

LUNG CANCER IASLC NEWS

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

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IMMUNOTHERAPY

Ongoing Clinical Challenges: Defining Immunotherapy Benefit for Patients With NSCLC and Poor Performance Status

By Valérie Gounant, MD, and Elisabeth Quoix, MD, PhD

Since the beginning of the 21st century, there have been two major innovations in the treatment of advanced NSCLC: the use of targeted therapies and the use of immune checkpoint inhibitors (ICIs). These modalities have revolutionized outcomes for patients with metastatic disease. However, the U.S. Food and Drug Administration (FDA) approvals for atezolizumab, nivolumab, and pembrolizumab were based on the results of phase III clinical trials, which restricted enrollment to patients with a performance status (PS) of 0 or 1, leaving the thoracic oncology community wondering about optimal treatment for patients with poor PS.

The prevalence of poor PS (2-4) patients at time of diagnosis is as high as 34%.¹ For patients with metastatic NSCLC and PS 3-4, there is no recommendation for chemotherapy, and best supportive care is the usual standard in

This article is the first in a two-part series on ongoing challenges using immunotherapy in special populations. The second part, with a focus on elderly patients, will run in the February issue and online (lungcancernews.org).

the absence of a molecular target. Most patients with PS 3-4 die within 2 to 4 months of diagnosis.

However, trials dedicated to patients with advanced NSCLC who harbor oncogenic drivers, including activating mutations, have been performed in populations with such poor general condition,^{2,3} and safety and efficacy were consistent with results observed in patients with good PS (so-called Lazarus syndrome), leading to general acceptance of these agents independent of PS. These trials have profoundly changed clinical practice; now, if oncogene-addicted tumors

are detected, these patients are treated with oncogene-specific tyrosine kinase inhibitors, regardless of PS.

Current Data

We have little data about safety and efficacy in poor PS patients. Currently, only four prospective trials including PS 2 patients have been published; three were in abstract form,^{4,5,6} and only one⁷ was an actual journal article. These included two phase II trials (CheckMate 171 with nivolumab⁴ and PePS2 with pembrolizumab⁵) and two phase III/IV trials (CheckMate 153 with nivolumab⁷ and CheckMate 817 with nivolumab and ipilimumab⁶). These trials did not select their populations based on biomarkers. The results of prospective trials in advanced NSCLC in PS 2 patients are summarized in Table 1 on page 3 (after Passaro⁸). These trials, apart from PePS2, also included elderly patients and/or PS 0-1 patients with comorbidities,

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EVOLVING STANDARDS OF CARE

Lung Cancer Leading the Charge for Tumor-Agnostic Targeted Therapies

By Robert C. Doebele, MD, PhD

Early in the drug development of targeted therapies, specific oncogene mutations were often associated with a single disease: *HER2* gene amplification with breast cancer, *BCR-ABL* fusions with chronic myelogenous leukemia, *EGFR* mutations with lung cancer, and *BRAF* mutations with melanoma. Thus, drug development and approval proceeded in both a mutation- and tumor-specific context for each of these indications. Through the efforts of The Cancer Genome Atlas, the Genomics Evidence Neoplasia Information Exchange, and other large-scale pan-tumor sequencing efforts, as well as through the implementation of multiplexed next-generation sequencing panels in the clinic, it has become clear

that specific oncogene mutations often occur in more than one tumor type. This revelation has opened the door for novel, tumor-agnostic, drug-development strategies.

BRAF

BRAF inhibitors alone or in combination demonstrate significant clinical benefit in patients with melanoma whose tumors harbor *BRAF* V600E. However, an early and prominent setback for the concept of tumor- (or tissue-) agnostic therapeutic approaches came in the form of lack of activity of

BRAF inhibitors in colon cancers harboring *BRAF* V600E mutations. Ultimately, this disappointing clinical finding was elegantly explained by inadvertent activation of *EGFR* by *BRAF* inhibitors.¹ Recent clinical trial data support this mechanism with triplet combination therapy of *BRAF*, *MEK*, and *EGFR* inhibition demonstrating improved activity.² *BRAF* V600E mutations also occur in lung cancers. In an early example of lung cancer providing a testing ground for tumor-agnostic strategies, dabrafenib and trametinib demonstrated significant clinical activity with an objective response rate (ORR) of 63% and a durable median

progression-free survival (mPFS) of 9.7 months, leading to European Medicines Agency approval in 2017 and later U.S. Food and Drug Administration (FDA) approval.³ Since this time, *BRAF* inhibitors with or without *MEK* inhibition have demonstrated clinical activity in hairy cell leukemia and anaplastic thyroid cancers harboring *BRAF* V600E mutations. Despite these successes across multiple tumor types, there is no tumor-agnostic approval yet for *BRAF* V600E mutations.

ALK

Oncogenic *ALK* gene fusions were first identified in anaplastic large cell lymphoma in 1994.⁴ However, the first clinical trial of an *ALK* inhibitor in cancer did not begin until after the discovery of

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Dr. Robert C. Doebele

IASLC 2020

Meetings Schedule

Sixth AACR-IASLC International Joint Conference: Lung Cancer

Jan. 11-14, 2020 | San Diego, CA | #Lung20

IASLC 2020 Targeted Therapies of Lung Cancer

Feb. 19-22, 2020 | Santa Monica, CA
#TTLC20

European Lung Cancer Congress 2020

April 15-18, 2020 | Geneva, Switzerland
#ELCC20

Lung Cancer Hot Topic: Liquid Biopsy

May 2020

IASLC 2020 World Conference on Lung Cancer

August 9-11, 2020 | Singapore | #WCLC20

IASLC 2020 North America Conference on Lung Cancer

October 15-17, 2020 | Chicago, IL
#NACLC20

Lung Cancer Hot Topic: Immunotherapy

November 2020



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Ongoing Clinical Challenges

from page 1

making it difficult to draw specific conclusions for PS 2 patients, which already constitute a very heterogeneous population. Heightening heterogeneity by the inclusion of elderly patients and PS 0-1 patients with comorbidities introduces even more complexity and ambiguity in interpreting the results.

The incidence of grade 3 to 4 treatment-related adverse events (TRAE; primary endpoint) was 6% for the PS 2 population and 12% for the overall population (including PS 0-1 patients and patients aged 70 years and older) in CheckMate 171; comparable figures in CheckMate 153 were 9% for PS 2 and 6% for the overall population. In CheckMate 817, combination immunotherapy was more toxic, but the safety profile was similar between cohort A with PS 0-1 patients (35% grade 3-4 TRAE) and cohort A1 with PS 2 patients (28% grade 3-4 TRAE) (139/198 patients) and PS 0-1 patients with comorbidities.

Overall survival (OS) was worse in PS 2 patients compared to the entire population in CheckMate 171 (5.4 vs. 9.9 months) and in CheckMate 153 (4 vs. 9.1 months). In CheckMate 817, in the PS 2 population, progression-free survival (PFS) was 3.6 months, with response rate (RR) of 20%, with median duration of response of 14.2 months. As expected, PFS was longer in those patients whose tumors had a high PD-L1 expression and/or high tumor mutation burden (TMB). In PePS2, RR was 19% in patients with PD-L1 expression of less than 1%, 33% in patients with PD-L1 expression of 1% to 49%, and 47% in patients with PD-L1 expression of 50% or higher. Median PFS and OS in those with PD-L1 expression of 50% or higher were 8.5 and 16.6 months, respectively. Thus, in selected populations, immunotherapy may be quite useful in PS 2 patients. This observation must be confirmed in dedicated studies confined to PS

Table 1. Results of Prospective Trials in Advanced NSCLC with ECOG PS 2 Patients

| First author | Trial | Drug | Setting | PD-L1 stratific. (%) | No PS 2 patients | ORR (%) | PFS (mos) | mOS (mos) | 6-mos OS (%) | Grade3-4 3-4 toxicity (%) |
|--------------|---------------------|------------------------|---------|----------------------|------------------|---------|-----------|-----------|--------------|---------------------------|
| Popat | Phase II CM 171 | Nivolumab | ≥ 2 L | No | 38 | 11 | | 5.4 | 46 | 6 |
| Spigel | Phase III-IV CM 153 | Nivolumab | ≥ 2 L | No | 128 | 20 | | 4 | 41 | 12 |
| Barlesi | Phase III-IV CM 817 | Nivolumab + ipilimumab | 1L | No | 139 | 20 | 3.6 | NA | NA | 28%* |
| Middleton | Phase II PePS2 | Pembrolizumab | 1/2 L | < 1 | 27 | 19 | 3.3 | 9.8 | NA | NA |
| | | | | 1-49 | 15 | 33 | 6.8 | NR | NA | NA |
| | | | | ≥ 50 | 15 | 47 | 8.5 | 16.6 | NA | NA |

* This result is not only for the PS2 population but for whole population of cohort A1 with PS2 and patients with PS 0 to 1 and co-morbidities.

Abbreviations: PS, performance status; stratific, stratification; ORR, objective response rate; PFS, progression-free survival; mos, months; OS, overall survival; CM, CheckMate; NR, not reported.

2 patients, either pretreated or not, with or without the addition of chemotherapy. It is worth noting that, although all of the crucial phase III studies proving the benefits of ICIs were limited to PS 0-1 patients, FDA authorization for the use of ICIs do not restrict the use of these agents to PS 0-1 patients.

Although there are no dedicated trials for PS 3 patients, we previously observed Lazarus-type responses to anti-PD-1 ICIs in two patients with NSCLC in very poor condition but with very high PD-L1 expression.⁹ Such patients improved from PS 3 or higher before the initiation of immunotherapy, to PS 0, after only 1 month of ICIs; now after more than 24 months of follow-up, major tumor shrinkage continues. Recently, others have similarly suggested that pembrolizumab can be considered in critically ill patients with NSCLC and PD-L1 expression of 50% or more.¹⁰

Challenges and Potential Next Steps

The main challenge is to select poor PS populations who are more likely to derive a benefit from immunotherapy. In particular, it is necessary to define predictive biomarkers in this population: these include tumor biomarkers (e.g., molecular profile, PD-L1, and TMB) and patient biomarkers (e.g., inflammatory and nutritional markers). Several trials dedicated

to PS 2 are currently recruiting. However, only two of these trials select the population based on PD-L1 status: these include the trial of the Swiss Group for Clinical Cancer Research (NCT03620669) and the SAVIMMUNE trial (NCT04108026) orchestrated by the French Cooperative Thoracic Intergroup (IFCT).

The role of chemotherapy and immunotherapy in combination must also be defined in the poor-PS population. A phase I trial evaluating the feasibility of weekly low-dose carboplatin and paclitaxel with pembrolizumab for patients with advanced NSCLC and PS 2-3 is ongoing.¹¹ ♦

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LETTER TO THE EDITOR

Patient-Driven Research

I was so glad to see the article by Dr. Amy Moore on PDX models in the October issue. As a Co-Founder of the EGFR Resisters, our collaboration with the GO2 Foundation for Lung Cancer is empowering patients to participate in studies that will directly accelerate research in EGFR-positive lung cancer. We are thrilled to be a part of supporting this cutting-edge research that will help researchers understand what is causing the cancer to become treatment resistant. (Note: This trial is currently enrolling, so please refer all eligible patients. Clinical Trial ID: NCT03872440)

After a dramatic response to initial therapy, it is devastating to develop resistance to treatment. There is a sense of urgency to understand the underlying mechanisms of drug resistance in EGFR-positive lung cancer and to identify new therapeutic options. We must convert that devastation to hope.

I can tell you firsthand that research matters. It means more and better treatment options for those in our community. It is our lifeline, our future, and it is hope. Many of us are depending on the next promising research advance so that we can continue to see and reach meaningful milestones with our families and friends.

Our goal is to change EGFR-positive lung cancer into a manageable chronic disease.

Our hope is that combining the collective patient voice with quality research will lead to longer and better lives for people with EGFR-positive lung cancer. ♦



Jill Feldman
EGFR Resisters Co-Founder

Robust Survival Duration Shown in NSCLC With Pembrolizumab

By Suresh Ramalingam, MD

Immune checkpoint inhibition is now part of routine care for patients with advanced-stage NSCLC. Randomized clinical trials have established the efficacy of checkpoint inhibitors as monotherapy and in combination with chemotherapy. One of the main features with immune checkpoint inhibition is the durability of clinical responses in a subset of patients; long-term survival is now possible for patients with advanced-stage NSCLC, even with metastatic disease. It is in this context that the publication by Garon et al. assumes significance. Although the results describe a cohort of highly

selected patients enrolled to a phase I study, the 5-year survival rate of approximately 30% for the patients who received pembrolizumab is a new milestone in lung cancer for metastatic disease. This robust survival duration was noted in patients with high PD-L1 expression in the first-line setting. This group represents approximately 25% to 30% of all cases of advanced NSCLC. Whether response to immunotherapy translates into cure for this subset of patients is subject to debate, which will be answered by continued follow-up.

For now, the focus shifts to understanding the specific biologic attributes of the long-term survivors. Knowledge regarding the immune milieu of long-

term survivors can lead to the development of novel approaches to improve outcomes for all patients with NSCLC. Combination approaches hold promise, as has already been evidenced by the integration of chemotherapy and radiotherapy with immune checkpoint inhibition. There is no doubt that more work needs to be done; however, it is also appropriate to reflect on the magnitude of progress to date, and the difference this makes for our patients' lives. ♦

Disclosure: Dr. Ramalingam is a co-author of this study; he has received honorarium for participating in advisory board meetings/Consultation for Merck, Astra Zeneca, Bristol Myers Squibb, and

Roche. He has received research support (to institution) from Astra Zeneca, Bristol Myers Squibb, and Merck.

About the Author: Dr. Ramalingam is a professor of Hematology and Medical Oncology at Emory University School of Medicine, Winship Cancer Institute.

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Tumor-Agnostic Targeted Therapies

from page 1

ALK gene fusions in lung cancer in 2007.⁵ Currently there are five approved *ALK* inhibitors for NSCLC, but no tumor-agnostic approval despite the presence of *ALK* oncogenes in neuroblastoma, inflammatory myofibroblastic tumors, and many others.⁶ The My Pathway basket trial (NCT02091141) is evaluating the activity of alectinib in patients with *ALK*-positive tumors.

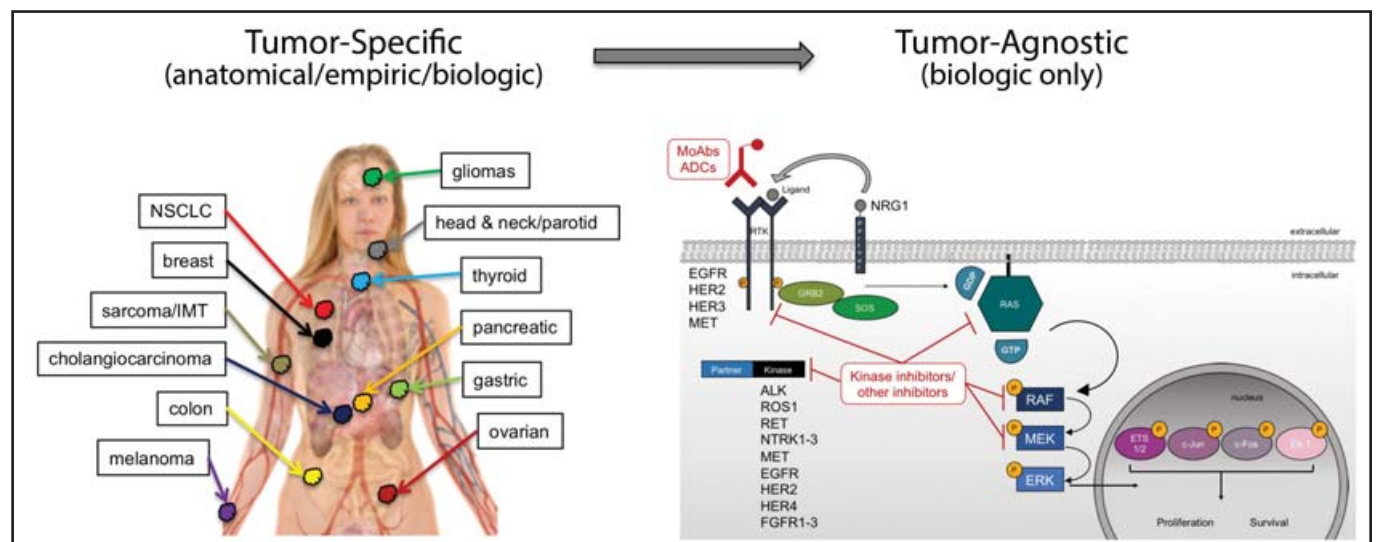
ROS1

ROS1 fusions were first identified in glioblastoma in 1987.⁷ The discovery of *ROS1* fusions in lung cancer and the readily available *ROS1* inhibitor crizotinib, which already had safety and efficacy data in *ALK*-positive NSCLC, facilitated rapid development of crizotinib as the first approved *ROS1* inhibitor in *ROS1*-positive NSCLC.⁸ Similar to *ALK* research, *ROS1* fusions have been identified in a number of other tumor types.⁹ The STARTRK-2 (NCT02568267, entrectinib) and AcSé (NCT02034981, crizotinib) basket trials are evaluating the role of *ROS1* inhibitors in *ROS1* fusion-positive tumors.

NTRK1/2/3

Gene fusions involving the *NTRK1* gene, which encodes the TRKA receptor tyrosine kinase, were discovered in 1982 in a single colorectal cancer specimen¹⁰; however, *NTRK1* gene fusions in lung cancer were first identified much later.¹¹ Early preclinical data suggested that TRK

Figure. Models for Drug-Development Strategies



inhibitors would have activity irrespective of tumor type and would target the related gene fusions involving *NTRK2* (TRKB) and *NTRK3* (TRKC), supportive of a tumor-agnostic therapeutic approach for this oncogene family.¹² A review of the literature suggested that *NTRK1/2/3* fusions occur across a number of tumor histologies, and given the relative rarity of these oncogenes overall,¹³ a basket trial design was pursued from the onset for TRK inhibitors. In 2018, larotrectinib was the first TRK inhibitor to be approved for the treatment of *NTRK1/2/3* fusion-positive cancers. This was based on a cohort of 55 adult and pediatric patients representing 17 unique different histologies that harbored *NTRK1/2/3* fusions.¹⁴ The ORR was 75% by independent review, and mPFS was not yet reached. Overall, the therapy was well tolerated with most common adverse events (AEs)

being transaminitis, dizziness, fatigue, nausea, and notable increase in body weight, which may be an on-target effect of TRKB inhibition. This trial represented a number of firsts in oncology including the first oncogene-targeted, tumor-agnostic therapy to be approved (pembrolizumab for MSI-high tumors was the first tumor-agnostic therapy approved), the first cancer drug to be approved simultaneously for both adult and pediatric patients, and the first cancer drug to be approved for a family of oncogenes.

Entrectinib was the second agent to gain approval (Japan) for *NTRK1/2/3* fusion-positive cancers. Entrectinib is an *ALK/ROS1/TRK1* inhibitor designed to have activity in the central nervous system (CNS), an important feature for tumors with a high propensity for brain metastases, such as lung cancer. Integrated analysis from 54 patients

with *NTRK* fusion-positive disease from ALKA-372-001 (EudraCT 2012-000148-88), STARTRK-1 (NCT02097810), and STARTRK-2 (NCT02568267) included only adult patients with 19 different histologies represented.¹⁵ The ORR was 57%, and the mPFS was 11 months. The intracranial ORR (IC-ORR) in 11 patients with CNS metastases was similar to the overall ORR at 54.5%. Entrectinib was well tolerated; the most common AEs included dysgeusia, constipation, fatigue, dizziness, and weight gain. Analysis of 10 patients with NSCLC with *NTRK1/3* fusions (no *NTRK2* fusions were identified in NSCLC) demonstrated an ORR of 70%, median PFS of 14.9 months, and intracranial ORR of 66.7%.¹⁶ Notably, these results were similar to the entrectinib data for *ROS1*-positive NSCLC with an ORR of 77.4%, mPFS of 19.0 months, and IC-ORR of 55%.¹⁷ Thus,

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A DEEPER DIVE

Novel Insights on ctDNA Dynamics During Targeted Therapy and Immune Checkpoint Blockage in NSCLC

By Christian Rolfo, MD, PhD,
MBA, Dr.h.c.

Liquid biopsy (LBx) is a new, powerful tool for the molecular profiling of patients with NSCLC that can help oncologists with appropriate treatment selection in oncogene-addicted NSCLCs. Circulating tumor DNA (ctDNA) assays for detection of both *EGFR* sensitizing and resistance mutations have already entered clinical practice in NSCLC,¹ and recently, the NILE study provided evidence that a 73-gene next-generation sequencing (NGS) panel can detect biomarkers (including *EGFR*, *ALK*, *ROS1*, *BRAF*, *RET*, *MET*, *HER2*, and *KRAS*) at a rate similar to standard-of-care tissue genotyping tests, with a faster turnaround time; it can also provide the opportunity to rescue patients who were incompletely genotyped or whose initial tissue analysis proved negative for “actionable” biomarkers.²

LIQUID BIOPSY EXPERT VOICES

In addition to tumor genotyping, LBx may potentially allow real-time monitoring of response in patients with cancer. This application may be particularly useful in patients treated with targeted agents favoring early identification of mechanisms of acquired resistance that inevitably occur after initial response, as well as in those treated with immune checkpoint inhibitors (ICIs) in which radiographic interpretation of response might be challenging, thereby overcoming the limits of conventional radiologic assessment methods. Recently, the American Association for Cancer Research published two interesting papers addressing this issue.

Phallen et al. evaluated the role of serial ultrasensitive LBx with targeted error correction sequencing (TEC-Seq) as an early non-invasive detection tool of response in

patients with metastatic NSCLC with *EGFR* or *HER2* mutations during treatment with different classes of TKIs. They collected serial blood draws from 28 patients with metastatic NSCLC at baseline and over the course of treatment until disease progression, evaluating the changes of a new metric, cell free tumor load (cFTL), which was defined as the contribution of the most abundant alterations in ctDNA at any particular time point. Changes in cFTL were compared with tumor burden assessed in patients with detectable sequence clones (24 patients) or the qualitative assessment of change from aneuploidy to normal ploidy in those without detectable sequence clones (4 patients). They reported that both ctDNA levels and clonal heterogeneity dramatically reduced in responding patients due to the selective pressure of targeted therapy with a significant reduction of cFTL

compared to baseline levels (average of 10.8% at baseline vs. 0.18% at a median time of 19 days after treatment start; $p < 0.001$); they also noted a decrease of plasma aneuploidy scores (average decrease of 92%; $p = 0.002$), and a reduction of average number of observed alterations (from 3.6 to 1.1 mutations per patient; $p < 0.01$). In contrast, patients with stable disease (SD) and progressive disease exhibited a less pronounced (average of 2.24% at baseline vs. 1.04% after treatment; $p = 0.03$) or limited variation of cFTL (average of 14.23% at baseline vs. 11.84% after treatment; $p = 0.6$), respectively, and no significant change in the number of mutations observed. Despite the limited sample number, this study further confirmed the findings of previous reports suggesting a potential role for LBx as a non-invasive drug-monitoring method,^{3,4} allowing an earlier identification of mechanisms of



Dr. Christian Rolfo

acquired resistance compared with conventional radiologic methodologies. However, to date, it is unclear whether this might be associated with changes in the treatment strategy before radiographic progression or not. The randomized phase II EORTC APPLE trial (NCT02856893) will likely provide further evidence on the utility of this strategy.

Interestingly, cFTL reduction at a median of 19 days was a more accurate predictor of clinical outcome compared with initial CT imaging performed after an average of 47 days ($p < 0.0001$), allowing a more precise evaluation of patients with nonmeasurable disease or with radiographic SD. This, in turn, may allow a better characterization of these patients and, in turn, overcome the limits of conventional radiographic methodologies. Finally, the authors reported that, in a subset of patients, the effect of the first dose of treatment after 4 to 12 hours showed a 110-fold increase in the rate of emerging mutations, with a relative stability of ctDNA amounts. This finding may potentially affect future combinatorial strategies, allowing us to add different inhibitors to *EGFR* blockade based on emerging mechanisms of resistance.

In a companion study, Anagnostou et al.

evaluated the role of noninvasive monitoring of ctDNA using the TEC-Seq approach in a longitudinal study of T-cell receptor (TCR) repertoire during immune checkpoint inhibition. The study included 24 patients with metastatic NSCLC treated with ICIs and 14 patients with resectable NSCLC (stage I-IIIa) receiving nivolumab as neoadjuvant treatment. At least two serial samples (range 2-8) were collected for all patients. To avoid the potential effect of clonal hematopoiesis,⁵ ctDNA analysis was focused only on genetic alterations identified through NGS in paired-matched tissue samples. In the metastatic cohort, 19 of 24 patients had ctDNA detectable levels (median mutant allele fraction of 1.87%) either at baseline or other time points, whereas 7 of 14 patients in the early-stage cohort had detectable ctDNA (median allele fraction of 0.34%). They identified three patterns of molecular response in ctDNA: molecular response, corresponding to a dramatic reduction of ctDNA to undetectable levels; molecular resistance, associated with limited fluctuations or a rise of ctDNA levels; and molecular acquired resistance, where tumor-specific variants were undetectable at the time of response followed by increase in mutant allele fraction at the time of acquired resistance. Reduction of ctDNA to undetectable levels was associated with longer PFS ($p = 0.001$) and OS ($p = 0.008$) compared with no evidence of ctDNA elimination. Once again, in patients with radiographic SD (12 patients), the molecular response pattern correlated with clinical benefit from immune checkpoint blockade and better predicted the magnitude of therapeutic response than CT imaging. Furthermore, molecular response was associated with major or partial pathologic response in the neoadjuvant cohort, whereas molecular resistance was associated with no pathologic response.

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IN REFERENCE TO:

Phallen J, Leal A, Woodward BD, et al. Early Noninvasive Detection of Response to Targeted Therapy in Non-Small Cell Lung Cancer. *Cancer Res.* 2019;79(6):1204-1213.

Anagnostou V, Forde PM, White JR, et al. Dynamics of Tumor and Immune Responses during Immune Checkpoint Blockade in Non-Small Cell Lung Cancer. *Cancer Res.* 2019;79(6):1214-1225.

Moreover, 24 patients with metastatic disease had available samples from both tumor infiltrating lymphocytes and peripheral blood lymphocytes for analysis of TCR clonal dynamics. Consistent with the cDNA analysis, distinct patterns in TCR clonotype dynamics were observed with a significant oligoclonal expansion in peripheral blood of pre-existing intratumoral T-cell clones, followed by a significant decrease after acquired resistance. In contrast, in patients with primary resistance, no evidence of TCR clonal expansion of intratumoral TCR repertoire was observed.

The results of this study have several potential clinical implications. First, ctDNA dynamics might complement standard imaging approaches in the therapeutic management of patients with NSCLC treated with ICIs,^{6,7} allowing a better characterization of pseudo-progression or mixed/dissociated responses. In addition, the clearance of ctDNA, if validated in large prospective studies, might represent a valid tool that would allow a better selection of patients who can benefit from elective discontinuation strategies after selected treatment duration and might help to identify patients who can benefit from combinatorial approaches instead of single-agent ICI therapy. Finally, this study further confirms that more clonal T cell repertoire is predictive of response ICIs targeting PD-1/PD-L1⁸ and TCR clonal dynamics might guide treatment management.

Further prospective studies in large patient population should validate these preliminary data and may support the incorporation of dynamic ctDNA analysis in clinical trials evaluating targeted therapies and immunotherapy in NSCLC. ♦

About the Author: Dr. Rolfo is professor of Medicine and director of Thoracic Medical Oncology and Early Clinical Trials at University of Maryland Greenebaum Comprehensive Cancer Center and University of Maryland School of Medicine. He is vice-president of the International Society of Liquid Biopsy.

EXPERT PERSPECTIVE

Improved Turnaround Times for Biopsy Results Matters More Than Type of Biopsy

Regarding “Liquid Biopsy for Assessing Response or Progression in Advanced NSCLC” by Dr. Geoffrey R. Oxnard published in the October issue of the *IASLC Lung Cancer News*, I would like to comment on the issue of turnaround time (TAT), which is a topic that is extremely critical in the treatment of patients with cancer.

Significant improvement has been observed regarding TAT since the Guardant360 became commercially available in 2014. This test uses next-generation sequencing (NGS) to determine the genomic alterations in blood after cell-free DNA (cf-DNA) from cancer cells is captured. Initially, the test consisted of 58 genes, with a TAT of approximately 10-12 calendar days. The test was increased to 73 genes, but its TAT has been reduced to only 7 calendar days as demonstrated in the prospective

NILE study.¹ The first 10 patients had a median cf-DNA TAT of 14 days (range 11-30 days) versus the last 10 patients, who had a median TAT of 7 days (range 5-9 days). As a pioneer in this field, the Guardant Health test has been challenged by other competitors, such as Biodesix’s Genestrat, which uses digital droplet polymerase chain reaction (ddPCR) technology and has an average TAT of 3 days. This test analyzes six actionable genomic abnormalities (*EGFR*, *ALK*, *ROS1*, *RET*, *BRAF*, and *KRAS*) in lung cancer. Inivata also uses NGS with its InvisionFirst-Lung test to analyze 36 genes relevant to patients with advanced NSCLC, with a TAT of 7 calendar days or fewer from blood draw. As a clinician, this is amazing. We can diagnose driver mutations, resistant mutations, and, perhaps in the future, monitor our patients in a seamless manner. Only rarely do we

have to rush to change therapy for a patient who has been well monitored. Hence, to wait just 3-7 calendar days to obtain a “genomic snapshot” of our patients is probably as good as it gets. The TAT for NGS in tumor tissue has also significantly improved, with some vendors in the private sector reporting NGS in 5 calendar days. In my opinion, to wait more than 14 calendar days for an NGS report, regardless of whether derived from blood or tissue specimen, is unacceptable. ♦

– Edgardo S. Santos Castillero, MD, FACP

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Dr. Edgardo S. Santos Castillero

EXPERT PERSPECTIVE

The Application of Liquid Biopsy in Lung Cancer: The View from China

The application of liquid biopsy in lung cancer is increasing in China.

For patients with insufficient tumor tissue, liquid biopsy could provide tumor cell-derived genomic landscape for precision therapy. Due to its minimally invasive nature, liquid biopsy can also be repeated serially for longitudinally monitoring treatment response, detecting the emergence of drug resistance, and tracking tumor evolution.¹ Here, inspired by the October *IASLC Lung Cancer News* article “Liquid Biopsy for Assessing Response or Progression in Advanced NSCLC” by Dr. Geoffrey R. Oxnard, we briefly discuss how liquid biopsy has been used in China, as well as its challenges and drawbacks.

The successful development of targeted therapy for advanced NSCLC is based on molecular classification, including *EGFR* sensitizing mutations, *ALK/ROS1/RET* rearrangements, and *BRAF^{V600E}* mutations. Genomic profiles are recommended to be evaluated in treatment-naïve patients with advanced NSCLC in China, especially in those with non-squamous NSCLC. For patients with insufficient tumor tissue, circulating-free DNA (cfDNA) or circulating-tumor DNA (ctDNA) is

strongly recommended for *EGFR* mutation detection according to guidelines by the Chinese Society of Clinical Oncology (CSCO). Super-ARMS has been approved by National Medical Products Administration (NMPA) for *EGFR* mutation detection using ctDNA. Other validated PCR-based assays, including cobas and digital droplet PCR (ddPCR) are also acceptable. CSCO guidelines also moderately recommend validated next-generation sequencing (NGS) multiplex panels for initial molecular diagnosis using ctDNA for patients without obtainable tumor tissue specimens.

For patients for whom first- or second-generation *EGFR*-TKI treatment fails, T790M secondary mutation is the predominant acquired resistance mechanism,² which can be effectively inhibited by the third-generation *EGFR*-TKI osimertinib.³ ctDNA has been advocated as a feasible source to identify T790M mutations, as a complement to routine tissue-based genotyping according to the guidelines. ctDNA is also clinically available to comprehensively understand the acquired resistance mechanisms of osimertinib to further guide subsequent personalized therapy.^{4,5} Furthermore, dynamic monitoring of ctDNA or



Dr. Fei Zhou



Dr. Caicun Zhou

T790M mutations in plasma is being used to predict efficacy and clinical outcomes of patients treated with *EGFR*-TKIs, allowing longitudinal monitoring of patients during treatment.^{6,7} However, serial ctDNA for assessing response or progression has not been used routinely in China, just serving as a complement to imaging and clinical evaluation or for scientific purposes.

Despite considerable promising advances that liquid biopsy has made, challenges remain. For *EGFR* mutation detection using ctDNA, although high specificity and concordance with tumor tissue have been achieved with super-ARMS, sensitivity varies from 76%-82%.^{8,9} Therefore, negative results should be interpreted with caution, and a more sensitive method (such as ddPCR or NGS approach) or using DNA from tissue biopsy should be performed to rule out false negatives. On the other hand, NGS-based approaches could provide more comprehensive molecular profiles of tumors rather than PCR-based approaches; however,

continued on page 9

SUPPORTIVE CARE

Palliative Care: Combating Stigma and Enhancing Quality of Care—A Worldwide Perspective

Jennifer Temel, MD, and colleagues¹ showed in a small but well-conducted phase III trial that a proactive, intensive palliative care program compared to our more typical reactive approach could lead to improved outcomes in advanced NSCLC, including better quality of life, decreased anxiety and depression, fewer hospitalizations at the end of life, more use of hospice, and improved survival, at minimal cost. But take-up of this strategy has been slow and sporadic, hindered by issues of reimbursement and by the stigma the term “palliative care” carries. In this issue as well as in those following, the *IASLC Lung Cancer News* has gathered multiple perspectives on the role of formal palliative care programs around the world and their challenges and successes. ♦

– Corey J. Langer, MD, FACP



Dr. Corey J. Langer

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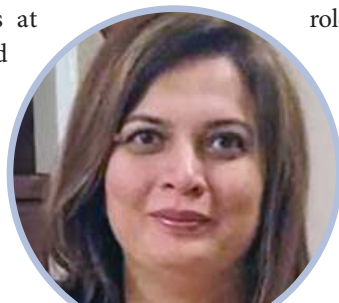
SUPPORTIVE CARE

Palliative Care in Canada



By Jehanara Chagani, RN, MSc(N),
CHPCN(C)

In Canada, palliative care is promoted as an approach that puts recipients and their families at the center of services and decision making. The provision of palliative care is supported in combination with other treatment plans and is offered in all settings. The “Framework on Palliative Care in Canada” summarizes the provision of



Ms. Jehanara Chagani

palliative care, setting the World Health Organization's definition in the Canadian context by developing a set of guiding principles. These principles highlight that palliative care should be integrated, holistic, equitable, high quality, and evidence based. Palliative care should recognize the diversity of Canadians, improve quality of life, and be a responsibility of all Canadians including caregivers, all levels of government, communities, not-for-profit organizations, healthcare providers, and the general population.¹

Despite these efforts, many challenges persist:

- Only 15% of Canadians who die at home receive palliative home care services.¹
- People with end-stage cancer are three times more likely to receive palliative care compared to patients with other life-limiting illnesses.²
- There is still a stigma surrounding the term palliative care, as it is used interchangeably with end-of-life care. The lack of a common definition of palliative care, limited resources and funding, lack of awareness, and reluctance

from patients and healthcare providers to discuss palliative care and the dying process contributes to the delay for palliative care services²

Role of Nurses in Palliative Care

Palliative care is a highly valued and specialized form of nursing practice. Nurses provide palliative care in various roles, including as nurse practitioners, care coordinators, home care nurses, and advanced practice nurses. They engage with patients and their families, assess suffering and survival, support patients as they progress through the process of dying and death, and ensure that patients remain comfortable and die in the environment of their choice.³

Some nurse-led initiatives to improve palliative care include:

- Strengthening palliative care through early identification of patients with palliative care needs and leading the goals of care discussions in long-term care facilities and homes. For example, nurses at the Central West Palliative Care Network, in partnership with its Local Health Integration Network, led the initiative for identification of those patients who would benefit from early palliative care in order to improve the experience of patients and caregivers. The partners developed the Early Identification and Prognostic Indicator Guide to help healthcare providers identify people who could benefit from palliative care. The initiative resulted in an increased percentage of patients benefiting from early palliative care

services from 5% to 10% and in a reduction in hospital admission/readmission, as well as an improved experience for patients and their families.²

- Providing palliative care to patients in the home, clinics, shelters, and mental health facilities as nurse practitioners. For example, as part of the Ontario government plan, “The Attending Nurse Practitioners in Long-Term Care Homes (LTCH)” initiative will fund 75 nurse practitioner full-time positions over 3 years to provide services in LTCHs including reduction of unnecessary hospital admissions and improved patient experience through adequate palliative care provision.⁴
- Advocating for patients with palliative care needs and their caregivers earlier in their disease trajectory and connecting them to the appropriate resources.
- Building capacity in healthcare professionals through formal and informal educational initiatives. Some of the formal initiatives are courses run by nurses, including “Learning essential approaches to palliative care” and “Fundamental of Palliative Care.”

- Educating the public on the basics of palliative care and advance care planning to help eliminate the stigma.

Palliative care has progressed and improved significantly in Canada since its inception. Such progress includes the expansion of palliative care to patients' homes, growing awareness of palliative care with conditions other than cancer, and increasing emphasis on early and integrated care. Nurses have played an essential role in this progress and will continue to be an integral part in improving and strengthening palliative care in Canada. ♦

About the Author: Ms. Chagani is an advanced practice nurse-clinical nurse specialist with Central West Palliative Care Network, in Ontario, Canada. She supports patients, families, nurses, physicians and other healthcare providers in optimizing hospice palliative care through capacity building, education, consultation, research and symptom management.

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Advanced Practice Nurses (nurse practitioners and clinical nurse specialists) also provide co-consultation to patients and healthcare professionals to optimize awareness and availability of palliative care services.

Expert Perspective from page 7

no NGS approach in oncology has been approved by NMPA currently. Furthermore, NGS is still costly and time-consuming, requiring approximately 2 weeks for results turnaround. Finally, we agreed with Dr. Oxnard that some other challenges, including how best to quantify mutations levels and define meaningful changes of ctDNA for monitoring treatment, must still be addressed to ensure reliable treatment decisions in the clinical setting. ♦

– Fei Zhou, MD, and
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Tumor Agnostic Targeted Therapies

from page 4

entrectinib has significant systemic and intracranial activity in both *NTRK* and *ROS1* fusion–positive NSCLC.

Future Potential Tumor-Agnostic Targets

There are numerous potential tumor-agnostic indications on the horizon, all of which will likely include important driver oncogenes in lung cancer. *RET* gene fusions have been identified in lung cancer, papillary thyroid cancer, colorectal cancer, and other tumor types. There are ongoing studies of selective *RET* inhibitors for patients with cancers harboring *RET* fusions including selpercatinib (LOXO-292; LIBRETTO-001, NCT03157128) and pralsetinib (BLU-667; ARROW, NCT03037385). The *FGFR1-4* inhibitor erdafitinib was recently FDA approved for urothelial carcinoma harboring pre-specified *FGFR* alterations including *FGFR* fusions that have previously been identified in NSCLC and other cancers. Erdafitinib is being evaluated in tumors with *FGFR* fusions, mutations, or amplification in the National Cancer Institute MATCH study (NCT02465060). *KRAS G12C* mutations, which occur most frequently in NSCLC but are found in numerous other malignancies, represent another exciting tumor-agnostic opportunity; recently developed, mutation specific inhibitors such as MRTX849 (NCT03785249) and AMG 510 (NCT03600883), have demonstrated preliminary antitumor activity in NSCLC.¹⁸ Finally, gene fusions involving *NRG1* were identified initially in NSCLC¹⁹ but recently have been identified in pancreatic, ovarian, and gallbladder cancers, among others.²⁰

Conclusion

Tumor-agnostic therapeutic strategies represent the true embodiment of a precision medicine approach to cancer by specifically targeting biologically relevant pathways, irrespective of old tumor classification systems. Currently, *NTRK* fusions represent the only tumor-agnostic indication for targeted therapies in cancer, with the recent approvals of larotrectinib and entrectinib. These recent successes demonstrate the willingness for regulatory agencies to consider novel indications and provide a roadmap for future tumor-agnostic oncogene targets. Multiple opportunities still exist for new tumor-agnostic indications for other oncogenes in cancer, including *ALK*, *ROS1*, *RET*, *FGFR*, *NRG1*, *KRAS G12C*, and others. The future success of tumor-agnostic strategies will depend on several factors including the implementation of cross-tumor trial teams to facilitate enrollment beyond organ-specific tumor sites and, most importantly, the broad deployment of multiplexed next-generation sequencing panels to identify eligible patients. ♦

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A DEEPER DIVE



Rebuilding Choice Architecture for Incurable but Treatable Lung Cancer: Rethinking the Future of Hospice Care in the United States

By Maggie Salinger, MD, MPP, and Arif Kamal, MD MBA, MHS, FAAHPM, FASCO

Hospice is a nationally known interdisciplinary program that provides comfort care for the terminally ill. Yet, despite being lauded for its positive effects on both quality of life and healthcare costs, hospice continues to be an under-utilized resource.¹⁻³ Fewer than half of Medicare beneficiaries leverage hospice's end of life (EoL) services, and, of those who do, nearly one-third postpone comprehensive palliation until death is less than a week away.³ The issue of low and delayed hospice uptake is linked to unfavorable choice architecture in the lead-up to enrollment, where simplistic eligibility criteria mandate that patients select either disease-directed therapies or comfort-focused ones—a distinction that has become all the more obsolete with the evolution of therapies that are better targeted and better tolerated, particularly in lung cancer. Thus, with an eye toward reduced spending and improved patient autonomy, policy makers have been considering ways to eliminate

has occurred within the Veterans Health Administration (VHA). Since 2009, the VHA's Comprehensive End of Life Care Initiative (CELICI) has invited veterans to receive hospice care in conjunction with disease-directed therapies. Through a recent study in *JAMA Oncology*, Mor and colleagues leveraged this large-scale programmatic shift and the fact that its rollout would vary across time and space to perform a quasi-experimental examination of CELICI's effects.⁴ The study should be applauded not only for its clever design and promising results, but also for its significant contribution to broader economic, political, and philosophical discussions.

Using a cohort of more than 13,000 patients with newly diagnosed stage IV NSCLC at VHAs across the country (years 2006 through 2012), Mor's team constructed a modified difference in differences regression to compare patients with high levels of hospice exposure to those with low levels of exposure according to the rate of palliative care consults at each site. The outcomes they examined in the 6

or aggressive treatment.⁴

Their design stands out among other studies on the topic both because of its large sample size and its ability to circumvent the selection bias inherent in a comparison of individuals opting into or out of hospice. These strong suits amplify the significance of their findings, which show that promotion of patient autonomy through palliative integration is not only possible, but also practical.

Mor et al.'s analysis revealed that people in high hospice exposure groups received more concurrent care (e.g., palliative consult plus radiation therapy) and less aggressive care (17.5% vs. 7.4% and 28.3% vs. 35.5% in the highest vs. lowest quintiles, respectively). The quintile with highest exposure was also the least expensive, yielding savings on the order of a couple hundred dollars per day.⁴

These differences in cost were evident despite the fact that hospital length of stay was similar among quintiles.⁴ Thus, savings seemed to come from a hospice-associated reduction in people's demand for aggressive interventions. Framed differently, financial gains were not predicated on restricted access to cancer therapies, nor were they dependent upon allowance of only one therapeutic modality at a time.

Implications for Systemic Change

The implication for policy makers is that we need not marshal patients into silos; we may still be able to provide affordable care when hospice is offered as a complementary ser-



Dr. Maggie Salinger



Dr. Arif Kamal

vice rather than solely as a substitute for active anti-neoplastic treatment. One risk of generalizing these findings, however, is that fewer than 20% of veterans received concurrent care in the highest quintile, and the magnitude of savings associated with hospice exposure diminished over time.⁴ Therefore, it would be difficult to predict the financial outcomes in a broader Medicare context where concurrent care could someday become more widely available, including in earlier stages of disease.

Further expansion of concurrent care would likely be accompanied by major policy changes, most notable among them being the possibility of Medicare Advantage (MA) swapping its carve-out model for a carve-in operation. This move toward a more integrated approach would be advantageous for a variety of reasons, but so too it might it also have deleterious effects.

As noted above, such policy changes would afford patients and providers greater degrees of autonomy and therapeutic flexibility. Alongside this ethical benefit, we would expect to see an increase in hospice uptake because at least some of its palliative services would become available by default. This would be a significant deviation from the current status-quo, in which patients must opt in to the program, agree to forgo medical treatment, and have a life expectancy of less than 6 months.

Shifting to a carve-in approach would also affect the quantity and quality of EoL services. Importantly, it would no longer be



this false dichotomy between medical and palliative care at the EoL.

Much of the innovation in this space

months following diagnosis were per capita costs and patterns of healthcare utilization, including receipt of concurrent and/

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the case that hospice enrollees are transitioned out of MA plans and into traditional Medicare. Because integration would heighten MA's financial responsibility at the EoL, its contracted payers would fold hospice-related costs into their capitated payment plans. Replacing the current per diem basis of payment would alleviate concerns about the duration of hospice care and instead direct attention to its quality.⁵ However, the associated need for payers to recalculate risk scores would be complicated by the fact that any change in the choice architecture for hospice enrollment would bring with it a change in the demand for its palliative services, the extent and cost of which would be difficult to estimate.

There is also general uncertainty about which hospice interventions reap the most benefit. As a result, policymakers have no clear guidance for how to go about streamlining a program that, historically, has been so adept at tailoring its care. And although it is true that Mor et al.'s study implies we can have our cake and eat it too, we know that some traditional elements of hospice are actually going to be cost inefficient in the eyes of insurance payers. As an example, carve-in plans are unlikely to offer year-long bereavement support to family members of decedents.

The potential for mismatch between the socially determined value of an initiative and its economically calculated worth extends far beyond the topic of hospice redesign. But because death is a destiny we all share and an event of great import to all cultures, perhaps this particular policy issue could bring unity to a divided Congress and serve as a roadmap for navigating other philosophical complexities in the healthcare reformation of the United States. ♦

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SUPPORTIVE CARE

Palliative Care for Patients With Lung Cancer in China



By Hui Tan, MPH

Lung cancer is the most prevalent cancer and the leading cause of death from cancer in China.¹ Approximately two-thirds of patients with lung cancer die within 2 years due to advanced disease (stage IIIB and IV) at time of diagnosis. Many patients with lung cancer experience multiple physical symptoms, including fatigue, shortness of breath, pain, appetite loss, insomnia, nausea, and dry cough.² Multiple studies have demonstrated that better patient outcomes are associated with palliative care. However, compared to Western countries, palliative care is extremely limited in China.³

There are only a few comprehensive palliative care programs or units at Chinese tertiary hospitals in large cities. For example, at Hunan Cancer Hospital, the interdisciplinary lung cancer care team (including oncology nurses) and palliative unit deliver palliative radiation therapy, chemotherapy, and surgery, targeted therapy, and pain control for patients with advanced lung cancer. In addition, Chinese medicine, acupuncture, and massage play an important role in palliative care because they improve quality of life and reduce side effects of

chemotherapy. Regarding psychosocial distress, nurses generally provide psychosocial care to patients with cancer simply because there are no social workers in Chinese hospitals. A recent nursing study showed that 38.6% of Chinese patients with lung cancer reported a relatively high level of psychosocial distress during hospitalization.⁴ There are few nursing models, nursing clinical guidelines, and nurse training resources available for managing psychosocial distress in China, so implementing universal psychosocial distress screening is still premature.^{4,5}

Words Matter

Another barrier to palliative care is the stigma associated with end of life. Death and dying is a major taboo in Chinese culture. When “palliative care” was first introduced in China, the name “Lin Zhong Guan Huai (临终关怀)” was used, which translates to “terminal care.” Understandably, this term is regarded by patients, families, and healthcare professionals as unlucky and constitutes a major impediment to referral. Recognizing this challenge, Dr. Li adopted the term “Gu Xi Guan Huai (姑息关怀),” which means “care to alleviate suffering.” This name is now widely used in China along with another name, “Huan He Yi Liao (缓和医疗),” which has a similar meaning. Even though the term for palliative

care has been changed, patients are often referred relatively late in the course of their disease to a palliative care unit.⁶ This underscores the need to develop training programs for palliative care in China; palliative care education should focus not only on physicians and their nurses but also on patients and their families. ♦

About the Author: Hui Tan is a nurse manager in the Department of Thoracic Neoplasm Chemotherapy, Hunan Cancer Hospital, the Affiliated Hospital of Xiangya School of Medicine, Central South University, China, and is a visiting scholar at the Yale University School of Nursing.

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ADVOCACY AND SURVIVORSHIP

A Balancing Act: Managing Patients' Expectations

By Leah Lawrence

Many patients newly diagnosed with lung cancer have difficulty navigating the world of cancer when unexpectedly and unwillingly thrust into it. In addition to understanding their diagnosis, prognosis, and treatment options, patients are also bombarded with an abundance of information on the internet, direct-to-consumer advertising of new cancer therapies, and headlines in the media touting miracle cures.

“It can be overwhelming,” said Janet Freeman-Daily, a lung cancer survivor and patient advocate.

Ms. Freeman-Daily was particularly taken aback in January 2019, when other patients with lung cancer began contacting her after seeing a headline written by the *Jerusalem Post* that read “A Cure For Cancer? Israeli Scientists May Have Found One.”¹

In the article, the chief executive officer of Accelerated Evolution Biotechnologies Ltd. said that, based on the results of a recent study, the company would be able to offer a “complete cure for cancer” within a year's time. However, only by scrolling to the last paragraph of the article could a reader see that the company had just completed a mouse experiment testing the new approach.

“There are so many people desperate for hope that they may see a headline talking about a ‘cure’ without reading the body of the article, and share it on social media,” Ms. Freeman-Daily said. “More people see it and do the same thing. It can be dangerous.”

The seductive headline teasing a cure-all for cancer led to myriad other news and social media outlets picking up the story. The timing of this was particularly tragic because in the week prior to the article's publication, hundreds of journal-

ism professionals, including those specializing in health news, were laid off,² Ms. Freeman-Daily noted.

“I would like to see the press become much more aware of the impact they can have on people,” Ms. Freeman-Daily added. “They should not be using the word ‘cure’ in a headline or the article when it is not yet proven.”

Another recent headline read, “Terminally-Ill British Mother, 40, Who Kept Her Lung Cancer Secret From Her Young Daughter Shocks Medics After Tumour Shrinks by 75% Following Alternative Treatment in Mexico.”³ In the article, the woman credits the alternative therapies for shrinking her tumor. These included treatments focused on heat, light, and laser therapies, according to the article, including hyperbaric oxygen therapy, coffee enemas, saunas, and infrared lamp therapy. Only by scrolling far

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DIAGNOSTIC ONCOLOGY

REPORTS FROM THE IASLC PATHOLOGY COMMITTEE

PD-L1 in Cytology Specimens

By Anjali Saqi, MD, MBA; Deepali Jain, MD, FIAC; Lukas Bubendorf, MD; Keith Kerr, MB, ChB, MRCPATH, FRCPath, FRCP(Ed); and Andre Moreira, MD, PhD

Lung cancer is a leading cause of cancer-related deaths worldwide. In the 21st century, there have been two significant developments in the systemic management of lung cancers. The first was the introduction of tyrosine kinase inhibitors (TKIs) reserved for patients with confirmed driver mutations. The second, as well as the most recent, is the incorporation of immune checkpoint inhibitors as a standard of care in the armamentarium. There are multiple immune checkpoint inhibitors, and each has its respective predictive PD-L1 immunohistochemical (IHC) biomarker test—companion or complementary—that interrogates patient eligibility.

Although promising data have continued to expand indications for immune checkpoint inhibitors, enrollment into clinical trials is frequently restricted to those with biopsy/histology specimens. This criterion affects clinical adoption and may cause question over the validity of testing on cytology samples, which comprise a significant proportion and are often the only available specimens upon which lung cancer diagnoses are rendered. We believe that cytology-type samples, when prepared appropriately, are valid material for clinical PD-L1 testing.

In an effort to address the shortcomings and lack of data, several studies across different laboratories and countries have examined PD-L1 testing on cytology specimens, including as part of the Blueprint Phase 2 Project that compared staining of five PD-L1 IHC assays on clinical samples.¹⁻¹² These studies have addressed several questions, which are summarized here.

1. Can cytology specimens be used for PD-L1 testing?

The overall consensus is that cytology specimens are suitable for PD-L1 testing.

2. Are results of PD-L1 cytology specimens equivalent to those of surgical biopsies and resections?

Results of PD-L1 testing on cytology specimens are highly concordant with those of histology specimens, including among squamous cell carcinomas, adenocarcinomas, and NSCLCs.

3. Which PD-L1 assays can be used on cytology preparations?

All assays have been tested on cytology specimens. Akin to testing on their histology counterparts, cytology specimens with assays 22C3, 28-8, and SP263 are similar, whereas SP142 and 73-10 demonstrate relatively lower and higher sensitivities, respectively, for tumor cell staining.

4. What types of cytology specimens can be stained with PD-L1?

PD-L1 testing is feasible on all cytology preparations, including fine needle aspirations (FNAs) and exfoliative specimens (i.e., effusions, bronchoalveolar lavages [BAL], brushings) used in the diagnosis and staging of lung cancer.

5. Which cytology preparations have been evaluated for PD-L1?

Most published PD-L1 studies on cytology specimens, including as part of the Blueprint Phase 2, have been performed on cell blocks. Although concordant with matched histology specimens and promising, there are limited data on the use of Papanicolaou-stained slides (i.e., smears and liquid-based cytology [LBC]) relative to cell blocks.

6. What are the advantages of cytology specimens?

First and foremost, cytology specimens represent a significant proportion of lung cancer specimens and, therefore, provide greater access to patients for potential systemic therapy options. Second, the back-and-forth or fanning tissue-disruptive motion of FNA acquisition is advantageous for sampling a broader area than is feasible with a relatively localized sampling with a biopsy. Similarly, effusions and BALs can detect cells from different areas. These sampling modalities may capture tumor heterogeneity.

An advantage specific to cell blocks is preservation of some degree of architecture. This is particularly helpful for matching and localizing cells of interest on serial slides, identification of cell membrane staining, as well as providing histological cues for those without formal training or limited exposure to interpreting cytology.

7. What are potential drawbacks of cytology specimens?

Several limitations apply to all small specimens (small biopsy and cytology) rather than specifically to cytology. Most predictive assays frequently have mini-

mum tumor cell/tissue requirements. Small specimens may suffer from low yield and insufficient cellularity following tissue allocation for various tests set forth by guidelines for advanced-stage lung adenocarcinomas. When interpreting PD-L1 results, differentiating between relatively small tumor cells without significant nuclear pleomorphism and macrophages, especially when both are similar in size and singly dispersed, can be challenging. Some PD-L1 assays require tabulation of immune cells; there is poor reliability on histology specimens. Moreover, in a limited sample, assessing whether immune cells are associated with the tumor or not may not be feasible and should be evaluated only in the context of sufficient and intact tissue fragments.

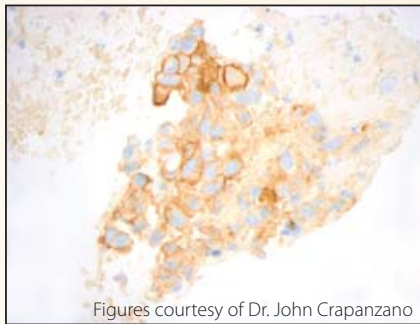
There are drawbacks unique to cytology specimen subtypes other than formalin-fixed paraffin embedded (FFPE) cell blocks, including cell blocks with ethanol pre-fixation, smears, and LBC. First, on smears and LBC, membranous staining may be less pronounced, and the distinction between membranous and cytoplasmic staining could be blurred and compromised by overlapping cells. Also, non-FFPE preparations require

Table. PD-L1 in Cytology

| Year | Study | Assay(s) | N | Diagnoses | Specimen type(s) | Preparation | Fixation | Concordance with FFPE | Matched specimens |
|------|------------------------|---------------|-----------|--|-------------------------------------|-----------------------|--|-----------------------|----------------------------------|
| 2017 | Skov et al. | 28-8 22C3 | 86 pairs | ADCA SQCA NSCLC Other | EBUS FNA EUS-FNA Effusion | Cell blocks | Formalin | 85% - 95% | Matched histology |
| 2017 | Heymann et al. | 22C3 | 214 | ADCA SQCA NSCLC | EBUS FNA Effusion | Cell blocks | Formalin | 91% | In 23 matched specimens |
| 2018 | Ilie et al. | ASL48 22C3 | 70 pairs | ADCA SQCA | BAL Effusion | Cell blocks LBC | Formalin NovaPrep | 90% | Matched histology |
| 2018 | Jain et al. | SP263 | 26 pairs | ADCA SQCA | Brushing Washing | LBC | CytoRich Red (Papanicolaou-stained) | 88% | Matched histology |
| 2018 | Russell-Goldman et al. | EIL3N | 56 pairs | ADCA SQCA NSCLC Small cell Other | FNA Effusion Brushing Rinse | Cell blocks | Formalin | Moderate to high | Matched histology |
| 2018 | Wang et al. | 22C3 | 1419 | ADCA SQCA NSCLC | EBUS FNA EUS Effusion BAL | Cell blocks | Formalin Methanol / Ethanol | | |
| 2018 | Noll et al. | 22C3 | 41 pairs | ADCA SQCA NSCLC | EBUS FNA | Smears Cell blocks | Alcohol (Papanicolaou-stained) | 97% 82% | Matched histology |
| 2019 | Hernandez et al. | 22C3 | 52 pairs | ADCA SQCA NSCLC | EBUS FNA Effusion Brushing | Cell blocks | Formalin | 67% | Matched histology |
| 2019 | Torous et al. | 22C3 | 232 | ADCA SQCA NSCLC | EBUS FNA Effusion Washing BAL | Cell blocks | CytoLyt | | |
| 2019 | Lozano et al. | 22C3 | 113 pairs | NSCLC | EBUS FNA EUS-FNA | Smears | Alcohol (Papanicolaou-stained) | 97.30% | Matched cell block and histology |
| 2019 | Gagne et al. | 22C3 | 1249 | ADCA SQCA NSCLC ADSQ Other | | Cell blocks | Ethanol Formalin | | |

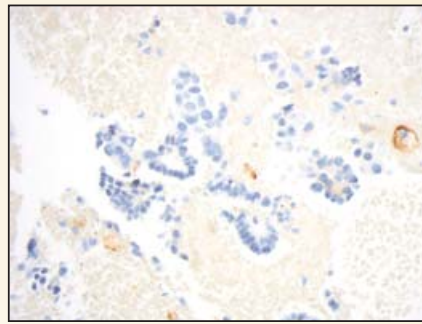
Abbreviations: ADCA, adenocarcinoma; SQCA, squamous cell carcinoma; NSCLC, non-small cell lung cancer; FNA, fine needle aspiration; EBUS, endobronchial ultrasound-guided FNA; EUS, endoscopic ultrasound-guided FNA; BAL, bronchoalveolar lavage; LBC, liquid-based cytology; FFPE, formalin fixed paraffin embedded.

**Fig. 1. PD-L1 Staining (Cell Block):
Staining Present in Adenocarcinoma**



Figures courtesy of Dr. John Crapanzano

**Fig. 2. PD-L1 Staining (Cell Block):
Staining Present in Macrophages**



additional rigorous validation and possible modifications of protocols and workflows, which may result in suboptimal adoption by laboratories.

8. Which type of cytology preparation should be used for PD-L1 staining?

FFPE cell blocks are currently the recommended cytology preparations for PD-L1 testing based on the greatest available data, including part of the Blueprint Phase 2 comparability study. Moreover, use of a standardized method that closely parallels histology provides initiative to integrate cytology into clinical trials, perform inter-laboratory comparisons and outcomes analyses, digitally scan/evaluate slides without a z-axis, and incorporate other efforts frequently restricted to histology specimens.

9. What are possible future directions?

Dual/multiplex staining that highlights and differentiates the tumor cells and macrophages can potentially aid in a more accurate assessment. The role of digital analysis and automated scoring requires further exploration. Most importantly, incorporation of FFPE cell blocks into clinical trials is essential. ♦

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MEETING HIGHLIGHTS

First-Ever IASLC School of Nursing Held at Latin American Lung Cancer Regional Meeting in Mexico City

By Enza Esposito Nguyen, DNP

The IASLC held its ninth Latin American Lung Cancer (LALCA) regional meeting in Mexico City this past October. Interest in this meeting has grown consistently, with more than 800 attendees participating this year. Each year, pre-conference schools are offered to provide in-depth content



Dr. Enza Esposito Nguyen

coverage for specialty groups within the organization. This year, three schools were offered: IASLC School of Thoracic Oncology, IASLC School of Pathology, and for the first time, IASLC School of Nursing (SON). The proposal for the SON was conceived by Luis Raez, MD, FACP, FCCP, and Christian

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Managing Patients' Expectations

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down in the story is it revealed that she had been placed on targeted therapy with alectinib prior to traveling to Mexico.

"The media plays a huge role in responsibly reporting these stories because any person interviewing her should point out that she was also on conventional therapy and at least ask her if she thinks that might have anything to do with her impressive results," said Corey J. Langer, MD, director of Thoracic Oncology and professor of Medicine at Perelman Center for Advanced Medicine, University of Pennsylvania, and Editor of the *IASLC Lung Cancer News*.

Closer to Home

Dr. Langer said that managing patient expectations can also be difficult when discussing direct-to-consumer advertising of evidence-based treatments that patients have seen on television or in magazines.

"Commercials for some of these newer drugs, particularly marketing for Merck's Keytruda and Bristol Myers Squibb's Opdivo, give patients a lot of hope," Dr. Langer said. "They often depict actors as patients who look a lot happier and healthier than a lot of my patients."

According to Dr. Langer, these commercials sometimes create unrealistic expectations with patients or imply that these drugs are destined to work better than other approaches.

"These commercials sometimes obligate me to bring patients down from an emotional high, and that is never good," he said. "It can create an adversarial relationship between the patient and the caregiver."

In some cases, Dr. Langer has even had patients come in begging for these drugs without even realizing that they are already being treated with them.

"Patients are getting bombarded, and

it is hard for them to discern what is bonafide from what is hyped," Dr. Langer said. "Giving a balanced perspective on some of this research doesn't make good TV, but it is what is necessary."

Where to Turn

To help patients weed through all of the available information on lung cancer, Dr. Langer often points them to patient advocacy groups or reliable online sources of information.

Ms. Freeman-Daily will often suggest that patients visit LCSMChat.com to find sources for trusted lung cancer information.⁴

When discussing the hype of some media articles, Ms. Freeman-Daily said that she has been accused of "trying to kill hope," but wanted to clarify that killing hope is not her intention at all.

"I want to help patients with stage IV lung cancer understand that there is no cure and that no one therapy is going to work for everybody," Ms. Freeman-Daily explained. "I encourage patients to work with their physicians to choose the treatment that is backed by evidence and that will provide the best possible outcome." ♦

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Dr. Richard Pazdur Discusses Project Facilitate and the Expanded-Access Program

In June 2019, the U.S. Food and Drug Administration (FDA) Oncology Center of Excellence launched Project Facilitate, a call center that assists oncology healthcare professionals with the submission process involved in obtaining unapproved therapies for individual patients with cancer via the Expanded Access program.¹ Richard Pazdur, MD, director of the FDA Oncology Center of Excellence fielded questions from the *IASLC Lung Cancer News* on the impetus behind this pilot project as well as its potential benefits to patients and the broader cancer care community.

Q: What is Expanded Access?

A: Expanded Access is a potential pathway for a patient with an immediately life-threatening or serious disease or condition to gain access to investigational therapies for treatment outside of clinical trials when there are no comparable or satisfactory alternative therapy options available. In those cases in which patients do not fit the trial requirements or live too far from a trial site, healthcare professionals can request permission from the FDA to treat a patient with an investigational medical product through Expanded Access.

Q: What is Project Facilitate, and what gap is it intended to address? How will the program's success be determined?

A: Navigating the Expanded Access process can be complex, particularly for oncologists who don't have experience working with clinical trials or these types of requests. Project Facilitate is a call center that is a single point of contact where FDA oncology staff help oncology healthcare providers through the process to submit an Expanded Access request for an individual patient. Experienced FDA oncology staff support oncologists and other healthcare professionals with their questions, assist in filling out the appropriate paperwork, and act as a facilitator for the process. As with all Expanded Access requests, the drug manufacturer has the right to approve or disapprove the physician's request. We will also need to determine if oncology healthcare providers are using Project Facilitate. There are several factors that will be used to evaluate the program, including use of the call center as represented by the number of calls to Project Facilitate.

Q: If Project Facilitate is deemed successful, are there plans to expand the program?

A: The FDA has been working to improve the Expanded Access framework, including the development of an updated and more streamlined application form. Project Facilitate is part of our continued commitment to Expanded Access, and we hope that the pilot program will simplify the process for oncology healthcare providers and will ultimately benefit patients. As Project Facilitate is a pilot program, it is too early to determine if the program will be expanded to areas outside of oncology.

Q: The FDA has also published new guidance on broadening cancer trial eligibility. How many patients are expected to be affected by that guidance, and will it reduce the need for Expanded Access?

A: The first option for patients for whom available treatments have been exhausted is to enroll in a clinical trial. However, in clinical trials testing treatments for cancer, some eligibility criteria have become commonly accepted over time or used as a template across trials without a clear scientific or clinical rationale or justification. In other cases, eligibility criteria can be deliberately restrictive, even though it is not clinically merited.

In March 2019, the FDA published four draft guidances and one final guidance regarding cancer trial eligibility criteria.² These guidances provide recommendations on how sponsors could safely and effectively broaden the criteria for the inclusion of certain patient populations in clinical trials, when appropriate, for pediatric patients and patients with HIV, Hepatitis B and C Virus Infections, brain metastases, prior or concurrent malignancies, or organ dysfunction. It is too early to tell how many patients will be affected, but we hope that our recommendations will help to shift the design of oncology clinical trials to be more representative of the patients who may ultimately benefit from novel treatments.

In cases in which patients do not fit the trial requirements or live too far from a trial site, healthcare professionals can request permission from the FDA to treat a patient with an investigational medical product through Expanded Access.³

Q: Are there benefits to the FDA and the greater research community to having a program like Project Facilitate, apart from improving access for individual patients?

A: The pilot program includes a central office for oncology requests so that the FDA can follow up on individual requests and gather data, such as how many patients received the investigational medical products and if not, why the requests were denied. The FDA will use these data to determine how the process is benefiting patients and healthcare professionals. In addition, the data could assist in encouraging sponsors to open clinical trials to study drugs for additional indications. ♦

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Names and News

Jeffrey Bradley, MD, FASTRO, is the new executive vice chairman of the



Department of Radiation Oncology at Winship Cancer Institute of Emory University. Previously Dr. Bradley was the S. Lee Kling Endowed Professor of Radiation Oncology, clinical director of the Kling Proton Center, and chief of the Radiation Oncology Thoracic Cancer Service at Washington University School of Medicine in St. Louis. Dr. Bradley has served as the Lung Cancer Committee Chairman for NRG Oncology (the largest of the four adult National Clinical Trials Network Groups sup-

ported by the National Cancer Institute) since 2010, a role he will continue.

Stephen M. Hahn, MD, FASTRO, has



been nominated to be the next commissioner of the U.S. Food and Drug Administration by President Trump. If approved by the Senate, Dr. Hahn will vacate his position as chief executive officer of The University of Texas MD Anderson Cancer Center, which he has held since 2017. He is also the Gilbert H. Fletcher Memorial Distinguished Chair and professor of radiation oncology there. Previously, he was the chair

of Radiation Oncology at the University of Pennsylvania. Dr. Hahn specializes in lung cancer and sarcoma.

Vassiliki Papadimitrakopoulou, MD, has left The University of Texas MD



Anderson Cancer Center, where she was a professor of medicine in the Department of Thoracic/Head and Neck Medical Oncology, to join Pfizer Oncology as the Clinical Development Leader. Dr. Papadimitrakopoulou is also a member of the FDA's Oncologic Drugs Advisory Committee and was co-principal investi-

gator of the Master Lung Protocol Study.

Alice Shaw, MD, has joined Novartis as the vice president, global head of



Translational Clinical Oncology. Previously, Dr. Shaw was the director of Thoracic Oncology and the Paula O'Keeffe Endowed Chair in Thoracic Oncology at Massachusetts General Hospital, as well as a professor of medicine at Harvard Medical School. Dr. Shaw's research in *ALK* and *ROS1* rearrangements in NSCLC and in targeted-therapy resistance has led to novel treatment strategies. ♦

ADVOCACY AND SURVIVORSHIP

STARS Patient Research Advocate Training Program Seeks Patients and Caregivers

By Adam Mohrbacher

Patients with lung cancer and their caregivers are becoming more empowered and knowledgeable than ever. As a result, lung cancer now has a growing group of patients who have lived long enough to become advocates for their disease. Some are evolving into research advocates—volunteers with a personal connection to cancer who are passionate about helping translate research findings into meaningful outcomes for patients and their families. Lung cancer research advocates provide the perspective of the collective lung cancer patient community in order to help research focus on the questions most important to patients and to create studies that will extend lives and improve quality of life for people who have lung cancer. However, learning the complex mechanisms of action regarding different cancer therapies and details of clinical trial design can be a steep learning curve for many patients, even those who are strongly motivated.

Over the past year, the IASLC launched a new program designed to further empower aspiring patient research advocates (PRAs) called STARS: Supportive Training for Advocates in Research and Science. STARS aims to train, develop, and nurture lung cancer patient research advocates (PRAs) in the science and



From left to right, back to front: Caleb Egwuenu, Lillian Leigh, Shelly Engfer-Triebebach, Kim MacIntosh, Sue McCullough, Laura Greco, Jill Hamer-Wilson, Jill Feldman, Dusty Donaldson, and Dr. Upal Basu Roy.

realities of lung cancer research. In the program, PRAs work with mentors (experienced research advocates) and receive training to increase their scientific literacy and ability to provide accurate scientific translation to their patient-caregiver communities. Additionally, the program equips its participants to connect and communicate with lung cancer researchers and research agencies in order to bring the patient perspective to studies and policy. It involves a 6-month commitment on the part of both mentors and PRAs, culminating in each PRA presenting on a scientific focus topic to the rest of the STARS cohort. PRAs also must develop a plan for how they intend to use the skills acquired during STARS to com-

municate with the public or their lung cancer community during November's annual Lung Cancer Awareness Month event. Finally, both mentors and PRAs attend the IASLC World Conference on Lung Cancer (WCLC), which will be held in Singapore in 2020. At WCLC, they attend relevant presentations geared toward enhancing their knowledge of lung cancer research and treatments as

well as several activities that are exclusive for STARS participants.

"I firmly believe that research advocacy is a community endeavor. That's what the STARS program helped accomplish," said Upal Basu Roy, MPH, PhD, vice president of research for the LUNGevity Foundation, who also served as a mentor for STARS inaugural year. "Not only [does it] train future patient research advocates, but [it] also creates a long-lasting community that can co-learn and co-evolve, with the goal of ensuring that lung cancer research incorporates the patient voice."

Preparation for the second year of STARS is now well underway, with the application period scheduled to open in early February 2020. Healthcare professionals are encouraged to recommend the program to any established patient with lung cancer or caregiver advocate looking to increase their scientific capabilities and advocacy.

To apply to the STARS program, visit www.iaslc.org/stars. ♦

First-Ever IASLC School of Nursing

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Rolfo, MD, PhD, MBA, who recognized the significant contribution of nurses to the care of patients with lung cancer through the trajectory of their illness. They also recognized that there was a gap in specialty education for nurses.

As the event chair, I worked closely with local nursing delegates to assess the educational needs of thoracic nurses and identify regional nursing experts to present. The program was developed to provide an overview and updates on nurses' roles in clinical trials, access to care, lung cancer staging, biomarker testing, lung cancer screening programs, survivorship, and nutrition. Case-based presentations provided an opportunity for nurses to discuss the care of patients in the post-operative setting and in those receiving chemotherapy, targeted therapies, or radiation therapy; pain and symptom management; management of immune-mediated adverse side effects; and stigma of palliative care.


Approximately 40 nurses from Mexico,

Panama, and Brazil pre-registered. There was such enthusiasm for the SON that a total of 75 attendees were present, including several medical oncologists and thoracic surgeons who joined the SON to bring back information to the nurses with whom they work. Nursing participants appreciated the extent to which they shared common issues relating to the care of patients with complex cases of lung cancer, incorporation of palliative care early in the continuum of care, and management of the diverse family unit. In addition, nurses from each of the countries represented shared similar experiences in barriers to care delivery and gaps in access to care. All participants expressed interest in opportunities to participate in ongoing webinars and regional meetings to support their practice.

The next IASLC regional meeting is scheduled for November 2021 in Montevideo, Uruguay, with the goal of offering the second LALCA-SON. This SON program can serve as a model for other regional meeting around the globe to support and develop the practice of thoracic nursing worldwide. ♦

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This is an investigational trial. TTFields has not been approved by the US FDA for treatment of NSCLC.

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