Highlights from IASLC WCLC 2016

By Lori Alexander, MTPW, ELS, MWC

With more than 2,500 presentations at the IASLC World Conference on Lung Cancer (WCLC) 2016, in Vienna, Austria, it is impossible to report on all new developments in the prevention, diagnosis, and treatment of lung cancer. However, some themes did emerge, most notably tobacco control and smoking cessation, improvements in diagnosis and prognosis, and advances in targeted therapy and immunotherapy.

**Tobacco Control and Smoking Cessation**

Tobacco control remains a crucial topic in the lung cancer community, and the issue was at the forefront of WCLC 2016. Perhaps the most inspiring of the presentations on tobacco control belonged to President of Uruguay Tabaré Vázquez, MD, who spoke at Monday’s Plenary Session. Before the session, Heinz Fischer, former president of Austria, welcomed Dr. Vázquez as well as WCLC delegates. Dr. Vázquez is widely recognized—and revered—for his stance against the tobacco industry. Uruguay won a landmark decision this year when an international arbitration tribunal ruled against the claim by Philip Morris International that two of Uruguay’s tobacco-control measures violated the terms of a Bilateral Treaty between Uruguay and Switzerland. The tribunal dismissed all of Philip Morris International’s claims and awarded Uruguay $7 million for its legal costs.

“Uruguay just exerted its sovereign right to protect its people’s life and health,” said Dr. Vázquez.

Vera Luiza da Costa e Silva, MD, PhD, Secretariat for the World Health Organization’s Framework Convention on Tobacco Control, also spoke at the Plenary Session. She addressed the tobacco industry’s condemnation of tobacco control efforts, in that the multibillion-dollar transnational industry warns against a “nanny state” and supports “an adult’s right to choose,” while at the same time aggressively and deceptively advertising its product.

Immunotherapy in Advanced Non-Small Cell Lung Cancer: A New Paradigm Post-IASLC WCLC 2016

By Melody Watson

The first plenary session on the last day of IASLC WCLC 2016 covered one of the most exciting areas in NSCLC research today: immunotherapy. The first speaker, Julie R. Brahmer, MD, from the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, US, presented key patient-related outcomes from KEYNOTE-024, a pivotal clinical trial comparing the PD-1 inhibitor pembrolizumab to “standard” platinum-doublet chemotherapy in untreated patients with stage IV NSCLC and PD-L1 tumor proportion score (TPS) ≥ 50%.

In addition to previously documented improvements in response rate, progression-free, and overall survival, pembrolizumab resulted in a significantly greater improvement in quality of life and patient-reported outcomes (PROs) compared with chemotherapy (+6.9 vs -0.9, p=0.002). Also pembrolizumab yielded significantly longer median time to deterioration in EORTC QLQ-LC13 composite endpoint of cough, chest pain, and dyspnea (HR: 0.66; 95% CI: 0.44–0.97; p=0.029). Pembrolizumab was also associated with better scores across almost all EORTC QLQ-C30 functioning scales, aside from cognitive functioning, compared with chemotherapy, as well as almost all EORTC QLQ-C30 symptom scales.

The next speaker, Shirish M. Gadgeel, MD, from the Karmanos Cancer Institute/Wayne State University, Detroit, US, presented the results of subgroup analyses of the OAK trial, a phase III clinical trial of atezolizumab, a PD-L1 blocking monoclonal antibody, versus docetaxel in patients with advanced, platinum-exposed NSCLC. Participants in this trial were not restricted on the basis of PD-L1 status, and could have received 1–2 prior lines of chemotherapy. In the primary analysis of OAK trial, atezolizumab resulted in a significantly longer median overall survival (primary endpoint), compared with docetaxel. This overall survival benefit was reported for the PD-L1 subgroups TC3 or IC3, TC2/3 or IC2/3, IC1/2/3 or IC1/2/3, as well as TC0 and IC0 (HRs of 0.41, 0.67, 0.74, and 0.75, respectively). In addition, an overall survival benefit from atezolizumab was shown in patients with non-squamous NSCLC (median 15.6 vs 11.2 months; HR: 0.73; 95% CI: 0.60–0.89; p=0.0015) as well as in patients with squamous disease (median 8.9 vs 7.7 months; HR: 0.73; 95% CI: 0.54–0.98; p=0.0383), regardless of PD-L1 status. The overall survival benefit from atezolizumab was similar in patients with CNS metastases (HR: 0.54), to that observed in patients with no CNS metastases (HR: 0.75) as well as theITT population (HR: 0.73). Additionally, an overall survival advantage of atezolizumab continued on page 11
PD-L1 Blueprint Project

By Fred R. Hirsch, MD, PhD

In the new era of immunotherapy in thoracic cancer, evaluating PD-L1 status remains a clinical challenge. In recognition of the potential confusion generated by having multiple predictive assays related to the same “family” of drugs, a workshop led by the U.S. Food and Drug Administration (FDA), the American Association for Cancer Research (AACR), and the American Society of Clinical Oncology (ASCO) was held in 2014 to discuss this matter. Several pharmaceutical and diagnostic companies with interest in the field as well as other academic organizations participated in this workshop. As a result of the workshop, the PD-L1 Blueprint Project was established, with the primary goal of comparing the PD-L1 assays used in clinical trials in terms of analytical and diagnostic performance. The consortium behind the Blueprint Project included representatives from Bristol-Myers Squibb (BMS), Merck, Genentech/Roche, AstraZeneca, Dako, Ventana, and AACR, as well as the International Association for the Study of Lung Cancer (IASLC), which is coordinating the project.

The first phase of the project, a feasibility study of a relative small number of cases (38), has just been published in the Journal of Thoracic Oncology. The study showed that 3 of 4 assays (Dako’s 28-8 linked to nivolumab, Dako’s 22C3 linked to pembrolizumab, and Ventana’s SP 263 linked to durvalumab) were very similar in analytical performance for PD-L1 expression on tumor cells, while the fourth assay, Ventana’s SP-142, linked to atezolizumab, consistently showed PD-L1 expression in fewer tumor cells compared to the other three assays. All assays expressed PD-L1 on immune cells, but with much greater variation compared to tumor cell expression. With respect to diagnostic comparability using selected cutoff values for the interchangeability among assays can be drawn. Therefore, a much larger ongoing phase II study is currently attempting to address this clinically important question and to compare performance of assays between large tumor specimens, smaller biopsies, and cytology.

The major strength of the PD-L1 Blueprint Project is the unique partnership among the different pharmaceutical companies and diagnostic companies, with IASLC as the coordinating organization.

In addition, this year, issue by issue, we will highlight various international advocacy groups whose shared purpose is to destigmatize lung cancer and to make sure thoracic oncology receives its fair share of funding and publicity. We promise, as well, to focus on new technology in both the surgical and radiation oncology spheres and to explore the potential impact such approaches may have on therapeutic outcome and morbidity; in particular, we will discuss how new technology might be harnessed to our evolving understanding of thoracic cancer biology. As we line up content for the new year, we welcome all suggestions and constructive criticisms.

2017 promises to be a very exciting year, particularly in the United States and parts of Europe where new political regimes with unorthodox, often radical agendas have assumed power. In this environment, preserving the integrity of science and the scientific method is key to our progress in thoracic oncology; and it is also key, I believe, to the longevity and quality of life of our patients. Their trust in us and in our objectivity and compassion is sacred. We cannot fail them. ✦
Breakthrough Therapy Designation and Mechanisms of Expedited Review

The U.S. Food and Drug Administration (FDA) is responsible for reviewing the evidence of safety and efficacy for all new drugs before they can be made available to patients. Increasing the efficiency and speed of the approval process for drugs that treat serious diseases, including lung cancer, is an important part of improving patient access to lifesaving medications. The FDA currently employs 4 distinct mechanisms to expedite the review of potentially important drugs:

1. **Fast Track Designation** can be granted to promote the development and approval of drugs to treat serious conditions with unmet clinical need. This designation provides for more frequent communications and meetings between the drug company and the FDA to support the approval process, as well as eligibility for Accelerated Approval, Priority Review, andRolling Review.

2. **Breakthrough Therapy Designation** may be applied to drugs that have preliminary clinical evidence of being a substantial improvement over existing treatments in the management of serious conditions. The manufacturers of Breakthrough Therapies receive all Fast Track benefits plus intensive guidance and organizational commitment from the FDA for creating an efficient drug development program. Examples of recently approved thoracic oncology agents with recent Breakthrough Therapy designation include pembrolizumab for the first-line treatment of metastatic PD-L1-expressing non-small cell lung cancer (NSCLC) and crizotinib for ROS-1 positive NSCLC.

3. **Accelerated Approval** regulations allow drugs for serious conditions with unmet clinical need to be approved based on a surrogate endpoint, such as tumor size or response, rather than on more traditional clinical endpoints like patient survival. This process can significantly decrease the amount of time required to gather the necessary data on efficacy to gain approval. Accelerated approval is conditional; to retain approval, drug companies are required to conduct phase 4 confirmatory trials to confirm the clinical benefits of these agents. Examples of recent accelerated approvals in thoracic oncology include alectinib for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib, and osimertinib for patients with $EGFR$ T790M mutation-positive NSCLC who have progressed on or after $EGFR$ TKI therapy.

4. **Priority Review** is granted to drugs for serious conditions that would offer significant improvements in safety or efficacy over standard treatments. The FDA strives to take action on applications under Priority Review within 6 months, as opposed to 10 months under Standard Review.

The Breakthrough Therapy designation is important for increasing the availability of oncology drugs that demonstrate large early clinical effects. The early involvement and coordination of experienced, senior FDA personnel can significantly reduce the time necessary for development and approval. Criteria for this designation include the following: (1) the drug is intended to treat a serious condition, and (2) preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over currently available therapy. Although the Breakthrough Therapy designation is often used for oncology agents, drugs treating any serious or life-threatening conditions, including non-oncologic illnesses, are also candidates for this designation.

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organization. More recently, Pfizer/Merck Serono has been added to the consortium since this company is conducting clinical trials with avelumab. Furthermore, the Blueprint Project is the only study to compare all the clinical PD-L1 assays as they are used in the clinical trials; three of these are FDA approved for clinical practice (Dako’s 22C3 and 28-8, and Ventana’s SP-142).

Currently, pembrolizumab (Merck & Co.) is approved with a “companion diagnostic,” e.g., 22C3 required for use of the drug, while the two other assays (28-8 and SP-142) are not required for use of their respective drugs, e.g., nivolumab and atezolizumab, but approved as “complimentary assays.” The approval and clinical development of PD-L1 assays not only hinges on the different antibodies used, but also the interpretation of different staining platforms specific to each of the assays. As currently constituted, there is a high risk of random matching of antibodies, staining platforms, and drug selection, which might yield results that do not have clinical validity. The phase II component of the Blueprint Project is anticipated to give a much better understanding of similarities and differences between the assays and their clinical interchangeability.

Reference
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“We cannot work with or permit the tobacco industry to play any part in public health measures,” said Dr. da Costa e Silva. “Despite all its [the tobacco industry’s] protestations, she added, “it is not fit to offer one crumb of advice against those of us who fight against the epidemic it has so effectively and cruelly engineered around the world.”

Several other WCLC sessions addressed tobacco control specific to various countries and regions, and many European countries continue to struggle with implementing policies.

“Up to now, strategies of tobacco control, which were successful in Australia, North America, and Western Europe, have been introduced only in a few Central European countries,” said Manfred Neuberger, MD, Vienna, Austria, who co-chaired the Meet the Expert Session “Strategies to Improve Tobacco Control in Central European Countries.”

Dr. Neuberger said that, according to a ranking system in which many factors were considered (e.g., tobacco price increases, smoking restrictions, and advertising bans), Austria, Germany, Cyprus, the Czech Republic, Greece, and Lithuania are lagging in their tobacco-control efforts and need to fight more strongly against the tobacco industry’s influence.

Smoking cessation was also discussed extensively in several sessions, including the nursing session “Prevention,” in which speakers explored the role of nurses in smoking cessation (see page 11). In addition, speakers in sessions on lung cancer screening emphasized the importance of providing smoking-cessation services in the context of lung cancer screening programs. Integrating smoking cessation into these programs has been termed a “teachable moment” because of the associated high success rates. Of note, a recent study showed that smoking cessation significantly reduced overall mortality among smokers enrolled in lung cancer screening programs. The beneficial effect appeared to be threefold to fivefold greater than that achieved by earlier detection in the National Lung Screening Trial. In addition, the integration of smoking-cessation services with lung cancer screening yields a significant cost benefit, reducing the overall expense of providing CT-based screening.

Improved Diagnosis and Prognosis

WCLC sessions provided an opportunity to highlight new publications on molecular testing and staging; most notably updates of the “Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors,” a joint guideline developed by the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) in 2013, and the 2016 edition of the IASLC Staging Manual in Thoracic Oncology.

The update to the molecular testing guideline was prompted by several factors, including newly discovered biomarkers with existing or potential targeted therapies (ROS1, MET, ERBB2, BRAF, RET, KRAS, and PIK3CA) and new markers of resistance (e.g., T790M), as well as advances in biotechnology—immunohistochemistry (IHC), next-generation sequencing, circulating cancer cells, and cell-free DNA (cfDNA)—and reconsideration of testing in squamous and small cell cancers. The revisions to the guideline are based on evidence from an unbiased review of published literature since 2013 and include recommendations from an expert panel of renowned world-wide leaders in the field.

The speakers at the Special Session, all members of the Expert Panel, provided a summary of the updated guidelines, noting that the 2013 recommendations are largely unchanged. Unfortunately, no new targets for squamous or small cell cancer have been identified, so testing remains limited to patients with advanced-stage lung cancers with an adenocarcinoma component. In the setting of acquired resistance, testing for the EGFR T790M mutation is recommended, as it occurs in approximately 50% of patients with disease progression on an EGFR inhibitor. In addition, T790M-specific therapy is available (osimertinib). With regard to testing at the time of initial diagnosis, the new guidelines recommend adding ROS1 testing for all patients and adding testing for BRAF, ERBB2, MET, and RET if a larger panel is being obtained. PD-L1/PD-L1 testing is important, but the Expert Panel determined that a separate guideline is needed for this testing. With regard to how to bow to test, IHC is acceptable for ALK and ROS1 testing but not for EGF testing; and next-generation panels are preferred over multiple single assays. Despite the evolving clinical utility of liquid biopsies and their potential advantages, published data are lacking.

The new guidelines are scheduled for publication in early 2017 in the Journal of Thoracic Oncology, the Journal of Molecular Diagnosis, and Archives of Pathology & Laboratory Medicine.

The newly revised staging classification for lung cancer was the focus of several sessions. Ramón Rami-Porta, MD, PhD, Barcelona, Spain, Executive Editor of the IASLC Staging Manual in Thoracic Oncology, noted updates in the classification since the proposed revisions were presented at WCLC 2015 in Denver, primarily within the tumor (T) classification, with few changes to the node (N), and no changes to the metastasis (M) categories. Dr. Rami-Porta reviewed the new changes, focusing on how the updates will likely influence daily clinical practice. The new classification system has a greater focus on tumor size, and tumor size is now a descriptor in all T categories. Additionally, adenocarcinoma in situ (Tis [AIS]), squamous cell carcinoma in situ (SCIS), and minimally invasive adenocarcinoma (T1mi) each has its own coding in the TNM classification. These small tumors behave differently from larger ones and deserve further study with regard to growth rate, tumor density, intensity of uptake in positron emission tomography, optimal type of resection, alternative nonsurgical therapies, molecular characterization, and genetic signatures. Dr. Rami-Porta also discussed determination of tumor size for part-solid tumors. For this presentation, it is the size of the solid component of the tumor that determines prognosis. Measuring the entire size of the tumor would be misleading in classification and prognosis.

Advances in Targeted Therapy and Immunotherapy

Targeted therapy and immunotherapy were the focus of several of the highest-ranked abstracts submitted to WCLC 2016. Three phase III trials on targeted therapy—AURA3, BRAIN, and ASCEND-4—presented at the Presidential Symposium are changing practice for lung cancer specialists.

AURA3, the first randomized phase III trial of a third-generation EGFR inhibitor, showed that osimertinib was associated with a significantly longer progression-free survival (the primary endpoint) compared with standard-of-care chemotherapy for patients with acquired T790M resistance (median, 10.1 vs 4.4 months; p<.001) with fewer grade 3 or higher adverse events. The study was published online in the New England Journal of Medicine simultaneously with the presentation.
EGFR tyrosine kinase inhibitors have demonstrated efficacy in EGFR-positive NSCLC. Use of these inhibitors, in lieu of brain radiation, for brain metastases has been controversial. The inhibitor, icotinib, resulted in a significantly longer median intracranial progression-free survival (the primary endpoint) than WBI + chemo (median, 8.9 vs 4.8 months; p < .014). Icotinib was also associated with longer progression-free survival (6.8 vs 3.4 months, p < .001) and a higher intracranial objective response rate (67.1% vs 40.9%, p < .001). However, overall survival was not significantly different between the treatment arms.

The ASCEND-4 trial was designed to evaluate the second-generation ALK inhibitor ceritinib, which is approved in Europe and the United States as second-line therapy following failure of, or intolerability to, crizotinib in patients with ALK-positive NSCLC. Based on an interim analysis of available data, the trial met its primary endpoint, with ceritinib resulting in a significantly longer trial median progression-free survival compared with standard of care (16.6 vs 6.8 months, p < .014). There was a trend toward longer median overall survival in the ceritinib arm (not evaluable vs 26.2 months; p < .056), even though 72.4% of patients in the standard-of-care arm subsequently received an ALK inhibitor following disease progression. The intracranial objective response rate was higher in the ceritinib arm (72.7% vs 27.3%).

The four highest-ranked abstracts on immunotherapy were presented in Wednesday’s Plenary Session (see coverage on page 1), and the use and study of immunotherapeutic agents continues to burgeon. “As of a month ago, immunotherapy surpassed chemotherapy as first-line treatment for advanced non-small cell lung cancer in selected patients,” said Roy Herbst, MD, PhD, Yale School of Medicine, and Smilow Cancer Hospital, New Haven, US. “So we have a totally new paradigm for treatment.”

Reference

INTERVIEW WITH SHAKUN MALIK, MD
BY ERIK J. MACLAREN, PhD

2017 Mesothelioma Clinical Trials Planning Meeting

Malignant mesothelioma is one of the most difficult cancers to control using existing therapies. Due to the rarity of this disease, randomized trials for potential new treatments are lacking. In order to facilitate clinical trials in patients with malignant mesothelioma, the NCI, the IASLC, and the Mesothelioma Applied Research Foundation have organized a Clinical Trials Planning Meeting (CTPM) for mesothelioma in March 2017. This meeting will bring together experts in the field to evaluate the most current data and propose clinical trials for promising agents. IASLC Lung Cancer News spoke with one of the co-chairs of the mesothelioma CTPM, Shakun Malik, MD, Head of Thoracic Cancer Therapeutics at the NCI Cancer Therapy Evaluation Program (CTEP), about recent advances in mesothelioma treatment and the goals of the meeting.

Q: Are there any advances on the horizon for the treatment of mesothelioma?
A: Yes, we are hoping so. There are a number of ongoing trials that are producing encouraging preliminary results, including immunotherapies as single agents and or in combination as first-line treatments and or in second-line treatment for recurrent metastatic disease. Anti-mesothelin antibodies, including antibodies and antibody-drug conjugates, are also promising.

Q: What are the prospects for using a master protocol along the lines of the Lung-MAP (SWOG S1400) trial in mesothelioma?
A: This is one of the agenda items that we are going to be discussing in the upcoming CTPM. The most important consideration for designing any master protocol is whether there are multiple cancer targets that have shown some preliminary, preclinical, or clinical evidence of activity in that particular disease. A master protocol like Lung-MAP in squamous cell lung cancer was based on data from The Cancer Genome Atlas that identified a number of potential targets for which the drugs were available, and conducting a master protocol simultaneously was thought to be more efficient than conducting clinical trials with each of the targets separately.

Q: How can the NCI and FDA influence the development of treatments for mesothelioma?
A: The NCI funds CTPMs, like the mesothelioma meeting in March, to bring together people from academia, the NCI, the FDA, and the pharmaceutical industry to discuss the current science and preliminary evidence that will support initiating trials that have a strong scientific rationale and that are feasible. The NCI leadership mandate for these meetings is to come up with proposals for 2 to 3 trials that could eventually be funded through the National Clinical Trials Network. The eventual goal is to provide patients with more drug options that are clinically meaningful. The FDA presence at these types of meetings helps us understand how to efficiently navigate the approval process. Lung-MAP is a good example of coordination, not only between the NCI and the FDA, but also a public-private partnership with the pharmaceutical industry. It really is a team effort, and everyone has worked together to make such efforts happen.
Lung Cancer in Never-Smokers: An Epidemiologic Perspective

By Chee-Keong Toh, MD, and Daniel SW Tan, MD

The recent decade has seen much interest in lung cancer in never-smokers (LCNS), in most part attributed to the expanding number of therapeutically tractable alterations enriched within this clinical phenotype. However, equally relevant are studies directed at understanding the etiology of LCNS, for which very little is known. Although environmental factors for secondhand smoke, such as cooking fumes, have been suggested, none have been firmly established. Further, while it has been suggested that there is a rising incidence of LCNS in recent years, it remains unclear if this is due to actual increased numbers, or whether this is a reflection of successful smoking cessation efforts resulting in significantly reduced incidence and mortality of lung cancer, with increased proportional representation of never-smokers.

One of the earliest publications that explored the epidemiological patterns of lung cancer in nonsmokers found that, while in 98% of males and in 70%–90% of European and American females the cancer was predominantly smoking-associated, this was true in only 6%–57% of Asian females. Further studies suggest that only 1.9% and 13% of newly diagnosed male and female lung cancer patients in the United States were never-smokers. Longitudinal collection of reliable data is limited, as many cancer registries, including the US Surveillance, Epidemiology, and End Results (SEER), do not collect information on patients' smoking history. Nevertheless, increasing interest in LCNS started in 2000s when the EGFR TKIs made their way into clinical trials, with early clinical data indicating that never-smokers have an enriched response to EGFR TKIs.

At that time of these published studies, our group and others began to report the clinical differences between never-smokers and smokers. Even without treatment with a TKI, we noticed a significant trend in the differences between smokers and never-smokers, including their survival. Adding to the enthusiasm was the discovery of EGFR mutations and the dramatic responses of some patients to the EGFR TKI. Weaving the clinical, epidemiologic, and molecular characteristics together, the link between oncogenic drivers, never-smoking status, and marked clinical response to targeted therapy began to unfold. Many studies have since corroborated the findings that EGFR mutations were predictive of significant response and progression-free survival to EGFR TKI and that the EGFR mutations were more common among females, never-smokers, and those of Asian ethnicity.

More recently, studies have been exploring the prevalence of driver alterations in the never-smoker cohort. While other targetable candidates have been discovered across different populations, none have been as striking in terms of discrepancies in geographic distribution of EGFR mutations in different ethnic backgrounds, which to date remains unexplained. In line with the two presented abstracts on increasing proportions of never-smoking NSCLC, we have also found similar trends in the increase in the proportion of never-smokers among our predominantly Chinese NSCLC patients in Singapore, comparing two time periods of 1999–2002 and 2009–2012 (manuscript in preparation), suggesting that this trend of increasing prevalence of never-smokers is observed even in a population where smoking rates are generally low.

To confirm if there is indeed an absolute rising incidence of LCNS, additional epidemiologic studies are required as well as continued follow-up of large-scale cohort studies. Further, current and future research priorities include understanding the mechanisms underlying the development of LCNS, identifying modifiable risk factors such as environmental exposure or diet, and rational enrichment strategies for high-risk cohorts to implement effective screening programs.

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Alectinib ( Alecensa) received a positive opinion from the European Medicines Agency (EMA) for Medicinal Products for Human Use (CHMP) for the treatment of adult patients with advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) whose disease has progressed following treatment with crizotinib. Based on this positive CHMP recommendation, a final decision is expected from the European Commission in early 2017. The EMAs recommendation is based primarily on data from the pivotal studies NP28673 and NP28761. (12/17/16)

Osimertinib ( Tagrisso), received approval by the Australian Therapeutic Goods Administration for the treatment of NSCLC in patients carrying the T790M mutation. The U.S. FDA approved osimertinib for treatment of lung cancer in September 2016, while NICE recommended the drug be made available under the Cancer Drugs Fund in October. (12/22/16)

Pembrolizumab (Keytruda)
• in combination with chemotherapy (pemetrexed plus carboplatin), was accepted for review by the US FDA for first-line treatment of patients with metastatic or advanced non-squamous NSCLC regardless of PD-L1 expression and with no EGFR or ALK tumor aberrations. This is the first application for regulatory approval of pembrolizumab in combination with another treatment. The FDA granted a Priority Review with a Prescription Drug User Fee Act (PDUFA), or target action, date of May 10, 2017. The supplemental Biologics License Application (sBLA) will be reviewed under the FDA Accelerated Approval program. (01/10/17)
• received a positive opinion with recommendation of approval by the European Medicines Agency (EMA) for Medicinal Products for Human Use (CHMP) for first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression and no EGFR- mutation or ALK-translocation. Pembrolizumab is currently approved in Europe for the second-line treatment of patients with locally advanced or metastatic NSCLC whose tumors express PD-L1 and who have received at least one prior chemotherapy regimen. Patients with EGFR- or ALK-positive tumor mutations should also have received targeted therapy before receiving pembrolizumab. A final decision regarding pembrolizumab by the European Commission is expected in early 2017. (12/16/16)
• received acceptance for restricted use by the Scottish Medicines Consortium within NHS Scotland, the publicly funded healthcare system in Scotland, for treatment of locally advanced or metastatic NSCLC in adults whose tumors express PD-L1 and who have received at least one prior chemotherapy regimen. Pembrolizumab, compared with a standard taxane monotherapy, was determined to significantly improve overall survival in adults with advanced NSCLC tumors that express PD-L1 and that progress after platinum-doublet chemotherapy. (01/16/17)

US National Cancer Institute (NCI) launched a new drug formulary (“NCI Formulary”) to enable investigators at NCI-designated Cancer Centers to have quicker access to approved and investigational agents for use in preclinical studies and cancer clinical trials. The NCI Formulary is a public-private partnership between NCI and pharmaceutical and biotechnology companies. Fifteen targeted agents from six pharmaceutical companies are included in the NCI Formulary, as of press time, the majority of which are used in clinical lung cancer research. (01/11/17) NCI Formulary url: https://nciformulary.cancer.gov/available_agents/default.htm

Varenicline (Chantix) labeling was updated by the U.S. FDA, including removal of the boxed warning regarding serious neuropsychiatric events. The removal of the boxed warning is based on the outcomes of EAGLES (Evaluating Adverse Events in a Global Smoking Cessation Study), the largest smoking cessation clinical trial in patients without and with a history of psychiatric disorder. Additional labeling revision includes updates to the warning regarding neuropsychiatric safety and the addition of information on the superior efficacy of varenicline compared with bupropion or nicotine patch. (12/16/16)
Impact of Clinical Pathways on Lung Cancer Management

Q&A with Ronan J. Kelly, MB BCh, MBA

Q: What is the impetus for the development of clinical pathways?

A: The incidence of cancer in the US is expected to increase by 45% in the next 2 decades, from 1.6 million in 2010 to 2.3 million in 2030. Direct medical costs associated with cancer care are also expected to increase from $125 billion in 2010 to at least $173 billion in 2020, and this may be a conservative estimate. This price escalation is not sustainable, and there are a number of systemic failures, which drive up costs, in our cancer care delivery system that need to be rectified. The Institute of Medicine estimates that approximately 30% of all healthcare dollars are spent on unnecessary tests, procedures, and doctor visits. Clinical pathways are a set of systems-based tools or protocols for creating greater cohesion in cancer care by standardizing decision-making, therapeutic selection, and care delivery. Essentially, they are seen as a method to reduce unnecessary and costly treatment variations. Pathway developers say their pathways are chosen based on efficacy, toxicity, and cost, in that order.

Q: What evidence exists to show that such pathways reduce costs, reduce medical errors, and improve outcomes, including survival?

A: One of the best-known studies in non-small cell lung cancer comes from The US Oncology Network, which reported no differences in overall survival in patients treated in the adjuvant setting or in the first-line and second-line metastatic setting when treated on or off their level 1 pathway, but costs were reduced by 35% when treated on pathway vs off pathway. We do, however, need more evidence to show that pathways not only reduce costs and medical errors but also improve survival. Studies to date have been small and have used observational designs or retrospectively identified control groups. Future studies performed by large independent groups to assess the long-term clinical and economic outcomes in real-world setting are needed. We also need to pursue a collaborative, national approach in the US to reduce the unsustainable administrative burden associated with clinical pathways and to ensure they are consistent and transparent.

Q: What are the impediments to the implementation of such pathways?

A: All countries are struggling with the appropriate amount to spend on healthcare. Each country has its own regulatory body to evaluate new cancer drugs, and each country uses different thresholds to determine what is considered good value or cost-effective prior to approving a new treatment. In the US there is no explicit “line in the sand” used for a maximally acceptable incremental cost-effectiveness ratio (ICER), which is a statistic used to summarize the cost-effectiveness of a health care intervention. Three different approaches—adjusting the ICER for dialysis into current dollars, using three times a country’s gross domestic product, and an inflation-adjusted index—suggest an acceptable threshold range of $150,000 to $200,000 per quality-adjusted life-year gain (QALY). For a number of years, I and others have proposed that cost-effectiveness analyses must be used to form policy around national healthcare plans, recognizing that each country will have different thresholds.

A: It was anticipated that the biggest challenges to pathway adoption would not be technical or operational, but rather cultural, and that oncologists would reject standardization and measurement over their own autonomy and clinical judgment. Some success has been achieved by fostering a collaborative approach where physicians are directly involved in pathway development, and aligned incentives are agreed upon up front. As we move forward, pathway development success is more about changing entrenched physician behavior patterns rather than merely revising formularies. While large oncology groups like UPMC and The US Oncology Network have been able to win consensus among their oncologists, achieving this throughout an entire insurer’s network will be more difficult. Concerns still exist; a recent ASCO task force highlighted that, in many cases, clinical pathways are undermining physicians’ ability to optimally care for their patients with cancer and they are limiting patient choice.

The ASCO task force raised a number of concerns regarding how clinical pathways are developed and implemented in practices. Key points from the policy statement include the following: (a) Oncology pathways are not developed or applied consistently by insurers, thereby resulting in wide variations in quality and utility; (b) Pathways are often too rigid and often overemphasize cost control; (c) Pathways overemphasize drugs, but do not include other critical aspects of care such as diagnostics, laboratory investigations, or palliative care services; (d) Lack of transparency in the pathway development process may lead to conflicts of interest; and (e) No system is in place to guarantee the integrity of the various pathways coming to market or to ensure they are implemented in a manner that supports high-quality patient care.

Q: Will the status of the Affordable Care Act influence the institution of such pathways? Or do you believe these algorithms are inevitable regardless of the existence of the Act?

A: I believe these algorithms are inevitable; the current marketplace and the Affordable Care Act have led to an increase in high-deductible health plans, which have exacerbated the significant financial hardships experienced by patients with expensive chronic conditions such as cancer. Clinical pathways are seen as a way to decrease costs, which hopefully will make care more affordable for patients. A recent ASCO policy statement on clinical pathways estimates that 60 individual health insurance plans in the US are currently implementing oncology pathways; this means that approximately 170 million individuals covered by those plans will potentially be treated under an oncology pathway if they develop cancer.

Q: In the 80s, the cost of one year of hemodialysis was approximately $50,000. What, if any, is the current threshold for cost per life year gained? Should there be such thresholds? What ethical issues does this analysis raise?

A: It is anticipated that the biggest challenges to pathway adoption would not be technical or operational, but rather cultural, and that oncologists would reject standardization and measurement over their own autonomy and clinical judgment. Some success has been achieved by fostering a collaborative approach where physicians are directly involved in pathway development, and aligned incentives are agreed upon up front. As we move forward, pathway development success is more about changing entrenched physician behavior patterns rather than merely revising formularies. While large oncology groups like UPMC and The US Oncology Network have been able to win consensus among their oncologists, achieving this throughout an entire insurer’s network will be more difficult.
The Fourth IASLC Screening Strategy Advice Committee CT Screening Workshop

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

The Fourth IASLC Screening Strategy Advice Committee (SSAC) computed tomography (CT) screening workshop was held on December 3, 2016, prior to IASLC WCLC 2016. This workshop provided a comprehensive international forum for all lung cancer clinical specialties to meet and discuss the advances in CT screening trials and imaging technology as well as future implementation plans.

This workshop focused on high-impact issues emerging in the area of lung cancer screening. Foremost among those issues was emphasizing the critical obligation to provide smoking cessation services in the context of lung cancer CT screening programs. This integration of smoking cessation with the provision of lung cancer screening has been termed a “teachable moment” and relates to the high reported success of smoking cessation when offered in the context of lung cancer screening. This integration has been found to result in a significant cost benefit, reducing the overall expense of providing the CT-based screening service. Further discussions addressed additional measures to reduce the cost of delivering this screening service by evolving more efficient clinical screening management approaches. The session also focused on radiological imaging and workup based on the experience of the international screening trials, and provided an overview of the innovative approaches of qualitative imaging quality control for lung cancer screening as well as opportunities for developing data registries. The second session explored opportunities for IASLC to support critical research in this area, such as by creating international registries of CT images/c clinical data. The third session highlighted the advances of utilizing of lung cancer CT screening scans for coronary heart disease (CHD) and chronic obstructive pulmonary disease (COPD) within future screening programs. These discussions will focus on the benefits of undertaking screening for the big 3 tobacco-related diseases: lung cancer, CHD, and COPD.

The fourth session provided the opportunity to discuss a global implementation plan for CT screening programs, potentially leveraging US, Canadian, and UK experience to understand how this process can be optimized in other national settings.

The fifth and final session was a roundtable discussion, concentrating on five major questions of:

- Identification of the hard-to-reach community for lung cancer screening
- Use of quantitative imaging in screening setup, and whether accreditation is needed
- CT screening data registries and the possibilities for international collaboration
- The development of international guidelines for the workup of CT-detected nodules

Drug Approval Processes Around the World: Focus on China

By Caicun Zhou, MD

As part of an ongoing series, IASLC Lung Cancer News is exploring how drug approval processes differ country by country, and continent by continent. In China, the drug registration process includes the following steps:

- Application to the China Food and Drug Administration (CFDA) for clinical trial approval, which is similar to the Investigational New Drug Application (IND)/Clinical Trial Applications (CTA) in Western countries
- Performance of the relevant clinical trial according to the Chinese Good Clinical Practice (GCP) and Regulations so as to secure Chinese patients’ data and clinical study report
- Application to the CFDA for marketing authorization, e.g., Imported Drug License (IDL) or Local Production Permit, a process similar to the New Drug Authorization (NDA) or Biological License Authorization (BLA)/Marketing Authorization Applications (MAA) used in Western countries

The Center for Drug Evaluation (CDE) under the CFDA is responsible for technical review, and the CFDA takes charge of administrative review and final approval.

The review and approval timeline defined in the current regulations is theoretical. … actual review and approval timelines are longer and vary from product to product.

During IND/NDA review, CFDA is empowered by regulations to perform on-site (research site, clinical site/GCP and manufacturing site/GMP) inspection. The on-site inspections are mandatory for local manufacturers, but for imported drugs applications inspections occur only as needed.

The review and approval timeline defined in the current regulations is theoretical. If there are no formal queues during the process, the timeline is usually about 125 days. However, from a practical point of view, because of the heavy workload in CDE due to a shortage of review resources compared with a large volume of applications, the actual review and approval timelines are longer and vary from product to product.

Ultimately, the CFDA is responsible for protecting the public health by ensuring the safety and efficacy of medical products and medical devices.

Recent Changes and Future Trends

In August 2015, The State Council, the Chief administrative authority of the People’s Republic of China, issued directives to reform the review and approval system, including accelerating the review and approval process for development and marketing authorization of new drugs with clinical value and generic drugs with clinical value and urgent need.

Accordingly, the CFDA took major measures on the review and approval process and system reform as follows:

- Priority Review and Approval: this applies to applications with obvious clinical value, for example, the application for drugs preventing or treating AIDS, TB, viral hepatitis, orphan diseases, malignant tumors, pediatric disease, and other serious diseases
- Communications on drug R&D and scientific review with CDE: the CFDA has published the relevant guideline to define the formal meeting type, the process, requirement, and timeline for consulting and preparation, which will grant more communication opportunities to industry
- Improvement on clinical data quality: the CFDA has requested preapproval GCP-inspection for all NDAs (both for imported drugs and local production) from the end of 2015

With these activities and reform measures, the CFDA hopes to encourage drug innovation, standardize evaluation and drug approval, and improve drug quality.
by starting with a clinical problem and that researchers need to work backward must be found and then targeted, and do we find the right target in the right up with another question: “But how cancer the way forward?” and promptly Charles Rudin, MD, PhD, of

With regard to endpoints, Dr. Mok said that overall survival should be avoided in the study population. An interaction agent in a biomarker-selected popula-

Researchers then sought to determine relevant biomarker as the available bio-
makers (IHC and FISH) were not helpful in patient selection,” said Dr. Mok. The primacy of EGF mutation ultimately emerged. He said that it is essential to know the expected efficacy of a new agent in a biomarker-selected population and the incidence of the biomarker in the study population. An interaction test should confirm the predictive power. With regard to endpoints, Dr. Mok said that overall survival should be avoided as a primary endpoint when significant crossover is expected in the biomarker-selected population.

Charles Rudin, MD, PhD, of Memorial Sloan-Kettering Center, New York, US, asked the question “Is molecular-based therapy for lung cancer the way forward?” and promptly answered “Yes.” However, he followed up with another question: “But how do we find the right target in the right context?” He said that driver mutations must be found and then targeted, and that researchers need to work backward by starting with a clinical problem and figuring out why it fails. Finding some targets is more difficult, he added, and many may be hiding in regulation of the epigenome. Dr. Rudin also noted that resistance to targeted therapy must be addressed.

Yu Shyr, PhD, of Vanderbilt University School of Medicine, Nashville, US, provided an overview of drugs recently approved by the FDA for lung cancer, noting that the indications have often become specific to the results of molecular testing. He then discussed several biomarker-based trial designs, including enrichment, stratified, hybrid, umbrella, and basket designs. With the enrich-

ment design, the biomarker is assessed and patients who test negatively for the biomarker are excluded; patients who test positively for the biomarker are then randomly assigned to treatment groups. The stratified design involves stratifying participants according to biomarker status and then randomly assigning to treatment. With a hybrid design, only certain biomarker subgroups are randomly assigned, while others are assigned to the standard of care. Dr. Shyr noted that, with an umbrella trial design, within one tumor type or histology, patients are grouped based on biomarker status to different randomizations (targeted treatments); with a basket trial design, patients are grouped based on biomarker status to identical treatment regardless of the tumor type or histology.

Francesco Pignatti, MD, of the European Medicines Agency (EMA), discussed the challenges related to the identification of small subgroups of molecularly defined patients. Given this situation, he said that it may be difficult to generate sufficient efficacy and safety data to assess benefit and risk, and that randomized controlled trials may not be feasible. Dr. Pignatti said that when assessing evidence from clinical trial data in small populations, researchers must use all available evidence, i.e., from small randomized controlled trials, multiple endpoints, multiple trials and sources, and external controls.

Dr. Pignatti also discussed greater involvement of patients when weigh-
ing benefits and risks. Some patients may be willing to take on higher risks to potentially achieve a small benefit. “If a significant group of reasonable and well-informed patients accepts this sort of trade-off, this may support a favorable benefit-risk profile,” he said. He also described Medicines Adaptive Pathways for Patients (MAPPs), a prospectively planned, adaptive approach to bringing drugs to market and further develop-

MAPPs balance timely access with providing adequate evolving infor-
mation on benefits and harms, he said, and increase dialogue with stakeholders through the development process.
The closing plenary session at IASLC WCLC 2016 featured several highly regarded oncologists who have devoted the greater part of their careers to thoracic oncology. These “giants” reflected on their work and the changes they have seen in the key areas of chemotherapy, thoracic surgery, radiation therapy, pathology, EGFR inhibitors, and translational research.

Chemotherapy
Advances in cytotoxic chemotherapy agents have lagged behind advances in other cancer treatments, said Thierry Le Chevalier, MD, Gustave Roussy Hospital and Marie Lannelongue Hospital, Paris Sud, France. He noted that few cytotoxic drugs have been approved for lung cancer since 2000 and that there has been a lack of progress in the treatment of small cell lung cancer. “We have used the same disappointing doublet since the early 80s,” he said. In addition, shifts in the population of patients with non-small cell lung cancer (NSCLC) are also changing the role of chemotherapy, with an increasing number of nonsmokers, women, and patients with mutation-driven tumors.

Although chemotherapy remains the systemic standard of care for most people with NSCLC, it is usually given with palliative intent. A subset of patients can be cured with chemotherapy, but it is mostly when chemotherapy is used in combination with surgery or radiation therapy. Dr. Le Chevalier described the findings of several of his studies with colleagues, which have shown that adjuvant cisplatin-based chemotherapy significantly improves outcomes for patients who had complete resection of NSCLC, with the greatest benefit found for patients with stage II or III disease.

Dr. Le Chevalier continues his research in assessing biomarkers to help better define patients who are more likely to benefit from postoperative chemotherapy. His research earned him the IASLC Paul A. Bunn, Jr. Scientific Award in 2005.

Surgery
In reflecting on surgical milestones in cardiothoracic surgery, Peter Goldstraw, MD, FRCS, of Royal Brompton Hospital, London, UK, echoed Dr. Le Chevalier’s comments about the shifting population of patients with lung cancer.

“In the 1970s it was unusual to operate on anyone over the age of 70, few patients were female, and lung cancer was almost totally a smokers’ disease,” said Dr. Goldstraw. “Now the eighth decade of life is the commonest decade of presentation, lung cancer is almost as frequent in females as in males, and 15% of cases are in lifelong nonsmokers.”

Dr. Goldstraw also noted that resection rates have improved and patient survival is longer because of the large number of specialist surgeons. Surgeons are now safely operating on older patients with more comorbidities and resections are less extensive, due to earlier diagnosis, improved preoperative assessments, and changes in the disease and its presentation. Surgical approaches, including conventional thoracotomy, are less invasive now, he added, and operative mortality is lower. Survival also improved as adjuvant therapy became the standard of care for resected NSCLC, as Dr. Le Chevalier noted.

Dr. Goldstraw is Emeritus Professor of Thoracic Surgery at the National Heart and Lung Institute, Imperial College, UK, and has received numerous awards in recognition of his contributions in cardiothoracic surgery. He received the 2007 IASLC Merit Award and served as IASLC President in 2011–2013. He is the Executive Editor of the *IASLC Staging Manual in Thoracic Oncology*, published in 2009, the first-ever lung cancer-specific staging publication.

Radiation Therapy
Radiation oncologist David Ball, MD, FRANZCR, of Peter MacCallum Cancer Centre, Royal Melbourne Hospital, Melbourne, Australia, highlighted improvements in radiation therapy for lung cancer. He began by delineating the dismal prognosis for lung cancer in the early 1970s, presenting the findings from a study from that period showing that radiation therapy alone, chemotherapy alone, and radiation therapy plus chemotherapy were no more effective, with respect to survival duration, than a so-called wait-and-see approach.

“Survival has improved tenfold compared with 40 years ago. Yet the active agent today is exactly the same as it was then with the same mechanism of action: megavoltage photons,” he said.

Key contributors to this improvement include the digital revolution, starting with computed tomography (CT) being used for 3-dimensional delineation of the target and organs at risk. It also enables accurate dose computation by correcting for tissue inhomogeneities. The addition of chemotherapy to radiation therapy has further improved outcomes, with shorter radiation therapy regimens now preferable to longer regimens. Another development is the increased use of hypofractionation due to the advent of stereotactic ablative radiotherapy.

Dr. Ball received the 2011 IASLC Merit Award and currently serves as a member of the IASLC TNM Staging Committee. He also chairs the Australian Lung Cancer Guidelines Working Party and has been Editor-in-Chief of the *Journal of Medical Imaging and Radiation Oncology* since 2007.

Pathology
The establishment of lung cancer cell lines revolutionized the field of thoracic pathology and deepened our understanding of lung cancer biology, said Adi F. Gazdar, MD, of University of Texas Southwestern Medical Center, Dallas, US. In the case of NSCLC, discoveries such as EGFR activating mutations and *EGFR T790M* mutation have resulted in targeted treatment for these mutations. Identification of such mutations has also transformed the classification of tumors, including the recognition that a tumor usually consists of mixtures of subtypes. Dr. Gazdar discussed an expression signature he and his colleagues have developed that can be used as an adjunct for histologic classification of NSCLC.

“Targeted Therapies
Frances A. Shepherd, MD, of Princess Margaret Cancer Centre, University of Toronto, Canada, is widely recognized for her involvement in the development of several large international randomized trials of novel agents directed against EGFR and other molecular targets. In her presentation, she compared the molecular landscape at the turn of the last century to the current situation, noting the progress made along the way and some of the lessons learned. For example, she commented that only in the last 10 years have we become fully aware that EGFR inhibitors cause G1 arrest and consequently reduce the effectiveness of chemotherapy or that patient selection is important for treatment with EGFR inhibitors.

Dr. Shepherd emphasized the importance of understanding the difference between quantitative and qualitative interactions when assessing treatment response. To illustrate her point, she used the SATURN maintenance study of erlotinib in patients with EGFR wild-type disease as an example of a quantitative interaction; even though erlotinib resulted in a statistically significant overall survival benefit, it was not clinically relevant because the benefit was so small. She underscored the need to evaluate the clinically relevant benefit and the statistical benefit together when assessing a treatment.

Dr. Shepherd concluded by talking about EGFR inhibitor resistance, including some of the exciting outcomes from studies of newer agents, such as osimertinib, that combat this problem, as well as the latest fourth-generation drugs and the need for broad molecular profiling.

As head of the Tumor Cell Biology Section at the National Cancer Institute, Dr. Gazdar collected, cataloged, and analyzed more than 2,200 human cancer specimens, mostly lung cancers and lymphomas. IASLC honored him with the Mary J. Matthews Pathology/Translational Research Award in 2003.

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Role of Nurses in the Care of Patients with Lung Cancer
By Lori Alexander, MTPW, ELS, MWC

WCLC 2016 offered focused education for nurses and allied health professionals through its nursing track, as well as through special nursing workshops held before the official start of the conference. The sessions addressed a range of topics, including the use of technology and social media, preparing patients for treatment, managing toxicities of newer treatments, and smoking cessation.

The International Thoracic Oncology Nursing Forum (ITONF) presented “Innovating Lung Cancer and Mesothelioma Care,” an extensive educational workshop that covered such topics as immunotherapy, clinical trials, vaping and smoking cessation, and social media and e-health. One highlight of the workshop was “Leveraging Technology and Social Media in Nursing,” presented by Anne Ireland, MSN, RN, AOCN, CENP, City of Hope National Medical Center, Duarte, US. Ms. Ireland discussed specific technologies that will provide opportunities for better data collection and integration, including wearable health-tracking devices, video capabilities, and real-time communication.

“Health and fitness apps have created an entirely new way of communication between providers and patients, making remote monitoring and health promotion easier and more cost-effective,” Ireland said. “The opportunity to use apps for health promotion and monitoring seems endless and provides for ease of access not previously possible.”

Such technology was also a topic at “Supporting Patients Receiving Treatment,” where Roma Maguire, Professor of eHealth, University of Surrey, Guildford, UK, discussed the use of mobile phone technology to remotely monitor patients. Ms. Maguire described mobile systems for patient-reported outcomes, including wearable health-tracking devices, video capabilities, and real-time communication.

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Evolving Standards of Care

Efforts Aim to Make Clinical Trial Information More Accessible
By Cynthia L. Kryder, MS

Clinical trials are essential to the development of new, potentially lifesaving therapies for patients with cancer. Well-designed clinical trials contribute to medical advances and evidence-based medicine. Nevertheless, the Cancer Research Institute estimates that only 3% to 6% of patients with cancer who are eligible for clinical trials actually participate. For patients with advanced lung cancer, access to emerging treatments through a clinical trial may be the best therapeutic option.

Streamline the Data
Increasing patients’ awareness of clinical trials, helping them to understand the benefits of clinical trial participation, and guiding them to suitable clinical trials are important aspects of cancer care. However, existing databases such as ClinicalTrials.gov and the European Union Clinical Trials Register, which are designed primarily for healthcare professionals and are often filled with medical jargon, can be hard for patients to navigate and understand.

In the United States, streamlining clinical trial information to make it more accessible to patients is one goal of the Cancer Moonshot effort, a $1 billion US initiative to facilitate cancer research. One element of the Cancer Moonshot is the National Cancer Institute (NCI) application programming interface (API), which allows outside organizations to access specific clinical trial data in the NCI database and integrate this information with their own unique applications. In addition, the NCI recently released its own streamlined interface where consumers, healthcare providers, and advocates can more easily find NCI-supported clinical trials (see text box).

In recent years, organizations have emerged that will match patients with suitable clinical trials based on a patient-provided profile. Antidote, a patient advocacy group, and Cure Forward, a digital health company, are two examples. Both organizations use the NCI API to integrate NCI data into their own databases. MolecularMatch offers a searchable online database that connects patients with personalized treatment options based on their particular molecular and genetic profiles. Moreover, through the online portal, MolecularMatch Lab, pathology laboratories and others can match patients’ test results to personalized cancer treatments, including clinical trials and experimental drugs, in real time.

Another organization making information about clinical trials in cancer immunotherapy more accessible is the nonprofit Cancer Research Institute (CRI). Through a partnership with EmergingMed, CRI developed the Cancer Immunotherapy Clinical Trial Finder, a searchable online database that features studies using immunology along with the full national database of cancer treatment trials from all sponsors.

Several searchable online databases are available where patients and healthcare professionals can search for clinical trials outside of the United States. These include Cancer Research UK, the European Organisation for Research and Treatment of Cancer, the European Union Clinical Trials Register, and NHS Choices. The World Health Organization (WHO) maintains the International Clinical Trials Registry Platform (ICTRP) search portal, through which users can search for trials registered in multiple countries, including Australia, Brazil, China, Cuba, Germany, Iran, Japan, the Netherlands, the Republic of Korea, and New Zealand.

Harness the Power of Social Media
As social media platforms have become tools to enable patients with cancer to gather and exchange information and provide support, the next logical step may be to use social media to communicate with patients about clinical trials. The results of a recently published pilot study suggest that Twitter could be a way to increase awareness of clinical trials and enhance recruitment. Physicians at the Abramson Cancer Center of the University of Pennsylvania analyzed a random sample of more than 1,500 tweets out of a total of 15,346 unique tweets that contained the phrase “lung cancer” during two weeks in January 2015. Although the majority of the tweets analyzed (56%) were focused on prevention or psychological support, the next largest category of tweets (about 18%) was about clinical trials. Most of the clinical trial tweets were about human research into a specific drug or device; 79% were about immunotherapy and 86% included embedded links to news articles. Interestingly, only one tweet linked readers to a patient recruitment website.

The hashtag has made Twitter a popular platform for patients with cancer. The Healthcare Hashtag Project created standardized hashtags for diseases, conferences, Twitter chats, and ontologies, and has enabled disease-specific communities to flourish on Twitter. The most widely recognized hashtag for lung cancer, #LCSM (Lung Cancer Social Media), evolved from a simple hashtag into an online community with a website and biweekly Twitter chats (#LSCMChat). In fact, the topic of a recent #LSCMChat was a live question-and-answer session with the NCI on immunotherapy and clinical trials.

Social media interactions such as these can increase awareness and boost recruitment in clinical trials, enabling more patients with advanced lung cancer to gain access to promising new treatments that are only available to those enrolled in clinical trials. *

WHERE TO SEARCH FOR CLINICAL TRIALS

Antidote: https://antidote.me/
Cancer Research Institute Clinical Trial Finder: https://platform.emergingmed.com/find-clinical-trials/cri#partnerhome
Cancer Research UK: http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial
ClinicalTrials.gov: https://clinicaltrials.gov/
Cure Forward: https://www.cureforward.com/
EmergingMed: https://www.emergingmed.com
European Organisation for Research and Treatment of Cancer: http://www.eortc.org/clinical-trials/
European Union Clinical Trials Register: https://www.clinicaltrialsregister.eu/ctr-search/search
MolecularMatch: https://www.molecularmatch.com/
National Cancer Institute-Supported Clinical Trials: https://www.cancer.gov/about-cancer/treatment/clinical-trials/search
NHS Choices: http://www.nhs.uk/Conditions/Clinical-trials/Pages/clinical-trial.aspx
World Health Organization International Clinical Trials Registry Platform: http://apps.who.int/trialsearch/

REQUEST FOR APPLICATIONS
2017 ALCF-IASLC Joint Fellowship Award for the Early Detection of Lung Cancer
Application Submission Deadline: March 1, 2017

The Bonnie J. Addario Lung Cancer Foundation (ALCF), in collaboration with the International Association for the Study of Lung Cancer (IASLC) announce their second joint Fellowship Award to support novel, innovative and translational research with potential of high clinical impact on the early detection of lung cancer.

The ALCF-IASLC Fellowship Award supports an early career scientist’s training and research on early detection modalities in an established lung cancer research laboratory of their choice, anywhere in the world.

This Award aims to identify brilliant, young “out of the box” thinkers/researchers who can deliver a meaningful and measurable result for the early detection of lung cancer that has a high probability of near-term benefit to lung cancer patients or individuals at risk, as well as to provide an opportunity for young researchers to learn new cutting-edge technologies and take this expertise back to their home country.

For further information, visit https://www.iaslc.org/fellowship/announcement

References
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

Conquering Thoracic Cancers Worldwide

Through education, international collaboration, and groundbreaking research, the IASLC is the leader in the global fight against lung cancer.

More information at IASLC.org.

The IASLC Foundation supports global research discovering new approaches to conquer thoracic cancers.
IASLC.org/Foundation
Nothing Plain about Plain Packaging
By Kenneth Michael Cummings, PhD, MPH

Cigarette packaging designs with different logos, imagery, size configurations and color schemes have been an important marketing tool used by manufacturers to attract different groups to try specific cigarette brands and sub-brands. For example, slim and elegant packaging with feminine imagery is used to attract young female smokers to a particular brand. Lighter-colored packs are often used to convey that a brand is less strong and, by analogy, less harmful, which is attractive to smokers concerned about how smoking might affect their health. Recently, the World Health Organization called on countries everywhere to step up efforts to limit cigarette advertising by introducing plain packaging. The recent WHO report on plain packaging can be found at: http://www.tobaccolabels.ca/wp/wp-content/uploads/2016/06/WHO-2016-Plain-packaging-of-tobacco-products-evidence-design-and-implementation-World-Health-Organization.pdf.

Governments have attempted to counteract the impact of cigarette marketing through a number of actions, including banning certain forms of cigarette promotions such as broadcast marketing, forbidding the distribution of free samples, and requiring health warnings on cigarette packs. In 2001, Canada became the first country to require pictorial warnings on cigarette packs in lieu of less impactful test-only warnings. By 2014, 77 countries and territories had adopted pictorial health warnings (http://www.tobaccolabels.ca/healthwarningsinfo/statusreport/). Plain packaging came next, with Australia introducing the world’s first regulation in 2012.

Plain packaging is often called “standardized” packaging. In Australia, the plain packaging regulations restricted cigarette companies in their use of logos, colors, and brand images on packs, and instead required a standard color and plain font. The regulations have also restricted the physical dimensions of cigarette packaging, including minimum pack size, which has effectively prohibited “super slim” packages (see Figure 1).

Research conducted before and after the Australian plain packaging legislation has demonstrated three primary effects of plain packaging: 1) it reduces the appeal of cigarette smoking, especially among non-smoking youth; 2) it reduces false health beliefs that some brands are less harmful than others; and 3) it enhances the impact of the health warnings already on the package. This evidence is further bolstered by cigarette companies’ own internal market research, which has demonstrated the importance of packaging as a form of marketing, including evidence showing the important role of pack color and design in influencing consumer perceptions and behaviors.

Australia has seen historic declines in smoking since plain packaging was introduced along with new health warnings and a large tax increase. A government-commissioned review of the impact of the packaging changes found that smoking rates fell an additional 0.55 percentage points between December 2012 and September 2015—a drop attributed to the packaging changes only, and not to the other anti-tobacco policies the country implemented around that time. Moreover, regardless of any short-term impact, the requirement of plain packaging is likely to have a greater long-term impact, as new generations will grow up without the promotional images and messages on cigarette packs that were so common in the past.

What’s Next?
A number of other countries have committed to implementing plain packaging, including the United Kingdom and France in 2017. Several other countries, including Norway, Hungary, Slovenia, Sweden, Finland, Canada, New Zealand, Singapore, Belgium, and South Africa, have also announced that they are considering similar legislation. Not surprisingly, cigarette manufacturers are not too happy about plain packaging and have attempted to block such legislation by threatening costly lawsuits against governments on the grounds that such legislation violates international trade and trademark laws. The Australian legislation has already withstood multiple legal challenges, and a similar lawsuit in the United Kingdom was rejected by the high court of England. A summary of legal cases to date can be found at: http://www.tobaccolabels.ca/plain-packaging/industry-positions/.

Public health researchers are also looking at additional ways to limit the appeal of cigarettes by banning menthol as a flavoring additive, lowering the nicotine content of cigarettes to reduce the abuse liability of smoking, and requiring inserts inside cigarette packages that would remind smokers about the dangers of smoking and the benefits of not smoking, as well as providing information and advice on how to stop smoking.

None of these measures can come soon enough, as cigarette smoking accounts for 80%–90% of all lung cancer deaths worldwide. Cigarette marketing is a massive driver of cigarette use, which is exactly why cigarette companies are willing to shell out billions of dollars every year to persuade people to buy their products. As noted by one cigarette company executive more than 60 years ago, “The rise and fall of every brand of consequence has been traced in detail and their year to year success or failure shown to be the direct result of consumer advertising.” (A study of Cigarette Advertising made by J.W. Burgard, 1953; https://www.industrydocumentslibrary.ucsf.edu/tobacco/docs/#id=qymm0104)

Kenneth Michael Cummings, PhD, MPH, is co-leader of the Tobacco Research Program at the Hollings Cancer Center, Medical University of South Carolina, US.
Names and News

Peter Hammerman, MD, PhD, has been appointed Global Head, Oncology Translational Research at Novartis Institutes for BioMedical Research (NIBR). Previous to this appointment, Dr. Hammerman was a Medical Oncologist and Physician Scientist at Dana-Farber Cancer Institute and Assistant Professor, Medicine, Harvard Medical School, Boston, US.

Roy S. Herbst, MD, PhD, received the 2016 IASLC Paul A. Bunn, Jr. Scientific Award, which is given to an oncologist who has made outstanding scientific contributions to thoracic cancer research. Dr. Herbst is Ensign Professor of Medicine; Professor of Pharmacology; Chief of Medical Oncology; Director of the Thoracic Oncology Research Program; and Associate Director for Translational Research at the Yale Cancer Center and Yale School of Medicine, New Haven, US.

Keith Kerr, BSc, MB ChB, FRCPATH, FRCP, received the 2016 IASLC Mary J. Matthews Pathology/Translational Research Award, which is given to a scientist for lifetime scientific achievements in pathology/translational research of thoracic malignancies. Dr. Kerr is Honorary Professor of Pulmonary Pathology at Aberdeen University Medical School in Scotland, UK.

Dr. Benjamin Levy has been appointed Clinical Director, Johns Hopkins Kimmel Cancer Center at Sibley Memorial Hospital and Medical Director of the Thoracic Oncology Program in Washington, D.C. Prior to this appointment, Dr. Levy was Director of Thoracic Medical Oncology, Mount Sinai Health Systems and Associate Director, Cancer Clinical Trials Office, Mount Sinai Hospital; Assistant Professor of Medicine, Icahn School of Medicine, New York, US.

Keunchil Park, MD, PhD, received the 2016 IASLC Merit Award, which is given to lung cancer specialists who have made extraordinary contributions to the IASLC’s development. Dr. Park is Professor, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine in Seoul, South Korea.

Ugo Pastorino, MD, received the Joseph W. Cullen/Early Detection Achievement Award in 2015. He is the 79th IASLC Merit Award, which is given to lung cancer specialists who have made extraordinary contributions to the IASLC’s development. Dr. Pastorino is Director, Thoracic Surgery Division, Istituto Nazionale Tumori, Milan, Italy; and Faculty Member, School of Specialization in Thoracic Surgery, General Surgery, and Medical Oncology and at the European Association for Cardio-Thoracic Surgery.

John C. Ruckdeschel, MD, has been appointed Director, University of Mississippi Medical Center Cancer Institute, Jackson, MS. Prior to this appointment, Dr. Ruckdeschel was Medical Director, Oncology Program and Services, Intermountain Healthcare, Greater Salt Lake City Area, US.

Gerard A. Silvestri, MD, MS, FCCP, is the 79th President of the American College of Chest Physicians, effective November 2017. Dr. Silvestri is Hillenbrand Professor of Thoracic Oncology and Vice-Chair of Medicine for Faculty Development at the Medical University of South Carolina in Charleston, US.

Sumitra Thongprasert, MD, received the 2016 IASLC Merit Award, which is given to lung cancer specialists who have made extraordinary contributions to the IASLC’s development. Dr. Thongprasert is Professor Emeritus, Faculty of Medicine, Chiang Mai University; Senior Consultant in Oncology, Bangkok Hospital Chiang Mai; and Director, Bangkok Hospital Chiang Mai Center of Excellence in Cancer, Bangkok, Thailand.

Immunology and Precision Medicine

“Translational research will be essential for the development of new drugs and to guide us to use the right drugs in the right patients in the right ways,” said Nagahiro Saijo, MD, PhD, CEO of the Japanese Society of Medical Oncology.

Dr. Saijo talked about his work in translational lung cancer research and began by discussing tumor immunology, including its history as well as studies of immunization in the 1970s that he had conducted. He also addressed the issue of T-cell activation, including PD-1/PD-L1 blockade in lung cancer, and commented on crucial translational issues that remain in immuno-oncology, such as whether killer T-cells actually exist (nobody has yet isolated them) and the fact that no one has been able to quantitatively demonstrate the killing of tumor cells in humans.

Dr. Saijo discussed studies he conducted on molecular mechanisms of cytotoxic drug sensitivity/resistance and their role as potential biomarkers, as well as drug discovery for molecular targets. He also described his studies on targeted therapies and pharmacogenetics, in particular the development of a nationwide genomic screening project (LC-Scrum-Japan) for precision medicine, incorporating both industry and academia.

Dr. Saijo is a founder and the first president of the Japanese Society of Medical Oncology (JSMO). He also served as IASLC President in 2007–2009 and was recognized in 2011 with the IASLC Paul A. Bunn, Jr. Scientific Award. He also received the prestigious European Society for Medical Oncology (ESMO) Lifetime Achievement Award in 2015.

A Look to the Future

Lawrence H. Einhorn, MD, of Indiana University, Indianapolis, US, provided an overall view of advances in lung cancer management from both past and future perspectives, including targeted treatment such as ALK inhibitors, and immunotherapy.

His predictions for the future included no development of new chemotherapy drugs, but continued research on antibody-drug conjugates, the development of a genomic assay for lung cancer (similar to the assays used in breast cancer) that will help determine which patients with node-positive disease will have a high chance of cure with surgery alone, and the development of a molecular signature to identify patients who need adjuvant therapy. Dr. Einhorn ended his talk with a description of the new CRISPR-Cas-9, a unique technology that enables editing of parts of the genome by removing, adding, or altering sections of the DNA sequence, and its potential applications in lung cancer.

Dr. Einhorn began changing the face of cancer treatment in 1974, when he added cisplatin, then an experimental drug, to the chemotherapy regimen for testicular cancer. With this advance, an almost universally fatal disease became curable. He is looking to do the same with lung cancer; he and his team of investigators are applying a personalized approach to platinum-based therapy that may potentially lead to a new standard of care.
SAVE THE DATE!
October 15–18, 2017 | Yokohama, Japan

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