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FOR THORACIC SPECIALISTS

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INSIDE

IMMUNOTHERAPY

AACR 2018: First-Line Management of Advanced NSCLC Enters New Era

By Corey Langer, MD, *IASLC Lung Cancer News* Editor

The therapeutic landscape irrevocably altered on April 17, 2018, when three pivotal trials—KEYNOTE 189, CheckMate 227 and Impower 150—were presented during a plenary session at the American Association for Cancer Research (AACR) Annual Meeting in Chicago. As of that point, immunotherapy (IO) had not yet established primacy in the management of treatment-naive advanced NSCLC, but these trials have cemented its role. *(Please note that additional graphics are available online at lungcancernews.org.)*

KEYNOTE 189: Pembrolizumab Makes Waves

Leena Gandhi, MD, PhD, on behalf of the investigators of KEYNOTE 189, presented the results of a randomized phase III trial isolating the role of pembrolizumab in combination with pemetrexed and a platinum-based drug in patients with advanced nonsquamous NSCLC in the absence of *EGFR* or *ALK* alterations.[1]

Patients were randomly assigned 2:1 to either the pembrolizumab triplet or to chemotherapy/placebo for four cycles, after which patients on the investigational

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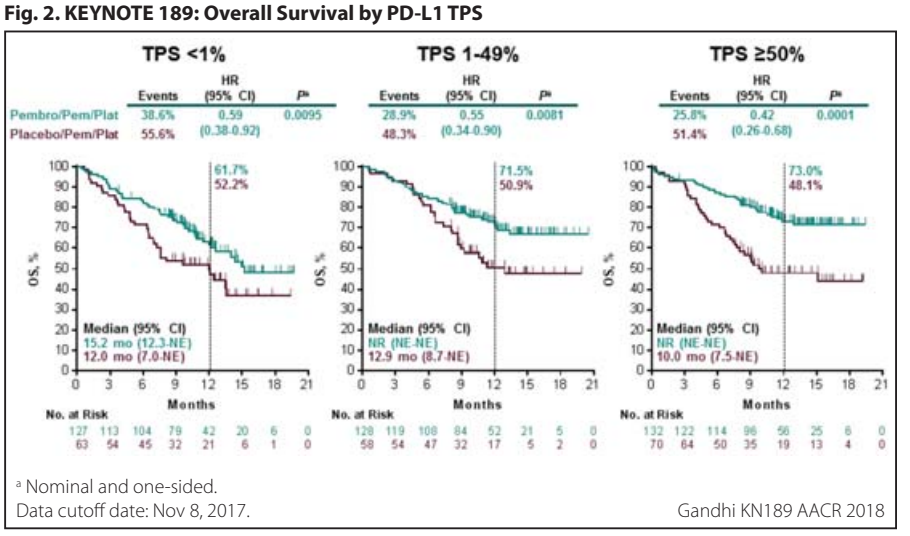
Fig. 2. KEYNOTE 189: Overall Survival by PD-L1 TPS



[a] Nominal and one-sided.
Data cutoff date: Nov 8, 2017.

Gandhi KN189 AACR 2018

EVOLVING STANDARDS OF CARE

Oncologic Biologic Biosimilars Are Coming to Market: Are You Ready?

Biosimilars have proven themselves to the U.S. FDA, but clinicians are still wary.

Healthcare providers are more than familiar with the use of brand name and generic drugs, but the passage of the Biologics Price Competition and Innovation (BPCI) Act of 2009 introduced a new player in the world of pharmaceuticals: the biosimilar.

In 2017, the U.S. Food and Drug Administration (FDA) approved the first biosimilar for cancer treatment, Mvasi™ (bevacizumab-awwb, Amgen Inc.). Mvasi is a biosimilar to Avastin® (bevacizumab, Genentech) and was approved for treatment of patients with certain colorectal cancers, nonsquamous NSCLC , glioblastoma, metastatic renal cell carcinoma, and cervical cancer. Although approved, Mvasi is not yet available for clinical use.

"There will be tremendous pressure to consider using biosimilars soon," said Corey J. Langer, MD, FACP, professor of medicine at The Hospital of The University of Pennsylvania and editor of the *IASLC Lung Cancer News*. "The presumption is that they are equivalent, but there is always a kernel of doubt."

According to Dr. Langer, oncologists have been "burnt" in the past thinking that new compounds are as good as or better than reference products, only to have problems emerge post-approval.

"With bevacizumab, I have nearly 20 years of experience working with the drug," he said. "I have a comfort level with it, and personally, I can't immediately export that comfort level to a biosimilar."

What Is a Biosimilar?

A biosimilar is a biologic product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product.

The BPCI created an abbreviated licensure pathway for biosimilars to come to market. According to the FDA, this pathway was established as a way to provide more treatment options, increase access to lifesaving medications, and potentially lower healthcare costs through competition. The BPCI was designed similarly to the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act), which encouraged generic competition for drugs. However, in contrast to generic drugs, which are small-molecule compounds made through chemical means, biosimilars are generally large, complex molecules produced through biotechnology in a living system, such as a microorganism, plant cell, or animal cell.

Dr. Richard Markus

"Unlike generic products, with biosimilars the manufacturer has to start with their own cell system and create their own process to make each biologic product unique," said Richard Markus, MD, vice president, Global Development at Amgen. "The biosimilar is highly similar, but a unique product according to that manufacturer's cell system and process."

According to Dr. Markus, the FDA evaluates a manufacturer's biosimilar

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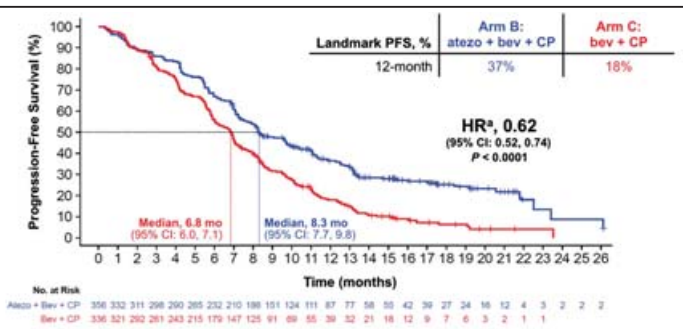
AACR 2018 from page 1

arm received maintenance therapy with pemetrexed and pembrolizumab, whereas the control group received pemetrexed/placebo (Fig. 1, online). At the time of disease progression, patients in the control group were offered crossover therapy to pembrolizumab. A total of 616 patients were enrolled. Those who received pembrolizumab attained a statistically significant and clinically meaningful improvement in overall survival (OS), with an unprecedented hazard ratio (HR) of 0.49 (Fig. 2, page 1; Fig 3 online). Median OS was not reached in the pembrolizumab arm compared to 11.3 months for the pemetrexed/placebo group; the respective 1-year survival rates were 69% and 49% (HR 0.49, 95% CI [0.38, 0.64]; p < 0.0001) with median progression-free survival (PFS) of 8.8 and 4.9 months, respectively (HR 0.52). The response rate in the investigational arm was 48% vs. 19% in the control arm (p < 0.00001). This benefit was observed across the board regardless of PD-L1 expression status, although the magnitude of benefit was more pronounced in those with higher levels of PD-L1 expression. For those with PD-L1 expression tumor proportion scores (TPS) of 50% or higher, the rate of response in the investigational arm was 62% vs. 23% in the control arm (HR 0.42, p < 0.0001). For TPS 1% to 49% and TPS < 1%, response rates were 48% vs. 21% (HR 0.55, p < 0.0001) and 32% vs. 14% (HR 0.59, p < 0.0001), respectively. Toxicities, particularly kidney injury, were heightened in the experimental arm but were manageable. Treatment discontinuation for adverse events (AEs) occurred in 13.8% of patients in the investigational arm compared to 7.9% in the control arm. Immune-related AEs occurred in 22.7% of patients in the investigational arm vs. 11.9% in the control arm.

Fig. 4. IMpower150 Demonstrated PFS Benefit in Arm B vs. C in the ITT-WT

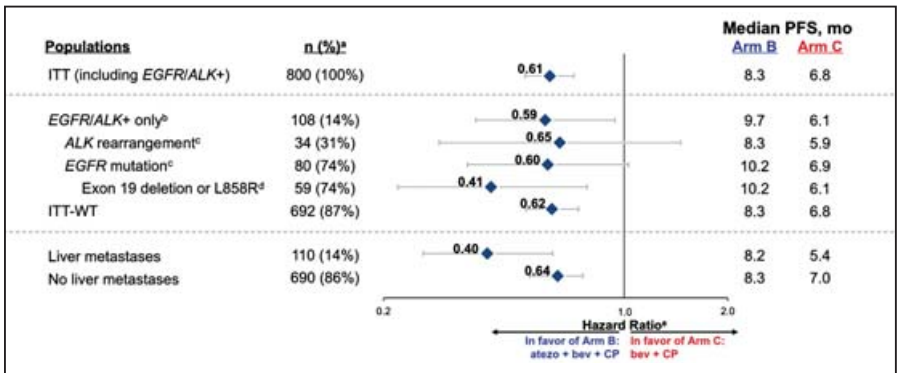


- OS positivity has since been reached (March 2018) and will be presented at an upcoming meeting

Abbreviations: atezo, atezolizumab; bev, bevacizumab: CP, carboplatin + paclitaxel.

[a] Stratified HR. Data cutoff: September 15, 2017. Reck M, et al. ESMO IO 2017 [LBA_PR1].
Kowanetz M, Socinski M, et al. AACR 2018 IMpower150: Efficacy Across Subgroups

Fig. 5. IMpoewr150: PFS Benefit in Arm B was Observed in Key Population

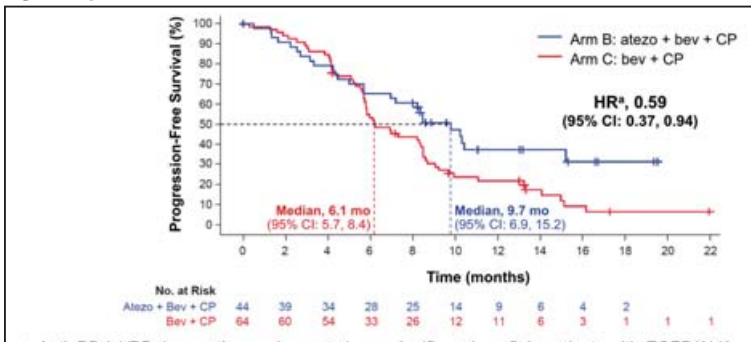


Abbreviations: atezo, atezolizumab; bev, bevacizumab; CP, carboplatin + paclitaxel.

[a] Prevalence % for ITT, *EGFR/ALK*+ only, ITT-WT, liver metastases, and no liver metastases out of ITT (n=800); prevalence % for *ALK* rearrangement and *EFGR* mutation out of *EGFR/ALK*+ only (n=108); prevalence % for exon 19 deletion of L858R out of *EFGR* mutation (n=80).
[b] Patients with a sensitizing *EFGR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.
[c] 6 patients had both *EFGR* mutation and *ALK* rearrangement.
[d] Other *EFGR* mutations include L861Q, G719X, S7681, exon 20 insertion, T790M, and other.
[e] Stratified HRs for ITT and ITT-WT populations; unstratified HRs for all other subgroups.
Data cutoff: September 15, 2017

Kowanetz M, Socinski M, et al. AACR 2018 IMpower150: Efficacy Across Subgroups

Fig. 6. IMpower150: PFS for Arm B vs. C in *EGFR/ALK*+ Patients



- Anti–PD-L1/PD-1 *monotherapy* has not shown significant benefit in patients with *EGFR/ALK* genetic alterations
- Most other clinical trials of PD-L1/PD-1 inhibitors in 1L NSCLC exclude patients with *EGFR* mutations

Abbreviations: atezo, atezolizumab; bev, bevacizumab: CP, carboplatin + paclitaxel.

[a] Unstratified HRs. Data cutoff: September 15, 2017

Kowanetz M, Socinski M, et al. AACR 2018 IMpower150: Efficacy Across Subgroups

This study has upended standard practice in the United States and promises to have a ripple effect globally. There are many unanswered questions, however. Pembrolizumab is approved as a single agent in advanced NSCLC for use with PD-L1 expression levels of 50% or higher based on the results of KEYNOTE 024, which showed superiority to chemotherapy in this setting.[2] KEYNOTE 189 did not compare the efficacy of combination pembrolizumab and chemotherapy to pembrolizumab alone, however. This point remains controversial, and its urgency is amplified by a recent press release on KEYNOTE 042, which reportedly demonstrated improved OS for single-agent pembrolizumab vs. chemotherapy in patients with any degree of PD-L1 expression.[3] Fortunately, the upcoming INSIGNIA trial—as outlined by Roy S. Herbst, MD, PhD, the discussant of KEYNOTE 189 at AACR—will address the issue of sequencing, directly comparing single-agent pembrolizumab in PD-L1–positive nonsquamous NSCLC to the three-drug combination; patients receiving pembrolizumab at the time of disease progression will go onto chemotherapy alone (pem/carbo) or on to a combination of pembrolizumab with chemotherapy.[4] In addition, KEYNOTE 189 did not address the role of IO/chemotherapy combinations in those with *EGFR* mutations or *ALK* translocations or in those patients eligible for angiogenesis inhibition.

Impower150: Relevance for Oncogenic Drivers

In this regard, IMpower150, which was presented by Mark Socinski, MD, fills a void.[5] Up until the emergence of IO in advanced NSCLC, the combination of paclitaxel and carboplatin with bevacizumab was considered by many a "state-of-the-art" regimen in advanced non-squamous NSCLC. The study E4599 demonstrated therapeutic superiority with improved response rates, PFS, and OS for this three-drug regimen compared to paclitaxel/carboplatin alone.[6] In IMpower 150, eligible patients were randomly assigned to the E4599 regimen of paclitaxel/carboplatin and bevacizumab or the same regimen in combination with atezolizumab. A third arm substituted atezolizumab for bevacizumab.

More than 1,200 patients were enrolled on this trial. In the intent-to-treat wild-type population, 356 patients randomly assigned to the four-drug atezolizumab arm realized a median PFS of 8.3 months and 1-year PFS of 37% compared to 6.8 months and 18%, respectively, for the 336 patients on the control arm (Figs. 4-6; HR 0.62, 95% CI [0.52, 0.74]; p < 0.0001).

As we observed in KEYNOTE 189, those with higher levels of PD-L1 expression had relatively greater benefit; the HR in the 20% of patients with very high levels of PD-L1 expression was 0.39, with median PFS of 12.6 vs 6.8 months for the atezolizumab combination and the control group, respectively. In addition, the PFS benefit was similar for those with *EGFR*/*ALK* alterations, with an HR of 0.59 and median PFS of 9.7 and 6.1 months, respectively. In those with "actionable" *EGFR* mutations, the PFS benefit was even more pronounced with an HR of 0.41 and a PFS of 10.2 and 6.1 months, respectively.

A recent press release confirmed an OS advantage for the four-drug regimen.[7] At a related presentation at the ESMO Immuno Oncology Congress, the median OS was 19.2 months for the atezolizumab arm compared to 14.4 months for the control arm (HR 0.775, 95% CI [0.619, 0.970]; p = 0.0262). Given the results of KEYNOTE 189, it is unclear whether there will be much uptake for the four-drug regimen due to its complexity and the inherent toxicities of taxanes, including hair loss and neuropathy. However, this study is unique in addressing patients with oncogenic drivers and has clinical relevance for those whose disease is TKI refractory.

Dr. Socinski told IASLC *Lung Cancer News* that this trial "tests the theory that VEGF inhibition may augment the effectiveness of anti–PD-L1 therapy. The trial provides validation for this strategy, creating a new option for bevacizumab-eligible patients, particularly in certain subsets such as *EGFR* mutated and *ALK*-translocated patients."

CheckMate 227: Using TMB to Determine Therapy

Finally, there are many investigators who firmly believe that IO combinations will ultimately displace chemotherapy in the management of advanced NSCLC. CheckMate 227, presented by Matthew D. Hellmann, MD, provides evidence that such an approach may have substantial merit in those with high tumor mutation burden (TMB) defined as > 10 mutations (mut)/Mb.[8] In this study, patients with high TMB who received combination nivolumab and ipilumumab (nivo/ipi) had

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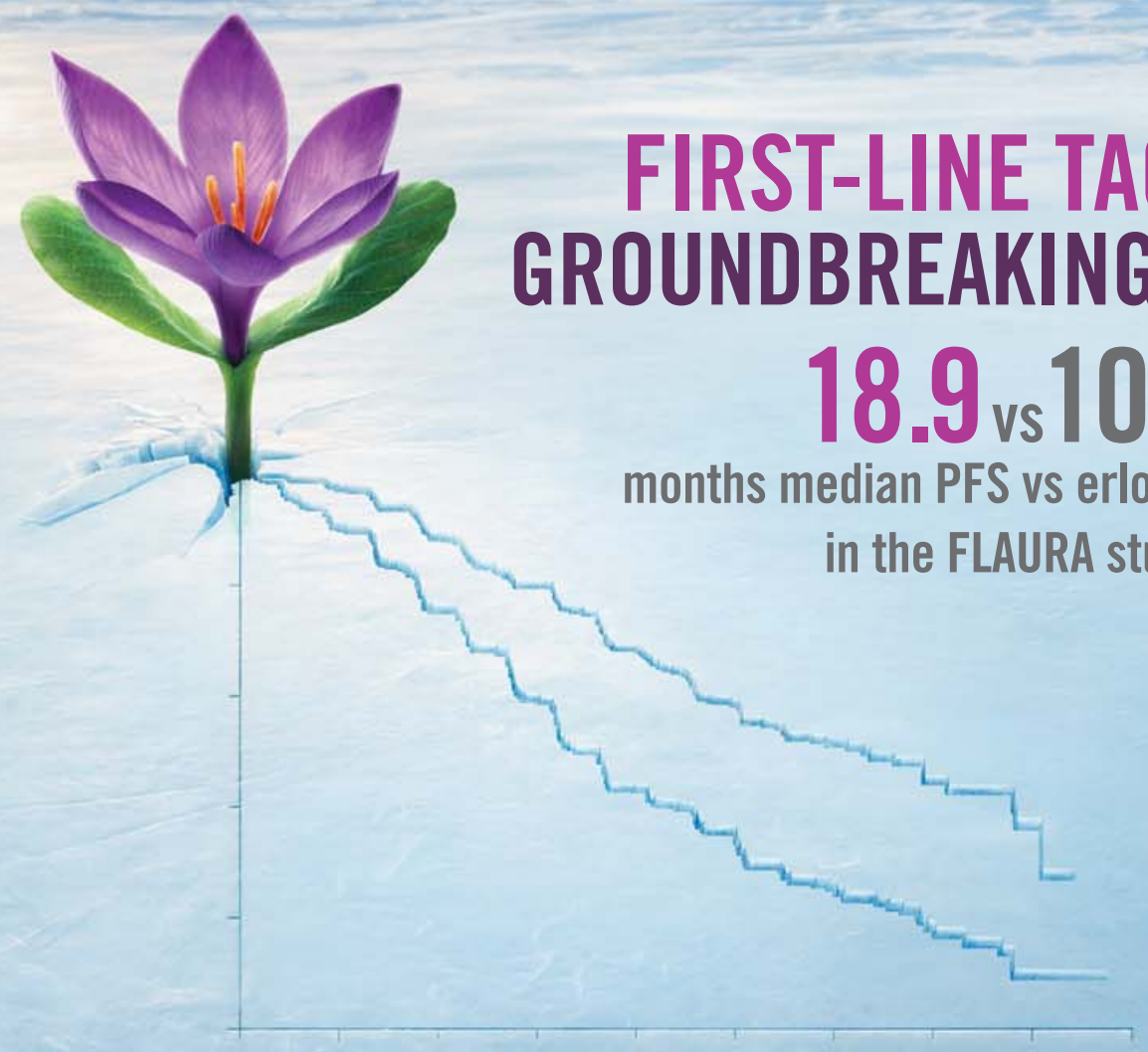
NEW INDICATION FOR THE TREATMENT OF METASTATIC EGFRm NSCLC



FIRST-LINE TAGRISSO®
GROUNDBREAKING EFFICACY

18.9 vs 10.2

months median PFS vs erlotinib/gefitinib in the FLAURA study

INDICATION

TAGRISSO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

SELECT SAFETY INFORMATION

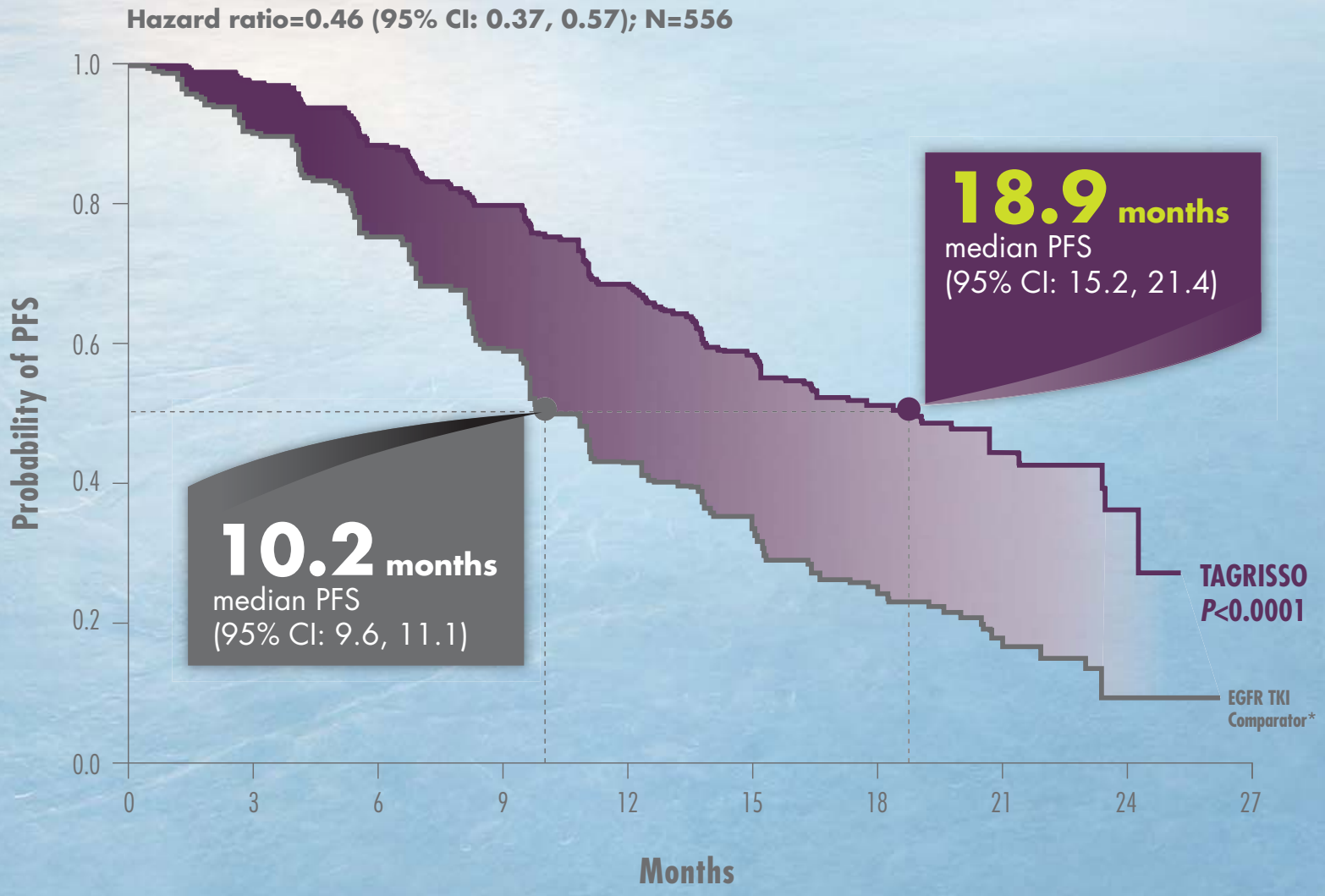
- There are no contraindications for TAGRISSO
- Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 TAGRISSO-treated patients; 0.4% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed

Please see Brief Summary of Prescribing Information on adjacent pages.

TAGRISSO®
osimertinib

CHOOSE FIRST-LINE TAGRISSO:

TAGRISSO nearly doubled median PFS and cut the risk of progression or death by 54% vs EGFR TKI comparator[1]



*In the FLAURA study, all US patients in the comparator arm received erlotinib.[2]

SELECT SAFETY INFORMATION

- Heart rate-corrected QT (QTc) interval prolongation occurred in TAGRISSO-treated patients. Of the 1142 TAGRISSO-treated patients in clinical trials, 0.9% were found to have a QTc > 500 msec, and 3.6% of patients had an increase from baseline QTc > 60 msec. No QTc-related arrhythmias were reported. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia
- Cardiomyopathy occurred in 2.6% of the 1142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) ≥10% from baseline and to <50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO

AstraZeneca

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A NEW STANDARD OF CARE

FOR THE TREATMENT OF METASTATIC EGFRm NSCLC

PFS

Demonstrated unprecedented 18.9 months median PFS vs 10.2 months for EGFR TKI comparator[1]

- Hazard ratio=0.46 (95% CI: 0.37, 0.57), *P*<0.0001

ALL SUBGROUPS

Delivered consistent PFS results across all subgroups[3]

- Including patients with or without CNS metastases

Osimertinib (TAGRISSO) is an NCCN-recommended first-line therapy option[4]

Randomized, double-blind, active-controlled trial in 556 patients with metastatic EGFRm NSCLC who had not received prior systemic treatment for advanced disease. Patients were randomized 1:1 to either TAGRISSO (n=279; 80 mg orally, once daily) or EGFR TKI comparator (n=277; gefitinib 250 mg or erlotinib 150 mg orally, once daily). Crossover was allowed for patients in the EGFR TKI comparator arm at confirmed progression if positive for the EGFR T790M resistance mutation. Patients with CNS metastases not requiring steroids and with stable neurologic status were included in the study. The primary endpoint of the study was PFS based on investigator assessment (according to RECIST v1.1). Secondary endpoints included ORR, DOR, OS, and safety.[1,3]

SELECT SAFETY INFORMATION

- Keratitis was reported in 0.7% of 1142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist
- Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose
- Most common adverse reactions (≥20%) were diarrhea, rash, dry skin, nail toxicity, stomatitis, fatigue and decreased appetite

Abbreviations: CNS, central nervous system; **DOR**, duration of response; **EGFRm**, epidermal growth factor receptor mutation-positive; **NSCLC**, non–small-cell lung cancer; **ORR**, overall response rate; **OS**, overall survival; **PFS**, progression-free survival; **RECIST**, Response Evaluation Criteria In Solid Tumors; **TKI**, tyrosine kinase inhibitor.

REFERENCES: 1. TAGRISSO [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2018. **2.** Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer. *N Engl J Med.* 2018;378(2):113-125 [protocol]. **3.** Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer. *N Engl J Med.* 2018;378(2):113-125. **4.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC V.3.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed March 1, 2018. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. To view the most recent and complete version of the guideline, go online to NCCN.org.

LEARN MORE AT TagrissoHCP.com

TAGRISSO®
osimertinib
First-line treatment of metastatic EGFRm NSCLC

TAGRISSO® (osimertinib) tablets, for oral use

Brief Summary of Prescribing Information.

For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

First-line Treatment of EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

TAGRISSO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

DOSAGE AND ADMINISTRATION

Patient Selection

Select patients for the first-line treatment of metastatic EGFR-positive NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor or plasma specimens *[see Clinical Studies (14) in the full Prescribing Information]*. If this mutation is not detected in a plasma specimen, test tumor tissue if feasible.

Information on FDA-approved tests for the detection of EGFR mutations is available at http://www.fda.gov/companiondiagnostics.

Recommended Dosage Regimen

The recommended dosage of TAGRISSO is 80 mg tablet once a day until disease progression or unacceptable toxicity. TAGRISSO can be taken with or without food.

If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

Administration to Patients Who Have Difficulty Swallowing Solids

Disperse tablet in 60 mL (2 ounces) of non-carbonated water only. Stir until tablet is dispersed into small pieces (the tablet will not completely dissolve) and swallow immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 120 mL to 240 mL (4 to 8 ounces) of water and immediately drink.

If administration via nasogastric tube is required, disperse the tablet as above in 15 mL of non-carbonated water, and then use an additional 15 mL of water to transfer any residues to the syringe. The resulting 30 mL liquid should be administered as per the nasogastric tube instructions with appropriate water flushes (approximately 30 mL).

Dosage Modifications

Adverse Reactions

Table 1. Recommended Dosage Modifications for TAGRISSO

Target Organ	Adverse Reaction[a]	Dosage Modification
Pulmonary	Interstitial lung disease (ILD)/Pneumonitis	Permanently discontinue TAGRISSO.
Cardiac	QTc[†] interval greater than 500 msec on at least 2 separate ECGs[b]	Withhold TAGRISSO until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then resume at 40 mg dose.
	QTc interval prolongation with signs/symptoms of life-threatening arrhythmia	Permanently discontinue TAGRISSO.
	Symptomatic congestive heart failure	Permanently discontinue TAGRISSO.
Other	Adverse reaction of Grade 3 or greater severity	Withhold TAGRISSO for up to 3 weeks.
	If improvement to Grade 0-2 within 3 weeks	Resume at 80 mg or 40 mg daily.
	If no improvement within 3 weeks	Permanently discontinue TAGRISSO.

[a] Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0).
[b] ECGs = Electrocardiograms
[†] QTc = QT interval corrected for heart rate

Drug Interactions

Strong CYP3A4 Inducers

If concurrent use is unavoidable, increase TAGRISSO dosage to 160 mg daily when coadministering with a strong CYP3A inducer. Resume TAGRISSO at 80 mg 3 weeks after discontinuation of the strong CYP3A4 inducer *[see Drug Interactions (7) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease/Pneumonitis

Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 TAGRISSO-treated patients; 0.4% of cases were fatal.

Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed *[see Dosage and Administration (2.4) and Adverse Reactions (6) in the full Prescribing Information]*.

QTc Interval Prolongation

Heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with TAGRISSO. Of the 1142 patients treated with TAGRISSO in clinical trials, 0.9% were found to have a QTc > 500 msec, and 3.6% of patients had an increase from baseline QTc > 60 msec *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. No QTc-related arrhythmias were reported.

Clinical trials of TAGRISSO did not enroll patients with baseline QTc of > 470 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

Cardiomyopathy

Across clinical trials, cardiomyopathy (defined as cardiac failure, chronic cardiac failure, congestive heart failure, pulmonary edema or decreased ejection fraction) occurred in 2.6% of the 1142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal.

A decline in left ventricular ejection fraction (LVEF) ≥ 10% from baseline and to less than 50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment.

Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

Keratitis

Keratitis was reported in 0.7% of 1142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist.

Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, osimertinib caused post-implantation fetal loss when administered during early development at a dose exposure 1.5 times the exposure at the recommended clinical dose. When males were treated prior to mating with untreated females, there was an increase in preimplantation embryonic loss at plasma exposures of approximately 0.5 times those observed at the recommended dose of 80 mg once daily. Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose *[see Use in Specific Populations (8.1, 8.3) in the full Prescribing Information]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

QTc Interval Prolongation *[see Warnings and Precautions (5.2) in the full Prescribing Information]*

Cardiomyopathy *[see Warnings and Precautions (5.3) in the full Prescribing Information]*

Keratitis *[see Warnings and Precautions (5.4) in the full Prescribing Information]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the Warnings and Precautions section reflect exposure to TAGRISSO in 1142 patients with EGFR mutation-positive NSCLC who received TAGRISSO at the recommended dose of 80 mg once daily in two randomized, active-controlled trials [FLAURA (n=279) and AURA3 (n=279)], two single arm trials [AURA Extension (n=201) and AURA2 (n=210)], and one dose-finding study, AURA1 (n=173) *[see Warnings and Precautions (5) in the full Prescribing Information]*.

The data described below reflect exposure to TAGRISSO (80 mg daily) in 558 patients with EGFR mutation-positive, metastatic NSCLC in two randomized, active-controlled trials [FLAURA (n=279) and AURA3 (n=279)]. Patients with a history of interstitial lung disease, drug induced interstitial disease or radiation pneumonitis that required steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 msec on electrocardiogram were excluded from enrollment in these studies.

Previously Untreated EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer

The safety of TAGRISSO was evaluated in FLAURA, a multicenter international double-blind randomized (1:1) active controlled trial conducted in 556 patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive, unresectable or metastatic NSCLC who had not received previous systemic treatment for advanced disease. The median duration of exposure to TAGRISSO was 16.2 months.

The most common adverse reactions (≥20%) in patients treated with TAGRISSO were diarrhea (58%), rash (58%), dry skin (36%), nail toxicity (35%), stomatitis (29%), and decreased appetite (20%). Serious adverse reactions were reported in 4% of patients treated with TAGRISSO; the most common serious adverse reactions (≥1%) were pneumonia (2.9%), ILD/pneumonitis (2.1%), and pulmonary embolism (1.8%). Dose reductions occurred in 2.9% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval as assessed by ECG (4.3%), diarrhea (2.5%), and lymphopenia (1.1%). Adverse reactions leading to permanent discontinuation occurred in 13% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (3.9%).

Tables 2 and 3 summarize common adverse reactions and laboratory abnormalities which occurred in FLAURA. FLAURA was not designed to demonstrate a statistically significant reduction in adverse reaction rates for TAGRISSO, or for the control arm, for any adverse reaction listed in Tables 2 and 3.

Table 2. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA*

Adverse Reaction	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
	Any Grade (%)	Grade 3 or higher (%)	Any Grade (%)	Grade 3 or higher (%)
Gastrointestinal Disorders				
Diarrhea[a]	58	2.2	57	2.5
Stomatitis	29	0.7	20	0.4
Nausea	14	0	19	0
Constipation	15	0	13	0
Vomiting	11	0	11	1.4
Skin Disorders				
Rash[b]	58	1.1	78	6.9
Dry skin[c]	36	0.4	36	1.1
Nail toxicity[d]	35	0.4	33	0.7
Pruritus[e]	17	0.4	17	0
Metabolism and Nutrition Disorders				
Decreased appetite	20	2.5	19	1.8
Respiratory, Thoracic and Mediastinal Disorders				
Cough	17	0	15	0.4
Dyspnea	13	0.4	7	1.4
Neurologic Disorders				
Headache	12	0.4	7	0
Cardiac Disorders				
Prolonged QT Interval[f]	10	2.2	4	0.7
General Disorders and Administration Site Conditions				
Fatigue[g]	21	1.4	15	1.4
Pyrexia	10	0	4	0.4
Infection and Infestation Disorders				
Upper Respiratory Tract Infection	10	0	7	0

* NCI CTCAE v4.0
[a] One grade 5 (fatal) event was reported (diarrhea) for EGFR TKI comparator
[b] Includes rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, rash follicular, erythema, folliculitis, acne, dermatitis, dermatitis acneiform, drug eruption, skin erosion.
[c] Includes dry skin, skin fissures, xerosis, eczema, xeroderma.
[d] Includes nail bed disorder, nail bed inflammation, nail bed infection, nail discoloration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.
[e] Includes pruritus, pruritus generalized, eyelid pruritus.
[f] The frequency of "Prolonged QT Interval" represents reported adverse events in the FLAURA study. Frequencies of QTc intervals of >500 ms or >60 ms are presented in Section 5.2.
[g] Includes fatigue, asthenia.

Table 3. Laboratory Abnormalities Worsening from Baseline in ≥ 20% of Patients in FLAURA

Laboratory Abnormality[a,b]	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or Grade 4 (%)	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or Grade 4 (%)
Hematology				
Lymphopenia	63	5.6	36	4.2
Anemia	59	0.7	47	0.4
Thrombocytopenia	51	0.7	12	0.4
Neutropenia	41	3.0	10	0
Chemistry				
Hyperglycemia[c]	37	0	31	0.5
Hypermagnesemia	30	0.7	11	0.4
Hyponatremia	26	1.1	27	1.5
Increased AST	22	1.1	43	4.1
Increased ALT	21	0.7	52	8
Hypokalemia	16	0.4	22	1.1
Hyperbilirubinemia	14	0	29	1.1

[a] NCI CTCAE v4.0
[b] Each test incidence, except for hyperglycemia, is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (TAGRISSO range: 267 - 273 and EGFR TKI comparator range: 256 - 268)
[c] Hyperglycemia is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TAGRISSO (179) and EGFR comparator (191)

DRUG INTERACTIONS

Effect of Other Drugs on Osimertinib

Strong CYP3A Inducers

Coadministering TAGRISSO with a strong CYP3A4 inducer decreased the exposure of osimertinib compared to administering TAGRISSO alone *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Decreased osimertinib exposure may lead to reduced efficacy.

Avoid coadministering TAGRISSO with strong CYP3A inducers. Increase the TAGRISSO dosage when coadministering with a strong CYP3A4 inducer if concurrent use is unavoidable *[see Dosage and Administration (2.4) in the full Prescribing Information]*. No dose adjustments are required when TAGRISSO is used with moderate and/or weak CYP3A inducers.

Effect of Osimertinib on Other Drugs

Coadministering TAGRISSO with a BCRP substrate increased the exposure of the BCRP substrate compared to administering the BCRP substrate alone *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Increased BCRP substrate exposure may increase the risk of exposure-related toxicity. Monitor for adverse reactions of the BCRP substrate, unless otherwise instructed in its approved labeling, when coadministered with TAGRISSO.

Drugs That Prolong the QTc Interval

The effect of coadministering medicinal products known to prolong the QTc interval with TAGRISSO is unknown. When feasible, avoid concomitant administration of drugs known to prolong the QTc interval with known risk of Torsades de pointes. If not feasible to avoid concomitant administration of such drugs, conduct periodic ECG monitoring *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on data from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1) in the full Prescribing Information]*, TAGRISSO can cause fetal harm when administered to a pregnant woman. There are no available data on TAGRISSO use in pregnant women. Administration of osimertinib to pregnant rats was associated with embryolethality and reduced fetal growth at plasma exposures 1.5 times the exposure at the recommended clinical dose *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically-recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

When administered to pregnant rats prior to embryonic implantation through the end of organogenesis (gestation days 2-20) at a dose of 20 mg/kg/day, which produced plasma exposures of approximately 1.5 times the clinical exposure, osimertinib caused post-implantation loss and early embryonic death. When administered to pregnant rats from implantation through the closure of the hard palate (gestation days 6 to 16) at doses of 1 mg/kg/day and above (0.1 times the AUC observed at the recommended clinical dose of 80 mg once daily), an equivocal increase in the rate of fetal malformations and variations was observed in treated litters relative to those of concurrent controls. When administered to pregnant dams at doses of 30 mg/kg/day during organogenesis through lactation Day 6, osimertinib caused an increase in total litter loss and postnatal death. At a dose of 20 mg/kg/day, osimertinib administration during the same period resulted in increased postnatal death as well as a slight reduction in mean pup weight at birth that increased in magnitude between lactation days 4 and 6.

Lactation

Risk Summary

There are no data on the presence of osimertinib or its active metabolites in human milk, the effects of osimertinib on the breastfed infant or on milk production. Administration to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death *[see Use in Specific Populations (8.1) in the full Prescribing Information]*. Because of the potential for serious adverse reactions in breastfed infants from osimertinib, advise women not to breastfeed during treatment with TAGRISSO and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating TAGRISSO.

Contraception

TAGRISSO can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of TAGRISSO *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

Infertility

Based on animal studies, TAGRISSO may impair fertility in females and males of reproductive potential. The effects on female fertility showed a trend toward reversibility. It is not known whether the effects on male fertility are reversible *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

Pediatric Use

The safety and effectiveness of TAGRISSO in pediatric patients have not been established.

Geriatric Use

Forty-three percent (43%) of the 1142 patients in FLAURA (n=279), AURA3 (n=279), AURA Extension (n=201), AURA2 (n=210), and AURA1, (n=173) were 65 years of age and older. No overall differences in effectiveness were observed based on age. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (13.4% versus 9.3%) and more frequent dose modifications for adverse reactions (13.4% versus 7.6%) in patients 65 years or older as compared to those younger than 65 years.

Renal Impairment

No dose adjustment is recommended in patients with mild, [creatinine clearance (CLcr) 60-89 mL/min, as estimated by the Cockcroft Gault method (C-G)], moderate, (CLcr 30-59 mL/min) or severe (CLcr 15-29 mL/min) renal impairment. There is no recommended dose of TAGRISSO for patients with end-stage renal disease *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Hepatic Impairment

No dose adjustment is recommended in patients with mild hepatic impairment [total bilirubin ≤ upper limit of normal (ULN) and AST > ULN or total bilirubin between 1 to 1.5 times ULN and any AST] or moderate hepatic impairment (total bilirubin between 1.5 to 3 times ULN and any AST). There is no recommended dose for TAGRISSO for patients with severe hepatic impairment *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

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Biosimilars from page 1

product by looking at a totality of evidence that includes the analytic structure of the compound, functional and pharmacokinetic similarity, and clinical trial data that demonstrate equivalent efficacy, safety, and immunogenicity to the reference product (Fig.).

For Mvasi, Amgen conducted a phase III, double-blind clinical trial where patients with nonsquamous NSCLC were randomly assigned to Mvasi (328 patients) or Avastin (314 patients).[1] The primary efficacy evaluation showed clinical equivalence between Mvasi and Avastin with a risk ratio of objective response rate for Mvasi compared with Avastin of 0.93 (90% CI [0.80, 1.09]) in the intent-to-treat population. In addition, the frequency, type, and severity of adverse events between the two biologics proved similar.

Based on the understanding of the mechanism of action of Mvasi, Amgen was able to obtain FDA approval for conditions other than nonsquamous NSCLC as well. Mvasi is approved as a biosimilar but not as an interchangeable product. An interchangeable biosimilar must meet additional requirements and, if approved, may be substituted for the reference product without involvement of the prescriber (Sidebar).

Clinicians' Concerns

In addition to proven safety and efficacy, concern exists about the quality control of biologic biosimilars, according to Edgardo S. Santos, MD, FACP, medical director of cancer research and associate professor of clinical biomedical science at the Charles E. Schmidt College of Medicine at Florida Atlantic University.

"We don't know if these products are produced in the United States or are coming from a global facility," said Dr. Santos, who is also chair of the IASLC Publications Committee.

According to Dr. Markus, Amgen has manufacturing facilities in the United States but also in other locations throughout the world.

"All facilities have to meet FDA inspection as a biologic facility," Dr. Markus said. "Amgen uses the same manufacturing network for biosimilars as it does for its [reference] products."

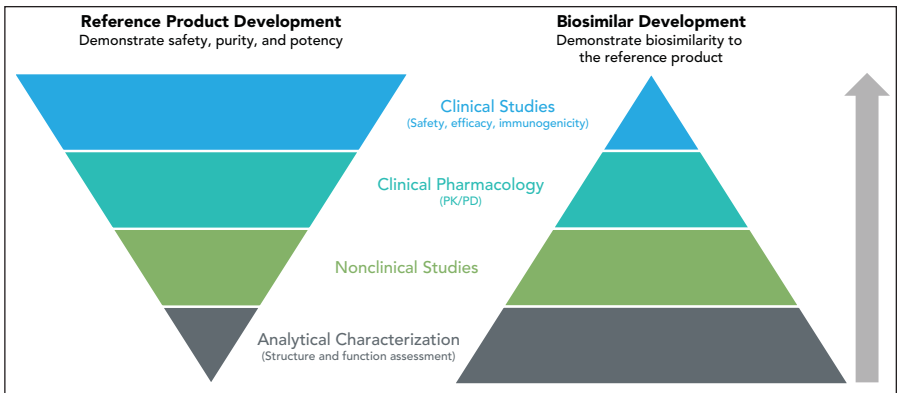
In addition, although Mvasi is the only biosimilar for Avastin approved by the FDA, there are many more biosimilars of Avastin in development. That means that there may be choices available to the treating physician or hospital with respect to biosimilars.

Dr. Santos worries that a multitude of biosimilars for the same reference drug will cause confusion for clinicians.

"If a biosimilar is on the market, and clinicians start to use it and see similar efficacy to the reference product, I do not know why we must continue to invest in more biosimilars for the same compound," Dr. Santos said. "We see the same phenomenon for reference drugs, and we end up with three or four drugs that all have the same efficacy for the same indication."

However, additional options could help avoid a monopoly and promote competition for pricing, Dr. Santos added.

Figure.



To attain FDA approval, a biosimilar may require a greater preponderance of analytical characterization and nonclinical studies than its reference product but might need fewer clinical trials/pharmacology studies.

Cost

"Competition that can lower healthcare costs" is one of the intended outcomes of approving more biosimilars, according to a statement from FDA Commissioner Scott Gottlieb, MD, in the announcement of the approval of a second oncologic biosimilar Ogivri (trastuzumab-dkst, Mylan GmbH) for Herceptin® (trastuzumab, Genentech).[2]

A biosimilar company that is able to gain even a small share of the market for a biosimilar product will make a lot of money. Looking across all treatments, it is estimated that biologics can cost an average of more than $16,000 per year, a 20-fold increase from the $730 per year cost of traditional pharmaceuticals.[3] At the midway point of 2016, Roche (which owns Genentech) reported a group revenue of approximately $25 billion supported largely in part by sales of three biologics: rituximab, trastuzumab, and bevacizumab.[4]

"Lowering costs is a laudable goal," Dr. Langer said. "Oncology care is very expensive, potentially unsustainable, one could argue. Anything that can reduce the cost without sacrificing therapeutic efficacy would be welcome."

However, Drs. Langer and Santos are both concerned that if biosimilars are introduced to the market at significant cost savings, then insurance payers may decide to no longer cover the higher cost of the reference product before the biosimilars have proven themselves in a real-world setting.

According to Dr. Santos, this situation is already occurring for Neupogen® (filgrastim), a growth factor used in the treatment of neutropenia. The first bio-

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FDA CORNER

FDA Fosters Understanding about Approval Process for Biosimilars

By Leah Christl, PhD, *Associate Director for Therapeutic Biologics and Director of the Therapeutic Biologics and Biosimilars Staff, Center for Drug Evaluation and Research, FDA*

Dr. Leah Christl

All FDA-approved biologics, including reference and biosimilar products, undergo a thorough evaluation so that patients can be assured of the efficacy, safety, and quality of these products. Biosimilars must meet the rigorous approval standards required by law. The goal of a biosimilar development program is to demonstrate biosimilarity between the proposed biosimilar product and the reference product, not to independently establish the safety, purity, and potency (safety and effectiveness) of the proposed product. State-of-the-art technology is used to compare the structure and function of the products, such as chemical identity and bioactivity, to demonstrate that the proposed biosimilar and the reference product are highly similar. A manufacturer must also demonstrate that its proposed biosimilar product has no clinically meaningful differences from the reference product in terms of safety and effectiveness. Generally, this is demonstrated through human pharmacokinetic and pharmacodynamic studies, an assessment of clinical immunogenicity, and, if needed, additional clinical studies. Any differences between the proposed biosimilar product and the reference product are carefully evaluated by the FDA to ensure the biosimilar meets the FDA's approval standards.

The manufacturing of biosimilars is closely regulated by the FDA. The statute requires the applicant to demonstrate that the facility in which the biosimilar product is manufactured, processed, packed, or held meets standards designed to assure that the biosimilar product continues to be safe, pure, and potent. The manufacturing controls and facility requirements apply to biologics regardless of whether it is a reference product or a biosimilar.

Slight differences (i.e., acceptable within-product variations) are expected during the manufacturing process for biologics, regardless of whether the product is a biosimilar or a reference product. For both reference and biosimilar products, lot-to-lot differences (i.e., acceptable within-product variations) are carefully controlled and monitored.

The FDA recently launched an education campaign to help increase understanding of biosimilar and interchangeable products among healthcare professionals. An interchangeable product is expected to produce the same clinical result as the reference product in any given patient. In addition, for a product administered to a patient more than once, there must be no additional risk or reduced efficacy if a patient switches back and forth between an interchangeable product and a reference product, compared to using the reference product without switching. A product approved as an interchangeable product means that the FDA has concluded it may be substituted for the reference product without consulting the prescriber. It is important for healthcare providers to understand that the FDA undertakes a comprehensive evaluation to ensure that biosimilar and interchangeable products meet the respective rigorous standards for approval. Healthcare providers and patients can expect that there will be no clinically meaningful differences between taking a reference product and a biosimilar when these products are used as intended. As with other drug products, healthcare providers should review the prescribing information in the labeling for detailed information about the approved uses. All campaign materials and other information about biosimilar products can be found at www.fda.gov/biosimilars. ✦

THOUGHT-LEADER PERSPECTIVE

Q&A Dr. Howard 'Skip' Burris III Shares His Views on Clinical Trial Eligibility Criteria, Payer Involvement

Howard A. "Skip" Burris III, MD, is the chief medical officer and president of clinical operations at Sarah Cannon, the Cancer Institute of HCA Healthcare, where he leads clinical, strategic, and drug-development initiatives. Dr. Burris also is an associate with Tennessee Oncology, PLLC.

In the interview below, Dr. Burris discusses the "extended journey" that a clinical trial represents for both a patient and an insurer. Because of the abundance of new therapies, the cancer community—comprised of patients, clinicians, industry, and private and federal insurers—must come together, in Dr. Burris's words, "to really figure out the most effective way to deliver the right therapy to the right patient at the right time." We are heading toward a future where the typical players find new roles, but real-world obstacles to clinical trial participation—including patient perception about the payer's role, increasing administrative burden for clinicians, and outdated exclusion criteria—must first be dealt with through collaboration and change.

Q: Do insurers affect patient enrollment to clinical trials and/or provision of trial treatments? If so, how?

A: There is the perception by many patients that their insurance companies might not cover clinical trial participation. That perception even extends to Medicare and to the interpretation of the Affordable Care Act regarding regular care in daily practice of patients with cancer. Medicare covers standard of care related to clinical trials as well as those related to research-specific aspects of trials billed to the sponsoring pharmaceutical or biotechnology company; therefore, the vast majority of patients on clinical trials receive the study treatment for free. Medicare has been a strong advocate for patients going on clinical trials, because this arrangement is better for the advancement of science and is, secondarily, better for them as payers.

I think that some of this perception is based on examples involving lack of payment by private payers in noncancer specialties—for example, a cardiology trial for a new stent or a urology trial for a sexual-dysfunction pharmaceutical agent. It is inaccurate to say that trial participation in those situations was elective or optional, but the therapies under study weren't investigational drugs or devices for patients with a life-threatening disease.


Dr. Howard 'Skip' Burris III

Insurance companies can take a more positive and proactive approach to lessen or eliminate the perception that clinical trial participation will not be covered. For example, every patient with cancer could have a case manager and/or advocate at the insurance company who recommends participation in a clinical trial, especially for those patients with relapsed disease.

Q: What are the challenges and strategies to enroll more participants into clinical trials?

A: Despite the vast number of trials available, the number one reason patients are not enrolled onto a clinical trial is that there isn't a clinical trial available specifically for them (regarding the particular disease setting) in their treating physicians' locations. As patients with cancer are divided into smaller and smaller subsets based on molecular markers, there are that many more trials enrolling patients. Take lung cancer—we used to talk about NSCLC versus SCLC, but now we can divide these into a dozen or more molecular subgroups. Despite the increased number of ongoing trials, it can become quite challenging for clinicians to offer all of those various trials at their individual sites. At Sarah Cannon, for example, the trial menu has doubled for a very small increase in the number of patients participating because, as patients are subdivided into more narrow classifications, more trials must be open. This results in an administrative burden for clinicians, as reimbursement for trial participation is on a per-patient basis for the work performed. Managing your trial menu can be a real challenge.

The second biggest challenge to enrollment is the clinical trial eligibility criteria. Inclusion/exclusion criteria can be very strict, but in truth, many of these do not accurately match the patient population. We treat a very narrow, select group of patients on study, but once a drug is approved, it is then exposed to the broader population where there is not inclusion/exclusion criteria. There will be advantages to exposing the broader population while the trials are being conducted.

HIV and hepatitis are great examples of two comorbid conditions that have traditionally been reasons for trial exclusion. We now know, however, that patients receiving newer medicines for these conditions respond very well, so those exclusion criteria should likely be lifted. Exclusion criteria have also been very stringent regarding cardiac events, but the average patient with lung cancer, for

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similar approved by the FDA was Zarxio (filgrastim-sndz), which is a biosimilar for Neupogen.

"There are insurance companies that do not allow use of Neupogen as growth factor support and not even Neulasta® (the pegylated form of filgrastim), which has shown better efficacy than Neupogen in head-to-head comparison with greater patient convenience," Dr. Santos said. "This will occur for other drugs as well."

According to Dr. Markus, Amgen has not announced a cost for Mvasi. However, he added that as oncologists and physicians begin to embrace biosimilars, they should not do it based on cost alone, and they should not do it blindly.

"Even though a product is approved, physicians will need to understand [biosimilars] a bit to feel confident about using them," Dr. Markus said. "There may eventually be a choice in which commercially available biosimilar agent they use and they, or an expert in their hospital system, should make their choice based on evaluation of the quality of the data, the clinical trial designs, and the results. They should also consider the fact that these agents are manufactured in a quality facility, just like they would before using a new biologic agent." ✦

References:

1. Thatcher N, et al. Randomized, double-blind, phase 3 study evaluating efficacy and safety of ABP 215 compared with bevacizumab in patients with non-squamous non-small-cell lung cancer. *J Clin Oncol.* 2016: 34(suppl 15):9095-9095.
2. FDA approves first biosimilar for the treatment of certain breast and stomach cancers. U.S. Food and Drug Administration website. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm587378.htm. Accessed February 15, 2018.
3. Shapiro RJ, Singh K, Mukim M. The Potential American Market for Generic Biological Treatments and the Associated Cost Savings. Sonecon LLC: Washington, DC, February 2008.
4. Pagliarulo N. Roche sales buoyed by cancer drugs. BioPharmaDive website. http://biopharmadive.com/news/roche-sales-buoyed-by-cancer-drugs/423032/. Accessed February 15, 2018.

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EVOLVING STANARDS OF CARE

Exploring Barriers to Combined-Modality Therapy for LS-SCLC

By Anna Farago, MD, PhD

Small cell lung cancer (SCLC) accounts for approximately 15% of all new lung cancer diagnoses in the United States. Approximately 30% of patients with newly diagnosed SCLC have limited-stage (LS) disease based on the Veterans' Administration Lung Study Group staging system; this means that the radiographically evident disease is localized within the hemithorax in a distribution treatable within a radiation field. For these patients, the optimal treatment is concurrent chemotherapy and radiation. This strategy is supported by several studies, including a meta-analysis published by Pignon and colleagues,[1] which demonstrated that concurrent chemotherapy and radiation improves local control and improves 3-year overall survival by approximately 5% compared to chemotherapy alone. Furthermore, multiple studies have shown that the optimal timing of radiation is to start within the first two cycles of chemotherapy.

In a recent brief report in *JAMA Oncology*, Pezzi et al.[2] explored barriers to combined-modality therapy for LS-SCLC. Using the National Cancer Database (NCDB), the authors analyzed initial management of all LS-SCLC cases between 2004 and 2013, with the goal of estimating utilization rates and factors associated with chemotherapy and radiation therapy delivery for LS-SCLC.

Dr. Anna Farago

The authors reviewed more than 70,200 cases with a median follow up of 62.3 months. They found that 55% of patients received chemotherapy and radiation as their initial treatment, 20.5% received chemotherapy alone, 3.5% received radiation alone, and 20% received neither. Notably, the NCDB did not provide information about whether chemotherapy and radiation were delivered concurrently or sequentially. Overall, outcomes were better for those patients who received combined modality therapy versus those who received chemotherapy alone, radiation therapy alone, or no therapy (median survival 18.2, 10.5, 8.3, and 3.7 months, respectively).

Differences in Outcomes Explained

Although one might speculate that the different outcomes among the four groups could reflect both selection bias (with more fit patients receiving combined modality therapy) and the superior anticancer activity of combined modality therapy, the authors sought to identify specific factors that were associated with differences in outcomes.

Access to health insurance and type of health insurance emerged as factors associated with overall survival. On multivariable analysis, the authors found that being uninsured was associated with a lower likelihood of patients receiving either chemotherapy or radiation therapy. Interestingly, Medicare/Medicaid insurance had no effect on chemotherapy use but did result in a decreased likelihood of radiation therapy delivery. Lack of health insurance, Medicaid, and Medicare coverage were all independently and significantly associated with a shorter overall survival on adjusted analysis (HR 1.19, 1.27, and 1.12, respectively), whereas chemotherapy and radiation therapy were associated with a survival benefit (HR 0.55 and 0.62, respectively).

The authors also found that the type of facility was associated with differences in outcomes. Patients who received care at an academic/research program had superior outcomes compared to those who received care at a community cancer center, comprehensive community cancer program, or integrated network cancer program (HR 1.19, 1.08, and 1.07, respectively; compared to a reference HR of 1 for the academic/research program). The authors noted that similar trends have been observed for outcomes of patients with NSCLC. They speculated that possible explanations could include patient selection, coordination of care, and access to subspecialists.

Implications for Clinical Practice

This study represents an important step toward better understanding of barriers to care for patients with LS-SCLC. In practice, concurrent chemotherapy and radiation for LS-SCLC poses several challenges for patients. Among these are time and cost associated with transportation for appointments, as well as scheduling

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example, is a little older than age 70, so it would not be shocking if he or she has experienced a cardiac event. In addition, cardiac exclusion criteria likely pertained, in many ways, to some of the older chemotherapies that were much harsher. We really need to re-evaluate whether those criteria should be lifted because of the lessened toxicity with newer therapies.

Q: Do you believe there are international models for clinical trial coverage and support that could be adapted in the United States?

A: Most models provide some sort of universal healthcare coverage, but how clinical trial participation is determined is quite varied. For example, in England, the pharmaceutical and biotechnology companies are expected to pay all of the trial costs. In other parts of Western Europe, the government will pay for the standard-care costs, acknowledging that the trial sponsors are paying the therapeutic costs. These same countries often have country-wide initiatives to encourage trial participation, the thought being that the best and newer therapies are available through trials, particularly for patients with relapsed or refractory disease. Generally, the clinical trial rates are much better for the countries that have socialized medicine or universal healthcare. In contrast, usually in Eastern European countries, trial accrual is much higher than in the United States because of the lack of available standard therapy—trials are the best option for care provision.

Q: How can medical societies leverage their influence with insurers to make sure "standard" care as part of clinical trials is covered?

A: Medical societies have a role in educating payers/insurers that participation in a clinical trial is part of a standard-of-care development and should be the first option for patient care, not a last resort. Medical societies can encourage a shift to value-based care from volume-based care. For example, the new immunotherapies for lung cancer have been very successful, but in reality, these therapies are not helping the majority of patients; long-term benefit is seen in probably only 30% of total patients. Although exciting and commercially successful, medical societies must encourage data collection and review to further drive research.

Medical societies should also include payers in discussions about guidelines, standard of care, and trials. The clinical trial community consists first and foremost of patients but also the clinicians providing care, the pharmaceutical and biotechnology companies providing the therapies, and the payers. We are approaching 20 million cancer survivors in the United States over the next 2 years; thus, we must realize that the clinical trial community has to come together to solve its problems and overcome obstacles.

Medical societies should also include payers in discussions about guidelines, standard of care, and trials. The clinical trial community consists first and foremost of patients but also the clinicians providing care, the pharmaceutical and biotechnology companies providing the therapies, and the payers.

Q: Do you foresee a time where industry/federal/academic partnerships will finally take hold in the realm of clinical research and patient care?

A: I do, although this might move to be simply out of necessity. At the end of the day, while there will be a shift in roles regarding who is in charge of selling a new drug, who is charge of paying for delivery of a new drug, and who is charge of discovering the pathways to develop a new drug, the end result is still the provision of the best clinical care for patients. Eighty-five percent of patients are in the community, but the definition of "community" in this context extends beyond every small rural town into big American cities. The thought leaders in these cities are reaching out to institutions like Sarah Cannon to gain access to clinicians and patients involved in research. With the cost of new drugs averaging $10,000 a cycle, getting the most value by selecting the right therapy is an important challenge. All the conversations are coming together about challenges like this, but there must be synergy among all of the groups involved. Concerns about the cost of drugs, access to healthcare, and the number of providers and physicians that we have—all of these problems are ripe for community cohesion and partnership as a means to solve them. ✦

RADIATION THERAPY

The Role for Trimodality Therapy in Stage III NSCLC

By Leah Lawrence

The use of trimodality therapy—the combination of chemoradiotherapy followed by surgery—remains controversial for patients with locally advanced cN2-N3 NSCLC.

According to the National Comprehensive Cancer Network guidelines, definitive chemoradiation therapy is the standard of care for the majority of patients with stage III NSCLC, and trimodality treatment is used only in selected patients with minimal N2 disease.

Results of the Intergroup 0139 study, one of the first randomized studies of concurrent chemoradiotherapy and trimodality approaches, showed that the 5-year progression-free survival was improved in patients who underwent trimodality treatment compared with bimodality therapy alone (hazard ratio = 0.77; 95% CI[0.62, 0.96]); however, this benefit did not translate into an overall survival advantage.[1]

"In a subset analysis of the study, they showed that patients who underwent a lobectomy did have a survival benefit with trimodality treatment, but this was an unplanned analysis," said Melissa A.L. Vyfhuis, MD, PhD, of the University of Maryland Medical Center.

The lack of overall survival benefit may have, in part, been due to the trial's high mortality rate seen with pneumonectomies. Furthermore, in the trial, they used a lower radiation dose of 45 Gy prior to surgical resection to offset the chance of an increase risk in morbidity or mortality associated with higher doses, according to Dr. Vyfhuis.

"In the setting of stage III disease, we now know that [45 Gy] is not sufficient for cure," Dr. Vyfhuis said. Practically speaking, if the tumor is deemed not resectable after such a low dose of radiation, then the patient would have to go back and receive additional radiation therapy, but now having sustained a significant break (typically 1 to 2 weeks) in their radiation treatments, which could affect clinical outcomes.

In our experience, patients who attain mediastinal nodal clearance after neoadjuvant chemoradiation, no matter how bulky or extensive the disease was initially, can benefit from trimodality therapy.

–Melissa A.L. Vyfhuis, MD, PhD

According to Dr. Vyfhuis, at the University of Maryland, she and her colleagues give a definitive dose of radiation (≥ 60 Gy) with concurrent chemotherapy, even if a patient was scheduled to undergo surgery; however, she acknowledged that not a lot of institutions routinely offer this dose as part of trimodality therapy.

"At University of Maryland, our surgeons have extensive experience operating on patients after the administration of a definitive dose (≥ 60 Gy) of radiation. This has resulted in low rates of postsurgical morbidity and mortality, especially for those patients undergoing a lobectomy," Dr. Vyfhuis explained.

Dr. Vyfhuis and colleagues recently published the results of a study that showed that trimodality treatment with a radiation dose of at least 60 Gy significantly improved survival and freedom from recurrence in patients with locally advanced NSCLC.[2]

The retrospective analysis included data from 355 consecutive patients with locally advanced NSCLC treated with curative intent between January 2000 and December 2013. Those patients who received trimodality therapy had a significantly longer median survival compared with patients with either unplanned or planned bimodality treatment (59.9 vs. 20.1 vs. 17.3 months, respectively; $p < 0.001$). The addition of surgery also benefited patients with stage IIIb ($p < 0.001$) and N3 ($p = 0.010$) nodal disease, especially when mediastinal nodal clearance was achieved.

"A median survival of approximately 60 months is essentially unheard of in stage III disease," Dr. Vyfhuis said, adding that as a retrospective study some selection bias may be present. "In our experience, patients who attain mediastinal nodal clearance after neoadjuvant chemoradiation, no matter how bulky or extensive the disease was initially, can benefit from trimodality therapy."

How Does It Fit?

The current standard of care for patients with stage III NSCLC may soon be changing however, according to Martin J. Edelman, MD, chair of the department of hematology/oncology at Fox

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challenges, particularly with twice-daily radiation. Supporting patients through these obstacles is a crucial element to providing optimal care. The Pezzi et al. study now further directs our attention to how insurance coverage may influence barriers to care.

The reasons for a lower likelihood of radiation therapy for patients with Medicare or Medicaid are not well understood at this point, but further research is certainly indicated to help determine whether the barriers for these patients are financial, logistic, or other. Reimbursement from insurance carriers may be a relevant factor. There are programs such as 340B and the Medicaid Drug Rebate Program that allow hospitals to deliver chemotherapy with competitive reimbursement. However, these programs do not provide financial assistance for radiation therapy delivery. The authors speculate that this may partially explain why patients with government insurance were less likely to receive radiation therapy in this cohort. Based on this study, it is important to consider whether expanding the financial assistance for radiation therapy delivery may enable more patients to receive this important element of their care.

Based on this study, it is important to consider whether expanding the financial assistance for radiation therapy delivery may enable more patients to receive this important element of their care.

By better understanding barriers to care for patients with LS-SCLC and working to overcome them, we hope ultimately to provide optimal evidence-based care for all medically eligible patients. ✦

About the Author: Dr. Farago is an instructor of medicine at Harvard Medical School and an assistant of medicine at Massachusetts General Hospital.

References:

1. Pignon JP, Arriagada R, Ihde DC, et al. A Meta-Analysis of Thoracic Radiotherapy for Small-Cell Lung Cancer. *N Engl J Med.* 1992;327:1618-1624.
2. Pezzi TA, Schwartz DL, Mohamed ASR, et al. Barriers to Combined-Modality Therapy for Limited-Stage Small-Cell Lung Cancer. *JAMA Oncol.* 2018 Jan 4. [Epub ahead of print].

BREAKING NEWS BRIEF

Nivolumab in the News

The dosing schedule for nivolumab now includes a flat dose of 480 mg infused every 4 weeks (Q4W) for a majority of approved indications, including patients who received prior therapy for metastatic NSCLC. The U.S. Food and Drug Administration (FDA) approval provides an alternative to the previously available option of 240 mg every 2 weeks (Q2W). The approval also allows for a shorter 30-minute infusion across all approved indications. Nivolumab is now available in a new 240 mg vial.

In addition, the FDA has accepted a Biologics License Application for nivolumab for priority review. The application includes treatment of patients with SCLC who have received two or more prior lines of therapy and whose disease has progressed. The FDA action date is August 16, 2018.

The application submission was based on the safety and efficacy data from the phase I/II CheckMate -032 trial that evaluated nivolumab alone vs. nivolumab plus ipilimumab in advanced or metastatic solid tumors. Of 401 patients, the objective response rate was 11% for patients treated with nivolumab alone and 22% for those treated with the combination. Of the 211 patients with evaluable TMB, objective response rates for the combination vs. nivolumab alone, respectively, were 46% and 21% for those with high TMB, 16% and 7% for those with medium TMB, and 22% and 5% for those with low TMB. One-year survival rates for the combination were 62% (high TMB), 20% (medium), and 23% (low); survival at 1 year for nivolumab alone was 35% (high), 26% (medium), and 22% (low). Patients were treated until disease progression or unacceptable toxicity. ✦

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GLOBAL INITIATIVES

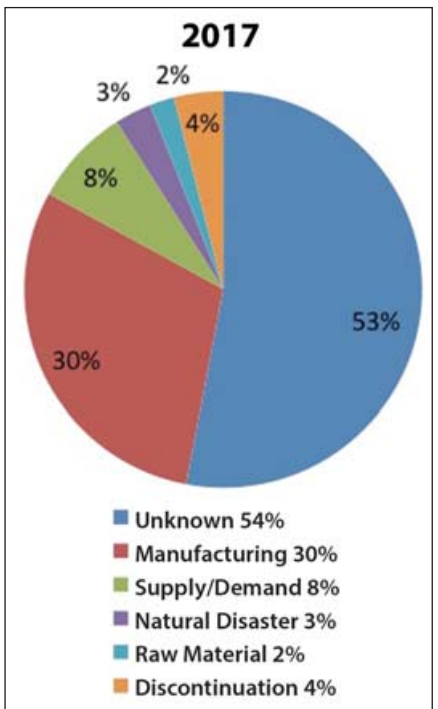
Managing Medication Shortages of Life-Saving Oncologic Therapeutics

Natural disasters, such as Hurricane Maria, may have contributed to more acute shortages than previously experienced.

By Jorge Garcia, PharmD, MS, MHA, MBA, and Dina B. Dumercy, PharmD, BCOP, BCPS

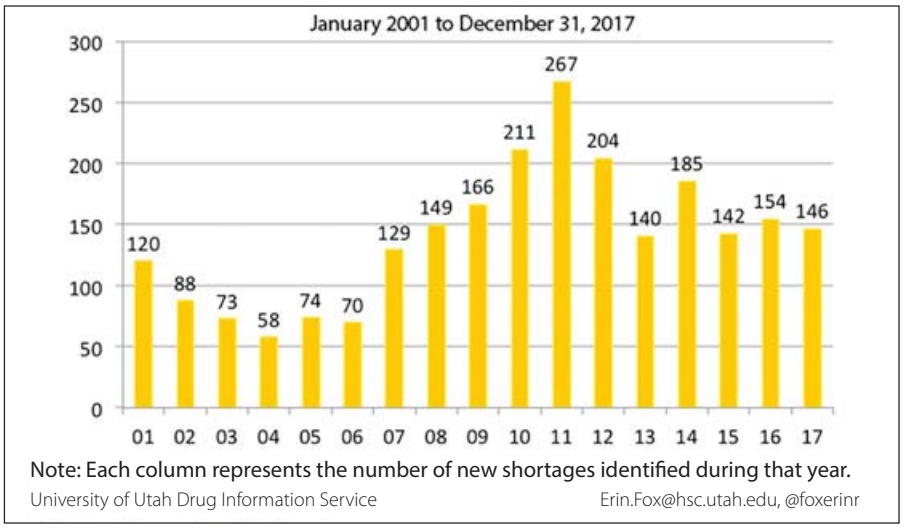
Drug shortages in oncology date back to the late 1980s, when there was a scarcity of paclitaxel. Since then, with an increase in the number of therapeutic options and the evolution of the market dynamics, and further compounded by the need for intravenous (IV) fluids to deliver chemotherapy/immunotherapy, healthcare professionals face continuous drug-shortage challenges regarding the treatment of their patients with cancer. Mechanisms often responsible for shortages include: ingredient shortage, drug recalls, and low revenue margins (all of which discourage production); lack of ability to stockpile; tougher manufacturing standards (which puts some manufacturers out of compliance); industry consolidation; and natural disasters (Fig. 1). As a result, oncology healthcare professionals face significant moral and ethical dilemmas when having to make decisions regarding treatment interruption, transitions to less-effective treatments, or rationing of life-saving treatments.[1] Although the current number of drug shortages is not the highest seen in recent years (Fig. 2), the industry has witnessed significant effects with regard to specific types of products (e.g., IV fluids) facing severe shortages. Strategies to successfully navigate the drug shortages must be multidimensional in approach, including careful management of supply and inventory, enhanced communication with stakeholders and suppliers, and operation within a safe and ethical framework. Drug shortages have created the need to evaluate alternative treatment options and administration strategies, as well as renewed attention on how to mitigate threats to clinical trials. Furthermore, with more pronounced drug shortages, there are major concerns regarding the effects on clinical outcomes associated with the treatment changes.

Fig. 1. Reasons for Shortages as Determined by UUDIS During Investigation



University of Utah Drug Information Service
Erin.Fox@hsc.utah.edu, @foxerinr

Fig. 2. National Drug Shortages – New Shortages by Year



Note: Each column represents the number of new shortages identified during that year.
University of Utah Drug Information Service Erin.Fox@hsc.utah.edu, @foxerinr

A Complex Universe of Factors

The U.S. Food and Drug Administration (FDA), the American Society for Health-System Pharmacists (ASHP), and numerous other organizations have provided recommendations on the management of supply and inventory. Although general, these recommendations apply across multiple specialties, including oncology. The transition to the use of IV push, when appropriate, can be made safer by the institution of specific administration instructions, provision of ready-to-administer dosage forms to nurses, and flexibility within the electronic record to facilitate ease of ordering and conversion of fluids. Researchers and pharmacists have the opportunity to critically evaluate the design of clinical trials to determine the feasibility of drug substitutions and to minimize the waste associated with products on shortage. For example, this can be accomplished by asking study sponsors to provide supplies needed to prepare investigational medications, including fluids, or by requesting assistance with accessing critically short medications by alternative means. In the hospital or in large oncology practice settings, moving stock supplies to a central location for closer inventory control and to support provision of medication in the final solution for administration may minimize waste. The use of technology such as syringe pumps can help support appropriate administration duration for agents that cannot be given rapidly, minimizing the use of the IV fluid bags.

With the rapidly changing availability of medication, the new paradigm is to provide constant updates and to facilitate close communication between the prescribers, pharmacists, nurses, patients, and suppliers. With agents that are available with multiple dosage forms, when one formulation is on shortage, alternative options often become rapidly unavailable. In January 2018, this was experienced acutely with etoposide when, within minutes, wholesalers ran out of products that were identified as alternatives. This had immediate consequences. For example, in patients with SCLC, this meant an acute need to reassess alternatives to our standard therapy, cisplatin/etoposide. Corey Langer, Editor of the *IASLC Lung Cancer News* indicates that although his institution seemed to be shielded initially from this problem, that is no longer the case, at least as of February 2018; he and his colleagues, like many others, are now contending with the same issue.

One of the more challenging aspects of dealing with medications in limited supply is how to determine which patients warrant higher priority to

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EDITOR'S NOTE

In SCLC, simply substituting oral etoposide for intravenous is not necessarily desirable. The available literature suggests increased toxicity with potentially less efficacy. Fortunately, there are number of studies, including two phase III trials, one led by Nasser Hanna[1] and another led by Primo Lara,[2] that have shown de facto therapeutic equivalence between cisplatin/etoposide and cisplatin/irinotecan with similar response, progression-free, and overall survival rates for patients with extensive-stage SCLC. In other situations, with other agents, such substitutions may not be so easy.

–Corey Langer, MD, Editor

Shortages in both chemotherapy drugs and reconstitution solutions (e.g., normal saline, dextrose 5% water) are posing tremendous challenges to clinicians: ethical issues and best clinical practice are compromised. Oncologic patients may not only be precluded from receiving standard-of-care therapy but also from the opportunity to participate in clinical trials. Recently, we have been forced to use oral etoposide, as well as irinotecan, in the first line for SCLC. As a result, one of my patients developed cisplatin/irinotecan-induced syndrome of inappropriate antidiuretic hormone secretion (only one report in literature), and now that patient faces a third change in his first-line therapy. The lack of D5W solution has kept us from enrolling patients in an SCLC clinical trial. Initiatives must be undertaken at the federal level, through legislation along with pressure on manufacturers, to mitigate this huge healthcare problem as soon as possible. Importing products from overseas and extending expiration dates are among the safe ideas being discussed.

–Edgardo Santos, MD, IASLC Publications Committee Chair

1. Hanna N1, Bunn PA Jr, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol*. 2006;24(13):2038-2043.
2. Lara PN Jr1, Natale R, Crowley J, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. *J Clin Oncol*. 2009;27(15):2530-2535.

Medication Shortages from page 12

receive the medications in question. In 2012, the Ontario Ministry of Health and Long-Term Care published the Ethical Framework for Resource Allocation During the Drug Supply Shortage.[2] This framework promotes the use of ethical principles to make recommendations, such as ensuring standard of care and best practice whenever possible, using alternative treatments with similar benefits, exercising solidarity in sharing resources across health sectors, and distributing the drug in short supply to those who are in greatest need and who are most likely to benefit. It also recommends that the allocation of strategies be based on the clinical situation, be nondiscriminatory (e.g., not based on social status), and be geared to minimize any possible waste.

Dr. Jorge Garcia

Dr. Dina B. Dumercy

Medication shortages affect institutions differently based on geographic location, existing contracts, access to secondary and tertiary wholesalers, allocations, and patient population, among other factors. Designing mitigation plans and executing such plans from a clinical and operational perspective, along with monitoring intended and unintended outcomes, incur significant costs associated with clinicians' time and other financial resources. Although we hope the end of drug shortages is on the horizon, current mitigation efforts should focus on strategies to minimize waste, support proactive communication, and promote best practices. ✦

Resources:

- Shortage Resources. American Society of Health-System Pharmacists website. ashp.org/Drug-Shortages/Shortage-Resources.Accessed February 3, 2018.
- FDA Drug Shortages. U.S. Food and Drug Administration website. www.accessdata.fda.gov/scripts/drugshortages. Accessed February 3, 2018.

References:

1. Jagsi R, Spence R, Rathmell K, et al. Ethical Considerations for the Clinical Oncologist in an Era of Oncology Drug Shortages. *Oncologist*. 2014;19(2):186-192.
2. Ethical Framework for Resource Allocation During the Drug Supply Shortage. Ontario Ministry of Health and Long-Term Care website. health.gov.on.ca/en/pro/programs/drugs/supply/docs/ethical_framework.pdf Accessed February 3, 2018.

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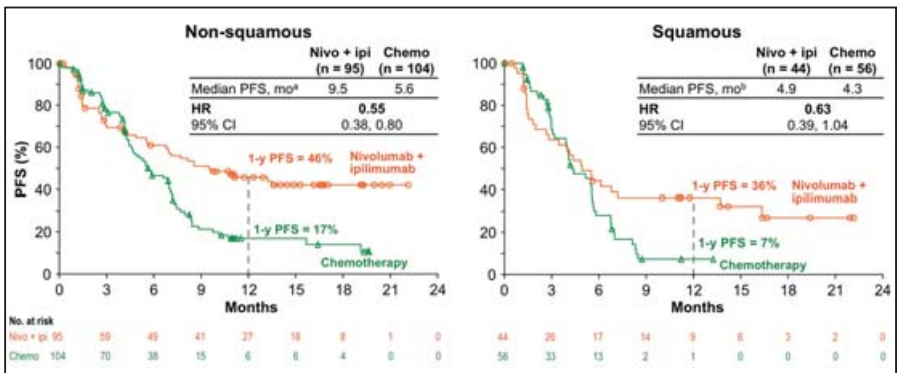
significantly improved PFS compared to patients who received standard platinum-based chemotherapy (HR 0.58, 95% CI [0.41, 0.81]; p < 0.001). This prespecified cohort was part of a much larger study in which individuals with chemotherapy-naive stage IV or recurrent NSCLC and no known sensitizing *EGFR* or *ALK* alterations were enrolled in two groups based on PD-L1 expression. Patients with ≥ 1% PD-L1 expression were randomly assigned 1:1:1 to nivo/ipi, nivo alone, or to platinum-based chemotherapy; patients with < 1% expression were randomly assigned 1:1:1 to nivo/ipi, nivo combined with platinum-based chemotherapy, or to chemotherapy alone. Patients were treated until disease progression or unacceptable toxicity, with a maximum treatment period of up to 2 years. TMB was determined from tumor tissue using the validated FoundationOne CDx assay. The co-primary endpoint included PFS by blinded independent central review for nivo/ipi vs. chemotherapy for patients with TMB > 10 mut/Mb. At a minimum follow-up of 11.5 months, PFS was significantly longer for the nivo/ipi group vs. the control group in patients with high TMB (median PFS of 7.2 months vs. 5.4 months and 1-year PFS of 43% vs. 13%, respectively (Figs. 7 and 8); HR 0.58, 95% CI [0.41, 0.81]; p = 0.0002). This benefit was observed regardless of tumor histology, PD-L1 expression level, age, or gender. There was similar degree of benefit in both PD-L1 negative and PD-L1 positive patients (HR 0.48 and HR 0.62, respectively). Conversely, in patients with TMB < 10 Mut/MB, the HR for PFS was 1.07 (95% CI [0.84, 1.35]). Objective overall response rate was 45% for the nivo/ipi group vs. 27% for the control group for patients with TMB > 10 mut/Mb. Preliminary median OS favored the nivo/ipi arm at 23 vs. 16.4 months, respectively, with 1-year OS of 67% vs. 58%; this difference was not yet significant (HR 0.79, 95% CI [0.56, 1.10]).

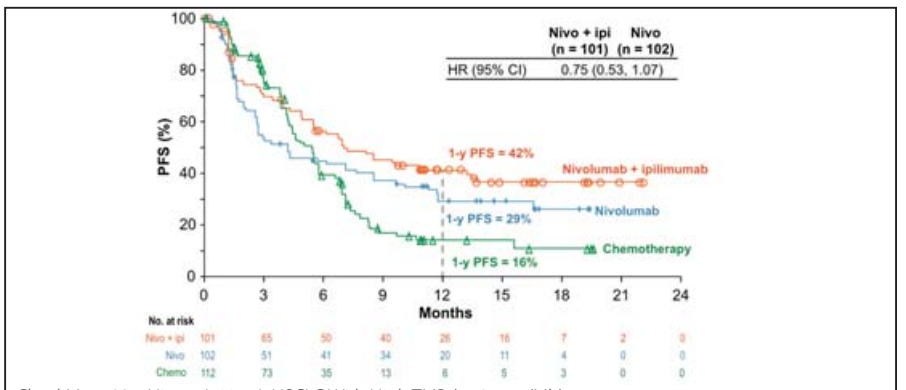
Others have voiced reservations regarding TMB. To paraphrase the comments of David L. Rimm, MD, PhD, the discussant of the study that has established 10 Mut/Mb as the threshold for TMB analysis (CheckMate 568[9]): TMB is provocative but not yet ready for prime time. Dr. Rimm indicated that, although there is a clear-cut correlation with PFS, we have not yet seen significant OS data. The test itself must be standardized. It costs 5 to 10 times more than immunohistochemistry (IHC) testing and requires a lot more tissue. In addition, as long as it depends on next-generation sequencing, results are generally delayed. All of these concerns are valid, but cost must be put into proper context. Although it is more expensive than IHC, next-generation sequencing, which helps determine TMB results, yields far more information than IHC, including crucial information on potential oncogenic drivers. In addition, its cost pales in comparison to the cost of a single cycle of single-agent immunotherapeutics or the empiric combination of pembrolizumab, pemetrexed, and carboplatin. ✦

Fig. 7. CheckMate 227: PFS in Patients With High TMB (≥10 mut/Mb) by Tumor Histology



[a] 95% CI: nivo + ipi (5.6 mo, NR), chemo 4.5, 7.0 mo); [b] 95% CI: nivo + ipi (2.7, 13.7 mo), chemo (3.2, 5.6 mo)
CheckMate 227: Nivo + Ipi in 1L NSCLC With High TMB (≥10 mut/Mb)

Fig. 8. CheckMate 227: PFS: Nivolumab + Ipilimumab vs. Nivolumab in Patients With High TMB (≥10 mut/Mb) and ≥1% PD-L1 Expression



CheckMate 227: Nivo + Ipi in 1L NSCLC With High TMB (≥10 mut/Mb)

References:

1. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. KEYNOTE-189: Randomized, Double-Blind Phase 3 Study of Pembrolizumab or Placebo Plus Pemetrexed and Platinum as First-Line Therapy for Metastatic NSCLC. Paper presented at: American Association for Cancer Research Annual Meeting; April 14-18, 2018; Chicago, IL.
2. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. *N Engl J Med*. 2016;375:1823-1833.
3. KEYTRUDA® (pembrolizumab) Monotherapy Met Primary Endpoint in Phase 3 KEYNOTE-042 Study, Significantly Improving OS as First-Line Therapy in Locally Advanced or Metastatic NSCLC Patients Expressing PD-L1 in at Least 1 Percent of Tumor Cells. MERCK website: investors.merck.com/news/press-release-detailes/2018/KEYTRUDA-pembrolizumab-Monotherapy-Met-Primary-Endpoint-in-Phase-3-KEYNOTE-042-Studay-Significantly-Improving-OS-as-First-Line-Therapy-in-Locally-Advanced-or-Metastatic-NSCLC-Patients-Expressing-PD-L1-in-at-Least-1-Percent-of-Tumor-Cells/default.aspx. Published April 9, 2018. Accessed April 27, 2018.
4. Herbst R. In discussion of: Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. KEYNOTE-189: Randomized, Double-Blind Phase 3 Study of Pembrolizumab or Placebo Plus Pemetrexed and Platinum as First-Line Therapy for Metastatic NSCLC. Paper presented at: American Association for Cancer Research Annual Meeting; April 14-18, 2018; Chicago, IL.
5. Kowanetz M, Socinski MA, Zou W, et al. IMpower150: IMpower150: Efficacy of Atezolizumab Plus Bevacizumab and Chemotherapy in 1L Metastatic Nonsquamous NSCLC Across Key Subgroups. Paper presented at: American Association for Cancer Research Annual Meeting; April 14-18, 2018; Chicago, IL.
6. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355(24):2542-2550.
7. Phase III IMpower150 Study Showed Genentech's TECENTRIQ (Atezolizumab) and Avastin (Bevacizumab) Plus Carboplatin and Paclitaxel Helped People With Advanced Lung Cancer Live Longer Compared to Avastin Plus Carboplatin and Paclitaxel. Genentech website. gene.com/media/press-releases/14710/2018-03-25/phase-iii-impower150-study-showed-genent. Published March 25, 2018. Accessed April 27, 2018.
8. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab + Ipilimumab vs Platinum-Doubled Chemotherapy as First-line Treatment for Advanced Non-Small Cell Lung Cancer: Initial Results from CheckMate 227. Paper presented at: American Association for Cancer Research Annual Meeting; April 14-18, 2018; Chicago, IL.
9. Rimm DL. In discussion of: Tumor Mutational Burden (TMB) as a Biomarker for Clinical Benefit form Dual Immune Checkpoint Blockade With Nivolumab + Ipilimumab in First-Line Non-Small Cell Lung Cancer: Identification of TMB Cutoff From CheckMate 568. Paper presented at: American Association for Cancer Research Annual Meeting; April 14-18, 2018; Chicago, IL.

BREAKING NEWS BRIEF

The FDA has accepted a supplemental Biologics License Application (sBLA) and granted Priority Review for **atezolizumab**, in combination with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of people with metastatic nonsquamous NSCLC. The FDA is expected to make a final decision regarding approval in early September 2018. ✦

For more news about atezolizumab, see Breaking News on page 19.

Trimodality Therapy from page 11

Chase Cancer Center, and formerly of the University of Maryland Greenebaum Comprehensive Cancer Center.

In 2017, results of the phase III PACIFIC trial showed that the administration of the anti–PD-1 antibody durvalumab after definitive chemoradiotherapy more than tripled the median progression-free survival compared with chemoradiotherapy followed by placebo (16.8 vs. 5.6 months; $p < 0.001$).[3] The results were presented at the 2017 European Society for Medical Oncology Congress and published in *The New England Journal of Medicine*.

Based on these results, the standard of care today for a patient with locally advanced NSCLC is chemoradiotherapy followed by immunotherapy, according to Dr. Edelman.

"The trial was done predominantly in Europe, a little bit differently than we might have done it in the United States, but results were impressive," Dr. Edelman said. "We do not yet have overall survival results, but I would be surprised if they do not echo the substantial improvements in progression-free survival that was published."

The integration of immunotherapy into treatment regimens for patients with stage III disease only further complicates matters. Many questions remain, Dr. Edelman said.

"We still do not know the optimal chemotherapy regimen to use in combination with radiation," Dr. Edelman said. "We feel following chemoradiotherapy with immunotherapy is good, but do not know if immunotherapy should follow immediately."

Trimodality care should be restricted to experienced institutions that have high volume and an experienced multimodality team.

–Martin J. Edelman, MD

With so many questions remaining about bimodality therapy, it is hard to know where surgery would fit in.

According to Dr. Edelman, an ideal candidate for trimodality treatment would be someone who is relatively fit, with an otherwise good performance status. Ideally, the patient would require a lobectomy and not a pneumonectomy or another type of complex procedure, and would have mediastinal nodal disease that is not bulky.

"Those patients in the correct hands should have a very low operative mortality," Dr. Edelman said.

However, outside of these situations, the standard of care remains bimodality therapy, he added.

"The problem with trimodality studies is how one integrates all three modes of treatment is very difficult, and each study has to be evaluated by itself because no two of them held all features constant," Dr. Edelman explained.

When he was at the University of Maryland, using a radiation dose of 60 Gy with chemotherapy was feasible. If a patient did not go on to surgery, this meant that the proper definitive radiation dose had been administered. However, this approach may not be feasible in all institutions.

"Trimodality care should be restricted to experienced institutions that have high volume and an experienced multimodality team," Dr. Edelman said. "Patients who are felt to be suitable for this treatment should be selected prior to initiation of any treatment." ✦

References:

1. Albain KS, Swann RS, Rusch VR, et al. Radiothearpy plus chemotherapy with or without surgical resection for stage III non-small cell lung cancer. *Lancet*. 2009;374:379-386.
2. Vyfhuis MAL, Bhooshan N, Burrows WM, et al. Oncological outcomes from trimodality therapy receiving definitive doses of neoadjuvant chemoradiation (≥60 Gy) and factors influencing consideration for surgery in stage III non-small cell lung cancer. *Adv Radiat Oncol.* 2017;2:259-269.
3. Antonio SJ, Villegas, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med.* 2017;377:1919-1929.

"The IASLC Atlas on EGFR Testing in Lung Cancer addresses the essential topics related to the testing of EGFR mutations."

– the Editors

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

IASLC Atlas of EGFR Testing in Lung Cancer

Edited by Tony S. Mok, MD, David P. Carbone, MD, PhD, and Fred R. Hirsch, MD, PhD

In the *IASLC Atlas of EGFR Testing in Lung Cancer*, pathologists are provided with "know-how" information on EGFR testing, and clinicians are provided with the "know-why" information about how to interpret the results. From the retrieval and handling of tumor samples to the different available assays, and from interpretation of results to reporting and quality assurance, the Atlas is a comprehensive yet user-friendly compendium for the general oncology readership.

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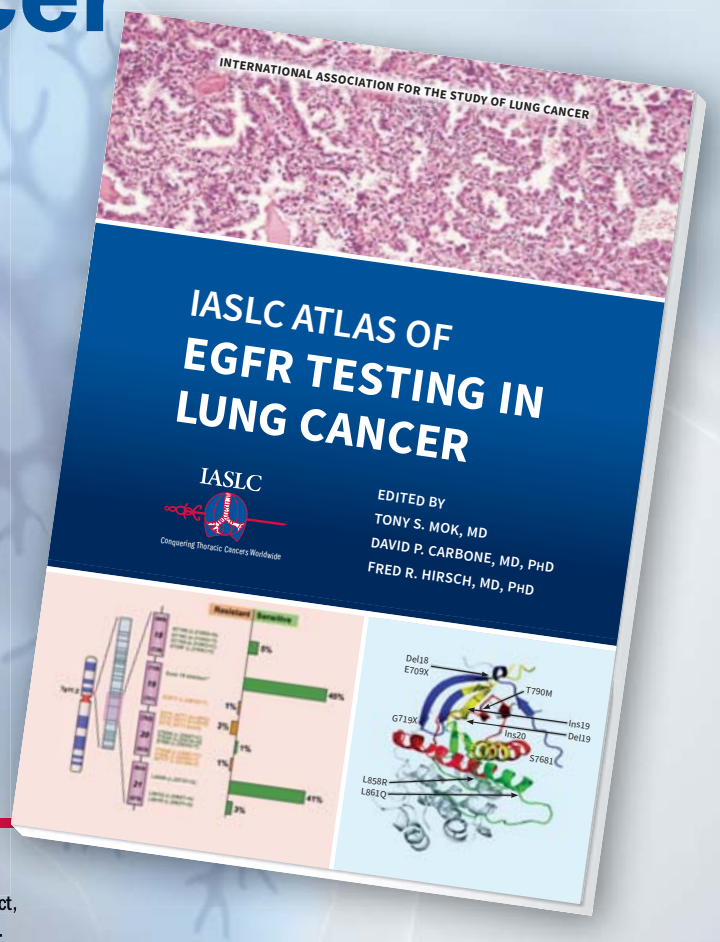
- 8 chapters, including in-depth focus on EGFR testing and assays, sample management, and *EGFR* gene mutations
- Current bibliography of EGFR citations

The first and most comprehensive publication of its kind, the *IASLC Atlas of EGFR Testing in Lung Cancer* presents today's key issues regarding the testing of *EGFR* mutations.



Available online for individual download from https://www.iaslc.org/EGFR

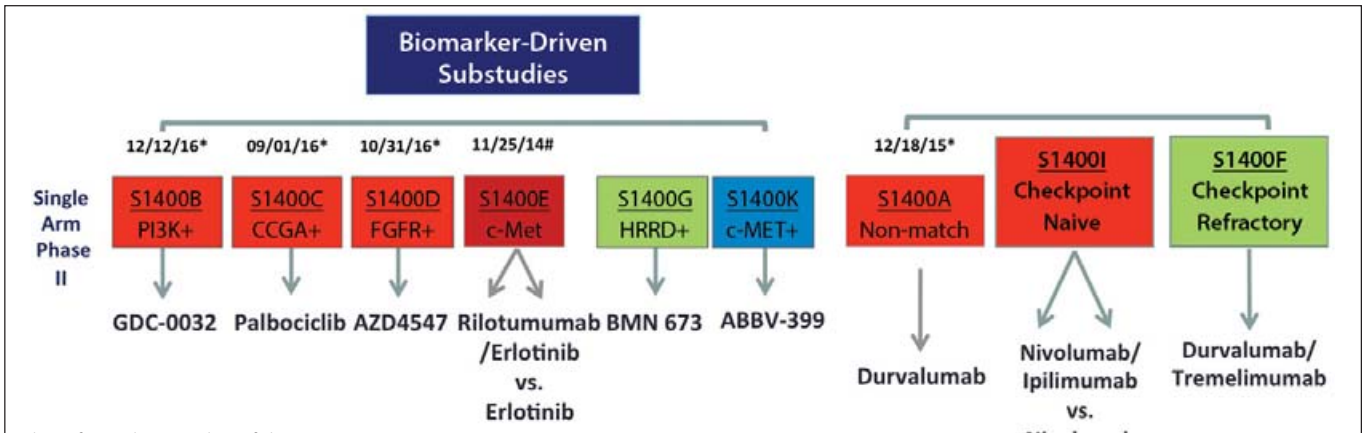
To order print copies of the EGFR Atlas, please email publications@iaslc.org with EGFR Atlas as the subject, the requested quantity along with order shipping information. Orders will be filled subject to availability.

EVOLVING STANDARDS OF CARE

The Lung Master Protocol: Results and Updates

By Vassiliki Papadimitrakopoulou, MD

Figure. Current Lung-MAP Schema



*date of completion; # date of closure.

Abbreviations: CCGA, cell-cycle gene alterations; HRRD, homologous recombination repair deficiency.

The Lung Master Protocol Trial (Lung-MAP) was designed in 2014 as a phase II/III trial overseen by a private–public collaboration among institutions participating in the National Cancer Institute's (NCI's) National Clinical Trials Network, the Foundation for the National Institutes of Health (FNIH), patient advocacy organizations, and numerous pharmaceutical companies. It uses an umbrella design that enables the conduct of multiple complex clinical trials targeting different biomarkers using one overarching protocol.[1] The trial leverages molecular profiling of tumors to identify and treat patients with histologically common (squamous cell lung cancer) but molecularly diverse tumors within independent substudies designed to provide a registration potential. Thus, it overcomes the difficulties of accruing patients with rare subsets of molecular alterations onto individual trials.

When the trial was activated in June 2014, Lung-MAP originally had four biomarker-driven substudies and one non-match substudy. The biomarker-driven substudies independently evaluated:

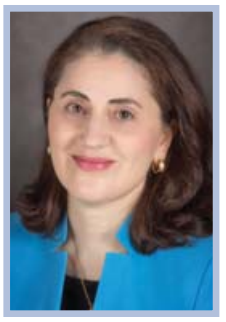
1. Taselisib for *PIK3CA* mutations [S1400B],
2. Palbociclib for *CDK4/6* alterations [S1400C],
3. AZD4547 for *FGFR* alterations [S1400D], and
4. Rilotumumab and erlotinib for c-MET overexpression [S1400E].

Patients who did not have any of those alterations were enrolled in the non-match substudy evaluating durvalumab, an anti–PD-L1 immunotherapy agent. Initially, the first three substudies included docetaxel as a randomized standard-of-care control arm. The fourth study using erlotinib as the control arm was closed in September 2014. Since trial activation in June 2014, the protocol has been amended multiple times to stay current with advances in lung cancer treatment and to remove the standard-of-care control arm from the master protocol. The trial was also modified from a phase II/III trial to one that includes both phase II and phase III substudies. The phase II studies allow investigational agents to be evaluated in single-arm trials and improve the efficiency of assessment if these drugs are found to be either highly effective or ineffective.

Adaptation to Change

Lung-MAP is open at more than 700 sites in the United States and Canada. As of January 5, 2018, 1,407 patients have been registered to screening; 1,244 patients have biomarker results, and 529 patients have registered to a substudy. The results of completed substudies have been presented and are included in summary in the table.[2-6] The prevalence of putative driver alterations is similar to the incidence previously described in primarily early-stage, resected cohorts such as The Cancer Genome Atlas. The current schema of the protocol is shown in the figure.

Three new substudies (S1400G, S1400K, and S1400F) are now part of Lung-MAP. S1400G evaluates talazoparib (PARP inhibitor) for homologous recombination repair deficiency, S1400F evaluates combination durvalumab and tremelimumab (anti–CTLA-4) in patients with immune checkpoint–refractory disease without a biomarker match, and S1400K evaluates ABBV-399 (antibody–drug conjugate) for c-MET–overexpressing tumors. More recent modifications to the trial are intended to allow all histologies to be eligible and to add screening biomarkers for immunotherapy combinations as well as exploratory biomarker testing. These changes along with clinical trials specifically targeting immune checkpoint inhibitor resistance are expected in upcoming trial revisions.



Dr. Vassiliki Papadimitrakopoulou

Additionally, the rapidly changing treatment landscape of NSCLC demands flexibility and adaptability in a master protocol. The substudy modularity inherent in the Lung-MAP design has allowed the protocol to adapt efficiently to rapid changes in the standard of care with the relatively recent approvals of nivolumab and other PD-1/PD-L1 inhibitors for the treatment of lung squamous cell carcinoma in the second-line setting. As described above, the matched substudies were converted into single-arm phase II trials while retaining a pathway for regulatory drug approval. The flexibility of the substudy concept has also enabled the development of a new combination immunotherapy option for patients with checkpoint-refractory disease without a biomarker match. As our understanding of intrinsic and acquired immune checkpoint inhibitor resistance evolves and more precise determinants of response beyond tumor PD-L1 expression are identified, it is envisioned that more personalized, biomarker-driven immunotherapy trials will become part of the Lung-MAP design. ✦

Table. Updated Results of Completed Lung-MAP Substudies

Substudy Closure Date	Final Accrual	Response: Patients (%)	PFS Median (95% CI)	OS Median (95% CI)
S1400A (non-match) 12/18/15	Total: 116 Durvalumab: 78 Docetaxel: 38	11 (16%)	2.9 (1.8, 4.1)	11.6 (10.1, 15.4)
S1400B PI3K 12/12/16	Total: 39 Taselisib: 31 Docetaxel: 8	1 (4%)	2.8 (1.7, 4.0)	5.9 (4.1, 11.5)
S1400C (CCGA+) 9/1/16	Total: 54 Palbociclib: 37 Docetaxel: 17	2 (6%)	1.8 (1.6, 2.9)	7.2 (4.0, 14.6)
S1400D (FGFR+) 10/31/16	Total: 45 AZD4547: 35 Docetaxel: 10	2 (7%)	2.7 (1.4, 4.5)	7.5 (3.6, 9.3)
S1400E (MET+) 11/26/14	Total: 9 Rilotumumab + Erlotinib: 4 Erlotinib only: 5	3 (5%)	2.7 (1.9, 2.9)	7.7 (6.7, 9.2)

Abbreviations: PFS, progression-free survival; OS, overall survival; CI, confidence interval; CCGA, cell cycle genetic alterations.

About the Author: Dr. Papadimitrakopoulou is a professor of medicine in the Department of Thoracic/Head and Neck Medical Oncology at The University of Texas MD Anderson Cancer Center.

References:

1. Herbst RS, Gandara DR, Hirsch FR, et al. Lung Master Protocol (Lung-MAP)-A Biomarker-Driven Protocol for Accelerating Development of Therapies for Squamous Cell Lung Cancer: SWOG S1400. *Clin Cancer Res.* 2015;21:1514-1524.
2. Herbst R, Redman M, Gandara DR, et al. OA 14.07 Progress in Lung Squamous Cell Carcinoma from the Lung-MAP Master Protocol (S1400) Sub-Studies S1400A, S1400B, S1400C and S1400D. *J Thorac Oncol.* 12:S1783-S1784.
3. Wade JL, Langer CJ, Redman M, et al. A phase II study of GDC-0032 (taselisib) for previously treated PI3K positive patients with stage IV squamous cell lung cancer (SqNSCLC): LUNG-MAP sub-study SWOG S1400B. *J Clin Oncol.* 2017;35:9054-9054.
4. Edelman MJ, Redman MW, Albain KS, et al. A phase II study of palbociclib (P) for previously treated cell cycle gene alteration positive patients (pts) with stage IV squamous cell lung cancer (SCC): Lung-MAP sub-study SWOG S1400C. *J Clin Oncol.* 2017;35:9056-9056.
5. Aggarwal C, Redman MW, Lara P, et al. Phase II study of the FGFR inhibitor AZD4547 in previously treated patients with FGF pathway-activated stage IV squamous cell lung cancer (SqNSCLC): LUNG-MAP sub-study SWOG S1400D. *J Clin Oncol.* 2017;35:9055-9055.
6. Papadimitrakopoulou V, Redman MW, Borghaei H, et al. A phase II study of durvalumab (MEDI4736) for previously treated patients with stage IV squamous NSCLC (SqNSCLC): Lung-MAP Sub-study SWOG S1400A. *Ann Oncol.* 2017;28.

EVOLVING STANDARDS OF CARE

Highlights of the 8th Edition of the TNM Staging System: Practicalities and Tools

By Hisao Asamura, MD, Masaya Yotsukura, MD, and Ramon Rami-Porta, MD, on behalf of the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee

Dr. Hisao Asamura | Dr. Masaya Yotsukura | Dr. Ramon Rami-Porta

The IASLC Staging and Prognostic Factors Committee (SPFC) proposed revisions to the lung cancer staging system for the 8th edition of the *TNM Classification of Malignant Tumors*. The Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) accepted these revisions, and the 8th edition of the *TNM Classification* was implemented in January 2017. In the United States, implementation was delayed until January 2018; now, the new edition has been enacted worldwide.

TNM staging is a tumor classification system that, in principle, reflects the anatomic extent of the tumor based on the extent of the primary tumor (T), the nodal spread (N), and the distant metastases (M). Revisions from the 7th to 8th editions were made to achieve refined prognostic capabilities and to help clinicians stratify tumors based on expected prognosis. All of these changes were based on prognostic analyses of data from the IASLC database—which included 70,697 evaluable patients with NSCLC and 6,189 with small cell lung cancer—and on clinical judgment.

What Is TNM?

- The determination of the anatomic extent of the tumor according to three components:
  - Primary tumour (T)
  - Lymph nodes (N)
  - Metastasis (M)
- Components have categories: T1a, N3, M1c, etc.
- Categories are defined by descriptors: size, location, invasion, etc.

T Descriptors

In the T component of lung cancer, the T1 category was divided into three subcategories (T1a-T1c) according to 1-cm cutoff points of the greatest dimension. The T2 category now includes tumors larger than 3 cm but no more than 5 cm and was divided into T2a and T2b based on 1-cm cutoff points. Tumors larger than 5 cm but no more than 7 cm were classified as T3, and tumors larger than 7 cm were classified as T4. Adenocarcinoma in situ (Tis(AIS): tumors without a solid part on CT image or a pathologic invasive part) and minimally invasive adenocarcinoma (T1mi: tumors with a solid part of ≤ 0.5 cm on CT image or a pathologic invasive part of ≤ 0.5 cm) were introduced. Sub-solid tumors 3 cm or less in the greatest dimension were recommended to be classified according to the size of the solid part on CT image or the pathologic invasive part. Involvement of main bronchus without carina was categorized as T2 regardless of distance to the carina. Total atelectasis and total obstructive pneumonitis were downgraded from T3 to T2. Invasion of the diaphragm was upgraded from T3 to T4.

N Descriptors

The N component featured no changes. However, analyses of the IASLC database revealed prognostic implications of the number of involved lymph nodes and of involved nodal stations. Exploratory analyses of survival showed that N1a (involvement of a single N1 nodal station) had better prognosis than N1b (involvement of multiple N1 nodal stations). N2a1 (involvement of a single N2 nodal station without N1 involvement) had a similar prognosis to N1b. N2a2 (involvement of a single N2 nodal station with N1 involvement) correlated with a worse prognosis than N2a1 but a better prognosis than N2b (involvement of multiple N2 nodal stations).

M Descriptors

M1 categories were refined based on the number of the extrathoracic metastases. Single extrathoracic metastasis was categorized as M1b, and multiple extrathoracic metastases were categorized as M1c. M1a has not changed from the 7th edition, which included metastasis restricted to the thoracic cavity. Prognosis of M1a and M1b diseases were similar; however, due to the difference of anatomic extension of the tumor, M1a and M1b were categorized as different entities.

Stage Grouping

Based on the T, N, and M categories, stage grouping was determined to achieve best prognostic stratifications. Stage IA was divided into stages IA1, IA2, and IA3, correlating with T1a, T1b, and T1cN0M0 tumors. Only T2aN0M0 and T2bN0M0 tumors were categorized as stage IB and IIA, respectively. T1-T2N1M0 and T3N0M0 tumors were grouped as stage IIB. Stage IIIA included T1-T2N2M0, T3N1M0, and T4N0-N1M0 tumors. Stage IIIB included T1-T2N3M0 and T3-T4N2M0 tumors. Stage IIIC was newly introduced to include T3-T4N3M0 tumors. Stage IV was subcategorized into stage IVA (any T, any N, and M1a or M1b), and stage IVB (any T, any N, and M1c).

Tools and Teaching Aids

For a better understanding of the new classification system, reading the *TNM Classification of Malignant Tumors, 8th Edition,* is strongly recommended. At least for lung cancer, the contents of the staging system are essentially the same among different publications. The following books have been published and can be used for reference:

- *UICC TNM Classification of Malignant Tumors, 8th Edition* by the Union for International Cancer Control. [1]
- *AJCC Cancer Staging Manual, 8th Edition* by the American Joint Committee on Cancer.[2]
- *Staging Manual in Thoracic Oncology, 2nd Edition* by the IASLC.[3]
  - The IASLC Staging Manual in Thoracic Oncology is available in English, Chinese, Japanese, German, Spanish, and Italian as a free mobile application in the Apple iTunes and Google Play stores.

The IASLC has launched several resources intended to extend the understanding of and to be a handy reference for the 8th edition of TNM. These include:

- *Staging Handbook in Thoracic Oncology.*[4]
- Staging Laminate Reference Cards, *8th Edition.*
- Poster: 8th Edition Lung Cancer TNM Staging Summary.
- Poster: 8th Edition TNM Classification of Lung Non-Mucinous AIS, Minimally Invasive Adenocarcinoma (MIA), and Lepidic Predominant Adenocarcinoma (LPA).
- The IASLC Staging Database T-Component/N-Component/M-Component TNM Stage Slide Catalog, Informative Captions, and Citations.
- The IASLC Lung Cancer Staging Project: Articles regarding the 8th Edition of the TNM Classification for Lung Cancer, Thymic Tumors, and Mesothelioma.

To obtain any of these tools, visit iaslc.org, select the Research & Education

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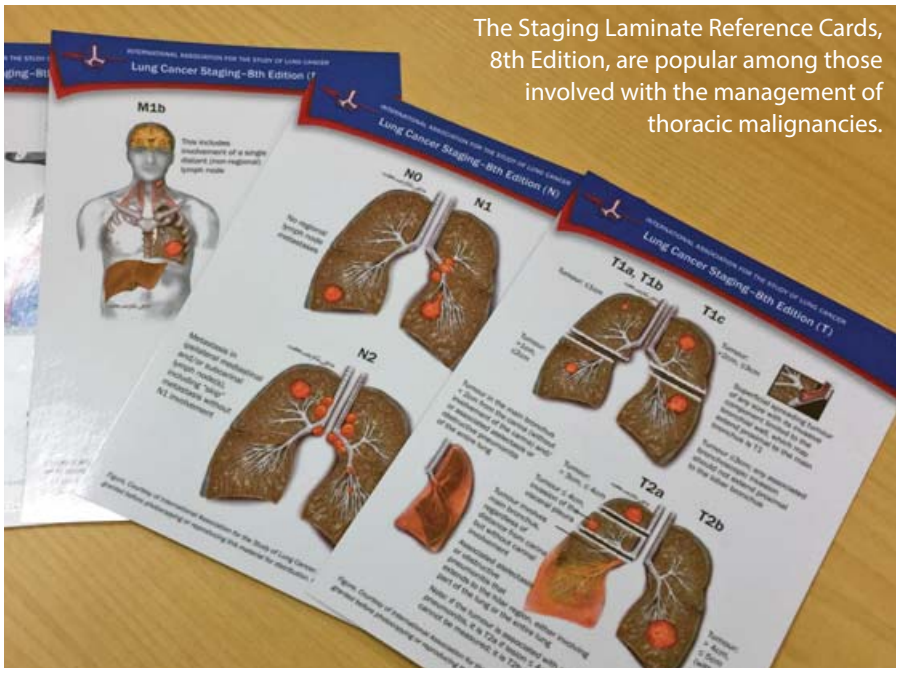

The Staging Laminate Reference Cards, 8th Edition, are popular among those involved with the management of thoracic malignancies.

TNM Staging System from page 16

tab, and choose Staging from the pull-down list. Protocol information is available there, as well as individual links to the various products and resources under the main link for the IASLC 8th Edition Staging Educational Materials. All of these tools can assist with implementation of the protocol in routine daily care.

The educational materials provided by the IASLC differ in nature and in practical use:

- *The Staging Handbook in Thoracic Oncology*[4] is a pocket-sized book that can be easily carried around for instant availability of the basic TNM information, including the descriptors of the three components of anatomic tumor extent. It also includes an atlas with figures describing the different categories.
- The Staging Laminate Reference Cards, 8th Edition, are the perfect size to be kept in the pockets of a white coat or surgical suit for a quick reference to the different categories of the three components of anatomic extent of lung cancer. These are very popular among those involved with the management of thoracic malignancies.
- The posters of the TNM and of the pathologic details of the newcomers into the TNM system (AIS, MIA, and LPA) are static elements intended to be on the walls of physicians' offices, radiology reading rooms, and pathology review rooms for a quick reference during clinical discussions and while reviewing reports including the clinical and/or pathologic TNM classification.
- The IASLC Staging Atlas in Thoracic Oncology app allows users to have all the basic TNM information and color figures of the categories at the palm of their hands in a very elegant format. It is not an interactive application, but it provides a quick reference if one does not have the books, laminated cards, or posters accessible.
- The IASLC Slide Catalogue, with captions and citations, is a unique tool provided by the IASLC. It is intended to facilitate the understanding and dissemination of the TNM classification in the most accurate way. The slides contain IASLC material extracted from the original articles that informed the changes implemented for the 8th edition of the TNM classification. They are offered to help in the preparation of educational presentations.
- The Protocol is also available, and it is a fundamental tool for those who intend to apply for grants to enable their contribution to the IASLC Staging Projects. This document includes a detailed description of the project, formatted in such a way that allows the text to be copied and pasted into grant forms. This tool has been underutilized in the previous editions.
- Finally, the IASLC Staging Articles contain the science behind the revisions introduced in the 8th edition of the TNM classification. These articles provide all of the data used for the revision, the methodologies applied, the results of the numerous analyses and their interpretation. Any questions that one may have reading the core information included in the laminates, posters, and apps can be resolved by reading these landmark papers. ✦

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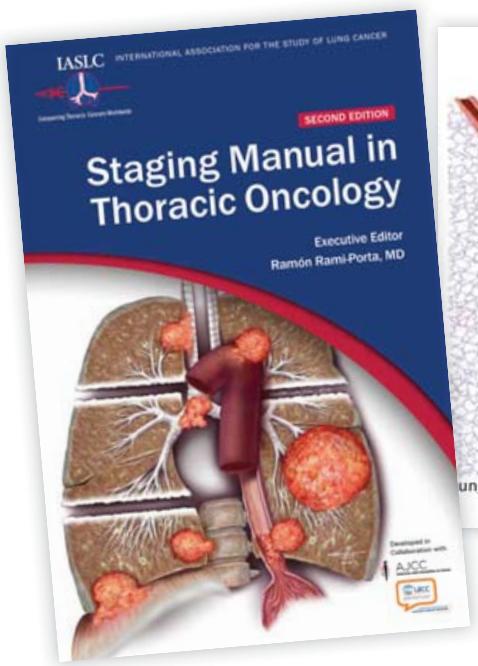
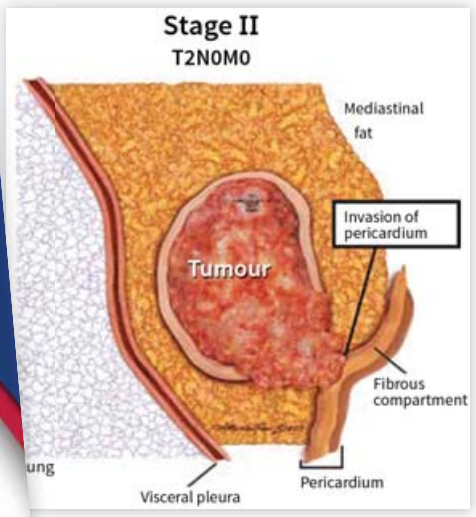
References:

1. Union for International Cancer Control. Briely JD, Gospodarowicz MK, Wittekind CH, eds. *TNM Classification of Malignant Tumors, 8th ed.* Oxford UK and Hoboken, NJ: John Wiley; 2017
2. American Joint Committee on Cancer. Amin MB ed. *AJCC Cancer Staging Manual, 8th ed.* Springer; 2017.
3. International Association for the Study of Lung Cancer. Rami-Porta R, ed. *Staging Manual in Thoracic Oncology, 2nd Ed.* North Fort Myers: Editorial Rx Press; 2016.
4. International Association for the Study of Lung Cancer. Rami-Porta R, ed. *Staging Handbook in Thoracic Oncology, 2nd Ed.* North Fort Myers: Editorial Rx Press; 2016.





The Staging Manual shows detailed illustrations that describe the different TNM classifications.

EDITOR'S NOTE

The new 8th edition of the TNM staging system for NSCLC remains highly challenging. Having a tool to help navigate the path to accurate staging is essential. Virtually all our treatment decisions hinge on proper, readily reproducible staging, so it is crucial that staging be done correctly. This goal requires the mutual engagement of pathology, radiology, and all disciplines of oncology.

–Corey Langer, MD, Editor

BREAKING NEWS BRIEF

CMS Coverage for Only FDA-Approved NGS Companion Diagnostics

The **Centers for Medicare & Medicaid Services** (CMS) have finalized a National Coverage Determination (NCD) to cover in-vitro diagnostic next-generation sequencing (NGS) laboratory tests that are U.S. Food and Drug Administration (FDA) approved as companion diagnostics for patients with advanced cancer, defined as recurrent, metastatic, relapsed, refractory, or stage III or IV cancer. This definition was expanded to include relapsed, refractory, and/or stage III after public comments were considered but prior to NCD finalization. This decision also extends to repeat testing when the patient has a new primary diagnosis of cancer.

This decision was made following parallel review with the FDA, which granted its approval of the FoundationOne CDx (F1CDx™) test in November 2017, at which time CMS issued a proposed NCD for NGS cancer diagnostic tests. F1CDx™ can detect mutations in 324 genes and two genomic signatures in any solid tumor. It is also a companion diagnostic for 15 targeted therapies.

Medicare coverage determinations for other NGS diagnostic tests for patients with advanced cancer will be made by local Medicare Administrative Contractors. The final decision also extends coverage to repeat testing when the patient has a new primary diagnosis of cancer.

Regarding existing or developmental diagnostic tests, including laboratory-developed tests, that are not FDA approved, the CMS stated in its press release on the NCD decision, "We strongly encourage continuing and publishing the results of these important studies, especially on the endpoints of overall survival, progression-free survival, objective response, and patient-reported outcomes relevant to the quality of life for Medicare beneficiaries. This is not only important to ensure that patients, caregivers, and their providers can make informed decisions, but also to continue to develop and publish results to develop new technologies in the healthcare system."

The FDA recently released two guidance statements with their recommendations regarding NGS-related testing products. The first guidance provides information about how product developers can use public databases, such as the National Institutes of Health's ClinGen, to support accuracy of clinical evaluation of their products. The second guidance provides recommendations for designing, developing, and validating NGS-based tests so as to ensure FDA approval. Both documents are available on FDA.gov. ✦

MEETING HIGHLIGHTS

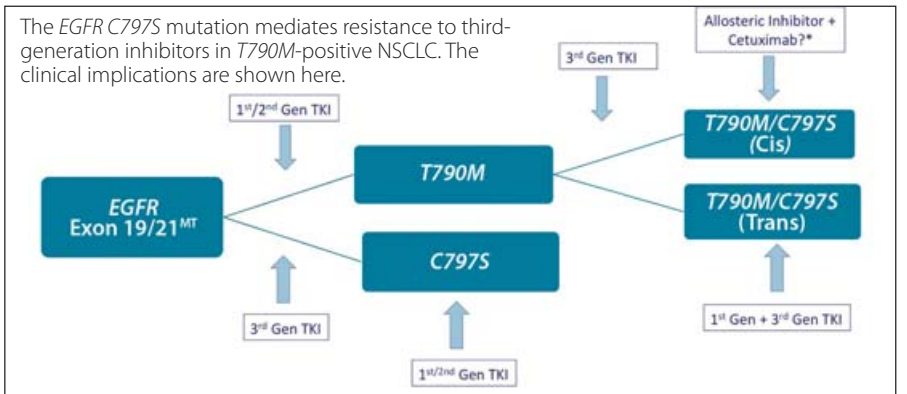
EGFR-Targeted Therapy: A New Beginning

Highlights from the IASLC 18th Lung Cancer Targeted Therapies Meeting keynote address.

By Suresh S. Ramalingam, MD

EGFR-targeted therapy has entered a new phase as the result of several important advances in recent years. It is now well established that *EGFR* tyrosine kinase inhibitors (TKIs) are the preferred standard of care for patients with exon 19 or 21 *EGFR* mutations. TKI therapy provides superior response rates and progression-free survival (PFS) over platinum-based chemotherapy. This finding was followed by studies that described *T790M* as the mechanism of acquired resistance to EGFR TKIs in 50% to 60% of patients, which led to the development of osimertinib, a third-generation EGFR TKI that inhibits T790M as well as the common activating mutations.[1]

Figure. *C797S*-mediated Resistance: Clinical Implications



Abbreviations: Gen, generation; TKI, tyrosine kinase inhibitor.
*Jia Y, Yun CH, Park E, et al. Overcoming *EGFR(T790M)* and *EGFR(C797S)* resistance with mutant-selective allosteric inhibitors. *Nature*. 2016;534(7605):129-132.

Osimertinib was proven to be superior to platinum-based chemotherapy in the setting of *T790M*-mediated acquired resistance. More recently, osimertinib was shown to be superior to erlotinib/gefitinib as first-line therapy for *EGFR*-mutated NSCLC, with a new benchmark PFS of approximately 19 months. It was also associated with more favorable activity against brain metastasis, less skin toxicity, and lower treatment-related serious adverse events. Consequently, osimertinib has emerged as a standard first-line therapy option for patients with an *EGFR* mutation. The mechanisms of resistance to osimertinib are just now beginning to be understood (Fig.), and several novel osimertinib-based combination approaches are under investigation.

Availability of plasma cell–free DNA platforms has greatly enhanced the ability to detect resistance mechanisms and shed light on prognosis. Emerging data

continued on page 19

MEETING HIGHLIGHTS

The Long Road Home

By Fadlo R. Khuri, MD, FACP

This lecure was delivered on the evening of February 23, 2018 at the 19th Lung Cancer Targeted Therapies Meeting. It is part of a series of annual talks given by senior leaders in the field of lung cancer research, about the field of thoracic oncology, their careers and the directions they have chosen. Previous speakers have included Paul Bunn and Larry Einhorn.

The courses of leadership and life are innately dynamic—one must adapt to circumstances while adhering to core principles to truly make a difference. I have been privileged to devote my career to understanding the biology of lung and aerodigestive cancers and to improving the prevention, treatment, and quality of life for patients with these diseases. This opportunity would never have been afforded to me without the American University of Beirut (AUB), the quintessential American institution of higher education abroad and a well-known liberal arts institution in the Middle East. Founded in 1866, the AUB has educated four generations of my family, so I was deeply honored—after my clinical research contributions and helping develop major programs at the University of Texas MD Anderson Cancer Center[1,2] and Emory University's Winship Cancer Institute[3,4]—to be selected in March 2015 to become the 16th president of AUB.

Global Contributions

In a region beset with instability and strife, AUB plays a critical role in the development of opportunities for tomorrow's leaders amid these daunting challenges. Almost half of the world's displaced persons live in the Middle East. War, deprivation, and estrangement are widespread. It is incumbent upon those who have been provided significant opportunities to help create them for others. I am confident that the time is ripe to develop and participate in a new Marshall Plan for education in the Middle East.[5]

Dr. Fadlo R. Khuri

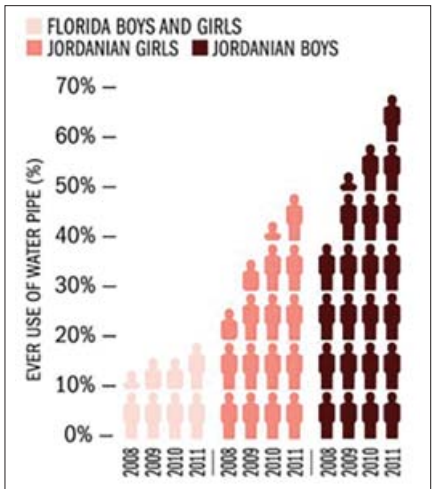
With a world-class leadership team and stabilized tuition fees and budgetary expenses, AUB has embarked on an aspirational voyage to create greater opportunities for some of the best and brightest individuals, many of whom would otherwise not have the ability to obtain college, medical, and postgraduate education. They will join our community of scholars and practitioners—a community that models a just, resilient, and relevant mini-society—dedicated to transforming the societies around us and improving the human condition through education, service, and research.

In the next 10 to 15 years, low-income counties will bear the vast majority of the cancer disease burden. Whereas U.S. smoking rates have fallen from 45% in 1965 to below 15%, smoking in the Middle East has done the opposite.[7,8] Lebanon, in particular, has the third highest per capita smoking rate in the world. The use of the water pipe is epidemic in Lebanon, Jordan, and other Arab countries, such that some studies demonstrate that up to 70% of Jordanian youth have attempted the water pipe (Fig.).[9]

In this context, AUB has developed a comprehensive effort to make the campus tobacco free by the start of academic year 2018-2019. We have also developed new National Cancer Treatment Guidelines for Lebanon, launched in February 2018, as a model for middle-income countries with broad disparities in wealth distribution. Through these and other measures, we intend to affect health and education, such that AUB's motto, "That they may have life and have it more abundantly," continues to apply to those most in need of our support. ✦

About the Author: Dr. Khuri is a professor in the Department of Hematology and Medical Oncology at Emory University School of Medicine. He is the 16th President of the American University of Beirut in Lebanon.

Figure. Prevalance of Water Pipe Usage Is Virtually at Epidemic Proportion in Parts of the Middle East



Sources: Vardavas C, Filippidis F, Agaku I. http://tobaccocontrol.bmj.com. Accessed April 11, 2018.
McKelvey KL, Wilcox ML, Madhivanan P, et al. *Eur J Public Health*. 2013;23(5):862-867.
Florida Department of Health; 2012 Florida Youth Tobacco Survey.
tobaccoatlas.org. Accessed April 11, 2018.)

References:

1. Khuri FR, Nemunaitis J, Ganly I, et al. A controlled trial of intratumoral ONYX-015, a selectively-replicating adenovirus, in combination with cisplatin and 5-fluorouracil in patients with recurrent head and neck cancer. *Nature Med*. 2000;6(8):879-885.
2. Khuri FR, Wu H, Lee JJ, et al. Cyclooxygenase-2 overexpression is a marker of poor prognosis in stage I non-small cell lung cancer. *Clin Cancer Res*. 2001;7(4):861-867.
3. Sun SY, Rosenberg LM, Wang X, Zhou Z, Yue P, Fu H, Khuri FR. Activation of Akt and eIF4E survival pathways by rapamycin-mediated mammalian target of rapamycin inhibition. *Cancer Res*. 2005;65(16):7052-7058
4. Owonikoko TK, Ramalingam SS, Miller DL, et al. A Translational, Pharmacodynamic, and Pharmacokinetic Phase IB Clinical Study of Everolimus in Resectable Non-Small Cell Lung Cancer. *Clin Cancer Res*. 2015;21(8):1859-1868.
5. George C. Marshall and the Marshall Plan: A Model of Transformational Diplomacy. U.S. Department of State website. web.archive.org/web/20050616023457/http://www.state.gov/r/pa/dc/rks/47848.htm. Accessed March 20, 2018.
6. World Health Organization. *World health statistics 2016: monitoring health for the SDGs, sustainable development goals*. Geneva, Switzerland: WHO Press; 2016.
7. Ng M, Freeman MK, Fleming TD, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. *JAMA*. 2014;311(2):183-192.
8. Vardavas CI, Filippidis FT, Agaku IT. Determinants and prevalence of e-cigarette use throughout the European Union: a secondary analysis of 26 566 youth and adults from 27 Countries. *Tob Control*. 2015;24(5):442-448.
9. McKelvey KL, Wilcox ML, Madhivanan P, Mzayek F, Khader YS, Maziak W. Time trends of cigarette and waterpipe smoking among a cohort of school children in Irbid, Jordan, 2008-11. *Eur J Public Health*. 2013;5:862-867.

EVOLVING STANDARDS OF CARE

NCCN Guidelines Updated for 2018: Keeping Pace with Data

By Gregory J. Riely, MD

The changes seen in the 2018 update of the National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for the treatment of patients with NSCLC reflect the rapid and significant progress we have observed in the treatment of lung cancer over the past 12 months. The currently posted NCCN Guidelines include all of the new approaches to treat patients with NSCLC that have so radically changed the NCCN recommendations.[1]

2018 Updates

This latest update of the NCCN Guidelines contains new recommendations for identifying the "right patient for the right drug," which has been the hallmark of lung cancer therapies for the past 10 years. To personalize therapy, the guidelines emphasize the need for knowledge of pretreatment tumor histology, molecular genotype, and immunophenotype prior to choosing therapy.

Recent additions include recommendations for osimertinib (category 2A) as an option for the first-line treatment of *EGFR*-mutant NSCLC, alectinib (category 1) as an option for the first-line treatment of *ALK*-positive NSCLC, ceritinib as an option (category 2A) for the first-line treatment of ROS-1 positive NSCLC, combination dabrafenib/trametinib (category 2A) for patients with *BRAF* V600E-mutant NSCLC, and pembrolizumab (category 2A) as a single agent for the first-line treatment of patients with NSCLC who have PD-L1 expression of 50% or greater. Additionally, the 2018 NCCN Guidelines recommend the use of pembrolizumab in combination with carboplatin and pemetrexed as a treatment option for patients with metastatic NSCLC, based on the initial positive results from a phase II trial that were confirmed in a recent phase III trial.[2] The clinical research data to support these recommendations were all presented or published in the last year.

In the 2018 update, a new section, "Principles of Molecular and Biomarker Analysis," educates physicians about the continued development of molecular testing by describing the important molecular aberrations that must be identified and the best practices for testing. The NCCN Guidelines also continue to keep pace with new data for the "Emerging Targeted Agents for Patients with Genetic Alterations" section, describing recent studies that support testing and treatment for patients with *MET* exon 14 alterations, *HER2* mutations, and *RET* gene rearrangements. Other recent additions are briefly outlined in the *Summary of the Guidelines Updates* (see the NCCN Guidelines for NSCLC, available at nccn.org).


Dr. Gregory J. Riely

ASCO Guidelines

The American Society of Clinical Oncology (ASCO) also issues guidelines for the treatment of NSCLC, although their guidelines have separate committees focusing on the treatment of early-stage disease or stage IV NSCLC, and guidelines are issued separately. The ASCO guidelines for systemic therapy of stage IV NSCLC are very rigorous in their assessment of evidence and, in the absence of strong evidence, are less likely to make a recommendation, compared to the NCCN Guidelines, which include a significant number of recommendations based on expert consensus. The ASCO guideline updates are issued less frequently (e.g., the most recently published guidelines, which became available on August 14, 2017, included a systematic review of evidence from February 2014 to December 2016). Because of the time needed for ASCO's systematic review and the writing

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EGFR-Targeted Therapy from page 18


Dr. Suresh S. Ramalingam

suggest that early clearance of the mutation in plasma with TKI therapy is associated with favorable outcomes[2]; to the contrary, persistence of mutations in the plasma despite therapy is associated with shorter PFS and a lower response rate. The latter group of patients may be candidates for novel combination approaches even before the emergence of molecular resistance. There is also increasing evidence that co-mutations are frequently present in patients with *EGFR* activation mutations and could affect outcomes with TKI therapy.[3] Further investigations into the role of co-mutations and the development of innovative treatment options based on these observations will likely result in better patient outcomes.

Immune checkpoint inhibitors that are widely used for the treatment of NSCLC have yielded disappointing results for patients with an *EGFR* mutation. Mutated tumors generally have lower PD-L1 expression and lower mutation burden. Chemotherapy is the preferred treatment for patients with *EGFR* mutations after acquired resistance to targeted agents. Elucidating the factors that drive the lack of sensitivity to checkpoint inhibitors is a crucial issue, and novel combination approaches are urgently needed in this patient population.

Whereas exon 19 and 21 mutations are the most common *EGFR* mutations, accounting for nearly 85% of all *EGFR* mutations, options for patients with less-common mutations are increasing. Afatinib was recently approved for patients with three distinct, uncommon *EGFR* mutations (*L861Q*, *G719X*, and *S768I*). Poziotinib and TK-788 are promising agents for patients with exon 20 insertion mutations. Poziotinib has demonstrated promising early results with a high response rate in a small cohort of patients[4]; data on PFS and duration of response are awaited. Currently, there are no targeted options for this molecular subset of patients.

The role of EGFR TKIs in patients with early-stage NSCLC is under investigation in randomized clinical trials. It is hoped that these studies will demonstrate the ability to cure more patients with the use of EGFR-targeted therapies. ✦

About the Authors: Dr. Ramalingam is a member of the IASLC Board of Directors. Dr. Ramalingam is Roberto C. Goizueta Distinguished Chair for Cancer Research at Emory University School of Medicine, and the deputy director at Winship Cancer Institute of Emory University.

References:

1. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res*. 2013; 19(8):2240-2247.
2. Mok T, Wu YL, Lee JS, et al. Detection and Dynamic Changes of EGFR Mutations from Circulating Tumor DNA as a Predictor of Survival Outcomes in NSCLC Patients Treated with First-line Intercalated Erlotinib and Chemotherapy. *Clin Cancer Res*. 2015;21(14):3196-3203.
3. Blakely CM, Watkins TBK, Wu W, et al. Evolution and clinical impact of co-occurring genetic alterations in advanced-stage EGFR-mutant lung cancers. *Nat Genet*. 2017;49(12):1693-1704.
4. Robichaux JP, Elamin YY, Tan Z, et al. Mechanisms and clinical activity of an EGFR and HER2 exon 20-selective kinase inhibitor in non-small cell lung cancer. *Nat Med*. 2018 Apr 23. [Epub ahead of print].

BREAKING NEWS BRIEFS

In late April 2018, the U.S. Food and Drug Administration approved **osimertinib** in the first-line setting for patients with metastatic NSCLC and either *EGFR* exon 19 deletions or exon 21 L858R mutations. In addition, a Premarket Approval supplement for the cobas *EGFR* Mutation Test v2 was granted, allowing the test to be used as a companion diagnostic with osimertinib in the first-line setting. The test was previously FDA approved for use with osimertinib for second-line treatment and beyond for patients with NSCLC who have *EGFR* exon 19 deletions or L858R-sensitizing mutations.

Approval of osimertinib in the first-line setting was based on the multicenter, international, randomized, double-blind FLAURA trial of 556 patients. All patients had *EGFR* exon 19 deletions or exon 21 L858R mutations and previously untreated (for advanced disease) unresectable or metastatic NSCLC. The estimated median progression-free survival (PFS) was 18.9 months (95% CI [15.2, 21.4]) in the osimertinib arm and 10.2 months (95% CI [9.6, 11.1]) in the standard-of-care arm, which used either gefitinib or erlotinib (HR 0.46, 95% CI [0.37, 0.57]); $p < 0.0001$). Confirmed overall response rates were 77% and 69%, and estimated median response durations were 17.6 and 9.6 months, both respectively. At the time of the primary PFS analysis, there were too few deaths to estimate or compare survival outcomes.

Health Canada has approved **atezolizumab** as a monotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC whose disease has progressed on or after platinum-based chemotherapy—making atezolizumab the only anti–PD-L1 therapy approved in Canada for lung cancer. Approval was based on results from the phase III OAK and the phase II POPLAR studies.

The National Institute for Health and Care Excellence in England also recently recommended the drug for patients with advanced NSCLC whose disease has progressed after chemotherapy, regardless of PD-L1 expression status. Roche is providing a confidential discount to National Health Service patients, who can use the therapy for up to 2 years. ✦

GLOBAL INITIATIVES

Israel's Parliament Hosts IASLC CEO Dr. Fred R. Hirsch

By Shani Shilo, DMD, PhD, and
Nir Peled, MD, PhD, FCCP

On March 6, 2018, the Israeli parliament, the Knesset, held a Science and Technology Committee meeting devoted to lung cancer, new technologies, and their effects on the future of care. The meeting was an initiative of the Israel Lung Cancer Foundation and was led by the parliament member Uri Maklev and three additional members. The Israeli Lung Cancer Foundation initiated this meeting after the annual health basket committee rejected reimbursement for high-risk cohorts on the national screening protocol (annual low-dose CT scans) due to prioritization of issues regarding other health technologies. In addition, this was the first time there was a dedicated committee in the Israeli parliament to discuss lung cancer innovations.

Shani Shilo, DMD, PhD, founder and CEO of the Israeli Lung Cancer Foundation, opened the meeting, sharing her experience as a caregiver to her spouse. Dr. Shilo's husband was misdiagnosed as having *ALK*-positive disease and was later diagnosed by hybrid next-generation sequencing (intron 19 deletion). His disease has completely responded to treatment for nearly 7 years. Through Dr. Shilo's initiation of the Israel Lung Cancer Foundation, she has been able to affect reimbursement approvals during the past several years to establish a sharing community with thousands of caregivers and patients, who provide one another with support and information.

Nir Peled, MD, PhD, FCCP, the Foundation's co-founder and president, elaborated on new technologies. Additional speakers included Dr. Abed Agbaria, from the management committee of the patient foundation, Yair Bar, MD, PhD, head of the Israeli Physician Lung Cancer Group, and Amir Onn, MD, head of the Head of the Institute of Pulmonology, Physiology, and Exercise at Sheba Medical Center.

IASLC CEO Fred R. Hirsch, MD, PhD, provided the international perspective. His talk emphasized the importance of communication and collaboration to improve lung cancer early diagnosis and treatment. He described the salutary effects of lung cancer screening on stage shift, reduced lung cancer mortality, and decreased expenses in comparison to the current expenses associated with treatment of patients with advanced disease. Further, he underscored the importance of early diagnosis and availability of study drugs.

"The meeting with the Knesset was a very important meeting for the Israeli lung cancer community. I fully support them in their efforts to implement the best preventive measures and highest-quality lung cancer care in Israel," Dr. Hirsch said. "It was also an important meeting for the IASLC regarding interaction with politicians and participation in a government system. It is a part of the society's new strategic plan to facilitate implementation of preventive measures and optimal treatment care in various countries via discourse at the government level."

A member of the patient foundation, a caregiver for her mother with small cell lung cancer, discussed the difficulties of managing her loved one, the need for new treatments, and the high burden of care on patients' families. Additionally, an exhibition entitled "Breath Friends" was displayed. This exhibition, which was photographed by Meir Rakocz, DMD, MHA, a patient himself, showed the faces of patients with lung cancer along with their caregivers and exhibited both the versatility of patients with lung cancer and the hope this new era of therapies has brought.

The Israeli healthcare services provides molecular profiling to all patients with NSCLC, per the IASLC guidelines; however, the Israeli Lung Cancer Foundation is now pushing for next-generation sequencing for all patients with advanced NSCLC. Fortunately, the availability of all drugs is generous in Israel and stands in parallel to the situation in the United States. Drug registration is very efficient and happens immediately after U.S. Food and Drug Administration approval. Reimbursement may even precede drug registration in unique circumstances.

Lung cancer screening, although a topic of importance, was not allowed to be mentioned, as the Foundation had appealed to the high court of justice to have it incorporated in the Israeli health system and received a notice from the law council of the Knesset to forego discussion of this topic during the meeting.

Follow-up meetings are planned. ✦

Drs. Fred R. Hirsch (left) and Nir Peled participated in the first dedicated-committee discussion in the Israeli Parliament about lung cancer innovations.

Dr. Shani Shilo (center), from the Israeli Lung Cancer Foundation with two of her colleagues, standing next to Dr. Shilo's portrait in the "Breath Friends" exhibit by Meir Rakocz.

About the Authors: Dr. Shilo is founder and CEO of the Israeli Lung Cancer Foundation. Dr. Peled is head of The Cancer Institute, Soroka Medical Center and Ben-Gurion University, Beer-Sheva, Israel; head of the Thoracic Oncology Assembly, European Respiratory Society; committee co-chair, Prevention, Screening & Early Detection of Lung Cancer, IASLC and the co-founder and president of the Israeli Lung Cancer Foundation.

NCCN Guidelines from page 19

process, ASCO's guidelines have not yet incorporated the first-line use of osimertinib for patients with *EGFR*-mutant NSCLC, the first-line use of alectinib for *ALK*-positive disease, or the data to support the combination of pembrolizumab with chemotherapy.

The NCCN Guidelines Process

NCCN is a not-for-profit alliance of 27 leading cancer centers whose mission is "improving the quality, effectiveness, and efficiency of cancer care." NCCN is perhaps best known for the development of guidelines for treatment of patients with a variety of cancers, including small cell lung cancer and NSCLC. The goal of the NCCN Guidelines is to outline evidence-based, consensus-driven treatment to ensure that all patients get the best outcome. Key assets of the NCCN Guidelines include the staff who coordinate all aspects of review and development as well as the nature of the multidisciplinary panel, including thoracic surgeons, medical oncologists, radiation oncologists, pathologists, and molecular pathologists.

The NCCN Drugs & Biologics Compendium (NCCN Compendium®), which is derived from the Guidelines, is recognized by public and private insurers alike, including, but not limited to, the Centers for Medicare and Medicaid Services (CMS) and UnitedHealthcare, as an authoritative reference for oncology coverage policy. Annual reviews by NCCN member institutions serve as the foundation for changes in guidelines, and these are supplemented by a systematic review and submissions of recommendations from professional societies and others. Because the NCCN Guidelines are used by so many, the guidelines panel reacts quickly to incorporate new findings into its treatment recommendations. On this basis, the NCCN Guidelines for NSCLC were updated nine times in 2017 and already twice in 2018. The NCCN Guidelines, which are rapidly updated based on strong evidence and expert consensus, are presented in a clear, algorithmic fashion and are broadly accessible to guide oncologists in the best care available for patients today. ✦

NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

About the Author: Dr. Riely is vice chair of the Clinical Trials Office, Department of Medicine at Memorial Sloan Kettering Cancer Institute. He is also an NCCN panel member for NSCLC.

References:

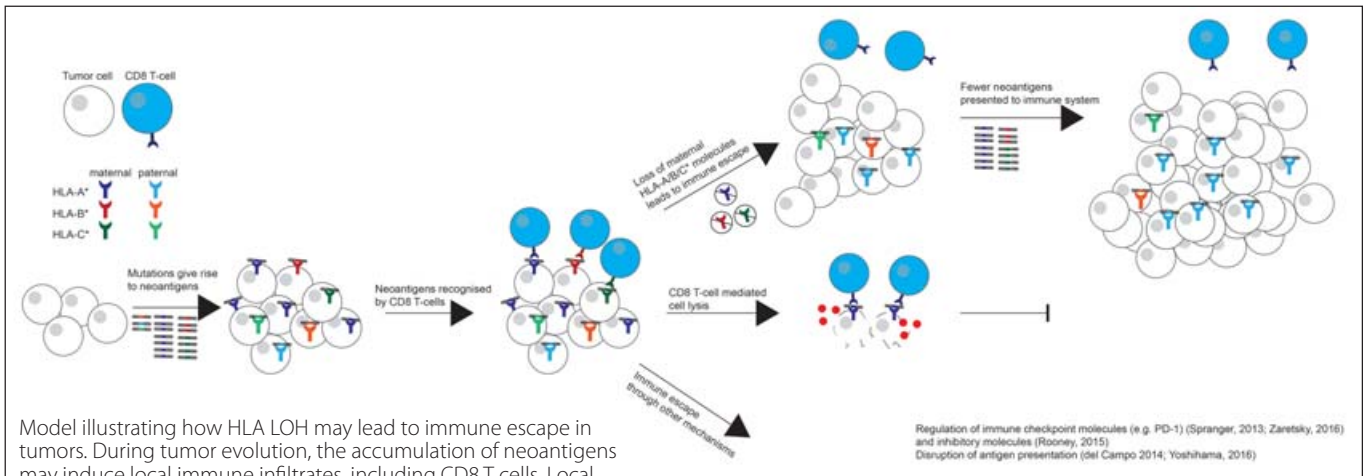
1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Clinical Practice Guidelines in Oncology for the Treatment of Patients with NSCLC, 2017. © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. Accessed. Accessed February 14, 2017. To view the most recent and complete version of the guideline, go online to NCCN.org.
2. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, nonsquamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol*. 2016;17:1497-1508.

EVOLVING STANDARDS OF CARE

HLA LOH As an Immune Evasive Mechanism in TRACERx NSCLC

By Rachel Rosenthal, PhD, MSc, and
Charles Swanton, FRCP, BSc, PhD

Figure. Model of HLA Allele-Specific Loss in NSCLC



Model illustrating how HLA LOH may lead to immune escape in tumors. During tumor evolution, the accumulation of neoantigens may induce local immune infiltrates, including CD8 T cells. Local immune infiltrates may act as a selection barrier for tumors. Subclones with HLA LOH may be positively selected, as these can evade killing by avoiding CD8 T-cell recognition. Alternatively, other subclones may evade killing through other mechanisms.

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An evolving tumor and the immune system continuously adapt to each other. As a tumor develops increasing numbers of somatic alterations and disregulated genes, it must also find ways to avoid immune detection and elimination by activated immune cells.[1] One route to withstand immune predation is through the disruption or prevention of antigen presentation, as reductions in antigen presentation can limit immune recognition. Indeed, a high proportion of cancer types have been found to acquire detrimental human leukocyte antigen (HLA) mutations,[2] down-regulate HLA expression,[3-5] or abolish the function of the stabilizing molecule beta-2 microglobulin (B2M).[6-8]

Another means of HLA disruption is via loss of heterozygosity (LOH) at the HLA locus, wherein the maternal or paternal HLA haplotype is lost, impairing the immune system's ability to recognize tumor antigens.[9] This particular mechanism of immune evasion was recently documented in the case study of a patient who developed a resistant lesion after being treated with tumor-infiltrating lymphocytes composed of T-cell clones targeting KRAS G12D.[10] The resistant lesion was found to have lost the HLA allele responsible for presenting the targeted neoantigen.

However, the polymorphic nature of the HLA locus has hampered the determination of copy number events affecting the locus, such as losses and amplifications, rendering a large-scale study of HLA LOH in human tumor samples and its effects on the tumor–immune system relationship infeasible. In a recently published study, we present a novel computational tool, Loss Of Heterozygosity in Human Leukocyte Antigen (LOHHLA), which can be used to determine HLA allele-specific copy number from sequencing data.[11]

To determine the prevalence of HLA LOH events in NSCLC (Fig.), we applied LOHHLA to the first published cohort from the Tracking Non–Small Cell Lung Cancer Evolution through Therapy (TRACERx) study. TRACERx is a multicenter, prospective cohort study, through which surgically resected NSCLC tumors are subject to high-depth, multiregion, whole-exome sequencing in order to investigate tumor evolution, intratumor heterogeneity, and the effects on clinical outcome.[12]

HLA LOH was identified in 40% of NSCLC samples. This was in contrast to other forms of HLA disruption, such as HLA mutations, which were only observed at a frequency of 3% in the TRACERx cohort. This observation suggests that HLA LOH may be a far more prevalent form of immune evasion. The multiregion aspect of the TRACERx dataset also allowed for the timing of HLA LOH events, as those that were identified in only a subset of tumor regions were subclonal in nature and occurred later in tumor evolution. Likewise, events that could be identified in every tumor region were considered early events in tumor evolution. Indeed, mapping specific HLA LOH events to tumor phylogenetic trees revealed that LOH at the HLA locus often occurred late in tumor evolution, on the branches of the phylogenetic tree. Strikingly, HLA LOH events sometimes mapped to multiple branches of the phylogenetic tree, suggesting that the loss had occurred at multiple time points over the course of a single tumor's evolutionary history. A formal statistical analysis revealed that focal loss at the HLA locus occurred more frequently than expected by chance, suggesting strong selective pressure for the event late in tumor evolution, potentially in response to a shift in the equilibrium between immune recognition and evasion.

HLA LOH events were found to associate with a high subclonal mutation and increased APOBEC-mediated mutagenesis. Furthermore, and consistent with LOH at the HLA locus facilitating the accumulation of subclonal neoantigens, there was a significant enrichment for subclonal neoantigens predicted to bind to the lost HLA alleles as compared to the kept alleles, suggesting that disrupting HLA expression could be an effective mechanism of evading immune detection.

TRACERx tumors exhibiting LOH at the HLA locus also had increased PD-L1 positivity. Because the PD-L1 ligand binds to the inhibitory receptor PD-1, the expression of PD-L1 may reflect a response to an active immune system. Validation using expression data from NSCLC samples in The Cancer Genome Atlas confirmed that tumors harboring HLA LOH events had increased immune cell infiltration, reflective of an active immune microenvironment. These data are consistent with the hypothesis that HLA LOH facilitates immune escape later in tumor evolution in response to increased immune pressure.

Targeting neoantigens predicted to bind to HLA alleles already lost in the tumor may not effectively elicit a T-cell response. Furthermore, as HLA allele–specific loss has already once been observed in an immunotherapy-resistant lesion, it will be intriguing to investigate how frequently HLA LOH results in acquired immunotherapy resistance. Indeed, a

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BREAKING NEWS BRIEF

Dacomitinib Shows Promise in First-Line Setting

Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency took steps in early April toward increasing the first-line treatment options for patients with locally advanced or metastatic *EGFR*-mutated NSCLC based on the results from the phase III ARCHER 1050 study. The FDA recently accepted a New Drug Application from Pfizer Inc. for dacomitinib, a pan-human EGFR TKI, for first-line treatment; priority review was granted. Likewise the European Medicines Agency accepted the Marketing Authorization Application for the same indication.

The study of interest compared dacomitinib (227 patients) with gefitinib (225 patients) and found that patients who received dacomitinib had a progression-free survival of 14.7 months vs. 9.2 months for those treated with gefitinib. This translated to a 41% reduction in risk of disease progression or death for dacomitinib (HR 0.59 95% CI [0.47, 0.74]; $p < 0.0001$) as first-line therapy in this setting. ✦

EDITOR'S NOTE

With the recent approval of osimertinib in the front-line setting in similar patients, based on the very positive results of the FLAURA trial, it is unclear how much uptake there will be for dacomitinib if/when this agent garners approval.

–Corey Langer, MD, Editor

ADVOCACY AND SURVIVORSHIP

Motivated, Engaged, and Organized: The New Molecular Cohorts of Lung Cancer

By D.R. Camidge

Just as physicians and scientists no longer treat lung cancer as a single disease because of molecular distinctions, patient advocacy groups also are becoming organized along molecular lines.

In 2015, Janet Freeman-Daily, Lisa Goldman, and Tori Tomalia—all *ROS1*-positive NSCLC survivors—co-founded a private Facebook group, "ROS1 Positive (ROS1+) Cancer." They named themselves "The ROS1ders." Similar Facebook groups now exist for those affected by *ALK* rearrangements, *EGFR* mutations, and *HER2/EGFR* exon 20 mutations (Figure online).

"Facebook has provided an intuitive platform to launch our group, collect initial data from members, and to communicate with members all over the world," said Ivy Elkins, a 4-year survivor of exon 19 *EGFR*-mutated NSCLC and one of the seven co-founders of the EGFR Resisters group (egfrcancer.org). "The group began in 2017 after a LUNGevity HOPE summit got us talking about what the options were for treatment if osimertinib stopped working."

Ms. Freeman-Daily feels that it is key for patients to control the advocacy organizations related to their diseases. She noted that not only can these patient-run groups provide online support and information related to treatment, side effects, and relevant trials, but they also can "drive research directly focused on their disease type by partnering with research labs, clinicians, and industry, as well as other advocacy groups."

Reaching out to the Bonnie Addario Lung Cancer Foundation, the ROS1ders initially wanted to spearhead the creation of a clinical trial examining treatment options for those patients who experience disease relapse during or after treatment with crizotinib. However, it became clear that there was a lack of knowledge about specific mechanisms of resistance to inform such a trial. "We had to take a step back to identify the real need—one that we, as a group, could actually do something about," said Ms. Freeman-Daily. Since then, the ROS1ders have developed the methodology to direct standard-of-care biopsies from their members to key academic labs for analysis. In addition, they have started to make patients and their families begin the discussion about the provision of additional tumor tissue through limited postmortem examinations. They have also generated novel ROS1 cell lines through the distribution of collection kits and instructions to distant sites, with live cells successfully returned to academic labs for in vitro culture.

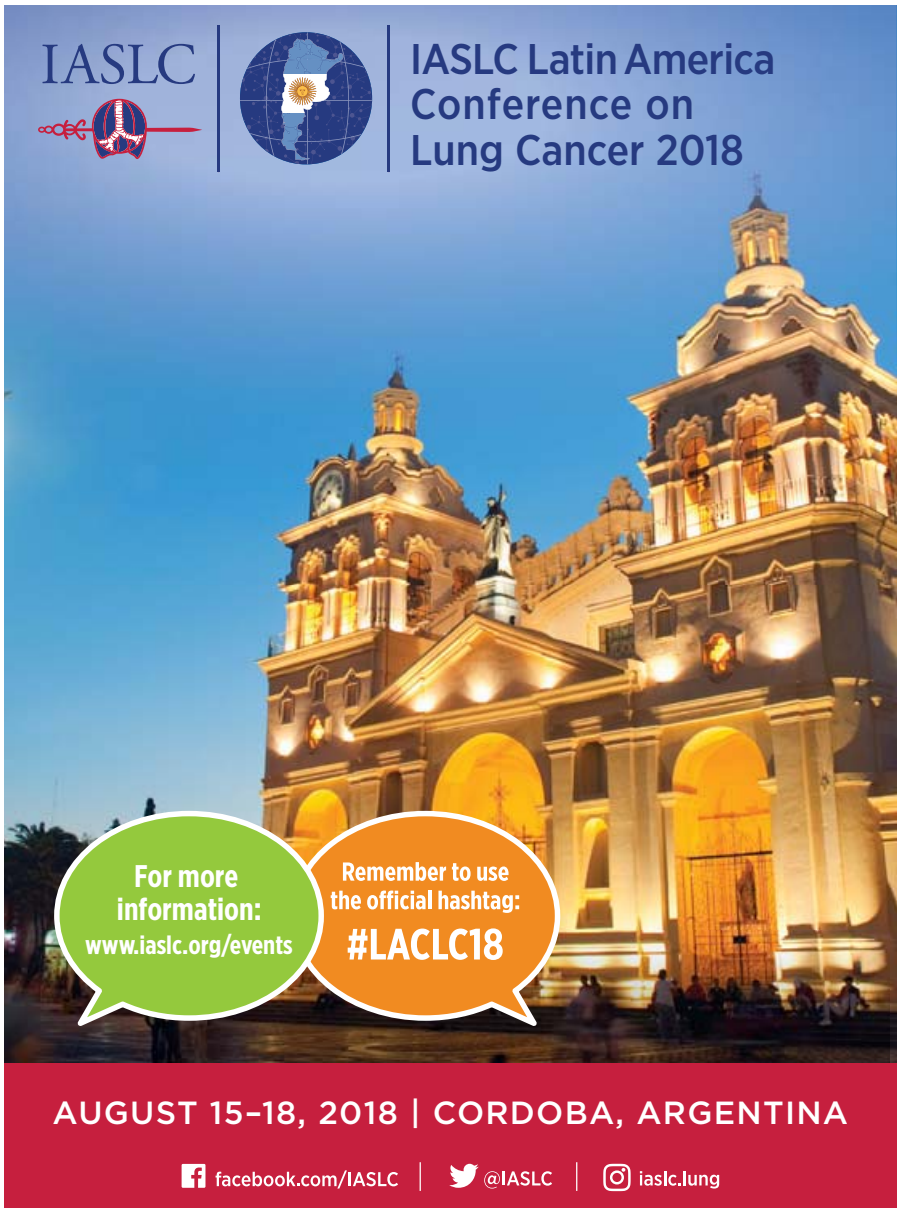
Many of the groups capture detailed information on members. The ROS1ders submitted a poster to the 2018 AACR meeting that describes their projects, including one that compares and contrasts the characteristics of more than 200 patients with *ROS1*-mutated NSCLC across 21 countries, multiple times the size of the largest previously published series on *ROS1*-positive NSCLC. Similarly, the EGFR Resisters had a poster at this year's IASLC Targeted Therapies Meeting, describing the medical details of more than 200 of their members.

Driving Research Through Partnerships

Sometimes starting a group requires outside help. Following his brother Kevin's diagnosis with Exon 20 *EGFR*-mutant NSCLC, Bob Hanlon reached out to Marcia Horn at the International Cancer Advocacy Network. Together with Kevin, they developed the Exon 20 Group (exon20group.org) and rapidly assembled a team of what Horn called "'all possible stakeholders," including 121 patients from 20 countries whose tumors harbored *EGFR* or *HER2* exon 20 mutations. Companies such as Takeda, Spectrum, and Rain Therapeutics, which are developing drugs for *EGFR* and *HER2* exon 20 mutant diseases have become partners on the initiative. "We want their trials to address our members' needs; for example, including cohorts for those patients whose disease did not respond to other drugs directed against exon 20 mutations," said Ms. Horn.

Some groups are effecting change through financial means. Outreach by the *ALK* Positive group, which has more than 900 members, has raised nearly $400,000. In 2018, together with LUNGevity, they issued a request for research applications specifically for *ALK*-related research projects, encouraging applicants to make use of the unique resources offered by such a large and engaged patient group.

Patient groups realize that the three things their members really own—their tissue, medical history, and personal story—can be leveraged to speed up progress in their disease; as a result, partnered research approaches are set to become increasingly common for many specific subsets of lung cancer in the future. ✦



BREAKING NEWS BRIEF

Rova-T Enters Phase III Trials after Disappointing Phase II Results

AbbVie will not seek accelerated U.S. Food and Drug Administration (FDA) approval for rovalpituzumab tesirine (Rova-T) in third-line relapsed/refractory (R/R) SCLC. Rova-T is an antibody–drug conjugate that targets the DLL3 protein, expressed in more than 80% of SCLC tumors.[1]

The step back was a result of the phase II data from TRINITY, a multicenter, open-label, single-arm study of patients whose SCLC tumors expressed DLL3 and who had received at least two prior treatments, including at least one platinum-based regimen. Of 177 patients, the objective response rate for Rova-T (based on RECIST criteria v1.1) was 16%, and overall survival at 1 year was 17.5%.

"We continue to believe Rova-T has potential for patients with small cell lung cancer and other DLL3-expressing cancers," said Mike Severino, MD, executive vice president of research and development and chief scientific officer for AbbVie in the company's March press release. "Although the results from the study were not what we hoped for, we look forward to receiving data from the ongoing phase III studies in the first- and second-line settings and remain committed to developing Rova-T for the treatment of patients with small cell lung cancer." ✦

References:

1. ClinicalTrials.gov (2016). Study of Rovalpituzumab Tesirine (SC16LD6.5) for Third-line and Later Treatment of Subjects With Relapsed or Refractory Delta-Like Protein 3-Expressing Small Cell Lung Cancer (TRINITY). Accessed April 11, 2018. https://clinicaltrials.gov/ct2/show/NCT02674568?term=SC16LD6.5&rank=2.

The 2018 Heine H. Hansen Award recipient was *IASLC Lung Cancer News* Associate Editor **Fabrice Barlesi, MD**. The award was presented at the 2018 European Lung Cancer Congress (ELCC), sponsored by the European Society for Medical Oncology (ESMO) and the IASLC. Dr. Barlesi is professor of medicine at the University of Aix Marseille and head of the Multidisciplinary Oncology and Therapeutic Innovations Department at Assistance Publique Hôpitaux de Marseille, in France.

Dr. Barlesi's Heine H. Hansen Award Lecture at ELCC, "The Power of Triple H," was a brief discussion not just of the history of lung cancer but of its future. Building on the work of Heine Hansen and others, lung cancer trials are more comprehensive and multifaceted than ever, which is scientifically exciting. Challenges remain, however, regarding stigma associated with the disease, the complexity of precision medicine, and societal expectations. Dr. Barlesi's lecture is summarized here.

Heritage: Heine Hansen was 12 years old when the relationship between tobacco exposure and lung cancer was made, and he was 57 when the realization that patients with lung cancer should be treated with chemotherapy was made. Lung cancer specialists should work to protect the heritage—the groundbreaking work of the true pioneers in the field—to provide optimal outcomes for patients with lung cancer, who still need advocates. Data from a public survey in the United Kingdom showed that 70% of respondents felt like lung cancer was self-inflicted because it affects smokers. In a similar survey in the United States, 25% of respondents felt like patients with lung cancer deserved less respect than obese patients.

Human: Heine Hansen was the first to say that we should integrate biologic hypotheses and translational research into our trials. This inclusive outlook paved the wave for modern trials, such as the IFCT/UNICANCER SAFIR02, which is a multiarm trial that aims to compare the superiority of targeted therapies based on molecular testing compared to standard treatment. The PIONeeR trial, a public/private consortium, will compare patients based on treatment response or disease progression and will allow for treatment of patients with different combinations of immunotherapy agents.

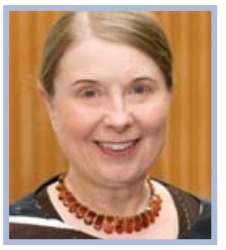
Hard: Questions and challenges abound in lung cancer. Society and patients have moved beyond the expectation of lung cancer as a chronic disease to the expectation of a cure. This is complicated by multiple perspectives and therapeutic options, but we must not forget to educate and enlist the help of general practitioners. In addition, precision medicine is complicated for patients and can result in missed opportunities in terms of trial participation and optimal treatment. Careful communication is needed to aid patient decision making. ✦

Names and News

Primo N. Lara, Jr., MD, has been named director of the National Cancer Institute–designated UC Davis Comprehensive Cancer Center, leading a team of more than 300 scientists serving more than 10,000 new adult and pediatric patients yearly. As director, Dr. Lara will hold the Codman-Radke Chair in Cancer Research and will serve as executive associate dean for cancer programs. Dr. Lara was selected for the position after a national search; he has served as acting director since July 2016.

Dr. Lara is active in medical education and training, serving as principal investigator of the NCI-funded K12 Paul Calabresi Clinical Oncology Training Grant, which trains junior faculty scholars to be independent, patient-oriented cancer researchers. He also chaired the IASLC Education Committee from 2011-2013 and the American Society of Clinical Oncology's Continuing Medical Education Subcommittee in 2012-2013.

Pasi A. Janne, MD, PhD, was awarded the Second AACR-Waun Ki Hong Award for Outstanding Achievement in Translational and Clinical Cancer Research. The award is given to a cancer researcher who has conducted highly meritorious laboratory, translational, or clinical cancer research anywhere in the world at a relatively early state in his or her career. Dr. Janne is the director at the Lowe Center for Thoracic Oncology, director at the Belfer Center for Applied Cancer Science at Dana-Farber Cancer Institute, and professor of medicine at Harvard Medical School in Boston. He delivered his lecture, "Developing Combination Precision Therapies for Lung Cancer," at the AACR meeting this past April.



IASLC past-president **Frances Shepherd, MD,** has been awarded the 2018 Canada Gairdner Wightman Award for outstanding career leadership in medicine and medical science. Dr. Shepherd is a professor in the Department of Medicine, Scott Taylor Chair in Lung Cancer Research, and senior staff physician at the Princess Margaret Cancer Centre. She has led numerous translational research studies evaluating new targeted therapies and antiangiogenesis agents in lung cancer, and she has developed several large international randomized trials for novel molecular agents. Dr. Shepherd is past recipient of the IASLC Lung Cancer Research Award as well as of numerous other international awards. ✦

TRACERx NSCLC from page 21

recent publication has since investigated the HLA locus of patients treated with checkpoint blockade therapy and found that a subset of patients harboring an HLA LOH event had poorer survival.[13]

Dr. Rachel Rosenthal

Dr. Charles Swanton

Given the prevalence of LOH events detected in the treatment-naive cohorts analyzed thus far, it may be important to consider HLA LOH when designing patient-specific immunotherapy approaches, such as tumor-infiltrating lymphocyte (TIL)–based therapies and neoantigen vaccines. For example, in every patient in the TRACERx study who exhibited HLA LOH, there were predicted neoantigens binding to the lost haplotype. This observation suggests that considering HLA LOH when identifying putative neoantigens that may elicit an effective T-cell response may improve clinical response to immunotherapy. ✦

About the Authors: Dr. Rosenthal is a scientist in the Translational Cancer Therapeutics Laboratory, University College London, United Kingdom. Prof. Swanton is a clinician scientist with the Translational Cancer Therapeutics Laboratory, the Francis Crick Institute, United Kingdom.

References:

1. Hanahan D and Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* 2011;144:646-674.
2. Shukla SA, Rooney MS, Rajasagi M, et al. Comprehensive analysis of cancer-associated somatic mutations in class I HLA genes. *Nat Biotechnol.* 2015;33:1152-1158.
3. Hicklin DJ, Marincola FM, Ferrone S. HLA class I antigen downregulation in human cancers: T-cell immunotherapy revives an old story. *Mol Med Today.* 1999;5:178-186.
4. Garrido F, Ruiz-Cabello F, Aptsiauri N. Rejection versus escape: the tumor MHC dilemma. *Cancer Immunol Immunother.* 2017;66:259-271.
5. Campoli M, Chang CC, Ferrone S. HLA class I antigen loss, tumor immune escape and immune selection. *Vaccine.* 2002;20 Suppl 4:A40-A45.
6. Benitez R, Godelaine D, Lopez-Nevot MA, et al. Mutations of the beta2-microglobulin gene result in a lack of HLA class I molecules on melanoma cells of two patients immunized with MAGE peptides. *Tissue Antigens.* 1998;52:520-529.
7. D'Urso CM, Wang ZG, Cao Y, et al. Lack of HLA class I antigen expression by cultured melanoma cells FO-1 due to a defect in B2m gene expression. *J Clin Invest.* 1991;87:284-292.
8. Drake CG, Jaffee E, Pardoll DM. Mechanisms of immune evasion by tumors. *Adv Immunol.* 2006;90:51-81.
9. Koopman LA, Corver WE, van der Slik AR, Giphart MJ, Fleuren GJ. Multiple genetic alterations cause frequent and heterogeneous human histocompatibility leukocyte antigen class I loss in cervical cancer. *J Exp Med.* 2000;191:961-976.
10. Tran E, Robbins PF, Lu YC, et al. T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer. *N Engl J Med.* 2016;375:2255-2262.
11. McGranahan N, Rosenthal R, Hiley CT, et al. Allele-Specific HLA Loss and Immune Escape in Lung Cancer Evolution. *Cell.* 2017;171:1259-1271 e11.
12. Jamal-Hanjani M, Wilson GA, McGranahan N, et al. Tracking the Evolution of Non-Small-Cell Lung Cancer. *N Engl J Med.* 2017;376:2109-2121.
13. Chowell D, Morris LGT, Grigg CM, et al. Patient HLA class I genotype influences cancer response to checkpoint blockade immunotherapy. *Science.* 2018;359(6375):582-587.

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