentation at ALTG 2019.

Figure 1. Timeline of clinical studies of immunotherapy treatment in malignant pleural mesothelioma.

in the IND-227 study and showed a limited improvement in OS. The OS increased from 16.1 to 17.3 months (HR=0.79) at the cost of toxicity (Gr 3-4) of 6 vs 18%.[89]

CONCLUSIONS

The last decade has focused on improvements in molecular analysis of MPM, diagnostic procedures, and optimal selection of patients for the available therapies. Also, the importance of differentiation of subgroups of MPM and the impact of (germline) BAP1 expression.

One of the new approaches is the combination of chemotherapy and IO drugs. It is expected that adding chemotherapy to the IO will boost the effect, especially in the patient group which is less responsive to IO therapy. There are currently several studies that are in phase III setting, which are expected to complete enrollment in 2023. Finally, it will become clear how to implement surgical resection in this disease.

References

1. Royal College of Physicians. National Mesothelioma Audit report 2020 (audit period 2016-18), London RCP, 2020.
2. Alpert N, van Gerwen M, Taioli E. Epidemiology of mesothelioma in the 21(st) century in Europe and the United States, 40 years after restricted/banned asbestos use. *Transl Lung Cancer Res*. 2020;9(Suppl 1):S28-S38.
3. Baumann F, Ambrosi JP, Carbone M. Asbestos is not just asbestos: an unrecognised health hazard. *Lancet Oncol*. 2013;14(7):576-578.
4. Baumann F, Carbone M. Environmental risk of mesothelioma in the United States: An emerging concern-epidemiological issues. *J Toxicol Environ Health B Crit Rev*. 2016;19(5-6):231-249.
5. Yang H, Bocchetta M, Kroczynska B, et al. TNF-alpha inhibits asbestos-induced cytotoxicity via a NF-kappaB-dependent pathway, a possible mechanism for asbestos-induced oncogenesis. *Proc Natl Acad Sci U S A*. 2006;103(27):10397-10402.
6. Yang H, Rivera Z, Jube S, et al. Programmed necrosis induced by asbestos in human mesothelial cells causes high-mobility group box 1 protein release and resultant inflammation. *Proc Natl Acad Sci U S A*. 2010;107(28):12611-12616.
7. Hillegass JM, Shukla A, Lathrop SA, et al. Inflammation precedes the development of human malignant mesotheliomas in a SCID mouse xenograft model. *Ann N Y Acad Sci*. 2010;1203:7-14.
8. Qi F, Okimoto G, Jube S, et al. Continuous exposure to chrysotile asbestos can cause transformation of human mesothelial cells via HMGB1 and TNF-alpha signaling. *Am J Pathol*. 2013;183(5):1654-1666.
9. Gaudino G, Xue J, Yang H. How asbestos and other fibers cause mesothelioma. *Transl Lung Cancer Res*. 2020;9(Suppl 1):S39-S46.
10. Xue J, Patergnani S, Giorgi C, et al. Asbestos induces mesothelial cell transformation via HMGB1-driven autophagy. *Proc Natl Acad Sci U S A*. 2020;117(41):25543-25552.
11. Heintz NH, Janssen-Heininger YM,

Mossman BT. Asbestos, lung cancers, and mesotheliomas: from molecular approaches to targeting tumor survival pathways. *Am J Respir Cell Mol Biol*. 2010;42(2):133-139.
12. Carbone M, Yang H. Molecular pathways: targeting mechanisms of asbestos and erionite carcinogenesis in mesothelioma. *Clin Cancer Res*. 2012;18(3):598-604.
13. Comertpay S, Pastorino S, Tanji M, et al. Evaluation of clonal origin of malignant mesothelioma. *J Transl Med*. 2014;12:301.
14. Jube S, Rivera ZS, Bianchi ME, et al. Cancer cell secretion of the DAMP protein HMGB1 supports progression in malignant mesothelioma. *Cancer Res*. 2012;72(13):3290-3301.
15. Yang H, Pellegrini L, Napolitano A, et al. Aspirin delays mesothelioma growth by inhibiting HMGB1-mediated tumor progression. *Cell Death Dis*. 2015;6(6):e1786.
16. Carbone M, Baris YI, Bertino P, et al. Erionite exposure in North Dakota and Turkish villages with mesothelioma. *Proc Natl Acad Sci U S A*. 2011;108(33): 13618-13623.
17. Baumann F, Buck BJ, Metcalf RV, McLaurin BT, Merkler DJ, Carbone M. The Presence of Asbestos in the Natural Environment is Likely Related to Mesothelioma in Young Individuals and Women from Southern Nevada. *J Thorac Oncol*. 2015;10(5):731-737.
18. Roushdy-Hammady I, Siegel J, Emri S, Testa JR, Carbone M. Genetic-susceptibility factor and malignant mesothelioma in the Cappadocian region of Turkey. *Lancet*. 2001;357(9254):444-445.
19. Carbone M, Emri S, Dogan AU, et al. A mesothelioma epidemic in Cappadocia: scientific developments and unexpected social outcomes. *Nat Rev Cancer*. 2007; 7(2):147-154.
20. Testa JR, Cheung M, Pei J, et al. Germline BAP1 mutations predispose to malignant mesothelioma. *Nat Genet*. 2011;43(10):1022-1025.
21. Carbone M, Yang H, Pass HI, Krausz T, Testa JR, Gaudino G. BAP1 and cancer. *Nat Rev Cancer.* 2013;13(3):153-159.
22. Carbone M, Arron ST, Beutler B, et al. Tumour predisposition and cancer syndromes as models to study gene-environment interactions. *Nat Rev Cancer*. 2020;20(9):533-549.
23. Carbone M, Harbour JW, Brugarolas J, et al. Biological Mechanisms and Clinical Significance of BAP1 Mutations in Human Cancer. *Cancer Discov*. 2020; 10(8):1103-1120.
24. Baumann F, Flores E, Napolitano A, et al. Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival. *Carcinogenesis*. 2015;36(1):76-81.
25. Pastorino S, Yoshikawa Y, Pass HI, et al. A Subset of Mesotheliomas With Improved Survival Occurring in Carriers of BAP1 and Other Germline Mutations. *J Clin Oncol*. 2018:JCO2018790352.
26. Panou V, Gadiraju M, Wolin A, et al. Frequency of Germline Mutations in Cancer Susceptibility Genes in Malignant Mesothelioma. *J Clin Onco*l. 2018;36(28):2863-2871.
27. Hassan R, Morrow B, Thomas A, et al. Inherited predisposition to malignant mesothelioma and overall survival following platinum chemotherapy. *Proc Natl Acad Sci U S A*. 2019;116(18): 9008-9013.
28. Carbone M, Adusumilli PS, Alexander HR, Jr., et al. Mesothelioma: Scientific clues for prevention, diagnosis, and therapy. *CA Cancer J Clin*. 2019;69(5):402-429.
29. Bononi A, Giorgi C, Patergnani S, et al. BAP1 regulates IP3R3-mediated Ca(2+) flux to mitochondria suppressing cell transformation. *Nature*. 2 017;546(7659): 549-553.
30. Bononi A, Yang H, Giorgi C, et al. Germline BAP1 mutations induce a Warburg effect. *Cell Death Differ*. 2017; 24(10):1694-1704.
31. Kobrinski DA, Yang H, Kittaneh M. BAP1: role in carcinogenesis and clinical implications. *Transl Lung Cancer Res*. 2020;9(Suppl 1):S60-S66.
32. Yoshikawa Y, Emi M, Nakano T, Gaudino G. Mesothelioma developing in carriers of inherited genetic mutations. *Transl Lung Cancer Res*. 2020;9(Suppl 1):S67-S76.
33. Bononi A, Goto K, Ak G, et al. Heterozygous germline BLM mutations increase susceptibility to asbestos and mesothelioma. *Proc Natl Acad Sci U S A*. 2020;117(52):33466-33473.
34. Hung YP, Dong F, Watkins JC, et al. Identification of ALK Rearrangements in Malignant Peritoneal Mesothelioma. *JAMA Oncol*. 2018;4(2):235-238.
35. Xu J, Kadariya Y, Cheung M, et al. Germline mutation of Bap1 accelerates development of asbestos-induced malignant mesothelioma. *Cancer Res*. 2014;74(16):4388-4397.
36. Carbone M, Gazdar A, Butel JS. SV40 and human mesothelioma. *Transl Lung Cancer Res*. 2020;9(Suppl 1):S47-S59.
37. Ivanov SV, Miller J, Lucito R, et al. Genomic events associated with progression of pleural malignant mesothelioma. *Int J Cancer*. 2009;124(3):589-599.
38. Guo G, Chmielecki J, Goparaju C, et al. Whole-exome sequencing reveals frequent genetic alterations in BAP1, NF2, CDKN2A, and CUL1 in malignant pleural mesothelioma. *Cancer Res*. 2015;75(2):264-269.
39. Nasu M, Emi M, Pastorino S, et al. High Incidence of Somatic BAP1 alterations in sporadic malignant mesothelioma. *J Thorac Oncol*. 2015;10(4):565-576.
40. Yoshikawa Y, Emi M, Hashimoto-Tamaoki T, et al. High-density array-CGH with targeted NGS unmask multiple noncontiguous minute deletions on chromosome 3p21 in mesothelioma. *Proc Natl Acad Sci U S A*. 2016;113(47):13432-13437.
41. Bueno R, Stawiski EW, Goldstein LD, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. *Nat Genet*. 2016;48(4):407-416.
42. Goparaju CM, Blasberg JD, Volinia S, et al. Onconase mediated NFKβ downregulation in malignant pleural mesothelioma. *Oncogene*. 2011;30(24): 2767-2777.
43. Pass HI, Mew DJ, Carbone M, et al. Inhibition of hamster mesothelioma tumorigenesis by an antisense expression plasmid to the insulin-like growth factor-1 receptor. *Cancer Res*. 1996;56(17):4044-4048.
44. Beck AK, Pass HI, Carbone M, Yang H. Ranpirnase as a potential antitumor ribonuclease treatment for mesothelioma and other malignancies. *Future Oncol*. 2008;4(3):341-349.
45. Mutti L, Peikert T, Robinson BWS, et al. Scientific Advances and New Frontiers in Mesothelioma Therapeutics. *J Thorac Oncol*. 2018;13(9):1269-1283.
46. Guo Z, Carbone M, Zhang X, et al. Improving the Accuracy of Mesothelioma Diagnosis in China. *J Thorac Oncol*. 2017;12(4):714-723.
47. Galateau Salle F, Le Stang N, Nicholson AG, et al. New Insights on Diagnostic Reproducibility of Biphasic Mesotheliomas: A Multi-Institutional Evaluation by the International Mesothelioma Panel From the MESOPATH Reference Center. *J Thorac Oncol*. 2018;13(8):1189-1203.
48. Mao W, Zhang X, Guo Z, et al. Association of Asbestos Exposure With Malignant Mesothelioma Incidence in Eastern China. *JAMA Oncol*. 2017;3(4):562-564.
49. Goldberg M, Imbernon E, Rolland P, et al. The French National Me sothelioma Surveillance Program. *Occup Environ Med*. 2006;63(6):390-395.
50. McFadden DE, Clement PB. Peritoneal inclusion cysts with mural mesothelial proliferation. A clinicopathological analysis of six cases. *Am J Surg Patho*l. 1986;10(12):844-854.

51. Chapel DB, Schulte JJ, Husain AN, Krausz T. Application of immunohistochemistry in diagnosis and management of malignant mesothelioma. *Transl Lung Cancer Res*. 2020;9(Suppl 1):S3-S27.
52. Churg A, Sheffield BS, Galateau-Salle F. New Markers for Separating Benign From Malignant Mesothelial Proliferations: Are We There Yet? *Arch Pathol Lab Med*. 2016;140(4):318-321.
53. Carbone M, Shimizu D, Napolitano A, et al. Positive nuclear BAP1 immunostaining helps differentiate non-small cell lung carcinomas from malignant mesothelioma. *Oncotarget*. 2016;7(37):59314-59321.
54. Husain AN, Colby TV, Ordonez NG, et al. Guidelines for Pathologic Diagnosis of Malignant Mesothelioma 2017 Update of the Consensus Statement From the International Mesothelioma Interest Group. *Arch Pathol Lab Med*. 2018;142(1):89-108.
55. Chapel DB, Husain AN, Krausz T, McGregor SM. PAX8 Expression in a Subset of Malignant Peritoneal Mesotheliomas and Benign Mesothelium has Diagnostic Implications in the Differential Diagnosis of Ovarian Serous Carcinoma. *Am J Surg Pathol*. 2017;41(12):1675-1682.
56. Facchetti F, Lonardi S, Gentili F, et al. Claudin 4 identifies a wide spectrum of epithelial neoplasms and represents a very useful marker for carcinoma versus mesothelioma diagnosis in pleural and peritoneal biopsies and effusions. *Virchows Arch*. 2007;451(3):669-680.
57. Cristiano S, Leal A, Phallen J, et al. Genome-wide cell-free DNA fragmentation in patients with cancer. *Nature*. 2019;570(7761):385-389.
58. Adams D, Lin SH, Pass HI, et al. Circulating stromal cells as a potential blood-based biomarker for screening invasive solid tumors. *Journal of Clinical Oncology*. 2020;38(15_suppl):3535-3535.
59. Sina AA, Carrascosa LG, Liang Z, et al. Epigenetically reprogrammed methylation landscape drives the DNA self-assembly and serves as a universal cancer biomarker. *Nat Commun*. 2018;9(1):4915.
60. Flores RM. The mesothelioma surgery shift. *J Thorac Cardiovasc Surg*. 2016 Feb;151(2):485-6. doi: 10.1016/j.jtcvs.2015.10.054. Epub 2015 Oct 23.PMID: 26621318 No abstract available.
61. Flores RM, Pass HI, Seshan VE, Dycoco J, Zakowski M, Carbone M, Bains MS, Rusch VW. Extrapleural Pneumonectomy (EPP) versus Pleurectomy/Decortication (P/D) in the surgical management of malignant pleural mesothelioma (MPM): Results in 663 patients. *J Thorac Cardiovasc Surg*. 2008 Mar; 135(3):620-6.
62. Treasure T, Lang-Lazdunski L, Waller D, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. *The Lancet Oncology* 2011;12:763-72.
63. Lim E, Waller D, Lau K et al. Extended pleurectomy decortication and chemotherapy versus chemotherapy alone for pleural mesothelioma (MARS2): a phase 3 randomised controlled trial. *Lancet Respir Med. 2024;Jun; 12(6):457-466.* https://doi.org/10.1016/S2213-2600(24)00119-X
64. Rintoul RC, Ritchie AJ, Edwards JG, Waller DA, Coonar AS, Bennett M, Lovato E, Hughes V, Fox-Rushby JA, Sharples LD, MesoVATS Collaborators. Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): an open-label, randomised, controlled trial. *Lancet*. 2014 Sep 20;384(9948):1118-27. doi: 10.1016/S0140-6736(14)60418-9. PMID: 24942631.
65. Taioli E, Wolf AS, Flores RM. Meta-analysis of survival after pleurectomy decortication versus extrapleural pneumonectomy in mesothelioma. *Ann Thorac Surg*. 2015 Feb;99(2):472-80. doi: 10.1016/j.athoracsur.2014.09.056. PMID: 25534527.
66. Tomek S, et al. Chemotherapy for malignant pleural mesothelioma: past results and recent developments. *Br J Cancer*. 2003;88(2):167-174.
67. Byrne MJ, et al. Cisplatin and gemcitabine treatment for malignant mesothelioma: a phase II study. *J Clin Oncol*. 1999;17(1):25-30.
68. Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. *Ann Oncol*. 2004;15(2):257-260.
69. Nowak AK, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. *Br J Cancer*. 2002;87(5):491-496.
70. Vogelzang NJ, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol*. 2003;21(14):2636-2644.
71. van Meerbeeck JP, et al. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. *J Clin Oncol*. 2005;23(28):6881-6889.
72. Castagneto B, et al. Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma (MPM). *Ann Oncol*. 2008;19(2):370-373.
73. Ceresoli GL, et al. Pemetrexed plus carboplatin in elderly patients with malignant pleural mesothelioma: combined analysis of two phase II trials. *Br J Cancer*. 2008;99(1):51-56.
74. Ceresoli GL, et al. Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma. *J Clin Oncol*. 2006; 24(9):1443-1448.
75. Santoro A, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaive patients with malignant pleural mesothelioma: results of the International Expanded Access Program. *J Thorac Oncol*, 2008;3(7):756-763.
76. de Gooijer CJ, et al. Switch-maintenance gemcitabine after first-line chemotherapy in patients with malignant mesothelioma (NVALT19): an investigator-initiated, randomised, open-label, phase 2 trial. *Lancet Respir Med*. 2021;9(6):585-592.
77. van den Bogaert DP, et al. Pemetrexed maintenance therapy in patients with malignant pleural mesothelioma. *J Thorac Oncol*. 2006;1(1):25-30.
78. Maruyama R, et al. Triplet chemotherapy with cisplatin, gemcitabine and vinorelbine for malignant pleural mesothelioma. *Jpn J Clin Oncol*. 2005;35(8):433-438.
79. Hillerdal G, et al. Treatment of malignant pleural mesothelioma with carboplatin, liposomized doxorubicin, and gemcitabine: a phase II study. *J Thorac Oncol*. 2008;3(11):1325-1331.
80. Zalcman, G., et al., Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2016;(387):1405-1414.
81. Kindler HL, Ismaila N, and Hassan R. Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline Summary. *J Oncol Pract*. 2018; 14(4):256-264.
82. Fennell DA, Casbard AC, Porter C, Rudd R, Lester JF, Nicolson M, Morgan B, Steele JP, Darlison L, Gardner GM and Nixon LS. A randomized phase II trial of

oral vinorelbine as second-line therapy for patients with malignant pleural mesothelioma. in American Society of Clinical Oncology. 2021.
83. Upham JW, Garlepp MJ, Musk AW, Robinson BW. Malignant mesothelioma: new insights into tumour biology and immunology as a basis for new treatment approaches. *Thorax*. 1995 Aug;50(8):887-93. doi: 10.1136/thx.50.8.887.
84. Brosseau S, Danel C, Scherpereel A, Mazières J, et al. Shorter Survival in Malignant Pleural Mesothelioma Patients With High PD-L1 Expression Associated With Sarcomatoid or Biphasic Histology Subtype: A Series of 214 Cases From the Bio-MAPS Cohort. *Clin Lung Cancer*. 2019 Sep;20(5):e564-e575.
85. Kosari F, Disselhorst M, Yin J, Peikert T. et al. Tumor Junction Burden and Antigen Presentation as Predictors of Survival in Mesothelioma Treated With Immune Checkpoint Inhibitors. *J Thorac Oncol*. 2021 Nov 17;S1556-0864(21)03319-0. doi: 10.1016/j.jtho.2021.10.022. Online ahead of print.
86. Fennell D, Kirkpatrick E, Cozens K and Nye M. Trials 23018 Vol 19 Article number 233.
87. Baas P, Scherpereel AK, Nowak A et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial *Lancet.* 2021 Jan 30;397(10272):375-386.
88. Popat S, Curioni-Fontecedro A, Dafni U, Shah R. A multicentre randomised phase III trial comparing pembrolizumab versus single-agent chemotherapy for advanced pre-treated malignant pleural mesothelioma: the European Thoracic Oncology Platform (ETOP 9-15) PROMISE-meso trial *Ann Oncol*. 2020 Dec;31(12):1734-1745. doi: 10.1016/j.annonc.2020.09.009. Epub 2020 Sep 22. PMID: 32976938.
89. Chu Q, Perrone F, Greillier L et al. Pembrolizumab plus chemotherapy versus chemotherapy in untreated advanced pleural mesothelioma in Canada, Italy and France: a phase 3, open-label, randomized controlled trial. *Lancet.* 2023;Dec16;402.(10419):2295-2306.

24

ADVANCES IN THE TREATMENT OF THYMIC MALIGNANCIES

Frank Detterbeck[1] **and Giuseppe Giaccone**[2] | [1]Yale University School of Medicine, New Haven, USA; [2]Weill Cornell Medical College, New York, USA

INTRODUCTION

Thymic neoplasms are rare tumors. An age-standardized incidence of 2.5-2.8 per million is reported in well documented population studies;[1,2] lower rates are reported from registries such as the Surveillance Epidemiology and End Results (SEER) database which misses smaller thymomas (previously thought to be benign).[3,4] As with all rare tumors, progress is hampered by the limited number of cases and care that is delivered in a disseminated manner. In a systematic review of literature prior to 2010, 85% of papers involved case reports or cohorts of <30 patients, only 5% retrospective cohorts of >100 patients, and a handful of small prospective studies.[5] Approximately 30% of patients with thymoma are associated with autoimmune disorders, the most common being myasthenia gravis. Autoimmune disorders are rare in thymic carcinomas. Second tumors are also more common in patients with thymic epithelial tumors.

Particularly in the past decade, interested clinicians and researchers have developed regional and international infrastructure to foster collaboration; this has had a major impact on treatment for thymic malignancies. The regional organization with the longest history is the Japanese Association for Research on the Thymus (JART); other major groups include the European Society of Thoracic Surgeons (ESTS) thymic group, the Chinese Alliance for Research in Thymoma (ChART), the Korean Association for Research on the Thymus (KART), and the Réseau Tumeurs THYMiques et Cancer (RYTHMIC). International infrastructure is provided by the International Association for the Study of Lung Cancer (IASLC, which has a focus on all thoracic malignancies despite its name) and the International Thymic Malignancy Interest Group (ITMIG). These groups have organized collective databases and research studies. ITMIG has defined standards that provide a foundation for communication and collaboration.[6-15] Furthermore, regional and international tumor boards have been established by RYTHMIC and ITMIG.

CLASSIFICATION

Stage

Stage classification describes the anatomic extent of disease. A consistent nomenclature is a critical foundation for collaboration among different centers; progress was hampered by the use of many different stage classification systems prior to the first official stage classification for thymic malignancies which took effect in 2017. This was based on a joint effort by the IASLC and the ITMIG, leading to assembly of a global database of over 10,000 cases, formation of a multidisciplinary international committee, and extensive statistical analysis.[16-19] Currently a new database of similar size is being analyzed to develop refinements to the stage classification for the 9th edition of TNM.[20]

The thymic stage classification system involves tumor (T), node (N), and metastasis (M) components. The T component categories reflect increasing levels of invasion into structures adjacent to the thymus (Table 1).[19] Contrary to many (empiric) prior staging

systems, invasion through the "thymic capsule" was not included because this has no prognostic impact. Nodal involvement is divided into N1 (anterior mediastinal and anterior cervical nodes that are close to the thymus) and N2 (middle mediastinal and deep cervical nodes), as defined by a thymic node map.[18,21] Pleural and pericardial implants are designated as M1a, extrathoracic metastases as M1b.[18] The various TNM categories are assembled in stage groups (Figure 1).[17]

Table 1. T, N, M Categories and Descriptors

Category	Definition (Involvement of):[a]
T1 a	Encapsulated or unencapsulated, with or without extension into mediastinal fat
b	Extension into mediastinal pleura
T2	Pericardium
T3	Lung, Brachiocephalic Vein, Superior Vena Cava, Chest Wall, Phrenic Nerve, Hilar (extrapericardial) pulmonary vessels
T4	Aorta, Arch Vessels, Main Pulmonary Artery, Myocardium, Trachea, or Esophagus
N0	No nodal involvement
N1	Anterior (perithymic) nodes
N2	Deep intrathoracic or cervical nodes
M0	No metastatic pleural, pericardial or distant sites
M1 a	Separate pleural or pericardial nodule(s)
b	Pulmonary intraparenchymal nodule or distant organ metastasis

Each T category defines a "level of invasion"; A tumor is classified according to the highest T level of involvement (one or more structures in that level) with or without any invasion of structures of lower T levels.

[a]Involvement must be pathologically proven in pathologic staging

Stage	Invasion of/metastasis to:	T	N	M
I	Anterior fat	**T1**a	N0	M0
	… with mediastinal pleura	**T1**b	N0	M0
II	Pericardium	**T2**	N0	M0
IIIA	Lung, veins, phrenic n, chest wall	**T3**	N0	M0
IIIB	Aorta, main PA, heart, trachea	**T4**	N0	M0
IVA	N1 (anterior region)	T any	**N1**	M0
	M1a (pleural/pericardial implants)	T any	N0, 1	**M1a**
IVB	N2 (deep region)	T any	**N2**	M0, 1a
	M1b (extrathoracic/distant sites)	T any	N any	**M1b**

Figure 1. Stage Grouping (8th Edition of TNM Staging). Grid of T, N, and M categories assembled into stage groups.[17] PA, pulmonary artery; phrenic n, phrenic nerve.

Histology

The classification of thymic malignancies has been debated for decades; the World Health Organization (WHO) recognized 3 histotypes of thymic malignancies: thymoma, thymic carcinoma (TC), and neuroendocrine tumors of the thymus (NETT). All thymomas are classified as malignant; the term "benign thymoma" should not be used.[22-24]

The WHO divides thymomas into 5 subgroups: A, AB, B1, B2, and B3. However, most thymomas are a mixture of subtypes. Therefore, an adequate assessment is needed to define the subtype (≥5 sections of a surgical specimen),[7,25,26] and the subtype should be reported by the major subtype and additional subtypes in 10% increments.[22] The subtype should not be defined based on a limited biopsy alone.[10,22] Controversial aspects of the thymoma classification were resolved through international workshops conducted by ITMIG; these were incorporated in the current WHO definitions.[22-24,27] Major differences among histological subtypes are related to the lymphocytic vs epithelial component and cell atypia. Thymic epithelial cells are recognized as the tumor cells, whereas the contribution of thymocytes is unclear.

Retrospective studies have reported a relationship between histological subtype and prognosis; however, higher grade tumors are associated with a higher stage. The most definitive analysis of the impact of the thymoma subtypes involved 4,221 cases from the ITMIG worldwide database.[28] Univariate associations with OS or recurrence were largely explained by differences

in age, stage, and R status. Multivariate analysis demonstrated only a difference in recurrence of type AB vs either type B1+B2 or B3, and only among stage I tumors.[28]

Genetic Characteristics

A major step forward in understanding the molecular characterization of thymic epithelial tumors comes from inclusion of thymic malignancies in The Cancer Genome Atlas Project (TCGA) of the US National Institute of Health (NIH), performed on 117 resected tumors. The TCGA integrates whole exome sequencing, DNA methylation, chromosomal alterations, mRNA, miRNA and proteomics analyses, and clinical characteristics in a state-of-the art multi-platform approach. By transcriptomic analysis, the tumors fell into 4 distinct molecular groups that largely correlated with WHO subtypes: a B-like cluster, a thymic carcinoma-like cluster, an A-like cluster, and an AB-like cluster. The WHO AB tumors partially mapped to the A-like cluster, suggesting that distinct subtypes of AB tumors may need to be distinguished, or that the distinction of the A- and AB-like clusters may be only partial.[29]

The most frequent mutation is a unique L404H substitution in the GTF2i gene, as was previously described in a smaller study.[30] This mutation is more commonly found in less aggressive histological subtypes (over 70% of thymomas type A and AB), but recent studies employing enrichment and targeted sequencing reported 40% GTF2i mutations also in type B thymomas.[31] More aggressive histological types commonly display mutations in TP53, which is prognostically unfavorable.[32] Tumor mutational burden is very low in these tumors, but significantly higher in thymic carcinomas compared to thymomas.[29] Rare subsets of thymic tumors carry potentially targetable mutations in genes such as c-Kit in about 10% of thymic carcinomas.[33]

The study of these rare tumors has been hampered by the lack of preclinical models, and most studies have been performed on human material obtained at resection. Only a handful of cell lines are currently available, but recently a knock-in mouse model for the GTF2i mutation has been created, which hopefully will help study the biology and potentially drug testing.[34]

TREATMENT

Localized Thymoma

Localized disease refers to a thymic tumor that is confined to the prevascular (anterior) mediastinal space with or without invasion of the mediastinal fat (Stage I). Abutment against the lung or pericardium should be included when there is no invasion into these structures.

Surgical Resection

Surgical resection is the primary treatment modality of localized thymic malignancies.[35-37] The ITMIG published empiric standards for surgical resection.[7] Every effort should be made to achieve a complete resection, including any adjacent potentially invaded tissues. The surgeon should mark areas of concern with stitches as the resection proceeds as well as areas of disruption of the loose areolar mediastinal tissue that do not represent a resection margin and might be misinterpreted. The use of a "mediastinal board" (a drawing of the mediastinum upon which the specimen is placed) is encouraged, which greatly facilitates orientation and communication between the surgeon and the pathologist.[7] For stage I, thymomas removal of adjacent lymph nodes is encouraged; for stage III-IV, a systematic dissection of N1 is recommended and a systematic sampling of N2 nodes is encouraged. The latter is true for any thymic carcinoma.[7]

Sternotomy is the most commonly used incision, but minimally invasive approaches are becoming popular (Video-assisted, Robotic assisted, subxiphoid).[38] ITMIG standards mandate that minimally invasive resections must be R0 en-bloc resections without disruption of the specimen (either during handling or removal).[8] Several non-randomized comparisons (NRCs) found no difference in perioperative results (operative time, complications);[39-41] a systematic review noted a decrease in postoperative stay from 9 to 8 days.[40] The rate of complete resection is equivalent.[39,40] Although the follow-up in most studies is

too short to provide confidence, there is no indication that overall (OS) or recurrence are compromised by a minimally invasive approach.[39-41] A surgeon's comfort level is an important consideration. The benefit of a minimally invasive approach is minimal, and before embarking on a less familiar technique, the surgeon should question whether their clinical volume is sufficient to allow a learning curve to eventually be overcome.[8]

Is a total thymectomy needed in patients without myasthenia gravis, as opposed to resection of the thymoma alone? Several adjusted NRCs have suggested no difference in morbidity and mortality, and an equivalent R0 resection rate.[42-49] However, there are conflicting results regarding long-term outcomes, with most suggesting no difference but some reporting lower freedom from recurrence and overall survival (OS).[42-49] However, the degree of adjustment for confounders in these studies is limited.

Adjuvant Radiotherapy

The role of adjuvant radiotherapy (RT) for resected localized thymic malignancies was variable in the past, based on a controversial rationale and institutional tradition.[36] For R0 resected thymoma, adjuvant RT has not been recommended by clinical guidelines for several years for Masaoka/Masaoka-Koga (M/MK) stage I thymoma, but has been vaguely suggested for consideration for M/MK stage II thymoma.[50,51]

Data does not support the use of adjuvant RT for localized disease. None of the NRCs reporting stage specific outcomes found a benefit in TNM stage I (M/MK stage I,II).[52-58] Furthermore, none of the NRCs of outcomes by R status found a benefit of RT after R0 resection.[56-62] Furthermore, the potential benefit of RT after R0 resection is low given a 10-year local recurrence rate in the tumor bed of 2% for TNM stage I and 6% for stage II (calculated from overall recurrence rates and the proportion of local recurrences).[17,36]

Locally Invasive Thymoma

Locally invasive tumors are those directly invading pericardium (T2), lung, phrenic nerve, innominate vein, great vessels, or chest wall (T3) and less often structures such as aorta, myocardium, trachea, and esophagus (T4).[19]

Surgical Resection

It is widely accepted that every effort should be made to accomplish a complete resection, including invaded structures.[50,51,63] Frozen section interpretation can be difficult; while intraoperative frozen section can be useful, it should not necessarily trump the surgeon's judgment.[7] In the ITMIG-IASLC database, an R0 resection was achieved in nearly 90% of stage III patients.[19]

Involvement of one phrenic nerve generally calls for resection unless the patient has limited pulmonary reserve. Although temporary phrenic paralysis is seen in most patients even with preservation, after recovery there is better lung function with preservation (forced expiratory volume in 1 second of 96% vs 76% of preoperative values).[64] However, preservation is associated with higher recurrence rates but no difference in OS.[64,65]

Vascular invasion adds complexity but should not be a deterrent to complete resection. If necessary, there should be no hesitation to resect the innominate vein or replace the superior vena cava (SVC) with a tube graft.[66-69] A substantial proportion of patients experience no recurrence >5 years after SVC resection.[66-70] Long recurrence free survival (RFS) has been reported in experienced centers in selected cases involving resection of the right atrium, myocardium, aorta or intrapericardial pulmonary artery.[71-74]

When should surgery be the first therapeutic modality for locally invasive thymic malignancy? A practical approach may be to proceed to primary surgery when there is no concern about the ability to achieve an R0 resection (i.e., the amount of invasion is limited, and additional tissue can be easily resected if intraoperative findings are worse than anticipated). If surgery may result in an R1 or R2 resection, general consensus is that preoperative therapy is a better approach than primary surgery.[50,51,63] In the ESTS (surgical) database, 25% of stage III thymomas underwent induction therapy and 69% received adjuvant therapy.[75]

Adjuvant RT

The role of adjuvant RT for locally invasive thymic malignancies has been controversial. Multivariate analyses and adjusted NRCs show mixed results regarding OS; a somewhat more consistent benefit is suggested regarding disease- or cause-specific survival.[52-62,76-85] However, in all studies major confounders were not accounted for (e.g., R-status, performance status, comorbidities). Many studies did not include a landmark analysis to account for the inherent selection bias (early postoperative deaths are systematically excluded from the RT arms but not the surgery-only arms). Thus, the available data must be viewed as inconclusive.

Clearly more research is needed, ideally prospective and focused on local recurrence rates. In a 2011 survey of ESTS surgeons, the majority (~70%) administered adjuvant RT or chemoradiotherapy to resected stage III thymoma.[86] Postoperative RT for R0 resected M/MK stage III thymoma and thymic carcinoma is recommended in the 2016 European Society of Medical Oncology (ESMO) guidelines and consideration thereof suggested in the 2017 and 2023 National Comprehensive Cancer Network (NCCN) guideline.[50,51,87]

Preoperative Therapy

Preoperative therapy is a common treatment strategy for locally invasive thymic malignancies that are deemed potentially difficult to resect upfront in an R0 fashion. However, this assessment is generally made in a subjective and variable manner. Data does not support size as a predictor of R0 resection.[19] In studies involving mostly preoperative chemotherapy, about 2/3rd of patients experienced a radiographic response, and in about 2/3rd of patients undergoing surgery an R0 resection was achieved.[5,88-101] Long-term outcomes are generally quite encouraging - OS rates at 5 and 10 years are ~75% and 50% for these locally invasive tumors. A variety of chemotherapy regimens have been used. Most studies involved chemotherapy alone, but some included concurrent chemoradiotherapy. There is no clear signal favoring one regimen or combination of modalities.

In summary, evidence is suggestive but debatable whether preoperative therapy improves outcomes, although radiographic and pathologic response rates are substantial. It is unclear whether preoperative therapy should involve chemotherapy alone or with radiotherapy. How to select patients for preoperative therapy is undefined. A rationale-based approach might be to proceed directly to resection for locally advanced tumors deemed to have a high chance of an R0 resection. In patients in whom this is questionable, preoperative therapy is reasonable.

Pleural Dissemination

Multimodality Treatment with Surgery

Selected patients with pleural implants undergo surgical resection. Typically, preoperative chemotherapy is given, less often adjuvant chemo- or radiotherapy. Despite the extent of the disease, a macroscopic complete resection is able to be accomplished in over half of the patients. Most often the resection has entailed a complete thymectomy with all involved adjacent tissues (e.g., pericardium, lung, vessels) and local pleurectomy together with all pleural or diaphragmatic implants; extrapleural pneumonectomy is now performed only rarely. Patient selection is clearly important but undefined. Conflicting data exists regarding whether a smaller number of lesions is important.[102-105]

The 5- and 10-year OS of about 75% and 50% after curative-intent multimodality therapy is encouraging.[82,101-102] Long-term outcomes seem to be better among series involving more recent time periods. Follow-up intervals of up to 10 years without recurrence are reported.[110] However, most patients experience a recurrence with an average interval of approximately 3.2 years.[102,107-109,113] Often, re-resection of the recurrence is undertaken.

At the time of resection, intrapleural therapy is sometimes used with the rationale of addressing microscopic disease on pleural surfaces. Most often this has involved heated cisplatin chemotherapy (typically 42° C over 1 hour, sometimes combined with an anthracycline); heated povidone-iodine has also been

used. Perioperative mortality has been low. Grade ≥3 morbidity is reported in 10-25%.[105,107,109.,119-121] OS is slightly higher in studies with vs without intrapleural therapy and the rate of recurrence appears better, although ~50% of patients experience a recurrence (with an average interval of approximately 4 years).[107,109,119,120] However, this can easily be due to selection. Thus, intrapleural therapy appears to be a reasonable but not clearly better treatment approach.

Palliative Treatment

Chemotherapy is moderately effective as a palliative treatment. In the past decade, the number of prospective phase II studies has increased dramatically. However, no single optimal regimen has emerged; no RCTs comparing one regimen to another have been done. The NCCN and ESMO guidelines for thymoma recommend cyclophosphamide, adriamycin, cisplatin (CAP), or CAP with prednisone, cisplatin, doxorubicin, vincristine and cyclophosphamide (ADOC), cisplatin and etoposide (PE), etoposide, ifosfamide and cisplatin (VIP), and CbTx (carboplatin and paclitaxel) and CODE (cisplatin, vincristine, doxorubicin, and etoposide.[50,87] These regimens reported a response rate of over 50%. Carboplatin-paclitaxel is often preferred for patients with thymic carcinoma, where the response rate is 22-36%.[123,124] The CAP regimen, as well as other anthracycline containing regimens, are still widely used and they may yield better outcomes compared to regimens that do not contain anthracyclines, however no randomized study has ever compared these regimens.

Reported long-term outcomes are variable (likely reflecting differences in the setting, stage, histotype). More recent studies tend to show slightly better results. In general, long-term results are better for thymoma than for TC. Progression-free survival (PFS) is ~16 months for thymoma and ~8 months for TC; 2-year OS is ~60-70% for thymoma and ~40-50% for TC.

Multiple prospective studies have assessed ≥2nd line chemotherapy. Generally, the response rates, PFS, and OS results are only slightly less than for 1st line treatment. Targeted therapies have been investigated; response and PFS results are low.[125] Driver gene mutations are relatively uncommon in thymic malignancies and do not clearly identify which patients will respond to targeted therapy.[126] Angiogenesis inhibitors, such as sunitinib and lenvatinib, have shown a response rate of 26% and 38%, respectively, in thymic carcinomas.[127,128]

Immunotherapy with immune checkpoint inhibitors has also been explored, almost exclusively in TC. Results include an ORR of ~25%, a PFS of only ~6 months and a 2-year OS of ~50% in a pretreated population of TC treated with pembrolizumab. Long term survival in a pembrolizumab phase II study has been demonstrated (approximately 20% at approximately 5 years).[129] Adverse grade ≥3 autoimmune toxicities are seen in ~15% (this is >70% in patients with thymoma).[130-132] Novel combinations[133] and targeted agents are being investigated. In addition, recently a handful of randomized trials have been activated in this disease.

SUMMARY

The past decade has seen a transformation of the state of the science regarding thymic malignancies. The evidence-base previously consisted predominantly of case series and only a handful of prospective studies. Now there are many prospective studies, a few RCTs, and many adjusted NRCs that provide a much better basis for treatment recommendations. Standardization of terms, a worldwide stage classification system, and infrastructure for collaborative studies through the organization of interested clinicians in several national and international organizations provided an essential foundation. The development of collaborative databases, and the willingness to fund clinical trials in rare disease was also a critical component.

The major currently used treatment approaches and the underlying evidence is summarized in Table 2. While treatment is no longer essentially empiric and based on institutional traditions, it is also clear that much work still needs to be done. It is always challenging in a rare disease to carry out research.

Table 2. Summary of Treatment Strategies and Evidence in Stage I-IVA Thymoma

Description	Localized	Locally Advanced	Intrapleural implants
TNM stage	**I**	**II, III**	**IVA**
Neoadjuvant therapy	Not used	Sometimes used; Data is suggestive but confounded; May be best used when achieving an R0 resection might be difficult	Sometimes used; Not well studied
Primary treatment	R0 resection	R0 resection	Macroscopic complete resection if possible; chemotherapy or chemoradiotherapy if not
Adjuvant RT	Not recommended; Data suggests no benefit	Often used; Inconclusive, conflicting data with strong confounders; Strongest indication is R1,2 resection or close margin	Often used to bed of resected pleural implants; Impact undefined
Adjuvant chemotherapy	No data	Rarely used; Limited role unless partial or no resection performed	Usually given if not done preoperatively; Data establishes feasibility but impact undefined

Summary of major treatment strategies; the available data, and patient selection factors. See text for details.

The degree of progress that has been achieved is remarkable, and a testament to the power of collaboration and building an infrastructure to support it. It sets the stage for significant further progress in the next decade.

References

1. Mariusdottir E, Nikulasson S, Bjornsson J, Gudbjartsson T. Thymic epithelial tumours in Iceland: incidence and histopathology, a population-based study. *APMIS*. 2010;118(12):927-933.
2. Engel P, Marx A, Muller-Hermelink HK. Thymic tumours in Denmark. A retrospective study of 213 cases from 1970-1993. *Pathol Res Pract*. 1999;195(8): 565-570.
3. Engels EA, Pfeiffer RM. Malignant thymoma in the United States: demographic patterns in incidence and associations with subsequent malignancies. *Int J Cancer*. 2003;105(4): 546-551.
4. dos Santos Silva I, Swerdlow A. Thymus cancer epidemiology in England and Wales. *Br J Cancer*. 1990;61:899-902.
5. Detterbeck F. The Creation of the International Thymic Malignancies Interest Group as a Model for Rare Diseases. In: Govindan R e, ed. *2012 ASCO Educational Book*. Alexandria, VA: American Society of Clinical Oncology; 2012:471-474.
6. Huang J, Wang Z, Loehrer P, Okumura M, Detterbeck F. Standard Outcome Measures for Thymic Malignancies. *J Thorac Oncol.* 2010;5:2017-2023.
7. Detterbeck F, Moran C, Huang J, et al. Which Way is Up? Policies and Procedures for Surgeons and Pathologicsts Regarding resection Specimens of Thymic Malignancy. *J Thorac Oncol*. 2011;6(7 Suppl 3):S1730-S1738.
8. Toker A, Sonett J, Zielinski M, Rea F, Tomulescu V, Detterbeck F. Standard Terms, Definitions, and Policies for Minimally Invasive Resection of Thymoma. *J Thorac Oncol*. 2011;6(7 Suppl 3):S1739-S1742.
9. Marom E, Rosado-de-Christenson M, Bruzzi J, Hara M, Sonett J, Ketai L. Standard Report Terms for Chest Computed Tomography Reports of Anterior Mediastinal Masses Suspicious for Thymoma. *J Thorac Oncol*. 2011;6(7 Suppl 3):S1717-S1723.
10. Marchevsky A, Marx A, Strobel P, et al. Policies and Reporting Guidelines for Small Biopsy Specimens of Mediastinal Masses. *J Thorac Oncol*. 2011;6(7 Suppl 3):S1724-S1729.
11. Gomez D, Komaki R, Yu J, Ikushima H, Bezjak A. Radiation Therapy Definitions and Reporting Guidelines for Thymic Malignancies. *J Thorac Oncol*. 2011;6(7):S1743-S1748.
12. Girard N, Lal R, Wakelee H, Riely G, Loehrer P. Chemotherapy Definitions and Policies for Thymic Malignancies. *J Thorac Oncol*. 2011;6(7 Suppl 3): S1749-S1755.
13. Benveniste MFK, Korst RJ, Rajan A, Detterbeck F, Marom EM. A Practical Guide from the International Thymic Malignancy Interest Group (ITMIG) Regarding the Radiographic Assessment of Treatment Response of Thymic Epithelial Tumors using Modified RECIST Criteria. *J Thorac Oncol*. 2014 9(9, Supplement 2):S119-124.
14. Carter B, Tomiyama N, Bhora F, et al. A Modern Definition of Mediastinal Compartments. *J Thorac Oncol*. 2014 9(9, Supplement 2):S97-S101.
15. den Bakker M, Roden A, Marx A, Marino M. Histologic classification of thymoma: a practical guide for routine cases. *J Thorac Oncol*. 2014 9(9, Supplement 2):S125-S130.
16. Detterbeck F, Asamura H, Crowley J, et al. The IASLC/ITMIG Thymic Malignancies Staging Project-Development of a Stage Classification for Thymic Malignancies. *J Thorac Oncol*. 2013;8:1467-1473.

17. Detterbeck F, Stratton K, Giroux D, et al. The ITMIG/IASLC Thymic Epithelial Tumors Staging Project: Proposal for an Evidence-Based Stage Classification System for the Forthcoming (8th) Edition of the TNM Classification of Malignant Tumors. *J Thor Oncol*. 2014 9 (9, Supplement 2):S65-S72.
18. Kondo K, van Schil P, Detterbeck F, et al. The ITMIG/IASLC Thymic Epithelial Tumors Staging Project: Proposals for the N and M Components for the Forthcoming (8th) Edition of the TNM Classification of Malignant Tumors. *J Thorac Oncol*. 2014 9(9, Supplement 2):S81-S87.
19. Nicholson A, Detterbeck C, Marino M, et al. The ITMIG/IASLC Thymic Epithelial tumors Staging Project: Proposals for the T component for the Forthcoming (8th) Edition of the TNM Classification of malignant tumors. *J Thor Oncol*. 2014 9 (9, Supplement 2):S73-S80.
20. Ruffini E, Rami-Porta R, Huang J, et al. The International Association for the Study of Lung Cancer Thymic Epithelial Tumor Staging Project: Unresolved Issues to be Addressed for the Next Ninth Edition of the TNM Classification of Malignant Tumors. *J Thor Oncol*. 2022;17(6):838-851.
21. Bhora F, Chen D, Detterbeck F, et al. The ITMIG/IASLC Thymic Epithelial Tumors Staging Project: A Proposed Lymph Node Map for Thymic Epithelial Tumors in the Forthcoming 8th Edition of the TNM Classification for Malignant Tumors. *J Thor Oncol*. 2014 9 (9, supplement 2): S88-S96.
22. Marx A, Strobel P, Badve S, et al. ITMIG Consensus Statement on the Use of the WHO Histological Classficiation of Thymoma and Thymic Carcinoma: Refined Definitions, Histological Criteria and and Reporting. *J Thorac Oncol*. 2014;9(5):596-611.
23. Marx A, Chan JKC, Chalabreysse L, et al. The 2021 WHO Classification of Tumors of the Thymus and Mediastinum: What Is New in Thymic Epithelial, Germ Cell, and Mesenchymal Tumors? *J Thorac Oncol*. 2022;17(2):200-213.
24. *WHO Classification of Tumours 5th Edition*. Vol 5. 5 ed. France: International Agency for Research on Cancer (IARC); 2021.
25. Moran CA, Suster S. On the histologic heterogeneity of thymic epithelial neoplasms. Impact of sampling in subtyping and classification of thymomas. *Am J Clin Pathol*. 2000;114(5):760-766.
26. Weydert J, De Young B, Leslie K. Recommendations for the Reporting of Surgically Resected Thymic Epithelial Tumors. *Am J Clin Pathol*. 2009;132(1): 10-15.
27. Marx A. Tumours of the thymus. *WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart 4th edition* 2015.
28. Weiss C-A, Yao X, Deng Y, et al. The Impact of Thymoma Histotype on Prognosis in a Worldwide Database. *J Thorac Oncol*. 2015;10(2):367-372.
29. Radovich M, Pickering CR, Felau I, et al. The Integrated Genomic Landscape of Thymic Epithelial Tumors. *Cancer Cell*. 2018;33(2):244-258.e210.
30. Petrini I, Meltzer PS, Kim IK, et al. A specific missense mutation in GTF2I occurs at high frequency in thymic epithelial tumors. *Nat Genet*. 2014;46(8): 844-849.
31. Higuchi R, Goto T, Hirotsu Y, et al. Primary Driver Mutations in GTF2I Specific to the Development of Thymomas. *Cancers (Basel)*. 2020;12(8).
32. Wang Y, Thomas A, Lau C, et al. Mutations of epigenetic regulatory genes are common in thymic carcinomas. *Sci Rep*. 2014;4:7336.
33. Barachini S, Pardini E, Burzi IS, Sardo Infirri G, Montali M, Petrini I. Molecular and Functional Key Features and Oncogenic Drivers in Thymic Carcinomas. *Cancers (Basel)*. 2023;16(1).
34. He Y, Kim IK, Bian J, et al. A Knock-In Mouse Model of Thymoma With the GTF2I L424H Mutation. *J Thorac Oncol*. 2022;17(12):1375-1386.
35. Detterbeck FC, Parsons AM. Thymic tumors. *Ann Thorac Surg*. 2004;77(5): 1860-1869.
36. Detterbeck F, Parsons A. Thymic Tumors: A Review of Current Diagnosis, Classification, and Treatment. In: Patterson GA CJ, Deslauriers J, Lerut A, Luketich JD, Rice TW, Pearson FG, ed. *Thoracic and Esophageal Surgery, 3rd Edition*. Philadelphia: Elsevier; 2008:1589-1614.
37. Detterbeck FC, Counts S, EM M. Thymic Neoplasms: A Comprehensive Review of the Diagnosis, Classification, and Treatment. 2021.
38. Ruffini E, Guerrera F, Brunelli A, et al. Report from the European Society of Thoracic Surgeons prospective thymic database 2017: a powerful resource for a collaborative global effort to manage thymic tumours. *Eur J Cardiothorac Surg*. 2019;55(4):601-609.
39. Burt BM, Yao X, Shrager J, et al. Determinants of Complete Resection of Thymoma by Minimally Invasive and Open Thymectomy: Analysis of an International Registry. *J Thorac Oncol*. 2017;12(1):129-136.
40. Friedant AJ, Handorf EA, Su S, Scott WJ. Minimally Invasive versus Open Thymectomy for Thymic Malignancies: Systematic Review and Meta-Analysis. *J Thorac Oncol*. 2016;11(1):30-38.
41. Agatsuma H, Yoshida K, Yoshino I, et al. Video-Assisted Thoracic Surgery Thymectomy Versus Sternotomy Thymectomy in Patients With Thymoma. *The Annals of Thoracic Surgery*. 2017;104(3):1047-1053.
42. Nakagawa K, Asamura H, Sakurai H, Watanabe S, Tsuta K. Does the mode of surgical resection affect the prognosis/ recurrence in patients with thymoma? *J Surg Oncol*. 2014;109(3):179-183.
43. Onuki T, Ishikawa S, Iguchi K, et al. Limited thymectomy for stage I or II thymomas. *Lung Cancer*. 2010;68(3): 460-465.
44. Tseng YC, Hsieh CC, Huang HY, et al. Is thymectomy necessary in nonmyasthenic patients with early thymoma? *J Thorac Oncol*. 2013;8(7):952-958.
45. Narm KS, Lee CY, Do YW, et al. Limited thymectomy as a potential alternative treatment option for early-stage thymoma: A multi-institutional propensity-matched study. *Lung Cancer*. 2016;101:22-27.
46. Nakagawa K, Yokoi K, Nakajima J, et al. Is Thymomectomy Alone Appropriate for Stage I (T1N0M0) Thymoma? Results of a Propensity-Score Analysis. *The Annals of Thoracic Surgery*. 2016;101(2):520-526.
47. Gu Z, Fu J, Shen Y, et al. Thymectomy versus tumor resection for early-stage thymic malignancies: a Chinese Alliance for Research in Thymomas retrospective database analysis. *J Thorac Dis*. 2016; 8(4):680-686.
48. Bae MK, Lee SK, Kim HY, et al. Recurrence after thymoma resection according to the extent of the resection. *J Cardiothorac Surg*. 2014;9:51.
49. Tassi V, Ceccarelli S, Zannori C, et al. Could thymomectomy be a reasonable option for non-myasthenic thymoma patients? *J Thorac Dis*. 2017;9(10): 3817-3824.
50. Girard N, Ruffini E, Marx A, Faivre-Finn C, Peters S. Thymic epithelial tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26 Suppl 5:v40-55.
51. NCCN. NCCN Clinical Practice Guidelines in Oncology: Thymomas and Thymic Carcinomas 2017; Version 1.2017. Accessed April 21, 2017, 2017.

52. Utsumi T, Shiono H, Kadota Y, et al. Postoperative radiation therapy after complete resection of thymoma has little impact on survival. *Cancer.* 2009;115(23):5413-5420.
53. Zhang C, Wang Q, Hu L, et al. The Prognostic Value of Postoperative Radiotherapy for Thymoma and Thymic Carcinoma: A Propensity-Matched Study Based on SEER Database. *Cancers (Basel)*. 2022;14(19).
54. Mou H, Liao Q, Hou X, Chen T, Zhu Y. Clinical characteristics, risk factors, and outcomes after adjuvant radiotherapy for patients with thymoma in the United States: analysis of the Surveillance, Epidemiology, and End Results (SEER) Registry (1988-2013). *Int J Radiat Biol*. 2018;94(5):495-502.
55. Forquer JA, Rong N, Fakiris AJ, Loehrer PJ, Sr., Johnstone PA. Postoperative radiotherapy after surgical resection of thymoma: differing roles in localized and regional disease. *Int J Radiat Oncol Biol Phys*. 2010;76(2):440-445.
56. Patel S, Macdonald OK, Nagda S, Bittner N, Suntharalingam M. Evaluation of the role of radiation therapy in the management of malignant thymoma. *Int J Radiat Oncol Biol Phys*. 2012;82(5):1797-1801.
57. Liu Q, Gu Z, Yang F, et al. The role of postoperative radiotherapy for stage I/II/III thymic tumor-results of the ChART retrospective database. *J Thorac Dis*. 2016;8(4):687-695.
58. Jackson MW, Palma DA, Camidge DR, et al. The Impact of Postoperative Radiotherapy for Thymoma and Thymic Carcinoma. *J Thorac Oncol*. 2017;12(4): 734-744.
59. Zhou D, Deng XF, Liu QX, Zheng H, Min JX, Dai JG. The Effectiveness of Postoperative Radiotherapy in Patients With Completely Resected Thymoma: A Meta-Analysis. *Ann Thorac Surg*. 2016;101(1):305-310.
60. Boothe D, Orton A, Thorpe C, Kokeny K, Hitchcock YJ. Postoperative Radiotherapy in Locally Invasive Malignancies of the Thymus: Patterns of Care and Survival. *J Thorac Oncol*. 2016;11(12):2218-2226.
61. Fernandes AT, Shinohara ET, Guo M, et al. The role of radiation therapy in malignant thymoma: a Surveillance, Epidemiology, and End Results database analysis. *J Thorac Oncol*. 2010;5(9):1454-1460.
62. Lim YJ, Song C, Kim JS. Improved survival with postoperative radiotherapy in thymic carcinoma: A propensity-matched analysis of Surveillance, Epidemiology, and End Results (SEER) database. *Lung Cancer*. 2017;108:161-167.
63. Ruffini E, Van Raemdonck D, Detterbeck F, et al. Management of Thymic Tumors: A Survey of Current Practice among Members of the European Society of Thoracic Surgeons. *J Thorac Oncol*. 2011;6(3):614-623.
64. Yano M, Sasaki H, Moriyama S, et al. Preservation of phrenic nerve involved by stage III thymoma. *Ann Thorac Surg*. 2010;89(5):1612-1619.
65. Hamdi S, Mercier O, Fadel E, et al. Is sacrifying the phrenic nerve during thymoma resection worthwhile? *Eur J Cardiothorac Surg*. 2014;45(5):e151-155.
66. Chen KN, Xu SF, Gu ZD, et al. Surgical treatment of complex malignant anterior mediastinal tumors invading the superior vena cava. *World J Surg*. 2006;30(2):162-170.
67. Okereke IC, Kesler KA, Rieger KM, et al. Results of superior vena cava reconstruction with externally stented-polytetrafluoroethylene vascular prostheses. *Ann Thorac Surg*. 2010;90(2):383-387.
68. Sun Y, Gu C, Shi J, et al. Reconstruction of mediastinal vessels for invasive thymoma: a retrospective analysis of 25 cases. *J Thorac Dis*. 2017;9(3):725-733.
69. Yagi K, Hirata T, Fukuse T, et al. Surgical treatment for invasive thymoma, especially when the superior vena cava is invaded. *Ann Thorac Surg*. 1996;61:521-524.
70. Shimizu N, Moriyama S, Aoe M, Nakata M, Ando A, Teramoto S. The surgical treatment of invasive thymoma: Resection with vascular reconstruction. *J Thorac Cardiovasc Surg*. 1992;103: 414-420.
71. De Giacomo T, Patella M, Mazzesi G, Venuta F. Successful resection of thymoma directly invading the right atrium under cardiopulmonary bypass. *Eur J Cardiothorac Surg*. 2015;48(2): 332-333.
72. Amirghofran AA, Emaminia A, Rayatpisheh S, Malek-Hosseini SA, Attaran Y. Intracardiac invasive thymoma presenting as superior vena cava syndrome. *Ann Thorac Surg*. 2009;87(5): 1616-1618.
73. Ried M, Neu R, Schalke B, von Susskind-Schwendi M, Sziklavari Z, Hofmann HS. Radical surgical resection of advanced thymoma and thymic carcinoma infiltrating the heart or great vessels with cardiopulmonary bypass support. *J Cardiothorac Surg*. 2015;10:137.
74. Fujino S, Tezuka N, Watarida S, Katsuyama K, Inoue S, Mori A. Reconstruction of the aortic arch in invasive thymoma under retrograde cerebral perfusion. *Ann Thorac Surg*. 1998;66:263-264.
75. Leuzzi G, Rocco G, Ruffini E, et al. Multimodality therapy for locally advanced thymomas: A propensity score-matched cohort study from the European Society of Thoracic Surgeons Database. *J Thorac Cardiovasc Surg*. 2016;151(1):47-57 e41.
76. Ma J, Sun X, Huang L, et al. Postoperative radiotherapy and tumor recurrence after complete resection of stage II/III thymic tumor: a meta-analysis of cohort studies. *Onco Targets Ther*. 2016;9: 4517-4526.
77. Chen YD, Feng QF, Lu HZ, et al. Role of adjuvant radiotherapy for stage II thymoma after complete tumor resection. *Int J Radiat Oncol Biol Phys*. 2010;78(5):1400-1406.
78. Omasa M, Date H, Sozu T, et al. Postoperative radiotherapy is effective for thymic carcinoma but not for thymoma in stage II and III thymic epithelial tumors: the Japanese Association for Research on the Thymus Database Study. *Cancer*. 2015;121(7):1008-1016.
79. Tateishi Y, Horita N, Namkoong H, Enomoto T, Takeda A, Kaneko T. Postoperative Radiotherapy for Completely Resected Masaoka/Masaoka-Koga Stage II/III Thymoma Improves Overall Survival: An Updated Meta-Analysis of 4746 Patients. *J Thorac Oncol*. 2021;16(4):677-685.
80. Khorfan R, Bharat A, Odell DD. Management and Long-Term Outcomes of Advanced Stage Thymoma in the United States. *Ann Thorac Surg*. 2021;111(1):223-230.
81. Rimner A, Yao X, Huang J, et al. Postoperative Radiation Therapy Is Associated with Longer Overall Survival in Completely Resected Stage II and III Thymoma-An Analysis of the International Thymic Malignancies Interest Group Retrospective Database. *J Thorac Oncol*. 2016;11(10):1785-1792.
82. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. *Ann Thorac Surg*. 2003;76(3):878-884.
83. Lim YJ, Kim HJ, Wu HG. Role of Postoperative Radiotherapy in Nonlocalized Thymoma: Propensity-Matched Analysis of Surveillance, Epidemiology, and End Results Database. *J Thorac Oncol*. 2015;10(9):1357-1363.
84. Weksler B, Shende M, Nason KS, Gallagher A, Ferson PF, Pennathur A. The role of adjuvant radiation therapy

for resected stage III thymoma: a population-based study. *Ann Thorac Surg*. 2012;93(6):1822-1828; discussion 1828-1829.
85. Lim YJ, Kim E, Kim HJ, et al. Survival Impact of Adjuvant Radiation Therapy in Masaoka Stage II to IV Thymomas: A Systematic Review and Meta-analysis. *Int J Radiat Oncol Biol Phys*. 2016;94(5):1129-1136.
86. Ruffini E, Fang W, Guerrera F, et al. The International Association for the Study of Lung Cancer Thymic Tumors Staging Project: The Impact of the Eighth Edition of the Union for International Cancer Control and American Joint Committee on Cancer TNM Stage Classification of Thymic Tumors. *J Thorac Oncol*. 2020;15(3):436-447.
87. NCCN. NCCN Clinical Practice Guidelines in Oncology: Thymomas and Thymic Carcinomas. 2023; V.1.2023:http://www.nccn.org, December 15, 2022.
88. Korst RJ, Bezjak A, Blackmon S, et al. Neoadjuvant chemoradiotherapy for locally advanced thymic tumors: A phase II, multi-institutional clinical trial. *J Thorac Cardiovasc Surg*. 2014;147(1):36-46.e31.
89. Liou DZ, Ramakrishnan D, Lui NS, Shrager JB, Backhus LM, Berry MF. Does size matter? A national analysis of the utility of induction therapy for large thymomas. *J Thorac Dis*. 2020;12(4):1329-1341.
90. Kunitoh H, Tamura T, Shibata T, et al. A phase II trial of dose-dense chemotherapy, followed by surgical resection and/or thoracic radiotherapy, in locally advanced thymoma: report of a Japan Clinical Oncology Group trial (JCOG 9606). *Br J Cancer*. 2010;103(1):6-11.
91. Mineo TC, Mineo D, Onorati I, Cufari ME, Ambrogi V. New predictors of response to neoadjuvant chemotherapy and survival for invasive thymoma: a retrospective analysis. *Ann Surg Oncol*. 2010;17(11):3022-3029.
92. Marulli G, Lucchi M, Margaritora S, et al. Surgical treatment of stage III thymic tumors: a multi-institutional review from four Italian centers. *Eur J Cardiothorac Surg*. 2011;39(3):e1-7.
93. Lucchi M, Ambrogi MC, Duranti L, et al. Advanced Stage Thymomas and Thymic Carcinomas: Results of Multimodality Treatments. *Ann Thorac Surg*. 2005;79(6):1840-1844.
94. Wang S, Jiang J, Gao J, et al. Induction Therapy Followed by Surgery for Unresectable Thymic Epithelial Tumours. *Front Oncol*. 2021;11:791647.
95. Lucchi M, Melfi F, Dini P, et al. Neoadjuvant chemotherapy for stage III and IVA thymomas: a single-institution experience with a long follow-up. *J Thorac Oncol*. 2006;1(4):308-313.
96. Rea F, Marulli G, Di Chiara F, et al. Multidisciplinary approach for advanced stage thymic tumors: long-term outcome. *Lung Cancer*. 2011;72(1):68-72.
97. Wei Y, Gu Z, Shen Y, et al. Preoperative induction therapy for locally advanced thymic tumors: a retrospective analysis using the ChART database. *J Thorac Dis*. 2016;8(4):665-672.
98. Cardillo G, Carleo F, Giunti R, et al. Predictors of survival in patients with locally advanced thymoma and thymic carcinoma (Masaoka stages III and IVa). *Eur J Cardiothorac Surg*. 2010;37(4):819-823.
99. Park S, Park IK, Kim YT, et al. Comparison of Neoadjuvant Chemotherapy Followed by Surgery to Upfront Surgery for Thymic Malignancy. *Ann Thorac Surg*. 2019;107(2):355-362.
100. Kanzaki R, Kanou T, Ose N, et al. Long-term outcomes of advanced thymoma in patients undergoing preoperative chemotherapy or chemoradiotherapy followed by surgery: a 20-year experience. *Interact Cardiovasc Thorac Surg*. 2019;28(3):360-367.
101. Rea F, Marulli G, Girardi R, et al. Long-term survival and prognostic factors in thymic epithelial tumours. *Eur J Cardiothorac Surg*. 2004;26(2):412-418.
102. Kimura K, Kanzaki R, Kimura T, et al. Long-Term Outcomes After Surgical Resection for Pleural Dissemination of Thymoma. *Annals of Surgical Oncology*. 2019;26(7):2073--2080.
103. Okuda K, Yano MMDP, Yoshino I, et al. Thymoma patients with pleural dissemination: Nationwide retrospective study of 136 cases in Japan. *Ann Thorac Surg*. 2014;97:1743-1749.
104. Murakawa T, Karasaki T, Kitano K, et al. Invasive thymoma disseminated into the pleural cavity: mid-term results of surgical resection. *Eur J Cardiothorac Surg*. 2015;47(3):567-572.
105. Chappuy B, Drevet G, Clermidy H, et al. Subtotal Pleurectomy with Intrathoracic Chemo Hyperthermia (HITHOC) for IVa Thymomas: De Novo Versus Recurrent Pleural Disease. *Cancers (Basel)*. 2022;14(20).
106. Nakamura S, Kawaguchi K, Fukui T, et al. Multimodality therapy for thymoma patients with pleural dissemination. *General Thoracic and Cardiovascular Surgery*. 2019;67(6):524-529.
107. Aprile V, Bacchin D, Korasidis S, et al. Surgical treatment of pleural recurrence of thymoma: is hyperthermic intrathoracic chemotherapy worthwhile? *Interact Cardiovasc Thorac Surg*. 2020;30(5):765-772.
108. Kaba E, Ozkan B, Erus S, Duman S, Cimenoglu B, Toker A. Role of Surgery in the Treatment of Masaoka Stage IVa Thymoma. *Annals of Thoracic and Cardiovascular Surgery*. 2017;24(1):oa.17-00108.
109. Dolan DP, Polhemus E, Lee DN, et al. Hyperthermic intraoperative chemotherapy (HIOC) for Stage IVa thymic malignancy may improve 5-year disease-free survival. *J Surg Oncol*. 2023;127(4):734-740.
110. Park S, Ahn MJ, Ahn JS, et al. A prospective phase II trial of induction chemotherapy with docetaxel/cisplatin for Masaoka stage III/IV thymic epithelial tumors. *J Thorac Oncol*. 2013;8(7):959-966.
111. Choe G, Ghanie A, Riely G, et al. Long-term, disease-specific outcomes of thymic malignancies presenting with de novo pleural metastasis. *The Journal of Thoracic and Cardiovascular Surgery*. 2020;159(2):705-714.e701.
112. Rena O, Mineo TC, Casadio C. Multimodal treatment for stage IVA thymoma: a proposable strategy. *Lung Cancer*. 2012;76(1):89-92.
113. Moser B, Fadel E, Fabre D, et al. Surgical therapy of thymic tumours with pleural involvement: an ESTS Thymic Working Group Project. *Eur J Cardiothorac Surg*. 2017.
114. Yano M, Sasaki H, Yukiue H, et al. Thymoma with dissemination: efficacy of macroscopic total resection of disseminated nodules. *World J Surg*. 2009;33(7):1425-1431.
115. Hamaji M, Burt B. Long-term outcomes of surgical and non-surgical managements of stage IV thymoma: a population-based analysis of 282 patients. *Semin Thorac Cardiovasc Surg*. 2015;27(1):1-3.
116. Lucchi M, Davini F, Ricciardi R, et al. Management of pleural recurrence after curative resection of thymoma. *J Thorac Cardiovasc Surg*. 2009;137(5):1185-1189.
117. Fabre D, Fadel E, Mussot S, et al. Long-term outcome of pleuropneumonectomy for Masaoka stage IVa thymoma. *Eur J Cardiothorac Surg*. 2011;39(5):e133-138.
118. Masaoka A. Staging System of Thymoma. *J Thorac Oncol*. 2010;5(10):S304-S312.

119. Markowiak T, Neu R, Ansari MKA, et al. Surgical Cytoreduction and HITOC for Thymic Malignancies with Pleural Dissemination. *Thorac Cardiovasc Surg*. 2021;69(2):157-164.
120. Ambrogi MC, Korasidis S, Lucchi M, et al. Pleural recurrence of thymoma: surgical resection followed by hyperthermic intrathoracic perfusion chemotherapydagger. *Eur J Cardiothorac Surg*. 2016;49(1):321-326.
121. Ried M, Potzger T, Sziklavari Z, et al. Extended surgical resections of advanced thymoma Masaoka stages III and IVa facilitate outcome. *Thorac Cardiovasc Surg*. 2014;62(2):161-168.
122. Yellin A, Simansky DA, Ben-Avi R, et al. Resection and heated pleural chemoperfusion in patients with thymic epithelial malignant disease and pleural spread: a single-institution experience. *J Thorac Cardiovasc Surg*. 2013;145(1):83-87; discussion 87-89.
123. Lemma GL, Lee JW, Aisner SC, et al. Phase II study of carboplatin and paclitaxel in advanced thymoma and thymic carcinoma. *J Clin Oncol*. 2011;29(15):2060-2065.
124. Hirai F, Yamanaka T, Taguchi K, et al. A multicenter phase II study of carboplatin and paclitaxel for advanced thymic carcinoma: WJOG4207L. *Ann Oncol*. 2015;26(2):363-368.
125. Conforti F, Pala L, Giaccone G, Pas TD. Thymic epithelial tumors: From biology to treatment. *Cancer Treatment Reviews*. 2020;86:102014.
126. Dapergola A, Gomatou G, Trontzas I, et al. Emerging therapies in thymic epithelial tumors (Review). *Oncol Lett*. 2023;25(2):84.
127. Thomas A, Rajan A, Berman A, et al. Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial. *Lancet Oncol*. 2015;16(2):177-186.
127. Sato J, Satouchi M, Itoh S, et al. Lenvatinib in patients with advanced or metastatic thymic carcinoma (REMORA): a multicentre, phase 2 trial. *Lancet Oncol*. 2020;21(6):843-850.
129. Giaccone G, Kim C. Durable Response in Patients With Thymic Carcinoma Treated With Pembrolizumab After Prolonged Follow-Up. *J Thorac Oncol*. 2021;16(3):483-485.
130. Giaccone G, Kim C, Thompson J, et al. Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. *The Lancet Oncology*. 2018;19(3):347-355.
131. Cho J, Kim HS, Ku BM, et al. Pembrolizumab for Patients With Refractory or Relapsed Thymic Epithelial Tumor: An Open-Label Phase II Trial. *J Clin Oncol*. 2019;37(24):2162-2170.
132. Conforti F, Zucali PA, Pala L, et al. Avelumab plus axitinib in unresectable or metastatic type B3 thymomas and thymic carcinomas (CAVEATT): a single-arm, multicentre, phase 2 trial. *Lancet Oncol*. 2022;23(10):1287-1296.
133. Conforti F, Pala L, De Pas T, He Y, Giaccone G. Investigational drugs for the treatment of thymic cancer: a focus on phase 1 and 2 clinical trials. *Expert Opin Investig Drugs*. 2022;31(9):895-904.

25

NURSE AND ALLIED HEALTH PROFESSIONALS

Melissa Culligan,[1] **Pippa Labuc,**[2] **Morten Quist,**[3] **Ftanou Maria,**[2] **Mary Duffy,**[2] **Kahren M. White,**[4] **and Anne Fraser**[5] | [1]Temple-Fox Chase Cancer Center, Philadelphia, USA; [2]Peter MacCallum Cancer Centre, Melbourne, Australia; [3]University of Copenhagen, Copenhagen, Denmark; [4]Private Practice, Sydney, Australia; [5]Auckland Hospital, Auckland, New Zealand.

FUTURE FOCUSED: THE IMPACT OF NURSES AND ALLIED HEALTH PROFESSIONALS ON PATIENTS WITH THORACIC MALIGNANCIES

The journey of nurses and allied health (NAH) in the thoracic cancer setting has been a long but largely unrecognized one. The journey for Nursing and Allied Health members within the IASLC reflects this challenge. As the support for IASLC grew internationally there was much talk about the focus of the multidisciplinary team, much to the excitement of NAH professionals working in this space and impacting on patient care and outcomes. It was then with great dismay that we learned that a multidisciplinary team meant that medical oncologists would include radiation oncology. However, there is nothing like a challenge for nurses and allied health professionals, and quickly we began to make our presence felt. Huge strides were made from the 2015 meeting in Denver, and the IASLC met the challenge!

True multidisciplinary team care is vital across the whole patient trajectory. NAH professionals were impactful in the palliative treatment and care settings in the early days of managing thoracic malignancies, and they are now even more so as patients live longer and NAH has an impact on their survivorship and quality of life.

Where teams can utilize all members' expertise, not only does this positively affect patient and families experience, outcomes, and survivorship, the team becomes stronger as they learn from each other and harness different types of knowledge.

The Nursing & Allied Health Professionals Committee that sits within the IASLC also has members on other committees offering links and support. We aim for diversity across professions, global regions, and gender. Key aims for the committee remain high-quality evidence-based education and publications, promotion of NAH-led research, international mentorship, and to ensure our presence is felt, respected, and valued.

One of our foundation members, Mary Duffy, mentioned two key phrases in her IASLC Lectureship Award for Nurses and Allied Health Professionals speech in 2020; 'nimble' and 'future focused.' For me personally (A. Fraser) this summed up my own career in thoracic oncology; the challenges professionally, academically, and clinically... being nimble and having the ability to keep up with a rapidly changing research and care. I could never have imagined the changes I would see when I started clinics 15 years ago. For me the phrase 'future focused' captures the excitement of working in this clinical area. The opportunities seen for research within the NAH fields are vast! The quality of research improves year on year as NAH recognize their own worth in the extraordinary work they are undertaking.

For those of you who still believe the multidisciplinary team contains a medical oncologist and a radiation oncologist, we would like to introduce you to some members of your true multidisciplinary team, and why they are so

important to the diagnosis, treatment, and survivorship experience of thoracic oncology patients.

The past decades have seen many advancements in the treatment of thoracic cancer, which have resulted in us now being in an era where survivorship in this patient group is a reality. While these improved treatments have resulted in increased survival rates, it has not come without its own challenges.

Long-term lung cancer survivors experience the lowest global quality of life and highest levels of symptom burden, specifically dyspnea, cough, fatigue, pain, and reduced appetite, of all tumor groups. These patients also present clinicians with new challenges that were not previously common in this population, in particular how do they transition back into meaningful everyday roles, including returning to work.

To ensure that all of these treatment advancements are not for nothing, clinicians now need to ensure that not only are they treating the disease, but that holistic care is provided to ensure that symptom burden is well managed and tolerated, and that quality of life is optimized.

In order to provide holistic care, an individual's physical, emotional, and social needs must be addressed through specialist intervention, which is delivered by the right person, at the right time. Multidisciplinary care, consisting of medics, nurses, and allied health professionals is pivotal to achieve this.

Nurses and allied health professionals play a key role in delivering noninvasive interventions to manage both cancer-related symptoms and side effects, consisting of education, behavior change, and rehabilitation.[1] These interventions are well recognized as empowering patients to self-manage their symptoms and achieve self-efficacy, resulting in functional optimization and increased quality of life.

THORACIC ONCOLOGY NURSING

Thoracic oncology nursing encompasses a vast array of clinical specialties as well as multiple different roles in the care of thoracic oncology patients. Nurses provide the foundation of care for all patients, regardless of their specific malignancy, disease stage, or treatment pathway. Nurses touch the lives of every thoracic oncology patient, from the time of initial diagnosis until the end of life.[2] Patients may not need to see radiation oncology or thoracic surgery specifically, but they will always need thoracic oncology nurses involved in their care throughout their journey, no matter which road they follow.

Where We are Now?

In thoracic oncology, nurses provide care at the bedside, in outpatient settings, and in patients' homes. Thoracic oncology nurses work in specialty areas including but not limited to radiation oncology, medical oncology, thoracic surgery, palliative care, survivorship, clinical research, patient navigation, lung cancer screening, smoking cessation, and supportive care. Nurses work with all members of the multidisciplinary team to ensure that patients and their families are receiving optimal and timely care, based on each individual patients' specific needs.[2] With the numerous diagnostic and treatment advances in the field of thoracic oncology, specifically in lung cancer and mesothelioma, the impact nurses have on patient outcomes has never been greater. The need for patient education, symptom management, care coordination, and supportive care highlights the central role nurses play now and will need to continue to play in the future.[3] Globally, thoracic oncology nurses have risen to the challenge of caring for and supporting their patients with the highest levels of knowledge, compassion, and commitment. It is important for experienced nurses to provide mentorship to new nurses entering the field, in all specialty areas. Developing and participating in educational programs, nationally and internationally, will play a key role in providing exceptional patient care and elevating the view that other multidisciplinary team members have of the role their nursing colleagues play in the care of all patients.[1-3]

Future Focus for Thoracic Oncology Nursing

As the field of thoracic oncology continues to advance and become

increasingly more complex for patients and other specialists to navigate, the demands for educated and experienced thoracic oncology specialty nurses will also increase. It is critical for nurses to become involved in organizations like the IASLC in order to developed collaborative relationships with likeminded professionals, to stay abreast of the latest treatment advances and to contribute to the development of evidence-based patient care through collaborative, multidisciplinary research efforts.[4-6]

OCCUPATIONAL THERAPY

Occupational therapists work with people of all ages and abilities to do the things they need and want to do in all aspects of life.[7,8] The primary goal of occupational therapy is to enable people to participate in the occupations of everyday life, enabling patients' ongoing participation in valued and meaningful activities.[9,10] Occupational therapists are integral members of the lung cancer multidisciplinary team, having an active role in the management of common refractory symptoms experienced by people with lung cancer, including fatigue and breathlessness.[11-13]

Where We are Now?

There remains a dearth of robust research into occupational therapy interventions in oncology, and more specifically lung cancer, with a number of small qualitative studies investigating how people with life-limiting illness engage in their occupational performance roles, and studies investigating the role of the occupational therapist in oncology and palliative care.[14] There are known knowledge gaps in occupational therapy interventions for people with cancer, with even fewer papers specifically related to lung cancer. A study by Bentley et al[15] identified that people with lung cancer or mesothelioma had significant unmet occupational therapy needs at diagnosis. This study identified the need for further research to examine the efficacy of occupational therapy interventions. A randomized clinical trial by La Cour et al and others[16,17] investigated the efficacy of the 'Cancer Home-Life intervention.' This is one of the few randomized clinical trials to be completed in occupational therapy interventions for people living with cancer. However, results showed the intervention was not effective and highlighted the need to pay more attention to intervention development and feasibility testing.

Future Focus for Occupational Therapy

There remain a limited number of occupational therapists internationally who specialize or have the ability to specialize through support from their institution in lung cancer. As a first step the profession of occupational therapy need to identify lung cancer practice as a sub-specialty to oncology practice. Occupational therapists need to design robust research that demonstrate the efficacy of interventions, supports the development of new interventions, and leads to improvements in occupational therapy interventions for people living with lung cancer. The aim of occupational therapy interventions is to improve the function, occupational engagement, and outcomes for people living with lung cancer.

PSYCHOLOGY

A diagnosis of lung cancer impacts not just physical health but also the psychological and emotional wellbeing of both the person with cancer and their loved ones. People with lung cancer have been found to experience greater disease burden, increased rates of anxiety and depression, and are at greater risk of suicide compared to people with other types of cancer.[18-21] Psychologists are crucial members of the lung multidisciplinary team. Psychologists work with people with cancer, loved ones, and multidisciplinary care teams, to address the person's psychosocial needs across the cancer trajectory from diagnosis, through treatment, survivorship, and end of life.

Where We are Now?

Psychologists working in lung cancer use interventions including cognitive behavior therapy, existential psychotherapies, mindfulness interventions, and family and couple therapy to address issues such as anxiety, depression, scanxiety, sleep diffi-

culties, pain, fatigue, fear of progression, death anxiety, stigma, intimacy changes, grief, cognitive problems smoking cessation, communication and relationship concerns.[23,24] Psychologists also work with the oncology team to develop complex behavior and discharge plans. They also provide multidisciplinary teams with mental health education, reflective practices, debriefs, and communication training.

Future Focus for Psychology

As there are very few psychologists working in oncology worldwide, very few people with cancer who need them have access to them. In addition to workforce investment, given the high rates of distress, it is essential that members of the multidisciplinary team routinely assess for emotional distress and are trained in Mental Health First Aid. To ensure equity, access, and a greater reach of mental health interventions, more research into the impacts of digital mental health interventions is needed. Given the growing number of survivors treated with immunotherapies and targeted therapies, more research is also needed to understand the psychological impacts of these novel therapies. Lastly, the involvement of psychologists within the IASLC community ensures that they learn from the multidisciplinary team and promote collaboration and partnerships but also ensures that mental health care is integral to quality cancer care.

References

1. McPhillips D, Evans R, Ryan D, et al. The role of a nurse specialist in a modern lung-cancer service. *Br J Nurs*. 2016;24:S21-7.
2. Serena A, Castellani P, Fucina N, et al. The role of advanced nursing in lung cancer: A framework-based development. *Eur Journ of Onc Nurs*. 2015;19;740-746.
3. Charalambous, A. Specialized cancer care roles: From clinical practice to research and beyond. *Asia Pac J Oncol Nurs*. 2020;7:232-234.
4. Kerr S, Mambwere M, Hardvella G. Nurse led lung cancer diagnostic/supportive follow-up clinical different approach to optimize lung cancer pathway. *Eur Respir J*. 2018; 52:PA2074.
5. Temel JS, Pirl WF, Lynch TJ. Comprehensive symptom management in patients with advanced-stage non-small cell lung cancer. *Clin Lung Cancer*. 2006;7; 241-249.
6. Sung MR, Patel MV, Djalalov S, et al. Evolution of symptom burden of advanced lung cancer over a decade. *Clin Lung Cancer*. 2017;18:274-280.e6.
7. Bentley R, Hussain A, Maddocks N, Wilcock A. Occupational therapy needs of patients with thoracic cancer at the time of diagnosis: Findings of a dedicated rehabilitation service. *Support Care Cancer*. 2013;21:1519-1524.
8. Occupational Therapy Australia. (2019). "About Occupational Therapy." http://aboutoccupationaltherapy.com.au/.
9. Sviden GA, et al. Involvement in everyday life for people with a life threatening illness. *Palliative and Supportive Care*. 2010;8:345-352.
10. Hammill K, et al. Occupational therapy for people living with a life-limiting illness: a thematic review. *British Journal of Occupational Therapy*. 2014;77(11):582-589.
11. White KM. Occupational therapy interventions for people living with advanced lung cancer. *Lung Cancer Management.* 2013;2(2):121-127.
12. Cooper J and Littlechild B. A study of occupational therapy interventions in oncology and palliative care. *International Journal of Therapy and Rehabilitation.* 2004;11(7):329-333.
13. Bye RA. When clients are dying: occupational therapists' perspectives. *The Occupational Therapy Journal of Research.* 1998;18(1):3-24.
14. Eva, G. and D. Morgan. Mapping the scope of occupational therapy practice in palliative care: A European Association for Palliative Care cross-sectional survey. *Palliative Medicine.* 2018;32(5):960-968.
15. Bentley R, et al. Occupational therapy needs of patients with thoracic cancer at the time of diagnosis: findings of a dedicated rehabilitation service. *Support Care Cancer.* 2013;21:1519-1524.
16. la Cour K, Oestergaard LG, Brandt Å, et al. Process evaluation of the Cancer Home-Life Intervention: What can we learn from it for future intervention studies? *Palliat Med*. 2020;34:1425-1435.
17. Pilegaard, M. S., et al. (2018). The 'Cancer Home-Life Intervention': A randomised controlled trial evaluating the efficacy of an occupational therapy-based intervention in people with advanced cancer. *Palliat Med* 32(4):744-756.
18. Kleine AK, Hallensleben N, Mehnert A, Hönig K, Ernst J. (2019). Psychological interventions targeting partners of cancer patients: A systematic review. *Crit Rev Oncol Hematol*. 2019;140;52-66.
19. Carlson LE. Mindfulness-based interventions for coping with cancer. *Ann N Y Acad Sci*. 2016;1373;5-12.
20. Haun MW, Sklenarova H, Villalobos M, et al. (2014). Depression, anxiety and disease-related distress in couples affected by advanced lung cancer. *Clin Lung Cancer*. 2014;86; 274–289.
21. Anguiano L, Mayer DK, Piven ML, Rosenstein D. A literature review of suicide in cancer patients. *Cancer Nursing*. 2012;53:E14–E26.
22. Ftanou M, Pascoe MC, Ellen S. Psychosocial interventions for end-of-life care: An invited commentary. *Australian Psychologist*. 2017;52:340-345.
23. Rodin G, Lo C, Rydall A, et al. Managing cancer and living meaningfully (CALM): A randomized controlled trial of a psychological intervention for patients with advanced cancer. *J Clin Oncol*. 2018;36:2422-2432.
24. La Cour K, et al. Activity and meaning making in the everyday lives of people with advanced cancer. *Palliative and Supportive Care*. 2009;7:469-479.

IASLC
INTERNATIONAL
ASSOCIATION
FOR THE STUDY
OF LUNG CANCER
Conquering Thoracic Cancers Worldwide

ISBN 978-1-947768-03-1

9 781947 768031 90000>

Editorial Rx Press

PO Box 974
N. Eastham, MA, USA 02651