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Tobacco Control Legislation in the Netherlands

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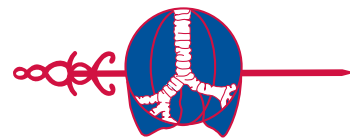
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LUNG CANCER IASLC NEWS

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

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PERSPECTIVE

Paul A. Bunn, Jr, MD: Recipient of 2016 Karnofsky Award

The David A. Karnofsky Memorial Award from the American Society of Clinical Oncology (ASCO) recognizes oncologists who have made outstanding contributions to the research, diagnosis, or treatment of cancer. Dr. Paul A. Bunn, Jr, Distinguished Professor, Division of Medical Oncology/University of Colorado, James Dudley Chair in Lung Cancer Research, is the 2016 Karnofsky Award recipient and was interviewed by IASLC Lung Cancer News. The following "perspective" constitutes an abridged summary of Dr. Bunn's reflections and comments:

Although the Karnofsky Award is given to individuals, cancer research is an inherently collaborative endeavor, one in which current progress is possible only due to the efforts of those who came before. Historically, representatives from the field of thoracic cancer research have been underrepresented as recipients of this award, and my selection can be seen

as a recognition that the sustained efforts of many individuals has led to important recent advances in lung cancer.

Efforts by members of the International Association for the Study of Lung Cancer Pathology and Staging Committees to improve the systematic pathology classification and the TNM IASLC staging of lung cancers have helped clinicians to choose the best treatments for each individual patient. Spiral computed tomography (CT) scans have reduced mortality by improving early detection, and the push by IASLC, government, and non-government agencies to reduce smoking rates has made a huge impact on reducing the incidence of lung cancer. Advances in radiation and surgery have improved cure rates with decreased mortality and morbidity. Molecular therapies, targeted therapies, and immunotherapies have helped improve the outcomes for advanced patients considerably.

Obviously, I am not responsible for all of these advances, and so I view this award as a tribute to all who have contributed to advances in prevention, early detection, pathology, staging, and treatment of lung cancer.

The history of systemic cancer treatments began after the end of World War II with the discovery that nitrogen mustard could be used to treat leukemias and lymphomas. In the 1950s, Sidney Farber showed that antifolates like methotrexate could be used to treat acute lymphoblastic leukemia. Subsequently, Drs. Emil "Tom" Frei III and Emil J. Freireich and others tested combinations of chemotherapeutic agents to try to cure leukemia, and Dr. Vincent DeVita and colleagues showed that combination chemotherapy could



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INTERNATIONAL REGIONAL INITIATIVES

Goals, Challenges, and Progress of Cancer Core Europe

By Prof. Fabien Calvo, MD, PhD

Today, cancer research is facing several challenges. The genomics era has ushered in a host of new molecular therapies; however, most of these targeted agents work for a limited subset of patients. Pooling data among centers, to analyze which sequences and combination of treatments perform best for which type of patient, is a powerful way to improve our understanding of the tumors and clinical decision-making. Furthermore, when only a few percent of patients qualify for a clinical trial, many patients must be seen. These are strong arguments for cancer centers to work together collectively.

In 2014, six centers decided to create Cancer Core Europe, and to fund a non-profit legal association taking research in cancer medicine into a new era. Six Comprehensive Cancer Centers in six different countries are founding members of this working consortium: Cambridge



Cancer Center in the UK, Karolinska Institutet in Sweden, Gustave Roussy Cancer Campus Grand Paris in France, the DKFZ and the National Center for Tumors in Heidelberg, Germany, the Netherlands Cancer Institute, NKI, in Amsterdam, and the Val d'Hebron Institute of Oncology, VHIO, in Barcelona, Spain. As a mix of both university hospitals backed by extensive basic and translational research programs and large, private cancer institutes with strong early clinical trials programs,

continued on page 2

MEETING PREVIEW

IASLC 17TH WORLD
CONFERENCE ON
LUNG CANCER

December 4-7, 2016
VIENNA, AUSTRIA

CONFERENCE PRESIDENT:
ROBERT PIRKER, MD



WCLC 2016 Together Against Lung Cancer

Dear Colleagues,

We are inviting you to take part in the IASLC 17th World Conference on Lung Cancer in Vienna, December 4-7, 2016. This Conference will be the first of the Annual Conferences, following the World Conference in Denver in 2015. We expect more than 6,000 participants from all parts of the world.

The members of the Program Committees are working closely with IASLC and ICS Events to develop a well-rounded, timely, and informative Conference Program. The motto "WCLC 2016 Together Against Lung Cancer" stresses the multidisciplinary nature of this World Conference. The Conference will be both an educational and scientific event. The three main topics are Active Prevention, Accurate Diagnosis and Advanced Care. Although lung cancer remains the leading cause of cancer worldwide, with more than 1.8 million newly diagnosed cases each year, we are currently experiencing many advances and innovations in the field of lung cancer research. This includes, but is not limited to, improved diagnosis through the WHO 2015

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From the Editor / Corey J. Langer, MD, FACP

Welcome to the second issue of *IASLC Lung Cancer News*.

In concert with the American Society of Clinical Oncology Meeting and in a tribute to his lifelong contributions to thoracic research, we have included a perspective by Dr. Paul A. Bunn, Jr, recipient of the 2016 Karnofsky Award, along with select previews of the meeting itself. We also highlight a number of relevant and timely topics with respect to low-dose computed tomography (LDCT) lung cancer screening. Drs. Gerard Silvestri and Denise Aberle, in separate, but related articles, discuss the clinical ramifications of the National Lung Cancer Screening Trial (NLST), which demonstrated a 20% decrease in lung cancer mortality in a high-risk population. They review the potential for extending these findings to other “at-risk” cohorts, the optimal timing of screening, and the “ideal” management of indeterminate nodules, which are observed in 1 in 4 subjects. Drs.

John Field, James Mulshine, and Fred R. Hirsch discuss the technical challenges to implementation of LDCT lung cancer early detection both in the US and potentially worldwide; and Drs. Brigit Toebes, Wanda de Kanter, and Willem Bantema reflect on recent changes in tobacco legislation in the Netherlands. In a complementary article, we include an interview with Dr. Laura Bierut on the genetics of tobacco addiction.

We also highlight the ongoing work of the Blueprint Project, led by Dr. Fred R. Hirsch and others, which will attempt to impose some degree of interchangeability and consistency on PD-L1 testing. Dr. Peter Ujhazy discusses the promise of the NCI Small Cell Lung Cancer Grants program in this orphan disease, and we feature a timely interview with Dr. Richard Pazdur on new parameters influencing FDA approval of cancer agents. We round out topical articles with an update on NCCN Guidelines



and the myriad changes made over the past 6–12 months. Finally, we include previews of the upcoming WCLC 2016, LALCA, APLCC meetings, as well as the Chicago Multidisciplinary Symposium in Thoracic Oncology.

We welcome feedback and article suggestions, particularly regarding events or controversies taking place outside North America. Ultimately, we seek to generate an interactive, easily accessible format that reflects the international nature of our society and its global influence.

Have a good summer! ♦

Corey J. Langer, MD, FACP
Professor of Medicine
University of Pennsylvania
Editor, *IASLC Lung Cancer News*

Cancer Core Europe from page 1

Cancer Core Europe is large enough to see significant numbers of patients, yet small enough to minimize administrative weight to work together effectively. Altogether 60,000 new patients are seen, 1 million outpatient visits are performed annually, and 300,000 treatments are delivered annually, and data from 1,500 ongoing clinical trials enriches joint research projects. Patients mainly have breast, lung, prostate, and colorectal tumors, but all cancer types and rare tumors are seen in large numbers in these reference centers. “Lung cancer still represents the most lethal form of cancer. To tackle this major health issue, collaborative approaches are key. Cancer Core Europe brings together different stakeholders with various strengths (clinical trial recruitment, science, imaging) to help address this issue,” says Prof. Jean-Charles Soria from Gustave Roussy.

Together, the increasingly complex molecular classification of cancers and the need for molecular/genomics information about patient tumors coupled with useful clinical data makes it nearly impossible for cancer centers to make meaningful research advances on their own—collaborative work like that being carried out by Cancer Core Europe is vital. Joint clinical trials are able to include more of the “right” patients with cancers matching the target in question. Combining various fields of expertise, Gustave Roussy (clinical trials, genomics, and immunotherapy), NCT-Heidelberg (genomics, imaging, bioinformatics, and data sharing), NKI-Amsterdam



(genomics, data sharing and immunology), Cambridge Cancer Centre (clinical imaging, clinical trials, and circulating free DNA genomics), Karolinska (genomics and proteomics), and VHIO (early-phase clinical trials, and genomics) bring the entire arsenal of research tools to bear on fighting cancer.

We believe the consortium will make great strides in these areas by working together, rather than individually. Cancer Core Europe’s principal aims focus on five areas. Clearly, joint early-phase clinical trials and data sharing are the cornerstones, and molecular diagnostics, immunotherapy, and imaging in the clinical setting complement the other two. Putting in place a data sharing platform is key; tumor genomic data, patient clinical and treatment outcomes information, as well as associated clinical images (PET, MRI, etc.) will be included. A common metadata repository with translations is the backbone to reference all of this rich data, allowing clinicians to make queries. The platform will be built in such a way that allows data owners to retain control of their data, and also respects data protection issues. We will offer robust and reproducible molecular diagnostics in all Cancer Core Europe

centers that have been cross-validated, starting with a common gene panel, but moving to include tumor exome, whole genome, and circulating free tumor DNA sequencing. This will be an important tool to implement for use in joint clinical trials. A standardized immuno-monitoring program will support clinical trials research, as will the development of better patient monitoring using innovative imaging modalities. Developing an advanced training program for junior MD-PhD researchers that involves the pharmaceutical industry is also underway.

Cancer Core Europe carries out innovative research to drive the development of new treatments and earlier diagnoses for patients and more effective cancer prevention for Europe’s citizens. Starting with a small core group will allow Cancer Core Europe to set up the needed infrastructure to support the integrated basic, translational, and clinical research that is carried out. Once the foundation is firmly established, more European cancer centers will be invited to join the consortium. “Europe has unique challenges due to different countries and local organizations, but our willingness to surmount these challenges also makes the collaboration all the more important for European cancer research,” says Prof. Alexander Eggermont, Chairman of the consortium. We hope that Europe will support collaborative efforts like these in the future, since it’s a very effective way to advance research in the era of personalized medicine. ♦



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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.

Karnofsky Award from page 1

cure Hodgkin disease and other lymphomas. Despite these improvements, however, the field of oncology lacked a biological rationale to direct research into new treatments.

In 1975, the National Cancer Institute (NCI) shifted its focus from relatively rare leukemias and lymphomas to solid tumors, which were much more common and did not respond well to traditional chemotherapy. Dr. John Minna headed up a new intramural branch of the NCI at the Veterans Administration Medical Center in Washington, DC, tasked with developing treatments for lung cancer. The research team he assembled for this research included Adi Gazdar, Daniel Ihde, Mary Matthews, Martin Cohen, and me. It was during this time that I came to appreciate what has become the guiding principle of my career; namely, that it is necessary to understand the biology of a disease in order to treat it.



Dr. Minna believed that the best way to understand the biological basis of cancer was to study tumor cells. Unfortunately, lung cancer cells cannot easily be removed from patients, so we began to systematically attempt to culture tumor cell lines from patients treated at the facility. These cell lines became the basis of the NCI human cell lines, and most were derived from lung cancer patients, although some came from other solid tumors as well. At that time, a few oncogenes were already known; however, it was soon discovered that most of these tumor-derived cell lines, especially those from small cell lung cancer, were missing pieces of chromosomes. This, in turn, led to the discovery of tumor suppressor genes such as p53 and Rb, which are located in those missing pieces of genetic material.

While these biologic studies were underway, clinical trials using chemotherapy demonstrated that many small cell lung cancer patients could be cured with a combination of chemotherapy and radiation therapy, and the combinations of agents could prolong survival in patients with advanced small cell lung cancer. The development of effective chemotherapy for non-small cell lung

cancers lagged behind the developments in small cell lung cancer, and platinum doublets had lower response rates. Nonetheless, these platinum doublets made small improvements in the cure rates in early stages and some survival benefits in advanced stages.

Our research into lung cancer cell lines also revealed that non-small cell lung cancer tumor cells frequently secreted epidermal growth factor (EGF) and overexpressed EGF receptors (EGFRs). This discovery led to a number of new treatments based on attacking either the growth factor or the receptor such as the monoclonal antibody cetuximab originally developed by Drs. John Mendelsohn and Gordon Sato; these were among the first targeted therapies. Originally, targeted therapies were given to all patients without testing for the presence of appropriate targets, which resulted in only 10% of all patients responding to these antibodies. Several studies indicated that assessment of EGFR expression by IHC or FISH might predict superior benefit in high expressing patients.

Studies from our SPORE in Colorado showed that overexpression of EGFR, squamous angiogenic dysplasia, and overexpression of PGE2 developed in the dysplastic bronchial epithelium during the early carcinogenic process. Prostacyclin overexpression could prevent lung cancer development in animal models. Serial assessment of dysplastic changes by bronchoscopy could identify changes that associate with chemoprevention in former smokers leading to the possibility of preventing lung cancers by smoking cessation and by chemoprevention.

Another form of anti-EGFR therapy was the discovery of small molecule tyrosine kinase inhibitors (TKIs) that could bind to the EGFR ATP binding pocket. Early studies showed dramatic response in patients who did respond; the magnitude of those responses was dramatic due to activating mutations in their *EGFRs* as demonstrated by Drs. Bruce E. Johnson, Thomas J. Lynch, and others in 2004. The finding that EGFR TKIs were most effective in *EGFR* mutant tumors and that such therapy was superior to initial chemotherapy inaugurated the molecular treatment era for lung cancer that has now been expanded to many other oncogenic drivers. Additionally, while these therapies do not cure patients, subsequent studies have identified many of the causes of resistance and novel second- and third-generation TKIs are providing additional benefit in these patients. This finding once again illustrates the importance of using the underlying biology, in this case the presence or absence of

EGFR mutations, to direct the appropriate course of treatment.

More recently, there have been successes in lung cancer treatment using inhibitors that target immune checkpoint proteins such as programmed cell death-1 (PD-1) and its ligand, PD-L1. These immunotherapies have been successful in producing extremely durable responses in some patients. Unlike molecular therapies, these immunotherapies may be able to produce complete responses (cures), though this remains to be seen. Like the molecular therapies, verifying the presence of the target, in this case PD-L1, improves the chances of getting a response, although better biomarkers are needed.

The push to find a cure for cancer has received renewed attention since President Obama called for a “National Cancer Moonshot” to eliminate cancer in his 2016 State of the Union Address. Many people are wondering if this effort can be successful, but that depends on

how you define success. If you would consider the Moonshot successful if it contributes additional resources that will move research forward and improve care for patients in the long term, then the effort will likely be successful. However, if you would only consider the Moonshot a success if it produces a cure for cancer by 2020, you might be disappointed.

It is a great honor for me to win the Karnofsky award, but obviously many fabulous investigators conducted the work required for these advances. I consider this award as honoring all those investigators and patient volunteers who have contributed to these improvements in lung cancer outcomes. ♦

☞ *The ILCN congratulates Dr. Bunn on his receipt of this prestigious honor. He has been a major leader in the field of thoracic oncology, a scientific visionary with a practical clinical background. His work has helped advance the field and has contributed to cures in thousands of individuals affected with lung cancer.*

—Corey J. Langer, MD, Editor

MEETING HIGHLIGHTS

IASLC and APLCC Present 7th IASLC Asia Pacific Lung Cancer Conference

By Nicola M. Parry, DVM

From May 13 to 15, 2016, the 7th International Association for the Study of Lung Cancer (IASLC) Asia Pacific Lung Cancer Conference (APLCC) took place at The Empress Convention Center in Chiang Mai, Thailand.

Held bi-annually, this conference is a collaborative effort between the IASLC and Asia-Pacific Oncologists with an interest in thoracic oncology. Combining the strengths of both organizations, the conference attracts a varied audience that comprises physicians and scientists in basic and clinical fields of thoracic oncology research. By bringing together this diverse group of professionals, the conference plays a key role in providing timely updates from Western and Asia-Pacific faculty members in the practical clinical management and multidisciplinary care of patients with thoracic malignancies, as well as in the results of basic and clinical research.

According to conference chairperson, Sumitra Thongprasert, MD, Chiang Mai University, Thailand, APLCC 2016 attracted “more than 800 healthcare professionals and key opinion leaders from the region and around the world.” Dr. Thongprasert emphasized that the meeting thereby aimed to foster sharing of knowledge



in the field of thoracic oncology, and ultimately advances the treatment of patients with lung cancer, in particular in Asia. She also added that the conference provided excellent opportunities for networking.

This year’s conference theme was “Optimizing Strategies for Cure in Lung Cancer.” During the 3-day program, experts in thoracic oncology presented updates on a variety of topics that address the scientific and educational needs of clinician attendees who care for patients with thoracic malignancies. The format included plenary sessions, oral and poster presentations, and industry-supported symposia—all designed to maximize learning and networking opportunities.

Throughout the conference, attendees shared updates on social media using the dedicated #APLCC2016 hashtag. Conference delegates were also encouraged to visit the exhibit hall where a range of commercial exhibitors exposed delegates to the latest technologies and therapies. ♦

LUNG CANCER SCREENING

Update on Low-Dose CT Lung Cancer Screening Implementation in the United States

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

Over the last fifteen years, the use of low-dose computed tomography (LDCT) for early lung cancer detection in high-risk individuals has moved from the seminal study arising from an NIH-funded R01 grant,¹ to the publication of the validation results of the National Lung Screening Trial (NLST),² to the endorsement of the United States Preventive Services Task Force.³ Now in mid-March 2016, the Center for Medicare and Medicaid (CMS) has announced the details of its reimbursement approach (Table 1) for annual LDCT for lung cancer screening (<https://www.medicare.gov/coverage/lung-cancer-screening.html>).

Given the previous pace of progress with early lung cancer screening, this represents a swift transition, but the foundation of research supporting this transition has been considerable in volume and international in scope. For example, the rate of Stage I detection reported by the I-ELCAP at 81% seemed remarkably high compared to the expected 15%, but subsequent reports from the NLST (63%), the Dutch/Belgian NELSON (73.7%) and now the UK pilot study (66.7%), have consistently confirmed that routine early stage detection of lung cancer can be realized.^{1,2,4,5} Concerns have been reported about challenges with high rates of unproductive diagnostic workup rates from 28% with NLST, but more recent reports of 12% with the NELSON study suggest more efficient approaches are possible. The new American College of Radiology LungRADs approach leverages the College's vast experience with breast cancer screening; when these criteria were applied retrospectively to the NLST cases, they were also able to achieve a low (12%) false-positive workup rate.^{6,7} Another recent report by I-ELCAP involved the re-analysis of archival data from the outcomes of over 20,000 subjects who had undergone screening and for which clinical outcome was known. In their retrospective analysis, the data suggested that nodules smaller than 7 mm could be followed with an LDCT one year later without sacrificing curability of screen-detected lung cancers.⁸

Fortunately, screening subjects demonstrate the ability to deal adaptively with the complex information inherent to the screening process. For participants in the NLST receiving a false-positive or a significant incidental finding with their screen result, they reported no significant difference in their health-related quality of life or anxiety outcomes at 1 or at 6 months after screening compared

to individuals with negative screening results.⁹

Additional efforts to ensure quality in implementing lung cancer screening services are being conducted by the lung cancer patient advocacy group, Lung Cancer Alliance (LCA), which established in 2012, the National Framework for Screening Excellence in the Continuum of Care. This is a consortium of medical centers adhering to responsible best practices for safe and effective lung cancer screening. Currently, 400 institutions have joined this national network and been designated by LCA as Screening Centers of Excellence. This consortium is demonstrating how lung cancer screening can be scalable and replicable in different care settings by following best-practice criteria. LCA convenes annual screening conferences and maintains regularized contact with the national network to ensure there is a forum to exchange timely information on policy, research, best practices, and lessons learned. This forum and furthering the national dialogue on the screening process is critical to ensure optimal dissemination of this new preventive service.¹⁰

Fortunately, research to further improve the screening process continues to emerge at a rapid pace. For example, 2 reports recently evaluated the use of computer-assisted diagnostic (CAD) software systems to analyze the CT data for the presence of potential lung cancers. Yankelevitz and co-workers used computer-assisted visualization of potential lung cancers in a test set of 50 lung cancers, which was then analyzed by 4 different CAD tools. For baseline cancer detection, the systems varied between 56% and 70% accuracy in detecting the nodules, which were on average 4.8 mm.¹¹ When comparable analysis was performed on scans acquired a year later, the systems ranged between 74% and 82% accuracy in detecting lung cancer in nodules that were on average 11.4 mm. Overall, the CAD systems detected 70% of lung cancers that were not initially detected by the radiologist, but failed to detect about 20% of the lung cancers when they were identified by the radiologist.¹¹ An earlier study from the Dutch/Belgian group also found that CAD performed well. An analysis of 400 low-dose chest CT examinations from the NELSON trial documented 78.1% sensitivity of nodule detection for double reading by radiologist and 96.7% for CAD tool analysis.¹² The conclusion based on these 2 studies is that CAD is

Table 1. Eligibility Requirements for Centers for Medicare and Medicaid Services Reimbursement of Annual, Low-Dose CT in Tobacco-exposed Individual.

Age 55–77.
They're asymptomatic (they don't have signs or symptoms of lung cancer).
They're either a current smoker or have quit smoking within the last 15 years.
They have a tobacco smoking history of at least 30 "pack-years" (an average of one pack a day for 30 years).
They get a written order from their physician or qualified non-physician practitioner.

From <https://www.medicare.gov/coverage/lung-cancer-screening.html>.



Figure 1. An interactive map to locate Screening Centers of Excellence can be found at www.lungcanceralliance.org/am-i-at-risk/where-should-i-be-screened/lung-cancer-screening-centers.

likely to emerge as an important tool in improving the accuracy of radiological detection of lung cancer in the screening setting, but additional research is needed to fully validate how integrating CAD into the screening process can be most beneficial.

Lung cancer screening is a complex process that involves a number of steps all of which could contribute to the success or failure of the screening process.¹³ This brief report only touches on a few examples. Clearly, comprehensive, ongoing analysis to ensure the quality, accessibility and consistency of the delivery of this service is essential. In addition to the National Framework, the American College of Radiology, the Quantitative Imaging Biomarker Alliance, and CMS are establishing approaches to address the various components of the screening process.^{6,14} As Canada and China are now considering nationwide implementation of screening, growing experience with this new service should enable continued optimization of the screening process.^{15,16} ♦

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LUNG CANCER SCREENING

A Practical Approach to the Evaluation of Pulmonary Nodules

By Gerard A. Silvestri, MD, MS, FCCP

A recent population-based study suggested the incidence of pulmonary nodules detected by CT is around 1.5 million per year. This finding is no surprise given the increasing use of chest CT for myriad of medical conditions and may increase even further as lung cancer screening is implemented nationally. The evaluation of pulmonary nodules is important because identifying malignant nodules should be performed as rapidly as possible while avoiding unnecessary and invasive testing for benign lesions. There are essentially 3 options for patients with pulmonary nodules, serial imaging, biopsy or PET scan, or surgical resection. The choice of the most appropriate option is based on the clinician's pretest probability that the nodule is malignant. For a calculated pretest probability of cancer

The evaluation of pulmonary nodules is important because identifying malignant nodules should be performed as rapidly as possible while avoiding unnecessary and invasive testing for benign lesions.

of less than 5%, serial imaging would be the preferred strategy. For nodules with a probability of cancer between 5% and 65%, PET scan or needle biopsy is indicated. Those with a high pretest probability of cancer (>65%) should be referred for surgical resection.

Several models are available for calculating the pretest probability of cancer in a pulmonary nodule. One model relies on 3 patient and 3 radiographic characteristics to stratify risk; where age, smoking history, and a history of extrathoracic malignancy are the patient factors, and edge characteristics of the nodule, upper lobe location, and size are the radiographic factors. Thus, an elderly smoker with a large, spiculated, upper lobe nodule has a much higher likelihood of cancer than a young, never smoking patient with a small, well circumscribed lower lobe nodule. McWilliams et al, extended this model to a population of patients with screen detected nodules. They confirmed the previous risk factors but also discovered patients with multiple pulmonary nodules are less likely to be diagnosed with cancer in the nodule in question. Other models incorporate PET findings when they are available. In addition, the findings of a completely calcified pulmonary nodule or the absence of growth over a 2-year period confirm benignity.

Once the pretest probability of cancer is calculated, clinicians should consider the advantages and disadvantages of each option. For nodules that have a low pretest probability of cancer, serial imaging for 2 years with chest CT is recommended. It has the advantage of being the least invasive option. Growth at any point during surveillance should lead to further testing with either biopsy or surgical resection. Both the American College of Chest Physicians (ACCP) and the Fleischner Society have provided guidance as to how often and for how long pulmonary nodules should be surveilled. In general, the larger the nodule or the higher the risk of cancer, the shorter the time interval between scans. The only downside of serial imaging is that a malignant nodule has the potential to grow between scans, though the penalty for missing tumor growth is unclear and must be weighed against invasive testing with its potential complications. For intermediate risk nodules, the choices are either PET scan or CT-guided transthoracic needle biopsy. PET scan has a relatively high sensitivity and specificity. However, both false positive and negative PET scans occur and clinicians should interpret the findings with caution. Focal pneumonia, granulomatous disease, among other entities can show uptake on PET and can cause clinicians to proceed with invasive testing when malignancy is not present. Conversely, false-negative PET scans occur, particularly in slow-growing malignancies such as adenocarcinoma in situ and carcinoid. In patients referred for surgery with a high pretest probability of cancer, a PET scan for staging the mediastinum and to search for metastatic disease is appropriate. Transthoracic needle aspiration can help avoid unnecessary surgery in cases where a benign diagnosis is considered. The accuracy is high. However, the trade-off is an associated 15% pneumothorax rate, with 6% of patients requiring chest tube drainage. If there is a high degree of suspicion for cancer, a needle biopsy is not warranted because a negative biopsy will not be trusted, and the patient will be referred for surgery anyway.

While all three diagnostic approaches are valid in differing scenarios, patient preferences should be incorporated into the final decision. For example, a patient with low probability of cancer may insist the lesion be removed because of the anxiety associated with waiting between interval scans with the possibility that a cancer is growing.

In summary, a clinician's suspicion of the probability that a nodule is cancer guides all further testing. As the probability of malignancy rises, the need for invasive testing increases. Future work is likely to incorporate radiographic volumetric measurements of the nodule to assess growth between serial images and biomarker assessment (either bronchoscopic or blood) that will help differentiate benignity from malignancy by less invasive means. ♦

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EVOLVING STANDARDS OF CARE

"PD-L1 IHC Blueprint Project" Presented at the AACR Annual Meeting 2016

By Erik J. MacLaren, PhD

Immunotherapy with anti-PD-L1/PD-1 antibodies is rapidly changing the therapeutic landscape for patients with non-small cell lung cancer (NSCLC). However, selecting the most optimal patient population for those treatments remains a challenge. All pharmaceutical companies with a therapeutic antibody are pursuing a PD-L1 immunohistochemistry (IHC) assay either as a "companion" diagnostic or as a "complementary" diagnostic test. The challenge for the community is that each company pursues a unique assay for each drug, leading to several different PD-L1 IHC assays on the market for the same group of drugs. To better understand the different PD-L1 IHC assays and how they compare to each other, four different pharmaceutical companies (e.g., BMS, Merck, AstraZeneca, and Genentech/Roche), two diagnostic companies (e.g., DAKO/Agilent and Ventana/Roche) and two academic organizations: the International Association for the Study of Lung Cancer (IASLC) and the American Association for Cancer Research (AACR), established the "PD-L1 IHC Blueprint Project," which aims to compare the four "distinct" PD-L1 IHC assays used in association with the drugs; Nivolumab (BMS), Pembrolizumab (Merck), Durvalumab (AstraZeneca), and Atezolizumab (Genentech/Roche). The early results of this effort (feasibility component) were presented by Fred R. Hirsch, MD, PhD, University of Colorado and CEO of IASLC Hirsch FR et al: The PD-L1 IHC Blueprint Project, AACR 2016).

Observations from the "PD-L1 IHC Blueprint Project" demonstrated analytical similarities and differences between the four assays; while three assays (e.g., clones 22C3, 28-8, and SP 263) were quite similar in PD-L1 expression, one assay (e.g., SP 142) was different. However, when clinical diagnostic paradigms were compared, the study demonstrated salient differences, which could lead to erroneous classification of PD-L1 status when related to the different agents under investigation. Thus, the consortium recommended that until more scientific data are gathered, each assay should be applied as recommended to its specific drug, and "mixing and matching" of assays might lead to erroneous classification of the patient tumor's PD-L1 status.

A phase II of the PD-L1 IHC Blueprint Project is being planned as a validation study; this will include a much larger series of NSCLC tumors. ♦

MEETING PREVIEW

2016 ASCO Annual Meeting

By Erik J. MacLaren, PhD

This year's annual meeting of the American Society of Clinical Oncology (ASCO) is taking place June 3–7 in Chicago. The theme of the meeting this year is **Collective Wisdom: The Future of Patient-Centered Care and Research**, which helps to stress the need for collaborative efforts across disciplines to advance the field of oncology. More than 5,200 abstracts have been accepted for the 5-day program, and the 7 sessions previewed here are of particular interest to the thoracic cancer community.

Kicking off Friday afternoon, Julie R. Brahmer, MD, from the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, Maryland, will be participating in a meet-the-professor session titled "Prescribing and Managing Immunotherapy." Dr. Brahmer is an international leader in the field of immunotherapy for lung cancer and is known for her work on nivolumab, among other contributions to the field. Her presentation will focus on identifying and managing side effects in patients treated with immunotherapeutic agents.

On the morning of Saturday, June 4, Graham Warren, MD, PhD, from the Medical University of South Carolina in Charleston, South Carolina, will speak at the education session "Lung Cancer Screening and Prevention." Dr. Warren investigates the clinical effects of tobacco on the biology of cancer cells and cancer treatment outcomes, and his presentation will urge clinicians to promote smoking cessation in patients with cancer. "The most important take-home from my session will be that addressing tobacco use prior to, during, and following a cancer diagnosis is critical," said Dr. Warren. "There are very clear relationships between smoking and adverse cancer treatment outcomes, and providing evidence-based cessation support for all cancer patients who use tobacco will allow us to realize the clinical benefits of cessation both in our screening populations as well as in our patients undergoing cancer treatment."

Monday has a trio of lung cancer-relevant presentations, beginning with "What's Next in Cancer Immunotherapy?" an education session on Monday morning that will focus on the current status of immunotherapy trials, as well as targets and biomarkers in development. "Immunotherapy holds a lot of potential for improving outcomes in difficult-to-treat thoracic cancers," according to Charles M. Rudin, MD, PhD, from the Memorial Sloan Kettering Cancer Center

in New York City, who is not presenting at the session, but spoke to IASLC about the topic. Dr. Rudin is excited by the progress in immunotherapies, especially their potential to treat small cell lung cancer (SCLC). "SCLC is often remarkably responsive to initial chemotherapy, but upon recurrence is really quite resistant," he said. "Immunotherapies are likely to have a central role in the treatment of SCLC, and there are already exciting emerging data with combination PD-1 and CTLA-4 directed therapy." Looking to the future of treatment in SCLC, Dr. Rudin predicts immunotherapies—with a twist. "The immune microenvironment of small cell is different from other solid tumors, and there may be alternative immune regulators, beyond PD-1 and CTLA-4, that may be of particular relevance for SCLC."



Minimally invasive surgeries are reducing recovery times and morbidities for patients with stage I NSCLC, and the rapid adoption of SBRT in place of conventionally fractionated radiotherapy is increasing overall survival for our early stage patients.

—Charles B. Simone, II, MD



The meet-the-professor session "Stereotactic Body Radiation Therapy or Surgery for Early-Stage Non-Small Cell Lung Cancer" is also scheduled for the morning of June 6. The speakers will discuss and compare the current uses of SBRT and surgery in patients, as well as optimal adjuvant therapy for these treatments. *IASLC Lung Cancer News* spoke about this session with Charles B. Simone, II, MD, from the Perelman School of Medicine at the University of Pennsylvania in Philadelphia. Although he is not presenting himself, Dr. Simone, who investigates the use of SBRT in medically operable and medically inoperable patients with stage I NSCLC, expressed his enthusiasm for the subject. "With numerous trials comparing the two modalities now open or about to open, including the SABRTooTH trial (United Kingdom), POSTLIV trial (China), STABLEMATES trial (United States), and VALOR trial (Veterans Administration Hospitals), the debate on surgery vs SBRT for stage I NSCLC is only beginning, and

the upcoming session at ASCO on SBRT and surgery will be of great interest to all providers caring for patients with lung cancer," he said. "Minimally invasive surgeries are reducing recovery times and morbidities for patients with stage I NSCLC, and the rapid adoption of SBRT in place of conventionally fractionated radiotherapy is increasing overall survival for our early stage patients."

Monday afternoon, Jessica S. Donington, MD, of the New York University School of Medicine will join two other speakers in the education session "Local Therapies in the Management of Oligometastatic and Metastatic Non-Small Cell Lung Cancer." Dr. Donington, a thoracic surgeon, will discuss the indications for surgical intervention in NSCLC.

On the final day of ASCO 2016, the education session "Small Cell Lung

and will cover promising complementary avenues of immunotherapy that have the potential to make an impact in non-responders," he said. While Dr. Moon anticipates progress in using biomarkers to guide anti-PD-1 therapy, he also predicts new breakthroughs on the horizon for NSCLC including, "...the idea of personalized immunotherapy, or analyzing tumor infiltrating lymphocytes to determine which combination of checkpoint antibodies should be used to treat an individual patient." ♦

WCLC 2016 from page 1

Classification of Lung Cancer, the upcoming 8th TNM classification, characterization of clinically relevant molecular markers, and liquid biopsies. Therapeutic advances include novel targeted therapies, predictive biomarkers for guiding therapies, immune checkpoint inhibitors, new, more effective, multimodality treatments, novel developments in surgery, and novel approaches in radio-oncology. Overall, the Program will provide an excellent opportunity to update medical and scientific knowledge, to create new ideas for patient care and scientific research, and to initiate and strengthen co-operation.

Vienna is an excellent destination for the 17th WCLC. Vienna is among the top conference cities in the world and offers the full infrastructure required for big conferences including hotels of different categories, a modern conference center, excellent public transportation, and safety. Vienna can easily be reached by air from all parts of the world as well as by rail or car from many European countries. The rich cultural heritage and the modernity of Vienna as well as its special atmosphere during December will contribute to making WCLC 2016 a memorable event.

We are looking forward to welcoming you for the 17th WCLC in Vienna. ♦

Sincerely yours,

Robert Pirker, MD

Congress President

on behalf of IASLC, the Regional Organizing and the Program Committees



Small Cell Lung Cancer: The Next Challenge

By Peter Ujhazy, MD, PhD

The newfound optimism in the management of lung cancer that infused the research, clinical, and patient communities

12 years ago is still gaining momentum. Seminal findings on the predictive value of epidermal growth factor receptor mutations^{1,2} were followed by discoveries of other therapeutic targets (ALK, ROS1, BRAF, etc.) and by the development of clinically applicable agents. These ultimately resulted in significant increases in the overall survival for thousands of patients. More recently, breakthroughs in our understanding of the immune responses to cancer have led to interventions using checkpoint inhibitors that, at least in some patients, have secured long-term remissions. Combinations of these approaches with chemo- and radiation therapy should slowly but steadily improve the 5-year survival rates of our patients. The beneficiaries of these milestones are mostly patients diagnosed with non-small cell lung cancer.

Another Wave of Optimism: Small Cell Lung Cancer

Today, we are witnessing another wave of optimism, this time regarding the “orphan” in the family of lung cancers: small cell lung cancer (SCLC). A major clinical challenge for many decades, SCLC is finally receiving the attention it deserves. Reasons for the slow progress in SCLC research are many: short lifespan of patients after diagnosis; limited access to specimens leading to (still) limited genomic, epigenomic, proteomic, and metabolomics data; incomplete information on the biology of premalignant lesions and the disease itself; and the mysterious development of irreversible treatment resistance after a remarkably successful short-term response

to first-line chemotherapy. However, during the last 5 years several landmarks were achieved in the genomic and proteomic characterization of the disease.³ New precision medicine interventions such as targeting the DLL3 protein⁴ or immunotherapy with checkpoint inhibitors⁵ have opened the doors to a new era in the management of SCLC.

Strategic Opportunities in SCLC Research

In 2013, the US Congress through the Recalcitrant Cancer Research Bill mandated the NCI to develop a scientific framework to conduct and support research on SCLC. That same year, the NCI, then under the leadership of its director and a lung cancer scientist Dr. Harold Varmus, held a workshop with national and international experts to establish the major strategic opportunities in SCLC research. They were summarized in the following five points:

1. Creation of Better Research Tools for the Study of SCLC
2. Comprehensive Genomic Profiling
3. New Diagnostic Approaches
4. Therapeutic Development Efforts
5. Mechanisms Underlying Both High Rate of Initial Response and Rapid Emergence of Drug and Radiation Resistance

Scientific Framework for SCLC

The NCI followed with a Scientific Framework for SCLC report⁶ that delineates the implementation of programs targeting these five points. The IASLC played a critical role in these efforts by organizing a follow-up meeting in spring of 2015, in collaboration with the NCI, with the participation of 200 world experts in the disease. Finally, last year, the NCI released a series of three Program Announcements soliciting proposals in SCLC research addressing all five areas (PAR-16-049, PAR-16-050, and PAR-16-051).

The intent is to create an NCI SCLC Consortium with multiple projects focused on early detection, prevention, and treatment. There will be a coordinating center that will serve as the hub for biospecimen collection, virtual tissue banking, model development and distribution, biostatistical analysis, bioinformatics including genomic, proteomic, and metabolomics databases, and administration. The Consortium will take advantage of NCI resources including the collection of oncology agents, various research models such as patient-derived xenografts, DNA/RNA pellets, but also semantic services, metadata, and terminology support.

The Program Announcements are currently open for applications, and the first round signals a strong national and international interest in SCLC projects. The NCI will continue in its fruitful collaboration with the IASLC to organize biennial meetings in the rapidly evolving field of SCLC research.

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POINTS OF CONTROVERSY

What Have We Learned from the National Lung Screening Trial?

By Denise R. Aberle, MD

The seminal National Lung Screening Trial (NLST) showed that lung cancer screening using low dose computed tomography (LDCT) resulted in a 20% decrease in lung cancer mortality relative to chest radiography in older, heavy smokers. Additionally, there was a relative 6.7% decrease in all-cause mortality (due largely to improved lung cancer mortality), suggesting that LDCT screening did not significantly precipitate downstream mortality or that patients spared a lung cancer death did not die of comorbidities.

Cancer Network (NCCN) recommendations allow for younger smokers of lesser smoking intensity provided that they have at least one additional risk factor, such as family history of lung cancer, certain other cancers, underlying chronic obstructive pulmonary disease, or documented exposure to respiratory carcinogens⁷; limited studies in cohorts satisfying these criteria suggest that lung cancer rates are comparable to that of those enrolled on the NLST.⁸ Finally, models of lung cancer risk have been developed

frequency and duration of screening, for which there are insufficient data. Annual screening was performed for 3 years in the NLST, and microsimulation models comparing annual, biennial, and triennial intervals have concluded that annual screening is most efficient. However, retrospective analyses suggest that in some low risk groups, such as those with negative baseline screens or repeat normal screens, annual screening may not be necessary.¹⁵ Nor are there any data regarding screening beyond 3 years. Answers to these questions may be attainable with long-term follow-up of cohorts of varying risk.

The NLST has changed public policy on lung cancer screening and provides for the early detection of lung cancer to reduce lung cancer mortality. Initial implementation in the US is largely patterned after the original NLST eligibility criteria. The current mandate for data submission to a national registry provides us with a critical opportunity to initially extend eligibility criteria to better define the risk profiles of the

optimal screening cohort. The collection of outcomes data should also yield insights into diagnostic management in the setting of screen-detected nodules as well as the frequency and duration of screening. At a minimum, we have a road map to refine screening practice and incorporate new ideas as they emerge. ♦

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continued on page 10

“ The reduction of screening false positivity, which is among the greatest concerns with screening implementation, will require better definitions of screen positivity and strategies to map escalating management to degree of suspicion of the detected nodule. ”

ties. These mortality reductions came at the cost of an overall 24% CT screen positivity rate, of which 96.4% were false positive results.¹ Based on the NLST, CT screening for lung cancer is now a covered benefit in the United States by both third-party payers and Medicare, with the caveat that reimbursement is tied to submitting data on eligibility, screening, and outcomes to a central registry.^{2,3}

The NLST enrolled individuals aged 55–74 years with a ≥ 30 pack-year current or former smoking history; for former smokers ≤ 15 years must have elapsed from the time they quit (YSQ). Both the United States Preventive Services Task Force (USPSTF), which determines policy for coverage by third-party payers, and the Centers for Medicare and Medicaid Services (CMS) currently base screening eligibility on the NLST, with each slightly extending the upper age limit of eligibility. However, the wisdom of constraining both pack-years of smoking and YSQ has been challenged,^{4,5} based upon data from SEER (Surveillance, Epidemiology and End Results) that indicate that only 26.7% of individuals with lung cancer would satisfy NLST eligibility criteria.⁶ Indeed, Pinsky found that current smokers with 20-29 pack-years had similar lung cancer risk to LDCT-eligible former smokers⁵; those with less smoking intensity were disproportionately women and racial/ethnic minorities. Several lines of evidence indicate that our current rule-based eligibility based on only age and smoking criteria are insufficient to identify the majority of individuals who get lung cancer. The National Comprehensive

that improve on the NLST criteria; some expert groups suggest that risk prediction models are best suited to identify screening cohorts.^{9,10} By systematically extending eligibility criteria and capturing outcomes through national screening registries, we can ultimately improve lung cancer mortality and extend these benefits to a greater population who will be diagnosed with lung cancer.

The reduction of screening false positivity, which is among the greatest concerns with screening implementation, will require better definitions of screen positivity and strategies to map escalating management to degree of suspicion of the detected nodule. Following the NLST, in which small nodules 4–6 mm accounted for roughly half of positive screens, but less than 1% of lung cancers, the American College of Radiology established CT screening guidelines called LungRADS™.¹¹ This guideline predicates management on nodule size, consistency, and changes over time, and has been shown in retrospective and limited prospective studies to increase the positive predictive value of a positive screen and reduce medical resource utilization at the likely expense of missed or delays in diagnosis of lung cancer.^{12,13} Mathematical models have been developed that may provide greater classification performance than rule-based approaches for indeterminate nodules, but our experience with diagnostic prediction models in the setting of the indeterminate nodule remains early.¹⁴

Additional unanswered questions with implementation are the optimal

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SMOKING CESSATION AND TOBACCO CONTROL

Q&A with Dr. Laura Bierut

Tobacco smoking dramatically increases the risk of developing lung cancers, and it has long been recognized that nicotine addiction is one of the biggest obstacles to changing current smokers' behavior. *IASLC Lung Cancer News* recently spoke with Laura Jean Bierut, MD, Professor of Psychiatry, from the Washington University School of Medicine in St. Louis, Missouri, about the link between smoking and genetics, the success of current anti-smoking policies, and how e-cigarettes might impact smoking in the coming years.

Q: Is there a heritable, genetic component to either tobacco addiction or lung cancer?

A: Yes, there is no doubt that genetic variation in the population affects both smoking behaviors and the development of lung cancer. Genetic studies have identified variants with the strongest influence on the risk of developing lung cancer or COPD in a region of Chromosome 15, and these are precisely the same variants that have been identified as influencing smoking behaviors. The variant that we know the most about is a single nucleotide polymorphism called "rs16969968," and it causes an amino acid change in the alpha-5 nicotinic receptor [CHRNA5]. This variant actually alters the conductance of the receptor in the cell, which is an elegant real-world demonstration of pharmacogenetics. There are other genetic risk variants in other regions of the genome, too, and all of these fall in chromosomal regions containing nicotinic receptors and enzymes involved in nicotine metabolism.

Q: Does the rs16969968 variant have any implications for smoking prevention or cessation strategies?

A: This variant plays essentially no role in whether an individual initiates smoking or not, which is strongly driven by environmental factors. However, if a person with the high-risk allele does begin smoking, they will smoke a higher number of cigarettes per day, have a higher intensity of smoking, and have a higher age of smoking cessation than those with the low-risk variant, increasing their risk for lung cancer.

The problem with smoking cessation pharmacotherapy using nicotine replace-

ment therapy is that it works modestly, at best, and the vast majority of smoking cessation is done without any medication. However, data suggest that people with the high-risk variant rs16969968 have the greatest difficulty quitting and stand to benefit the most from medication, although the evidence is still controversial. This makes sense since this variant affects nicotine receptor function. Improved implementation of pharmacotherapy, using patients' genetics as a guide, could have a huge public health impact.

Q: What other interventions, aside from smoking cessation programs, work best for preventing or curtailing tobacco addiction?

A: Policies like age restrictions for purchasing tobacco, increased taxation, and indoor smoking bans have made a tremendous impact already. Even in places where taxation and clean air policies have not decreased overall smoking rates, they have reduced the amount of cigarettes people smoke because of the increased cost of tobacco products and the decreased opportunities to smoke during the day. This is one of the great public health successes in the US. If you plot per capita cigarette consumption in the US and lung cancer rates on the same graph, you can see the clear relationship between declining smoking rates and reduced incidence of cancer (Figure 1).

Internationally, the US has historically been at the forefront of tougher anti-smoking legislation, and the public health benefits have been observed here first.

Europe has implemented similar policies and is catching up in terms of reduced smoking rates and cancer incidence, if they have not already overtaken us. China is on the other end of the spectrum. It has a state-owned tobacco industry, which has hindered the implementation of anti-smoking public policies, so smoking rates remain high, and the incidence of tobacco-related cancers is on the rise.

Q: Over the last several years, new smoking substitutes have been introduced to the market like electronic cigarettes [also known as e-cigarettes or electronic nicotine delivery systems]. How will these technologies affect the rates of smoking and lung cancer going forward?

A: E-cigarettes have only been out for about 10 years, so we don't know the answer to this question yet. It is a fact that combustible cigarette smoking is at its lowest rate ever among high school students, which is great. However, the rate of e-cigarette use is increasing among this same age group and has already surpassed that of combustible cigarette use. While the health risks of e-cigarettes are far less than those of combustible cigarettes, we cannot say that they are risk-free. The critical issue is whether or not those using e-cigarettes now will eventually progress to using combustibles. ♦

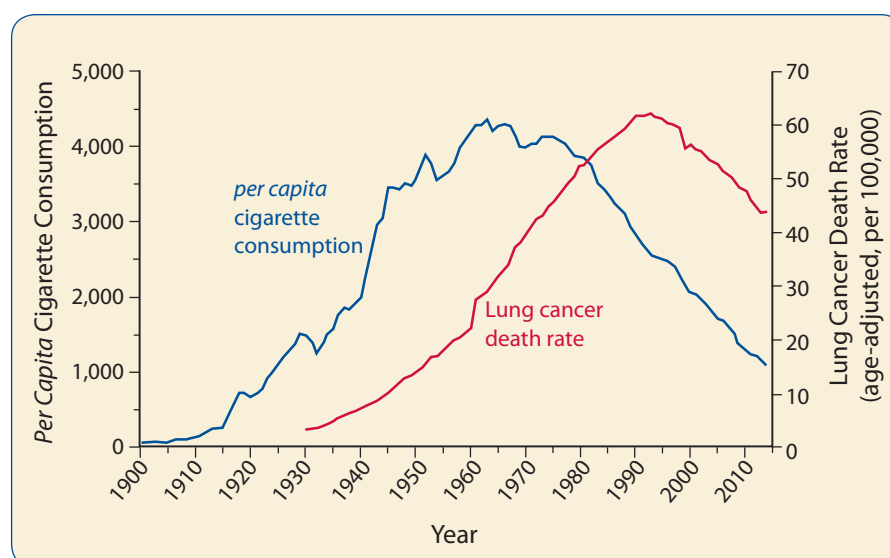


Figure 1. US Cigarette Use vs. Lung Cancer Deaths, 1900–2014. Death rate sources: Public-use data files, National Vital Statistics System, National Center for Health Statistics, Centers for Disease Control and Prevention; and Jemal et al., *CA Cancer J Clin*, 2010. Cigarette consumption sources: Tobacco Outlook Report, Economic Research Service, US Department of Agriculture; and Alcohol and Tobacco Trade and Tax Bureau, US Department of Treasury.

2016–2017 LUNG CANCER MEETINGS CALENDAR

2016

JUNE

American Society of Clinical Oncology (ASCO)
June 3–7
Chicago, IL, US

AUGUST

17th Annual International Lung Cancer Congress
August 4–6
Huntington Beach, CA, US

Latin American Lung Cancer Conference (LALCA)
August 25–27
Panama City, Panama

SEPTEMBER

IASLC Chicago Multidisciplinary Symposium in Thoracic Oncology
September 22–24
Chicago, IL, US

OCTOBER

ESMO 2016 Congress
October 7–11
Copenhagen, Denmark

DECEMBER

World Conference on Lung Cancer
December 4–7
Vienna, Austria

2017

JANUARY

Best of WCLC, Seoul
January 16
Seoul, South Korea

FEBRUARY

IASLC 17th Annual Targeted Therapies of Lung Cancer Meeting
February 22–25
Santa Monica, CA, US

MAY

IASLC and ESMO Present
7th European Lung Cancer Conference
May 5–8
Geneva, Switzerland

INTERVIEW WITH RICHARD PAZDUR, MD / BY ERIK J. MACLAREN, PHD


New oncology drugs have, for decades, followed a well-trodden path of sequential clinical trials to get from the laboratory to the patient. This model has proven its worth by delivering effective new treatments while also protecting patient safety, but newer “seamless” trial designs have the potential to modernize the drug testing process and allow patients to access promising new treatments more quickly. Richard Pazdur, MD, who has been the FDA’s Director of the Office of Hematology and Oncology Products since 2005, recently co-authored an article in the *New England Journal of Medicine*¹

discussing the main issues surrounding seamless drug development. *IASLC Lung Cancer News* spoke with Dr. Pazdur about how this new model will affect oncology drug development programs moving forward.

Q: Can you explain what are the most significant differences between conventional sequential trial designs used in the development of anticancer drugs versus the newer seamless approach used for drugs like pembrolizumab?

A: The primary difference is that seamless drug trials are intended to obtain information on drug dosing, activity, and efficacy in one trial and avoid the delays of conducting separate phase 1, phase 2, and phase 3 trials. Seamless design allows greater fluidity and flexibility in the clinical trial, and it eliminates some of the administrative burden on the part of the sponsor and participating institution. It is a much more fluid approach that allows expansion cohorts to be added after the early dose-finding phase of the trial to, for example, investigate activity in different diseases or to start examining various biomarkers to define which populations are most likely to respond to the drug.

Q: What changes in the drug development field have prompted the emergence of the seamless trial design in drug development now?

A: I think the reason why it is happening now is that the drugs are better, and there is also an urgency to get these drugs developed rapidly and get them on the market as expeditiously as possible. We have a better scientific rationale for the drugs that are being developed, and we are seeing activity much earlier than before, in phase 1 studies or the phase 1 components of these seamless trials. This creates an incentive to avoid the “start-stop” process of sequential trials and move toward a more fluid development process in which different disease cohorts can be added as the trial proceeds. The bottom line is that the drugs have gotten better.

Q: What are some of the disadvantages of the seamless trial design?

A: Well, as we emphasized in the NEJM article, one of the things that we really want to make sure of is that we do not lose patient protections that are afforded by the traditional phase 1, phase 2, phase 3 design. Specifically, we want to

make sure that patients are adequately informed, that there are revisions to the informed consent, and that there are more interactions between the investigators, the institutional review boards (IRBs), and the FDA. This will require a more open dialogue and more frequent communications on the part of the regulators, the IRBs, and the investigators. It will require more meetings; whether those are conducted in person or in teleconferences will depend on the specific situation, but there is going to be a need for greater communication. There are also unique issues that need to be addressed for seamless trials. Namely, there should be an adequate statistical plan for cohorts being added, including the number of patients to be added, and predefined measures of success and failure. We think these issues can be addressed with careful planning.

Q: Besides progression-free survival and overall survival, what other endpoints should be taken into account with respect to new drug approval?

A: One of the things we are looking at is response rate, obviously. Many times sponsors are coming in with single-arm trials from these expansion cohorts. They are not randomized populations, and response rate is the primary endpoint we look at in these situations. It is an endpoint we commonly see submitted to the agency for approval, especially for some “breakthrough therapy” drugs.

Q: Do regulators, researchers, and trial sponsors have any additional or different responsibilities when participating in seamless, rather than sequential trials?

A: Yes, and again, the key is greater openness and communication on the parts of the investigators, the IRBs, and the regulators. The FDA will also need to modify the format of its oversight teams, which have traditionally been disease-specific. Seamless trials may involve cohorts for several diseases, such as melanoma, sarcoma, lung cancer, breast cancer, all in one trial, so we may have to do some reorganizing of our staff for a specific protocol.

Q: Is there anything else you would like to share with our readers about seamless drug development?

A: I think this model provides an excellent springboard for studying populations that have been excluded from traditional trials, particularly pediatric patients. I’m very interested in highlighting pediatric populations as a possibility for expansion cohorts to investigators, especially after the adult dose has been established. One could also expand to cohorts in renally or hepatically impaired patients. I think that we are just at the beginning of how to look at these trials and use them more effectively in the broader picture of drug development. So far, seamless trials have been confined to the development of anticancer drugs, but I cannot see any reason why this could not be expanded to other diseases outside of oncology as well.

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MEETING PREVIEWS

7th IASLC Latin American Conference on Lung Cancer

By Nicola M. Parry, DVM

From August 25 to 27, 2016, the 7th International Association for the Study of Lung Cancer (IASLC) Latin American Lung Cancer Conference will take place in Panama City, Panama.

According to conference chairpersons, Edgardo S. Santos, MD, FACP, Lynn Cancer Institute, Boca Raton, Florida, and Roberto Iván López, MD, Hospital Punta Pacifica, Panama City, Panama, this annual conference attracts a varied audience that includes surgical oncologists, pulmonologists, radiation oncologists, medical oncologists, pathologists, radiologists, and affiliated healthcare professionals.

During this year's 3-day program, international and national experts will discuss the latest developments in basic and translational research, molecular diagnosis and prognostic factors, early diagnosis, targeted and individualized therapies, and surgical and clinical management of lung cancer in Latin America and worldwide. Although the official language of the conference is English, all sessions will be simultaneously translated into English and Spanish.

Dr. Santos notes that the IASLC School of Thoracic Oncology is a new event that will take place in conjunction with this year's meeting. This intense, 1-day workshop is aimed at physicians in training, junior investigators, or faculty physicians, and will be held on Wednesday, August 24, before the conference begins. During the workshop, experts will discuss topics related to lung cancer, including pathology, radiation oncology, pulmonology, surgery, biostatistics, and medical oncology.

2016 Multidisciplinary Symposium in Thoracic Oncology

By Jyoti Patel, Heather Wakelee, Everett Vokes, and Fred R. Hirsch

Please join us for the 2016 Multidisciplinary Symposium in Thoracic Oncology to be held Sept 22–24, 2016, at the Chicago Marriott Downtown Magnificent Mile, co-sponsored by IASLC and the University of Chicago. This dynamic conference will lead off with keynote speaker Julie Brahmer discussing immunotherapy in lung cancer, and will focus on the science of tumor immunology and perspectives on the future of immuno-oncology. Additional speakers will provide updates on recent meetings and the state of the art in treatment of thoracic malignancies from surgical, pulmonary medicine, radiation oncology, and medical oncology perspectives. We expect to highlight exciting new presentations; abstract submissions are currently open until August 1. We are particularly soliciting submissions focused on tobacco control, EGFR/ALK resistance, biomarker based surgical decision making, improvements in targeted radiation strategies, and outcomes/QoL/health services. A special session will provide an opportunity for junior investigators with high quality work in these areas to present their data with commentary by internationally known experts. We will also continue the exciting tradition of a multidisciplinary tumor board as well as debates on controversial topics. This conference is targeted to medical oncologists, pulmonologists, surgeons, and radiation oncologists in both academics and community practice, as well as basic scientists and advocates with an interest in thoracic oncology. We hope to see you in Chicago in September. ♦

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On Thursday, August 25, 2016, the conference will host a Young Investigators' Session, and will once again support the Framework Convention for Tobacco

Control, by hosting a half-day Tobacco Forum involving leaders from the tobacco industry, as well as legislators and government officials. For the first time, this forum will also include patients and family members. "It is our responsibility to listen to and understand the needs of the patients affected with lung cancer," said Dr. Santos.

The scientific program over the next 2 days includes plenary sessions, oral and poster presentations, roundtable discussions, and industry-supported symposia. According to Dr. Santos, "Immunotherapy and liquid biopsy, and how to utilize novel technology will be among the hottest topics this year, as well as targeted therapy." He also noted that key opinion leaders from Latin America and the United States will share

emerging data from innovative clinical trials in non-small cell lung cancer.

More than 600 delegates from Latin America are expected to attend this year's conference, along with a wide range of commercial exhibitors. Each morning and afternoon, light refreshments will be provided in the Exhibit Hall during networking breaks. These breaks provide opportunities for delegates to view the posters and to mingle with colleagues, exhibitors, and sponsors.

Drs. Santos and López encourage all healthcare professionals with an interest in thoracic malignancies to attend this conference, to help bring more hope to lung cancer patients, to increase access to novel therapies in Latin America, and to be unified in a mission to "make lung cancer a chronic disease." ♦

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SMOKING CESSATION AND TOBACCO CONTROL

Tobacco Control Legislation in the Netherlands

By Prof. Brigit Toebes, PhD, and Willem Bantema, MSc, in collaboration with Wanda de Kanter, MD

Critics have warned that Dutch legislation and policy increasingly lag behind that of other countries when it comes to regulating tobacco. There have been criticisms on multiple fronts, including the lack of a firm smoking ban in all (public and/or private) spaces, the absence of warning labels with pictures and/or plain packaging on tobacco products, limited taxes on tobacco products, lack of display bans, reduction of sale points, and the absence of a comprehensive tobacco control campaign. Arguably, the current position is caused by the emphasis that Dutch society tends to place on autonomy and individual freedom.

Historical Overview of Legislation, Regulation, and Policy

The Dutch Tobacco Act, first adopted in 1988, prohibits smoking in all public buildings and in public transport. In 2004, the scope of the law was widened to include non-hospitality workplaces, except in separately ventilated areas not serviced by employees. More recently, in July 2008, the law was again expanded, rendering shopping malls, tobacco shops, gaming establishments, and convention centers smoke-free. The 2008 amendment also covers restaurants, cafés, bars, festival tents, and nightclubs, except in separately ventilated areas that are not serviced. Employees may only be required to enter such smoking rooms in emergency situations.

The Netherlands joined the Framework Convention on Tobacco Control (FCTC) on 27 January 2005.

In 2014, a substantial increase in excise duties was introduced, directly affecting retail prices. As a result, the cost of a pack of 20 cigarettes surpassed the €6 mark. Notwithstanding this recent price increase, the Dutch government has announced additional increases in excise duties for cigarettes and rolling tobacco to be implemented from 2015 onwards. Since January 2015, smoking is prohibited in all bars, including small establishments (see details below). The exception, however, leaves the ability to smoke in designated rooms and on open terraces intact. Recently (February 2016), the Dutch House of Representatives voted in favor of new legislation that would ban smoking in all schools and colleges, as well as on playgrounds beginning in the year 2020.

Under pressure from civil society, municipalities in the Netherlands are gradually renouncing their collaboration with the tobacco industry with whom many had previously entered into (financial) partnerships.

Smoking Ban in Small Cafés

The aforementioned implementation of the smoking ban in the hospitality industry was the most successful in restaurants and least successful in bars. Two years after introducing the smoking ban in

Dutch bars, more than half of bar owners had violated the ban. This non-compliance attracted quite a lot of media attention and, on several occasions, resulted in court cases.

In February 2010, the Dutch Supreme Court ruled that the smoking ban must also apply to owner-run pubs and cafés without employees, thus rejecting an earlier ruling that small bar and café owners were exempt. Regardless of this ruling, the Dutch Minister of Health (Schippers) announced, in June 2011, an exemption to the smoking ban in small bars that do not serve food.

To combat non-compliance, fines for violations of the smoking ban were doubled in August 2011 to now reach €600 for the first violation, €1,200 for the second violation, €2,400 for the third violation and €4,500 for the fourth consecutive violation.

Dutch Court Cases in Which the FCTC Played a Role

Due to the Dutch “monist system,” treaties automatically form part of the Dutch legal order after their ratification. This means that the FCTC can be addressed directly in Court—which has now occurred on several occasions.

In 2012, the anti-smoking group Clean Air Nederland (CAN) took the Dutch State to court in an effort to enforce a ban on smoking in all bars. CAN argued that the current situation—

of abundant non-compliance—led to an unfair competitive disadvantage for bars that do obey the law, and that the State violated the FCTC (Article 8-2). CAN’s victory in the appeals process was confirmed by the Supreme Court on October 10, 2014. As a result, State Secretary for Health (Van Rijn) announced immediate enforcement of the smoking ban in small bars on 21 July 2014, which entered into force in January 2015. At the end of 2015, about 93% of the bars were in compliance with the ban. Clear legislation and active enforcement appear to be effective. Although this new legislation abolishes the exemption for small bars, smoking is still allowed in closed smoking rooms and on open terraces. A new court case addressing this matter (again initiated by CAN) is currently pending before court.

Furthermore, in 2015 the Court of First Instance in the Hague addressed a complaint submitted by the Youth Smoking Prevention Foundation concerning the interaction between the Dutch government and the tobacco industry (based on Article 5-3 FCTC and human rights law). While the Court argued that Article 5-3 is insufficiently specific for the Court to rely on, the government has responded by taking various measures to restrict the interaction between itself and the tobacco industry. ♦

MEETING HIGHLIGHTS

Best of the 16th World Conference on Lung Cancer in Peru

By Luis E. Raez, MD, FACP, FCCP

The International Association for the Study of Lung Cancer (IASLC) and the Peruvian Oncology Research Group (GECO) organized and hosted the “Best of the 16th World Conference on Lung Cancer (WCLC)” in Lima, Peru, on February 4–5 2016. The conference was very successful, with almost 250 doctors attending from several medical specialties including medical oncology, surgery, and pulmonary and radiation oncology, among others.

The meeting was chaired by Dr. Luis E. Raez from Memorial Cancer Institute (Florida, US), Dr. Luis A. Mass from the National Cancer Institute (Lima, Peru), and Dr. Denisse Bretel (Medical Director of GECO). Several IASLC speakers from the US including Drs. Fred Hirsch, Suresh Ramalingam, Luis E. Raez, Francisco Tarrazzi, and Ana Botero

also participated. In addition, other IASLC members from South America were part of the program, including Drs. Carlos Vallejos (Peru), Carlos Barrios and Gilberto Lopes (Brazil), and Andres Cardona (Colombia). They joined another 12 outstanding IASLC speakers from Peru.

The program featured a comprehensive review of lung cancer from epidemiology, tobacco control, and screening to presentations of the latest developments in diagnosis, surgery, and radiation as well as molecular diagnosis, immunotherapy, and targeted therapies. A large number of oncology fellows from several subspecialties attended. One of the major goals of WCLC meetings in Latin America is to motivate young oncologists from this region to join IASLC and the fight against lung cancer.



International IASLC Speakers for the Best of World Lung Cancer Conference in Lima, Peru, 2016. From left: Drs. Carlos Barrios, Luis A. Mass, Andres Cardona, Suresh Ramalingam, Carlos Vallejos, Fred Hirsch, Ann Botero, Francisco Tarrazzi, Luis E. Raez and Denisse Bretel.

IASLC has a venerated tradition of organizing successful meetings in Peru. In 2014 Dr. Raez and Dr. Vallejos organized the 6th Latin American Lung Cancer Conference (LALCA), the

largest LALCA meeting ever conducted with more than 750 physicians attending. We look forward to another successful Best of World Conference on Lung Cancer in Lima, Peru, in 2017. ♦

National Comprehensive Cancer Network NSCLC Guideline Updates for 2016: Non-Small Cell Lung Cancer

By Erik J. MacLaren, PhD

The table at right lists key updates to the National Comprehensive Cancer Network (NCCN) Guidelines for NSCLC as of February 2016. These guidelines are not determined solely by evidence, but also incorporate expert opinion and are subject to frequent updates.

Recommendations by NCCN fall into 1 of 4 categories of evidence and consensus. Over 80% of the categories of evidence and consensus in the NCCN NSCLC guidelines are Category 2A unless otherwise noted. **Category 1** recommendations reflect uniform expert consensus based on strong evidence, **Category 2A** recommendations reflect uniform expert consensus based on lower-level evidence, **Category 2B** recommendations are based on lower-level evidence accompanied by less-than-uniform expert consensus, and **Category 3** recommendations are the most controversial and subject of significant expert debate. When this designation is used, there is major disagreement about the appropriateness of the intervention. Such a category means the intervention is not approved.

This list of updates is not meant to be exhaustive, but rather to highlight some of the more significant changes to the NCCN NSCLC guidelines so far in 2016. The full-length version of these guidelines is updated several times a year and can be found at www.nccn.org. This resource contains information on the prevention, diagnosis, and management of NSCLC and is used as an invaluable reference by clinicians around the globe to keep up with real-time advances and updates in cancer care. *IASLC Lung Cancer News* will provide periodic summaries of ongoing updates. ♦

COMMENTARY

The updates reported in this article on the NCCN NSCLC Guidelines reflect the changes made in version 4.2016. This year I anticipate there will be many more versions of the guidelines, breaking last year's record of 7. This will occur because there are more and more targeted agents and immunotherapies undergoing investigation, either alone or in combination with other therapies. These real-time rapid updates of the NCCN guidelines are intended to assist all those individuals involved in therapeutic decision making in cancer care, including physicians, patients and their families, payers, pharmacists, nurses, and others. It should also be noted that the NCCN has a Drug and Biologics Compendium. This compendium is recognized by public and private insurers alike, including the Centers for Medicare and Medicaid Services (CMS) and United Healthcare, as an authoritative reference for oncology coverage policy. In addition, the NCCN believes strongly in encouraging patients to participate in clinical trials.

— David S. Ettinger, MD

BREAKING NEWS BRIEFS

- Clovis Oncology is shutting down patient enrollment in clinical trials of its lung cancer drug rociletinib, which targets *T790m*, a mutation responsible for acquired resistance in more than half of those initially treated with first-generation TKIs targeting *EGFR* mutations. This includes the pivotal trial TIGER-3. This decision came after a US FDA panel, ODAC, voted against recommending approval. Clovis expects to receive a complete response letter from the FDA rejecting the drug. In response, the company will cut 35% of its staff by the end of 2016 and also withdraw its previously filed application with the European Medicines Agency.
- Boehringer Ingelheim's supplemental new drug application for afatinib (Gilotrif) was approved by the US FDA for treatment of patients with advanced squamous cell carcinoma of the lung whose disease has progressed after platinum-based chemotherapy. The European Commission also approved the new indication (the drug is marketed under the product name Giotrif in Europe).

ALK Positive NSCLC

1. Ceritinib and alectinib are recommended as therapeutic alternatives to patients who are intolerant to crizotinib.
2. Ceritinib has been added as a subsequent treatment option (category 2A) for patients whose disease progresses on first-line treatment and who are brain symptomatic.
3. Alectinib has been added as a subsequent treatment option after crizotinib failure (category 2A).

Sensitizing *EGFR* Mutation Positive NSCLC

1. Gefitinib has been added as a first-line therapy option for patients in whom an *EGFR* mutation has been identified prior to first-line chemotherapy.
2. For patients in whom an *EGFR* mutation is discovered during first-line chemotherapy, adding erlotinib or afatinib to current chemotherapy is **no longer recommended**. Instead, erlotinib, afatinib, or gefitinib should be administered after chemotherapy is completed or interrupted.
3. Gefitinib has been added as a second-line therapy option (category 2A) for patients whose disease progresses on first-line treatment.
4. Osimertinib is now a subsequent therapy treatment option (category 2A) after disease progression on first-line *EGFR* TKI and is approved for patients with metastatic tumors positive for the *EGFR T790M* mutation.
5. Erlotinib is **no longer recommended** as a subsequent therapy for patients whose disease has progressed on *EGFR* TKI and who have multiple metastatic lesions.*
6. Afatinib plus cetuximab may be used in patients whose disease progresses on *EGFR* inhibitors.

Adenocarcinoma, Large Cell, NSCLC NOS

1. Immune checkpoint inhibitors are now the preferred agents for patients with ECOG performance status (PS) 0-2 whose cancer has progressed on first-line treatment.
2. Pembrolizumab is an approved treatment option (now category 1) for PS 0-2 NSCLC patients whose disease has progressed on first-line therapy and whose tumors express PD-L1 using an FDA-approved test.
3. In patients with advanced or metastatic PD-L1-positive NSCLC, pembrolizumab has been determined to improve survival compared to docetaxel.

Squamous Cell Carcinoma (SqCC)

1. Immune checkpoint inhibitors are now the preferred agents for patients with PS 0-2 whose disease has progressed on first-line treatment.
2. Erlotinib is **no longer recommended** as a post-first-line or switch treatment option.**
3. Pembrolizumab is an approved treatment option (now category 1) for PS 0-2 NSCLC patients whose disease has progressed on first-line therapy and whose tumors express PD-L1 using an FDA-approved test.
4. First-line platinum-based chemotherapy is recommended for patients with PS 0-2.
5. The combination regimen of cisplatin/gemcitabine/necitumumab has been added as a category 3 recommendation for first-line treatment of patients with metastatic SqCC.

Tumor Testing

1. It is now recommended that testing patients with NSCLC for *EGFR* and *ALK* mutational status should be done as part of broad molecular profiling to help identify other rare driver mutations and to determine the availability of appropriate drugs or clinical trials.

Emerging Agents

1. Dabrafenib plus trametinib is recognized as a targeted regimen with activity in tumors with *BRAF V600E* mutations.

* Erlotinib is FDA approved for metastatic *EGFR*-positive NSCLC regardless of the number of metastatic lesions, and NCCN continues to recommend its use in patients with an isolated lesion.

** Erlotinib is FDA-approved for first-line and maintenance treatment of locally advanced or metastatic NSCLC.

Names and News



Abbas El-Sayed Abbas, MD, has been appointed Thoracic Surgeon-in-Chief and Surgical Director of Lung Cancer, Thoracic Malignancy and Foregut Disease Programs for Temple University Health System, Philadelphia, US.

Dr. Abbas will continue as Vice Chair of Thoracic Medicine and Surgery at the Lewis Katz School of Medicine at Temple University, Director of Foregut Surgery program, Section Chief of Thoracic Surgery, and Associate Professor of Thoracic Medicine and Surgery.



Michael R. Blackburn, PhD, has been appointed Executive Vice President and Chief Academic Officer of The University of Texas Health Science Center at Houston (UTHealth), US. Dr. Blackburn has served as Vice Chairman of the

Department of Biochemistry and Molecular Biology at McGovern Medical School at UTHealth since 2011. In 2012, Dr. Blackburn was named joint Dean of The University of Texas Graduate School of Biomedical Sciences at Houston.



Paul A. Bunn, Jr, MD, received the 2016 David A. Karnofsky Memorial Award and Lecture, which is given annually to an oncologist who has made outstanding contributions to cancer research, diagnosis, and treatment.

Dr. Bunn is Distinguished Professor of Medicine and the James Dudley Endowed Professor of Lung Cancer at the University of Colorado School of Medicine, Denver, US.



Professor Jean-Yves Douillard, MD, PhD, has been appointed the first Chief Medical Officer of the European Society of Medical Oncology. Prof. Douillard was previously Professor of Medical Oncology at the

Integrated Centres of Oncology R. Gauducheau and University of Nantes Medical School, France, where from 2009–2011, he was Director of Clinical and Translational Research.



Waun Ki Hong, MD, FACP, DMSc (Hon), received the 10th AACR Margaret Foti Award for Leadership and Extraordinary Achievements in Cancer Research and the 2016 ASCO Special Recognition Award, which honors an individual whose

research and innovations have had a transforming and lasting effect in the areas of clinical oncology, cancer research, clinical trials, or patient advocacy activities. Dr. Hong is Professor of Medicine at The University of Texas MD Anderson Cancer Center, Houston, US.



Roman Perez-Soler, MD, has been named to the US National Cancer Institute's (NCI's) Board of Scientific Counselors for Clinical Sciences and Epidemiology, which provides advice on NCI intramural and extramural research programs. Dr. Perez-Soler is Chairman and Chief,

Department of Oncology, Montefiore Einstein Center for Cancer Care; Chief and Professor, Division of Medical Oncology, Department of Medicine at Albert Einstein College of Medicine; and Deputy Director of Albert Einstein Cancer Center, all in New York, US.



Cathy Pietanza, MD, has been appointed Global Director of Scientific Affairs for Oncology in Merck Research Laboratories. Prior to joining Merck, Dr. Pietanza was an Assistant Attending Physician at

Memorial Sloan-Kettering Cancer Center, New York, US, on the Thoracic Oncology Service, and also held an appointment at the Weill Cornell Medical College.



Umberto Ricardi, MD, has been elected President-Elect of the European Society for Radiotherapy & Oncology (ESTRO). Prof. Ricardi is Full Professor of Radiation Oncology and Chairman of the Radiation Oncology Department,

University of Turin, Turin, Italy.



Suresh Senan, MRCP, FRCR, PhD, received the 2016 Heine H. Hansen Award, which recognizes a lung cancer investigator who has made a special contribution to lung cancer research and education on an international

basis. Prof. Senan is Vice Chair of the Department of Radiation Oncology at the VU University Medical Centre, Amsterdam, the Netherlands, and is Professor of Clinical Experimental Radiotherapy.



Patrick Soon-Shiong, MD, FRCS (C), FACS, has been appointed Chairman of the Board of Directors of Altor BioScience Corporation. Dr. Soon-Shiong is the inventor of Abraxane, an albumin-bound nanoparticle of

paclitaxel approved for lung, breast, and pancreatic cancer. He announced the Cancer MoonShot 2020 Program in January 2016.



Charles Swanton, MD, PhD, received the Biochemical Society 2016 GSK prize in recognition of distinguished research leading to new advances in medical science. Prof. Swanton is Professor of Cancer Medicine and

Chair of Personalized Cancer Medicine, University College London, UK, and Co-Director, Cancer Research UK Lung Cancer Center of Excellence at University College London, and Manchester University, UK.



Stefania Vallone has been elected President of Lung Cancer Europe (LuCE), which provides a European platform for already existing lung cancer patient advocacy groups and supports the establishment of national

lung cancer patient groups in different European countries where such groups do not yet exist. Ms. Vallone, Italy, is a lung cancer patient advocate, who has also been active with Women Against Lung Cancer Europe.



Readers are invited to submit new content for a future Names and News column to Editor@iaslclungcancernews.net; submissions received will be subject to review and approval by the Editor, and selection for publication is not guaranteed.

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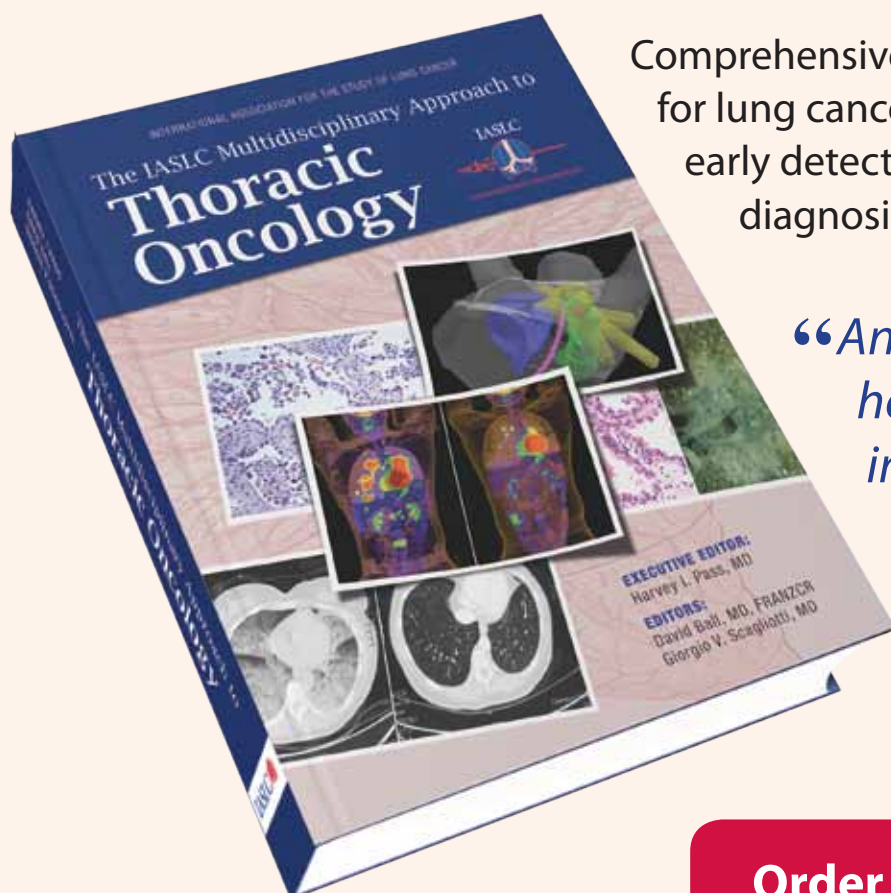
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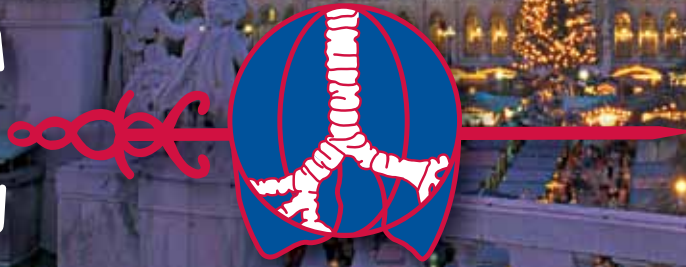
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