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FOR THORACIC SPECIALISTS

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LUNG CANCER IASLCNEWS

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

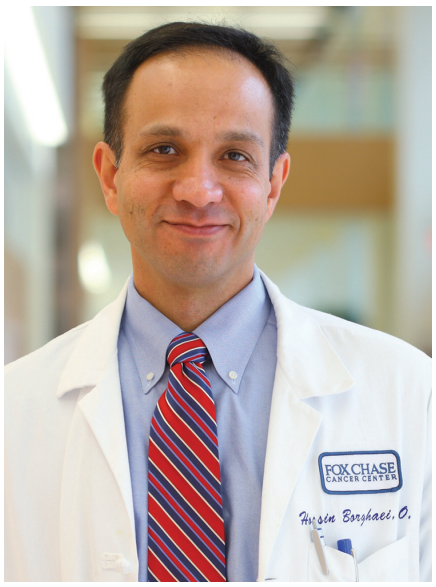
INSIDE

IMMUNOTHERAPY

Takeaways from KEYNOTE-021 and IMpower 150 on Combination Chemotherapy and Checkpoint Inhibition in NSCLC

By Hossein Borghaei, MS, DO

The role of checkpoint inhibitors in the management of recurrent or metastatic NSCLC is now well established. For patients who are treatment naive who do not have a driver mutation and who have a high PD-L1 expression (≥ 50% tumor proportion score), frontline pembrolizumab is the accepted standard of care based on the results of the KEYNOTE-024 study.[1] Based on the results of KEYNOTE-021 cohort G, a randomized phase II trial, the U.S. Food and Drug Administration has approved the triple combination of carboplatin, pemetrexed, and pembrolizumab in all patients with non–squamous cell NSCLC, regardless of PD-L1 expression levels.[2] The results of this trial indicate that the combination of a platinum-doublet chemotherapy and a checkpoint inhibitor is not only feasible from a safety standpoint, but it can also lead to better response rates and possibly better overall survival (OS) duration. However, many in the thoracic oncology community remain skeptical of the role of such combinations for first-line treatment of patients with advanced disease. In the absence of definitive phase III data, platinum-doublet chemotherapy remains a viable option for patients with less than 50% PD-L1 expression and no driver mutations.



Promising Results for OS, PFS

IMpower 150 is a randomized phase III trial designed to assess whether the addition of atezolizumab, a PD-L1 antibody, to a backbone of carboplatin, paclitaxel, and bevacizumab (C, P + B) could provide better clinical efficacy (see Fig. 1, page 6). As reported by Reck et al., this

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THOUGHT LEADER PERSPECTIVE

Q&A with the New IASLC President

Giorgio Vittorio Scagliotti, MD, Professor of Oncology at University of Torino and Head of the Department of Oncology and Chief of the Division of Medical Oncology at the San Luigi Hospital in Torino, Italy, earned his medical degree and completed his postgraduate training in respiratory medicine, internal medicine, and medical oncology at the University of Torino. He is a member of several scientific societies, including the IASLC, the Italian Society of Respiratory Medicine, The Italian Association of Medical Oncology, the European Respiratory Society, and the American Society of Clinical Oncology. Dr. Scagliotti was an IASLC Board member from 2003-2007 and was the 2016 Addario Lectureship Award recipient.

In the interview below, Dr. Scagliotti shares his vision for thoracic oncology and his perspective on international issues and the IASLC's involvement in solutions.

Q: Where is thoracic oncology going as a field?

A: Thoracic oncology is moving toward a step-by-step implementation of precision medicine, keeping in mind that not every therapeutic strategy should be centered on targeted therapies. While targeted therapies, at best, will constitute a therapeutic choice for 40% of our patients, other innovative approaches, such as immunotherapy, will have arrived on the therapeutic stage in a timely manner and can address the needs of those whose tumors do not harbor oncogenic drivers. Patient stratification issues in immunotherapy studies must be solved to identify and treat the optimal subgroup of patients. In addition, we must better understand the role of "omics" in early disease and the real contribution of this area of study to real-world diagnosis and management.

Q: How will the insights and challenges you've experienced as a leader in thoracic oncology in Europe influence your tenure as IASLC President?

A: The differences among European health care systems and those in the United States are still huge. Because the IASLC membership consists of so many different national perspectives, we should avoid discussing the pros and cons of each system. It is a matter of fact that drug accessibility in some European countries still represents a relevant societal issue, and critical drugs are not yet available for many patients. In addition, the average gap in time between drug approvals in the major European Union countries and the United States still exceeds 1 year.

Q: What special challenges do you anticipate in an era when the National Institutes of Health, the National Cancer Institute, and the European Medicines Agency budgets are threatened with cuts?

A: That is a critical problem to be solved. Scientific organizations, such as the IASLC, should become preferred partners for regulatory agencies to act as "institutional advisors." If we look carefully at our new strategic plan, this is an issue that

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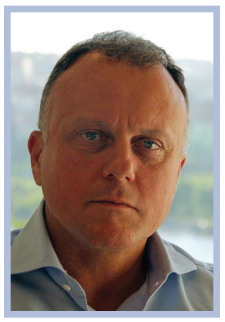
MEETING NEWS PREVIEW

Lung Cancer Immunotherapy Meeting to Discuss New Topics, Emerging Themes

By Federico Cappuzzo, MD, PhD

During the past few years, improvements in the knowledge of immune system biology have dramatically changed the therapeutic paradigm for NSCLC. Pembrolizumab has been recently approved by regulatory agencies as an upfront agent for patients with advanced NSCLC with 50% or greater programmed cell death ligand 1 (PD-L1) expression, and recent data strongly support combination immunotherapy and standard chemotherapy in patients with low or no PD-L1 expression. In the second-line setting, single-agent immunotherapy with nivolumab, pembrolizumab, or atezolizumab is now considered the standard of care.[1] A recent study showed that durvalumab enhances progression-free survival over placebo in patients with locally advanced NSCLC treated with concurrent chemoradiotherapy.[2] Several new agents are under investigation, and clinical trials are exploring the potential role of new drug combinations, the role of immunotherapy in early stages, and the role of immunoprevention.



In such an exciting and rapidly changing era, many questions are arising, such as optimal drug combinations, sequencing, enhanced patient selection, better biomarkers, and cost effects of all new treatments. Therefore, there is an urgent need to revise and critically analyze available data to help clinicians provide the best therapy options to patients.

The Live Educational Experience

The IASLC-sponsored Lung Cancer Immunotherapy meeting, to be conducted in Madrid, Spain, on March 22-24, 2017, will bring together leading experts who are engaged in developing novel therapeutic options for lung cancer, with a specific focus in immunotherapy. The meeting will review the status of immunotherapy in lung cancer, analyzing both preclinical and clinical data. The topics selected for this meeting include: review of immune checkpoint inhibitors and other immunotherapies, analyses of clinical trials in different lung cancer stages, relevant clinical issues including patient selection and treatment of special patient populations, analysis of data on biomarkers predicting sensitivity to immunotherapy, new combinations, and new therapeutic strategies. The meeting will also feature exciting developments in the treatment of early-stage lung cancers, small cell lung cancer, and mesothelioma.

The meeting will open on March 22 with a lecture on lung cancer treatment progress, followed by a lecture on tobacco- and e-cigarette–induced inflammation. On March 23, there will be a discussion of basic immunologic principles, followed by presentation of preclinical and phase I data. Entire sessions will be

The IASLC-sponsored meeting will be held in Madrid, March 22-24, 2018

dedicated to biomarkers, anti–PD-L1/PD-1 data, new combinations, and new immunotherapy agents—including vaccines—providing the most innovative and updated results. Finally, on March 24, discussion will focus on clinical management, early-stage disease, small cell lung cancer, and mesothelioma. The last part of the meeting will focus on immunoprevention. A nurses' workshop and advocates' workshop are scheduled for March 25. This symposium is also open to fellows and early-career faculty members who will present their scientific research as abstracts or oral presentations at the meeting.

The Organizing Committee includes some of the most eminent experts in the field of lung cancer, including IASLC President Giorgio Scagliotti, MD, PhD; IASLC Treasurer Tony Mok, BMSc,

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IASLC

IASLC Lung Cancer Immunotherapy Meeting 2018

MARCH 22-24, 2018 | MADRID, SPAIN

New IASLC President from page 1

we would like to face head-on. Obviously, conflicts of interest could complicate any potential solutions, but the IASLC is ready to propose solutions that will guarantee independent judgment.

Q: Please comment on the research "alliance" that seems to exist between industry, government, and academia. Is the model developed by France exportable to other countries or continents?

A: We should stop seeing pharmaceutical companies as enemies and academia as the only good conductors of research. We must sit down and write clear rules for cooperation among the different stakeholders and then strongly encourage that cooperation. The French model is pretty interesting, but we should be open to a more structured cooperation, especially among pharmaceutical companies and a network of research institutions to establish large research networks. The intellectual property issues can be solved in the pure interest of our patients.

Q: As we witness major therapeutic advances, can we contain or handle costs?

A: Affordability is a question not only for oncology but for medicine in general; it is a matter of fact that oncology will be the major therapeutic area to be affected by a huge increase of costs by 2020. My personal view favors innovation when the innovation is coming with real and meaningful increases in survival; whereas the "me-too" agents should be abandoned. I am not an expert in pharmacoeconomics, but I know that

every country in Europe is looking to different strategies for reimbursement, some of them really innovative, such as the "pay-for-value" approach introduced by the Italian regulatory agency.

Q: How will the IASLC expand its multidisciplinary mission? How about its international outreach, especially to developing countries?

A: Here is the core of IASLC's business. Our main goal is to understand the needs of different parts of the world and provide customized approaches to help physicians in those areas, in turn, provide state-of-the-art diagnosis and treatment for thoracic malignancies. This is obviously not an easy task, but we will engage all of our energies and resources.

Q: From a more general perspective, which roles should academic and medical societies, as well as patient advocacy groups, play in the advancement of science and medicine, now and in the future?

A: I truly believe all parties together should act as an army, with the only and ultimate aim of conquering lung cancer. ✦

LUNG CANCER IASLCNEWS

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IASLC MISSION

To embrace the study of the etiology, epidemiology, prevention, diagnosis, treatment, and all other aspects of lung cancer and other thoracic malignancies; to provide education and information about lung cancer and other thoracic malignancies to IASLC members, to the medical community at large, and to the public; to use all available means to eliminate lung cancer and other thoracic malignancies as a health threat for the individual patient and throughout the world.

Checkpoint Inhibition in NSCLC

from page 1

combination resulted in an improvement in progression-free survival (PFS) in all patients, even those with driver mutations (Fig. 2).[3] This is notable because prior immunotherapy studies that allowed patients with driver mutations (or that reported the demographic surrogate of never-smoker status) demonstrated either comparability or inferiority for this subgroup.

The survival data are not yet mature, but preliminary results indicate an improvement in OS with the four-drug combination (median OS of 19.2 vs. 14.4 months, HR: 0.77, p = 0.026). The reported results included the analysis of two of the three arms but did not include the full analysis of the third arm that featured C + P plus atezolizumab without bevacizumab.

PFS analysis of multiple subgroups indicates that this quadruple combination was more effective than the triplet combination. In the driver mutation–negative group, the median PFS improved from 6.8 to 8.3 months, and response rates improved to 64% from 48%. PFS benefit was seen across all PD-L1 levels, with PD-L1–high tumors (TC3 or IC3) showing the greatest improvement compared with TC/IC 0, 1, and 2 groups. However, even the TC/IC 0 group, which comprised 49% of the patients, still showed PFS improvement. A new potential biomarker (T–effector gene signature expression) was also evaluated in this trial, but the results as presented did not necessarily support the use of this new test for selection of patients who would benefit from this treatment above and beyond PD-L1 testing.

At this time, there is no convincing evidence that combinations are consistently improving OS in patients with high PD-L1 expression.

When to Change Standard of Care

As with many important trials, this study provided new results that could have an immediate effect on standard of care, but it also raised questions that remain unanswered:

- Does this quadruple regimen offer such a big improvement over what is available now that the additional cost and toxicity is justified?
- Is PFS an adequate endpoint for studies of this sort, or should we demand OS data before changing standard practice?
- What is the value in biomarker testing? Do the results of this study support the continued use of PD-L1 expression?
- Is cytotoxic chemotherapy capable of augmenting or inducing an immune response? Is what we see in this trial an indication that VEGF inhibition is capable of enhancing immunologic effects of checkpoint inhibitors?

The available data so far suggest that the addition of cytotoxic chemotherapy to a checkpoint inhibitor can enhance or modulate the effects of anti–PD-1/–PD-L1 inhibitors. This is now supported by the results of KEYNOTE-021, cohort G and IMpower150. There are a number of other phase III studies using a similar approach that are expected to report soon. The bigger question is, to what extent are we able to extend our patients' lives by offering them three- or four-drug therapies?

From my perspective, I do not believe that improved PFS alone is sufficient to consider one regimen superior to another. I still consider single-agent pembrolizumab to be the standard of care for patients with high PD-L1 expression. At this time, there is no convincing evidence that combinations are consistently improving OS in this population. For patients with lower levels of PD-L1 expression, one can argue that the higher response rates seen with these combinations justify their use, particularly for patients with high tumor burden.

Considering the fact that a sizable portion of patients with advanced lung cancer do not receive second-line therapy, it is important to use the best option upfront, but this best option is likely to be different for every individual patient—perhaps a reflection of the heterogeneity of the tumor that we are trying to defeat. ✦

KEYNOTE-189 Interim Results

On January 16, Merck announced that the phase III KEYNOTE-189 trial met its primary endpoints of overall survival (OS) and progression-free survival (PFS). Interim results demonstrated significantly longer OS and PFS for pembrolizumab, an anti–PD-1 therapy, in combination with pemetrexed and cisplatin or carboplatin vs. pemetrexed plus platinum chemotherapy alone. The safety profile of pembrolizumab in this combination was consistent with that previously observed. Results from KEYNOTE-189 will be presented at an upcoming medical meeting and submitted to regulatory authorities. ✦

Fig. 1. IMpower150 Study Design

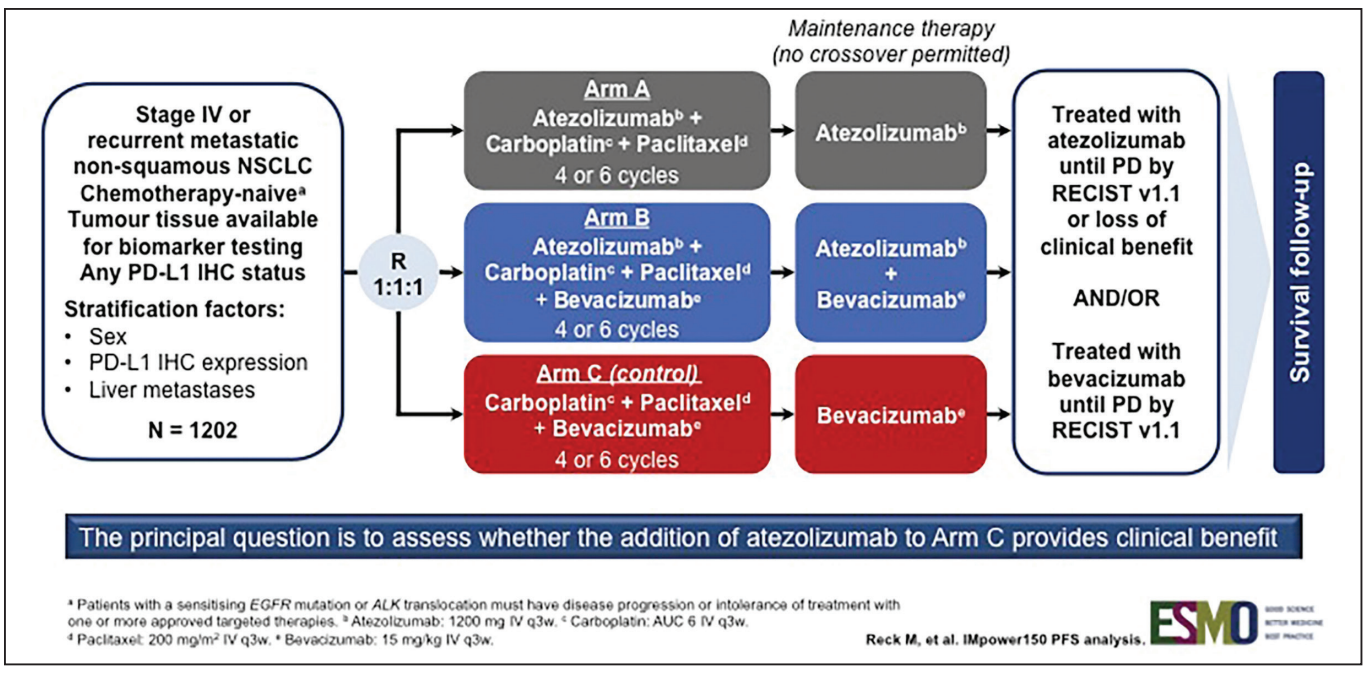
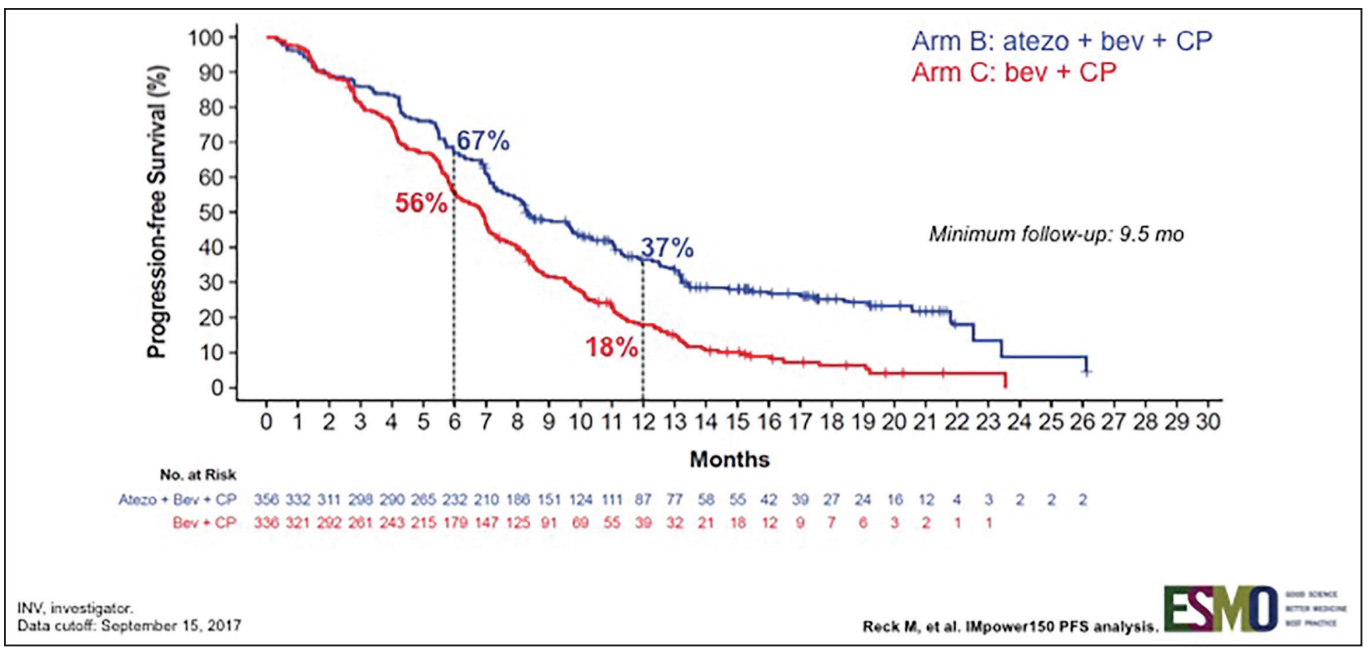


Fig. 2. INV-Assessed PFS in ITT-WT (Arm B vs. Arm C)



About the Author: Dr. Borghaei is an Associate Professor and Chief of Thoracic Medical Oncology at Fox Chase Cancer Center.

References:

1. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* 2016;375:1823-1833.
2. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol* 2016;17:1497-1508.
3. Presented at ESMO Immuno-Oncology Congress. Geneva, Switzerland: 2017.

Immunotherapy Meeting from page 3

MD; Roy Herbst, MD, PhD; Luis Paz-Ares, MD, PhD; and David Carbone, MD, PhD. Taken together, the upcoming meeting in Madrid promises to be a scientifically relevant event with an abundance of new topics and updates on emerging research themes. ✦

About the Author: Dr. Cappuzzo is Director of Oncology and Hematology Department at AUSL Romagna in Ravenna, Italy.

References:
1. M. Reck, MA Socinski, F Cappuzzo, et al. Primary PFS and safety analyses of a randomized phase III study of carboplatin + paclitaxel +/– bevacizumab, with or without atezolizumab in 1L non-squamous metastatic NSCLC (IMPOWER150). Abstract presented at: ESMO Immuno Oncology Congress 2017: December 7, 2017; Geneva, Switzerland.
2. 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.

FDA CORNER

FDA Corner: The Upcoming Lung Cancer Neoadjuvant Meeting

By Erik J. MacLaren, PhD

The development of immunotherapies and targeted therapies for use in lung cancers has provided less-toxic options for treating these malignancies. Researchers have begun investigating the possibility of using these newer drugs in the neoadjuvant setting, that is, systemic treatments given prior to surgical resection. According to Mark G. Kris, MD, of Memorial Sloan Kettering Cancer Center, an expert on neoadjuvant therapy in lung cancer, the benefits of neoadjuvant trials include being able to estimate endpoints in months rather than the usual 10 to 15 years for adjuvant trials. "There are many good reasons to run neoadjuvant trials," Dr. Kris said, "but the question is: How do you do it?"

On March 1 and 2, Dr. Kris will be serving as a co-chair of the IASLC-FDA Lung Cancer Neoadjuvant Meeting 2018 in Rockville, Maryland, with the objective of answering that important question.[1] "Every speaker has some experience in this space," he said. "We're trying to put all those people in the same room to come up with what we know, what we think are today's standards, and then what questions we need to ask to move forward."

Gideon Blumenthal, MD, Acting Deputy Director of the U.S. Food and Drug Administration's (FDA's) Office of Hematology and Oncology Products, and Nicole Drezner, MD, Medical Officer of the FDA's Office of Hematology and Oncology Products, have also been involved in organizing the meeting. Both spoke with the *IASLC Lung Cancer News* about the potential to use neoadjuvant therapies in lung cancer and the goals of this joint meeting.

Q: What are the potential benefits of neoadjuvant therapies to treat lung cancers? Is current interest in this topic justifiable since it is not (necessarily) part of standard practice?

Dr. Blumenthal: One of the advantages of neoadjuvant therapy is an earlier readout of a drug's effect on the primary tumor because radiographic and pathologic responses are available in real time. In contrast, in the adjuvant setting, it may take many years to see if a new drug has an effect on preventing or delaying relapse. With neoadjuvant trials, it may be possible to design smaller clinical trials with earlier readouts and robust correlative science. Additionally, earlier detection of lung cancers with better screening methods may increase the number of eligible patients for trials in earlier disease stages, such as in the adjuvant and neoadjuvant settings.

Gideon Blumenthal, MD

We have seen more interest now that active targeted therapies and immunotherapies in lung cancer are available. Available data suggest that giving certain systemic therapy prior to surgery is equivalent to giving it after surgery for patients with early-stage lung cancer. Also, there is precedent for accelerated approval in the neoadjuvant setting for early-stage breast cancer—the targeted therapy pertuzumab was granted accelerated approval in 2014 based on pathologic complete response in the neoadjuvant setting, and it was recently granted full approval based on confirmatory evidence in a large adjuvant trial.

Q: What are the goals of this workshop, and which issues will be addressed?

Dr. Drezner: This workshop will bring together key stakeholders involved in lung cancer clinical research—including regulators, clinicians, patients, industry, and investigators—to discuss the state of current and future neoadjuvant trial design, including incorporation of novel imaging and blood-based biomarkers.

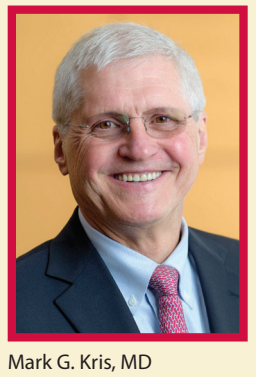
Nicole Drezner, MD

Another important issue to be discussed is the standardization of endpoints in neoadjuvant lung cancer trials and validation of novel endpoints by comparison with established endpoints. In the past year, for example, we have seen more trials using major pathologic response (MPR) as an endpoint when evaluating neoadjuvant therapy in the treatment of patients with early-stage NSCLC. Given the recent shift from cytotoxic chemotherapy to targeted therapies and immune checkpoint inhibitors to treat patients with NSCLC, the evaluation and determination of endpoints such as MPR may change with these new pharmacologic classes of drugs and improved patient outcomes.

Q: Why is the FDA helping to spearhead this workshop?

Dr. Drezner: The FDA Oncology Center of Excellence is charged with helping to expedite the development of oncology therapeutics and to support an integrated approach in the clinical evaluation of drugs, biologics, and devices for the treatment of cancer. At the FDA, we have a unique vantage point as we review applications and provide advice to industry and research sponsors on the design of clinical trials across the lifecycle of drug and diagnostic development. The FDA can also assist in standardizing the design of clinical trials and can aid in the validation or qualification of potential surrogate endpoints, thereby hastening the development process. Given the FDA's unique position interfacing with representatives from industry, clinicians, and patient advocacy groups and our commitment to making the drug approval process more efficient and innovative, we are excited to partner with the IASLC on this important workshop.

Expected Outcomes



Mark G. Kris, MD

With so many open questions around what Dr. Kris calls the "nuts-and-bolts" issues of designing neoadjuvant trials for lung cancers, this meeting will be an opportunity to begin setting standards going forward.

"Representatives from medical oncology, surgical oncology, pathology, radiology and radiation oncology, statistics, industry, and regulators will come together to discuss a wide range of topics pertaining to neoadjuvant endpoints in lung cancer trials," Dr. Blumenthal said. "Out of this meeting, we hope to potentially publish a white paper or draft guidance to help inform sponsors on best practices when designing neoadjuvant trials for early-stage lung cancer." ✦

Reference:
1. IASLC-FDA Lung Cancer Neoadjuvant Meeting 2018. International Association for the Study of Lung Cancer website. iaslc.org/events/iaslc-fda-lung-cancer-neoadjuvant-meeting-2018. Accessed January 8, 2018.

MEETING NEWS PREVIEW

Targeted Therapies Meeting Focuses on Upcoming Research Advances in Lung Cancer

Find participant discussion on Twitter: #LCTT18

By Chairs Suresh Ramalingam, MD, Paul Bunn, MD, PhD, Leora Horn, MD, MSc, and Roy Herbst, MD, PhD

Lung cancer research has reached an exciting point with the availability of a plethora of therapeutic strategies that have resulted in improved outcomes for patients. Recent advances include novel targeted therapies based on genomic characteristics of the tumor, and immunotherapy focused on overcoming T-cell exhaustion. Several agents that belong to these categories have received U.S. Food and Drug Administration approval in recent years. Consequently, lung cancer is no longer considered a single disease entity, and treatment decisions are made based on individual patient tumor characteristics.

The IASLC-sponsored 18th Annual Targeted Therapies in Lung Cancer meeting—conducted in Santa Monica, California on February 21-24, 2018—will bring together leading experts who are engaged in developing novel therapeutic options for lung cancer worldwide. This will include representation from academia, the pharmaceutical industry, and advocacy groups. The meeting will review the status of all anticancer agents that are in development for lung cancer. The topics selected for this meeting include: review of targeted therapies, such as those against *EGFR, ALK, ROS1, BRAF, MET, RET, TRK, HER2*; immune checkpoint inhibitors and other immunotherapies; and other novel therapies, such as DNA repair inhibitors, angiogenesis inhibitors, MEK/AKT inhibitors, and mTOR/PI3K inhibitors. The discussions will focus on monotherapy, emerging combinations, mechanisms of overcoming resistance, and biomarkers. The meeting will also discuss exciting developments in the treatment of early-stage lung cancers, SCLC, and mesothelioma. A number of other exciting compounds that serve patients in the realm of supportive care also will be discussed.

The meeting will include oral and poster presentations by young fellows in training and junior faculty, with a dedicated session for early-career investigators to discuss career development. The conference also will feature a keynote presentation by Suresh Ramalingam, MD, from Emory University and a dinner-lecture by Fadlo R. Khuri, MD, President of the American University of Beirut. Each session in the meeting includes time for extensive attendee discussion and feedback about research directions pursued for specific therapeutic strategies. ✦

Suresh Ramalingam, MD | Paul Bunn, MD, PhD | Leora Horn, MD, MSc | Roy Herbst, MD, PhD

EVOLVING STANDARDS OF CARE

Improved Turnaround Times for NGS Wait on Improved Technology

Availability of next-generation sequencing continues to improve, but current technology cannot speed turnaround time of results.

The standard of care for all patients diagnosed with advanced nonsquamous NSCLC is to undergo genetic testing at diagnosis.

"We now know that close to half of all patients with nonsquamous NSCLC will have an oncogenic driver mutation," said Anne S. Tsao, MD, director of the Mesothelioma and Thoracic Chemo-Radiation Programs at The University of Texas MD Anderson Cancer Center. "Some of the most common abnormalities that are targetable with drugs include *EGFR* mutations, *ALK* translocation, *ROS1* rearrangements, and genetic mutations of *BRAF V600E*, and *RET* rearrangements."

Cancers that test positive for these common abnormalities can undergo treatment with targeted therapies in place of systemic chemotherapy or immunotherapy. In the past, polymerase chain reaction (PCR) testing was a standard method to look for common mutations in NSCLC, but clinicians had to know what mutations they were looking for in advance. Fluorescence in situ hybridization (FISH) testing can be used to look for translocations in *ALK* and *ROS1*, and immunohistochemistry (IHC) can be used to test for PD-L1.

However, more recently, the advent of next-generation sequencing (NGS) has allowed clinicians to look for and identify a wider range of targetable mutations, amplifications, translocations, or rearrangements, all with one test. Unfortunately, turnaround time for NGS can take much longer than PCR, IHC, or FISH testing.

Timing of Tests

Performing genetic testing on tumor samples is one step in a multistep process, according to Lynette M. Sholl, MD, chief of the Pulmonary Pathology Division and Associate Director of the Center for Advanced Molecular Diagnostics at Brigham and Women's Hospital. When a patient presents, first something abnormal must be identified on a scan, and then a biopsy must be scheduled and performed. Material from the biopsy is sent to the pathology lab, where the diagnosis is confirmed, and then on to a molecular lab, where genetic testing is initiated.

"The timing from the initial realization that something is wrong until having a treatment plan in hand can potentially be quite lengthy because there are a lot of moving parts," Dr. Sholl said.

In some cases, this process can be sped up with the use of cell-free DNA testing—the examination of extracellular DNA circulating in the blood, known as a "liquid biopsy." When using cell-free DNA testing, clinicians do not need tissue from the biopsy and are often testing for one specific mutation, such as *EGFR*.

"It can be very variable, but under optimal conditions we have been able to confirm a diagnosis and get critical genomics within a week," Dr. Sholl said. "When not using cell-free DNA, more commonly from biopsy to genomics in hand, the process can range from 2 weeks to a month."

Ignacio I. Wistuba, MD, chair of the department of translational molecular pathology at The University of Texas MD Anderson Cancer Center, agreed, adding that in approximately 10% of cases it may take longer because of a small sample size or because of some artifact that must be worked out.

"In some cases, it may take even longer because people don't account for the time it takes the tissue to get to the lab," Dr. Wistuba said. "It may take 1 day if the lab is in the same institution, or it could take a couple weeks if the tissue needs to be shipped from pathology to the molecular lab."

These delays are more likely to occur in practices or hospitals that do not see a lot of patients with lung cancer, he explained. For patients with advanced disease who need treatment, these delays can be costly. In some cases, clinicians might send samples out for NGS and simultaneously perform cell-free DNA testing in the hope

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TARGETED THERAPY

ALK Testing in Europe

By Enriqueta Felip, MD, PhD

ALK-directed TKIs are effective first- and second-line therapies in patients with *ALK* rearrangements. Testing of all patients with stage IV adenocarcinomas of the lung for *ALK* aberrations is supported by international guidelines.[1,2] In Europe, there are also a number of published national guidelines supporting *ALK* testing in stage IV lung adenocarcinoma.[3-5] Although the break-apart fluorescence in situ hybridization (FISH) test remains a core approach to detect *ALK* rearrangements, immunohistochemistry is widely used and is rapidly being adopted as the primary test for prescribing ALK TKIs. Overall, the current consensus is that reflex testing for *ALK* gene rearrangement should become routine and that *ALK* testing should be carried out in parallel with *EGFR* mutation assessment for all patients with stage IV adenocarcinomas; this is more efficient in terms of tissue usage and testing turnaround time for both *EGFR* and *ALK* gene aberrations.[6]

Recent Data

Worldwide, there is no clear information regarding the penetrance of biomarker testing, including *ALK*, in patients with NSCLC. The French National Cancer Institute reported the results of the BIOMARKERS-France study, which assessed the characteristics, molecular profiles, and clinical outcomes of

17,664 consecutive patients with NSCLC who were screened during a 1-year period by this program. The investigators showed that routine nationwide molecular profiling of patients with advanced NSCLC was feasible.[7] In the discussion section, the authors mentioned that—considering that 39,000 new lung cancer cases (any stage and histology) are reported each year in France—18,000 patients with advanced non-squamous NSCLC represent the number of patients likely to be screened for *EGFR* mutations and *ALK* rearrangements according to current guidelines.

Recent preliminary results of the National Cancer Institute (NCI) Molecular Analysis for Therapy Choice (MATCH), a precision-medicine cancer treatment clinical trial, were presented in 2017.[8] In this trial, patients whose tumors, regardless of site of origin, have genetic changes that match one of the treatments in the study may receive that treatment if they meet other eligibility criteria. By July 16, 2017, 5,963 tumor samples from patients with a wide range of cancer types had been screened using next-generation sequencing (NGS). Although the study was not designed to determine biomarker penetrance in different tumor types, the number of included patients with lung cancer was relatively small (7.4%), compared with those with cancers of the colon and rectum (15.4%), breast (12.8%), prostate (2.6%), and other rarer cancer types (61.8%).

In a similar ongoing program in Europe, the EORTC SPECTAlung (NCT02214134) study aims to screen 3,500 participants with thoracic tumors—including lung cancer, malignant pleural mesothelioma, thymoma, or thymic carcinoma—at any stage during a 5-year period (2015-2019) to identify the molecular characteristics of their disease. If a particular molecular alteration is detected, these patients are then considered for linked targeted clinical trials.

ALK rearrangement determination, among other biomarkers, is a standard approach in stage IV lung adenocarcinoma. Biomarker testing in lung cancer is still a challenge due to the small tumor sample available in the majority of cases, as well as organizational and economic limitations in some cases. Furthermore, there is no common methodology for *ALK* testing, which may include immunohistochemistry, FISH, and NGS technologies. We must work to ensure the availability of biomarker testing in all patients with stage IV lung adenocarcinoma, and we must standardize the implementation of NGS technologies. ✦

About the Author: Dr. Felip is Head of the Thoracic Tumors Group, Specialist Physician in Medical Oncology, and Head of the Medical Oncology Service of the Thoracic Tumors Committee at Vall d'Hebron Hospital, Barcelona, Spain.

References

1. 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(suppl 5):v1-v27.
2. Leighl NB, Rekhtman N, Biermann WA, 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(32):3673-3679.
3. von Laffert M, Schirmacher P, Warth A, et al. ALK-Testing in non-small cell lung cancer (NSCLC): Immunohistochemistry (IHC) and/or fluorescence in-situ Hybridisation (FISH)?: Statement of the Germany Society for Pathology (DGP) and the Working Group Thoracic Oncology (AIO) of the German Cancer Society e.V. (Stellungnahme der Deutschen Gesellschaft für Pathologie und der AG Thorakale Onkologie der Arbeitsgemeinschaft Onkologie/Deutsche Krebsgesellschaft e.V.). *Lung Cancer.* 2017;103:1-5
4. Felip E, Concha Á, de Castro J, et al. Biomarker testing in advanced non-small-cell lung cancer: a National Consensus of the Spanish Society of Pathology and the Spanish Society of Medical Oncology. *Clin Transl Oncol.* 2015;17(2):103-112.
5. Marchetti A, Ardizzoni A, Papotti M, et al. Recommendations for the analysis of ALK gene rearrangements in non-small-cell lung cancer: a consensus of the Italian Association of Medical Oncology and the Italian Society of Pathology and Cytopathology. *J Thorac Oncol.* 2013;8(3):352-358.
6. Kerr KM and López-Ríos F. Precision medicine in NSCLC and pathology: how does ALK fit in the pathway? *Ann Oncol.* 2016;27 Suppl 3:iii16-iii24.
7. Barlesi F, Mazieres J, Merlio JP, et al. Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). *Lancet.* 2016;387(10026):1415-1426.
8. Harris L, Chen A, O'Dwyer P, et al. Update on the NCI-Molecular Analysis for Therapy Choice (NCI-MATCH/EAY131) precision medicine trial. 2017 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics. Abstract B080. Presented October 29, 2017.

LUNG CANCER PREVENTION AND TOBACCO CONTROL

Radon: A Modifiable Lung Cancer Risk Factor

By Douglas Arenberg, MD

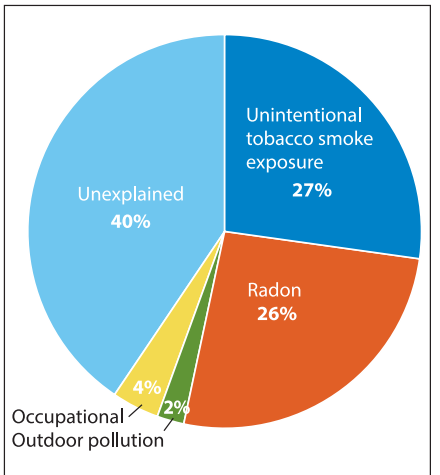
There has been rapid change over the past decade in the field of lung cancer. Advances such as histology-specific treatments, targeted agents, immunotherapy, screening, and biomarkers dominate scientific journal pages, and rightfully so. Now more than ever, we lung cancer specialists have more tools to work with to reduce suffering and death from lung cancer.

In the midst of such dizzying change, it is useful to step back and observe the big picture. A big-picture moment came for me, as an advocate for lung cancer screening, in realizing that (for my patients), I needed an increased focus on tobacco cessation and other risk-reduction tools. The goal of lung cancer screening—fewer lung cancer deaths—can be realized efficiently and with less risk by reducing exposure to known risk factors, most prominently tobacco smoke. Yet, in addition to tobacco smoke, we have irrefutable evidence from epidemiologic studies of other modifiable risk factors, specifically radon (Fig. 1). In achieving our big-picture goal, we would do well to understand all of the modifiable lung cancer risk factors and to work toward reducing them. In that regard, and in light of the fact that at the time of this article's writing (January) it is Radon Awareness Month, let us pause to recognize and understand the role of radon, its detection, and its mitigation in reducing lung cancer mortality.

Understanding Radon and Its Relation to Lung Cancer

Radon is a natural product of the decay of uranium in the earth's crust. It is almost universally present in the air we breathe. Although it is undetectable by the senses, it is dangerous to people living in dwellings where radon gas can accumulate. As radon decays, its daughter molecules are metals that deposit in the lung and, in turn, decay yielding both alpha and beta particle emissions that can damage DNA. On the surface, this may seem like a complex problem,

Fig. 1. Causes of Lung Cancer in Non-smokers



Adapted from American Cancer Society Facts & Figures 2006. Special section Environmental Pollutants.

continued on page 11

LUNG CANCER SCREENING

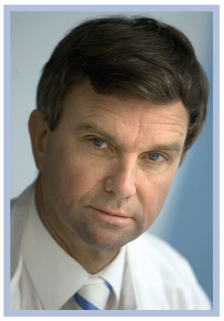
European Union Position Statement on Lung Cancer CT Screening: The Next 18 Months

By John K. Field, PhD, and Matthijs Oudkerk, MD, PhD

Lung cancer kills more Europeans than any other cancer. In 2014, 272,000 citizens of the twenty-eight countries in the European Union (EU) died from lung cancer, which is 20.1% of all cancer deaths.[1] When implemented in the general population, lung cancer screening using CT saves lives.

The European lung cancer CT screening community involved in randomized controlled trials has a long, collaborative history. In the past 12 to 15 months, this group of experts across multiple clinical disciplines in lung cancer CT screening—involving eight countries—decided that it needed to provide leadership and direction to the European policy makers on how lung cancer screening should be implemented.

John K. Field, PhD



Matthijs Oudkerk, MD, PhD

The expert group is fully aware that lung cancer screening has already started in the United States (using the U.S. Preventive Services Task Force's recommendation[2]) and that funding has been agreed to by Medicare. However, Europe is sitting on the fence while opportunistic lung cancer screening has already started.

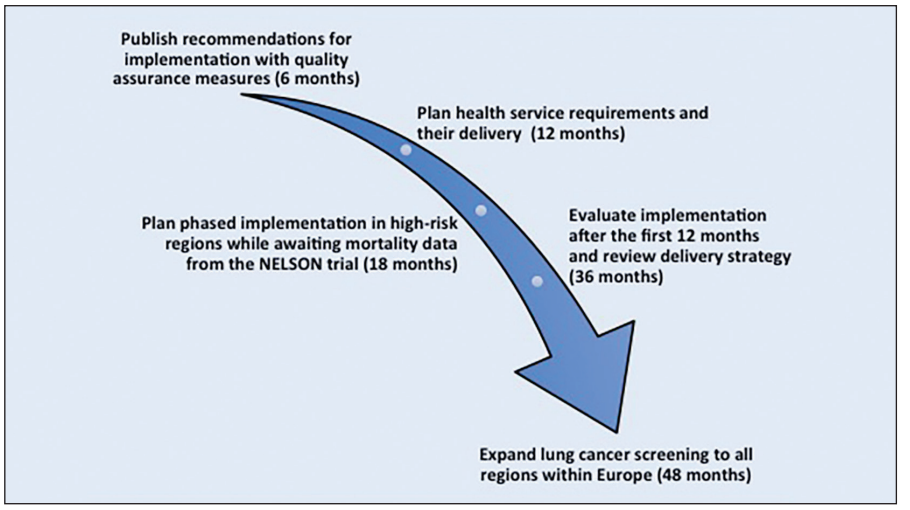
The EU position statement on lung cancer screening (EUPS), published in December 2017 in *The Lancet Oncology*,[3] has provided a set of nine recommendations on how to take lung cancer CT screening forward in Europe, dealing with many of the outstanding questions that were posed after the 2011 National Lung Screening Trial publication (see Recommendations).[4,5]

The EUPS expert opinion now argues that lung cancer specialists in Europe must start planning for implementation, as outlined in Fig. 1.[3]

Clearly, there are a number of major issues that must be resolved prior to implementation. These include, but are not limited to, (1) how the high-risk population is identified for screening—either general practitioner records or national questionnaires—and the use of risk-prediction models; (2) service provision of CT scanners for screening; (3) training of radiologists and radiographers; and (4) whether the radiology community will set up central reading resources and, if so, how quality assurance will be performed.

The expert group estimates that the above organizational issues will take approximately 18 months to resolve, and the group also recognizes that it is highly likely that the Dutch-Belgian Lung Cancer Screening trial (NELSON) will publish results during this 18-month timeframe.[5] NELSON results will be key because it is the largest European randomized lung cancer screening trial and was designed to investigate whether low-dose CT screening can reduce lung cancer mortality by 25% or greater when compared with no screening after 10 years of follow-up.[6]

Fig. 1. EU Position Statement on Lung Cancer CT Screening 'Call for Action'



Lung cancer kills more Europeans than any other cancer.

It should also be noted that the recommended protocol for the management of pulmonary nodules has been updated based mainly on the recent NELSON publications, as outlined in Recommendation 6: "Management of prevalent lung nodules in CT screening programmes, lung nodules at incident screening (newly detected), and CT-detected lung nodules in clinical practice should be managed with different protocols because of different pretest lung cancer probabilities."[3]

The EU lung cancer screening community considers the EUPS policy review to be an important planning document on how to best implement lung cancer screening in Europe, and the policy review

continued on page 11

Recommendations

1. Low-dose CT is the only evidence-based method for the early detection of lung cancer shown to provide a mortality reduction. On the basis of this evidence from randomized controlled trials, the EU position statement recommends that we start to plan for the implementation of lung cancer screening in Europe while cognizant of future publications that include the awaited NELSON trial data on mortality and cost-effectiveness and data from the six smaller European studies for developing implementation strategies in each of their own countries.
2. Future lung cancer low-dose CT programs should use a validated risk stratification approach so that only individuals deemed to be at high enough risk are screened. In the near future, incorporation of potential biomarkers and susceptibility genes into lung cancer risk models should be considered to improve the accuracy of risk stratification models.
3. All future screenees entering into early detection programs for lung cancer should be provided with carefully constructed participant information on the potential benefits and harms of screening to enable them to make an informed decision as to whether they wish to participate or not. Smoking cessation advice should be offered to all active smokers.
4. Future management of screen-detected solid nodules should utilize semi-automatically derived volume measurements and volume-doubling time, and should be quality assured.
5. National quality assurance boards should be set up by professional bodies to ensure adherence to all minimum technical standards, including semi-automated volumetry, and to standardize diagnostic criteria for screen-detected lung nodules, including radiation exposure limits.
6. Management of prevalent lung nodules in CT screening programs, lung nodules at incident screening (newly detected), and CT-detected lung nodules in clinical practice should be managed with different protocols because of different pretest lung cancer probabilities.
7. Although only evidence for annual low-dose CT lung cancer screening is available, recent research suggests the possibility of using a more personalized approach to lung cancer screening with a risk-based approach on the results of baseline and first screening rounds.
8. Management of lung nodules by lung cancer multidisciplinary teams should be done according to the EU position statement recommendations with the aim of minimizing harm and ensuring patients receive the most appropriate treatment.
9. The EU position statement expert group recommends that the planning for low-dose CT screening should be started throughout Europe because low-dose CT lung cancer screening has the potential to save lives. ✦

EU Position Statement from page 10

will be discussed with the health policy makers throughout the EU. Policy makers in Europe are on the verge of making a definitive decision regarding whether to implement lung cancer screening, but, unfortunately, none of the countries in Europe are currently prepared to move forward practically. ✦

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References:

1. Eurostat. Cancer statistics—specific cancers. http://ec.europa.eu/eurostat/statistics-explained/index.php/Cancer_statistics_-_specific_cancers#Lung_cancer. Accessed December 19, 2017.
2. U.S. Preventative Services Task Force. Final Recommendation Statement Lung Cancer: Screening. uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/lung-cancer-screening. Accessed December 14, 2017.
3. Oudkerk M, Devaraj A, Vliegenthart R, et al. EU Position Statement on Lung cancer Screening. *Lancet Oncol.* 2017;18(12):e754-e766.
4. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med.* 2011;365(5):395-409.
5. Field JK, van Klaveren R, Pedersen JH, et al. European randomized lung cancer screening trials: Post NLST. *J Surg Oncol.* 2013;108(5):280-286.
6. 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). *Int J Cancer* 2007:120(4):868-874.

An American Perspective on the European Lung Cancer Screening Implementation Plans

International sharing of best practices may improve quantitative imaging quality for low-dose CT for small nodules.

By James L. Mulshine, MD

It is heartening to learn of the decision by thought leaders to begin the process of initiating European implementation of lung cancer screening.[1] With this effort, the opportunity exists to offer potentially life-saving cancer detection services to cohorts that are at the highest risk for developing lung cancer. In addition, because so many European countries have already been conducting CT screening research efforts, there are many positive models of screening success to inform the process of optimizing screening across Europe. In addition, many European screening sites have also implemented high-quality tobacco-cessation programs as an integral part of their tobacco health efforts. Success from these complementary efforts can serve as a template to be scaled, as required, to ensure that maximal smoking-cessation benefit is achieved in conjunction with CT screening implementation.

One example of a screening resource that may be shared internationally to address quality issues with quantitative imaging in the screening setting is the Quantitative Imaging Biomarker Alliance Small Pulmonary Nodule Profile.[2] This is a document that describes a process to acquire a low-dose CT screening image that contains sufficient image quality to allow reliable measurement of the volume of pulmonary nodules of interest. This image-quality process employs an inexpensive precision-engineered phantom to test the image-acquisition process of the CT imaging platform used for the screening study. The acquired phantom image is analyzed by an automated cloud-based analysis resource that, within 5 minutes, completes a targeted analysis to determine if the imaging process is sufficiently robust to allow reliable measurement of relevant pulmonary nodules.

Discussions about this and other opportunities for international collaboration with lung cancer screening implementation were discussed at the recent IASLC 18th World Conference on Lung Cancer in Yokohama, Japan. The new European Union position statement on lung cancer screening and the expected outcome report from the Dutch-Belgian Lung Cancer Screening trial (NELSON) study will undoubtedly frame further important discussions regarding lung cancer screening to be covered at the IASLC 19th World Conference on Lung Cancer, in Toronto, Canada. ✦

About the Author: Dr. Mulshine is Acting Dean of the Graduate College and Professor in the Department of Internal Medicine, Rush Medical College, and Vice President for Research at Rush University Medical Center.

References:

1. Oudkerk MD, Deveraij A, Vliegenthart R, et al. EU Position Statement on Lung Cancer Screening. Lancet Oncol. 2017;18(12):e754-e766.
2. Rydzak CE, Armato SG, Avila RS, et al. Quality assurance and quantitative imaging biomarkers in low-dose CT lung cancer screening. Br J Radiol. 2017 Oct 27:20170401. doi: 10.1259/bjr.20170401. [Epub ahead of print] PMID: 28830225.

In Related News:

Look for an article in the April issue on management of incidental pulmonary nodules detected on CT by IASLC Board member Dr. Paul van Schil.

Radon from page 9

but radon detection and mitigation are actually quite simple. Whereas most of what we know about radon-related lung cancer risk comes from studies of high-level occupational exposure, there is strong epidemiologic evidence that residential radon exposure contributes to lung cancer risk.[1-3] Additionally, while the United States Environmental Protection Agency has set a cutoff level of 4 picocuries per liter (pCi/L) as a recommended action level,[4] most radon-attributable lung cancer deaths likely occur in people with exposures below this level,[5] simply because of the size of the exposed population. Therefore, current recommendations from United States Center for Disease Control and Prevention are that all homeowners should check their indoor radon levels.

In any given dwelling, radon levels are highest below grade (in the basement), but levels do not necessarily diminish on higher floors, especially in newer homes with more efficient air recirculation. Consequently, radon testing should be done in the lowest level of the home, particularly if the homeowner plans to use the basement as a living space. The cost of testing kits is not very high ($15 to $30, on average), and nearly every hardware store carries these kits. Both short- and long-term tests exist, and both should be used to assess the risk of radon exposure in any given home. Cancer risk arises from long-term exposure, so a short-term test showing low radon levels cannot be considered reassuring until long-term monitoring shows low average-exposure levels over a longer interval (6 months or more, with average levels ≤ 4 pCi/L). Homes with high radon levels can usually be easily structurally modified in a day. In the United States, most state health departments have a list of certified radon contractors. Furthermore, some states offer free testing kits. Excellent resources for physicians and consumers interested in more information can be found at epa.gov/radon.

Excellent resources for physicians and consumers interested in more information can be found at epa.gov/radon.

Tobacco cessation and radon mitigation may never not offer the immediate gratification of a major response to targeted agents or immunotherapy, but they are crucial to reducing the global public health risk of lung cancer and other related malignancies. ✦

About the Author: Dr. Arenberg is an Associate Professor of Medicine and Director of Lung Cancer Screening Program at University of Michigan Medical Center.

References:

1. Ruano-Ravina A, Rodriguez MC, Cerdeira-Carames S, Barros-Dios JM. Residential radon and lung cancer. *Epidemiology.* 2009;20(1):155-156.
2. Thompson RE, Nelson DF, Popkin JH, Popkin Z. Case-control study of lung cancer risk from residential radon exposure in Worcester county, Massachusetts. *Health Phys.* 2008;94(3):228-241.
3. Wilcox HB, Al-Zoughool M, Garner MJ, et al. Case-control study of radon and lung cancer in New Jersey. *Radiat Prot Dosimetry.* 2008;128(2):169-179.
4. Neuberger JS, Gesell TF. Residential radon exposure and lung cancer: risk in nonsmokers. *Health Physics.* 2002;83(1):1-18.
5. Gray A, Read S, McGale P, Darby S. Lung cancer deaths from indoor radon and the cost effectiveness and potential of policies to reduce them. *BMJ.* 2009;338:a3110.

IMMUNOTHERAPY

Management of Immunotherapy Toxicity in NSCLC

By Beth Eaby-Sandy, MSN, CRNP

When I started in thoracic medical oncology 15 years ago, we just had chemotherapy, and patient education was focused and streamlined. Chemotherapy could be toxic and life threatening, but we had specific warnings and guidelines to give to patients. We now have chemotherapy, targeted therapies, and immunotherapy drugs. Patient education has changed from a one-size-fits-all approach to one that must be tailored based on the class of drug.

Immunotherapy in NSCLC can present a challenge for patient education because often the patient has already endured chemotherapy and now expects the same side effects and risks to continue. Often, there is a sense of relief when a patient hears how well tolerated immunotherapy usually is, and that there is a much lower risk of nausea, hair loss, and lowered blood counts. In most instances, this is the case; however, 5% to 10% of patients who receive immunotherapy will experience significant immune-mediated adverse events.

These include, but are not limited to:

- Pneumonitis (seen more frequently in patients with NSCLC as opposed to other tumor types)
- Colitis
- Endocrinopathies (thyroid, adrenal, and pituitary)
- Rash/dermatitis
- Hepatitis/nephritis

There are several other less common immune-mediated toxicities that can occur, including several neurologic, hematologic, and cardiac toxicities. As an oncology community, we are still discovering more immune-mediated toxicities as these drugs become more widely used.

Management is based around the use of systemic steroids along with other supportive-care measures specific to each adverse event. There are several different management protocols recommended by clinicians, as well as the pharmaceutical industry. The National Comprehensive Cancer Network, American Society of Clinical Oncology, Society for Immunotherapy of Cancer, and others are working together to create a consensus-based clinical management strategy. The sidebar contains details of the most commonly seen toxicities and some management strategies that can be used.

There are several other less-common toxicities that can manifest with many different patient symptoms. In general, I tell patients that if they are feeling unwell or if something doesn't feel right, they should call and report the symptoms and let the oncology team decipher symptoms and related approaches.

The IASLC Nursing and Allied Health Committee has produced an immunotherapy toxicity identification and management tool, which is a great clinical piece to refer to while seeing patients with these toxicities. (For more information, see iaslc.org/toxicities or email info@iaslc.org.) As an oncology community, we will continue to learn about these toxicities and how to better identify and manage them. Proper patient education can lead to early detection of immune-mediated adverse events, mitigation of which is important before the events become life threatening. ✦

About the Author: Ms. Eaby-Sandy is a Nurse Practitioner at Abramson Cancer Center, University of Pennsylvania.

In Case You Missed It:
Read last month's immunotherapy update (http://bit.ly/2DFqpQc).

Common Toxicities (All Grades) and Their Associated Management Strategies

Pneumonitis

- Frequency with PD-1/PD-L1 inhibitors: 2% to 4%.
- Patients should immediately report: Increase in shortness of breath or nagging frequent cough.
- What it looks like on imaging: See Fig. 1A and Fig. 1B.
- Treatment: Steroids per recommended guidelines – generally oral prednisone at high doses (0.5-1.0 mg/kg)[1] with a minimum of 4-week taper schedule or intravenous (IV) corticosteroids if inpatient; consult with pulmonology; oxygen if required; and immune suppression when indicated for severe cases.

Fig. 1. Patients with Pneumonitis

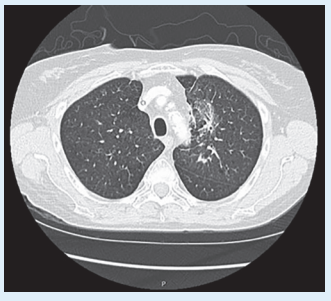


Fig. 1A. Patient Who Is Non-Symptomatic, Grade 1

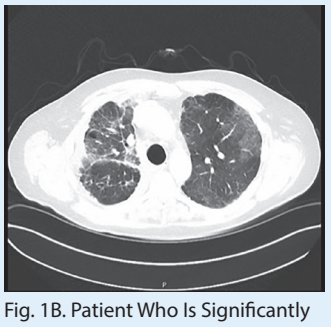


Fig. 1B. Patient Who Is Significantly Symptomatic, Unable to Wean off of Steroids, Grade 3

Colitis

- Frequency with PD-1/PD-L1 inhibitors: 1% to 3% (19% diarrhea/colitis reported for atezolizumab).
- Patients should immediately report: Worsening diarrhea associated with abdominal pain, cramping, or blood and/or mucus in the stool.
- What it looks like: Consider colonoscopy for diagnosis, otherwise, based on patient symptoms.
- Treatment: Steroids – generally oral prednisone at high doses (0.5-1.0 mg/kg)[1] with a minimum of 4-week taper schedule or IV corticosteroids if inpatient; consult with gastrointestinal (GI) specialist if not improving; antidiarrheal agents; stool culture; and immune suppression when indicated for severe cases.

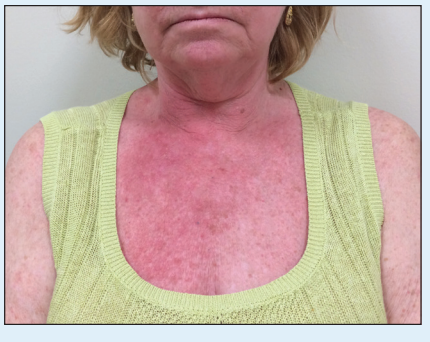
Endocrinopathies

- Frequency with PD-1/PD-L1 inhibitors: Up to 10%.
- Patients should immediately report: Heart palpitations, severe malaise, intolerance to temperature, loss of appetite, or increased thirst/urination. Often there are no real symptoms.
- What it looks like: Thyroid-stimulating hormone significantly up or down; adrenocorticotropic hormone levels or cortisol levels significantly depleted; brain MRI for suspected hypophysitis; fasting glucose if diabetes is considered.
- Treatment: Thyroid replacement; hormone replacement for depleted cortisol levels; monitoring labs; insulin for diabetes, and immune suppression when indicated for severe cases.

Dermatitis

- Frequency with PD-1/PD-L1 inhibitors: 1% to 9%.
- Patients should immediately report: Significant rash with hives or significant itching with or without rash.
- What is looks like: Typically erythematous, papular, on face, neck, and/or chest. Rarely pustular. Fig. 2 shows a rash from a PD-1 inhibitor. Rashes from anti–CTLA-4 drugs alone or combined with PD-1 inhibitors typically can cause more severe dermatitis.
- Treatment: Topical steroid creams; antipruritics; sunscreen; and oral steroids in severe cases only.

Fig. 2. Rash from a PD-1 Inhibitor



Nephritis and Hepatitis

- Frequency with PD-1/PD-L1 inhibitors: 1% to 5%
- Patients should immediately report: Decrease in urine output. Most patients will be asymptomatic unless sudden, severe inflammation occurs.
- What is looks like: Lab values show elevations in liver function tests or renal function.
- Treatment: Steroids (sometimes pulse for nephritis), generally oral prednisone at high doses (0.5–1.0 mg/kg)[1] with a minimum of 4-week taper schedule or IV corticosteroids if inpatient; further immune suppression in severe cases; consult GI or renal services for input. ✦

Note: % of toxicities are taken directly from the product inserts for pembrolizumab, nivolumab, and atezolizumab. Numbers reported are from all studies across different tumor types, but may be higher or lower depending on specific trials.

Reference:

1. Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Cancer*. 2016;13(8):473-486.

MEETING NEWS PREVIEW

Inaugural Africa Conference: Finding Parallels Among Disparate Realities

New collaborative meeting to provide educational, scientific updates to diverse audience from Africa and the Middle East.

By Joy Curzio, *ILCN* Managing Editor

As a global association, the IASLC understands the numerous variables, experiences, and perspectives that dictate a country's or region's ability to be a principal actor in scientific events. For many years, several countries in Africa have had fewer opportunities for international education, leading to diminished awareness of the problems those countries face and little to no discussion of potential solutions. For these reasons, the IASLC is sponsoring its first major educational event in Tangier, Morocco, April 29-May 1, 2018. The endeavor is led by the IASLC President Giorgio V. Scagliotti, MD, and Co-Chairs Prof. Abdelaziz Maaouni, Fred R. Hirsch, MD, PhD, and David P. Carbone, MD, PhD. The Scientific Committee Chair Federico Cappuzzo, MD, and the Educational and IASLC School of Oncology Chair Christian Rolfo, MD, PhD, MBA, are working in collaboration with local and honorary committees coordinated by Nabil Ismaili, MD, and Fadila Guessous, PhD. The aim of the conference is to provide all African regions, including the Middle East and northern parts of the continent, with guidance—based on diverse international perspectives—regarding management of lung cancers, mesothelioma, and thymic and other thoracic malignancies.

It was after presenting at several conferences in the Middle East and North Africa that Dr. Carbone noted that "there was a large group of enthusiastic young cancer physicians with limited ability to interact with global experts, limited ability to travel, and limited involvement with the international community represented by the IASLC." It was then that he proposed the idea for this meeting to the IASLC Board of Directors, which enthusiastically approved.

"I am excited about the opportunity to interact with dedicated and talented physicians in a region of the world new to the IASLC, and to work with these physicians to improve the quality and duration of life for their patients, as well as to provide opportunities for them to participate in global research efforts," Dr. Carbone said.

The IASLC CEO Dr. Hirsch noted that this specific meeting was in the planning stages for 1 to 2 years, but that provision of educational programs and scientific updates in this specific geographic region has been a long-standing goal of the association. In addition to the numerous clinical differences, there are also cultural differences that the IASLC is working to understand so that information is delivered clearly and concisely. "Bringing such a diverse group together is going to be interesting," Dr. Hirsch said. "Hopefully we will be able to harmonize the educational offerings to best support attendees."

The first day of the congress will include an update in general concepts for the different multidisciplinary specialties involved in thoracic oncology including, but not limited to, radiology, oncology, pathology, and pulmonology. A simultaneous session held by the IASLC School of Nursing Thoracic Oncology—the first event of its kind—will focus on the roles of Thoracic Nurse Navigators and research nurses in lung cancer, and will highlight possibilities for implementation of these types of approaches in Africa. Subsequent sessions will address general multidisciplinary updates, including patient advocacy and palliative care. In addition, there will be discussion of improved care coordination among African countries through the use of a cancer registry, providing specific successful case examples of the Middle East and Latin America regions.

We would like this meeting to be a networking forum for attendees to discuss and find parallels among the different realities in the African countries and Middle Eastern region.

–Christian Rolfo, MD, PhD, MBA

"We hope the attendees leave the conference with clear messages about standard-of-care treatments, with tools to increase the homogenization of the treatment among the different countries, and with new information about the advances in thoracic oncology treatment, diagnosis, and prevention," Prof. Rolfo said. "We would like this meeting to be a networking forum for attendees to discuss and find parallels among the different realities in the African countries and Middle Eastern region."

Presentation formats will include didactic lectures and roundtable forums; the latter will focus on general themes such as molecular pathology, treatment of advanced disease, toxicity management, and pharmaco-economics. One of the most important roundtables will be on smoking cessation and control in the general population and the negative public influence of the tobacco industry.

"Scientific societies should make investments to allow African institutions to get progressively close to the essentials of diagnosis and treatment of thoracic malignancies," the IASLC President Dr. Scagliotti said. "More relevantly, the IASLC should be at the forefront of any initiative to promote tobacco control and early detection of lung cancer."

Prof. Rolfo hopes that this inaugural meeting's success will solidify its spot on the IASLC's calendar for many years to come. Look for post-meeting recaps in the August issue of *Lung Cancer News*. ✦

Turnaround Times from page 8

of identifying one of the more common mutations quickly.

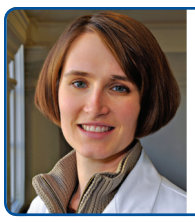
Wider Availability

Lower-volume centers may have a new NGS option with the recent U.S. Food and Drug Administration (FDA) and Centers for Medicare & Medicaid Services approval of the first breakthrough-designated, NGS-based in vitro diagnostic test, the FoundationOne CDx (F1CDx). The test can detect genetic mutations in 324 genes and two genomic signatures in any solid tumor type. *(See Breaking News on page 14 for details.)*

Unlike other companion diagnostics tests approved by the FDA that match one test to one drug, the F1CDx provides information on a wide variety of mutations that may help guide treatment of patients with cancer. At the same time as the approval, the Centers for Medicare & Medicaid Services (CMS) proposed coverage of the F1CDx.

According to the Dr. Sholl, approval of this product is unlikely to improve turnaround time for NGS because there is a fixed amount of time required to complete this type of testing.

"The chemistry required to perform the assay requires several days," she said. "That includes getting the specimen, extracting the DNA, pulling down part of the DNA that you want to sequence, performing the sequencing … when you tack on interpretation, quality control, and the actual reporting, it will be quite difficult to get turnaround time below 2 weeks."



The timing from the initial realization that something is wrong until having a treatment plan in hand can potentially be quite lengthy because there are a lot of moving parts.

–Lynette M. Sholl, MD

However, the CMS coverage approval could create some significant issues for the molecular testing community, Dr. Sholl said. This approval could be an indication that, moving forward, CMS may only pay for NGS if it is performed with an FDA-approved assay.

"For instance, if CMS decides it is only going to reimburse for testing using a certain provider and all other payers fall in line, that means that all patients are going to have to send samples to that provider," Dr. Sholl said. "That is not great for patients because there are dozens of labs across the country that can do this within the confines of a hospital, within the context of the type of care the patients are getting locally, and within the context of diagnostic scenarios that they deal with routinely in those settings. Labs will have to shut down because they won't be getting paid."

Dr. Sholl said that if the CMS requires FDA approval for all NGS, then the FDA must provide a feasible model for labs to submit local assays for approval with a timely turnaround time in terms of FDA review.

Despite the unknowns, the possibilities for the future of genetic testing in NSCLC are myriad. Moving forward, Dr. Wistuba said he had no doubt that NGS will be available in most centers throughout the world and will be the most widely used method for genetic testing.

"Hopefully, we are able to see more advances in technology that allow us to achieve more rapid turnaround time in the molecular lab," he added.

Dr. Tsao agreed, "It is only a matter of time before technology is capable of meeting very rapid turnaround times that will lead to more testing at a higher frequency."

As NGS becomes more widespread, Dr. Tsao hopes that more patients with other histologic subtypes of lung cancer may begin to get tested.

"For example, in small cell lung cancer actionable mutations haven't been identified yet," Dr. Tsao said. "[NGS] may introduce more options and more treatments for patients if we are able to discover additional targets that they may carry." ✦

BREAKING NEWS BRIEFS

The **FoundationOne CDx (F1CDx) test** received full U.S. Food and Drug Administration (FDA) approval. F1CDx is the first breakthrough-designated, next-generation sequencing–based in vitro diagnostic (IVD) test to detect genetic mutations in 324 genes and two genomic signatures in any solid tumor type. Simultaneous to FDA approval, the Centers for Medicare & Medicaid Services (CMS) proposed coverage of the F1CDx. The test is the second IVD to be approved and covered after overlapping review by the FDA and CMS under the Parallel Review Program, which facilitates earlier access to innovative medical technologies for Medicare beneficiaries. (11/30)

The FDA is making several efforts to advance the development of innovative targeted drugs and enable increased and more timely availability of individualized treatment approaches. **Two draft guidances** have been released: "Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease" and "Investigational IVD Devices Used in Clinical Investigations of Therapeutic Products." Respectively, these guidance documents offer drug developers an approach for enrolling patients to targeted therapy trials based on the identification of rare mutations when reasonable scientific evidence suggests the study drug could be effective for these mutations, and then clarifies the appropriate regulatory pathway for investigational in vitro devices used in clinical trials for therapeutic products. (*For more on this topic, read the April edition's FDA Corner.*) (12/15)

The FDA has accepted a supplemental New Drug Application (sNDA) for the use of **osimertinib** in the first-line treatment of patients with metastatic NSCLC whose tumors have activating *EGFR* mutations (exon 19 deletions or exon 21 [L858R] substitution mutations). Osimertinib is a third-generation, irreversible EGFR tyrosine kinase inhibitor with clinical activity against central nervous system metastases. The FDA has granted osimertinib Priority Review status and previously granted it Breakthrough Therapy Designation in the first-line treatment of patients with metastatic *EGFR* mutation–positive (*EGFR*m) NSCLC. sNDA acceptance was based on progression-free survival data for previously untreated patients with locally advanced or metastatic *EGFR*m NSCLC in the phase III FLAURA trial. (12/18)

The European Commission has granted a marketing authorization for **alectinib** as monotherapy for the first-line treatment of adult patients with ALK-positive advanced NSCLC. The approval is based on results from the phase III ALEX study, which showed alectinib significantly reduced the risk of disease worsening or death (progression-free survival) by 53% (HR = 0.47, 95% CI: 0.34-0.65, $p < 0.001$) compared to crizotinib. The study also showed that alectinib reduced the risk of tumors spreading to or growing in the brain or central nervous system compared to crizotinib by 84% (HR = 0.16, 95% CI: 0.10-0.28, $p < 0.001$). (12/21)

The FDA granted approval to **afatinib** for a broadened indication in first-line treatment of patients with metastatic NSCLC whose tumors have nonresistant *EGFR* mutations as detected by an FDA-approved test. Approval was based on durable response in 21 of 32 patients with nonresistant *EGFR* mutations (S768I, L861Q, and/or G719X) other than exon 19 deletions or exon 21 L858R substitutions enrolled in one of three clinical trials. Of 21 responders, the proportion of patients with response duration of ≥ 12 months was 52%, and the proportion with response durations of ≥ 18 months was 33%. (1/12) ✦

MEETING NEWS HIGHLIGHTS

5th AACR-IASLC International Joint Conference: Translational Progress through Basic Research

By Monte M. Winslow, PhD

Over 4 rainy days in San Diego, California, more than 220 participants from 15 different countries heard presentations that spanned a very wide range of basic, translational, and clinical lung cancer research. This joint conference between the IASLC and the American Association for Cancer Research (AACR) was driven by the attendees' deep interests in gaining a better understanding of all stages of lung cancer pathobiology. Truly hitting on multiple aspects of bench-to-bedside science, many presentations showed the clinical progress of observations made years ago through basic science.

The diverse and high-quality presentations were followed by vigorous question and answer periods, which were one of the highlights of the meeting.
–Monte M. Winslow, PhD

The content of the meeting covered many aspects of lung cancer initiation, evolution, diagnosis, treatment, and interaction with the tumor microenvironment. The diverse and high-quality presentations were followed by vigorous question and answer periods, which were one of the highlights of the meeting. An overarching theme of the meeting seemed to be heterogeneity at all levels. From differences in individual mutations to overall mutation burden, a greater understanding of these differences is leading to better patient treatment. Better biomarker stratification is leading to greater treatment precision in the clinic and to a deeper basic understanding of the mechanisms by which these alterations drive different aspects of carcinogenesis, and how this might, in turn, contribute to future clinical advances. Presenters also highlighted our lack of understanding of the molecular and cellular events associated with the earliest stages of disease, as well as the heterogeneous and diverse role of the noncancer cells within lung tumors.

As part of the conference, committed students and trainees presented interesting and relevant posters on a range of topics. This "next generation" of lung cancer biologists seemed particularly motivated, with a keen sense of urgency and the resilience needed to make major advances in basic, translational, and clinical lung cancer research.

Meeting Chair Charles Rudin, MD, PhD, of Memorial Sloan Kettering Cancer Center, summarized the meeting by saying, "As in prior years, this has been a great meeting, providing intellectual fodder for all attendees. Basic cancer researchers gained perspective on the clinical successes and challenges of lung cancer therapy, [and] clinicians got a glimpse into emerging biologic insights that may soon help them better treat patients in the clinic."

Featuring the widespread exchange in information and ideas among attendees, this conference has not only increased our knowledge of different aspects of lung cancer research but, importantly, it has led to new collaborations, new concepts, and an increased sense of global community driven by our common goals. ✦

About the Author: Dr. Winslow is co-chair of the conference and Assistant Professor in the Department of Genetics at Stanford University School of Medicine.

Names and News

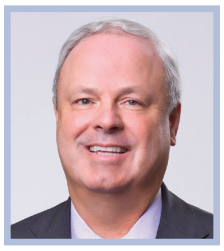
New IASLC Foundation Board Members

The addition of two IASLC Foundation Board members, **Bruce Ratner** and **Paolo Paoletti, MD,** was approved at the 2017 IASLC World Conference on Lung Cancer.

Mr. Ratner is the Executive Chairman of Forest City Ratner Cos., a New York-based real estate development company, which he started in 1985. As the founder of one of the largest urban real estate developers in the country, Mr. Ratner has developed 52 ground-up projects in the New York City area over more than 30 years. His MetroTech Center, an 11-building corporate campus occupied by more than 20,000 workers, has often been credited with helping to spur the renaissance of Downtown Brooklyn. Mr. Ratner serves on the boards of Weill Cornell Medical College, Memorial Sloan-Kettering Cancer Center, and the Museum of Jewish Heritage–A Living Memorial to the Holocaust, where he is Chairman. A graduate of Harvard College and Columbia Law School, Mr. Ratner holds honorary degrees from Brooklyn College, Medgar Evers College, Pratt Institute, and Long Island University.

Dr. Paoletti is the Chairman of the Board for Genmab, PsiOxus Therapeutics (Chairman of the Board), FORMA Therapeutics, and Nucana Biomed. He was formerly the first appointed president of GSK Oncology, where he was responsible for championing an organization of more than 2,000 professionals around the world dedicated to fighting the causes and effects of cancer. As the leader of the business unit, he had accountability for the overall oncology business within GSK and oversaw all activities from early drug discovery through clinical development, launch, and life cycle management. Dr. Paoletti has a degree in medicine from the University of Pisa (Italy), where he was professor of pulmonary diseases and authored more than 300 publications.

John V. Heymach, MD, PhD, has been named a Fellow (Medical Sciences) of the American Association for the Advancement of Science (AAAS). Dr. Heymach is the Chair of Thoracic/Head and Neck Medical Oncology and a Professor in the Departments of Thoracic Head and Neck Medical Oncology and Cancer Biology at The University of Texas MD Anderson Cancer Center. He also serves as leader of the Lung Cancer Program of the Cancer Center Support Grant and co-leads the MD Anderson Lung Cancer Moon Shot Program. He is a past recipient of the Damon Runyon Clinical Investigator Award, the Wilson Stone Award for Basic Science Research, and the Emil J. Frei Award for Translational Research.



Howard A. "Skip" Burris III, MD, has been elected to serve as the 2019-2020 President of the American Society of Clinical Oncology (ASCO) for the term beginning in June 2019. Dr. Burris is president of clinical operations and chief medical officer for Sarah Cannon, the Cancer Institute of HCA Healthcare. He is an associate of Tennessee Oncology, PLLC, where he practices medical oncology.

Laurie E. Gaspar, MD, MBA, has been elected as the 2019-2020 Treasurer of ASCO. Dr. Gaspar is Professor Emeritus in the Department of Radiation Oncology at the University of Colorado, with continued clinical interest in the management of brain tumors and lung cancer. She also conducts research in patient communication and advocacy, shared decision-making, and global issues in oncology.

Tony S. K. Mok, BMSc, MD, has been elected to an International Oncologist seat of the 2019-2020 ASCO Board of Directors. Dr. Mok is the Li Shu Fan Medical Foundation Named Professor of Clinical Oncology and chair of clinical oncology at The Chinese University of Hong Kong. He co-founded the Lung Cancer Research Group, and has led a number of multinational clinical trials. ✦

Funding Fellowships to Find a Cure: 'It's About the People'

By AnnMarie Estrada,
IASLC Foundation Director

When you think of the IASLC, you think about professional development, networking, and renowned international lung cancer conferences. When you consider the IASLC Foundation, what comes to mind? At first, you may think of fellowships and grants. When we look a little closer, we begin to understand that the IASLC Foundation is about the one of 16 people worldwide who have lung cancer and their families; those who need new medical breakthroughs, and those who are most hopeful for a cure. It's about the people who are counting on the knowledge-enhancing research that fellowships and grants provide to pave the way toward a cure.

In the past few months, I have had the privilege of working with several lung cancer survivors and advocates who are dedicated to spreading the word about the importance of IASLC Research Fellowships and Grants. They are fundraising within their own networks to support the IASLC Foundation charge to find a cure for lung cancer. Below are a some of these heroes:

- Kathy Weber, a 3-year survivor with undetectable disease. She started her outreach and fundraising in 2015 and, in 2017, she started a social media campaign that resulted in more than $10,000 raised in just 60 days. Kathy continues to fundraise; her goal is $60,000 to fully fund a fellowship.
- Ivy Elkins, a stage IV lung cancer survivor of 4 years, is dedicated to full-time patient advocacy and to helping other patients navigate their disease through facilitating a private global Facebook group.
- Lauren Fisher, widow of John Fisher and patient advocate, speaks publicly about the critical issue of screening and early detection and has raised enough money to fully fund a fellowship this year focused on early detection and screening.

Over the next several months, we will feature stories on the IASLC Foundation webpage (iaslc.org/foundation) about patients and their families, survivors, advocates, physicians, care teams, fellows, and young investigators. You will learn about the journeys each of these courageous individuals has gone through in the quest to treat and cure lung cancer. They have unique stories, and yet they are all intimately connected. Our goals are the same.

While in Yokohama, Japan, at the 18th World Conference on Lung Cancer, I had the opportunity to spend some time with Chris Draft, former NFL football player, who lost his wife to lung cancer in 2012. Mr. Draft is dedicating his life to lung cancer awareness and to helping lung cancer survivors through his charity, the Chris Draft Family Foundation (chrisdraftfamilyfoundation.org). He inspired me to look deeper into why the research is so important and why raising money for fellowships and grants is so critical to finding a cure. He reminded me, "It's about the people."

Individual contributions to the foundation are key to helping fund the research necessary to finding a cure. Our goal is to eradicate lung cancer and ensure that those people afflicted will go on to live long and productive lives.

Consider a contribution to the IASLC Foundation today. Go to iaslc.org/foundation or mail your gift to the IASLC Foundation, 13100 E. Colfax Ave., Aurora, CO 80011. Any questions about the IASLC Foundation can be directed to annmarie.estrada@iaslc.org. ✦

IASLC 2018 Meetings

SAVE THE DATE!

IASLC 18th Lung Cancer Targeted Therapies Meeting
February 21-24
Santa Monica, California

IASLC–FDA Lung Cancer Neoadjuvant Meeting 2018
March 1-2
Rockville, Maryland

IASLC Lung Cancer Immunotherapy Meeting 2018
March 22-24
Madrid, Spain

ELCC 2018: European Lung Cancer Congress
April 11-14
Geneva, Switzerland

IASLC Africa Conference on Lung Cancer 2018
April 29-May 1
Tangier, Morocco

IASLC Latin America Conference on Lung Cancer 2018
August 15-18
Cordoba, Argentina

IASLC 19th World Conference on Lung Cancer
September 23-26
Toronto, Canada

IASLC Asia Conference on Lung Cancer 2018
November 7-10
Guangzhou, China

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