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FOR THORACIC SPECIALISTS

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LUNG CANCER IASLCNEWS

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

INSIDE

LUNG CANCER LEADERSHIP

Interview with Bruce Johnson, MD, 2017-2018 ASCO President

Long-term IASLC member Bruce E. Johnson, MD, will serve as the 2017–2018 President of the American Society of Clinical Oncology (ASCO) upon the conclusion of the 2017 ASCO Annual Meeting. Dr. Johnson describes his experience, vision, and goals for the field of thoracic oncology and oncology in general for *IASLC Lung Cancer News* readers.

Bruce Johnson

Where is oncology going as a field?

The field of oncology is rapidly evolving as we develop treatments for subsets of our patients with cancer. The era when all patients with a specific type of cancer (lung cancer, colon cancer, and breast cancer) are treated in a similar fashion is rapidly coming to an end. The era of targeted therapies for subsets of patients has arrived; those with *HER2* positive breast cancer treated with traztuzumab, *KRAS* wild type colon cancer treated with cetuximab, and *EGFR* mutant lung cancer treated with an EGFR-TKI. The addition of immunotherapy to our therapeutic arsenal has opened up patient groups who can be identified for initial therapy with checkpoint inhibitors. Patients with lung cancer with greater than 50% of their tumor cells expressing programmed cell death-ligand 1 (PD-L1) and patients with colon cancer with microsatellite instability should be treated with checkpoint inhibitors. I anticipate this cycle will continue where patients will continue to have predictive biomarkers identified that will dictate their therapies.

What is the role of thoracic oncology in the evolution of oncology? How will the insights and challenges you've experienced as a leader in thoracic oncology influence your tenure as ASCO President?

I am proud to be the first ASCO President with an interest in thoracic oncology since David Johnson (2004-2005) and Paul Bunn (2002-2003) served more than a decade ago. My theme for the coming year is, "Delivering Discoveries, Expanding the Reach of Precision Medicine." Lung cancer has served as a model for precision medicine, with 5 subsets of non-small cell lung cancer now effectively targeted. Our field has

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LUNG CANCER SCREENING

Lung Cancer Screening Is Cost Effective

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

John K. Field James L. Mulshine

There is now robust and consistent evidence for the cost-effectiveness of lung cancer computed tomography (CT) screening as delineated in the recent analysis from ten Haaf and colleagues in PLOS Medicine.[1] They have used microsimulation modeling analysis based on the smoking behavior surveys of individuals born between 1940 and 1969 from Ontario, Canada. Over 570 potential screening scenarios were evaluated, which included parameters such as the age to start or stop screening, screening interval, eligibility criteria (with respect to smoking history and quit time) as well as whether or not former smokers were excluded from further screening. Smoking criteria were based on both the National Lung Screening Trial (NLST) and the NELSON data. The costings were conducted from a third-party health care provider using Ontario Health Care plan. The results were provided as net discounted costs and life-years gained for each scenario. Their analyses are presented in the Figure below and demonstrate the results of all of the simulations of various screening scenarios on the efficient frontiers. The authors worked on $50K Canadian dollars (CD) per life-year gained, which is acceptable as the threshold for the Canadian health care system (i.e., US $41K and UK £28K). It is of note that these figures are

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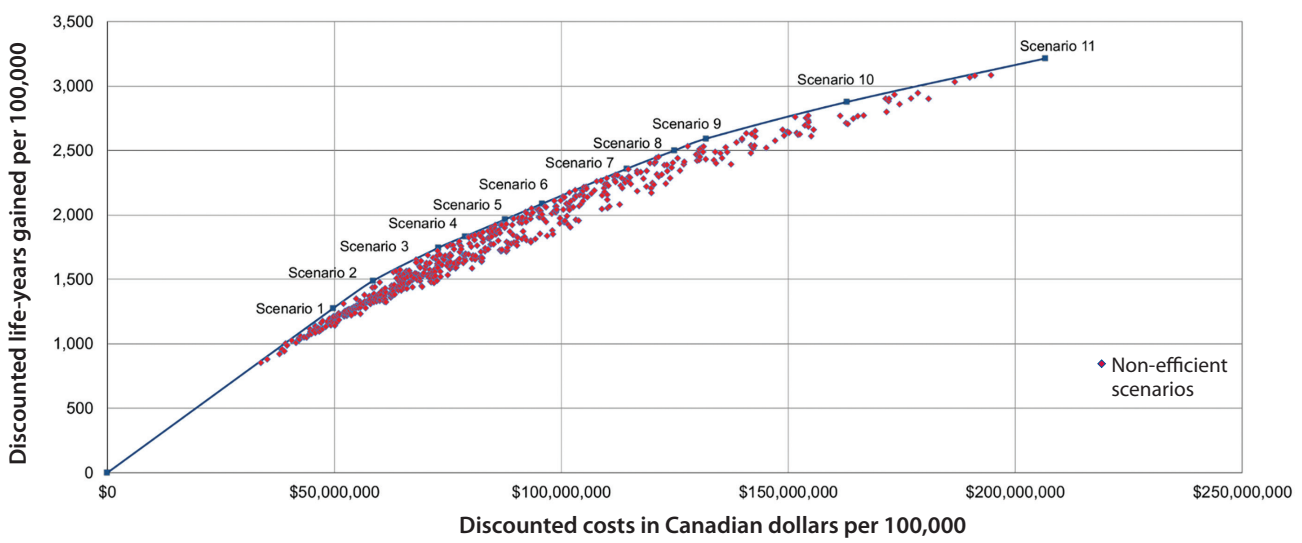


Figure. Microsimulation modelling of the cost effectiveness in the Ontario population in Canada. Source: *PLoS Med*. 2017;14(2):e1002225.

LUNG CANCER SCREENING

An Argument for a Large-Scale Low-Dose CT Lung Cancer Screening Trial in France

By Bernard Milleron, MD, and Sébastien Couraud, MD, PhD

Large-scale lung cancer screening trials have been successfully conducted in several countries, and formal screening recommendations have been made based on this key research. For example, the U.S. National Lung Screening Trial (NLST) demonstrated in 2011 that annual screening by low-dose computed tomography (CT) was associated with a 20% reduction in lung cancer mortality in a high-risk population.[1] Following these results, the U.S. Preventive Services Task Force recommended the implementation of such screening in the United States for adults aged 55 to 80 who are at high risk for lung cancer.[2] Many initiatives and trials have been established in other countries such as Australia, the United Kingdom, and Canada. In Europe, final results from the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) are expected in 2019. NELSON was designed to investigate whether screening by low-dose CT in high-risk populations will lead to a decrease in 10-year lung cancer mortality of at least 25% when compared with an unscreened control group. Of note, the selected population appears slightly at lower risk than in the NLST trial (50-75 years; smoked >15cig/d >25y OR >10cig/d >30y; quit since less than 10y). This point may be kept in mind for interpretation of further results.[3]

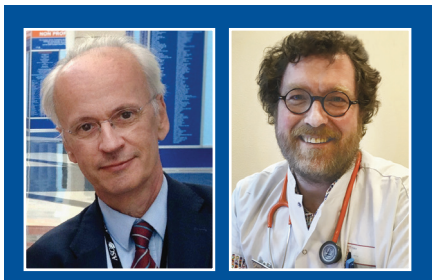
The French National Authority for Health (*Haute Autorité de Santé*, HAS) published a report in 2016 on lung cancer screening, which was based on a literature analysis.[4] Our group, gathering the French Pulmonology society, the French Thoracic Imaging society and the French intergroup IFCT, performed a similar literature analysis in 2013, which argued that lung cancer screening should be considered as a means to reduce lung cancer mortality and that comprehensive research in this field should be encouraged.[5] Interestingly, our conclusions were similar to those of many international societies but deeply different from those made by the later HAS report.

For example, HAS claimed that curative interventions for early-stage disease show limited success; however, data from a collaborative group, the International Early Lung Cancer Action Group, showed a survival rate of 92% for 302 patients with stage I disease who underwent surgical resection 1 month after diagnosis.[6] In addition, HAS posited that the natural progression of lung cancer is too fast to allow for detection of disease in early stages. In contrast, the first lung cancer screening trial to take place in the United Kingdom, the UK Lung Cancer Screening Trial, detected stage I/II lung cancers in 36 of 42 (86%) screened participants.[7] HAS reported that high-risk individuals who may benefit from screening are not characterized, whereas NLST demonstrated usefulness of screening in a well-characterized high-risk population (e.g., age and smoking history). An important and timely field of research in itself, these criteria could be optimized using biomarkers and/or risk-prediction models, such as the PLCO models.[8,9]

HAS reported that diagnostic interventions for false-positive cases identified by low-dose CT screening may result in severe complications or even death. However, very few patients identified in NLST underwent resection (4%), and diagnostic interventions for false-positive cases resulted in very few complications (0.4%) or death (less than 0.1%). However, it cannot be ignored that, of the total number of low-dose CT screening tests, 24.2% were classified as positive and 23.3% had false-positive results.[1] In the NELSON trial, a new process for CT interpretation was successfully tested. Using volume measurement and doubling time, the rate of positive disease detection decreased drastically, compared with the NLST study, to approximately 6%.[10]

HAS also pointed out the potential risk of radiation exposure from repeated CT scan imaging in arguing against large-scale screening, which is a valid point and should not be minimized. However, use of low-dose and very low-dose CT scanning decreased the radiation dose for each scan to an amount less than 6 months of environmental radiation in France. In addition, the target population for screening—individuals aged 55 to 80—is the population in which the risk of irradiation-induced cancer is lowest.[11]

Regarding prevention and mortality, HAS underscored the importance of tobacco smoking prevention, which is an obvious and significant way to reduce lung cancer incidence. HAS stated that the randomized trials it reviewed did not demonstrate a mortality reduction, but none of the trials was powered to detect a difference in this outcome.[5] Interestingly, the ITALUNG trial—which was also not powered for demonstrating a survival benefit—recently released final data showing a non-significant trend towards mortality reduction in the screening arm.[12]



Bernard Milleron Sébastien Couraud

Extrapolating Data into the Real World

The HAS report stated that lung cancer screening should be tested in a French setting before recommendations, which would otherwise be based on data from other countries, are made. The importance of this point has led us and other researchers to submit several proposals to the French National Cancer Institute during the past decade. Unfortunately, no large lung cancer screening trial has been approved by French authorities despite the mention of screening-focused goals in the third Cancer Plan (2014-2019), launched by the former French President François Hollande in February 2014.[13]

Previous screening efforts in France have resulted in very poor participation rates.[14] These existing data may affect health-policymakers' decisions about the implementation of yet another cancer screening trial and any associated costs. However, the economic strategy for a lung cancer screening program is drastically different from that for other screening programs because tobacco is both a well-identified risk factor and a taxable product. Any large-scale lung cancer screening strategy may be fully subsidized by increasing existing taxes on tobacco products. We recently estimated that just a 1% increase of the cigarette tax in France would fund a screening program with a 45% participation rate.[15]

The current outlook regarding adoption of a large-scale lung cancer screening trial using low-dose CT is bleak due to the position presented in the HAS report. However, investigation of

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At Press Time

IASLC Lung Cancer News mourns the loss of **Dr. Robert Comis**, long-time lung cancer researcher and leader, who passed away suddenly at the time of production of this issue. A remembrance of Dr. Comis will be featured in the next issue of *ILCN*.

LUNG CANCER IASLCNEWS

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IASLC MISSION

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

GLOBAL RESEARCH REPORT

The CRISPR-Cas9 Toolkit: Moving From Bench to Bedside

By Cynthia L. Kryder, MS

Decades of immunology research have shown that it is possible to harness the power of the immune system to fight cancer. In particular, recent discoveries regarding the regulation of T-cell responses have contributed to the development of genomically targeted agents and immune checkpoint therapies that have improved durable responses and long-term survival in patients with lung cancer.

The ability to precisely edit genes to engineer T cells to better fight cancer is seen as a potentially revolutionary medical tool. Progress is accelerating using a gene-editing technology called CRISPR-Cas9.

How CRISPR Works

The acronym for **C**lustered **R**egularly **I**nterspaced **S**hort **P**alindromic **R**epeats, CRISPR, comprises 2 components. One is the Cas9 enzyme that acts as a molecular scissors to snip DNA. Precisely where Cas9 cuts is controlled by the second component, which is a short strand of RNA that matches up precisely with the target region of intracellular DNA. This RNA strand acts like a global positioning system to guide Cas9 to the targeted site, where it makes a cut at an exact point in the DNA sequence (Figure). Once Cas9 has cut the DNA, it is then possible to disrupt the function of a particular gene, remove it completely, introduce precise changes to the DNA sequence, or insert a completely different gene.

The power of CRISPR lies in its programmable nature. Researchers can engineer unlimited versions of the RNA strand to guide Cas9 to any gene they wish. With this specificity, scientists can target and study particular DNA sequences anywhere in the genome.

Using CRISPR to Manipulate the PD-1 Immune Checkpoint in Lung Cancer

Cell-mediated immune responses involve T cells, which become activated via 2 signals: antigen recognition and a co-stimulatory signal. Once activated, T cells begin to proliferate and differentiate; cytotoxic T cells eliminate cells expressing the antigen that led to their activation. Some cancers manipulate inhibitory co-signaling pathways, otherwise known as immune checkpoints, which regulate the intensity of T-cell immune responses and prevent them from attacking the wrong targets. One such checkpoint, programmed cell death 1 (PD-1), primarily works to ensure that activated T cells do not target healthy tissue near the site of an infection. The PD-1 receptor is upregulated on T cells once they become activated; its ligands, PD-L1 and PD-L2, are present in normal tissue cells. Binding of PD-1 to its ligands exerts an inhibitory effect on T cells, thereby signaling the T cell not to instigate an immune system attack.[1] Thus, this checkpoint shields normal tissue from the immune attack.

> Whether the technology of CRISPR-Cas9 is deserved to call a pair of magic scissors in fields of clinical applications, there will be a long way to go. If with acceptable safety in phase I/II clinical trial, the scissors has to demonstrate a magic power by winning the game over PD-1 inhibitors, which would be a turn-point of cell therapy moving from bench to bedside.
>
> —**You Lu, MD**, West China Hospital, Sichuan University, Sichuan, China

Certain cancer cells protect themselves from immune attack by exploiting the PD-1 checkpoint pathway. Cancer cells have been found to express either PD-L1 or PD-L2, which binds to the PD-1 receptor on cytotoxic T cells. In the tumor microenvironment, binding of PD-1 to PD-L1 turns off the immune response necessary for tumor recognition and elimination, consequently shielding cancer cells from immune attack.[1]

Lu You, MD, Sichuan University, Sichuan, China, and colleagues are investigating whether it is possible to use CRISPR-edited autologous T cells to block the PD-1/PD-L1 pathway in order to improve antitumor responses in patients with metastatic non-small cell lung cancer (NSCLC).[2] In this first-in-human clinical trial, investigators will use CRISPR-Cas9 to disable the *PD-1* gene on T cells. The lymphocytes will be selected and expanded ex vivo and infused back into patients. The premise is that without the PD-1 protein, the edited T cells will be able to initiate an immune attack.

Patients will be assigned to 1 of 3 treatment groups to determine the maximal tolerated dose. The primary outcome measure is the number of patients with adverse events and/or dose-limiting toxicities. Response rate, progression-free survival, and overall survival are among the secondary endpoints. Biomarkers and immunologic markers will be collected and analyzed as well.

CRISPR-edited Cells versus CAR T Cells

CRISPR-edited cells should not be confused with those that have been genetically engineered ex vivo to produce chimeric antigen receptors (CARs) on the cell surface. CARs are proteins that allow the T cells to recognize a specific antigen and to kill cancer cells that harbor the antigen on their surfaces.

CAR-modified T cells (CAR-T cells) recognize their target antigen through the scFv binding domain, resulting in T cell activation in a major histocompatibility complex-independent manner. The most widely studied application of CAR-T cell therapy targets the CD19 antigen found in B cells and has shown remarkable efficacy in B cell malignancies, particularly in anti-CD19 CAR-T cells for B cell acute lymphoblastic leukemia with up to a 90% complete remission rate.[3] Similar success has not been obtained in patients with solid tumors.

Praise and Precautions

The implications of directly editing intracellular DNA to make permanent changes that affect the proteins that are produced are not fully known. Although CRISPR has been praised for its precision, DNA is complex, and it is possible for CRISPR to miss its target. In addition, CRISPR may inadvertently cut into stretches of DNA that look similar; such inaccurate editing

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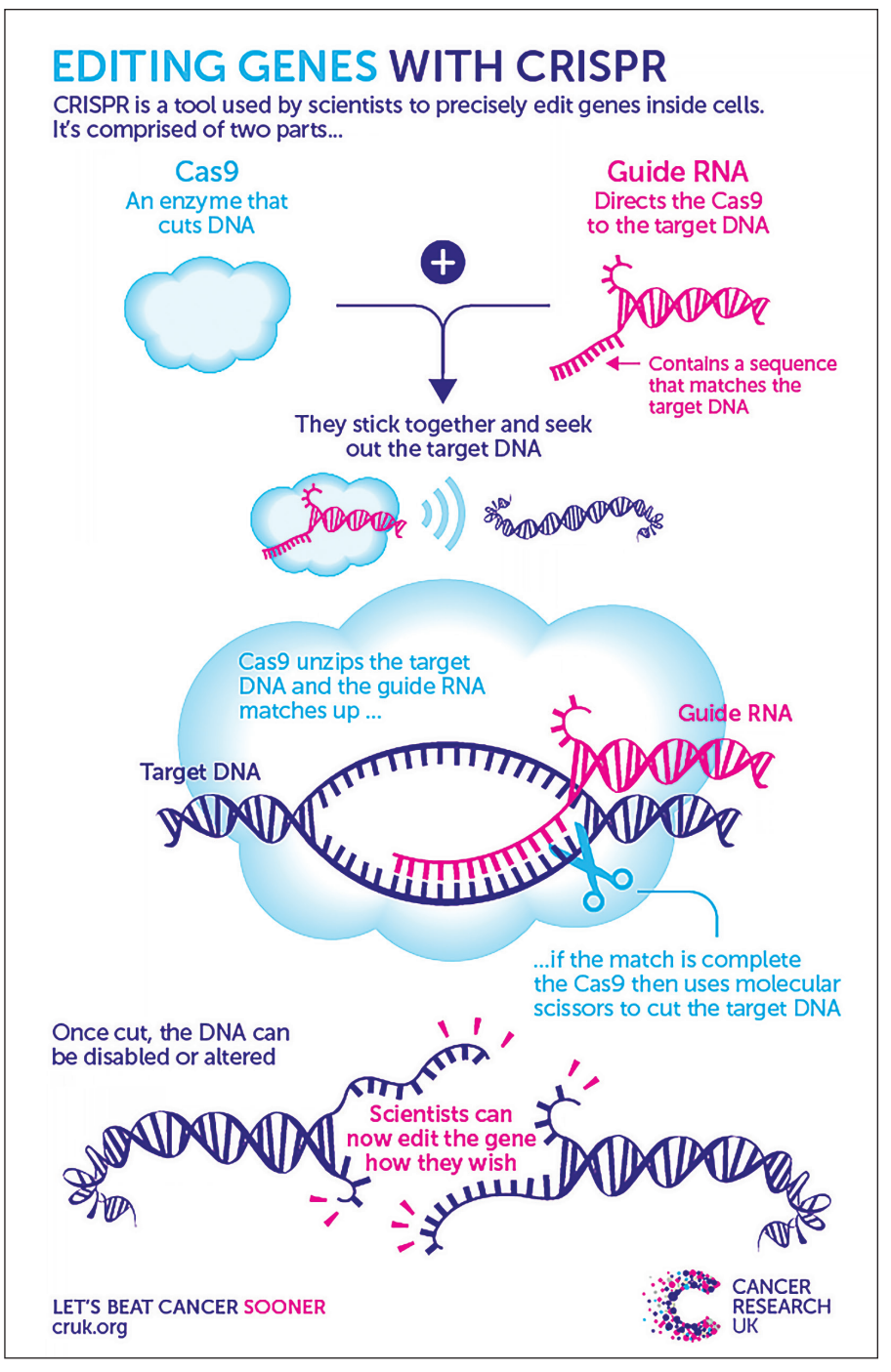

PERSPECTIVE

European Perspective on Molecular Testing

By Niki Karachaliou, MD, PhD


Niki Karachaliou

The identification of oncogenic driver alterations in non-small cell lung cancer (NSCLC), such as *EGFR* mutations and *ALK* rearrangements, each of which confers sensitivity to small tyrosine kinase inhibitors, has made EGFR and ALK testing a necessity in routine molecular pathologic diagnosis. Furthermore, next-generation sequencing (NGS) studies have divided NSCLC into molecular subtypes defined by distinct somatic alterations,[1,2] which have led to an increasing interest in identifying additional targetable alterations in this disease.[3] *EGFR* mutation testing is routinely available in 70% of the population worldwide, but it remains costly at a rate of $500 or more in the majority.[4] Various techniques like conventional Sanger sequencing, real-time PCR platforms, digital PCR, and NGS are used to detect *EGFR* mutations. Fluorescence in situ hybridization (FISH), immunohistochemistry (IHC) reverse-transcriptase PCR, and some forms of NGS platforms are used for *ALK* gene fusion detection (Figure). Following the results of the KEYNOTE-024 trial that led to the FDA approval of pembrolizumab for first-line therapy in patients with PD-L1 expression of 50% or higher PD-L1 testing by IHC has become another very important biomarker.[5] But it remains unclear which is best: PD-L1 testing, or PD-L1 plus other markers (e.g., tumor mutation burden, or neoepitopes,[6] or IFN-γ signatures[7]), to enhance response prediction and selection of patients for anti-PD1/L1 therapies.

In 2009, the Spanish Lung Cancer Group demonstrated that a large-scale screening study for *EGFR* mutations was feasible and reported a prevalence of 16.6% among Spanish patients with NSCLC.[8] As a result, the Spanish Association of Medical Oncology and the Spanish Association of Pathology recommend routine *EGFR* mutation and *ALK* rearrangement testing in all NSCLC of nonsquamous cell subtype, or nonsmokers regardless of histologic subtype. The analyses should be performed in laboratories participating in external quality control programs, and the results should be provided no more than a week after the pathologic diagnosis.[9] To this end, a nationwide platform funded by AstraZeneca was implemented in Spain for large-scale screening of *EGFR* mutations in the tissue and blood of patients with advanced NSCLC. Routine testing for other molecular abnormalities is not considered necessary in current clinical practice. In our molecular diagnostic laboratory, *EGFR* deletions in exon 19 and exon 21 point mutations in codon 858 are examined in tissue and blood with a 5' nuclease PCR assay in the presence of a protein nucleic acid clamp, designed to inhibit the amplification of the wild-type allele.[10] The analysis of the gatekeeper T790M mutation in exon 20 is always included in both pre-treatment[11,12] and post-treatment[13] tumor samples.

The Network Genomic Medicine (NGM) in Cologne, Germany, was the first group to screen for genomic alterations in all histological subtypes of lung cancer.[14] Since then, the NGM has made great progress, implementing genotyping by NGS and genomic-driven treatment trials (e.g., EUCROSS: NCT02183870).[15]

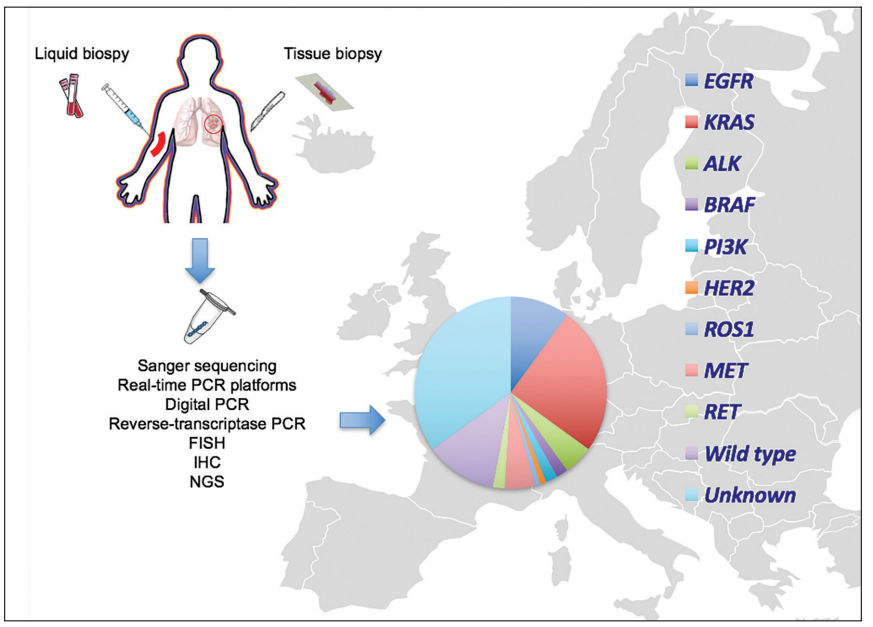

Figure. *ALK* gene fusion detection: fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), reverse-transcriptase (PCR), and forms of (NGS) platforms.

From April 2012 to April 2013, the French Cooperative Thoracic Intergroup (IFCT) screened 17,664 patients with advanced NSCLC for oncogenic drivers through a nationwide program funded by the French National Cancer Institute.[16] *EGFR* mutations and *ALK* rearrangements, as well as *ERBB2*, *KRAS*, *BRAF*, and *PIK3CA* mutations were assessed either concurrently or with a sequential approach in 28 certified regional genetics centers in France, using the Sanger sequencing method or a more sensitive validated allele-specific technique.[16,17] The Lung Cancer Mutation Consortium (LCMC) initiative clearly demonstrated a clinical benefit for patients who are molecularly profiled and receive a matched targeted agent.[16]

According to the consensus of the Italian Association of Medical Oncology and the Italian Association of Pathology and Cytopathology, all patients with NSCLC of nonsquamous cell subtype should be tested for *EGFR* and *KRAS* mutations within 2 to 5 days after the pathologic diagnosis. Negative cases should be prescreened for elevated ALK protein by IHC before final confirmation by FISH.[18] Through the Alliance Against Cancer,[19] a national molecular screening program evaluating the use of NGS in patients with advanced NSCLC is going to be initiated in Italy by June 2017.

The Swiss Lung Pathology Group recommends gene sequencing analysis (through various NGS platforms) for *EGFR*, *KRAS*, *BRAF*, and *HER2* mutations, as well as prescreening for elevated ALK and ROS1 protein by IHC (positive cases should be confirmed by FISH). For negative cases, sequential testing for *MET* amplification or *RET* rearrangements is highly recommended, as well as the evaluation of PD-L1 protein expression, *MET* exon 14 skipping mutations, and *NTRK1* rearrangements.

The above mentioned molecular diagnostic algorithms represent a shift in lung cancer diagnosis and treatment, but at the same time pose several challenges for Europe and beyond. For instance, there is a paradox between the development of minimally invasive techniques, resulting in small tissue samples and the need to obtain large enough samples for the analyses of a growing number of biomarkers. High-quality diagnostic samples, molecular profiles of various samples (including plasma genotyping), new sampling procedures, and high-sensitivity tests should all be combined to provide great amounts of information from increasingly smaller amounts of tissue. A Spanish Lung Liquid versus Invasive Biopsy Program (SLLIP) is currently running in Spain, with the primary objective of demonstrating the non-inferiority of cell-free circulating tumor DNA (cfDNA)-based versus tumor tissue-based genotyping as it pertains to the detection of clinically actionable biomarkers in first-line, treatment-naive, metastatic nonsquamous NSCLC. The Guardant360 cfDNA-targeted NGS panel is used for the cfDNA-based genotyping in the SLIPP study. The logistical challenges of implementing molecular diagnostics in clinical practice, including the access to targeted therapies, are also important issues.

In the United Kingdom, NGS is applied to samples from patients with advanced NSCLC to screen for clinically actionable known drivers, through the Cancer Research UK Stratified Medicine Program 2 (SMP2).[20] According to the results obtained, patients are recruited to The National Lung Matrix Trial (NCT02664935), a phase II umbrella study.[21] A similar umbrella study is ongoing in France: SAFIR02 Lung trial (NCT02117167).[22] Even with these initiatives for matching drugs to tumor profiles, the goals are not always reached: many patients are not able to go through a successful biopsy, actionable targets are detected in less than half of the patients, and only a minority of patients are finally treated with targeted therapies. A joint European strategy for NGS sequencing-based molecular diagnostics of lung cancer will definitively establish a database for the evaluation of personalized lung cancer therapy, increase access to new drugs, and develop models for reimbursement adapted to diverse national health care systems.✦

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FDA CORNER

INTERVIEW WITH COMMANDER JASON HUMBERT

FDA Warns of Fraudulent Cancer Drugs

On April 25, 2017, the US Food and Drug Administration (FDA) issued warning letters to 14 companies regarding more than 65 products being marketed with unproven or fraudulent claims. The products identified included pills, topical creams, ointments, oils, drops, syrups, teas, and a thermography device.[1]

The marketing and sale of fraudulent health products are serious issues that pose risks to consumers, particularly those coping with a serious diagnosis like cancer. Such treatments are often promoted with claims that they are "natural" remedies or that a single product can treat multiple conditions or diseases. The sale of untested and unapproved drugs is facilitated by the Internet, which allows those behind these products to easily change brand and company names and otherwise evade regulatory oversight.

The recent spate of warning letters is the product of a deliberate investigation by the FDA to identify products being deceptively marketed on the Internet and on social media platforms as cures, treatments, or diagnostics for cancer. The search was a collaboration between the FDA's Office of Regulatory Affairs, the Center for Food Safety and Applied Nutrition, and the Center for Drug Evaluation and Research. *IASLC Lung Cancer News* spoke with Commander Jason Humbert, a Senior Regulatory Operations Officer at the FDA's Office of Regulatory Affairs, about the efforts to identify and eliminate fraudulent products on the market.

How does the FDA identify and investigate fraudulent products being marketed to treat cancer?

The FDA considers a number of factors when determining whether a product's labeling is in violation of the *Federal Food, Drug, and Cosmetic Act*. In general, firms cannot claim that their products cure, mitigate, treat, or prevent cancer unless the FDA has determined the product is safe and effective for those intended uses.

The FDA monitors the marketplace—including social media, websites, and brick-and-mortar stores—for potentially fraudulent products (for example, products that may be unsafe or products about which the manufacturer makes false or misleading claims) through a variety of tactics such as market surveys, label reviews, reviewing adverse event reports, and testing of products.

It's important to note that the FDA does not do this alone. Other state and federal agencies such as state Attorneys General offices, the Federal Trade Commission, and the Department of Justice also take actions against companies making false marketing claims.

What consequences are faced by the companies that received warning letters from the FDA in April? Are they required to immediately stop marketing the suspected drugs? Are fines involved?

The companies have 15 days from receiving a warning letter to correct the violations or to provide a plan to the FDA for how they will correct the violations. Since these particular violations pertain to marketing claims, corrective action is likely to involve removing the claims from their labels and marketing materials.

If the companies fail to resolve violations cited in the warning letters, they may be subject to further FDA action, including seizure of illegal products, injunctions, and possible criminal prosecution.

In addition to the need to correct the violations outlined in the warning letters, the companies are under an ongoing requirement to comply with all applicable FDA requirements such as Good Manufacturing Practice regulations.

Are fraudulent cancer drugs a bigger or smaller problem than in the past, and why?

Over the past decade, the FDA has sent more than 90 warning letters to companies marketing hundreds of fraudulent products making cancer claims. With the ongoing popularity of online sellers and social media sites, consumers are regularly exposed to online marketing tactics and direct-to-consumer product sales, including those that claim to diagnose, treat, or cure cancer. Due to the nature of online marketing, some companies attempting to avoid compliance with FDA law simply start new websites and rename their fraudulent products. This is why the FDA urges consumers to remain vigilant and to protect themselves against health fraud by not purchasing these products and by always discussing cancer treatment options with their health care provider.

What other steps is the FDA taking to reduce the sales of these fraudulent therapies?

In general, if companies fail to resolve violations cited in warning letters that they receive, the FDA can and has taken further action, including seizure of illegal products, injunction, and criminal prosecution. As one example, in 2015, the FDA was granted a permanent injunction against a company illegally marketing a handheld laser device as a treatment for cancer and dozens of other conditions after the company and its representatives ignored FDA's warning letter and continued to illegally market and distribute its devices. The Department of Justice later charged three individuals, and a fourth individual agreed to plead guilty to conspiracy charges in a related criminal case.

Jason Humbert

Conclusion

Far from being relegated to the distant past of "patent medicines," products making false claims to diagnose and treat cancer continue to be sold to patients who are often seeking a magic bullet for difficult-to-treat tumors. These fake drugs pose a risk of unknown interactions with clinically proven treatments, putting patients at increased risk, and some patients may choose products falsely promising a miracle cure over more unpleasant treatments.

That the FDA continues to issue warning letters regularly underscores the crucial need for consumers to remain vigilant and educated about fraudulent cancer cures, which the FDA addresses by disseminating consumer information using media outlets, Consumer Updates, and information on FDA.gov, and working with consumer and trade groups.✦

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MEETING PREVIEW

2017 ASCO Annual Meeting

By Erik J. MacLaren, PhD

The Annual Meeting of the American Society of Clinical Oncology (ASCO) is taking place June 2–6 in Chicago, Illinois, and over 5,000 abstracts have been accepted for presentation at the meeting or for online release. The theme of this year's meeting is **Making a Difference in Cancer Care With You**, intended to foster a multidisciplinary approach and uniting the oncology community in the effort to improve cancer care. Several scientific and educational presentations of particular interest to those involved in lung cancer care and research are highlighted below.

On Saturday, June 3, an educational session titled "Prevention, Diagnostics, and Treatment of Lung Cancer in Low- and Medium-Resource Countries" will be chaired by **Fred R. Hirsch, MD, PhD**, CEO of IASLC, from the University of Colorado Comprehensive Cancer Center in Aurora, Colorado. Dr. Hirsch's research concerns the development of biomarkers for the diagnosis, prevention, and treatment of lung cancer, and he will give a presentation discussing biomarker testing in challenging venues with limited resources. **Hisao Asamura, MD**, Co-President of the 2018 World Conference on Lung Cancer and an expert in thoracic surgery from Keio University School of Medicine in Tokyo, Japan, will discuss considerations in choosing between wedge or anatomical resections in patients with lung cancer. Finally, Nicola Roxon, adjunct professor at Victoria University in Melbourne, Australia, and a former Minister for Health and Ageing as well as Australia's first female Attorney-General, will discuss national policy issues in smoking cessation. The session will include a panel discussion, including by the speakers, following their presentations.

On the previous day, Friday, June 2, two lung cancer-related sessions are scheduled. The first is starting with a session called "Upfront Management of Operable Non-Small Cell Lung Cancer," chaired by **Shirish M. Gadgeel, MD**, University of Michigan, Ann Arbor, Michigan. Dr. Gadgeel, whose research is supported by the National Cancer Institute (NCI) and the Southwest Oncology Group (SWOG), will speak about treating early-stage non-small cell lung cancer (NSCLC) with chemotherapy and targeted therapies. **Thomas A. DiPetrillo, MD**, from the Brown University Oncology Research Group in Providence, Rhode Island, and associate professor of radiation oncology, will also give a presentation on new radiation techniques for treatment of early-stage NSCLC. Finally, **Hiran Fernando, MBBS**, chief of thoracic surgery at Boston Medical Center in Boston, Massachusetts, will speak about advances in the surgical treatment of NSCLC.

On Friday afternoon, **Melissa Lynne Johnson, MD**, associate director of lung cancer research at the Sarah Cannon Research Institute in Nashville, Tennessee, will chair an extended educational session highlighting state-of-the-art uses for immunotherapies in lung cancer, how to manage toxicities, and the role of specific patient populations. Dr. Johnson will give a presentation titled "Are All Immunotherapy Drugs the Same or Is One the Best?" Other presentations in this session will cover immunotherapy sequencing, discussed by **Edward B. Garon, MD**, from the David Geffen School of Medicine at University of California Los Angeles in Los Angeles, California, and the role of immunotherapy in patients, presented by **Ben C. Creelan, MD**, from the Lee Moffitt Cancer Center in Tampa, Florida. **Dickran Garo Kazandjian, MD**, from the NCI will focus on pseudoprogression, and **Hossein Borghaei, DO**, from the Fox Chase Cancer Center in Philadelphia, Pennsylvania, will cover toxicity management with immunotherapies. Finally, **Aaron Scott Mansfield, MD**, from the Mayo Clinic in Rochester, Minnesota, will wrap up the session with a presentation titled "What Is the Role of PD-L1 Biomarker Testing in Clinical Practice?"

On Sunday, June 4, there are two sessions pertaining to lung cancer. The first entitled "Incorporating Precision Medicine Into Your Practice: How, Why, and When?," will be chaired by **Lee Steven Schwartzberg, MD**, from the University of Tennessee Health Science Center in Memphis, Tennessee; he is a leader in the field of precision medicine. **Edward S. Kim, MD**, a specialist in lung

Highlighted Lung Cancer-Related Abstract Presentations

Editor Note: Following is a partial list of abstract presentation sessions scheduled at the 2017 ASCO Annual Meeting. This is list offered for reader interest and is not inclusive of all lung cancer-related ASCO abstract presentations. Attendees of the ASCO Annual Meeting are encouraged to refer to the ASCO meeting program guide for the full range of abstract offerings.

June 3, 3 PM
Poster Discussion Session
Lung Cancer—Non-Small Cell Metastatic

Beyond PDL1: New Combinations and Molecular Predictors
Naiyer A. Rizvi - Discussant
Columbia University Medical Center

Predicting and Overcoming EGFR TKI Resistance
Myung-Ju Ahn - Discussant
Division of Hematology and Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine

June 4, 8 AM
Clinical Science Symposium
Old Targets, New Drugs: HER2 and MET

Abstract 8509
Efficacy, safety, and biomarker results of trastuzumab emtansine (TDM1) in patients (pts) with previously treated HER2-overexpressing locally advanced or metastatic non-small cell lung cancer (mNSCLC).
Tom Stinchcombe - First Author
Duke University

Abstract 8510
Ado-trastuzumab emtansine in patients with HER2 mutant lung cancers: Results from a phase II basket trial.
Bob T. Li - First Author
Memorial Sloan-Kettering Cancer Center
Leena Gandhi - Discussant
Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center

Abstract 8511
Impact of MET inhibitors on survival among patients (pts) with MET exon 14 mutant (METdel14) non-small cell lung cancer (NSCLC).
Mark M. Awad - First Author
Dana-Farber Cancer Institute

June 5, 8 AM
Oral Abstract Session
Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers

Abstract 8500
Gefitinib (G) versus vinorelbine+cisplatin (VP) as adjuvant treatment in stage II-IIIA (N1-N2) non-small-cell lung cancer (NSCLC) with EGFR-activating mutation (ADJUVANT): A randomized, Phase III trial (CTONG 1104).
Yi-Long Wu - First Author
Guangdong Lung Cancer Institute, Guangdong General

Abstract 8502
Prophylactic cranial irradiation (PCI) versus observation in radically treated stage III non-small cell lung cancer (NSCLC): A randomized phase III NVALT11 study.
Harry J.M. Groen - First Author
University of Groningen, University Medical Center Groningen

Abstract 8503
Nivolumab (nivo) ± ipilimumab (ipi) in advanced small-cell lung cancer (SCLC): First report of a randomized expansion cohort from CheckMate 032.
Matthew David Hellmann - First Author
Memorial Sloan-Kettering Cancer Center

Abstract 8504
Phase II study of maintenance pembrolizumab (pembro) in extensive stage small cell lung cancer (ES-SCLC) patients (pts).
Shirish M. Gadgeel - First Author
Karmanos Cancer Institute

Abstract 8505
Randomized trial of cisplatin and etoposide in combination with veliparib or placebo for extensive stage small cell lung cancer: ECOG-ACRIN 2511 study.
Taofeek Kunle Owonikoko - First Author
Emory University

Abstract 8506
Mature overall survival (OS) results from the LUME-Meso study of nintedanib (N) + pemetrexed/cisplatin (PEM/CIS) vs placebo (P) + PEM/CIS in chemo-naïve patients (pts) with malignant pleural mesothelioma (MPM).
Anna K. Nowak - First Author
School of Medicine, Faculty of Medicine and Health Sciences,
University of Western Australia

June 6, 9:45 AM
Oral Abstract Session
Lung Cancer—Non-Small Cell Metastatic

Abstract 9000
Progression after the next line of therapy (PFS2) and updated OS among patients (pts) with advanced NSCLC and PD-L1 tumor proportion score (TPS) >50% enrolled in KEYNOTE-024.
Julie R. Brahmer - First Author
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University

Abstract 9002
Efficacy of the addition of cisplatin to single-agent first-line chemotherapy in elderly patients with advanced non-small cell lung cancer (NSCLC): A joint analysis of the multicenter, randomized phase III MILES-3 and MILES-4 studies.
Cesare Gridelli - First Author
A.O.S.G. Moscati

Abstract 9004
Efficacy and safety results from AvaALL: An open-label, randomized phase III trial of standard of care (SOC) with or without continuous bevacizumab (Bev) treatment beyond progression (PD) in patients (pts) with advanced non-small cell lung cancer (NSCLC) progressing after first-line Bev and chemotherapy (chemo).
Jaafar Bennouna - First Author
Institut de Cancerologie de l'Ouest

Abstract 9005
CNS response to osimertinib in patients (pts) with T790M-positive advanced NSCLC: Data from a randomized phase III trial (AURA3).
Tony Mok - First Author
Chinese University of Hong Kong

Abstract 9006
Efficacy and safety of lorlatinib in patients (pts) with ALK+ non-small cell lung cancer (NSCLC) with one or more prior ALK tyrosine kinase inhibitor (TKI): A phase I/II study.
Alice Tsang Shaw - First Author
Massachusetts General Hospital

Abstract LBA9008
Alectinib versus crizotinib in treatment-naive advanced ALK-positive non-small cell lung cancer (NSCLC): Primary results of the global phase III ALEX study.
Alice Tsang Shaw - First Author
Massachusetts General Hospital
Next-Generation TKIs Move Up to First

cancer from the Levine Cancer Institute in Charlotte, North Carolina, will discuss NSCLC as a paradigm for precision medicine, while Dr. Schwartzberg will speak on using molecular testing in patients with cancer to produce useful results. Finally, **Deborah Schrag, MD**, from the Dana-Farber Cancer Institute in Boston, Massachusetts, will present a talk called "Aligning Value and Precision Medicine."

Sunday afternoon, **Christopher S. Lathan, MD,** from the Dana-Farber Cancer Institute will chair a session on tobacco cessation and screening recommendations in patients with lung cancer. **Irina Veytsman, MD**, from PinnacleHealth Cancer Center in Harrisburg, Pennsylvania, will give a presentation on implementing real-world smoking cessation programs. This will be followed by **Peter J. Mazzone, MD**, from the Cleveland Clinic in Cleveland, Ohio, who will describe how to develop a lung cancer screening program, while **Christopher S. Lathan, MD**, will wrap-up the session by discussing engagement with patients to address disparities in lung cancer screening.

The program for Monday, June 5, contains two final sessions relevant to lung cancer. The first is chaired by **Dr. Edward Kim**, titled "Clinical Pathways and New Drug Approvals: Maximizing Value Without Compromising Patient Care." Dr. Kim will give a presentation on the ways clinical pathways can influence the use of new drugs in practice. Attendees will then learn about cost-benefit analysis of expensive marginal drugs from **Eric S. Nadler, MD**, of Texas Oncology in Dallas, Texas. Finally, **Janet Freeman-Daily**, a lung cancer patient advocate from Gray Connections, will round out the session by discussing cost-benefit calculations from the patient's perspective.

The second lung cancer-related educational session on Monday is "Lung Cancer in the Older Population: Caring for the Whole Patient," chaired by **Craig H. Reynolds, MD**, from Florida Cancer Affiliates. He will speak on cultural issues impacting the care of dying patients. **Corey J. Langer, MD**, a professor of medicine from the University of Pennsylvania Abramson Cancer Center in Philadelphia, Pennsylvania, and editor of the *IASLC Lung Cancer News* will describe therapeutic challenges associated with interacting with older patients with lung cancer. Finally, attendees will hear Carolyn Jean Presley, MD, from the Yale Cancer Center in New Haven, Connecticut, discuss the current positive environment surrounding supportive care and decision making in older patients. ✦

GLOBAL RESEARCH REPORT

Dziadziuszko Follows in Footsteps of Thoracic Oncology Icon, Receives Award in Heine Hansen's Name

By Keightley Amen, BA, ELS

In 2015, the International Association for the Study of Lung Cancer (IASLC) and the European Society for Medical Oncology (ESMO) established an annual award to recognize Heine H. Hansen's lifetime of international contributions to lung cancer research and education.

This year, the HHH Award was bestowed upon an individual who met Hansen on multiple occasions and subsequently advanced Hansen's goals to enhance thoracic oncology research and bolster international collaboration in the lung cancer community.

Rafal Dziadziuszko accepted the honor and delivered a keynote address to an international audience of thoracic oncology specialists gathered at the European Lung Cancer Conference 2017, held May 5–8 in Geneva, Switzerland. He spoke poignantly about the influence Hansen and the IASLC had on his career.

"I met Heine Hansen on several occasions early in my career when he participated in events in Poland and Central-Eastern Europe to motivate us to join pan-European collaborations. This was before the Iron Curtain came down, when access to international research projects was limited," Dziadziuszko said. "He believed that our region needed to be fully integrated into European lung cancer research and motivated young oncologists to broaden their research capabilities. I feel I am one of his followers to realize this task."

Dziadziuszko serves as deputy head and national consultant in radiation oncology in the Department of Oncology and Radiotherapy at Medical University of Gdansk, Poland, as well as professor at the Medical University of Gdansk.

Like Hansen (1938–2011)–who was a former president of ESMO, a founder of IASLC, and a mentor to many in the field–Dziadziuszko has an impressive record of service and leadership.

- Co-author of more than 120 peer-reviewed publications and book chapters about lung cancer translational and clinical research
- Organization of academic clinical research studies in Central Europe
- Mentor of six past and ongoing PhD students
- Membership, committee service, and leadership in ESMO, IASLC, European Organisation for Research and Treatment of Cancer, European Society for Radiotherapy and Oncology, American Society of Clinical Oncology, American Association for Cancer Research, and Central and East European Oncology Group
- Chair of the non-small cell lung cancer (metastatic) track for the upcoming ESMO 2017 Congress, slated for September in Madrid, Spain

Rafal Dziadziuszko

"Dziadziuszko is a global leader with extensive international collaborations and a true follower of the ideas of Heine Hansen," said Fred R. Hirsch, chief executive officer of IASLC. "He is a brilliant researcher, a real clinical doctor who cares for his patients, and with a personality, which makes him very much liked and respected all over the world."

Dziadziuszko said he is thankful for his multidisciplinary team, as well as the impact the award will have in his current work, which aims to identify novel molecular targets for lung cancer, evaluate novel radiotherapy strategies in thoracic malignancies, and improve lung cancer screening.

"Together we have created a team focused on improvement of patient-centered practice with strong emphasis on translational and clinical research," he said. "The award motivates us to be more active and to further improve our performance." ✦

LUNG CANCER SURVIVORSHIP

Deb Violette, Lung Cancer Survivor and Advocate: Her Story

Editor's note: IASLC Lung Cancer News *is committed to including the patient's voice and experience of having lung cancer as part of our editorial breadth and mission. Here we are pleased to present Deb Violette's story. A courageous advocate and long-term survivor of lung cancer, Ms. Violette is also the president and CEO of Free Me From Lung Cancer, a non-profit organization committed to making lung cancer a national priority.*

Deb Violette

I was 44 years old when I was diagnosed with lung cancer. I had presented with recurring lung infections over the year leading to my diagnosis. In April 1998, I started to cough up blood. My doctor told me not to worry about it and put me on yet another round of antibiotics and scheduled to see me later in the week. His words "don't worry" did not settle me. I knew that there was something more serious than a lung infection. I went to my appointment and was seen by his assistant who after talking with me decided to send me to the hospital to get an x-ray.

My fear was confirmed and I was told I had lung cancer. The ensuing weeks were filled with doctor appointments and testing. Finally, I was informed I had stage III lung cancer. My course of treatment included chemotherapy, surgery to remove my right lower lobe, and radiation. Many thoughts ran through my mind. How do I tell my parents? My stepdad was fighting end-stage prostate cancer. How do I tell my employer? Will I lose my job? Will I be able to work? Will I survive this disease? These are the same questions every cancer patient faces.

Through my journey with lung cancer I knew that more needed to be done to help those diagnosed with the disease. As the days turned into months, I began to get my strength back. I joined a national organization and lobbied Congress for more funding. We were successful in getting money for research from the U.S. Department of Defense. During this time, I have become a major voice in the halls of the Maine State House helping to pass legislation to get funding for early detection, making it illegal to smoke in cars transporting children under the age of 18, supporting proclamations declaring November Lung Cancer Awareness Month, just to name a few.

I have represented lung cancer patients on a variety of panels including Lung SPORE, the U.S. Department of Defense's Congressionally Directed Medical Research Program, and the International Association for the Study of Lung Cancer Patient Advocate Committee. I currently sit on the Maine Cancer Foundation's Early Detection and Prevention Committee and Advisory Board member for the Maine Lung Cancer Prevention and Screening Initiative Program. I raised money for a national organization before starting my own foundation in 2012: Free ME from Lung Cancer.[1] Our mission is to reduce the suffering caused by a diagnosis of lung cancer by raising much-needed money for lung cancer research, early detection, and prevention. I am happy to say that we have funded over 20 low-dose CT scans for high-risk patients and will be funding our first $100,000 research grant this year.

My journey with cancer has spanned over 19 years. I know the devastating effects this disease has on the physical, emotional and psychological level. I wish I could say that my check-ups get easy with time but they don't. There is still fear that rises up at appointment time. The "what if" is always there. But, I will not let this disease define me—I shall define it. My disease has given me strength and shown me my passion, which is to help researchers find better treatment options, help change health care policy, and support those diagnosed with lung cancer and their families.

We have come a long way since I was diagnosed. The treatment I had is different compared to what most lung cancer patients are given today. We are living longer. Our voices are getting stronger and stronger; yet we still have to overcome the stigma long associated with this disease. No other cancer patient struggles with being asked if they smoked. We must stop the shame and blame of the patient for this disease—a disease that takes more lives than breast, ovarian, and cervical cancers combined.✦

Reference

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BREAKING NEWS BRIEFS

- Pembrolizumab (Keytruda) received FDA approval for use in combination with pemetrexed and carboplatin for the first-line treatment of patients with metastatic nonsquamous NSCLC, irrespective of PD-L1 expression. This approval was based on randomized phase II data from KEYNOTE-021, Cohort G1, in 123 previously untreated patients with metastatic nonsquamous NSCLC and no evidence of *EGFR* or *ALK* genomic tumor aberrations , which showed an improvement in overall response rate and in progression-free survival for patients receiving pembrolizumab plus pemetrexed and carboplatin compared to chemotherapy alone. (5/10/17)

- Brigotinib (Alunbrig) received FDA accelerated approval for use in patients with ALK-positive non-small-cell lung cancer (NSCLC) whose disease has progressed on or who are intolerant to crizotinib. Approval was based on a non-comparative, two-arm, open-label, multicenter clinical trial demonstrating a clinically meaningful and durable overall response rate (ORR) in crizotinib-exposed patients with locally advanced or metastatic ALK-positive NSCLC (the ALTA Trial; NCT02094573). (4/28/17)

- Lorlatinib was granted breakthrough therapy designation from the FDA for use in patients with ALK-positive metastatic NSCLC who had previously received one or more ALK inhibitors. Results were submitted to the FDA from the ongoing phase I/II study NCT01970865 (N = 54) presented at the 17th World Conference on Lung Cancer in 2016. Patients with ALK- or ROS1-positive NSCLC can develop resistance to TKI therapy, with the CNS as a common site of relapse. Lorlatinib is a selective brain-penetrant ALK/ROS1 TKI active against most known resistance mutations. (4/27/17)

- Pembrolizumab (Keytruda) received its second Med safe registration in New Zealand for PD-L1—positive patients with advanced NSCLC). Lung cancer is the leading cause of deaths due to cancer in New Zealand. In September 2016, funding of pembrolizumab was approved in New Zealand for treatment of advanced melanoma. (4/22/17)

CRISPR-Cas9 from page 3

may produce unintended results. Another concern is how modifying 1 gene will affect the function of other genes and molecules. Scientists will need to evaluate the effects of genetic edits in the laboratory to ensure they do not introduce genomic changes that have adverse health consequences.

Consider also that the process of extracting, genetically modifying, and multiplying cells ex vivo is a complicated and expensive process that may not be scalable. With regard to NSCLC, to justify their use, CRISPR-edited PD-1 knockout cells will need to demonstrate superior efficacy to already available anti-PD-1 antibodies.

Finally, all immunotherapies carry risk. Immune responses may be raised against normal tissues in addition to being raised against tumor cells, resulting in adverse events that may differ from adverse events commonly seen with other therapies. Adverse events reported in patients treated with immunotherapies commonly involve certain organ systems, including the skin, endocrine system, liver, gastrointestinal tract, nervous system, eyes, respiratory system, and hematopoietic cells.[4]

Exactly if and how the CRISPR-Cas9 gene-editing technique fits into the treatment of patients with advanced lung cancer remains to be determined. Although hopeful, researchers are proceeding with caution in the effort to move CRISPR-Cas9 from bench to bedside.✦

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NCI CORNER

INTERVIEW WITH MATTHEW HOLDERFIELD, PHD

NCI to Team Up with Cancer Research UK and the Cancer Research Technology Pioneer Fund on RAS Research

Matthew Holderfield

On April 19, 2017, Cancer Research UK (CRUK) and the Cancer Research Technology (CRT) Pioneer Fund announced a commitment of £2.5 million, or about $3.2 million, for a collaboration with the National Cancer Institute (NCI) as part of the RAS Initiative.[1]

The trio of human RAS oncogenes (*KRAS*, *NRAS*, and *HRAS*) are the most commonly mutated gene family in cancer, and about 35% of lung cancers are driven by activating mutations of *KRAS*.[2] Unlike oncogenic kinases such as ALK and EGFR, RAS proteins have not yet been successfully targeted by therapeutics and have been called "undruggable."

In 2013, the NCI launched the RAS Initiative and created a hub at the Frederick National Laboratory for Cancer Research (FNLCR) in Maryland to facilitate national and global collaboration among the RAS research community. *IASLC Lung Cancer News* spoke with Matthew Holderfield, PhD, the RAS Drug Discovery Group Lead at the FNLCR, about this new collaboration and what it means to the RAS Initiative as a whole.

Can you describe the purpose of the NCI RAS Initiative?

In short, the purpose is to develop effective treatments for patients with KRAS mutated cancers. The NCI RAS initiative has several strategies to achieve this. We conduct high throughput small molecule screening to identify new chemical leads that may develop into drugs. We do this ourselves or in collaboration with pharmaceutical companies with an interest in RAS. We also collaborate with academics and companies with ongoing drug discovery or basic research programs focused on targeting KRAS mutated cancers. We can provide reagents, technical support, or start a full collaborative research program, depending on the topic and level of interest.

To what extent is KRAS responsible for the growth and metastatic potential of advanced non-small cell lung cancer (NSCLC)?

This is a really interesting question. We know that KRAS is mutated in about 20%–30% of NSCLC. EGFR and NF1 mutations are also quite common in NSCLC, both of which promote growth by activating KRAS without mutating the KRAS gene itself. So, the actual number of tumors where KRAS plays a role is probably far greater than those with KRAS mutations. However, we also know that not all KRAS mutated cells are KRAS dependent, meaning that if KRAS is removed, some of those cancers will still divide. There are many redundant pathways that can promote cell division, and presumably some tumors will have mutations in other oncogenes independent of KRAS. We are really only starting to understand these mechanisms well enough to make predictions about KRAS dependence and there is a lot more work to be done in this area. Regardless, there are a lot of patients with tumors that activate KRAS, particularly in NSCLC.

Why is RAS considered "undruggable"? Is it a "fellow passenger" as opposed to an "oncogenic driver"?

RAS is definitely an oncogenic driver. The high number of mutations in cancer, and all the preclinical biology, validate that KRAS is an excellent and well-validated target. In this case, the term "undruggable" just means that people have tried to develop small molecule inhibitors without success. Kinases and G-protein coupled receptors are among the favorite targets because we understand how to design very good drugs for these proteins. Both types of enzymes have large clefts in the surface of the protein where small molecule substrates can bind. These clefts can be used as a "pocket" for a small molecule inhibitor to bind and disrupt protein function. Small proteins with few pockets or with very high affinity for substrates are not easy to drug. RAS seems to meet all these criteria for a difficult target. It is a relatively small protein with no obvious pockets for a small molecule to bind, with the exception of a single site that binds to GTP. Unfortunately, GTP binds very tightly to RAS, and there is a lot of GTP in the cell, so you would need a lot of drug to overcome GTP. It's no question that RAS is a difficult target, but I don't think it's impossible.

What will the CRUK and the CRT Pioneer Fund contribute to the RAS Initiative?

The CRUK Beatson Institute has already done some NMR screening to find fragments that bind to RAS. These are small compounds that aren't quite big enough to be a drug, but might be a starting point for developing a drug. This is an approach that we have not taken. So, it's a completely different way to get to a drug than we are currently pursuing and it's not something we would otherwise be working on. Additionally, they have enough chemistry support to really make some progress on the project. The NCI RAS initiative is focused primarily on RAS biology, and we depend on our collaborators for chemistry support. In this case, the CRUK Beatson Institute is well resourced for the project and they have some really smart scientists on the team.

Why has it been difficult to develop reliable assays for potential RAS agents?

I think the main reason is because there are no RAS inhibitors. It's difficult to develop an assay to find a RAS inhibitor if there are no RAS inhibitors to validate the assay. It's a chicken-or-egg problem that has really plagued the field. One way around this problem is to develop a lot of assays that test the same biology using orthogonal methods. If a potential RAS inhibitor scores positive in 1 assay, it could be an artifact; but a compound that scores in 5 different assays, each testing the function of the compound in slightly different ways, is much more likely to be an interesting drug candidate.

Are there realistic prospects for active intervention? Why have agents like the farnesyl transferase inhibitors failed in the past?

Definitely. I would not be working in the field if I wasn't optimistic about the possibilities. One significant challenge, and the reason FT inhibitors failed for KRAS mutated cancers, is redundancy. There are actually some very good FT inhibitors that effectively and potently prevent RAS farnesylation. However, mammals have evolved genetic and biochemical redundancies that cause KRAS to be get geranyl-geranylated when FT is inhibited. Essentially, the backup system kicks in and keeps KRAS functioning. So, even though the inhibitors work exactly as designed, KRAS dependent cells do not respond to FT inhibitors. Interestingly, another RAS isoform, HRAS, does not get geranyl-geranylated, and HRAS dependent cells are very sensitive to farnesyl transferase inhibitors. Unfortunately, HRAS mutations are far less common than KRAS mutations. Yet FT inhibitors are being evaluated for patients with HRAS mutated cancers. So I think the mechanism is still valid. We just have to find a similar vulnerability for KRAS, the protein that drives cancer progression in 20%–30% of cancers.

Conclusion

New resources and technologies are being brought to bear on the riddle of targeting RAS with small molecule drugs. Should the collaborators at the NCI's FNLCR and the CRUK Beatson Institute succeed in solving the chicken-or-egg dilemma of developing effective RAS drugs, as well as crafting reliable assays for their analysis, it will open new avenues for RAS drug discovery. Considering the current need for such agents, any progress toward targeting RAS proteins has the potential to have a significant impact in outcomes for many patients with lung cancer and other cancers. ✦

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LUNG CANCER RESOURCES

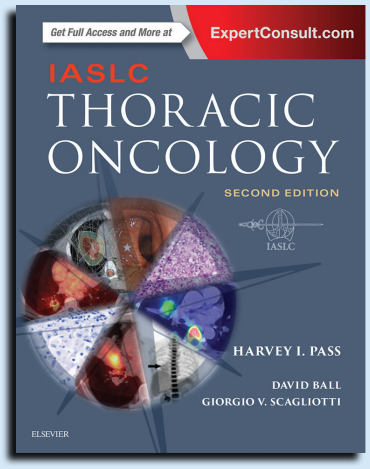
Announcement of New IASLC Publications

IASLC Thoracic Oncology (2nd ed.)

For the past 40 years the International Association for the Study of Lung Cancer has remained the only society exclusively dedicated to the study and treatment of lung cancer and other thoracic malignancies. These cancers are notoriously complicated, as was recently pointed out by their mutational burdens and histologic heterogeneity. New discoveries, novel trials, and changes in the standard of care are happening at an extraordinary rate, and medical, surgical, and radiation oncologists, as well as respiratory physicians, nurses, physician's assistants, and social workers, need reliable and up-to-date sources of information filtered by experts in the field.

The organization published the first edition of *The IASLC Multidisciplinary Approach to Thoracic Oncology* in 2014 with the hope that this would be the first step in consolidating this information in one comprehensive source. However, we never imagined the explosion of information that would occur over a 2-year period that would need to be presented to the reader. The genomic phenotyping of lung cancer has expanded remarkably, necessitating the discovery and validation of third-generation targeted agents. The staging system for lung cancer has been modified and externally validated. Histologic classification of the disease has helped to define high-risk patients in early-stage cancer. Radiation techniques are being refined and expanded with greater implementation in oligometastatic disease as well as for early-stage patients; and, most dramatically, immunotherapeutic strategies, not limited solely to checkpoint inhibition, now dominate many of the novel trials for metastatic disease as well as for neoadjuvant and adjuvant therapy. The plan with respect to the *The IASLC Multidisciplinary Approach to Thoracic Oncology* was always to be able to update, amend, and incorporate new ideas in later editions so that the basics were retained, but new discoveries were discussed by the "discoverers" themselves.

That is why we now have a new edition of the reference text, *IASLC Thoracic Oncology* and with our new publishing partner, Elsevier, hope to get information to the "treaters" of the future in "real time." This second edition, which includes updated material for more than 50 percent of the book, will help manage the wealth of new data so that the word gets out in a comprehensive, multispecialty, coordinated fashion. Novel findings are presented "hot off the press" in a way that academics and non-academics alike can keep up with thoracic cancer diagnostics and therapeutics so that the ultimate beneficiary is the patient.

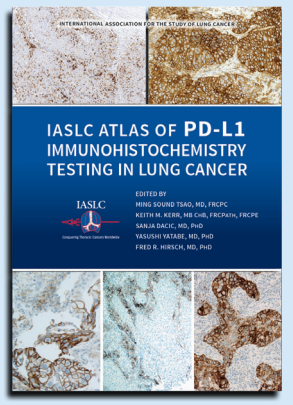


IASLC Thoracic Oncology is meant to provide both the practitioner and the fellow with an updated reference source that will be useful in dealing with lung cancer. It is also meant to further unify the international community through recognition that wars are won by forming allies; and in the battle against lung and other thoracic cancers, the IASLC stands for such an alliance. The battle is not only fought in the clinics and the hospitals but also on the educational front so as to supply the troops with successful plans for therapy. The editors' most profound wish is that the knowledge highlighted in the book and all of its associated future ventures will help to move the survival curves upward and toward the right.

—Executive Editor Harvey I. Pass, MD, with Editors David Ball, MD, FRANZCR, and Giorgio V. Scagliotti, MD, PhD

➲ Readers can obtain a copy of the *IASLC Thoracic Oncology* (2nd edition) by visiting Elsevier's Bookstore at https://www.us.elsevierhealth.com/ or at this year's ASCO meeting by visiting Elsevier's Booth in the exhibit hall (#5041).

IASLC Atlas of PD-L1 Immunohistochemistry Testing in Lung Cancer

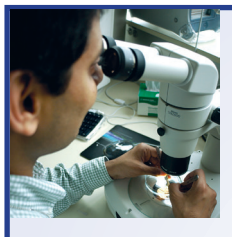


Despite very encouraging progress in the development and use of immunotherapy for patients with non-small cell lung cancer, much confusion remains regarding patient selection for each therapy. Programmed cell death ligand-1 (PD-L1) protein expression, as detected by immunohistochemistry (IHC) testing, has been widely used as a predictive biomarker assay for anti-PD-1/PD-L1 therapies. In fact, the PD-L1 IHC 22C3 pharmDx assay for determination of PD-L1 expression is approved by the US FDA for both first-line and second-line therapy with pembrolizumab. However, there is no clear understanding among physicians, thoracic pathologists, and clinical trialists regarding which assay to use for PD-L1 testing, and whether the various assays are interchangeable because each assay was codeveloped with discrete PD-1 and PD-L1 inhibitors. This complex biomarker scenario—the likes of which we have never faced before in lung cancer diagnostics—poses many challenges for pathologists, oncologists, and patients.

The International Association for the Study of Lung Cancer (IASLC) has recognized the importance and timeliness of this topic and convened an expert panel of authors to present current information about the emerging PD-L1 IHC assays, as well as to highlight both areas of clarity and debate. The newly published *IASLC Atlas of PD-L1 Immunohistochemistry Testing in Lung Cancer* is the result. The authors of this text have approached this topic with a wider lens, looking at the changing landscape of laboratory testing in general, as well as detailing the specifics of each assay and the current controversies regarding PD-L1 expression testing in lung cancer. Although this *Atlas* primarily aims to be a guide or resource for physicians and others involved in lung cancer diagnosis and treatment, it is the hope of the authors that this text will eventually give patients a more comprehensive understanding of the current biomarker scenario. Ultimately, we believe that through the creation of this *Atlas*, patients with lung cancer will receive the most state-of-the-art treatment options, based on up-to-date evidence, and will feel more confident and knowledgeable regarding their therapy.

—Editor Ming Sound Tsao, MD, FRCPC

➲ Readers can obtain a copy of the *IASLC Atlas of PD-L1 Immunohistochemistry Testing in Lung Cancer* by visiting https://www.iaslc.org/publications/iaslc-atlas-pd-l1-immunohistochemistry-testing-lung-cancer or contacting Pia Hirsch, pia.hirsch@iaslc.org



IASLC FOUNDATION

SPRING FUND DRIVE

The IASLC Foundation is kicking off its Spring Fund Drive. The Foundation experienced tremendous growth in 2016. Your donation supports IASLC fellowships for groundbreaking research.

The Spring Fund Drive will run from April through June, with the goal of gaining as many new donors as possible. From this we hope to grow the number of future fellowships offered.

Help Others Succeed – Make a Donation

Visit the IASLC Foundation webpage at IASLCFoundation.org to

- make a donation
- learn about the benefits of becoming an Annual Fund Individual Donor
- get general and comprehensive information about the IASLC Foundation: its mission and purpose, the programs it supports, the Spring Fund Drive

Interview with Bruce Johnson from page 1

dramatically transformed since 2004 with the discovery of the association between mutations of the epidermal growth factor receptor (*EGFR*) and treatment with EGFR-TKIs. This has been followed by the identification of *ALK* rearrangements and treatment with 4 different approved ALK tyrosine kinase inhibitors, *ROS1* rearrangements and treatment with crizotinib, V600E *BRAF* mutations and treatment with the combination of dabrafenib plus trametinib (now approved in Europe), and PD-L1 positive NSCLC (> 50%) and treatment with pembrolizumab. Thoracic Oncology is the flagship of Precision Medicine. I stated 5 years ago that a goal for the members of our Lung Cancer Program was to see more than 50% of our patients treated with agents other than chemotherapy by the time I retired from clinical medicine. I am very proud that we are nearing that mark in lung cancer; however, much more needs to be done.

What special challenges do you anticipate in an era when the NIH and NCI budgets are threatened with cuts?

The additional two billion dollars added to the NIH budget this year (2017) has been a welcome addition but is being done by a yearly appropriation. Despite this infusion of funds, our future remains uncertain with the administration proposing at the same time in May of this year that the budget of the NIH be cut by $5.8 billion dollars. The NIH and NCI have typically received bipartisan support from Congress. However, funding has been hampered by a series of continuing resolutions passed by Congress rather than the more traditional means of prioritization and funding through the appropriations process. I believe the real threat in these uncertain times is the lack of predictability faced by our young investigators either considering entering the field or staying in our field. The stability of funding to the scientific community and particularly our young investigators, really needs to be consistent with ongoing support from the federal government and other sources to make research a reasonable career choice. We look to our lawmakers to make rational decisions to continue to support our clinical and laboratory research which is critically needed for the continued advances and broader application of precision medicine.

Comment, if you can, on the research "alliance" that seems to exist between industry and academia?

The ongoing research in thoracic oncology has been vigorously supported by our industry colleagues. Those of us in thoracic oncology continue to benefit from the investment by the pharmaceutical industry developing drugs for different subsets of our patients. Our industry colleagues have been supportive of the precision medicine initiatives with multiple targeted agents now approved in NSCLC, including those targeting *EGFR* mutation, *ALK* rearrangements, *ROS1* rearrangements, *BRAF* mutations, and high levels of PD-L1 expression. My own personal experience working with the pharmaceutical industry has been highlighted by my interactions with GSK and now Novartis to target V600E *BRAF* mutant NSCLC. Mark Kris from Memorial Sloan Kettering Cancer Center and I chaired the Clinical Trials Committee of the Lung Cancer Mutation Consortium and were charged with helping identify targeted agents for subsets of our lung cancer patients. We did not have a regimen for *BRAF* mutant NSCLC so we approached GSK,which was successfully developing the BRAF inhibitor, dabrafenib, plus the MEK inhibitor, trametinib, for V600E *BRAF* mutant melanoma. The investigators from the Lung Cancer Mutation Consortium were already identifying the subset of patients with adenocarcinoma of the lung with *BRAF* mutations. GSK agreed to support the clinical trial if we identified the *BRAF* mutant lung cancer patients. We are now reporting a 63% response rate and a 10-month progression-free survival for the subset of patients with V600E mutations treated with the combination, which has been approved for use in Europe. We anticipate these meaningful industry collaborations will continue for our different subsets of patients with lung cancer.

What roles should academic/medical societies play in the advancement of science and medicine, now and in the future?

Our academic/medical societies play a critical role in the advancement and medicine. One of the pillars of the American Society of Clinical Oncology is the transformation of our cancer care delivery system by new investments in science which I enthusiastically support. The investments can come through both private and public support. Our societies play a critical role advocating for a consistent and increasing public investment in our research enterprise. I have participated in trips to Capitol Hill to meet with our elected representatives to advocate for continued and increasing federal funding. This is particularly critical for long-term studies that can continue to improve the outcomes of our patients with cancer and those at risk for cancer. The areas important for thoracic oncology that need to be supported by federal and foundation funding include ongoing work to develop methods to prevent smoking initiation and encourage smoking cessation, the leading cause of lung cancer. The other work that needs to be supported outside of industry includes lung cancer screening studies and important work on adjuvant therapies. These areas are critical for increasing the proportion of patients with early stage disease and to prevent those who undergo surgical resection from having disease recurrence. One must be mindful of the long-term research which is critical for our field.

I have been proud of my membership in the International Association for the Study of Lung Cancer. I vividly remember attending my first IASLC meeting in Toronto, Canada in 1985. I was one of 1,000 attendees at the 4th International meeting where I had 3 oral presentations and 3 poster presentations. I look forward to attending in Yokohama this fall and my ongoing work with both ASCO and the IASLC. ✦

Dr. Johnson is Chief Clinical Research Officer and Institute Physician at the Dana-Farber Cancer Institute, Boston, US, Professor of Medicine at Harvard Medical School, and Director of the Dana-Farber/Harvard Cancer Center Lung Cancer Program.

Lung Cancer Screening from page 1

significantly lower than the cost effectiveness figures from the NLST, (US $81K quality-adjusted life-year [QALY]), probably reflecting that the NLST did not have a standardized management process and the costly nature of the health care system in the US.[2]

Their results indicated that annual screening was more cost-effective than biennial screening and that scenarios that required higher levels of accumulated smoking exposure were more cost-effective. They opined that the annual scenario of individuals 55-75 years old who smoked >40 pack-years and who currently smoked or quit <10 years ago has an ICR of CD $41K.[1] An earlier lung cancer cost-effectiveness modeling study based on Canadian data, suggested CD $52K per QALY gained, which was improved by incorporating an adjunct smoking cessation program,[3] which improved the quit rate by 22.5% and further improved the incremental cost-effectiveness ratio to CD $24K per QALY.[3]

These results are consistent with the previously published actuarial approach by Pyenson et al,[4,5] which estimated the costs and benefits of annual lung cancer screening on a commercial insurance model for the 50- to 64-year-old high-risk individuals. From Pyenson's simulation, annual CT screening[5] of individuals with 30+ pack-years (PKY) of smoking was associated with a QALY cost of US $28K. However, incorporating the provision of standard smoking cessation measures into the model modestly increased cost but resulted in an improvement in the QALY's saved to somewhere between US $16K- US $23K.

Expressed another way, the cost of providing lung cancer screening as an insurance service in the US using an actuarial approach would be estimated at a cost of US $2.22 monthly per covered life compared to a calculated cost of US $1.02 in lung cancer screening if tobacco cessation services were included.[6]

Lung cancer cost-effectiveness has been mainly considered in the US context, which has a much more expensive health care system than that of Europe. The only cost-effectiveness data from a screening trial in Europe has come from the UK Lung Cancer Screening (UKLS), which was based on modeling using the baseline data, providing a figure of around UK £8.5K per QALY gained for screening.[7]

The modelling studies summarized above uniformly demonstrate that lung cancer CT screening is cost-effective. However, the major issue now is how best to implement lung cancer CT screening in different settings and how best to reduce the cost of delivering lung cancer screening in different international health care systems? ✦

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PERSPECTIVE

Clinical Labeling in Medicinal Products: An Interview With Dr. David Planchard About the Effects of *BRAF* Mutations on Non-small Cell Lung Cancer Outcomes and Therapeutic Selection

By David Planchard, MD, PhD

What was the rationale for conducting clinical research in *BRAF* mutation-positive NSCLC?

Recently, progress has been made in characterization of the oncogenic driver mutations that contribute to the molecular pathogenesis of lung cancers, including activating mutations in *EGFR* and *ALK* rearrangements. Moreover, lung cancer has one of the highest rates of genetic alterations when compared with other cancers. Some of the alterations are actionable via the administration of drugs that have already been approved, are available for off-label use for other indications, or are under investigation in clinical trials. Activating mutations in the *BRAF* gene, which are generally mutually exclusive from *EGFR* mutations or *ALK* rearrangements, act as an alternative oncogenic driver in NSCLC.

Most cancer cells harboring a $BRAF^{V600}$ mutation display a critical dependence on the activity of this oncogene for their growth and survival, and these cells are exquisitely sensitive to selective *BRAF* and *MEK* inhibitors, irrespective of tissue of origin. Several studies have reported poor outcomes for patients with NSCLC who have $BRAF^{V600E}$ mutations, as well as a decrease in response to platinum-based chemotherapy for these patients.[1-3]

Dabrafenib and trametinib target two different tyrosine kinases in the RAS/RAF/MEK/ERK pathway. Both dabrafenib and trametinib have demonstrated clinical benefit as monotherapies in randomized phase III studies when compared to chemotherapy for $BRAF^{V600}$ mutation-positive metastatic melanoma.[4,5] Preclinical research showed that the dabrafenib and trametinib combination was synergistic in enhancing cell-growth inhibition in the $BRAF^{V600E}$ mutation-positive NSCLC cell line. The combination of dabrafenib and trametinib was more effective in combination than either as single-agent therapy at inhibiting the MAPK pathway and inducing apoptosis. These effects in lung cancer cell lines were similar to those observed with the combination of dabrafenib and trametinib in $BRAF^{V600E}$ mutation-positive melanoma cells. Also, dabrafenib only inhibited ERK signaling in cells with mutant *BRAF*, whereas MEK inhibitors blocked the ERK pathway in both tumor and normal tissues.

These compelling clinical data for melanoma $BRAF^{V600}$ and preclinical data for NSCLC $BRAF^{V600}$ provided a rationale for conducting a study of BRAF and MEK inhibitors for patients with NSCLC.

How was France able to conduct and complete research on such a rare clinical entity?

The French National Cancer Institute funded a large-scale program in 28 molecular genetics centers and overseas entities for the systematic routine analysis of *EGFR* mutations and *ALK* rearrangements, as well as for *HER2*, *KRAS*, *BRAF*, and *PIK3CA* mutations in patients with advanced-stage nonsquamous NSCLC. In our phase II study with separate cohorts for treatment with dabrafenib alone or in combination with trametinib,[6,7] $BRAF^{V600E}$ mutational status was ascertained based on local testing in Clinical Laboratory Improvement Amendments (CLIA)-approved laboratories or their equivalents outside of the US. Clinical correlative work with the French Cooperative Thoracic Intergroup (data from the 28 molecular genetics centers) indicated that from April 2012 to April 2013, a genetic alteration was recorded in approximately 50% of the NSCLC analyses. As part of this program, 13,906 patients were tested for *BRAF* mutations; of these, 262 (2%) were positive for a *BRAF* mutation (80% were $BRAF^{V600E}$).[3] In 2015, molecular screening was performed in France on roughly 26,000 patients with NSCLC. This systematic molecular screening program, which included *BRAF* mutation status, clearly helped us to identify a high number of patients with NSCLC who harbored a *BRAF* mutation and who were potentially eligible for clinical trials.

With approval of both dabrafenib and trametinib for NSCLC, what other kind of "label changes" occurred based on this research? What was the process for the regulatory changes?

We conducted a phase II study examining the clinical activity of the BRAF inhibitor dabrafenib as a single agent (Cohort A) and in combination with MEK inhibitor trametinib (Cohort B) in patients with advanced NSCLC and $BRAF^{V600E}$ mutations whose disease had relapsed or progressed after prior therapy.[6,7] The third group (Cohort C) comprised treatment naïve patients who received the combination therapy in the first-line setting. The results demonstrated clinically meaningful antitumor activity with an objective response rate of 33.3% for Cohort A and 63.2% for Cohort B. The median progression-free survival was also longer for Cohort B when compared with Cohort A: 9.7 months vs. 5.5 months, respectively. This observation is consistent with those in metastatic melanoma studies. The most common adverse events (>20% incidence) were pyrexia, nausea, vomiting, peripheral edema, diarrhea, dry skin, decreased appetite, asthenia, chills, cough, fatigue, rash, and dyspnea.

Data from Cohort C for combination dabrafenib and trametinib in the first-line setting are not yet mature and will be presented in the near future.

These results indicated that inhibition of a *BRAF* mutation defines a new class of patients with a specific oncogenic driver. This trial was the first assessment of combined BRAF and MEK inhibition in NSCLC. The results were particularly noteworthy in light of scarce pre-existing data and the clear unmet need for effective targeted therapy for patients with *BRAF*-mutated NSCLC.

Based on the results of this phase II trial, the Committee for Medicinal Products for Human Use adopted a positive opinion on February 23, 2017, and recommended a change to the terms of the marketing authorization for the medicinal products Tafinlar (Novartis, dabrafenib) and Mekinist (Novartis, trametinib), stating specifically that "Trametinib in combination with dabrafenib is indicated for the treatment of adult patients with advanced NSCLC with a [$BRAF^{V600}$] mutation." On April 3, 2017, the European Commission approved dabrafenib in combination with trametinib for the treatment of patients with $BRAF^{V600}$-positive advanced or metastatic NSCLC.

Are the majority of patients with NSCLC and $BRAF^{V600E}$ mutations being treated on or off protocol in France at this point?

I would say that during the accrual periods for Cohort A (October 2010 to April 2014) and Cohort B (December 2013 to January 2015) most patients in France with $BRAF^{V600E}$ mutations were included in this phase II trial. Since the trial has closed, patients are now receiving combination dabrafenib and trametinib off label, or they have been enrolled in a French phase II basket study, "Phase 2 Study Assessing Secured Access to Vemurafenib for Patients With Tumors Harboring BRAF Genomic Alterations (AcSé)."[8] This trial is ongoing for patients with a $BRAF^{V600}$ mutation, regardless of histologic type. However, patients in the trial are treated with vemurafenib alone, which—based on the results from our phase II study—is not the optimal strategy in this setting. All reports of $BRAF^{V600}$ mutation cases that we have at Gustave Roussy are systematically discussed during a monthly thoracic molecular tumor board to decide the best strategy for these patients; if they are not eligible to be included in a clinical trial, the off-label use of combination dabrafenib and trametinib is often recommended.

David Planchard

Are similar processes being instituted for other uncommon mutations, such as the *MET* exon 14 skipping mutation?

For less common driver mutations such as the *MET* exon 14, *RET*, and *NTRK* mutations, it has become increasingly difficult to initiate and complete prospective trials. Multicenter registries might permit the generation of meaningful clinical data in a short time period, such as with patients with *RET* rearrangements who were treated with different multikinase inhibitors including cabozantinib, vandetanib, sunitinib, sorafenib, lenvatinib, nintedanib, ponatinib, and alectinib. However, prospective trials with larger sample sizes are needed, and collaboration among various investigators and centers around the world is crucial. In France, we are screening for these mutations in most centers, but we lack specific trials for these populations. Most inhibitors are used off label; crizotinib for patients with a *MET* exon 14 mutation is an example.

Are there other data on successful BRAF or MEK inhibitors, either alone or in combination, that might sway decision making regarding treatment?

I would say no because we do not have any data regarding combination

vemurafenib and cobimetinib for *BRAF*^{V600E} mutation-positive NSCLC. No prospective trials have been conducted in NSCLC that are similar to what has been done in *BRAF*^{V600} mutation-positive melanoma. The only prospective results we have for vemurafenib come from the histology-independent, phase II basket study of vemurafenib monotherapy for patients with non-melanoma cancers who harbor *BRAF*^{V600} mutations.[9] In France we also have conducted the previously mentioned closed basket trial of single-agent vemurafenib.[2] Final results are pending for both trials; however, neither trial specifically focuses on NSCLC, and no combination with a MEK inhibitor such as cobimetinib has been tested. To my knowledge, combination dabrafenib and trametinib is one of the best strategic options for patients with NSCLC who have *BRAF*^{V600} mutations. The next step in NSCLC *BRAF*^{V600} will be to test the benefit of immunotherapy treatments (anti-PD-1 or PD-L1) either alone or in combination with dabrafenib and trametinib as is currently done in melanoma. ✦

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MEETING SUMMARY

ELCC 2017 Unveils New Research Regarding Screening, Immunotherapy, Treatment Planning, and More

By Keightley Amen, BA, ELS

In early May, at the seventh annual European Lung Cancer Conference (ELCC) in Geneva, Switzerland, multidisciplinary lung cancer professionals gathered to learn about the latest research advances in the field.

Men Require More Frequent Screening for Lung Cancer

A study presented at ELCC retrospectively reviewed patients who underwent chest computed tomography (CT) screening to investigate gender differences in screening intervals, stage, and pathology in newly developed lung cancer.[1]

It found that the average time between a previous lung cancer scan and a scan that diagnosed lung cancer was significantly longer in women (5.6 years) than in men (3.6 years). However, lung cancer stage at diagnosis was higher in men: 82% of lung cancers diagnosed in women were stage I compared to 49% in men. In addition, pathological analyses showed that solid nodule (72%) was the most common finding in men and ground glass opacity nodule (45%) was the most common in women.

The study suggests that follow-up scans for women might be necessary only every two to three years.

White Blood Cell Counts May Predict Response to Immunotherapy

Another study presented at ELCC found that white blood cell counts can predict whether patients with lung cancer will benefit from immunotherapy.[2]

The researchers assessed 54 patients with non-small cell lung cancer (NSCLC) who received nivolumab 3 mg/kg every 14 days. They measured white blood cell counts at baseline, after two nivolumab cycles, and after four nivolumab cycles, then compared counts between nivolumab responders and non-responders.

White blood cell counts at baseline and during therapy predicted whether patients would respond. Furthermore, greater number and concentration of natural killer cells at baseline were associated with response, as were an increase in natural killer cells during treatment and a greater number and concentration of CD8-positive T cells that expressed PD-1.

Osimertinib Reduces Symptom Burden and Improves Functioning

A recent analysis of patient-reported outcomes from the AURA3 phase III clinical trial found that osimertinib treatment improves cancer-related symptoms in patients with advanced epidermal growth factor receptor (*EGFR*) mutation NSCLC who progressed after first-line EGFR tyrosine kinase inhibitor therapy.[3]

According to previously released results, patients taking osimertinib had significantly longer progression-free survival than those on chemotherapy (10.1 months versus 4.4 months). The latest analysis found that osimertinib also reduced the symptoms of lung cancer, primarily appetite loss, fatigue, breathlessness, and chest pain. Osimertinib also significantly improved global health status, physical functioning, role functioning, and social functioning.

Pretreatment with PD-1/PD-L1 Checkpoint Inhibitor Boosts Salvage Chemotherapy in Patients with Advanced NSCLC

Another study in NSCLC reported that patients with advanced disease who require salvage chemotherapy are 30% more likely to achieve a partial response if they have been pretreated with a PD-1/PD-L1 checkpoint inhibitor compared to those who have not.[4]

The retrospective analysis assessed patients with stage IV NSCLC and controls: 67 had been previously treated with a PD-1/PD-L1 inhibitor, and the remaining 15 served as controls. All had been pretreated with chemotherapy. CT scans within the first month and then every six weeks showed a significantly higher partial response rate in those who had received a PD-1/PD-L1 inhibitor compared to controls (27% versus 7%). Stable disease was seen in 51% of cases and 53% of controls, and progressive disease was seen in 22% of cases versus 40% of controls.

More Specific Criteria May Help Prolong Immunotherapy After Disease Progression

Additional research regarding immunotherapy has found that some patients with advanced lung cancer may benefit from prolonged immunotherapy even after the disease has progressed as evaluated by standard criteria. The ELCC presentation provided provide new, more specific criteria that may allow certain patients to continue treatment.[5]

The current Response Evaluation Criteria in Solid Tumours (RECIST) evaluates changes in tumor size and identifies whether patients are responding to treatment or progressing. According to RECIST, when a CT scan finds that a tumor is growing and a patient is progressing, treatment is changed to best supportive care or a different drug.

In a post hoc analysis of the phase 2 POPLAR trial, researchers assessed response to treatment with RECIST versus immune-related RECIST criteria. The study allowed patients to continue atezolizumab treatment if they had not progressed according to immune-related RECIST and had no major toxicities, even if RECIST indicated progression.

The newly reported research evaluated overall survival and performance status in the 61 patients who continued atezolizumab after standard progression. Tumors stabilized or shrunk in 82%; median overall survival was 11.8 months and objective response rate increased when immune-related RECIST was used.

Flu Vaccine May Be Contraindicated with PD-1/PD-L1 Checkpoint Inhibitors

Patients with cancer receiving PD-1/PD-L1 checkpoint inhibitors may be at increased risk of adverse events after receiving the seasonal influenza vaccination.[6]

Twenty-three patients with cancer who were receiving nivolumab or pembrolizumab were vaccinated with a trivalent influenza vaccination and followed for safety, efficacy, and frequency of immune-related adverse events (irAEs). Ten controls received the same vaccine.

All patients showed adequate immune response to the vaccine, none experienced severe adverse events attributable to the vaccine, and none developed influenza infection. However, there was an unusual high frequency of irAEs (52.2%), and six patients (26.1%) experienced severe grade 3 or 4 irAEs.

The most common were skin rashes and arthritis (13% each), followed by colitis and encephalitis (8.7% each), hypothyroidism, pneumonitis, and neuropathy (4.3% each).

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PATIENT CARE

Role of Molecular Testing for AHCP Caring for Patients with NSCLC

By Kimberly Rohan, ANP-BC

Kimberly Rohan

Treatment for patients with NSCLC today has become increasingly personalized over the past few years. It is paramount to be able to test a patient's tumor for mutations and other molecular aberrations to provide the most effective care. In 2004, the observation was made that somatic mutations in the kinase domain of *EGFR* strongly correlated with the sensitivity to EGFR TKIs.[1] This discovery led to a change in practice for those whose tumors had the *EGFR* mutation. More recently, very specific therapy has emerged for those patients who develop resistance to the TKIs (T790M). Currently, the known mutations and molecular translocations for lung cancer for which there are therapies include *EGFR, T790M, ALK, ROS1, BRAF*, and *MET*.

The issue for many is the lack of available tissue to run the various tests and to prioritize the sequencing of testing. Several blood-based tests are now available for those who cannot get enough tissue for testing. The sensitivity of these blood tests, or liquid biopsies, is about 46% with specificity of 97%, positive predictive value 78%, and negative predictive value 90%.[2] It is important that the patient understands the risks and benefits of blood testing versus tissue testing, which may require a repeat biopsy.

A multidisciplinary approach is key to ensuring that during biopsy adequate tissue is obtained to perform testing and the most efficient process is in place with the pathology department to ensure prompt testing.

The role of the Advanced Practice Practitioner (APP) in caring for these patients is to ensure that the testing is completed in a timely manner and that the patient understands the significance and clinical implications of the testing. By ensuring testing is properly completed, patients will receive appropriate treatment based on the molecular biology of their individual tumors, instead of suboptimal care. Research in the field of lung cancer and targeted therapies is moving very rapidly, requiring the APP to stay informed of the newest therapies, testing strategies, and management of the side effects of these new therapies. A multidisciplinary approach is key to ensuring that during biopsy adequate tissue is obtained to perform testing and that the most efficient process is in place with pathology departments to ensure prompt testing. Nurse navigators have become key members of the multidisciplinary team in educating patients, families, and other health care providers on the importance of these additional tests. Often these test results can take several days to return. This, therefore, requires diligence in tracking the results and ensuring the results are available to clinicians. Each team needs to determine who will share the results and how to make certain they will be available for all team members to view.

As the care of lung cancer patients continues to evolve, it is critical that APPs involved in the care of these patients stay informed. APPs are key members of the treatment team throughout the care continuum. Joining IASLC is one way for APPs to keep abreast of the ever-changing therapeutic landscape in the care of patients with lung cancer. ✦

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Screening Trial in France from page 2

screening in relation to lung cancer mortality is an important area of research. Hopefully, through creative approaches to funding and trial participation, France will be able to contribute to the growing volume of international data on this topic within the next few years. Maybe recent renewal in policy makers in France will result in significant changes in preventive medicine. ✦

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Names and News

Robert J. Cerfolio, MD, MBA, has been appointed chief of clinical thoracic surgery at NYU Langone Medical Center, New York, US. Dr. Cerfolio also will serve as director of the new Lung Cancer Center at NYU Langone's Perlmutter Cancer Center. Prior to his appointment, Dr. Cerfolio served as chief of the section of thoracic oncology and the James H. Estes endowed chair for lung cancer research at University of Alabama at Birmingham School of Medicine, Birmingham, US.

Steven M. Keller, MD, has been appointed Senior Principal Scientist, Oncology Clinical Research, at Merck, Kenilworth, US. Previous to this appointment, Dr. Keller was Director, Thoracic Surgery, Weiler Hospital; Professor of Cardiothoracic Surgery at the Albert Einstein College of Medicine; and faculty member, Montefiore Lung Cancer Preceptorship Program, New York, US.

Prof. Nir Peled, MD, PhD, FCCP, was elected Head of the European Respiratory Society Thoracic Oncology Assembly. Prof. Peled is a pulmonologist and medical oncologist. He is the head of the Thoracic Cancer Unit and The Center of Precision Cancer Care at Davidoff Cancer Center, and Associate Professor at the Sackler Faculty of Medicine, Tel Aviv University, Israel.

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