The addition of atezolizumab to standard chemotherapy for extensive-stage SCLC achieved what, for decades, had been beyond reach: an improvement in survival in this disease. Since the 1980s, our standard of care for SCLC has been a platinum chemotherapy agent plus etoposide. This regimen reliably provides an initial response that is often dramatic but is almost always short lived. IMpower133 was a global, randomized, double-blind, placebo-controlled trial designed to assess the effects of adding concurrent (and maintenance) atezolizumab to first-line carboplatin and etoposide in extensive-stage SCLC (Fig. 1). As presented at the IASLC 2018 World Conference on Lung Cancer, the study met both coprimary endpoints with a significant improvement in overall survival (OS) and progression-free survival (PFS). Median OS was 12.3 months with atezolizumab versus 10.3 months in the control arm (hazard ratio [HR] for death 0.70 [0.54, 0.91]; Fig. 2). The combination of atezolizumab, carboplatin, and etoposide was given a Category 1, preferred treatment recommendation in the National Comprehensive Cancer Network guidelines and awaits formal U.S. Food and Drug Administration approval.

Clinical Impact of IMpower133

In the context of more than 40 failed phase III trials, the improvement in survival seen in IMpower133 represents a tremendous achievement, and I have adopted this regimen as my new standard of care. PD-L1 expression was not used as a selection criterion, and blood-tumor mutational burden was
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IMPORTANT DEADLINES

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IMpower133 from page 1

not predictive of outcome. Although the search for a predictive biomarker continues, my current use of atezolizumab is for “all-comers” with extensive-stage SCLC.

There are limitations to the data, including patients with asymptomatic untreated brain metastases. Use of atezolizumab in this setting has not been explored; these patients were excluded from enrollment on IMpower133. No dataset perfectly encapsulates our daily clinic experience; we must extrapolate from available data. Because I would not expect these patients to derive less benefit from atezolizumab, I am comfortable with its use here, acknowledging the need for more data. IMpower133 also excluded patients with active autoimmune diseases, including paraneoplastic syndromes associated with SCLC. Here, I am very cautious, because worsening of these syndromes can be unsafe and can negatively affect quality of life.

How would I approach a patient who begins chemotherapy during hospitalization, where atezolizumab may not be available? I would likely add atezolizumab to the next possible cycle. Whenever feasible, however, I favor concurrent administration with the first cycle, to capitalize on the potential synergy between chemotherapy and atezolizumab. SCLC can have an unpredictable course, and delaying implementation may result in a lost opportunity. SCLC is an unforgiving disease and, too often, our first attempt at treatment is our only chance to affect the natural history of this highly lethal malignancy.

The Start of a New Chapter?
IMpower133 is only the first of several studies expected to read out over the next 2 years in SCLC. KEYNOTE-604 (NCT03066778) will assess the effects of pembrolizumab with chemotherapy, and CASPIAN (NCT0343872) will report the efficacy of durvalumab with or without tremelimumab in combination with chemotherapy. In addition, CheckMate 451 (NCT02538666) examines a maintenance approach after chemotherapy with nivolumab, nivolumab plus ipilimumab, or placebo. This is a different patient population—one that has completed chemotherapy and is well enough to enroll on a clinical trial—but hopefully this will also prove to be an effective strategy. Many more questions remain, including the role of consolidative thoracic radiation. Although the CREST study, which explored this approach in patients who responded to initial chemotherapy, did not meet its primary endpoint of improving 1-year survival, it did show an improvement in 2-year survival. It is important to note that consolidative radiation was not permitted in IMpower133, and additional study is needed not just to demonstrate efficacy but also to ensure safety when combining definitive radiation with atezolizumab and chemotherapy. Still, the potential is alluring, given the survival gains seen for patients with locally advanced NSCLC with durvalumab after chemoradiation. Examining the role of checkpoint inhibition after chemoradiation for limited-stage SCLC is also of great interest for the same reason.

Lest we forget the recalibrant nature of SCLC, two recent immunotherapy studies yielded disappointing results. CheckMate 311 compared second-line topotecan to nivolumab and, unfortunately, did not meet its primary endpoint of improving overall survival. In IFCT-1603, second-line atezolizumab monotherapy was associated with a disappointing PFS of 1.4 months, a 6-month PFS rate of 6.3%, and a response rate of only 2.3%.4 Rovalpituzumab teotinase, an antibody-drug conjugate targeting DLL3, was explored in the single-arm TRINITY study and resulted in a response rate (assessed by independent radiology committee) of only 12.4%, with a median survival of less than 6 months.5 These sobering results further underscore the need for additional study. With the survival gains seen in IMpower133, we have finally moved the needle in SCLC. It is now our charge to build upon these results and ensure that the next major advance is not another 30 years in the future.

MEETING PREVIEW
IASLC SCLC Meeting Program, Faculty to Reflect the Field’s Pivotal, Recent Major Advances

The upcoming April workshop promises to benefit early-career researchers, as well as experienced investigators excited about new perspectives and unique opportunities.

By Charles M. Rudin, MD, PhD

The 2019 IASLC Small Cell Lung Cancer (SCLC) Meeting will be held at Memorial Sloan Kettering Cancer Center in New York, New York, April 3 to 5, 2019. This international meeting will be dedicated to the memory of the recently deceased Dr. Adi Gazdar who, among his many areas of scientific impact, largely shaped the modern era of SCLC research (See in Memoriam on page 5.) This year’s conference—organized by program co-chairs Dr. Julie George (University of Cologne), Dr. Trudy Oliver (University of Utah), Dr. Taofeeq Owoinokoko (Emory University), and Dr. John T. Poirier (Memorial Sloan Kettering Cancer Center)—promises to build on the momentum of the prior two meetings, featuring exciting advances in both laboratory and clinical research on SCLC. The impetus for launching the biennial IASLC Small Cell Lung Cancer Meeting continued on page 5.
RET
RET is a receptor tyrosine kinase that induces cellular proliferation, migration, and differentiation when activated. RET fusions occur in 1.4% of NSCLC and are more likely to be present in younger, never-smoking patients with adenocarcinoma. Clinical data from a phase II trial on the use of cabozantinib for patients with RET fusion–positive disease revealed two patients with partial responses,12 and the final results in 25 patients with RET-positive disease revealed an overall response rate (ORR) of 28%.13 The results from a global, multicenter registry of 165 patients with RET-positive disease from Europe, Asia, and the United States were reported.14 Of note, the ORR to cabozantinib, vandetanib, and sunitinib was detailed as 37%, 18%, and 22%, respectively. The median progression-free survival (PFS) was 2.3 months, and median overall survival (OS) was 6.8 months in all patients. On the other hand, newer agents look more promising. The novel RET inhibitor LOXO-292 yielded an ORR of more than 70% in RET-altered NSCLC and was well tolerated, with most adverse events grade 1 (Fig. 1).15 BLU-667, another potent and selective RET inhibitor, has been found in both men and women with wide ranges of age and smoking history.24 A phase I study of entrectinib demonstrated antitumor activity in one patient with a NTRK1 fusion.25 In combined phase I/II trials evaluating larotrectinib in patients across tumor types and age groups who were TRK+ positive, 55 patients were enrolled.26 The study demonstrated an ORR of 75% based on independent review. In addition, 71% of responses were ongoing, and 55% patients remained progression free at 1 year, strongly suggesting substantial activity in patients with NTRK fusion–positive disease. Additional NTRK inhibitors are also in development.

Future Directions
Targeted therapies have led to improved outcomes for patients with lung cancer, and additional targets and treatments continue to emerge. Genomic sequencing using broad platforms and blood-based cell-free DNA have illuminated the intricacies of lung cancer. Understanding tumor biology helps to advance precision treatment to improve patient outcomes. Despite this progress, resistance invariably develops, resulting in even more complex and heterogeneous tumors. Further research is needed to understand mechanisms of resistance to prolong survival and quality of life. 

About the Author: Dr. Reckamp is a medical oncologist at the City of Hope Comprehensive Cancer Center.

References:
Adi Gazdar, MD, a true giant in the field of lung cancer research, passed away on December 29, 2018. Dr. Gazdar was the W. Ray Wallace Distinguished Chair in Molecular Pathology Research and professor of pathology at the Hamon Center for Therapeutic Oncology Research and pathology at UT Southwestern Medical Center. Adi Gazdar was one of the first “molecular pathologists” of lung cancer and helped lead the development of this area around the world through his publications, collaborations, and mentoring activities.

As head of the Tumor Cell Biology Section at the National Cancer Institute between 1969 and 1975, Dr. Gazdar collected, cataloged, and analyzed more than 2,200 human cancer specimens, focusing on lung cancers and lymphomas. After moving to UT Southwestern Medical Center, he collected and analyzed an additional 2,500 human tumor specimens. The total number of human cancer cell lines he established or helped to establish across cancer types is approximately 400—the world’s largest collection of human cancer cell lines. This work has facilitated numerous therapeutic advances and has led to the development of prognostic biomarkers in lung cancer and other cancer types. He was also a highly regarded tumor virologist, discovering the “Gazdar murine sarcoma virus” (Gz-MSV); his development of two human T-cell lymphoma lines led to the discovery of one of the first human retroviruses (HTLV-1); the other line was crucial for the initial isolation and characterization of the human HIV–AIDS virus.

Dr. Gazdar was an exceptional clinical and molecular pathologist. He played a critical role in the IASLC pathology panel/committee, which set the standards for the pathologic classification of human lung cancers. Dr. Gazdar was an active member of the IASLC for more than 35 years; he also served on the IASLC Board of Directors. In 2003, he was awarded the Mary J. Matthews Pathology/Translational Research Award for his scientific achievements in thoracic pathology research. Dr. Gazdar was an exceptional mentor, training numerous fellows in lung cancer biology and pathology. In 2015, the IASLC Adi Gazdar Lectureship Award for Translational Research was established through a generous donation from Dr. Gazdar and his wife Celia; this award allowed funding for several fellowships. “This award is a testimony to Adi’s commitment to the training of the next generation of translational molecular pathologists in lung cancer; he was an outstanding educator and mentor,” said Dr. Ignacio I. Wistuba, chair of Translational Molecular Pathology at The University of Texas MD Anderson Cancer Center, who is a former trainee and long-term collaborator of Dr. Gazdar.

“Dr. Gazdar’s contribution to lung cancer biology is of tremendous significance through establishment of NSCLC and SCLC cell lines and through other studies on which he led and participated,” said Fred R. Hirsch, MD, PhD, who is Executive Director for the Lung Cancer Institute at Mount Sinai. Dr. Hirsch, who was IASLC CEO from 2013 to 2018 and has been an active member of the society for 41 years, noted that Dr. Gazdar was a wonderful mentor to him throughout his career. “Dr. Gazdar was a unique human being with much wisdom, even beyond the scientific sphere. His interest in history and global cultures was both unique and engaging and made him an exceptionally interesting travel partner. He was liked by everyone, and he will be deeply missed.”

With more than 700 publication credits, the Institute for Scientific Information includes Dr. Gazdar in a list of the world’s most cited authors (88,255 citations with an h-index of 147)—comprising less than 0.5% of all authors of published research—based on the important scientific developments of the past 2 decades. Dr. Gazdar was extremely active in ongoing lung cancer research up until the time of his death, generating exciting new findings in subclasses of SCLC. He was a true gentleman as well as scientist and mentor. His soft-spoken and even-tempered manner was an inspiration among scientists. John Minna, MD, professor and director of the Hamon Center for Therapeutic Oncology Research, Internal Medicine, and Pharmacology, worked with Dr. Gazdar for decades. “He stimulated collaborations worldwide, and always said exactly what he thought about data or hypotheses, even if these ran against general thinking,” Dr. Minna told the IASLC Lung Cancer News. “Of course, in nearly every case, he was also right.” Dr. Gazdar is survived by his wife of 49 years, Celia Gazdar. The lung cancer community is saddened by the loss of this giant in the study of lung cancer.

IASLC SCLC Meeting Program

from page 3

Workshop in 2015 was two-fold: first, a recognition that new insights into the biology and vulnerabilities of this exceedingly lethal disease were emerging from both clinical and basic researchers; and second, a recognition that no international forum existed to promote interaction among this diverse community of investigators. The pace of discovery has continued to accelerate, which was reflected in a larger meeting in 2017. This year, with major advances in the capacity for animal modeling of disease, new insights into intratumoral heterogeneity, the emergence of novel therapeutic strategies, the clinical impact of immunotherapy, and many other advances, the conference co-chairs had a tough task trying to pack the highlights into the limited time available.

Structure and Program

The meeting will begin the evening of Wednesday, April 3, with an opening keynote lecture by Dr. Anton Berns of Netherlands Cancer Institute, whose laboratory was the first to generate a genetically engineered mouse model of SCLC. Sessions over the next day and a half will focus on: advances in SCLC pathology and biomarkers; new insights from genomic, transcriptomic, and metabolomic platforms; advances in understanding tumor initiation including cell of origin, analyses of tumor heterogeneity, and intratumoral cell-cell interactions; progress in genetically engineered mouse modeling of disease subtypes; and therapeutic advances in targeted agents, immune modulators, and other approaches. The invited faculty represent leaders in SCLC research from around the world. The meeting will conclude in the early afternoon of Friday, April 5.

From its inception, the goals of this meeting have included a “state-of-the-state” update on recent progress in SCLC research, a forward-looking perspective on key unanswered questions in the field, and promotion of research collaboration among investigators. With these goals in mind, we have maintained the structure of the meeting as a single track, rather than having parallel sessions focused on basic and clinical research. This format allows all participants to learn from and interact with investigators approaching the disease from distinct and potentially complementary angles. We believe this is ideal for early-career investigators and trainees getting up to speed in the area, as well as for active researchers seeking new perspectives and opportunities.

For more information, or to register for the meeting, please visit iaslclung.org/events and select the 2019 IASLC Small Cell Lung Cancer Meeting. We encourage abstract submissions for poster presentation by trainees.

About the Author: Dr. Rudin is chief, Thoracic Oncology Service, co-director, Druckenmiller Center for Lung Cancer Research, and Sylvia Hassenfeld Chair in Lung Cancer Research at Memorial Sloan Kettering Cancer Center.
Dramatic improvements in lung cancer outcomes can be attributed to recent advances in novel targeted therapy and immunotherapy. As the treatment paradigm for lung cancer evolves, concerns about the rising cost of these novel therapeutics has become a global dilemma. In Canada, the average price of lung cancer drugs increased by 17% between 2012 and 2017, whereas the gross domestic product per capita actually decreased by 19% during this time period (Fig. 1).\(^1,2\) Classic market forces do not consistently apply to cancer drug pricing, with higher prices paid for treatments of lower value, and next-in-class agents often costing as much or more than first-in-class agents.\(^3,4\)

**The Effects of Cost**

Payers around the world are struggling to provide timely access to breakthrough lung cancer therapies for our patients. Uptake of novel cancer therapies is limited by high drug acquisition and technology or testing costs. For example, in the Canadian universal publicly funded healthcare system, only nine out of 14 recently approved lung cancer drugs have received public funding due to budgetary constraints, often after significant delays.\(^5,6\) In other high-income nations, such as Spain and Japan, fewer than half of all newly approved drugs are funded and available to all patients.\(^6\) The proportion of available novel anticancer therapeutics drops dramatically in low- and middle-income countries (LMICs). Although prices may be subsidized or reduced in LMICs, recently developed treatments remain unobtainable for most patients with lung cancer in these areas. In countries with private or hybrid healthcare systems, patients experience the negative consequences of expensive cancer treatments directly. In the United States, for example, high out-of-pocket payments are a reality for many patients with advanced lung cancer and can affect adherence to therapy, potentially leading to treatment failure and drug resistance. A recent U.S. study found that patients with lung cancer receiving tyrosine kinase inhibitors (TKIs) were more compliant with therapy if their co-payments were less than $30 USD monthly, compared to those with higher co-payments.\(^6\) Previous studies have shown that patients diagnosed with lung cancer in the United States are almost four times more likely to declare bankruptcy, and that bankruptcy is associated with higher cancer mortality.\(^7\) Other research in the United States has shown that patients with lung cancer with less financial reserve experience worse quality of life and higher symptom burden.\(^8\)

**Costs and Decision Making**

To make informed policy decisions about costly advances in cancer care, a growing number of countries such as Canada and the United Kingdom have expanded the evaluation of novel therapies beyond clinical benefit and safety to include the economic effects on the healthcare system and the individual. In Canada, the patient perspective and system effect related to adoption of a new therapy, as well as the clinical benefit and economic effect, are all considered in decision making, as part of the Pan-Canadian Oncology Drug Review process.\(^9\) Cost-effectiveness evaluation helps us understand how treatment benefit relates to cost and can be expressed using the incremental cost effectiveness ratio (ICER)—the incremental cost of a novel therapy over the incremental benefit compared to the current standard of care. Thus, a treatment that significantly prolongs survival with low cost would be highly cost effective with a low ICER.

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**IN MEMORIAM**

Cancer Research Innovator, Trailblazer, and Mentor Dr. Waun Ki Hong Dies

Waun Ki Hong, MD, the “father of chemoprevention” and renowned cancer researcher and mentor, died on January 2, 2019, at the age of 76. Dr. Hong’s illustrious career began in the South Korean Air Force as a flight surgeon during the Vietnam War. After his military service, Dr. Hong completed his internship at Bronx/Lebanon Hospital in New York City and his residency at the Veterans Affairs (VA) Medical Center in Boston. During his 9-year tenure at the VA Medical Center as chief of Medical Oncology, he helped establish the hospital’s oncology training program, marking the beginning of his decades-long journey as a mentor to hundreds of physician-scientists.

Dr. Hong joined the University of Texas MD Anderson Cancer Center in Houston in 1984 as chief of the Section of Thoracic Head and Neck Oncology, later becoming the head of the Division of Cancer Medicine there until he retired in 2014. An IASLC member since 2006, Dr. Hong’s seminal work in head and neck cancer documenting the use of chemotherapy and radiotherapy as an effective alternative to laryngectomy for cancer of the larynx led to organ preservation across numerous cancer types. Dr. Hong also spearheaded the investigation of multiple agents to prevent cancer occurrence, later known as chemoprevention. In addition, he helped pioneer the concept of personalized therapy as one of the principal investigators of one of the first therapeutics trials in this realm—the Biomarker-Based Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial. During his career, Dr. Hong was the recipient of several notable awards including the David A. Karnofsky Award from the American Society of Clinical Oncology, the Gold Medal of Paris from the International Congress on Anti-Cancer Treatment, and the American Cancer Society Medal of Honor Award. A die-hard Boston Red Sox fan, perhaps the greatest honor came in 2015 when he threw out the first pitch at Fenway Park, which sailed right over the plate.

“Ki could initially appear quite awe inspiring, given the remarkable accomplishments and the matchless work ethic, but he really was a warm, kind, sensitive, and generous human being,” said Fadlo R. Khuri, MD, president of the American University of Beirut and a mentee of Dr. Hong’s. “He was an absolutely transformative mentor for me and for a whole host of individuals across more than 3 decades. There are few people one meets of whom it can be truly said that they the world and the lives of those in it substantially better. Waun Ki Hong was just such a rare individual. I will miss him the rest of my life.”

Dr. Hong is survived by his wife, Mi Hwa, his two sons, Edward and Burton, and four grandchildren. He will be missed by his many friends, colleagues, mentees, and patients.
The IASLC’s Spotlight on Screening

From a CT image archive that aims to accelerate early lung cancer detection to fostering global collaboration, the IASLC offers valuable resources and education.

By James L. Mulshine, MD, and John K. Field, PhD, FRCPath

The IASLC is supporting a new early thoracic CT image archive to encourage both quality measures and research for early lung cancer detection and management. This effort, the IASLC’s Early Lung Imaging Confederation (ELIC), is planned to have global reach by using a hub and spoke architecture (Fig. 1). A centerpiece of this is the development of ELIC as an innovative, international collaborative data environment to store, analyze, and aggregate CT images and associated de-identified clinical information. To enable quantitative analysis, the stored collection will consist of high-quality digital imaging and communications in medicine files of CT images, associated with a harmonized, minimal dataset of core clinical metadata. Analyses will be done at local/regional centers (spokes), and results will be assembled in a cloud-based IASLC hub. This environment is designed to allow local review of images without moving donated CT images outside of national borders to address the evolving international data-sharing requirements. The ELIC hub and spoke system will permit analysis of CT images and associated data in a highly secure environment, without any requirement to reveal data itself (i.e., privacy protecting). No identifiable data will ever leave sources under governance of the local primary investigator control. This cloud-based, open research environment will provide a global collaborative resource to accelerate progress by enabling precise, robust evaluation of CT images for the earliest evidence of emerging lung cancers and will potentially increase the frequency of curative screening management. ELIC may also establish a framework to conduct pilot clinical trials and will complement established successful IASLC efforts with lung cancer staging and pathology.

The preliminary feasibility test of this approach will be an effort to connect six of the world’s largest existing lung cancer screening registries to allow for rapid image analysis. The goal of this project will be to provide a global resource to facilitate setup and deployment of quantitative imaging tools that will enable rapid implementation of screening by new global lung cancer screening groups.

To enhance the developmental utility of ELIC, CT images accrued into the ELIC archive will be of sufficient quality so that the collection of data obtained from continued on page 9

Dr. James L. Mulshine
Dr. John K. Field

INDUSTRY AND REGULATORY NEWS

MYSTIC Fails to Meet Improved OS Endpoint

November 16, 2018 — Phase III OS results were announced for MYSTIC, a randomized, open-label, multicenter, international trial of durvalumab monotherapy vs. durvalumab plus tremelimumab, an anti-CTLA4 antibody, vs. platinum-based chemotherapy in treatment-naive patients with metastatic NSCLC.

In the primary analysis of patients with PD-L1 expression on 25% or more of their cancer cells (as determined by the VENTANA PD-L1 Sp263 Assay), neither durvalumab alone nor its combination with tremelimumab significantly improved survival compared with chemotherapy. A hazard ratio of 0.76 (97.54% CI: 0.564-1.019; nominal p = 0.036) was observed for durvalumab alone; the combination’s HR was 0.85 (98.77% CI: 0.611-1.173; nominal p = 0.202).

Does the IASLC Lung Cancer News provide nuanced commentary vital to your knowledge base? Is your specialty in thoracic oncology well represented? Do global perspectives enhance your understanding of global challenges in the field? Now in its fourth year of publication, the IASLC Lung Cancer News wants to know if it’s hitting the mark.

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http://www.iaslc.org/readersurvey
There was a time, remembered by us older pathologists, when the image of pathology was that of a rather peripheral specialty, sometimes perceived to have limited clinical relevance, delivered by physicians who were never seen, rarely heard, and were usually banished to some dark corner of their hospital. We pathologists, of course, knew differently, but still we were perceived as the “back room” members of clinical practice. My, how circumstances have changed. Pathology is now at the forefront in the multidisciplinary care of patients with lung cancer. Pathologic classification, at both morphologic and molecular levels, is now a cornerstone of the treatment of patients with lung cancer in this era of precision cancer medicine.

The Players and Their Roles

The Pathology Committee of the IASLC has been a key player in important developments in lung cancer diagnosis and classification for more than 40 years. Taking the lead from the IASLC’s culture of promoting research, education, and best practices in the clinical management of patients with lung cancer, the Committee and its members have led major initiatives. Among these are several iterations of the World Health Organization (WHO) Lung Cancer classification, which have included radical changes in the understanding of lung adenocarcinoma and the integration of immunohistochemical and molecular features in day-to-day diagnostics of lung cancer.

This was a collaborative endeavor involving both IASLC pathologists and the pharmaceutical industry. Credit is due to Dr. Fred Hirsch, a long-standing Pathology Committee member and past-CEO of the IASLC, for his tireless efforts and determination in bringing parties together and securing important funding for this complex work. The Blueprint project has clarified a number of difficult questions that have plagued the world of PD-L1 immunohistochemistry testing in lung cancer, including the technical comparability of several of the trial-validated assays, the possibility of high interobserver agreement in PD-L1 scoring, and the comparability of cytology and biopsy samples in this testing space.

The efforts of the committee continue under the leadership of our current Chair, Dr. Ignacio Wistuba of The University of Texas MD Anderson Cancer Center. Many important questions in lung cancer pathology need answers, and the committee members have established small working groups to address these myriad topics, with members working on several projects. Some questions are “old chestnuts” that have been hard to crack, such as the grading of lung cancer in both histology and cytology samples, recognition of invasion in early-stage adenocarcinomas, neuroendocrine tumor pathology, and the assessment of surgical margins in cancer resection specimens. Many address new questions prompted by the evolution of targeted therapies in lung cancer, especially immunotherapy. There are working groups looking at immune-related markers, tumor mutation burden, and assessment of major pathologic responses after neoadjuvant therapy.

Introducing a New Column

These undertakings come in addition to the creation of more IASLC atlases as well as contributions to future editions of the WHO classification, IASLC meetings, and other educational activities such as the IASLC webinar series. It is not difficult to see the enormous contribution that the IASLC Pathology Committee has made in the field of lung cancer pathology. In an effort to be transparent and to disseminate information in a timely manner, the IASLC Pathology Committee aims to make a regular contribution to the IASLC Lung Cancer News, highlighting interesting committees from the world of lung cancer pathology that we hope readers will find useful in daily practice. The care of patients with lung cancer truly is a multidisciplinary effort, and we all practice lung cancer medicine in different ways. Dr. Wendy Cooper, a pathologist from the Royal Prince Alfred Hospital, in Sydney, Australia, came up with a title for the article series that we all liked, as it reflects the close collaboration between pathology and oncology, delivering personalized medicine for patients with lung cancer: Diagnostic Oncology: Reports from the IASLC Pathology Committee. Each issue will feature an article for this new column, authored by a committee member. If you have questions for the committee or a topic suggestion, email IASLC Lung Cancer News Managing Editor Joy Curzio at curziocommunications@gmail.com. •

The IASLC Pathology Committee at the 2018 USCAP meeting in Vancouver, Canada.
Thoughts on IMpower 150: Latest FDA Approval for Atezolizumab Misses the Mark

On December 6, 2018, the U.S. Food and Drug Administration (FDA) approved atezolizumab in combination with bevacizumab and chemotherapy, specifically paclitaxel and carboplatin, in advanced nonsquamous NSCLC. As part of a larger phase III trial, this combination (PCBA) proved superior to the “standard” combination of bevacizumab/paclitaxel/carboplatin (PCB). In the wild-type population, the median PFS was 8.3 months compared with 6.8 months for the control arm, with a hazard ratio (HR) of 0.59 and further separation of the PFS curves beyond the median, presumably when patients had completed systemic chemotherapy and were on maintenance bevacizumab. This PFS benefit translated into an OS benefit in the intent-to-treat population: median OS of 19.8 months for PCBA vs 14.9 months for PCB with an HR of 0.76. Results were even more impressive in a subgroup of TKI-exhausted patients with oncogenic drivers, either EGFR mutation or ALK translocation, where the HR for OS dropped to 0.54 (median OS not reached vs 17.5 months).

Although these results on their own are astounding, it remains to be seen if this regimen offers any therapeutically advantageous combination over Pembrolizumab and pembrolizumab (PCP), which, in a similar population, resulted in an even more impressive PFS and OS benefit. The PCBA regimen is restricted to patients who are bevacizumab eligible, which would exclude many individuals with recent thromboembolic disease or recent history of hemoptysis. In addition, paclitaxel, in lieu of pemetrexed, is potentially more toxic with heightened risk of peripheral sensory neuropathy and alopecia. The addition of a fourth agent to a standard three-drug regimen can further exacerbate toxicity. Finally, the FDA approval explicitly omits the TKI- refractory population, which seemed to enjoy the greatest relative benefit in IMpower 150. Of note, this population was excluded from enrollment on the KEYNOTE-189 study, which led to pembrolizumab’s approval in combination with pemetrexed and carboplatin in advanced, nonsquamous NSCLC. In the absence of such an approval, the standard regimen in TKI-refractory patients remains elusive and controversial.

In this regard, we believe the FDA has missed the mark by failing to include the TKI-refractory population with oncogenic drivers in this important approval.

Corey Langer, MD, IASLC Editor
Fabrice Barlesi, MD, PhD, IASLC Associate Editor
Caicun Zhou, MD, PhD, IASLC Associate Editor
Edgardo S. Santos Castillero, MD, FACP, IASLC Publications Committee Chair

New Approval for Atezolizumab

December 6, 2018 — The U.S. Food and Drug Administration (FDA) approved atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin for management of metastatic nonsquamous NSCLC with no EGFR or ALK mutations in the first-line setting. Atezolizumab is also approved by the FDA for treatment of patients with metastatic NSCLC who experience disease progression during or following treatment with platinum-based chemotherapy, as well as for those patients who have EGFR or ALK mutations and have experienced disease progression during or after targeted therapy. (For more about the basis of this approval, see the Editors’ Note above.)

About the Authors: Prof. Multshine is a professor at Rush University and chair of the IASLC Early Detection and Screening Committee. Prof. Field has a personal clinical chair in Molecular Oncology at the University of Liverpool, UK.
NURSES & ALLIED HEALTH PROFESSIONALS

Nursing Care’s Technological Patient-Care Transformation

By John McPhelim, RN, BSc (Hons)

Nursing—particularly communication—in lung cancer care is transforming as a result of the innovative use of supportive health technologies. Cell phones, tablets, laptops, and desktop computers are growing increasingly popular in the use of safety monitoring and communication with patients across a variety of healthcare settings. Technology-based communication offers a wide range of benefits such as remote face-to-face interviews and interpretation of digital data, which facilitates convenient care, hastens medical interactions, and negates the requirement for patients to travel long distances. Robust and protocol-driven electronic health strategies are flourishing. The International Thoracic Oncology Nurses Forum Workshop at the IASLC World Conference on Lung Cancer, in Toronto, Canada, in September 2018, provided excellent examples of how technology can support the delivery of healthcare and how social media can be used, in the right circumstances, to share real-time data and information among health professionals while complementing patient communication.

Pamela Rose, a lung cancer specialist nurse at NHS Lanarkshire, in Scotland, United Kingdom, presented the findings of a project funded by the Scottish Government and Macmillan Cancer Support. Ms. Rose described the development of an electronic patient-reported outcomes measure that is intended to support patients’ use of an electric patient management system that facilitates communication between professionals and patients using a web-based platform. This service has been evaluated positively by users and has identified significant unmet needs in the participant group. Using this platform, patients complete an online assessment in advance of a consultation with their nurse specialist. This allows the nurse to prepare and focus on patient-identified needs. Furthermore, this electronic patient-reported outcomes measure has been very successful in identifying non-medical needs of patients, thereby delivering a rounded, holistic assessment that improves patient care and experience of care outcomes.

Liz Darlison, director of Mesothelioma UK, presented “Tag, Tweet, or Follow: Top tips for using social media in your clinical practice.” Platforms such as Twitter, Facebook, and similar electronic tools were demonstrated to be useful in a world where electronic interactions and communication are commonplace among patients. Using these tools can be of great value; however, their use must be carefully managed. Ms. Darlison highlighted the potential negative aspects to engaging in social media, so guarded caution is advised. (For more on this topic, see the article about social media and clinical trials below.)

Sarah Cubbin, a lung cancer nurse specialist at the Clatterbridge Cancer Centre, Liverpool, United Kingdom, shared her working practice in the use of an electronic platform to assess and monitor patients remotely using an agreed protocol with her oncology colleagues. This initiative demonstrated feasibility, effectiveness in assessing patient symptoms, and patient acceptance.

There are numerous ongoing investigations regarding the use of technology in the delivery of cancer care. Roma Maguire, PhD, MSc, BN, of University of Strathclyde, Glasgow, United Kingdom, has conducted a study in remote monitoring of symptoms in patients with mesothelioma in which outcome measures such as symptoms and quality of life were evaluated. She is currently conducting a remote electronic symptom-monitoring study in Europe in patients receiving systemic treatments; recruitment to date includes more than 2,000 participants.

Electronic technology is now habitual in a large percentage of the public’s everyday life, and communication via various modes of technology is now the norm for patients. Without question, now is the time for the nursing community to embrace such technologies to foster secure, pragmatic systems to support and enhance delivery of care. ✪

About the Author: Mr. McPhelim is a lead lung cancer nurse specialist at NHS Lanarkshire, Scotland, UK, as well as treasurer of the International Thoracic Oncology Nursing Forum.

ADVOCACY & SURVIVORSHIP

Improving Clinical Trials Through Clinician, Patient Use of Social Media

The National Cancer Institute featured a workshop in June 2018 titled “At the Crossroads of Social Media and Clinical Trials: A Workshop on the Future of Clinician, Patient, and Community Engagement.” The two-day conference brought together key stakeholders in this area including clinical trialists, internet researchers, patient navigators, advocates, and communication experts.

By DR Camidge

The viral spread of videos related to the “ALS Ice-Bucket Challenge,” in which individuals dumped a bucket of ice water over their heads and then tagged friends on social media as a way to fundraise for research, represents a prominent example of how a social media campaign can work to raise awareness of medical issues. However, creating a social media presence to generate free marketing for an idea, a person, institution, or project—such as an actively recruiting clinical trial—is frequently referred to as being “like given a free puppy.” Just as the puppy needs constant attention, so does a social media presence. To effectively create a go-to spot for information, optimal use of social media requires more effort than maintaining a website or engaging in email. Instead, it’s more akin to engaging in a constant conversation with a community consisting of multiple participants and observers.

“In the end, it’s about meeting people where they are,” said Yasmin Kloth, manager of the National Institute of Health’s All of Us Research Program’s social media program.

Clinical Trials: Social Media’s Potential for Value and Harm

In addition to being a means for healthcare professional outreach to patients, the conference discussed how patients themselves are also using social media to educate one another about new developments, including the pros and cons of clinical trials. Research by British researchers found that e-cigarettes were more effective for smoking cessation than nicotine-replacement therapy when combined with behavioral therapy. The randomized trial, the results of which were published in The New England Journal of Medicine on January 30, found an almost double sustained abstinence rate after 1 year among the smokers randomly assigned to the e-cigarette group: 18.0% vs. 9.9% for nicotine-replacement products (relative risk 1.83; 95% CI: 1.30-2.58, p < 0.001).

The study had several limitations, however, and the rate of continued e-cigarette use was fairly high. E-cigarettes may pose health risks, the severity of which are unknown, so long-term use could be problematic. ✪

Read the IASLC Lung Cancer News April issue for more details about this study.

broken news

E-cigs Help Smokers Quit, Health Risks Unknown

British researchers found that e-cigarettes were more effective for smoking cessation than nicotine-replacement therapy when combined with behavioral therapy. The randomized trial, the results of which were published in The New England Journal of Medicine on January 30, found an almost double sustained abstinence rate after 1 year among the smokers randomly assigned to the e-cigarette group: 18.0% vs. 9.9% for nicotine-replacement products (relative risk 1.83; 95% CI: 1.30-2.58, p < 0.001).

The study had several limitations, however, and the rate of continued e-cigarette use was fairly high. E-cigarettes may pose health risks, the severity of which are unknown, so long-term use could be problematic. ✪
In the following inter-
view, Jamie E. Chaft,
MD, a medical oncol-
yst at the Memorial Sloan Kettering Cancer Center, discusses new data on induction immunotherapy for patients with resectable NSCLC as well as the recently published summary paper on the IASLC–U.S. Food and Drug Administration (FDA) summit on neoad-
vjuvant therapies.1

Q: What are the implications of induc-
tion or neoadjuvant immunotherapy in patients with resectable NSCLC?
A: We now have data from multiple early-
phase studies of neoadjuvant immu-
otherapy that preoperative immunother-
ysis is both safe and feasible. These studies have helped alleviate the fears of high
rates of pneumonitis from thoracic sur-
ery shortly after a dose of anti–PD-1/–
PD-L1 therapy. Although these results are
useful, the practi-
cal implication of these studies comes from
the unanticipated efficacy seen after
just two doses of single-agent anti-
PD-1/–PD-L1 therapy. This observation has
spurred tremendous commitment from
industry to move drugs and drug combi-
nations into the neoadjuvant space.

Q: What advantages, if any, does induc-
tion therapy offer over “conventional”
adjuvant treatment?
A: Induction therapy offers practical
advantages of improved tolerability/drug
delivery, time for preoperative smoking
cessation, and the ability to monitor the
efficacy of the drug in vivo, both radio-
graphically during treatment and patho-
logically after treatment. The resection
specimen provides a unique opportu-
nity for systemic evaluation of treatment
response and the potential for identifica-
tion of surrogate markers of much later
clinical endpoints.

Q: Is major pathologic response (MPR; ≤
10% residual viable tumor in the sur-
gical specimen) a reasonable surrogate for
long-term benefit? Do you think the
FDA will allow this endpoint as a con-
duit to accelerated approval?
A: The FDA’s previously published
position, outlined in the joint IASLC–
FDA paper in the Journal of Thoracic Oncology,1 considers accelerated
approval based on surrogacy in a case-
by-case basis. A provisional surrogate
must measure response to the interven-
tion and be reasonably likely to predict
clinical benefit. MPR was developed to
fill a void in NSCLC, as pathologic com-
plete response (pCR) to chemotherapy is
too infrequent. MPR measures the effect
of neoadjuvant chemotherapy at a more
clinically relevant frequency and has
been associated with clinical outcomes.
Perhaps as our therapies improve, we
will have the opportunity to use pCR.
Until then, the systematic study of MPR
with collection of later clinical outcomes
should be a priority of the lung cancer
community with the goal of working with
regulatory authorities to bring
effective drugs to patients sooner.

Q: What are your thoughts on com-
bining platinum-based chemotherapy
with immunotherapy in this setting? Do
you think this approach might pose an
advantage over neoadjuvant immuno-
therapy alone?
A: The presented data on the combina-
continued on page 12

Rising Cost of Lung Cancer
Therapies from page 6
compared to a treatment that only mini-
mally affects survival or quality of life and
yet is expensive, leading to a high ICER.
However, there is no consensus on what
constitutes an acceptable ICER thresh-
old for funding a novel therapy, with
significant variation across countries and
disease types. The National Institute for
Health and Care Excellence in the United
Kingdom has a threshold of up to £30,000
per quality-adjusted life year (QALY) to
be considered cost effective for National
Health Service funding,2 although drugs
with higher ICERS have been recom-
manded for access through their Cancer
Drug Fund. In North America, the
$100,000 per QALY threshold has been
cited for oncology,3 although many drugs
exceed these thresholds, often running
over $220,000/QALY.1,12

Moving Forward
Many countries are increasingly using
managed-entry agreements, which allow
cost sharing between the payer (or gov-
ernment) and drug manufacturer when
there is uncertainty regarding benefit and
cost effectiveness. These programs strive
to ensure patient access to new drugs;
however, pricing in managed-entry agree-
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mement.
of ongoing trials. Without social media, some patients on clinical trials do not know what questions to ask their doctors or what the most useful resources are for caregiver information. At the very least, they might struggle to find a hotel or the best place to eat in a new city. More importantly, it is unknown whether a patient’s personal experiences in a trial, as discussed on social media, might mislead other potential participants or data might be prematurely revealed through discussion of these experiences. The patient-consenting process for trials was proposed as an ideal setting in which to ask trial participants to refrain from discussion on social media. However, several patients at the conference emphasized their right to freedom of expression.

“Social media isn’t going away. It’s the trials’ process, not the patients who should adapt,” said Gilles Frydman, founder of the Association of Cancer Online Resources and co-founder of Smart Patients, Inc. Certainly, trial patients can be requested to limit their public posts at the time of informed consent. Increasing community awareness that any individual source may be subject to implicit bias may be the better way to address this issue over time.

Plain and Simple Talk
The lack of user friendliness of some Internet sites (notably clinicaltrials.gov) and the lack of plain language that is easily comprehended by a non-specialist audience was repeatedly mentioned during the conference. Although social media could facilitate accrual, retention, and better adherence to follow-up schedules for a specific trial, there is a fine line in this setting between increasing awareness and coercion. In addition, it is unclear how investigational review boards, which previously have had to approve language used in patient-facing materials such as consent forms, should address trial-specific social media with every immediate interaction visible, potentially forever, in the public domain. One suggestion was to have broad plain-language templates approved in advance, with the specific words used on any given day being less important.

“Social media is organic and responsive—our old ideas of a fixed script or set of words vetoed to be presented to a patient in a paper consent form do not fit well with social media interaction. [Investigational review boards] in general are still grappling with best oversight practices for recruitment or other research activities conducted over social media,” said Luke Gelinas, chair of the Advarra IRB, and one of the speakers at the conference.

Overall, the potential of social media to change aspects of clinical trials dramatically was clear in the conference. Equally clear was that, as with anything new, nothing is ever simple. A considerable amount of work is ongoing to understand the best way to marry the use of social media and trial promotion going forward.

Conducting Trials Through Social Media
Conduct of meaningful research directly through social media appears very attractive given the potential for industrial-strength data to be generated. However, a Centers for Disease Control (CDC) study relating to the lifestyle habits of young LGBTQ people revealed the underlying complexities with this approach. In the study, choice of the right social media platform was vital, with participants’ favorite platforms varying by study population. Facebook and Twitter might be the most well-known platforms, but they are by no means the only forms of social media being used.

“If social media is used appropriately, it can be a cost-effective way to connect with otherwise hard-to-reach groups,” said Erin Fordyce, research methodologist at NORC at the University of Chicago, which helped coordinate the LGBTQ study with the Centers for Disease Control’s Division of Adolescent and School Health.

The study also highlighted the importance of recognizing the inherent bias present in any responders. Only a proportion of potential trial participants will be on social media, only a proportion will be using the specific platform involved in the trial, and only a proportion of those will choose to respond. Multiple tricks exist to ensure respondents are genuine and that multiple responders are in fact different people. In the former situation, responses that are uniform in their approach, such as “don’t know” should be discounted. Device identification methodologies also can be used to prove uniqueness or individual existence of respondents.

Crowd-Sourcing a Clinical Trial
For rare diseases, where a single center could never encounter enough examples of cases, social media offers the potential to reach out in a manner unrestricted by geography. A study conducted by PatientsLikeMe and Duke University for ALS revealed the huge potential for social media in this regard. Following a small published case report that had suggested benefit from a dietary supplement, PatientsLikeMe facilitated a virtual trial where patients gained access to the supplement themselves and then centrally cataloged their own experiences through Duke. This study showed no evidence of benefit from the supplement and reported results earlier and more cost effectively than an NIH-sponsored study, which showed the same result.

“Our ALS trial shows what the creative use of social media can achieve in terms of bringing the clinical trial paradigm into the 21st century!” said Paul Wicks, vice president of Innovation at PatientsLikeMe. “It’s easy to imagine that in the future, these approaches will be used more and more.”

Induction Immunotherapy
from page 11

Q: What are your thoughts on the NADIM trial in stage IIIA NSCLC, where the MPR rate exceeded 70% and the pCR rate exceeded 50% in patients receiving induction nivolumab, paclitaxel, and carboplatin?
A: The NADIM study showed remarkable rates of pathologic regression in high-risk resectable NSCLC with what was a very tolerable regimen. The pathologic response methodology was not presented with the data; therefore, it is unclear how these numbers would shift with external review. Regardless, the regimen was exceptionally effective. I hope these data will fuel enrollment of the ongoing phase III induction trials.

Q: Which biomarkers are most useful in this setting?
A: We are still learning about predictive biomarkers in this setting. The dataset in the neoadjuvant nivolumab study was incomplete, but tumor mutation burden associated well with pathologic regression. The LCMC3 effort with neoadjuvant atezolizumab will provide a very large dataset to evaluate the question of predictive biomarkers for single-agent immunotherapy. We will have to wait and see if any of these hold up when chemotherapy is added to immunotherapy.

Q: The IASLC just released a paper on this subject. What are the two most salient points for daily practice in the paper?
A: The IASLC–FDA summit on neoadjuvant therapies produced a summary paper outlining the discussion of many experts in the field. To me, the take-home messages are that neoadjuvant therapy should be a consideration for all patients for whom adjuvant therapy would be appropriate. The ability to monitor the effect of the treatment given against the patient’s tumor aids clinical decision making. Research opportunities and the collaborative potential to define a surrogate in this disease further these considerations.

References:
Nuances of PET Interpretation in Thoracic Oncology: More Than Just Lung Cancer

By Michael MacManus, MD, FRANZCR, and Tim Akhurst, MD, FRACP

18F-FDG PET/CT scans portray living biology and are indispensable in thoracic oncologic evaluations, including presurgical staging of NSCLC, patient selection and target-volume definition in curative-intent radiation therapy (RT), and the evaluation of patients with suspected recurrence after definitive therapy. FDG-PET is also superior to CT for response assessment after definitive chemoradiation.1 The indications for PET/CT will continually expand as thoracic oncology becomes more complex with new immunotherapies and tyrosine kinase inhibitors (TKIs) and with the increasing use of stereotactic ablative body radiotherapy (SABR).2 Physicians interpreting PET must be aware of the clinical state of the patient beyond a simple request for “lung cancer imaging,” and they must fully understand the nuances regarding acquisition and interpretation of PET/CT scans.

The Importance of Standardization, Timing
PET data, including semi-quantitative variables such as tumor standardized uptake value, are profoundly influenced by technical factors, including patient preparation (e.g., avoidance of strenuous exercise, adequate fasting, hydration, and hyperglycemia) and appropriate FDG dosing. Standardization of image-acquisition timing after FDG injection and use of the same scanner and reconstruction protocols for all patient examinations contribute to accurate reading of serial scans.

Lung cancer can progress rapidly, especially in locoregionally advanced cases. PET/CT scans must be current at the time of commencement of curative-intent treatment; outdated or incorrectly acquired scans should be repeated. One study showed that more than 30% of patients with NSCLC eligible for chemoradiation had disease that progressed significantly within a median of 3 weeks between PET/CT scans, mandating changes to therapy.2 Baseline PET scans may provide additional clinical information, including identification of recurrent laryngeal nerve palsies, cardiac disease, unsuspected second malignancies, as well as otherwise “occult” CT-undetectable metastases. Differential FDG-PET response of apparently infective lesions to antimicrobial therapy might unmask unsuspected cancer (Fig. 1).

RT Planning, Assessing Therapeutic Response
Incorporation of FDG-PET data into RT planning frequently changes RT target volumes, often allowing better management of small FDG-avid nodules or preventing unnecessary irradiation of atelectatic lung. PET/CT scans acquired in the raised-arm RT position can be used directly for tumor-volume contouring and definition of planning target volumes.4 If a staging PET/CT scan can also be used for RT target definition, the PET request should make this clear, enabling proper patient positioning and facilitating cost savings and patient convenience.

After curative-intent chemoradiation, the qualitative distinction between complete metabolic response (CMR; which is associated with a 5-year survival of approximately 50% of patients) and non-CMR (wherein prognosis is dramatically

An Interview with Dr. Federico Cappuzzo: Checkpoint Inhibitors Have Replaced Old Strategies

Federico Cappuzzo, MD, PhD, has been the director of Medical Oncology at AUSL della Romagna, Ravenna, Italy, since April 2016; in January 2017 he became the director of the Hematology and Oncology Department. The author of more than 200 papers, Dr. Cappuzzo is an extremely active member of the IASLC, having served in various leadership and faculty roles for numerous planning committees and meetings. The IASLC Lung Cancer News spoke with Dr. Cappuzzo about checkpoint inhibitors (CPIs) in the first- and second-line settings, as well as about the future therapeutic horizon.

Q: As CPIs move to front line, which regimen or regimens are now "standard" in the second-line setting in advanced NSCLC?
A: Of course this is an important question for clinical practice because CPIs are now mainly used in front-line settings in combination with chemotherapy, particularly with platinum-based chemotherapy. When this is ineffective, the standard second-line option is, unfortunately, docetaxel unless a CPI is used as a single agent in the front line, in which case the standard second-line regimen is platinum-based chemotherapy.

Q: Does this reinvigorate the role of combination docetaxel and ramucirumab in this setting?
A: Yes, we know that docetaxel alone is not an optimal treatment in the second-line setting for patients who have already received platinum-based chemotherapy. We also know that the combination of docetaxel with an antiangiogenic agent, such as ramucirumab or even nintedanib, could be a reasonable option that we can offer patients to ensure a more effective regimen.

Q: With respect to patients who have been on chemotherapy/CPI combinations front line, do you think there is a role for platinum re-challenge in patients whose disease has stabilized or responded to prior platinum regimen(s) and who experience disease progression on CPI alone or on pembrolizumab/pemetrexed?
A: Re-challenge of platinum-based chemotherapy is generally considered an option when we have a patient whose disease responds to the therapy and the duration of response is relevant—for example, lasting at least 1 year. I think that this concept remains applicable even in the era of immunotherapy, meaning that if we have a patient treated with a platinum-based chemotherapy and CPI combination whose disease responds to the therapy and maintains the response for a long time after chemotherapy is stopped, re-challenge with the platinum-based agent at the time of disease progression could be preferable to docetaxel. Of course, it’s only reason-
It is common knowledge that the number one cause of preventable deaths in the world is from tobacco use—overwhelmingly from cigarettes. Most of the deaths from tobacco use, particularly from smoking, are from cardiovascular disease, followed by cancer, and then chronic obstructive pulmonary disease (COPD). The most common cause of cancer deaths in advanced economies is smoking-related lung cancer. Approximately 25% of deaths from cardiovascular disease are from smoking, and approximately 80% of COPD deaths are from smoking. Therefore, if we are looking at general public health, we must turn our attention to the vector that is causing most of the top three causes of death.

The Current ENDS Market
Since the turn of the 1900s, this vector has been the cigarette. However, the cigarette industry is under significant challenge from other nicotine-delivery products. Most notably, the electronic cigarette, or electronic nicotine delivery systems (ENDS), has been a market disrupter for the past decade. ENDS come in a variety of forms such as e-hookahs, vaporizer pens, and tank systems. ENDS are different from cigarettes in that they use a battery to create an aerosol that contains nicotine, which is then inhaled. This aerosol is a liquid mixture of a variety of chemicals created from propylene glycol (PG), vegetable glycerin (VG), flavors, and nicotine. The ratio of the PG to the VG is important to the user, particularly if they want the big “vape cloud,” in which case they would use a higher proportion of VG.

Nuances of PET Interpretation
from page 13
cally worse), can help determine further disease management, including salvage surgery or immunotherapy. Knowledge of typical uptake patterns in lung and pleura after RT is essential to avoid mis-interpreting radiation-induced changes as persistent or progressive disease. After SABR for lung cancer, a nonmalignant pseudotumor may develop at the irradiated site; FDG-PET negativity can distinguish between a pseudotumor and local progression (Fig. 2). In the assessment of response to systemic therapy, the degree of partial metabolic response as assessed by semiquantitative analysis, such as PERCIST, which includes PET parameters unlike RECIST, can help determine whether to continue treatment.

Patterns of failure vary from progression at multiple sites to oligoprogression at a single or a limited number of sites. Delivery of locally ablative therapy to sites of oligoprogression identified by PET can allow continuation of otherwise efficacious therapy. FDG-PET has an important role in selection of patients suitable for metastasectomy or ablative techniques including SABR and radiofrequency ablation.

Newer Systemic Therapies
Therapy for lung cancer is evolving rapidly, with the advent of multiple novel systemically administered agents, each characterized by specific therapeutic and toxic effects that may influence PET/CT evaluation. Molecularly targeted therapies, especially TKIs targeted to activating mutations involving EGFR, EMLA-ALK, BRAF, and ROS1, have revolutionized the care of many patients with lung cancer who harbor the specific targets for these agents. Immunotherapy, particularly the immune checkpoint inhibitors, have generated well-founded excitement due to improvements in survival and the potential for prolonged disease-free survival in some patients with metastatic disease. Both TKIs and immune checkpoint inhibitors have associated toxicities that influence PET interpretation, including severe pneumonitis, which can be well visualized on FDG-PET. Changes in FDG uptake with the treatment of pneumonitis can provide objective evidence of therapeutic response (e.g., to steroids, Fig. 3) and contribute to clinical decision making for both the cancer and for treatment related toxicity. PET clinicians interpreting scans should be fully aware of the initiation of relevant systemic therapies and consider their effects on differential diagnosis.

Fig. 3. Pulmonary Toxicity of Immunotherapy
A male patient commenced immunotherapy with nivolumab and ipilimumab for lung metastasis from melanoma. In the left column, baseline CT, PET/CT, and PET maximum intensity projection images are shown, respectively. The patient developed increasing breathlessness, and PET/CT showed airspace consolidation that was FDG avid, consistent with pneumonitis (middle column). Immunotherapy was suspended, and the patient commenced high-dose steroids with rapid clinical improvement. Repeat PET/CT imaging showed resolution of inflammatory FDG uptake in pulmonary parenchyma, a therapeutic response in the lung metastasis, and new bilateral pleural effusions (right column).

References
ENDS and HTPs
from page 14

a tobacco industry. Then, Vuse became a market leader; this was initially an R.J. Reynolds Tobacco Company product that was subsequently purchased in the United States by British American Tobacco, which already had the ENDS product Vype. Altria (a U.S. company that had split off from Philip Morris but still sells Marlboro, which is the global market leader of cigarettes) sells MarkTen® as their ENDS product. Lorillard Tobacco Company had the ENDS product Blu, but it was sold to Imperial Tobacco when R.J. Reynolds Tobacco Company bought Lorillard Tobacco Company. Therefore, multiple companies, each with their roots in the sales of traditional combustible tobacco, are prominent in the marketing of ENDS. Additionally, there is Juul—at approximately 70% market share in July 2018 and growing, there will surely be more on this product in a future article.

HTPs: An Answer for Higher-Income Countries?

Heated tobacco products (HTPs) are another cigarette alternative. Purportedly, HTPs do not combust tobacco, but rather they simply heat tobacco in order to put nicotine into an aerosol. For users of ENDS and HTPs, it is all about the nicotine delivery and the resolution of withdrawal or cravings for nicotine. Unlike with ENDS manufacturers, the largest marketers of HTPs are the usual tobacco companies that have been known for decades. IQOS (or “I quit ordinary smoking”) by Philip Morris International, Ploom TECH by Japan Tobacco International, and glo® by British American Tobacco are the most common now, but this market is growing.

Ostensibly, by heating the tobacco rather than burning or combusting it, there are fewer carcinogens and, hopefully, fewer other harmful or potentially harmful constituents. Right now, these large, multinational tobacco industries are trying to position their HTPs to become market leaders. The CEO of Philip Morris has declared that his company wants to stop selling cigarettes in the United Kingdom and have them replaced by people smoking iQOS. In the United Kingdom, the United States, Canada, Australia, France, Japan, and many other developed economies with effective tobacco control programs, smoking of cigarettes continues to decrease. These multinational companies should stop selling their cigarettes in lower-income countries where there are still high rates of use and, thus, high rates of related morbidity and mortality.

Will New Products Result in Fewer Deaths?

It is true that both ENDS and HTPs seem to have fewer carcinogens, so their use should, theoretically, cause fewer cancers, particularly lung cancers. However, there is more controversy about other health effects, and there is great variability among various countries as to how they are perceived. ENDS are forbidden in many countries, particularly if they deliver nicotine.

However, countries such as the United Kingdom are strongly encouraging adults to switch to ENDS as a cigarette smoking-cessation tool because ENDS are believed to be less hazardous than cigarettes. A recent report from the United Kingdom states that it is plausible that the nationwide decrease in smoking prevalence is due to the availability of ENDS as cigarette smoking-cessation tools. Other countries fall elsewhere on the continuum of perceived risk/benefit, although a common shared belief is that ENDS are less deadly than cigarettes. The big question is that confounding many countries is the uptake of ENDS by youth and the unknowns that result from this uptake. For example, what are we to think about JUUL, an innovative ENDS in the United States that has approximately 60% of the market share and has created havoc in schools with its increasing prevalence of use? Even less is known about HTPs, particularly what they will mean for the market, whether they will be less harmful in long-term use than cigarettes, and whether youth and young adults will start using them.

The various regulatory options that governments might implement are another factor that must be considered. For example, the U.S. Food and Drug Administration is considering a rule that would significantly decrease the amount of nicotine that could be delivered by a cigarette. It is unclear, however, whether this would result in a decrease in the percentage of youth who start smoking or an increase in the number of adults who quit smoking. Equally unclear are the effects on rates of users of ENDS or HTPs and the ultimate public health outcome.

Additionally, there has been a worldwide movement to restrict flavors in tobacco products, particularly combustible products, to help stop smoking initiation by youth. However, this is tricky because adults also prefer flavored tobacco products, and such flavorings may be the attraction that aids adults in their transition from combustible tobacco products, such as cigarettes with low nicotine delivery, to ENDS or HTPs.

We can only hope that these recent changes will be effective in decreasing the deaths from tobacco.

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References:


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able to consider a platinum-based chemotherapy re-challenge as long as the patient tolerated the therapy well in the first-line setting and there is no residual toxicity.

Q: In a patient with nonsquamous NSCLC in such a scenario, would you consider resuming carboplatin, substituting a taxane for pemetrexed, and switching the CPI for an angiogenesis inhibitor? Why or why not?

A: We can certainly change the drugs that we’re using from the front-line setting, with the idea being that, regardless of what is used front-line, we will re-challenge with chemotherapy. If we have a patient who was already on an immunotherapy in the front-line setting, using a platinum-based chemotherapy regimen, replacing one of the agents and adding an antiangiogenic therapy (for example, bevacizumab) could be reasonable.

Q: What role is there for adding new immunotherapeutic agents (e.g., vaccines and CTLA4 inhibitors) to front-line CPIs in those with "smoldering progression"?

A: Combinations of different immuno-therapy agents in the first-line setting is very attractive considering that generally patients are reluctant to consider chemother-apy and frequently ask for a chemo-free combination. Recent data show that combination nivolumab and ipilimumab could be more effective than chemotherapy or chemotherapy/CPI combinations, particularly for patients with high tumor mutational burden (TMB). Additional data are needed, but this approach allows for avoidance of chemotherapy in the first-line, whereas an effective therapy—platinum-based chemotherapy—can be reserved for those whose disease progresses on CPIs.

Q: How long are you treating patients with CPI in the second line?

A: The duration of treatment in the second line with CPIs generally continues up to disease progression, toxicity, or patient refusal. Many studies have continued treatment for up to 2 years. Optimal duration is not defined, but we know from clinical studies that, in patients who benefit from the treatment, stopping therapy at 1 year is not recommended. So in my practice, we use CPIs up until progression in both the first- and second-line settings.

Q: Do some biomarkers (TMB, for example) influence your choices to (re) use CPIs in patients based on PD-L1 expression status?

A: In the future I think TMB will be used in clinical practice, but at the present time the only biomarker that we are using is PD-L1. In the first-line setting CPIs can be considered in combination with chemotherapy irrespective of PD-L1 expression. In the second-line setting, the efficacy of a CPI, even as a single agent, has been demonstrated in clinical trials irrespective of PD-L1 expression. This is not an optimal situation because we know that PD-L1 is not the optimal biomarker: a consistent proportion of patients with high levels of PD-L1 expression do not respond to immunotherapy, and some patients with no or low PD-L1 expression have shown positive effects of CPIs. We need additional biomarkers to refine patient selection, not only to identify those patients who will demonstrate a strong response to therapy but also to save patients who are not likely to respond from unnecessary treatment. However, at the present, based on the current data for TMB, PD-L1 remains the most standard biomarker.

Q: What do you see on the horizon in the next few years for CPI?

A: I think we will have additional combinations of existing and new immunotherapeutic agents. Of course, what we urgently need are agents for patients who have disease progression on the current CPIs because the fallback for these patients remains chemotherapy. We need new strategies and new drugs that we can employ as second-generation immunotherapeutic agents.
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