Osimertinib: A New Option in Non-Small Cell Lung Cancer

Q&A with Alice T. Shaw, MD, PhD, and Ranee Mehra, MD

By Erik J. MacLaren, PhD

Osimertinib is a second-generation anaplastic lymphoma kinase (ALK) inhibitor that was recently approved in the US as a second-line treatment for ALK-rearranged non-small cell lung cancer (NSCLC) after progression on the standard first-line therapeutic, crizotinib. Data from the J-ALEX trial, a Japanese phase 3 study directly comparing first-line efficacy and the safety of alectinib versus crizotinib, were presented at the 2016 ASCO Annual Meeting, showing that alectinib significantly increased progression-free survival (PFS) in patients. IASLC Lung Cancer News spoke with Alice T. Shaw, MD, PhD, from Harvard Medical School in Boston, Massachusetts, and Ranee Mehra, MD, from the Fox Chase Cancer Center in Philadelphia, Pennsylvania, to find out what these results might mean for the treatment of ALK-positive NSCLC.

Shaw: J-ALEX is almost a game changer. The results suggest that alectinib is superior to crizotinib as a first-line tyrosine kinase inhibitor (TKI) therapy, but there are some minor issues with this study that could impact extrapolation of the findings to all patients. Ultimately, we need to see the results from the global ALEX trial to confirm that PFS with alectinib is superior to crizotinib, and to determine the magnitude of the PFS benefit with alectinib.

Mehra: The hazard ratio (HR) of the alectinib arm versus the crizotinib arm in the J-ALEX trial was 0.34, which is very impressive, so I think that J-ALEX is indeed a game changer.

Q: Is the J-ALEX study a “game changer” in terms of how we treat ALK-positive NSCLC?

Shaw: I think we should wait for the global ALEX results before we start using alectinib routinely as first-line therapy. I do think, however, that there are specific scenarios in which we should use first-line alectinib. Specifically, I believe alectinib can and should be used as a first-line therapy in patients who have ALK+ lung cancer and brain metastases at diagnosis, given the results from the single-arm phase 2 studies of alectinib and what we now know from J-ALEX in terms of the benefit of alectinib over crizotinib in patients with brain metastases.

Q: Should we adopt alectinib front-line routinely, even in the absence of the concomitant data from the global ALEX study?

Mehra: I believe alectinib can and should be used as a first-line therapy in patients who have ALK+ lung cancer and brain metastases at diagnosis, given the results from the single-arm phase 2 studies of alectinib and what we now know from J-ALEX in terms of the benefit of alectinib over crizotinib in patients with brain metastases.

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Meeting Preview

IASLC WCLC 2016: Active Prevention, Accurate Diagnosis, Advanced Care

Dear Colleagues,

IASLC WCLC 2016, with the theme “Active Prevention, Accurate Diagnosis, Advanced Care,” will be a multidisciplinary conference covering all aspects of lung cancer. The conference will inform participants about the most recent scientific advances in the field of lung cancer and will provide updates on the state-of-the-art management of patients with lung cancer. Multiple sessions will cover multidisciplinary topics.

Major topics will include the 8th TNM classification, molecular diagnosis, extended surgical procedures, and advances in radiotherapy. With respect to systemic treatment, the focus will be on targeted therapies, e.g., third-generation EGFR tyrosine kinase inhibitors, and immunotherapy, particularly immune checkpoint inhibitors. These advances will be covered in scientific and educational sessions as well as in industry-supported symposia.

continued on page 4
FDA’s New Tobacco Rule

By Kenneth Michael Cummings, PhD, MPH

The US FDA recently finalized a new rule (http://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm388395.htm) that will extend its regulatory authority to all tobacco products, including small and large cigars, hookah tobacco (also called waterpipe tobacco), pipe tobacco, nicotine gels, dissolvable tobacco products, and electronic cigarettes (e-cigarettes).

What will the new rule do?

This new rule builds on groundwork, established in June 2009, giving the FDA authority to regulate cigarettes, cigarette tobacco, roll-your-own tobacco (RYO), and smokeless tobacco products, after Congress passed and the President signed the Family Smoking Prevention and Tobacco Control Act. This Act gave the agency authority to regulate the manufacturing, distribution, and marketing of tobacco products. The new regulations extend FDA authority to a wider range of tobacco products. Table 1 provides a quick summary of what the new tobacco rule will do.

Why did the FDA take this action?

Before the FDA finalized a rule deeming tobacco products to be subject to the Federal Food, Drug, and Cosmetic Act, tobacco products such as small and large cigars, pipe tobacco, hookah tobacco, nicotine gels, dissolvable tobacco products, and e-cigarettes could be sold without any review of their ingredients, how they were made, or their potential dangers. In addition, there was no federal law stopping retailers from selling e-cigarettes, hookahs, or cigars to youth under the age of 18. This new rule will allow the FDA to better fulfill its mandate to improve public health and to protect future generations from the risks of tobacco use. The tobacco product review process allows the FDA to evaluate important factors such as ingredients, product design, and health risks, as well as the appeal of products to youth and non-users.

What’s the bottom line?

Public health groups have been united in their view that the FDA should have the authority to regulate all tobacco products, not just cigarettes, RYO, and smokeless tobacco, as has been the case since the 2009 Family Smoking Prevention and Tobacco Control Act. That said, there remains a vigorous debate within the public health community as to how to implement the new tobacco rule. While there has been a decline in cigarette use by teens over the past decade, the increasing use of small cigars, hookahs, and e-cigarettes by teenagers has caused some public health groups to urge the FDA to aggressively restrict the marketing of these products, especially the use of flavoring agents that may make these products appealing to youth. Other public health groups have argued that the FDA ought to apply a light touch when it comes to regulating non-combustible tobacco products such as dissolvable tobacco products and e-cigarettes, since these products could conceivably serve as safer substitutes for combustible tobacco products, especially cigarettes. By treating all tobacco products the same from a regulatory prospective, some have worried that this would stifle development of safer products, unfairly favoring well-resourced tobacco manufacturers in meeting the FDA’s regulatory hurdles, and potentially misleading consumers into believing that all tobacco products are equally risky, which is not the case.

In the end, it is good that FDA has been given the authority to regulate all tobacco products. However, what this will ultimately mean in terms of public health benefit will depend in large measure by how the FDA chooses to implement this authority. Will the FDA recognize the continuum of risk that obviously exists between different classes of tobacco products and tailor its regulations accordingly, or will it instead apply its regulatory authority in a way that assumes all tobacco products are the same? Only time will tell.

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

Table 1. Provisions of the New Law.

The final rule will subject all manufacturers, importers and/or retailers of newly regulated tobacco products to any applicable provisions related to tobacco products in the Federal Food, Drug, and Cosmetic Act and FDA regulations, including:

- Registering manufacturing establishments and providing product listings to the FDA
- Reporting ingredients, and harmful and potentially harmful constituents
- Requiring premarket review and authorization of new tobacco products by the FDA
- Placing health warnings on product packages and advertisements
- Not selling modified risk tobacco products (including those described as “light,” “low,” or “mild”) unless authorized by the FDA

In addition, several provisions aim to restrict youth access to tobacco products, including:

- Not allowing products to be sold to persons under the age of 18 years (both in person and online)
- Requiring age verification by photo ID
- Prohibiting the sale of tobacco products in vending machines (unless in an adult-only facility)
- Forbidding the distribution of free samples
United States of America

There are now 2 distinct immunotherapy drugs approved, nivolumab and pembrolizumab, for the treatment of NSCLC after failure of platinum-based chemotherapy. Both nivolumab and pembrolizumab produce similar response rates and toxicity profiles. However, the toxicity profiles differ substantially from what oncology nurses are accustomed to seeing.

While fatigue, rash, and diarrhea may be mild common adverse events with these drugs, and are side effects that most oncology nurses or advanced practitioners are accustomed to trouble-shooting, immune mediated toxicities such as colitis, pneumonitis, dermatitis, and endocrinopathies can be severe and, at times, life-threatening. Nurses now must learn the signs and symptoms of these new toxicities, as well as the very different management strategies required to control them.

Several nursing educational platforms such as Medscape, Clinical Care Options, OncLive, Meniscus, the Oncology Nursing Society (ONS), and the Advanced Practitioner Society of Hematology and Oncology (APSHO), as well as others, have launched continuing education programs aimed to teach nurses about these new therapies and their toxicities.

Canada

Currently, there are two immunotherapy drugs used in Canada: nivolumab and pembrolizumab, which both carry the same indications as in the United States in the second-line setting for metastatic NSCLC.

The key to successful treatment using this new class of agents is communicating with patients and providing ample education based on particular symptoms that the patient might develop.

Cancer Care Ontario (CCO), the British Columbia Cancer Agency (BCCA), and other cancer nursing organizations in Canada have created guidelines for managing these unique side effects as well as patient education information in lay language.

Most of the cancer centers have also established a callback program to patients on these therapies. This is an ideal way to capture all patients starting on immunotherapy and to monitor them throughout their treatment. These individuals are flagged in a computerized system and nurses call them at certain time points to perform an assessment over the phone.

Key questions are added in a drop-down list based on the organ and body system to be assessed. This is an efficient way to capture immune-mediated adverse events through electronic documentation at the right time and to provide necessary and timely interventions.

United Kingdom

Currently, there are no immunotherapy drugs approved in the UK, although both nivolumab and pembrolizumab have been submitted for approval to both the National Institute for Health and Care Excellence (NICE) and the Scottish Medicine Consortium (SMC). These drugs are available in the private setting, in clinical trials, and on compassionate use programs while the UK awaits decisions regarding approval from NICE and SMC.

Nurses are just beginning to gain experience in managing patients on these new drugs. However, initial impressions are positive. Nurses have reported improvements in patient quality of life, with minimal toxicities from these drugs.

However, we must not be complacent, as these drugs can result in severe immune toxicities that can present at any point in the course of treatment. We have concentrated heavily on the nursing management of patients receiving immunotherapies at the National Lung Cancer Forum for Nurses (NLCFN) Conference held last year, and we are currently putting together an educational tool for nurses on immunotherapies.

Australia/New Zealand

In Australia and New Zealand, there is an expanded access program to use nivolumab for patients who have already received first-line chemotherapy and require second-line treatment. Pembrolizumab is available only to patients participating in clinical trials in Australia.

As far as educational resources for nurses and patients, we have relied heavily upon our melanoma nurse colleagues to educate and support us for the challenges coming our way as we start implementing this new class of drugs in the management of our metastatic lung cancer patients. We are very appreciative of the support given to us by the melanoma community.

For formal education support, the Australian Cancer Nurses Society (CNSA) has supported us with education days, as well immunotherapy components during our annual conferences, and immunotherapy education will be incorporated into our Australian Lung Cancer Conference in Melbourne this August.

Roswell Park Cancer Institute to Conduct First CimaVax Trial in the United States

Roswell Park Cancer Institute in Buffalo, New York, US, expects to be the site for the first US clinical trial of CimaVax, the groundbreaking lung cancer vaccine developed at Cuba’s Center for Molecular Immunology (CIM). Set to commence within the next 6 months, pending clearance from the FDA, the trial will evaluate the benefit of CimaVax plus nivolumab in patients with advanced non-small cell lung cancer (NSCLC) whose disease has progressed after first-line treatment and who are eligible to receive nivolumab, the standard current of care. The single-arm, single-institution trial will begin with a two-part phase I dose-ranging study to determine the optimal dose as well as the optimal vaccination schedule; it will then proceed to a phase II trial to assess efficacy and safety of the immunotherapy combination, explains Professor Mary Reid, PhD, MSPH, Director of Cancer Screening and Survivorship at Roswell Park Cancer Institute. “We plan to enroll 18 patients in each part of the phase I trial and 60 patients in phase II,” says Dr. Reid.

“The primary phase II endpoint will be overall survival at 1 year. Patients will remain on therapy as long as they continue to respond.”

CimaVax is an epidermal growth factor (EGF)-based vaccine that contains one of the most important ligands of the epidermal growth factor receptor (EGFR) coupled to a carrier protein, recombinant P64, and administered together with an adjuvant. The carrier protein and the adjuvant are necessary to break down the tolerance against EGF, a self-protein.1 Vaccination with CimaVax initiates a specific immune response that sequesters EGF, essentially starving the tumor of the ligand that feeds the EGF receptor, which stops tumor growth and slows or halts disease progression.

Development of the CimaVax vaccine for lung cancer began more than a decade ago because Cuba had no second-line therapies to offer patients, explains Dr. Reid. With no access to targeted agents or immunotherapies because of the trade embargo, Cuban patients with advanced lung cancer who failed first-line chemotherapy had no treatment options. Today, CimaVax is widely used in Cuba in the primary care setting, where patients with advanced lung cancer receive monthly vaccine injections from their primary care physicians.

In clinical trials in Cuba, CimaVax improved overall survival in patients with advanced NSCLC compared with controls.

In clinical trials in Cuba, CimaVax improved overall survival in patients with advanced NSCLC compared with controls.1,2 “The greatest benefit was seen in patients with high pretreatment circulating EGF ligand levels and those who demonstrated a good anti-EGF antibody response,” says Dr. Reid. In addition, among patients who achieved seroconversion, those who were 60 years continued on page 11.
Mehra: I would expect that the global ALEX results are going to be positive, based on the J-ALEX data, but there are probably pharmacogenomic differences between the populations included in these trials. Therefore, I think it is reasonable to see the global ALEX data and the exact benefit of the drug in the first-line setting before it becomes a standard of care. On a case-by-case basis, it may be something to consider now for patients with preexisting brain metastases.

Q: If alectinib becomes the standard first-line option, what do we give second-line or third-line?

Shaw: We do not know much yet about patients whose disease has progressed on first-line alectinib, but I would anticipate that 40% or 50% of these patients could have a secondary mutation in ALK that is causing resistance, such as G1202R or I1171 mutations. Other ALK inhibitors, particularly lorlatinib, do have activity against these mutations, so I envision that another ALK inhibitor could be an option in the second-line setting after progression on alectinib, depending on the resistance mechanism that is identified. Of note, ceritinib is inactive against G1202R. Chemotherapy is an option at any point, but I would argue that patients whose disease progresses on alectinib and who have an ALK resistance mutation should have another ALK inhibitor before going on to chemotherapy.

Mehra: Ceritinib is an FDA-approved agent in the second-line setting, although we do not have a lot of experience with its activity after alectinib. Anecdotally, there are case series experiences of ceritinib showing activity after failure on alectinib, so I think ceritinib is a reasonable standard option. We also have some emerging data about resistance mutations, which may help guide subsequent treatment selection. Ongoing trials of newer ALK inhibitors, such as lorlatinib and X-396, and immunotherapeutic agents are also reasonable options to explore before going on to chemotherapy.

Mehra: Although there was an imbalance in baseline brain metastases, the response rates of the two agents were similar. The benefit seemed to be in the PFS and the number of new events, so I do not think the imbalance in the baseline brain metastases would have affected the results too much. If performance status between the arms was imbalanced, there would have been more concern, but it was not.

Q: Should all patients with progressive disease on front-line alectinib be biopsied?

Shaw: Patients whose disease is progressing on alectinib should absolutely be biopsied because we are just beginning to understand the mechanisms of resistance to this drug. I also believe that repeat biopsies are crucial to picking the next agent for patients whose disease has progressed on first-line alectinib. We are hoping to develop liquid biopsies that can detect ALK resistance mutations in the blood and follow them serially over time. That may allow us to bypass the need for additional tissue biopsies.

Mehra: Repeat biopsies are mostly done only on tertiary care and research institutions, but I think this too will soon be an emerging standard of care. As we learn more about resistance mutations, biopsies will be important for deciding which next-generation drug to use. The challenges right now are that not all community centers have a mechanism to do repeat testing and that it is not always safe to do a biopsy in pretreated patients. Cell-free liquid biopsies could soon become a routine way to get these data.

References

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More than 2,000 abstracts have been submitted for selection as an oral or poster presentation. Poster presentations will be an important part of the Congress. Posters will be on display in the major exhibition hall, just beside the industry exhibition, for the whole of the assigned day, with presenters present at certain time slots during the morning and afternoon. This should facilitate interaction between presenters and participants.

IASCW CLC 2016 and the organizers of IASCW CLC 2016 are particularly honored that the President of Uruguay, Dr. Tabaré Vázquez, has accepted our invitation to deliver a keynote lecture on “Tobacco control in Uruguay” on Monday morning. The attendance of President Dr. Tabaré Vázquez promises to raise global awareness of IASCW CLC 2016 and of the importance of tobacco control. I kindly ask you to make sure to attend the keynote lecture of President Dr. Tabaré Vázquez, underscoring our support for Uruguay in its tobacco control initiatives as well as our commitment for primary prevention as the most efficient strategy to decrease the worldwide epidemic of lung cancer.

I particularly invite you to attend the Opening Plenary Session on Sunday evening, during which Nobel Laureate Dr. Harald zur Hausen will deliver a keynote lecture on Cancer Management in the 21st Century.

IASCW CLC 2016 will provide you with a great opportunity to share scientific advances and clinical experiences with colleagues from all over the world. It will be also an excellent opportunity for initiating and strengthening ongoing collaborations, which will benefit lung cancer patients around the globe. There will also be time to get to know each other, to make new friendships and to become part of the global IASCW community. The atmosphere at the Conference itself as well as the way of life in the Viennese host city should support these important goals.

Finally, I would like to provide you with some practical information regarding your participation at IASCW CLC 2016. Vienna is an international city in the heart of Europe and host to many international organizations, including the United Nations. Viennese and Austrians are friendly and helpful to foreigners, and Vienna is a safe city with an excellent public transport system. For travel within Vienna, you can use the Metro (U-Bahn) or streetcars (Straßenbahn). Travel to Vienna is also easy, and interruption of air travel due to weather conditions or for other reasons is very unlikely to occur. Although you can expect cool weather, with temperatures around 5 degrees Celsius, it will unlikely go below zero. Snow in early December is unlikely in Vienna, but it could snow in the more alpine regions of Austria. You may consider planning a few extra days to enjoy Vienna and its surroundings. Vienna, Salzburg, and Innsbruck can be reached easily by train. In addition, Bratislava, Budapest, and Prague are within 300 kilometers of Vienna and can also be reached by train. Please be aware that many tourists will visit Vienna in early December and that December 8 is a holiday in Austria. Therefore, please plan your trip well ahead. Your early registration will also save you money and make final arrangements easier for the organizers.

I hope you will be able to attend IASCW CLC 2016, and would like to warmly welcome you in Vienna.

Yours sincerely,

Robert Pirker, MD
IASCW CLC 2016 Congress President. 
Genetic Differences in Lung Cancers Arising in Smokers and Never-Smokers

By Adi F. Gazdar, MD

While all of the major histological forms of lung cancer are strongly associated with smoking, an important subset (about 20% worldwide, 10–15% in the US) arise in lifetime never-smokers. Lung cancer in never-smokers (LCNS) targets the female gender, East Asian ethnicity, and adenocarcinoma histology. While environmental smoke exposure (ESE), or secondhand smoke, is usually considered the major cause of LCNS, ESE is a weak carcinogen, and the other known risk factors are modest in effect or frequency. Thus, we do not understand the major cause or causes of LCNS.

A comparison of the genetic changes in lung cancers arising in ever and never-smokers may shed some light on the causes of LCNS. We know that there are major differences in the patterns of mutations involving specific genes, but as these are covered in other newsletters, they will not be discussed further here.

The major differences in tumor-acquired changes (other than the specific targeted genes) consist of two major types: the overall number of mutations and specific types of mutational change.

Tobacco exposure is a powerful carcinogen, and exposure over the decades between smoking initiation and tumor appearance results in numerous “driver” and “passenger” mutations in coding and non-coding regions of the genome. Thus, the three major forms of lung cancer are among the five tumor types with the largest number of mutations. These mutations are present throughout the respiratory epithelium. However, never-smokers have many fewer mutations (perhaps tenfold to one hundredfold less), and have a more limited distribution in non-malignant epithelium.

The other form of change involves the specific pattern of base pair substitutions involved in the resultant mutations. Of the four base pairs, six major forms of changes may occur, and are known as either transversions or transitions. Tobacco exposure results in a specific base pair change known as G>T:C>A transversions. By contrast, the commonest form of base pair substitution in never-smoker tumors is known as G:A:C>T transitions. Recently we have learned that the base pairs immediately preceding and following the substitution may also play a role in the pathogenesis of specific tumors. These findings greatly increase the number and complexity of the base pair changes, and we are still trying to understand their roles in lung cancers.

In addition to tumor-acquired genetic changes, genetic variations may predispose to cancer. The human genome, consisting of about 3 billion nucleotides, contains about 10 million genetic variations known as single nucleotide polymorphisms (SNPs). Genome-wide association studies (GWAS) scan the entire genome to identify genetic variants associated with lung and other cancers. Earlier studies had identified SNPs associated with an increased tendency to smoke and others associated with all forms of lung cancer. More recent work has focused on identifying SNPs associated with lung cancer in Asian women never-smokers. Pathway analyses involving the affected genes are being performed to try and elucidate the different roads to cancer in smokers and never-smokers.

Unlike individual SNPs, inherited gene mutations (such as BRCA gene mutations in breast cancer) may have high penetrance, resulting in greatly increased cancer risks. Modest numbers of high-risk families have been identified with lung cancer and potential or actual genes identified. One mutation in the EGFR gene, T790M, while rare in the general population, is present in up to 1% of lung cancers. Of interest, subjects who inherit this mutation are most at risk for lung cancer if they are women and never-smokers.

From these findings we can draw the following conclusions:

1) Lung cancers arising in smokers and never-smokers are different tumors at the genetic level.

2) These two distinct types of tumors share some etiologic factors, but the major cause or causes of lung cancers in never-smokers remain unknown.

3) Molecular studies, combined with clinical observations and epidemiological findings may shed further light on the origins and causes of lung cancers arising in never-smokers.

References


Erratum

In the article published in IASLC Lung Cancer News Volume 1, Number 2, National Comprehensive Cancer Network NSCLC Guideline Updates for 2016: Non-Small Cell Lung Cancer, the ending of second paragraph contained an error.

The corrected paragraph should read as follows:

Recommendations by NCCN fall into 1 of 4 categories of evidence and consensus. Over 80% of the categories of evidence and consensus in the NCCN NSCLC guidelines are Category 2A unless otherwise noted. Category 1 recommendations reflect uniform expert consensus based on strong evidence. Category 2A recommendations reflect uniform expert consensus based on lower-level evidence, Category 2B recommendations are based on lower-level evidence accompanied by less-than-uniform expert consensus, and Category 3 recommendations are the most controversial and the subject of significant expert debate. When this designation is used, there is major NCCN disagreement that the intervention is appropriate.
**INTERVIEW WITH DINAH S. SINGER, PHD**  / By Erik J. MacLaren, PhD

### Blue Ribbon Panel of the US National Cancer Advisory Board

During his State of the Union address in January 2016, President Barack Obama announced a new effort led by Vice President Joe Biden to accelerate research into cancer, known as the Vice President’s Cancer Initiative, or the National Cancer Moonshot.1 Among the goals of the Initiative are to identify areas of cancer research in which additional funding could allow investigators to accomplish in 5 years what would normally take a decade. IASLC Lung Cancer News spoke with Dinah Singer, PhD, Acting Deputy Director of the National Cancer Institute (NCI), Director of the Division of Cancer Biology, and Co-Chair of the Blue Ribbon Panel of the National Cancer Advisory Board (NCAB), about how this initiative is moving forward.

#### Q: What are the timeline, expectations, and priorities of the Vice President’s Cancer Initiative?

**A:** The president first announced the Vice President’s Cancer Initiative during the State of the Union address in January. In order to advise on the scientific component of the Initiative, the NCI and the National Institutes of Health (NIH) convened a Blue Ribbon Panel of experts on April 4, 2016, to generate recommendations on scientific opportunities and priorities. This panel has 28 members, representing the full spectrum of the cancer community, including researchers, clinicians, private sector representatives, and, of course, advocates. The report generated by the Blue Ribbon Panel is to be completed by August 2016, so our timeline is extremely accelerated.

The Blue Ribbon Panel has established seven working groups to address the different aspects of the cancer research continuum, from tumor biology and tumor evolution all the way through to implementation sciences. These working groups have been charged with identifying unique opportunities in their areas that could benefit from the additional attention and funding that we expect through the Vice President’s Cancer Initiative. In the end, the Blue Ribbon Panel will agree on five to 10 recommendations that could reasonably and feasibly be implemented quickly, so that within 5 years we will actually have results that can be delivered for patient benefits.

### Benefit of EGFR Mutation Analysis from Plasma Cell-Free DNA for Treatment of Advanced Non-Small Cell Lung Cancer

**By Tony S. K. Mok, BMSc, MD, FRCP**

Patients must first be identified as having an epidermal growth factor receptor (EGFR) mutation before they can benefit from EGFR tyrosine kinase inhibitors (TKI). Furthermore, to benefit from third-generation EGFR TKI such as osimertinib, it is essential to identify the presence of resistance exon 20 T790M mutations (T790M). The challenge is how to optimize detection of these mutations in all patients with advanced stage pulmonary adenocarcinoma. Limited by availability of adequate tumor samples, a significant portion of lung cancer patients are never tested for EGFR mutations. A recent Asian study showed that the testing rate of EGFR mutation analysis in 22,193 patients with advanced non-small cell lung cancer (NSCLC) was only 31.8%.1 There is much room for improvement.

A promising solution to the problem is plasma cell-free DNA (cfDNA) testing. Multiple studies on various platforms have consistently demonstrated good sensitivity and high specificity with EGFR mutation analysis on plasma cfDNA. We performed a prospective study on the matched tumor and plasma samples from FASTACT 2, a randomized study that compared intercalated combination of chemotherapy and erlotinib with chemotherapy alone in unselected treatment-naive patients, using the cobas 4800 blood test and reported concordance rate, sensitivity, and specificity at 88%, 75%, and 96%.2 With digital PCR, we analyzed matched pair samples from the ASPIRATION study, a single-arm first-line study of erlotinib in 204 patients with EGFR mutation. Results were similar, with concordance rate, sensitivity, and specificity at 78%, 77%, and 92%, respectively.3 Other studies have shown similar specificity, but the sensitivity is variable.

Luo et al4 conducted a meta-analysis of 20 studies and reported aggregate sensitivity of 67% and specificity of 92%. These data confirm the clinical applicability of EGFR mutation analysis on plasma cfDNA. When the result is positive for EGFR mutation, there is more than a 90% chance that it is a true positive and that the patient will benefit from EGFR TKI. When the plasma test is negative, it is essential to pursue tumor biopsy, as the false negative rate is about 30%. As plasma testing becomes more efficient and available, it should be integrated as a standard test for patients with advanced stage adenocarcinoma.

To detect T790M promptly at time of radiological progression to EGFR TKI is a clinical challenge. In addition to the limitation by accessibility and risk, many patients are reluctant to have a re-biopsy. Detection of T790M continued on page 7
The College of American Pathologists (CAP), International Association for the Study of Lung Cancer (IASLC), and Association for Molecular Pathology (AMP) published online in April 2013 the original “Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors” in Archives of Pathology & Laboratory Medicine, Journal of Thoracic Oncology, and The Journal of Molecular Diagnostics, respectively. This guideline contained 15 evidence (grade A/B) based recommendations for molecular analysis of lung cancers. The major recommendations were (1) to use molecular testing for epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) fusions to guide patient selection for therapy with an EGFR or ALK inhibitor, respectively, in all patients with advanced-stage adenocarcinoma, regardless of sex, race, smoking history, or other clinical risk factors, (2) to prioritize EGFR and ALK testing over other molecular predictive tests, and (3) to address how the testing should be performed.

Scientific knowledge on new biomarkers for targeted therapy like ROS1, RET, BRAF, and MET and new technology like next-generation sequencing continues to advance at an incredible pace due to discoveries from basic science, translational science, and clinical trials. Consequently, the Molecular Testing Guideline needed to be updated to communicate emerging clinical standards and to leverage the latest breakthroughs in lung cancer research. Moreover, a guideline that has not been reaffirmed and updated after 5 years or more is no longer considered current. The guideline revisions are designed to provide state-of-the-art molecular testing recommendations for pathologists, oncologists, and other cancer and molecular diagnostic laboratory professionals involved in the management of lung cancer.

The co-chairs Philip T. Cagle, MD, on behalf of CAP, Yasushi Yatabe, MD, and Neal Lindeman, MD, on behalf of AMP, along with a multidisciplinary expert panel from all three organizations, developed the following key questions about update and revision at a 2-day face-to-face meeting:

- What other genes, previously not addressed, should be tested in lung adenocarcinoma?
- Is immunohistochemistry reliable for screening for ALK translocations?
- What are the types and rates of secondary resistance in patients who are undergoing treatment with targeted tyrosine kinase inhibitors?
- What are the clinical performance characteristics of circulating DNA/CTC in plasma when used for diagnosis of primary lung adenocarcinoma or relapse?
- Are there biomarkers that are predictive of clinical outcome in a mous and small cell lung carcinoma?
- What key considerations are there regarding next-generation sequencing panels targeting key genes or regions of interest?

To address these questions, an extensive literature search strategy, containing inclusion and exclusion criteria, was developed, and an unbiased review of published experimental literature since 2013 was executed. Over 1,650 abstracts were captured in the initial literature search, and more than 450 of these were moved on to a full-text review. Tables were developed from extracted data for approximately half of the studies that went through the full-text review. Expert panelists then evaluated the extracted data to develop draft recommendations that addressed the key questions. The draft recommendations were then posted online for 5 weeks following multiple announcements from all three organizations to garner public comments, which were fully evaluated and discussed by the expert panel and co-chairs. The recommendations are now in the process of being revised based on the feedback from the open comment period. The final recommendations, once the manuscript is completed, will be jointly approved and once again published in Archives of Pathology & Laboratory Medicine, Journal of Thoracic Oncology, and The Journal of Molecular Diagnostics, with an expected publishing date in late 2016 or early 2017.

Molecular testing for the selection of optimal therapy for patients with lung cancer remains as crucial as today as when the “Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors” was originally published. However, what has shifted is the clinical situation as a result of the tremendous effort of researchers and patients all over the world. Therefore, the expanded list of genes and new methods in the updated Molecular Testing Guideline are both clinically relevant and necessary.

—Yasushi Yatabe, MD, PhD
Expert Panel Co-Chair, Lung Guideline Update Project

EGFR Mutation Analysis from page 6

mutation from plasma cfDNA is much more feasible than tissue testing. Oxnard et al. utilized the matched tumor and plasma samples from AURA study, and used BEAM digital PCR for detection of T790M mutation from plasma. The major advantage of this study is that the investigators included samples from both T790M positive and negative patients, and all enrolled patients had received osimertinib. Based on this database, they were able to report the diagnostic utility and correlate clinical response to osimertinib with the biomarkers. Sensitivity and specificity for detection of T790M was 70.2% and 69%, respectively. Tumor response rate in patients with tumor tissue positive for T790M mutation was 62%, while the response rate in plasma positive cases was 63%. In other words, the plasma test shares similar predictive power as the tissue sample test. Clinically, a false positive result poses significant consequences. Oxnard et al. were able to analyze the clinical outcomes of patients with positive T790M in plasma but negative in tumor sample. Out of 18 false positive cases, four patients attained partial response and five attained stable disease. This may potentially reflect on tumor heterogeneity. The tumor sample that tests negative for T790M may not be representative of the molecular status in all progressing sites.

The role of plasma cfDNA for detection of EGFR mutation at initial diagnosis and of T790M mutation at time of disease progression on EGFR TKI is well established. The remaining controversy is the application of plasma testing for monitoring of disease status. It remains unknown if persistent detection of EGFR mutation or early detection of T790M from plasma prior to radiological progression will have any impact on the course of the illness. We reported that the persistent presence of EGFR mutation after 3 months of therapy is associated with worse progression-free survival and overall survival.2 However, it is unknown if a change in therapy based on the plasma molecular status would influence survival. Further investigation on the role of molecular monitoring on plasma cfDNA is warranted.

Advances in technology have now allowed us to perform routine EGFR mutation analysis on plasma cfDNA. Both the US FDA and the European Medicines Evaluation Agency have granted approval for the use of a new panel of plasma samples as companion diagnostics for NSCLC for the detection of EGFR mutation. Liquid biopsy is now viable, and should be integrated into clinical practice. •

Professor Mok’s provided conflicts of interest are available upon request to editor@iaslcungcancersnews.net.

References
Osimertinib

from page 1

cancers harboring the T790M resistance mutation. In this setting, it produces a very good response rate, about 60%, and an excellent progression-free survival (PFS) outcome. Furthermore, it is associated with an acceptable toxicity profile, as it has low affinity for wild-type EGFR.

Cappuzzo: Osimertinib is an attractive agent because it is very potent; it has been designed particularly to overcome resistance to first- or second-generation EGFR TKIs, including erlotinib, gefitinib, or afatinib. Osimertinib is also active against brain metastases and leptomeningeal disease. These properties render this agent very attractive and very promising in patients with NSCLC.

Q: What are the prospects that osimertinib will displace standard first-line TKIs, and what level of evidence would secure its role in the first-line?

Gandara: We will have to await the results of the ongoing FLAURA trial,1 which compares osimertinib with investigator choice of either gefitinib or erlotinib, to answer these questions. Some critics will say that FLAURA did not go up against afatinib, the second-genera
tion TKI that has shown some evidence of superiority over gefitinib in the LUX LUNG 7 trial, so the impact of FLAURA, if it is positive, will be in the eyes of the beholder.

In terms of level of evidence, FLAURA is a large trial, with about 650 patients planned, and PFS as the primary endpoint. If it meets that endpoint in a clinically meaningful way, which would be an improvement by several months for osimertinib compared to control or a hazard ratio of 0.7 or lower, it will be sufficient to change practice. However, I should note that none of the trials comparing erlotinib or gefitinib to chemotherapy have ever demonstrated improvement in overall survival. If FLAURA were to show improvement in overall survival, that could certainly propel it forward in terms of therapy.

Cappuzzo: The activity of these agents has been investigated in TKI-naive patients,2 and the response rate, duration of response, and PFS in this population were quite impressive. To move to a first-line setting, certainly we need phase III trial data, which will clarify whether we can use osimertinib in the first-line. Preliminary data strongly suggest that this agent could become the new SOC in the front-line setting, but I repeat: we need a phase III trial to confirm such findings.

Q: If osimertinib does move to the first-line, where does that leave us in the second-line setting? Does chemotherapy become the “default” option?

Gandara: This issue, about what to do in second-line if osimertinib moves into first-line, is perhaps the most confounded right now. In my mind, there is no clear-cut answer, since checkpoint immunotherapy agents, although approved in the second-line setting, seem to produce relatively poor results in patients with EGFR-mutated lung cancers, likely due to the low mutational load in these oncogene-driven cancers. That would mean that platinum-based chemotherapy would become the second-line choice, unless a new TKI with activity against osimertinib resistance—for example, the C797S mutation—emerges in the near future.

Cappuzzo: We know that the main mechanism related to osimertinib failure is the occurrence of a new secondary mutation, C797S, but we do not yet have clinical data. Based on preclinical models, it seems that if the C797S mutation is present but T790M is not, the patient may still be sensitive to first-generation EGFR TKIs. Assuming that osimertinib becomes the standard front-line therapy, it will be crucial to understand whether the patient is still sensitive to other currently available agents. That will require prospective clinical data on this issue. I think chemotherapy remains an important option for patients with EGFR mutations, but only after failure on all available EGFR TKIs.

Q: Will we automatically be obtaining repeat biopsies or liquid biopsies in the setting of acquired resistance?

Gandara: This question has already been answered, in my opinion, with guidelines from 2013 onward, as those from IASLC, along with clinical practice patterns already showing that a repeat biopsy at time of resistance is critical in the decision-making process. Importantly, testing needs to extend beyond T790M, to look for other mechanisms of resistance in addition to T790M. We know that this occurs in about half of cases.

We are now in a transition phase between repeat tissue biopsy and so-called liquid biopsy for plasma cell-free DNA analysis. In some patients, repeat biopsy is simply not possible. Further, the ability to perform liquid biopsy through an NGS platform is revolutionary, and I believe it will become the SOC very soon. The sensitivity is very high now, and there are essentially no false positives. In fact, recent data suggest that if testing for T790M, for example, is negative in tissue repeat biopsy but positive in plasma, that it is the tissue that is a false negative, not the reverse.

That being said, a very small number of patients will have evolution to small cell lung cancer after a first-line EGFR TKI, and that can only be detected by biopsy at present.

Cappuzzo: We know that the biology of the tumor changes during treatment because of the occurrence of different secondary mutations, and that it is extremely important to identify the mechanism of resistance to determine the best subsequent therapy. It is, therefore, extremely important to repeat the biopsy of the tumor; however, we know that in clinical practice this is not always done. Liquid biopsy is a very attractive alternative, and many centers are already doing these tests. I strongly believe that this technology will become the SOC for our patients.

Q: What role, if any, do you think urine assays will play in NSCLC?

Gandara: Urine testing has recently been shown to be complementary to tissue and plasma, but right now has a more limited scope in terms of number of genes assessed. We will have to wait and see how this evolves, because eventually insurance companies or governmental agencies are going to want to pay for only one test: tissue biopsy or plasma cfDNA or urine, not two or three tests.

Cappuzzo: We can obtain information from the blood, but we can also try to obtain some information from the urine. It is possible that we could ultimately combine different tests because we know that there is not 100% overlap in the results of these different assays; by so doing, we could significantly reduce the risk of false-negative results. This is a very important consideration in clinical practice, ensuring that all patients have the opportunity to receive the right drug.

References

In Memoriam
Gregory A. Curt, MD

On July 31, 2016, the lung cancer and oncology research community lost a respected researcher and leader, Gregory Curt, MD, who died at the US Walter Reed National Military Medical Center following treatment for cancer at age 64. After graduating summa cum laude from Providence College in 1974, and from the University of Rochester School of Medicine, with distinction in research, in 1977, Dr. Curt completed his training at the New England Deaconess Hospital in Boston and, in 1980, began his oncology fellowship at the US National Cancer Institute (NCI) where he was later appointed Clinical Director (1989-2002). While NCI Clinical Director, Greg led the intramural program at NCI in translational research involving new therapeutic modalities including anti-cancer drugs, vaccines, and immunotoxins. Achieving the rank of Captain in the United States Public Health Service (PHS), Dr. Curt was awarded the Outstanding Service Medal of the US, Public Health Service in 1992. In 2002, Dr. Curt continued his dedication to cancer drug development as Senior Director and Alliance Manager at AstraZeneca Oncology, where he was responsible for AstraZeneca’s new partnerships with NCI in cancer prevention and treatment using novel drug combinations. Dr. Curt was the US Medical Science Lead for Strategic Alliances, Physician Lead for the US Oncology Phase 1 Team, and US Group Director for late-stage drug strategy in Global Medicines Development. He also served as Executive Director for External Relations in US Medical Affairs.

“Greg Curt, MD was a fabulous investigator, administrator, and individual. As Clinical Director of the NCI, his studies focused on the pharmacology of methotrexate and 5-azacytidine. During his later career at AstraZeneca, he was involved in early clinical development of their compounds and in their global alliances. The cancer community will miss his enthusiasm for novel therapies.”

—Paul A. Bunn, Jr, MD, FASCO
MEETING HIGHLIGHTS

Honoring Superb Advocacy at the 13th Annual Prevent Cancer Quantitative Imaging Workshop

By James L. Mulshine, MD

On June 13, 2016, the Prevent Cancer Foundation hosted the 13th Annual Quantitative Imaging Workshop: Lung Cancer, COPD and Cardiovascular Disease – Exploring the Intersections. A major focus of the meeting related to optimization of CT imaging issues as the nation begins to implement CT screening for lung cancer. It was appropriate then that the meeting started with the awarding of the 4th James L. Mulshine, MD Leadership Award, which recognized the remarkable efforts of Laurie Fenton Ambrose, President and CEO of the Lung Cancer Alliance, for her many accomplishments but most specifically for her efforts in guiding patient advocacy and other stakeholder groups in the successful efforts to gain coverage of lung cancer screening by the Centers for Medicare & Medicaid Services (CMS).

Two special guests gave the award to Ms. Fenton Ambrose: Professor Cheryl Healyton, Dean of the College of Global Public Health at New York University, and former Secretary of Defense Chuck Hagel. In their comments, they framed how Mrs. Fenton Ambrose has brought a strategic vision, energy, and a deep understanding of consensus building to advocacy of lung cancer patients and those at risk for lung cancer. These efforts included both an effective dialogue with the Secretary of Health and Human Services as well as the development of a broad consortium of supportive advocacy groups, academic institutions, and other interested institutions. Collectively, these efforts were pivotal to the issuance of a national coverage decision by the CMS.

Laurie Fenton Ambrose serves as the President and CEO of Lung Cancer Alliance. This foundation has developed a number of impactful lung cancer advocacy programs such as the National Framework for Screening Excellence, a consortial effort to implement high-quality lung cancer screening services among the 400 screening delivery healthcare institutions that have joined this effort.

Another highlight of the meeting was a crowdsourcing evaluation of the imaging performance of CT scanners from lung cancer screening sites. Ricardo Avila, CEO of Accumetra LLC, an advanced imaging technology company, described the preliminary results of the CT Imaging Protocol Challenge. This involved measuring identical objects at different screening sites using a variety of scanners, in this case 26 different screening sites using 53 different scanners. While considerable variability was found, by changing the CT scanner acquisition settings, a large fraction of the variability could fortunately be reversed. The CT image-quality reports were generated within 20 minutes of sending the data to the website, allowing sites to rapidly adjust their settings and submit new scans to see if there was an improvement.

This image-quality assessment experience stimulated a deep discussion over the course of the Workshop on defining processes to ensure accuracy with quantitative imaging measurement, not only for lung cancer screening management but also for CT-based lung cancer treatment response assessment. These discussions including representatives from the drug and imaging industry, the Quantitative Imaging Biomarker Alliance, the FDA, the National Cancer Institute, the National Institute of Standards, the National Photonics Initiative, lung cancer advocacy groups, and academics and representatives from a number of institutions that currently are offering lung cancer screening services. Next steps for the Workshop include a broader dialogue to align with efforts related to the Vice President’s Moonshot Initiative, with the goal of accelerating our progress in improving lung cancer outcomes. In parallel, discussions with COPD researchers and advocates as well as cardiovascular researchers and advocates about shared opportunities to optimize health information yield from the lung cancer screening encounter will continue, especially around image quality and health economics issues.

GLOBAL RESEARCH REPORTS

CONVERT: An International Randomized Trial of Concurrent Chemo-Radiotherapy Comparing Twice-Daily and Once-Daily Radiotherapy Schedules in Patients with Limited-Stage Small Cell Lung Cancer and Good Performance Status

By Prof. Corinne Faivre-Finn

The optimal timing and schedule of thoracic radiation in the management of limited-stage small cell lung cancer (LS-SCLC) continues to provoke debate. Since the publication of Intergroup 0096 in 1999, there had been controversy about the standard chemo-radiotherapy (cCTRT) regimen in LS-SCLC. Although twice-daily (BD) radiotherapy (RT) was associated with higher survival compared to once-daily (OD) RT, concerns regarding toxicity (i.e., a third of the patients developing grade 3 or more esophagitis), together with logistical issues in the delivery of BD RT and criticism about the low dose of RT used in the control arm of Intergroup 0096, led to the limited adoption of this regimen in routine practice.1

The CONVERT trial is the first multicenter, international, randomized phase III trial aiming to establish a standard chemo-radiotherapy regimen in LS-SCLC. It is the largest-ever trial completed in this group of patients. We reported the trial results at the 2016 Annual Meeting of the American Society of Clinical Oncology.2

In CONVERT, patients with LS-SCLC were randomized 1:1 to receive either 45 Gy in 30-BD fractions over 3 weeks or 66 Gy in 33-OD fractions over 6.5 weeks, starting on day 22 of cycle 1 chemotherapy (four to six cycles of cisplatin and etoposide, according to investigator’s prespecified choice), followed by prophylactic cranial irradiation, if indicated. RT was planned using either 3-D conformal or intensity-modulated radiation therapy (IMRT). The primary endpoint of the study was 2-year survival and all analyses were by intention to treat. The study enrolled 547 patients recruited from 73 centers in seven European countries and Canada between 2008 and 2013.

Patient characteristics were well balanced in both arms of the study. Median age was 63 years (15% were older than 70 years), almost 50% were female, and the majority of patients had a performance status of 0 or 1 and were ex-smokers or current smokers.

At a median follow-up of 45 months, 2-year survival was 56% compared to 51%, and median overall survival was 30 months compared with 25 months in the BD RT and the OD RT arms, respectively, a difference that did not prove to be statistically significant. Furthermore, continued on page 10
Liquid Biopsy Testing

On June 1, 2016, the U.S. Food and Drug Administration (FDA) approved the use of the cobas EGFR Mutation Test v2 to detect mutations in the epidermal growth factor receptor (EGFR) gene using patient plasma samples. IASLC Lung Cancer News spoke with Reena Philip, PhD, Director of the Division of Molecular Genetics and Pathology, and Eunice Lee, PhD, Chief of the Molecular Pathology and Cytology Branch, both in the Office of In Vitro Diagnostics and Radiological Health in the Center for Devices and Radiological Health, about the new liquid biopsy test.

Q: Can you explain for our readers what the cobas EGFR Mutation Test v2 is and how it works?

Philip: This is a polymerase chain reaction (PCR)-based test for detecting exon 19 deletions or L858R substitution mutations in EGFR in patients with non-small cell lung cancer to determine whether they are eligible for treatment with erlotinib. Previously, this test had been approved for use with formalin-fixed paraffin-embedded (FFPE) tumor specimens, and this new approval concerns its use with cell-free DNA (cfDNA) in plasma specimens, also known as “liquid biopsies.” The only caveat is that testing with plasma samples is to be considered reflex testing because the percent positive agreement (PPA) between tissue and plasma samples was low, 76.7%. This means that if EGFR mutations are detected in patients’ plasma samples, then the patients are eligible for treatment with erlotinib; however, if no mutations are detected, patients are still advised to go through the tumor tissue testing.

Q: Why would there be disagreement between testing results from tissue and plasma?

Philip: It is believed that the tumor cells shed cfDNA into the blood, and that tumor DNA can be detected by these devices in plasma samples only if there are sufficient amounts. That is why we think that around 77% PPA is reasonable, because perhaps for patients with early-stage disease, there will not be enough tumor DNA in the blood to be detected.

Q: How did the FDA arrive at the conclusion that this liquid biopsy is “ready for prime time”?

Philip: The approval was based on the totality of the data, including the device data and the results that were submitted by Astellas (Pharma Technologies) and Roche (Molecular Systems). These results supported the safety and effectiveness of the device for testing plasma samples. The data are available online in a document called the Summary of Safety and Effectiveness Data (SSED).1 Section 10 of that document shows data provided from the ENSURE trial that were used to support the cfDNA clinical claims.

Lee: In general, deciding which test to use should depend on the performance of the device and the claims that are associated with the device. In this case, as Dr. Philip mentioned, the PPA for the cobas EGFR test is about 77%, so it is important to have that reflex claim, whereby patients in whom mutations were not detected are then tested using tissue biopsy samples in order to determine their eligibility for erlotinib treatment.

Q: Are there pitfalls we need to avoid with liquid biopsy testing?

Lee: Right now, there is a lack of clinical data on treatment responses in patients identified by liquid biopsy. Companion diagnostic tests have been approved to detect mutations in tumor samples, and the clinical data used was based on tumor tissue testing. However, there is not perfect concordance between the tumor tests and the plasma tests. It is unclear how the patients who are identified by the plasma test would respond to the treatment, which was approved based on tumor testing. So it is important to get some clinical data that are associated with the plasma test.

Q: Is there anything else you would like to share with our readers?

Lee: I would add that the cobas EGFR test offers a minimally invasive alternative to tumor testing, particularly for patients who have positive results, and it avoids challenges that are associated with tumor biopsies like safety concerns and getting insufficient amounts of sample. However, it is key for the safe and effective use of these tests to establish the performance of the devices and to understand the risks that might be associated with how they are used. Therefore in this case, patients with negative results are reflexed to tumor testing, and would still have to undergo the tissue biopsy procedure.

Philip: I agree that liquid biopsies will allow for the analysis of cfDNA in a relatively non-invasive manner and have the potential to significantly advance personalized medicine. On July 19, 2016, a workshop called Liquid Biopsies in Oncology Drug and Device Development was co-hosted by the FDA and the American Association for Cancer Research (AACR).2 We discussed some of the issues underlying liquid biopsies and some of the analytical issues we briefly touched on earlier. 

References
• Everolimus (Afinitor) has been approved by the European Commission for treat-
mant of unresectable or metastatic, well-differentiated (grade 1 or grade 2) non-
ffunctional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin in
adults with progressive disease. Everolimus is the first approved therapy in all
European Union (EU) member states, plus Iceland and Norway, for this type of
lung NET, and one of few treatment options available for this type of GI NET.

The EU approval of everolimus was based on data from the RADIANT-4 trial
evaluating everolimus versus a placebo in patients with advanced, progressive, well-
differentiated nonfunctional NET of GI or lung origin. Everolimus was previously
approved (February 2016) by the FDA for treatment of adults with progressive,
well-differentiated nonfunctional NET of GI or lung origin that are unresectable,
locally advanced or metastatic.

“The approval of everolimus offers a treatment option to patients with NET of
GI or lung origin in the EU for whom evidence-based effective systemic ther-
apies were previously lacking,” says J.C. Yao, MD, corresponding author of the
RADIANT-4 trial.

• LOXO-101, a selective inhibitor of tropomyosin receptor kinase (TRK), was granted
Breakthrough Therapy Designation by the US FDA “for the treatment of unresect-
able or metastatic solid tumors with neurotrophic tyrosine receptor kinase (NTRK)-
fusion proteins in adult and pediatric patients who require systemic therapy and
who have either progressed following prior treatment or who have no acceptable
alternative treatments.”

Investigators enrolled 41 patients with tumors refractory to other available thera-
pies. No patients without a fusion showed activity. However, in those patients with
NTRK fusions present, 83% had a response. In patients with TRK mutation or
amplification, 60% were able to achieve disease control. While the patient number
was small and the findings early, study data provide the rationale for continued

A phase 2 basket trial (NCT02576431) is underway to evaluate LOXO-101 in
adults with cancer whose tumors harbor NTRK fusions.

• Olmutinib (BI 1482694/HM61713), which was granted Breakthrough Therapy Designation by the US FDA “for the treatment of unresect-
able or metastatic solid tumors with neurotrophic tyrosine kinase receptor (NTRK)-
fusion proteins in adult and pediatric patients who require systemic therapy and
who have either progressed following prior treatment or who have no acceptable
alternative treatments.”

This approval of olmutinib is a step forward for patients with lung cancer in
South Korea. This is a needed new treatment option for the majority of EGFR
mutation-positive lung cancer patients whose disease has become resistant to first-
line TKI therapy,” comments Professor Keunchil Park, Samsung Medical Center,
Sungkyunkwan University School of Medicine, Seoul, South Korea.

• Seribantumab (MM-121; Merrimack Pharmaceuticals) has received FDA Fast
Track designation for development to treat patients with heregulin-positive, locally
advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has
progressed following immunotherapy.

Seribantumab is designed to block heregulin-driven signaling and enhance

to the treatment of advanced lung cancer that may significantly extend patients’
lives. Furthermore, combining a vaccine that targets EGF with a checkpoint
inhibitor such as nivolumab may stimulate the immune system in a way that improves
patients’ response to nivolumab. “This approach is a great scientific opportunity
to push the treatment of lung cancer in a new direction,” asserts Dr. Reid.

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Next-Generation Sequencing Across the World: Reports from France, Germany, and China

Next-generation sequencing (NGS) technology has revolutionized genomic and genetic research as it fulfills its potential to tailor the treatment of cancer patients in general and non-small cell lung cancer (NSCLC) patients in particular to their cancer genome alterations. The role of NGS in drug development and clinical trials varies worldwide in response to regional and national support and organization. IASLC Lung Cancer News invited experts from France, Germany, and China to summarize their NGS molecular diagnostics networks, and to comment on the implications and accomplishments of their programs for the development of treatments for patients with thoracic malignancies.

NGS Lung Cancer Genotyping Program in France

By Frédérique Nowak, MS, PhD, and Jean-Charles Soria, MD, PhD

The development of precision medicine in oncology requires that molecular diagnostics be performed on as broad a scale as possible so as to ensure health care equity. To this end, as early as 2006, the French National Cancer Institute (INCa) and the French Ministry of Health decided to set up a specific molecular testing organization and created a nationwide network of 28 molecular genetics centers located throughout France. The centers were selected through competitive calls for proposals managed by INCa in 2006 and 2007. Each molecular genetics center is composed of several university hospital and cancer center laboratories with complementary expertise in all the DNA-based and RNA-based techniques required for molecular testing.

These centers perform molecular tests for all patients in their region, irrespective of the institutions (university hospitals, cancer centers, local public hospitals or private institutions) where the patients are being treated. The corresponding costs are covered by INCa and the French Ministry of Health.

The dynamics of access to molecular testing in France is monitored by INCa. In 2015, more than 60,000 cancer patients underwent molecular predictive tests. Among the 26,600 patients with advanced-stage or metastatic non-small squamous NSCLC who underwent EGFR screening in 2015, 3,100 (11.7%) had tumors with an EGFR mutation and were therefore eligible for EGFR-TKI treatment (Figure 1). Moreover, the 28 molecular genetics centers in 2015 identified 700 patients with an ALK rearrangement, 520 patients with a BRAF mutation, and 160 patients with a ROS1 rearrangement, giving them the possibility of access to, respectively, ALK inhibitors, BRAF inhibitors, and crizotinib, which is available in France for ROS1-positive patients.

Beyond offering widespread access and nationwide coverage, achieving, securing, and maintaining quality are crucial. For this purpose, INCa fosters multidisciplinarity and the development of a collaborative network between centers. INCa has also set up a quality assurance program based on the publication of guidelines and on the organization of national External Quality Assessment rounds for the tests that have a major therapeutic impact on patients.

The increasing number of actionable molecular abnormalities that have to be screened for each patient has led the centers to turn towards technologies allowing multiplex analysis in an “all-in-one” approach. Since 2013, INCa has supported the implementation of targeted Next Generation Sequencing (NGS) as part of routine clinical practice. The targeted analysis of a panel of genes is an adequate short-term approach that can be implemented within the existing organizational framework. Nevertheless, laboratories need to adapt to constantly evolving technologies, which is extremely challenging. Moreover, they need to acquire specific expertise in bioinformatics for data analysis. To this end, working groups have been set up by INCa to foster institutional communication and to facilitate the drafting of guidelines. Reference teams in bioinformatics have also been funded to support wet labs and their “embedded” bioinformaticians through network animation, release of validated data analysis tools, and training. The objective is to shift progressively from standard approaches towards targeted NGS for all patients by the end of 2016.

The next challenge is to make the most of the additional information obtained by targeted NGS in routine practice. New tools are required to assess the clinical significance of new variants. In this context, collecting information about rare mutations in relation to patients’ follow-up data becomes critical. Molecular Tumor Boards are also being organized more widely in the French territory to help clinicians in interpreting molecular data. Finally, targeted NGS allows an opportunity to offer access to experimental compounds; its broad use will be linked to a strategy aimed at improving accrual onto multicentric genom-ics-driven clinical trials. Daily testing for molecular subsets in metastatic NSCLC allows for, at the national level, creation of readily available cohorts that can then be referred to recruiting centers. In that regard, France was the top recruiter of the dabrafenib/trametinib phase II trial in BRAF V600 (+) NSCLC. In parallel, INCa is supporting the ACaé program, which offers, within the secure framework of a clinical trial, broad access to targeted therapies outside their approved marketing indication. Nevertheless, there is clearly room to grow. Data from the Biomarker France study show we can increase the enrollment of patients carrying “actionable” molecular alterations onto studies evaluating experimental compounds.

Such an organization for the nationwide provision of molecular tests is facing a fast-evolving scientific, medical, and technological environment. In this context, implementation of targeted NGS is one step. The recent development of checkpoint inhibitors also holds the potential for improving patient outcomes. Nevertheless, specific predictive biomarkers are required for the identification of patients most likely to respond to treatment, and they are currently under development. As these assays enter into clinical practice, it will require the accurate integration of new expertise within the existing organizational framework to provide a complete service offering for precision medicine.

References
Our growing understanding of the molecular basis of cancer has led to an evolution in personalized medicine and has created the need to offer molecular diagnostics to all patients with advanced lung cancer. To ensure patients with lung cancer in Germany have access to individualized therapies based on a comprehensive molecular analysis of their tumors, the Cologne Lung Cancer Group (LCGC) at the Center for Integrated Oncology (CIO) at the University Hospital Cologne established the Network Genomic Medicine (NGM) Lung Cancer in March 2010. The NGM Lung Cancer represents an interdisciplinary collaboration between lung cancer physicians and research scientists at the University Hospital Cologne and local hospitals, pathologists, and private oncology practices throughout Germany to deliver precision treatment to patients nationwide. The NGM is unique in that the German government had no role in its creation and has no involvement with regard to patient access, implementation, or oversight.

"The network aims to provide a comprehensive genomic workup for any patient with a nonresectable, malignant lung tumor and to direct them to appropriate treatment or clinical trial regardless of their geographic location or reimbursement status," explains Anne Schultheis, MD, Institute for Pathology, University of Cologne. Dr. Schultheis notes that, since 2014, a portion of the costs for the genomic analysis has been reimbursed by health insurers. Any unreimbursed cost is borne by the NGM.

Access to molecular testing through the NGM is limited only by awareness among local oncologists and pathologists. "Patients’ tumor biopsies generally are sent first to local pathologists who, if they, or the treating oncologists, are aware of the NGM, will pass on the biopsies of patients with nonresectable, advanced lung tumors so that we can perform a comprehensive genomic analysis," says Dr. Schultheis. Once in the network, patients with lung cancer gain access to the latest treatments and clinical trials.

The NGM is unique in that the German government has had no role in its creation and has no involvement with regard to patient access, implementation, or oversight.

Molecular analysis of tumor tissue is centralized at either the main laboratory at the Institute for Pathology at the University Hospital Cologne, or at a second regional laboratory. Directed by Reinhard Büttner, MD, the pathology team focuses on molecular diagnosis as well as on the determination of predictive markers, with special interest also in immunotherapy. When actionable mutations are detected and approved therapies are available, subsequent treatment is decentralized, enabling patients to receive treatment close to home. For patients with detected mutations for which no drug has yet been approved, NGM attempts to direct them to an appropriate clinical trial at a centralized location.

With its roots in academia, NGM can take advantage of the latest research findings from the experts at the LCGC study center. Led by Jürgen Wolf, MD, the LCGC study program develops clinical trials to treat genetically defined subgroups of lung cancer and to optimize immunotherapy in coordination with work groups in translational cancer genomics, molecular pathology, and molecular imaging at the University of Cologne. This ongoing exchange of information allows NGM to offer clinical studies to most patients with lung cancer who have a therapeutically relevant genetic aberration in their tumor.

Molecular testing is performed under very strict laboratory procedures. To detect all relevant changes in lung cancer tumor cells, the NGM has designed its own molecular diagnostic platform covering all known driver mutations. The current lung cancer-oriented platform is updated regularly based on new research findings and includes, among others, mutations in the genes EGFR, KRAS, BRAF, PIK3CA, HER2, p53, MET, and DDR2; translocations in ALK, RET, and ROS1; and amplifications in HER2, MET, and FGFR1. The NGM uses a multiplex test in combination with deep sequencing to detect rare gene mutations in the smallest tissue samples. This approach involves multiple techniques such as next-generation sequencing, immunohistochemical detection of protein expression, and fluorescence in situ hybridization (FISH).

In the future, the NGM plans to convert to a hybrid-capture genetic analysis technique that will increase the number of mutations that can be detected. This approach involves an analysis of multiple oncogenes and multiple genetic aberrations, not only for lung cancer but also for other malignant tumors. This process can potentially lead to the identification of new molecular markers that may be clinically relevant.

Over the past 6 years, NGM has evolved from providing services to patients in only one geographic region, North Rhine-Westphalia, to offering comprehensive genomic workups to any patient in the country. Currently, NGM is Europe's largest platform for molecular diagnostics. “Each year NGM screens about 4,500 patients with lung cancer (and about 2,000 patients with other tumors, such as melanoma, ovarian cancer, or gastrointestinal tumors) for genomic aberrations,” says Dr. Schultheis. “This number represents 35% of all newly diagnosed patients with lung cancer in Germany.” With such widespread access, increasing awareness among patients and providers becomes a challenge. “More hospitals and private oncologists need to be aware of the network and the importance of precision therapies,” Dr. Schultheis acknowledges.

The close cooperation between the NGM, the LCGC, and the University of Cologne as well as the partnerships with healthcare providers throughout the country has been a key to NGM’s success. “As an interdisciplinary network, we are working hand in hand to accomplish our goal of delivering personalized medicine to every patient in Germany with advanced lung cancer,” says Dr. Schultheis.

Current State of NGS-Based Lung Cancer Genotyping in China

By Yang Shao, PhD

The clinical application of next-generation sequencing (NGS) first kicked off in the field of prenatal genetic screening for birth defects in China around 2012. Four years later, it has become part of a routine program adopted by hospitals and expecting parents, and it has transformed into a billion-dollar industry. NGS-based genetic tests first appeared in the oncology clinic in 2014, with the lung cancer field one of the earliest adopters, for several reasons. First, the wide use of targeted therapies such as EGFR, ALK, and ROS1 inhibitors poses real needs for multi-gene-based genotyping tools.1–3 Second, molecular interactions between the tumors and the drugs such as sensitizing and resistance mechanisms are relatively better understood in lung cancer; identifying markers of sensitivity and resistance therefore provides a scientific basis for clinical decision-making. Third, lung cancer is the most prevalent cancer type in China and attracts a lot of industry attention. Comparing to Sanger sequencing, qPCR, or FISH-based techniques, NGS-based genetic testing offers several advantages, including higher sensitivity/ specificity, the capacity to provide a more well-rounded view of the tumor genetics, and the ability to offer a one-test-for-all-drugs approach.4 NGS also allows us to best utilize limited tissue samples, which is a frequent challenge. In addition, delineating a group of genetic alterations such as MET exon 14 skipping5 and rare EGFR sensitizing mutations6 can only be accomplished with NGS-based tests.

The majority of the commercially available NGS-based tests are gene panels ranging from several genes to several hundred genes; the price ranges from $700 to $18,000 per test (approximately $1,050 USD to $2,800 USD). Small gene panels usually focus on core NCCN recommendation genes, while large panels can encompass all known cancer-related genes. For example, “Sangtinel,” a popular liquid biopsy test offered by Geneseeq Technology Inc., China, includes 416 genes and several gene fusion events.

Several controversies exist in the commercial implementation of such tests: 1) How to best control and monitor the quality of various tests commercially offered? 2) Should the test exist as a laboratory-developed test (LDT) or as part of a commercial diagnostic kit? and 3) How large should the gene panels be? These questions have been intensively debated by experts in the field over the past year. NGS combined with liquid biopsy is another nascent and rapidly emerging field in China. Liquid biopsy tests exploit the presence of circulating tumor DNA in the blood. Since it is minimally invasive, liquid biopsy allows...
Today’s Age of Drug Development
Q & A with Kapil Dhingra, MD

IASLC Lung Cancer News recently spoke with Kapil Dhingra, MD, of KAPital Consulting LLC in Sparta, New Jersey, about oncologic drug development and the challenges and opportunities to anticipate in the future.

Q: What are the perils and pitfalls of oncologic drug development in the new millennium?
A: I don’t necessarily agree with the phrase “perils and pitfalls.” From my perspective, we are experiencing the golden age of oncologic drug development with a plethora of targeted drugs and immunotherapies at our disposal and even more in development. This is an exciting time and we need to maintain this momentum to harness the power of personalized medicine in the treatment of cancer.

That said, we are facing several challenges. We still have a relatively poor understanding of what makes cancer cancer and what makes cancer respond or not respond to treatments. The connection between the tumor cell, its microenvironment, and the immune system is complicated and the tools available to understand complex cancer biology remain poor. For instance, we have no way of knowing what goes on in a patient’s tumor once we’ve administered a drug.

Another big challenge is the competitive oncologic drug-development environment. There is tremendous pressure from all stakeholders on small and large companies to bring first-in-class drugs to market quickly. This competition often leads to suboptimal decision-making. Judicious acceleration of drug development while maintaining an objective perspective on the emerging early data on new drugs is critical to achieve the right balance.

Q: How do we address the risk-benefit equation in the development of targeted therapies and immunotherapies?
A: Nothing has really changed in a meaningful way as to how we assess risk versus benefit, whether we’re talking about chemotherapy, targeted therapies, or immunotherapies. With any drug, we still need to weigh its benefit against the price to be paid with regard to side effects. Our hope is that targeted therapies and immunotherapies will yield a better risk:benefit profile compared with chemotherapy. The key change is in our expectation that we are no longer interested in drugs that produce modest improvements in survival at the expense of significant toxicity.

Q: Is lung cancer unique in this regard?
A: No.

Q: Given the stakes in cancer therapy and the imminent lethality of cancer, shouldn’t some of the rigid rules developed by the FDA in the management of “benign” illnesses like hypertension or diabetes mellitus be relaxed?
A: In my opinion, the FDA has become much more enlightened over the past 5 or 6 years. The FDA has shown significant flexibility with oncologic drug trials by allowing sponsors to combine phase 1, 2, and 3 trials into one trial. Similarly, the FDA has been open to considering new ways to assess the efficacy of targeted therapies and immunotherapies. Keep in mind that the vast majority of novel oncology agents are approved not based on their effect on overall survival, but on other endpoints such as disease-free survival and progression-free survival. Even in the European Union, regulators have shown considerable flexibility in approving new targeted cancer drugs. This represents a change from the way drugs were approved in the past. In addition, mechanisms to accelerate the speed of approval of cancer drugs have been implemented. Consequently, in the last 5 years, more than 40 new agents to treat cancer have been approved. So, from that perspective, the FDA already has relaxed its traditional regulatory framework. We do need to shift our focus, though, with regard to toxicities when using these novel agents. It was perfectly acceptable to focus on grade 3 and 4 toxicities such as reversible myelosuppression when dealing with chemotherapy agents. But when we’re dealing with targeted therapies and immunotherapies that are given long term, we need to look at persistent grade 1 and 2 toxicities. A grade 2 skin rash or diarrhea that persists over a long period of time can adversely affect a patient’s quality of life far more than grade 3 myelosuppression, which is often asymptomatic. Also, with immunoncology drugs, we are seeing far more toxicities, e.g., autoimmunity, that linger long after a drug is stopped.

Q: Is there anything else you would like to share with our readers about oncologic drug development in the future?
A: The lung cancer drug development community needs to develop a more holistic approach to profile the patients’ tumors. This should include not just actionable mutations such as EGFR mutations and ALK fusions, but also the microenvironment and the homeostasis between the tumor and the patient’s immune system. Additionally, we need to develop more systematic and efficient means to test the large number of permutations and combinations of novel agents in the pipeline. Serial profiling of the tumor and the patient’s immune system will enable us to offer a more personalized approach to treatment of the majority of patients with lung cancer, rather than a minority of patients who qualify for such an approach today. I foresee a future where such profiling will be done not only at baseline, but also several times during the natural history of a patient to adapt his/her treatment regimen or regimens to the emerging changes in the behavior of the tumor.
Mark A. Socinski, MD, has been appointed Executive Medical Director of the Florida Hospital Cancer Institute, and will oversee the coordination of clinical cancer services for the Florida Hospital network. He will also be a member of the Institute’s Thoracic Oncology Program. Dr. Socinski was previously Professor of Medicine and Cardiovascular Surgery; Director of the Lung Cancer Section for the Division of Hematology and Oncology; Co-director of the Lung Cancer Center of Excellence; and Co-director of the Lung Cancer Program at the University of Pittsburgh Medical Center (UPMC) Cancer Pavilion, Pittsburgh, US.

Anton Berns, PhD, FAACR, was elected to the National Academy of Sciences (NAS). NAS membership is in recognition of distinguished and continuing achievements in original research. Dr. Berns is the Senior Group Leader of the Division of Molecular Genetics at the Netherlands Cancer Institute, Amsterdam, and is a former director of the NKI.

Jean-Marie Cuillerot, MD, has been appointed Vice President and Global Head of Clinical Development at Agenus, Inc, Lexington, US, overseeing ongoing clinical development of checkpoint targeted antibodies, including AGEN1884 targeting CTLA-4 and INCAGN1876 targeting GITR. Dr. Cuillerot was Global Head of Clinical Development, Immuno-Oncology, and Vice President of Clinical Immunotherapy/Immu-no-Oncology at EMD Serono Research and Development Institute, an affiliate of Merck Serono, and prior to that at Bristol-Myers Squibb.

Jeffrey Engelman, MD, PhD, has been appointed Vice President and Global Head of Oncology at the Novartis Institutes of BioMedical Research. Prior to joining Novartis, Dr. Engelman was Director of the Center for Thoracic Oncology and Molecular Therapeutics at Massachusetts General Hospital, Boston, US, and Harvard Medical School professor.

Glen Weiss, MD, MBA, was named 2016 Healthcare Leadership Awards’ Researcher of the Year by AZ Business magazine. Dr. Weiss is Director of Clinical Research, Director of Phase I and II Clinical Trials, Cancer Treatment Centers of America, Arizona, US, and is Clinical Associate Professor at University of Arizona College of Medicine.

David Spigel, MD, has been appointed chief scientific officer of Sarah Cannon Research Institute, Nashville, US, and will oversee the development and operations of Sarah Cannon’s clinical research program. Dr. Spigel joined Sarah Cannon in 2003 as the director of the lung cancer research program.

Laurie Fenton Ambrose received the 2016 James L. Mulshine, MD Leadership Award, which recognized her efforts in guiding patient advocacy and other stakeholder groups in the successful efforts to gain coverage of lung cancer screening by the Centers for Medicare & Medicaid Services (CMS). Ms. Ambrose is President and CEO of the Lung Cancer Alliance.

David H. Johnson, MD, received the 2016 ASCO Distinguished Achievement Award, which is given annually and recognizes leadership or mentorship by a scientist, practitioner, or researcher who has benefited patients with cancer or those who treat them. Dr. Johnson is Chairman of the Department of Internal Medicine at The University of Texas (UT) Southwestern Medical Center, Dallas, US.

The Victorian Comprehensive Cancer Centre, which opened this summer, is a new purpose-built facility for cancer research, treatment, care, and education in Melbourne’s Parkville biomedical precinct. In addition to the new facilities, ten world-leading cancer organizations have come together to form the VCCC Alliance to share knowledge and resources and to drive the next generation of cancer research, education, treatment, and care.

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In summary, NGS-based genotyping is a rapidly emerging and promising field in China that can bring tangible clinical benefits to patients and fulfill the vision of Precision Medicine, particularly in thoracic oncology. It has the potential to turbocharge translational research and speed up therapeutic innovation. ✦

References
**17TH WORLD CONFERENCE ON LUNG CANCER**

December 4 – 7, 2016

VIENNA, AUSTRIA

CONERENCE PRESIDENT:
ROBERT PIRKER, MD

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**IMPORTANT DATES**

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