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FOR THORACIC SPECIALISTS

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LUNG CANCER IASLCNEWS

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

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IMMUNOTHERAPY

Immunotherapy Succeeds in Squamous NSCLC, Establishing a New Frontline Standard of Care

By Kara Nyberg, PhD

Treatment advances for metastatic squamous cell carcinoma have long lagged behind those for other NSCLC subtypes, forcing patients with this difficult-to-treat disease to settle with platinum-based chemotherapy as the best treatment option. But the tide now appears to be turning. As presented at the American Society of Clinical Oncology (ASCO) meeting in Chicago this past June, two dedicated squamous cell carcinoma studies—KEYNOTE-407 and IMpower131—have shown that immunotherapy–chemotherapy combinations can improve outcomes over chemotherapy alone.[1,2] Importantly, KEYNOTE-407 provides irrefutable evidence that such combinations can significantly improve patient survival regardless of PD-L1 status, ushering in a new standard of care for squamous disease.

KEYNOTE-407: New Standard

The global phase III KEYNOTE-407 trial included 559 patients with squamous NSCLC without regard to tumor PD-L1 expression levels.[1] Individuals were randomly assigned to receive four cycles of carboplatin and paclitaxel or nab-paclitaxel, plus either pembrolizumab or placebo. Maintenance pembrolizumab or placebo was administered in accord with patients' initial treatment assignment.

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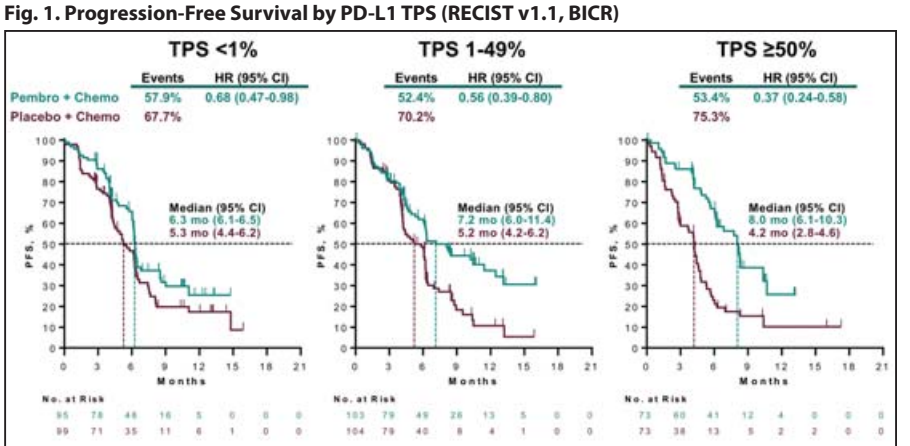
Fig. 1. Progression-Free Survival by PD-L1 TPS (RECIST v1.1, BICR)



Abbreviation: BICR, blinded, independent central review.
Data cutoff date: Apr 3, 2018.

Courtesy of Dr. Luis Paz-Ares

MEETING PREVIEW

WCLC Plenary Symposia to Include Practice-Changing Research Presentations

The conference's program is stacked with science and education for scientists, clinicians, and advocates alike.

By Leah K. Lawrence

The IASLC 19th World Conference on Lung Cancer (WCLC), the world's largest meeting dedicated to lung cancer and other thoracic malignancies, will take place this year from September 23 to 26 in Toronto, Canada.

With more than 7,000 delegates coming from more than 100 countries, this year's meeting is sure to include incredible science, education, and networking opportunities, according to Natasha B. Leighl, BSc, MSc, MD, a medical oncologist at the Princess Margaret Cancer Centre and IASLC WCLC 2018 co-president.

"The WCLC is a unique chance for lung cancer experts around the world and across disciplines to get together to take action against lung cancer," Dr. Leighl told the *IASLC Lung Cancer News*.

The 2019 WCLC offers valuable multidisciplinary content for thoracic oncology specialists and supportive care providers of all backgrounds and career levels.

This year's WCLC program was designed to include a number of multidisciplinary sessions, so attendees should examine speakers and individual presentation titles when planning their meeting agendas, according to Andrea Bezjak, MDCM, FRCPC, MSc, of the Princess Margaret Cancer Centre, and IASLC WCLC 2018 co-president.

"The whole program, from beginning to end, has a lot to offer attendees from various backgrounds," Dr. Bezjak said. "Whether an individual is a clinician, a scientist, a nurse, or an advocate, and whether an individual is new to lung cancer or very experienced, they should look at the program and plan to attend from the pre-symposium through the opening reception all the way to the closing plenary."

Highlighting Plenary Symposia

The meeting's pre-symposium sessions kick off the morning of Sunday, September 23, and include the Young Investigator Session and several industry symposia. Sunday evening, attendees can enjoy the IASLC Foundation Concert at 5:45 PM (EDT) and then gather with colleagues at the Opening Ceremony at 7:30 PM (EDT). The Welcome Reception and opening of the Exhibit Hall follows immediately thereafter, at 8:30 PM (EDT).

The bulk of the scientific presentations will begin Monday morning, September

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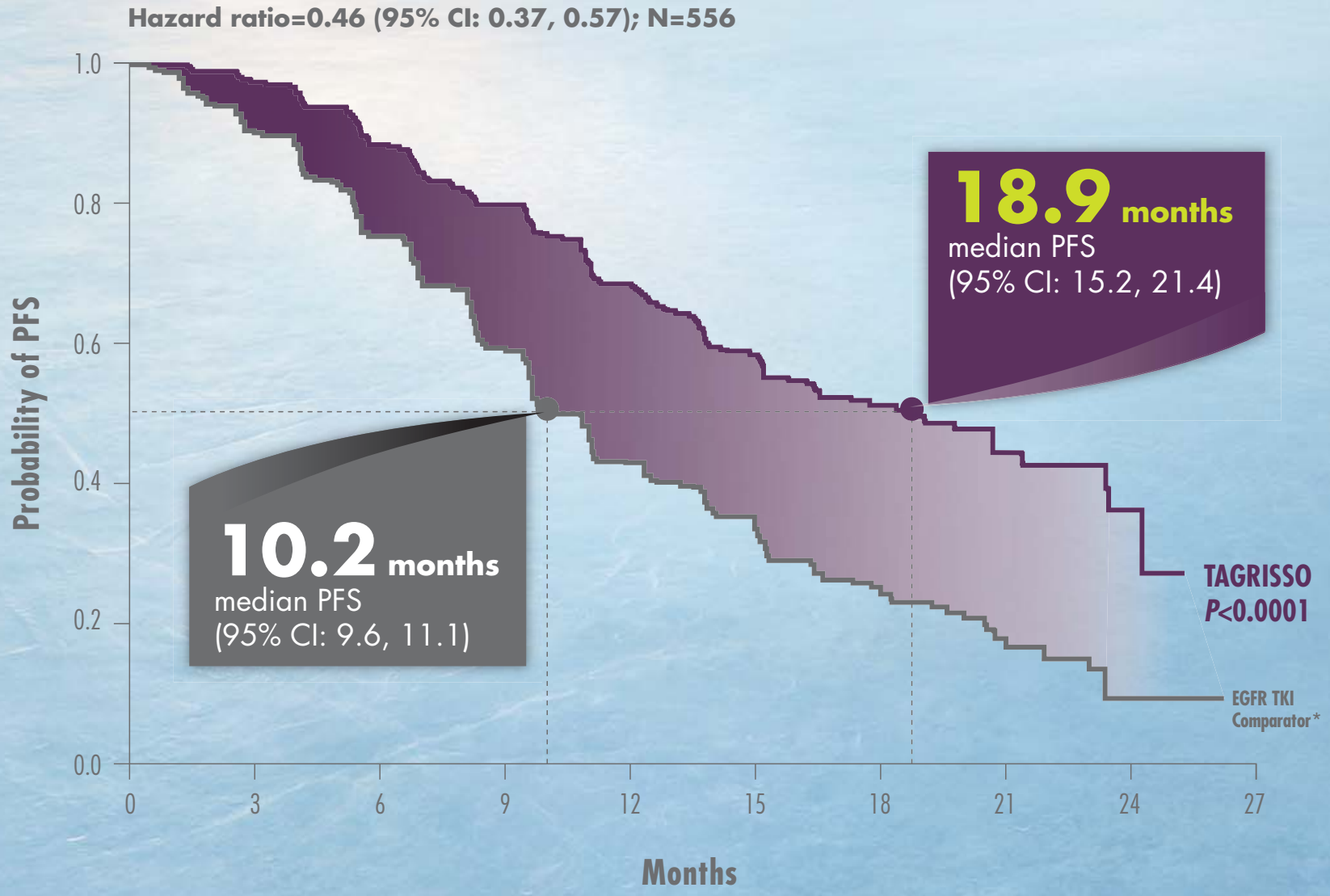
NEW INDICATION FOR THE TREATMENT OF METASTATIC EGFRm NSCLC

FIRST-LINE TAGRISSO® GROUNDBREAKING EFFICACY

First-line TAGRISSO cut the risk of progression or death by 54% vs EGFR TKI comparator (erlotinib/gefitinib)[1]



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

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

AstraZeneca

A NEW STANDARD OF CARE

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, 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 v.1.1). Secondary endpoints included ORR, DOR, OS, and safety.[1,3]

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
- 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.4.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed April 26, 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

Please see Brief Summary of Prescribing Information on adjacent pages.

TAGRISSO®
osimertinib

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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IMMUNOTHERAPY

KEYNOTE-042: No Hard and Fast Rules for First-Line Pembrolizumab Regarding PD-L1–Positive Disease

By Kara Nyberg, PhD

The KEYNOTE-042 trial demonstrated that single-agent pembrolizumab significantly improved overall survival compared with platinum-based chemotherapy in the first-line setting for patients with advanced NSCLC.

The pace of research focused on new therapies for advanced NSCLC has progressed from a trot to a sprint in recent years. Among immunotherapy options, pembrolizumab emerged as an early frontrunner, along with nivolumab and atezolizumab, in the second-line treatment setting. Pembrolizumab now appears to be surging ahead of other checkpoint inhibitors in the first-line setting based on the collective findings of multiple large phase III KEYNOTE trials.

The latest of these trials reported at the American Society of Clinical Oncology (ASCO) Annual Meeting this past June—KEYNOTE-042—demonstrated that single-agent pembrolizumab significantly improved overall survival (OS) compared with platinum-based chemotherapy in the first-line setting for patients with advanced NSCLC, even those with PD-L1 expression levels as low as 1%.[1] How the KEYNOTE-042 findings will translate to clinical practice and whether this heralds the end of frontline chemotherapy for patients with PD-L1–positive disease has yet to be fully determined.

The Past: The KEYNOTE Legacy

KEYNOTE-10 first established the value of pembrolizumab in NSCLC by showing that the PD-1 inhibitor significantly improved OS compared with docetaxel following prior platinum-based chemotherapy, earning it a place as a standard second-line treatment option.[2,3]

Then came the first-line studies. In KEYNOTE-024, which only allowed patients with PD-L1 expression of 50% or greater (roughly 30% to 35% of all patients with wild-type NSCLC), pembrolizumab monotherapy outperformed platinum-based chemotherapy in the first-line setting for both OS and progression-free survival (PFS).[4] Shortly thereafter, pembrolizumab became the first immunotherapy drug approved for the first-line treatment of patients with metastatic NSCLC with high PD-L1

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Placebo-treated patients could cross over to receive pembrolizumab monotherapy upon disease progression.

During a Clinical Science Symposium, KEYNOTE-407 investigator Luis G. Paz-Ares, MD, PhD, reported the results of the second interim analysis, which reflected sufficient events to gauge both overall survival (OS) and progression-free survival (PFS), the co-primary endpoints of the trial. The data showed that combining pembrolizumab with conventional chemotherapy in the first-line setting significantly prolonged median OS to 15.9 months compared with 11.3 months with chemotherapy alone (hazard ratio [HR] 0.64, 95% CI [0.49, 0.85]; p = 0.0008). Moreover, the OS benefit observed with the pembrolizumab-chemotherapy regimen persisted across all relevant patient subgroups, including those with tumor PD-L1 expression categorized as low (<1%; HR 0.61, 95% CI [0.38, 0.98]), intermediate (1%-49%; HR 0.57, 95% CI [0.36, 0.90]), and high (≥50%; HR 0.64, 95% CI [0.37, 1.10]).

The pembrolizumab-chemotherapy combination also proved superior to chemotherapy alone with regard to median PFS (6.4 vs. 4.8 months; HR 0.56, 95% CI [0.45, 0.70]; p < 0.0001), objective response rate (58.4% vs. 35.0% at the first interim analysis; p = 0.0004), and the median duration of response (7.7 vs 4.8 months).

Adverse events occurred at similar frequencies in the pembrolizumab–chemotherapy and chemotherapy-alone arms. However, immune-mediated adverse events and infusion reactions occurred more often with the addition of pembrolizumab to chemotherapy, as compared to without, both overall (28.8% vs. 8.6%) and for grades 3 to 5 adverse events (10.8% vs. 3.2%). The most common immune-mediated adverse events associated with the pembrolizumab arm included hypothyroidism (7.9%), hyperthyroidism (7.2%), and pneumonitis (6.5%).

"These data suggest pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel should become a new standard of care for the first-line treatment of metastatic squamous NSCLC across all levels of PD-L1 expression," concluded Dr. Paz-Ares.

Charles G. Drake, MD, PhD, who critiqued the KEYNOTE-407 results following Dr. Paz-Ares' presentation, agreed. "This trial is clearly a win," he said.

The KEYNOTE-407 results complement those of the momentous KEYNOTE-189 trial,[3] which demonstrated that adding pembrolizumab to first-line chemotherapy significantly improved median OS regardless of PD-L1 tumor expression in patients with metastatic nonsquamous NSCLC.

IMpower131: Atezolizumab with Chemotherapy Still Under Study

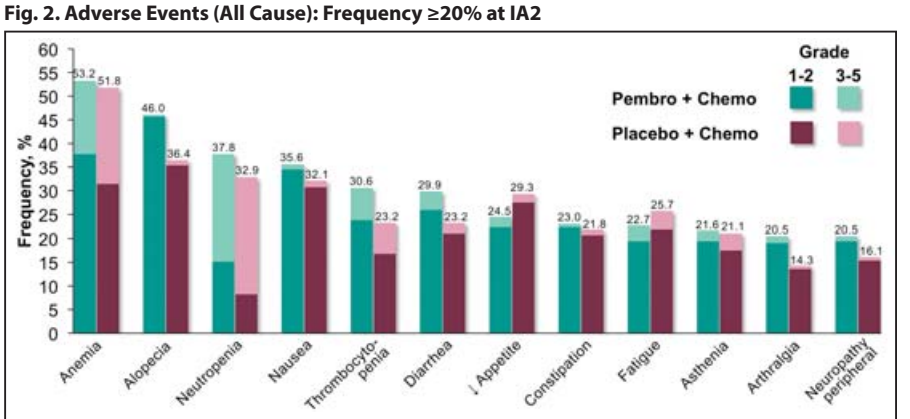
Whether atezolizumab and chemotherapy might represent another new frontline standard of care for patients with metastatic squamous NSCLC remains to be determined. Robert M. Jotte, MD, PhD, presented interim findings of the randomized phase III IMpower131 trial, in which 1,021 patients were randomly assigned to treatment with atezolizumab plus carboplatin/paclitaxel, atezolizumab plus carboplatin/nab-paclitaxel, or carboplatin/nab-paclitaxel (the control arm).[2] Patients received 4 or 6 cycles of chemotherapy with or without atezolizumab, followed thereafter by atezolizumab maintenance therapy or best supportive care.

Median PFS, one of the two co-primary endpoints, reached 6.3 months with atezolizumab plus carboplatin/nab-paclitaxel compared with 5.6 months for carboplatin/nab-paclitaxel alone (HR 0.71, 95% CI [0.60, 0.85]; p = 0.0001). The PFS rate at 1 year, which reflects additional separation of the Kaplan-Meier curves beyond the median values, was 24.7% for atezolizumab plus carboplatin/nab-paclitaxel and 12.0% for carboplatin/nab-paclitaxel alone. Among PD-L1–expressing subgroups, the PFS difference between these two respective regimens was greatest in the subgroup of patients with the highest level of PD-L1 expression (median PFS: 10.1 vs. 5.5 months; HR 0.44, 95% CI [0.27, 0.71]).

However, an initial look at median OS, the other co-primary endpoint, failed to show a difference in outcome between the control arm and the combination of atezolizumab and carboplatin/nab-paclitaxel in the intent-to-treat population (14.0 vs. 13.9 months). In the PD-L1 subgroups, median OS trended favorably for the atezolizumab-containing arm in the high PD-L1–expressing subgroup (23.6 vs. 14.1 months; HR 0.56, 95% CI [0.32, 0.99]) but—unexpectedly—unfavorably in the low PD-L1–expressing subgroup (12.4 vs. 16.6 months; HR 1.34, 95% CI [0.95, 1.90]).

"A new combination therapy needs to show an OS benefit before it's adopted as a standard of care," commented Tom Stinchcombe, MD, who discussed the IMpower131 findings. Longer follow-up is needed to see if an OS difference emerges over time that might favor the atezolizumab-containing combination. ✦

Fig. 2. Adverse Events (All Cause): Frequency ≥20% at IA2



Data cutoff date: Apr 3, 2018. Courtesy of Dr. Luis Paz-Ares

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Circulating Tumor Cell–Derived Patient eXplants: A New Tool for SCLC Research

By Caroline Dive, CBE, PhD, FMedSci, and Kris Frese, PhD

Small cell lung cancer (SCLC) is aggressive, disseminates early, and has a dismal prognosis.[1] Its genomic landscape which reveals little in the way of obvious druggable targets, presents a significant challenge. One obstacle to a more comprehensive understanding of the biology and behavior of this recalcitrant tumor has been the difficulty in routinely obtaining tumor biopsies of sufficient quantity and quality for productive research. Biopsies obtained at diagnosis are unlikely to represent the disease following relapse, which often occurs within only a few months after treatment with platinum-based doublet chemotherapy. As new therapeutics for SCLC will most likely be studied after debulking with first-line chemotherapy in a trial setting, it is the tumor biology with acquired chemotherapy resistance that we must better understand and target.

Several research groups, including that of the authors of this article, have demonstrated that in SCLC, the prevalence of circulating tumor cells (CTCs), detected using the EpCAM capture–based CellSearch platform, is high relative to other tumor types.[2,3] It was subsequently shown that, following CTC enrichment from a simple 10 mL peripheral blood draw, CTC-derived tumors could be generated when implanted subcutaneously in the flanks of immune-compromised mice.[4] These CTC-derived explant (CDX) tumors exhibited typical SCLC morphologic and histochemical properties, and their genomes correlated with those of the donor patient's CTCs. CDXs are highly proliferative and faithfully reflect the donor patient's depth and duration of response to platinum–etoposide double chemotherapy. The CDX approach has an advantage in that it can be implemented at the pre-treatment baseline and can be repeated when disease progresses after chemotherapy, which is when a tumor biopsy to generate a patient-derived xenograft is much more difficult to obtain.

Dr. Caroline Dive

Dr. Kris Frese

Benefits and Applications

CDXs are now being derived in multiple research laboratories worldwide. The value of CDX tumors for SCLC research has been exemplified.[5,6] There is now, to our knowledge, an extensive panel of over 60 SCLC CDX models in existence, encompassing baseline CDX from patients with disease that goes on to be chemosensitive or chemorefractory (progressing within 90 days of chemotherapy administration) and from patients with limited and extensive disease. Demonstrating the utility of CDX to investigate targeted therapies, baseline and progression CDX models have been used to examine the combination of the PARP inhibitor olaparib with the Wee1 inhibitor AZD1775. Although a range of responses were seen to this drug combination in 10 CDX models in vivo and/or in short-term cultures made from disaggregated CDX tumors, this combination demonstrated superior efficacy to chemotherapy for the majority of samples.[7] The olaparib/Wee1 combination cured multiple mice bearing one patient's CDX, and this "super-responder" model is providing insights for predictive biomarker discovery. Notably, a durable response seen at baseline was absent in the paired serial model made at progression, suggesting that, for this combination, durable benefit would be more likely in a clinical trial designed to facilitate early administration.

Using the CTC iChip technology,[8] Drapkin et al.[5] derived 17 CDX models, including paired pre- and post-treatment models from a patient recruited to a clinical trial. Importantly, this study showed

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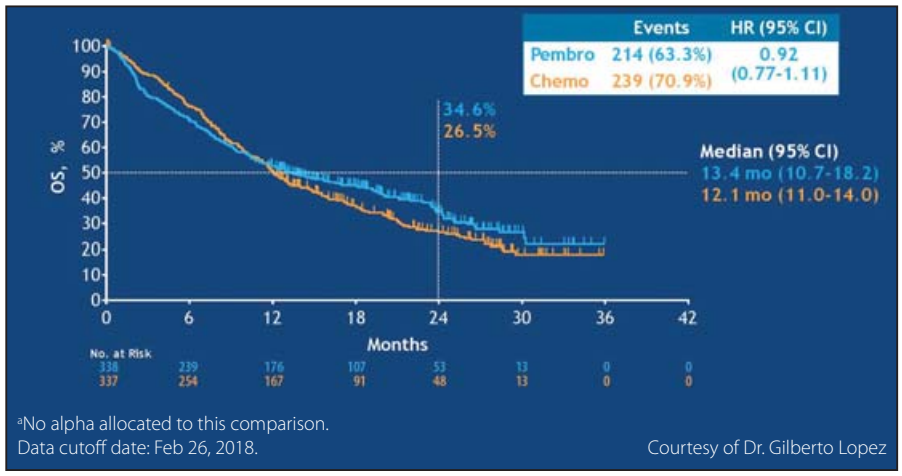
expression.[3] More recently, the KEYNOTE-189 and KEYNOTE-407 trials performed in patients with nonsquamous NSCLC and squamous NSCLC, respectively, showed that combining pembrolizumab with standard first-line platinum-containing chemotherapy improved OS and PFS compared with chemotherapy alone irrespective of PD-L1 tumor expression.[5,6] These results bolster earlier findings of the phase II KEYNOTE-021 study, which garnered pembrolizumab accelerated approval for use in combination with pemetrexed and carboplatin for the treatment of patients with previously untreated metastatic nonsquamous NSCLC.[7]

In light of this work, the next logical step was to see if survival could be extended and the toxicity of chemotherapy averted by leveraging pembrolizumab alone in patients with lower levels of PD-L1 expression (1% to 49%). Hence the rationale for the KEYNOTE-042 trial.

Fig. 1. Overall Survival: TPS ≥1-49% (Exporatory Analysis[a])



[a]No alpha allocated to this comparison.
Data cutoff date: Feb 26, 2018.
Courtesy of Dr. Gilberto Lopez

The Present: KEYNOTE-042

Lead investigator Gilberto Lopes, MD, MBA, of the University of Miami Sylvester Comprehensive Cancer Center, presented the KEYNOTE-042 findings at the ASCO Annual Meeting during the main plenary session. This randomized, open-label, phase III trial included patients with locally advanced or metastatic NSCLC of squamous or nonsquamous histology with PD-L1–positive expression but without sensitizing *EGFR* mutations or *ALK* alterations.

Like other pembrolizumab trials that came before it, PD-L1 tumor expression was assessed using the 22C3 immunohistochemistry assay. The investigators employed the tumor proportion score (TPS) for patient stratification and analysis. A PD-L1 score of ≥ 1% was mandatory for entry into the trial.

Researchers stratified the 1,274 patients included in KEYNOTE-042 by region (East Asia vs. other regions), ECOG performance status (0 vs. 1), histology (nonsquamous vs. squamous), and PD-L1 TPS (1% to 49% vs. ≥ 50%). Patients were randomly assigned to pembrolizumab or chemotherapy, consisting of up to six cycles of paclitaxel and carboplatin or pemetrexed and carboplatin with optional pemetrexed maintenance (nonsquamous histology only) at the investigator's discretion. OS comprised the primary endpoint of interest, which

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EVOLVING STANDARDS OF CARE

Updated Results from the Phase III ALEX Trial: Embracing Hazard Ratios

By D. Ross Camidge, MD, and Mary W. Redman, PhD

Dr. D. Ross Camidge

Updates of the primary analysis of the phase III ALEX trial were presented at the American Society of Clinical Oncology Annual Meeting this year.[1,2] ALEX was a first-line trial of crizotinib versus alectinib in advanced *ALK*-positive NSCLC, and the primary endpoint was investigator-assessed progression-free survival (PFS). After longer follow up, the PFS hazard ratio (HR) dropped from 0.47 to 0.43, with a median PFS of 10.9 months for crizotinib (previously 11.1 months) and 34.8 months (95% CI: 17.7-not evaluable; not calculable previously) for alectinib. Independent radiology review committee (IRC) PFS analyses were restricted to the primary analysis time-point, and in 2017 also demonstrated a statistically significant benefit (HR 0.5; medians 10.4 and 25.7 months, respectively). To some extent, this update is a victory lap for alectinib—its role as the first drug to be preferred over crizotinib in this population has been cemented. However, it also raises several interesting issues.

Investigator-Assessed Endpoints vs. IRC, Medians vs. Hazard Ratios

When a lesion is on the cusp of progression, an investigator's measurements could reflect some clinical bias, and such datasets are usually associated with longer PFS and higher response rates than an IRC's as in ALEX. However, investigator-assessed endpoints may also be viewed as data more reflective of treatment decisions in the real world. From a practical standpoint, the major reason whether quoting an investigator-assessed versus IRC-assessed datapoint matters is that when the inevitable cross-trial comparisons for other drugs—such as brigatinib, ensartinib, and lorlatinib, which are all completing "ALEX-like" studies—occurs, we must compare like with like.

Beyond the effects of investigator versus IRC adjudication, the major jump in the median PFS from the IRC-predicted value in 2017 to the investigator-assessed median in 2018 also reflects how medians are most informative when the chances of an event occurs uniformly over time. When a flattening of the Kaplan-Meier curves is observed because a proportion of patients become "long-term survivors," then the chance of an event is not uniform. If the flattening of the curves occurs around the estimate of the media (as in the alectinib arm of ALEX), more than a single time point can be associated with time points where 50% of patients have/have not experienced the event, and the confidence intervals around the median will be larger. As data mature resulting in more observed event times (less censoring), the point estimate of the median can shift tremendously in the horizontal direction even though the overall magnitude of benefit has changed relatively little. Consistent with this, although the change in the estimated alectinib arm median PFS from the IRC in 2017 to the investigator-assessed update in 2018 seems large, the median for the crizotinib arm, which has a more uniformly distributed PFS curve over time, did not differ that much either between investigator and IRC assessments or between the 2017 and 2018 analyses. Similarly, when next-generation ALK inhibitor drugs are examined in the pure second-line post-crizotinib setting, the median PFS estimates are incredibly robust for the same drug across trials because the durations of control are shorter and the PFS curve is steeper and more uniform over time. For example, the median PFS was 7.1, 8.1, and 8.9 months in three separate trials of alectinib in the post-crizotinib setting.[3-5]

Although the median is a convenient number to remember—as we start to see PFS curves that are more reminiscent of advanced breast cancer trials than the advanced NSCLC trials of only a few years ago—in reality, the hazard ratio is a better true estimate of benefit in first-line randomized trials and will likely become the number we embrace.

A Glimpse of Overall Survival Benefit?

The ALEX update consolidates the idea that the benefit seen in the first-line alectinib arm remains far superior to what might be expected from the thought experiment of adding the median PFS of first-line crizotinib to the median PFS of alectinib administered post-crizotinib. Why this is so remains hypothetical. Perhaps control of more subclones of disease at baseline, in the body and/or the brain, may lessen the development of biologic diversity over time and directly improve the natural history of the disease compared to chasing after resistance once it has manifested (when, with cells turning over, additional diversity will have been generated). If the administration order of drugs really does matter, such that one can't play catch up later, this suggests that the nonsignificant trend in ALEX toward improved overall survival with alectinib (HR 0.76; 95% CI [0.50, 1.15]) could turn out to be real. However, now that patients with advanced *ALK*-positive NSCLC are surviving for years, it will take a long time for these data to mature and for us to know for certain. ✦

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24. Dr. Bezjak will join Paul A. Bunn, Jr., MD, of University of Colorado School of Medicine, in co-moderating Monday's Plenary Session, "Patients First," starting at 8:15 AM (EDT).

The Plenary Session will open with a presentation by Lucy Kalanithi, MD, a Stanford physician whose husband, Paul Kalanithi, MD, died after a diagnosis with stage IV lung cancer. Dr. Paul Kalanithi authored the memoir *When Breath Becomes Air*, detailing his experience.

The session will also include presentations from many leaders in the field including David Carbone, MD, PhD, of The Ohio State University Comprehensive Cancer Center, Tony S. Mok, MD, FRCP, of the Chinese University of Hong Kong, and Solange Peters, MD, PhD, of the University of Lausanne, as well as from the IASLC President Giorgio Vittorio Scagliotti, MD, PhD, who will discuss current science and clinical trials that are critical to finding a cure for patients with lung cancer.

Tuesday's Presidential Symposium begins at 8:15 AM (EDT) and will include the presentation of the conference's top four abstracts.

Dr. Solange Peters speaking about global immunotherapy research at the 2017 WCLC.

"This symposium will include data from some of the top trials and will include results that will be practice changing," Dr. Leighl said.

Drs. Leighl and Bezjak also highlighted the importance of Wednesday's two Plenary Sessions. The first Plenary Session will begin at 8:15 AM (EDT) and will include speakers who will call members to action and discuss some of the challenges ahead in the field of lung cancer research and treatment.

The second Plenary begins at 3:15 PM (EDT) and will include an international and multidisciplinary panel of speakers who will summarize key messages from the conference.

"We will hear from the world experts on what they feel were the most important things that they heard about at the conference and their opinions of what the future holds," Dr. Leighl said.

Join and Attend

It is an exciting time to be a part of lung cancer research, according to Dr. Leighl. There has never been so much progress and collaboration, she said.

"The IASLC is a great organization, and it brings people together who are passionate about the treatment and science of lung cancer around the world," Dr. Leighl said.

Members of IASLC get a discount on attending the WCLC, an experience that is unmatched for people working toward the eradication of lung cancer.

"WCLC is an exciting chance for people who are passionate about lung cancer research to come together and collaborate," Dr. Leighl said. ✦

CDX for SCLC Research from page 7

that matched patient-derived xenografts and CDXs derived from solid and liquid biopsies at baseline were faithful to the patients' tumors in terms of shared mutations, supporting the low degree of clonal heterogeneity previously reported for SCLC.[9] This study also showed that, in the patient for whom serial CDXs were generated, these serial models accurately recapitulated the evolving drug sensitivities of the donor patient's disease to combination treatment with olaparib and temozolomide.[5]

CDX tumors can also be disaggregated, allowing short-term cultures to be derived.[7] Gene expression profiling of these cultures reveals relatively few changes in protein-coding genes, many of which are reversed when cells are re-implanted in mice. Furthermore, these tumors grow with similar kinetics to those that have never been exposed to plastic, indicating that brief culturing under permissive conditions does not select for more aggressive clones. These short-term cultures can be subjected to genetic manipulation via lentiviral infection and facilitate chemical and genetic screens, as well as mechanism-based hypothesis exploration. CDX cultures can also be modified to reporters that facilitate assessment of in vivo disease burden and metastatic dissemination.

CDX can now be added to the research toolkit, augmenting established cell lines, patient-derived xenografts, and genetically engineered mouse models to support exploration of SCLC biology (including, for example, mechanisms of vasculogenic mimicry[10]) to test novel treatments, identify mechanisms of chemoresistance, and develop predictive and pharmacodynamic biomarkers that can be translated for clinical implementation as CTC-based assays.[11] With a range of new candidate treatments entering SCLC clinical trials, CDXs derived from patients on clinical trials will facilitate studies to understand responses and resistance complemented by CTC-based biomarkers. This recalcitrant tumor has defeated all attempts to improve patient outcomes. It is our hope that the CDX approach, by allowing a more routine examination of the biology of SCLC throughout its disease course, will lead to new insights and next steps toward the collective overall goal of finding ways to extend patient survival. ✦

About the Authors: Prof. Dive is the deputy director of and a senior group leader at the Cancer Research UK Manchester Institute and professor of pharmacology at The University of Manchester. Dr. Frese is a clinical and experimental pharmacology preclinical team lead at the Cancer Research UK Manchester Institute.

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

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was tested sequentially for those with a PD-L1 TPS of ≥ 50%, ≥ 20%, and ≥ 1%—the latter representing the entire study population.

Patient baseline characteristics were well balanced across the two treatment arms. In both groups, participants had a median age of 63 years, 71% were men, 29% were enrolled in East Asia, 39% had squamous histology, 47% had a PD-L1 TPS of ≥ 50%, and 78% were current or former smokers.

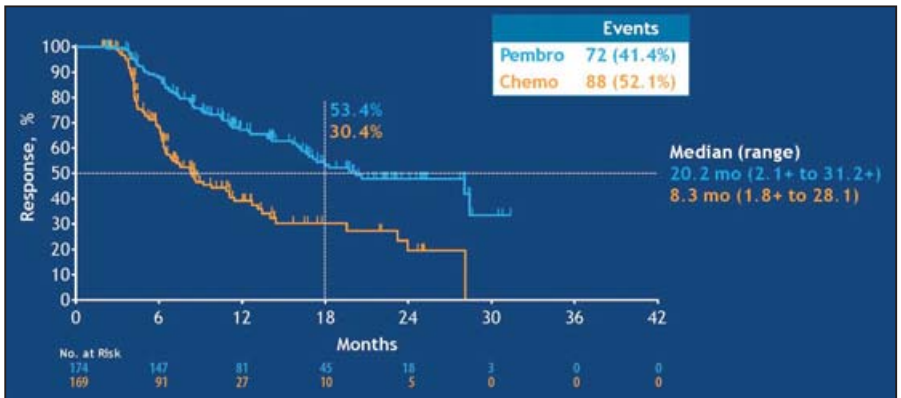
Pembrolizumab monotherapy excelled over chemotherapy across all TPS subgroups, with greater benefits seen with higher PD-L1 expression. Among patients with PD-L1 TPS of ≥ 50%, median OS reached 20 months with pembrolizumab versus 12.2 months with chemotherapy (hazard ratio [HR] 0.69, 95% CI [0.56, 0.85]; p = 0.0003). In the PD-L1 TPS ≥ 20% subgroup, median OS was 17.7 months with pembrolizumab vs. 13.0 months with chemotherapy (HR 0.77, 95% CI [0.64, 0.92]; p = 0.0020). Finally, among patients with PD-L1 TPS of ≥ 1%, comprising the entire study population, median OS reached 16.7 months with pembrolizumab versus 12.1 months with chemotherapy (HR 0.81, 95% CI [0.71, 0.93]; p = 0.0018).

PFS, the secondary endpoint of the trial, was not met. Although pembrolizumab improved median PFS in comparison with chemotherapy in patients with PD-L1 TPS of ≥ 50% (7.1 vs. 6.4 months; HR 0.81, 95% CI [0.67, 0.99]), the p value of 0.0170 did not meet the protocol-specified significance boundary. No significant PFS differences were observed between arms for patients with PD-L1 TPS of ≥ 20% and the entire cohort with PD-L1 TPS of ≥ 1%.

Despite a longer duration of treatment exposure, grades 3 to 5 treatment-related adverse events occurred much less often with pembrolizumab than with chemotherapy (17.8% vs. 41.0%). However, as expected, grades 3 to 5 immune-related adverse events and infusion reactions occurred more frequently among patients treated with pembrolizumab versus chemotherapy (8.0% vs. 1.5%). The respective rates of treatment discontinuation (9.0% vs. 9.4%) and treatment-related deaths (2.0% vs. 2.3%) proved to be comparable between the arms.

"These data, therefore, confirm and extend the role of pembrolizumab monotherapy as a standard first-line treatment for patients with PD-L1-expressing tumors," Dr. Lopes concluded. "This better safety and activity profile of pembrolizumab suggests that it is an appropriate treatment for patients at any level of PD-L1 positivity."

Fig. 2. Duration of Response: TPS ≥1% (RECIST v1.1, BICR)



Median duration of response for pembro vs chemo: 20.2 months vs 10.8 months for TPS 50%, 20.2 months vs 8.3 months for TPS 20%, and 17.4 months vs 8.2 months for TPS 1-49%.
Abbreviation: BICR, blinded, independent central review.
Data cutoff date: Feb 26, 2018. Courtesy of Dr. Gilberto Lopez

The Future: Pembrolizumab for All?

Given the totality of the KEYNOTE findings, the key question emerging is not whether pembrolizumab should be used in treatment-naive patients with advanced PD-L1–positive disease that lacks driver mutations—that seems to be a given at this point. Rather, the critical question is whether pembrolizumab should be used alone or in combination with chemotherapy.

"Is PD-L1 monotherapy really the answer for everyone with PD-L1 of 1% or higher?" posed Leena Gandhi, MD, PhD, of the New York University Perlmutter Cancer Center, who critiqued the KEYNOTE-042 findings following Dr. Lopes' presentation of the results.

In answer to this question, Dr. Gandhi referred to an exploratory analysis that Dr. Lopes showed during his KEYNOTE-042 presentation in which little survival advantage emerged with pembrolizumab versus chemotherapy in patients with a TPS of 1% to 49% (median OS: 13.4 vs. 12.1 months; HR 0.92, 95% CI [0.77, 1.11]). She argued that the OS benefit associated with pembrolizumab in KEYNOTE-042 is driven by the high PD-L1 subgroup (TPS ≥ 50%); the benefits are not as clear-cut for those with PD-L1 TPS of 1% to 49%.

Because of this, Dr. Gandhi still foresees an important role for frontline chemotherapy in selected patients with PD-L1–positive disease. "Patients with low or no PD-L1 expression likely should get some type of combination therapy," she said. Dr. Gandhi drew on data from KEYNOTE-189 and KEYNOTE-407 and emphasized that these two frontline trials documented clear, consistent improvements in OS, PFS, and response rates with first-line pembrolizumab and platinum-containing chemotherapy over chemotherapy alone in all patients, regardless of PD-L1 expression, which cannot be said for KEYNOTE-042.

All told, consensus seems to be emerging that in the absence of driver mutations, patients with PD-L1 expression of ≥ 50% should receive first-line pembrolizumab monotherapy, whereas those with lower expression levels would do best with a pembrolizumab-chemotherapy combination. However, these are not hard-and-fast rules. Patient-specific factors, such as high tumor burden or poor performance status, may prompt the decision to add or eliminate chemotherapy, as necessary, to optimize outcomes for each individual patient. ✦

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INDUSTRY AND REGULATORY NEWS

IMpower130: Atezolizumab Shows OS, PFS Benefit

According to results of the phase III IMpower130 study (NCT02367781), the addition of atezolizumab to carboplatin and nab-paclitaxel in the first-line setting for patients with advanced nonsquamous NSCLC was found to increase overall and progression-free survival rates compared with chemotherapy alone.

IMpower130 is multicenter, open-label, randomized study in which 724 patients were randomized (2:1) to receive either atezolizumab plus carboplatin and nab-paclitaxel (Arm A) or carboplatin and nab-paclitaxel alone (Arm B, control). The co-primary endpoints were overall survival (OS) and progression-free survival (PFS) in the intent-to-treat wild-type population. No new safety signals were reported at the data cutoff. Formal results will be presented at an upcoming meeting.

In addition, the U.S. Food and Drug Administration (FDA) recently 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 based on both a PFS and OS benefit seen in IMpower 150, in comparison to standard chemotherapy and bevacizumab. The FDA is expected to make a final decision regarding approval in early September 2018. *(Read the AACR recap on lungcancernews.org for details on IMpower150.)* ✦

EDITOR'S NOTE

Although the OS data are striking, there is no apparent benefit for those patients with PD-L1 TPS of < 50%. In this sense, KEYNOTE-042 confirms KEYNOTE-024, but it does not really alter the therapeutic landscape, although the results are likely to garner pembrolizumab expanded approval to patients with any degree of PD-L1 expression.

–Corey J. Langer, MD, Editor

GLOBAL INITIATIVES

Austria's Reversal of Smoking Ban in World Spotlight

Tobacco harms the health, the treasury, and the collective spirit of Austria. In May 2018, a smoking ban was scheduled to begin in all bars and restaurants in Austria; however, the ban was recently overturned by lawmakers from a new ruling coalition in the government, the People's Party and the Freedom Party.

In its discussions regarding the ban, the far-right Freedom Party argued that it was an example of too much interference from the government and that it restricted the people's freedom of choice. During the election campaign, party leader Heinz-Christian Strache, an avid smoker, promised a reversal of the ban.[1] After the election, Strache made this a non-negotiable condition for entering a coalition government with the conservative People's Party. People's Party leader Chancellor Kurz, a nonsmoker who supported tobacco control prior to the election, accepted this demand to form a functioning government.

The move has horrified Austria's medical establishment. Manfred Neuberger, MD, professor emeritus of environmental health at the Medical University of Vienna, told *BBC News* that it is "a public health disaster."[2]

"The decision is irresponsible," he said in the *BBC* interview. It was a victory for the tobacco industry. The new government made Austria into the ashtray of Europe."

Since then, and in just 3 weeks, half a million Austrians have signed a petition to ban smoking in bars and restaurants. If the petition acquires at least 900,000 signatures, the coalition has agreed to call a referendum on the topic, but not before 2022.[2]

In 2005, Austria became a party of the WHO Framework Convention on Tobacco Control (WHO FCTC), a legally binding public health treaty that contains provisions to reduce the health economic burden caused by tobacco use. According to Article 8 of the WHO FCTC, all treaty parties will provide protection from exposure to tobacco smoke. Guidelines regarding implementation of Article 8 came into existence in 2007; these guidelines established that each WHO FCTC member should provide universal tobacco exposure protection within 5 years of entry into the treaty. In a written statement from the WHO FCTC Convention Secretariat Vera Luiza da Costa e Silva regarding the reversal of the ban, it was noted that the guidelines reaffirm "that there is no safe level of exposure to tobacco smoke and that approaches other than 100% smoke free environments, including ventilation, air

filtration, and the use of designated smoking areas (whether with separate ventilation systems or not), have repeatedly been shown to be ineffective; and there is conclusive evidence, scientific and otherwise, that engineering approaches do not protect against exposure to tobacco smoke."

Austria's Smoking Habit

As of 2014, rates for adults (aged 15 or older) who smoked daily were comparable with rates in 1997 (24%) and increased slightly since 2006 (23%). These rates can be contrasted with the marked decline seen in 93% of Organisation for Economic Cooperation and Development countries during the same time period; on average, smoking rates decreased from 26% in 2000 to 19% in 2014.[3]

Outside of Austria, nearly all countries in Western and Northern Europe have complete smoking bans in the hospitality industry, according to Dr. Neuberger. In addition, a representative survey recently showed that 70% of the population of Austria is in favor of the ban,[4] which would protect employees and customers from the effects of second-hand smoke.

According to Dr. Neuberger, this type of ban would also make "it more difficult for the tobacco industry to seduce young people to start smoking."

"It is a shame that the government listened to lobbyists and merchants of 'Big Tobacco' and not to medical science," he told the *IASLC Lung Cancer News*.

In June 2018, lawsuits were filed at Austria's institutional court by innkeepers, waiters, and the government of Vienna against the cancellation of the smoke-free hospitality industry. The Ministry of Health then drafted an ordinance that limits exposure in smoking sections for underage trainees to no more than 1 hour per day. Guidance for enforcement of this ordinance was not provided, however.

Medical Societies as Catalysts for Change

The IASLC is dedicated to improving the health of patients and the community through effective tobacco control. Vienna was host city to the IASLC World Conference on Lung Cancer (WCLC) in 2016 and is scheduled to host it again in 2022. In 2016, despite the conference venue being smoke free for WCLC, restaurants and hotels were subject to individual management policies.

Controversy exists over the role of the IASLC or other cancer organizations as to how to address conference venues in the context of local tobacco control laws. Whereas some advocate that the IASLC should intervene to guarantee smoke-free hospitality in venues in 2022, others advocate that the IASLC should continue to support development of smoke-free laws, particularly in countries faced with strong opposition from the tobacco industry. Robert Pirker, MD, program director for lung cancer at Medical University of Vienna, Austria, said that Austrians need support from the organizations such as the IASLC now more than ever.

"The decision to reverse the planned ban of smoking in restaurants resulted in a huge outcry by doctors, medical societies, political parties, and even more so by the general public," Dr. Pirker indicated. "The public pressure on politicians to enforce stricter tobacco control, including a full ban of smoking in restaurants, is ever increasing."

The IASLC provides a rigorous evidence-based resource for clinicians and politicians to understand risks associated with lung cancer and the most effective methods for cancer treatment. Tobacco control is fundamental to the mission of the organization.

Dr. Pirker also said that doctors must "continue informing the public about the benefits of stricter tobacco control and to work with the public to achieve these goals, even in the absence of legal requirements."

In Dr. Pirker's opinion, complacency in the face of tobacco epidemic insulates the tobacco industry in Austria, resulting in more tobacco-related deaths each year. This is an area in which large international medical societies can potentially create change through increased efforts; Austria can still do more to make tobacco control and smoking cessation work for their citizens' wellbeing.

The IASLC Tobacco Control and Smoking Cessation Committee has discussed this issue at length and acknowledges complexity in how best to respond. One option is to not hold large conferences, such as the WCLC, in cities with poor tobacco control—a potentially significant financial loss for the local government. However, presence of the conference, with high-profile tobacco-control sessions and prominent messages at key points during the meeting—the Opening Plenary at WCLC in 2016, for example, featured Dr. Tabaré Vázquez, who spoke about the success of tobacco control in Uruguay—could jumpstart a campaign for better tobacco control and thereby better serve the local tobacco-control community, healthcare workers, and patients. There is no clear answer, but the Committee and the IASLC as a whole remain committed to the very best in prevention, diagnosis, and treatment of lung cancer and, therefore, to the most vigorous, critical, and effective tobacco control measures possible. ✦

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EVOLVING STANDARDS OF CARE

Global Insights on New Clinical Practice Guideline for the Management of Malignant Pleural Mesothelioma

By Hedy L. Kindler, MD


Dr. Hedy L. Kindler

The American Society of Clinical Oncology (ASCO) has issued its first-ever clinical practice guidelines on the management of patients with malignant pleural mesothelioma (MPM), based on a systematic review of the medical literature.[1] This comprehensive guideline consists of 63 recommendations on the diagnosis, staging, chemotherapy treatment, surgical cytoreduction, and radiotherapy treatment of MPM.

The ASCO mesothelioma guidelines were developed by a multidisciplinary expert panel, co-chaired by myself and Raffit Hassan, MD, with experts in medical oncology, thoracic surgery, radiation oncology, pulmonary, pathology, imaging, and advocacy. The panel conducted a literature search that included systematic reviews, meta-analyses, and randomized controlled trials, as well as prospective and retrospective comparative observational studies published from 1990 through 2017. Some phase II studies were also included to address clinical questions for chemotherapy management. The 222 studies identified comprised the evidentiary basis for the guideline recommendations. These recommendations were crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BridgeWiz software.[2] Ratings for the type and strength of recommendation and evidence quality were provided with each recommendation.

Five overarching clinical questions relevant to the management of patients with MPM were addressed:

- What is the optimal approach to obtain an accurate diagnosis?
- What initial assessment is recommended before initiating therapy?
- What is the appropriate first- and second-line systemic treatment?
- What is the appropriate role of surgical cytoreduction?
- When should radiation be recommended?

Panel Recommendations and Insights

The panel emphasized that mesothelioma should always be reported as epithelial, sarcomatoid, or biphasic because these subtypes have a clear prognostic significancer. Thus, for patients in whom antineoplastic treatment is planned, a thoracoscopic biopsy is recommended to allow for histologic confirmation of diagnosis and to enable more accurate determination of the pathologic subtype. Cytologic evaluation of pleural fluid is not considered sufficiently sensitive. It was recommended that histologic examination be supplemented by immunohistochemistry using selected markers expected to be positive or negative in MPM, along with other markers that address the differential diagnosis.

The panel recommended a CT scan of the chest and upper abdomen with intravenous contrast for initial staging and a PET/CT for those being considered for surgery. The indications for additional staging procedures including dedicated abdominal imaging, mediastinoscopy, endobronchial ultrasound, contralateral thoracoscopy, and laparoscopy were reviewed. Identifying measurement sites on CT per modified RECIST for mesothelioma[3] was deemed the optimal approach to tumor measurement.

The guideline panel recommended that chemotherapy be offered to patients with MPM because it improves survival

continued on page 13

Perspective: Patient Care in Egypt

By C.A.I.R.O Journal Club Executive Board

The one thing we know for sure about MPM is that very little is known about this disease entity. This malignancy poses a major challenge to thoracic oncologists because of limited effective treatment options. The incidence of MPM in Egypt is one of the highest in the world, and the incidence rate is rapidly increasing.[1]

We believe that the general approach of the ASCO recommendations does not apply well to low-resource settings like Egypt. First, some practice settings in Egypt lack expert pathologists who can confidently establish a MPM diagnosis. In addition, some recommended systemic therapies are not reimbursed by public health insurance in Egypt. Moreover, the clinical and epidemiologic characteristics of patients with MPM in Egypt are a bit different from Western countries; thus, clinicians in Egypt must tailor these recommendations wisely for patients with MPM.

We believe that one of the priorities of MPM management in Egypt should include establishing a strong awareness program for both patients and general physicians, which might help with diagnosing MPM at an earlier stage and better performance status, thereby enabling patients to benefit more from complex multimodal treatment strategies. Moreover, designing nationwide clinical trials that focus on innovative approaches for early diagnosis and better treatment is essential for optimizing care of patients with MPM in Egypt.

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The C.A.I.R.O Journal Club Executive Board consists of the following members: Ahmed Magdy Rabea, MBBch, Msc, PhD (Cairo University); Amr Shafik (Ain Shams University); Basel Refky, MS, MRCS, MD (Mansoura University); Emad Shash, MBBCh, MSc, MD (Cairo University); Khaled Abdel Aziz (Ain Shams University); Loay Kassem, BSc, MSc, PhD (Cairo University); Noha Rashad (Maadi Armed Forces Complex); Omar Abdel-Rahman, MBBCh, MSc, MD (Ain Shams University).

Perspective: Patient Care in Europe

By Paul Baas, MD, PhD

The 2018 ASCO guidelines for MPM are the first guideline this year to give a clear overview of the latest developments in the field. Compared to the MPM guidelines published by the European Respiratory Society and the European Society of Thoracic Surgeons in 2010[1] and those published by the European Society for Medical Oncology in 2015,[2] there are some differences.

Regarding the diagnosis of MPM, the European guidelines underscore the need for a tissue biopsy, which is not a focus of the ASCO guideline. This is partly because of the requirements for reimbursement for asbestos victims, which vary by country. The ASCO guidelines correctly focus in depth on the genomic sequencing data, and they state that some mutations can be found in higher incidence in MPM (i.e., *BAP1*, *TP53*, *NF2*, and *SETD2*). The major differences in guidelines are related to the ASCO recommendation of the use of surgical resections, whereas the European guidelines recommend a stricter approach because of the lack of phase III data showing an OS benefit to surgery. It is not expected that the rate of surgical resections for MPM in Europe will be altered by the ASCO guidelines.

Considering all the new guidelines in this era of immuno-oncology, it is unfortunate that no randomized studies have yet been reported.

The guidelines from the British Thoracic Oncology Group and the European Respiratory Society will be published soon.

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About the Author: Dr. Baas is a professor of Thoracic Malignancies and chief of the department of Thoracic Oncology of the Netherlands Cancer Institute, Amsterdam.

Treatment of MPM from page 12

and quality of life. However, in asymptomatic patients with epithelial MPM and a low disease burden who are not surgical candidates, a trial of expectant observation may be an initial option. In the absence of a clinical trial, pemetrexed plus platinum-based chemotherapy is the recommended first-line treatment, and bevacizumab may be added if there are no contraindications. For those unable to tolerate cisplatin, carboplatin may be substituted. Retreatment with pemetrexed-based chemotherapy may be offered if durable disease control with first-line therapy is achieved. Pemetrexed maintenance was not recommended due to insufficient evidence to support its use. Given the very limited activity of second-line chemotherapy, participation in clinical trials was encouraged.

The surgical recommendations addressed selected patients with early-stage disease who should be considered for maximal surgical cytoreduction and those who should not (including patients with sarcomatoid histology). Lung-sparing surgery (such as extended pleurectomy/decortication) was deemed the first choice due to decreased operative and long-term risk, whereas extrapleural pneumonectomy could be offered to highly selected patients at centers of excellence. Because surgical cytoreduction is not expected to yield an R0 resection, multimodality therapy with pre- or postoperative chemotherapy and/or radiation was advised.

The panel recommended that prophylactic irradiation of intervention tracts should not generally be offered to prevent tract recurrences, unless resected tracts were histologically positive. Radiation therapy was considered effective for palliation of symptoms. Adjuvant radiation could be offered to patients who underwent maximal cytoreduction, as it might be associated with a decreased local recurrence risk; this complex treatment approach should be confined to experienced centers of excellence.

It is hoped that these ASCO recommendations and the accompanying comprehensive literature review will enable more optimal treatment of patients with this relatively uncommon malignancy. ✦

About the Author: Dr. Kindler is a professor of medicine in the Section of Hematology/Oncology, University of Chicago.

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Perspective: Patient Care in China

By Renhua Guo, MD

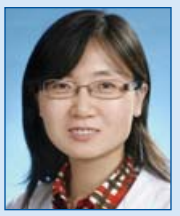
The ASCO guideline provides clinicians in China with detailed methods for diagnosis of MPM including thoracentesis, core needle biopsy, or thoracoscopic biopsy. These recommendations are both practical and affordable.

Regarding treatment, chemotherapy has been shown to improve patient survival and quality of life. The recommended first-line chemotherapy for patients with mesothelioma is pemetrexed plus platinum. Only vinorelbine is offered in the guidelines as second-line therapy, but is this the only option? Is maintenance therapy required for patients with a performance status of 0 to 2 and either partial response or stable disease? For a few of the patients with MPM whom I have treated, pemetrexed plus a platinum agent was used as first-line therapy followed by second-line chemotherapy with gemcitabine plus Endostar (a recombinant human endostatin). Patients with partial response and/or stable disease were offered maintenance treatment. One patient, who presented with advanced disease, has survived more than 9 years without recurrence.

The overall treatment response for patients with MPM remains poor. Whether the tumor genome has been sequenced, the related driver genes/mutations and the tumor mutation burden are poorly understood.

About the Author: Dr. Guo is deputy director of the Department of Oncology at the Hospital of Nanjing Medical University (Jiangsu Provincial People's Hospital).

By Dr. Jiuwei Cui



MPM is rare but highly aggressive malignancy associated with asbestos exposure. Its incidence has peaked in the United States and will continue to increase over the next few decades in Asia, due to ongoing asbestos exposure in many countries and a long latency period. Given the rarity of this malignancy, there are relatively few reports on treatment of patients with MPM in Asia. The recently released ASCO guidelines should provide updated evidence-based therapeutic options and provoke awareness among the public to improve the care quality of the patients with MPM in Asia, as well as in other countries in which MPM incidence is increasing.

The guideline will help clinicians in China to inform patients about appropriate treatment options and to protect them from potentially harmful or useless therapies on an individual basis. It also calls for more clinical trials to test new treatment technologies, as well as improved patient communication regarding participation in these trials. Future management of MPM will emphasize both locoregional and systemic control. Therefore, inclusion of patients in clinical trials evaluating multimodality treatment should be encouraged. In addition, multinational cooperation regarding translational research is essential to obtain meaningful answers regarding unsolved questions in a timely manner.

About the Author: Dr. Cui is chief, Cancer Center, the First Hospital of Jilin University.

INDUSTRY AND REGULATORY NEWS

On June 15, 2018, the China National Drug Administration (CNDA) approved **nivolumab** injection for the treatment of locally advanced or metastatic NSCLC after prior platinum-based chemotherapy for patients without *EGFR* or *ALK* tumor mutations. This is China's first and only PD-1 inhibitor. Approval was based on data from the phase III CheckMate-078 trial, in which 90% of the patients enrolled were Chinese. ✦

LUNG CANCER SCREENING

The IASLC Issues Liquid Biopsy Statement to Aid Understanding of Rapid Innovation

By Joy Curzio

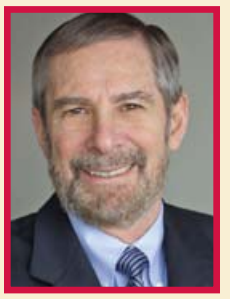
Liquid biopsy is a powerful tool that can determine a patient's molecular tumor profile and aid diagnosis, as well as therapeutic choices. Liquid biopsy can be applied as an alternative to tissue testing in cases where tumor testing is not possible or tissue is not adequate for multiple cancer types, including NSCLC. Because of the increasing relevance of this procedure for the optimization of NSCLC clinical management via the identification of predictive biomarkers, either prior to treatment or at progression, the IASLC has issued "The IASLC Statement Paper: Liquid Biopsy for Advanced Non-Small Cell Lung Cancer (NSCLC)," now available online in the *Journal of Thoracic Oncology*. The Statement Paper was authored by a multidisciplinary panel of thoracic oncology experts with interest and expertise in liquid biopsy and molecular pathology to evaluate available evidence with the aim of producing a set of recommendations to guide the use of liquid biopsy subsequent molecular analyses.

"It is important to gather experts to collect and interpret the vast amount of information available and to guide best practices ensuring that general oncologists and clinicians have access to the latest and best information in the emerg-

continued on page 15

NCI CORNER

The Budget Landscape with Dr. Douglas R. Lowy


Dr. Douglas R. Lowy

By Erik MacLaren, PhD

The National Cancer Institute (NCI) and researchers who rely on the funding it provides have spent much of the past year under the shadow of expected cuts in federal funding. President Trump's budget request last year proposed cutting the National Institutes of Health (NIH) budget overall by $7.7 billion to $26.9 billion, a reduction of 22%. After a 6-month delay, Congress passed a spending bill for 2018 that unexpectedly increased overall NIH spending by $3 billion, or 8.3%, to $37 billion, exceeding the initial funding proposals of both the U.S. House of Representatives and the Senate.

Although unexpected, the budget increase from Congress continues a trend of bipartisan support and 4 consecutive years of increasing appropriations for the NCI and NIH as a whole. Douglas R. Lowy, MD, the deputy director and former acting director of the NCI, explained the yearly funding process to the *IASLC Lung Cancer News*. "First, Congress decides how much to appropriate to the NIH via the regular appropriation," he said, including two main components: individual funding for special projects given to specific institutes and centers, and general funds, which are distributed based on the prior year's appropriation.

The 2018 spending bill will deliver an increase of $275 million for the NCI's "regular appropriation," bringing the total budget to $5.665 billion. In addition, the 21st Century Cures Act, passed in 2016, authorized $1.8 billion over 7 years to fund the Cancer Moonshot including $300 million to fully fund the Cancer Moonshot for 2018.[1] *(See the sidebar for more about the Cancer Moonshot.)*

In terms of allocating funding for specific diseases or research areas, such as lung cancer or immunotherapy, Dr. Lowy explained that the NCI does not predetermine spending, but instead relies primarily on the process of peer review to determine which specific proposals are funded based on factors such as scientific merit. "Advances in one cancer type often benefit other cancer types," he said. He also noted that "the NCI rapidly developed an extensive process for funding new awards related to the Cancer Moonshot, in line with the recommendations of the Blue Ribbon Panel," and these are posted to the NCI website.[2]

At the American Society of Clinical Oncology's annual meeting this past June, NCI Director Norman E. Sharpless, MD, discussed some of the ways the institute will use the budget increase.[3] Nearly half of the funding increase, $127 million, will go to the Research Project Grants (RPG) funding pool, which is the source of most investigator grants from individual R01s to program project grants like P01s. This is the biggest increase in the RPG pool since 2003, and Director Sharpless described the decision as the most direct way for the institute to support investigator-driven research. He also emphasized the importance of investigator-initiated discovery as opposed to a top-down approach. Additionally, the budget increase has allowed the NCI to set aside funding dedicated to early-career investigators and increase the number of R01s awarded to these investigators by at least 25%.

Other areas benefitting from extra funding include big data and the NCI's clinical trial networks. In order to create better tools to leverage large, complex datasets while protecting data privacy and security, the NCI is developing the Cancer Research Data Ecosystem, a project that received significant new targeted funding from the Cancer Moonshot. An additional $10 million will go to the National Clinical Trials Network and the National Community Oncology Research Program to increase per-patient reimbursements, offsetting higher costs to participating institutions.

This year, the White House's budget request for overall NIH funding is flat. Asked what researchers should expect in 2019, Deputy Director Lowy noted that the budget request is only the first step in a lengthy process. Congress recommended increases to NIH funding in 2018 above the President's budget, and this year, subcommittees in the House and Senate have once again proposed an increase to the NCI's appropriation. However, any optimism should be tempered by the uncertainties involved. "Of course, it remains to be seen what the actual appropriation will be," Dr. Lowy said. ✦

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NCI Selects Five Teams of Researchers to Expand Discovery of Predictive Biomarkers for Immunotherapy


Dr. Ignacio I. Wistuba

In October 2017, the United States National Cancer Institute (NCI) launched a major effort to expand the discovery and validation of predictive biomarkers on cancer immunotherapy. This $56.3-million NCI initiative is part of the U.S. Cancer Moonshot, launched by former President Barack Obama and Vice President Joe Biden and funded by the 21st Century Cures Act – Beau Biden Cancer Moonshot. This new program calls for the creation of four national Cancer Immune Monitoring and Analysis Centers (CIMACs) and a Cancer Immunologic Data Commons (CIDC) for systematic collection, processing, and analysis of blood and tumor samples using state-of-the-art immune profiling strategies from samples collected from patients enrolled on NCI-funded early-phase immunotherapy trials, including oncology research groups from the NCI's National Clinical Trial Network and the NCI Experimental Therapeutics Clinical Trials Network. The four CIMACs have been awarded to: Holden Maecker, PhD, and Sean Bendall, PhD, of Stanford Cancer Institute, Stanford; Sacha Gnjatic, PhD, of Precision Immunology Institute and the Tisch Cancer Institute at Icahn School of Medicine at Mount Sinai, New York; Ignacio I. Wistuba, MD, Chantale Bernatchez, PhD, and Gheath Al-Atrash, MDO, PhD, of The University of Texas MD Anderson Cancer Center in Houston; and Catherine J. Wu, MD, and Stephen Hodi, MD, of Dana-Farber Cancer Institute in Boston. Shirley Liu, PhD, and Ethan Cerami, PhD, also of Dana-Farber have been awarded an NCI-supported CIDC, which will collect the resulting data for exploration of biomarkers of immune response.

The centers are also part of the Partnership for Accelerating Cancer Therapies (PACT) announced early this year by the U.S. National Institutes of Health (NIH). The 5-year, $210-million public–private partnership aims to identify and develop biomarkers to guide and improve treatments that help the immune system attack cancer. In announcing the PACT, NIH leaders note that cancer immunotherapies have led to dramatic improvement in outcome for some patients, a success that must be extended to more people and a greater variety of cancers.

One of the challenges in developing biomarkers that can predict what treatment would be best for an individual patient is standardization of research tools and approaches. "It's important to have these dedicated centers that use standardized methods and assays to better understand how the immune system and tumors respond to treatment and to develop predictive biomarkers for novel immunotherapy approaches," Dr. Wistuba, who is chair of the IASLC Pathology Committee said. ✦

Liquid Biopsy Statement from page 13

ing field of liquid biopsies," said Fred R. Hirsch, MD, PhD, CEO of the IASLC.

The possibility of using a noninvasive method to understand and identify molecular targets and mechanisms of resistance for current drugs, both targeted agents and immunotherapies, can be extremely beneficial for patients, as will harnessing these strategies to identify new biomarkers. The future of liquid biopsies is undeniably exciting, but there is a need to more clearly understand the latest developments.

"The evolution of liquid biopsies in lung cancer in the past 2 years has been amazing, as evidenced by the U.S. Food and Drug Administration approval for use of circulating tumor DNA (ctDNA) for use with osimertinib in patients with *EGFR*T790M," said Christian Rolfo, MD, PhD, MBA, of the University of Maryland Greenebaum Cancer Center and lead author of the statement paper. "The major benefit is the real-time information provided by this noninvasive method. The future also looks very promising for new members of the liquid-biopsy family as exosomes," Dr. Rolfo noted.

Given the pace of scientific and therapeutic advances in thoracic oncology, including emerging technologies for liquid biopsy, collecting and distributing up-to-date information is critical for improving outcomes for patients worldwide. The IASLC is committed to serving as a global resource for all involved in lung cancer, the leading cause of cancer-related deaths worldwide.

"This statement is an important tool for clinicians to better understand the latest technologies in liquid biopsies but, more importantly, to answer several frequent questions about use, determination, reporting, and interpretation of the genomic data," Dr. Rolfo said. "The IASLC is committed to global thoracic oncology education and, with this statement, this goal has been achieved in relation to ctDNA," Dr. Rolfo concluded. ✦

Fig. 1. Patient with NSCLC Progressive or Recurrent Disease During Treatment With TKI

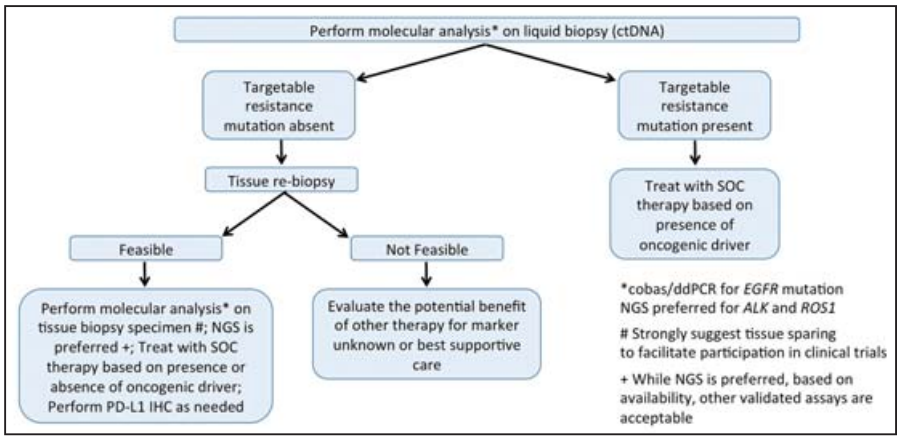
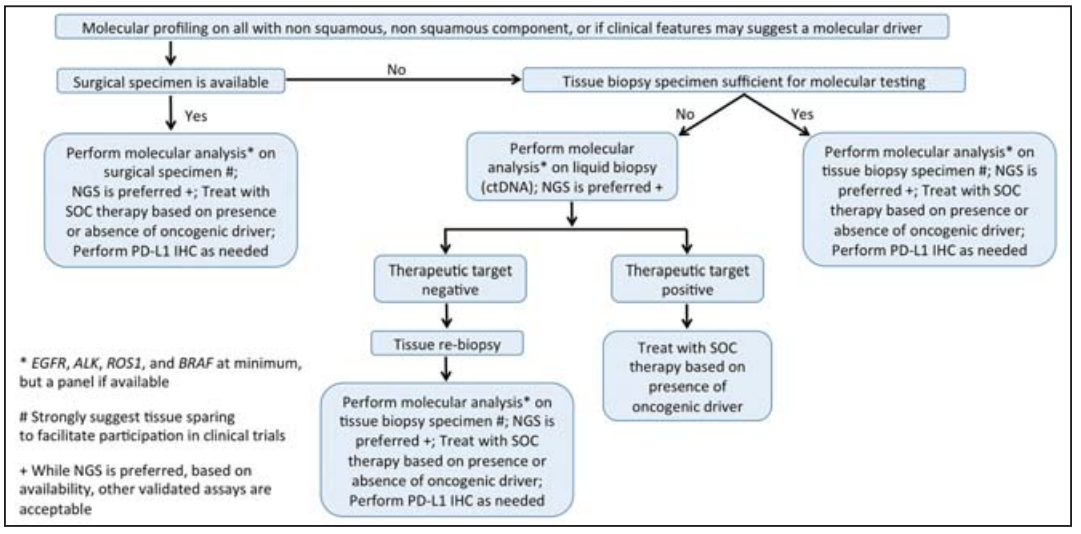
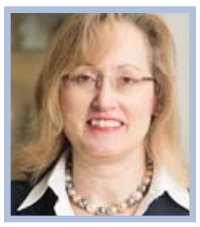


Fig. 2 Patient With Advanced Treatment-Naive NSCLC



Names and News

Leena Gandhi, MD, PhD, has become head of oncology for Eli Lilly and Company, where she will direct research of the company's immuno-oncology products. Previously, she was director of thoracic medical oncology at New York University (NYU) Langone Medical Center LLC. Prior to joining NYU Langone and the Perlmutter Cancer Center, Dr. Gandhi served at the Dana-Farber Cancer Institute, Brigham and Women's Hospital, where she was a medical oncologist and clinical investigator in the Lowe Center for Thoracic Oncology and in the Early Drug Development Center. Dr. Gandhi played a leading role in numerous clinical trials, including the pivotal KEYNOTE-189, which she presented at the American Association for Cancer Research meeting in April 2018.



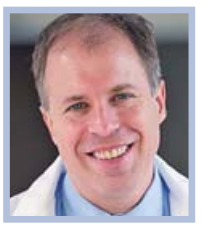
Julie R. Brahmer, MD, MSc, director of thoracic oncology program and professor of oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, has been recognized as 2018 Oncologist of The Year by Continental Who's Who, a business publisher.

Dr. Brahmer directs the Kimmel Cancer Center on the Johns Hopkins Bayview campus and is co-principal investigator on Johns Hopkins' National Clinical Trials Network. During the course of her career, Dr. Brahmer has attained expertise in the clinical investigation of lung cancer, and mesothelioma, and is considered one of the world's leading experts on immunotherapy.

An IASLC Board member, Dr. Brahmer is also founding board member for the National Lung Cancer Partnership, and she is on the Medical Advisory Board of the Lung Cancer Research Fund and LUNGevity.

As of April 2018, **Christian Rolfo, MD, PhD, MBA,** is the director of the Thoracic Medical Oncology and the Early Clinical Trials at the University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center (UMGCCC) and professor in medicine at the University of Marlyland School of Medicine. Previously, Dr. Rolfo was director of the Phase I–Early Clinical Trials Unit and the Clinical Trials Management Program at the Antwerp University Hospital in Belgium. He also served as senior staff for the Thoracic Oncology Cluster. Dr. Rolfo's focus of research includes molecular profiling, translational research in thoracic oncology, drug development, and liquid biopsies. He is on the IASLC education committee and on the membership committee of the European Society of Medical Oncology. He is also educational chair of the International Society of Liquid Biopsies.

Navneet Singh, MD, the IASLC's Regent from India, has been appointed chair of the IDEA working group for the American Society of Clinical Oncology. Dr. Singh will serve a 2-year term. Dr. Singh is also on the IASLC's Staging Committee, and he leads the multidisciplinary thoracic oncology group at PGIMER, where he specializes in targeted therapies and immunotherapies for advanced NSCLC.



Avrum Spira, MD, has been named global head of the new Lung Cancer Initiative within Johnson & Johnson, which will be based at Boston University's Medical Campus. This initiative is a 5-year research alliance with Johnson & Johnson Innovation LLC; it aims to develop biomarker-based early-screening tests for lung cancer. Dr. Spira is a School of Medicine professor of medicine, pathology, and bioinformatics, and is leading two separate ongoing research projects through the new initiative: Detection of Early Cancer Among Military Personnel (DECAMP) and the development of a precancer genome atlas to characterize molecular changes that lead to invasive lung cancer. ✦

INDUSTRY AND REGULATORY NEWS

On June 13, 2018, Health Canada approved **alectinib** as a monotherapy for the first-line treatment of patients with *ALK*-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC.

The approval was based on results from the phase III ALEX study, which demonstrated a reduced risk of disease progression or death by more than half (53%) with alectinib versus crizotinib. ALEX data also showed that alectinib reduced the risk of metastasis to the brain or CNS by 84% compared with crizotinib. ✦

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www.iaslc.org/events

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