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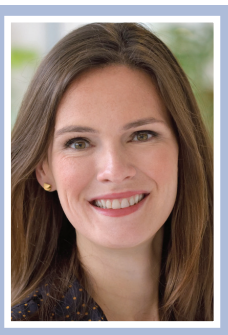
EVOLVING STANDARDS OF CARE

What Can We Offer a Patient with a Malignant Mesothelioma?

By Cornedine Jannette de Gooijer, MD; Maria Disselhorst, MD; and Paul Baas, MD, PhD

Until 2015, few changes occurred with respect to available therapies for malignant pleural mesothelioma (MPM). Luckily, a renewed interest in MPM with emphasis on immunotherapy has led to several phase II and III trials. The latest results and running trials in MPM are presented in the tables and are discussed in more detail in the article.



Dr. Cornedine Jannette de Gooijer

Dr. Maria Disselhorst

Dr. Paul Baas

Surgery

Whether to offer surgery to patients with MPM is subject to physicians' preferences and experience. The MARS 2 trial in the United Kingdom will evaluate the additional value of (extended) pleurectomy/decortication (P/D) to chemotherapy (NCT02040272). In this trial, 328 patients with MPM will be randomly assigned to chemotherapy with or without extended P/D. In the EORTC-1205 trial, the timing of chemotherapy (before or after) P/D will be examined in 64 patients (NCT02436733). Patients with limited-disease malignant peritoneal mesothelioma (MPerM) can participate in the MESOPEC study, in which adjuvant dendritic cell–based immunotherapy after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is being tested.

Chemotherapy

Evidence for maintenance chemotherapy in MPM is lacking. Maintenance pemetrexed has been under investigation since 2010, but no results have been published to date (NCT01085630). In the Netherlands, a study of switch-maintenance therapy with gemcitabine versus observation in the first-line setting in patients with nonprogressing disease after platinum/pemetrexed has finished accrual, and the first results are expected this year. To date, there is still no approved second-line treatment option. Retreatment with pemetrexed (plus platinum) can be considered.[1] Vinorelbine is under investigation in two randomized phase II studies, one comparing active symptom control to active symptom control with vinorelbine

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EVOLVING STANDARDS OF CARE

Checkpoint Inhibitors and Clinical Decision Making: A Q&A with Dr. Nasser H. Hanna

Q&A

Nasser H. Hanna, MD, is the Tom and Julie Wood Family Foundation Professor of Lung Cancer Clinical Research at Indiana University School of Medicine, and he specializes in the study and management of all forms of lung cancer. Dr. Hanna spoke with the *IASLC Lung Cancer News* in detail about the questions—asked and remaining—surrounding the use of checkpoint inhibitors (CPIs) in the front-line setting for squamous and nonsquamous NSCLC. In the interview below, Dr. Hanna shares information about his personal clinical decision-making process, and he highlights studies—published and ongoing—that provide a solid roadmap for therapeutic selection in each course of treatment.

Dr. Nasser H. Hanna

Q: As CPIs move to the front line, which regimen or regimens are now "standard" in the second-line setting in advanced NSCLC?

A: It is now standard of care to treat all patients with squamous cell NSCLC who are chemotherapy naive but are eligible for pembrolizumab with carboplatin and either paclitaxel or nab-paclitaxel plus pembrolizumab. Although many patients benefit from this combination, just about everyone will experience disease progression, which leads to the question of what to do in the second line for these patients. The standard-of-care treatment for nearly 2 decades in the second line for squamous cell has been docetaxel, which will continue to be an option for those patients who can tolerate treatment once every 3 weeks (usually at 60-75 mg/m^2 or once weekly, 3 weeks on/1 week off at 35 mg/m^2). Alternatively, patients can receive combination docetaxel/ramucirumab based on the results of the REVEL study.[1] This is very viable option for patients who are more fit and who do not have contradictions to ramucirumab, which is an antibody to the VEGF receptor.

For nonsquamous NSCLC, patients who have a PD-L1 tumor progression score (TPS) of at least 50% are eligible to receive pembrolizumab in the first line, and many of those patients will benefit for a time and then experience disease progression. For these patients, I think the standard of care will be carboplatin plus pemetrexed with or without bevacizumab. For patients with nonsquamous NSCLC who receive carboplatin plus pemetrexed plus pembrolizumab in the first-line setting and then subsequently experience disease progression, I think that, once again, docetaxel given once every 3 weeks, docetaxel given weekly for 3 weeks on/1 week off, and docetaxel plus ramucirumab are all options.

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CONQUERING THORACIC CANCERS WORLDWIDE

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(NCT02139904) and the other comparing pembrolizumab to gemcitabine or vinorelbine (NCT02991482).

Angiogenesis Inhibitors

Bevacizumab is the only angiogenesis inhibitor that has demonstrated a benefit in the management of MPM in phase III testing. It yielded a 2.7 month survival benefit in combination with first-line chemotherapy (pemetrexed/cisplatin) versus chemotherapy alone in 448 patients with MPM.[2] The addition of bevacizumab to chemotherapy is now considered a treatment option.[1] Nintedanib, an antiangiogenic tyrosine kinase inhibitor, showed promise in the phase II setting but failed to improve progression-free survival in combination with first-line chemotherapy in a phase III trial.[3,4]

Immunotherapy

Over the past few years, multiple promising phase II trials have been published on immune checkpoint inhibitors for MPM in the second or later line. Monotherapy PD-1 inhibitors (e.g., nivolumab and pembrolizumab), have yielded objective response rates (ORRs) of approximately 20%.[5-10] The PD-L1 checkpoint inhibitor avelumab had a somewhat lower ORR of 9%.[11] The only randomized phase IIB trial of immunotherapy with monotherapy tremelimumab (a CTLA-4 inhibitor) versus placebo failed to show any benefit.[12] Recently, two phase II trials testing nivolumab plus ipilimumab[13,14] and a trial testing tremelimumab plus durvalumab showed objective response rates between 25% and 38%.[15]

In the first line, a phase III study randomly selecting between standard chemotherapy and nivolumab plus ipilimumab is ongoing, and initial results are expected this year (NCT02899299). In further lines, a monotherapy PD-1 inhibitor is being tested in two phase III trials, versus either best supportive care (NCT03063450) or chemotherapy (NCT02991482).

Dendritic cell immunotherapy has attracted attention for its activity in mice and humans. Autologous monocyte–derived dendritic cells are pulsed with tumor lysate from five different mesothelioma cell lines and reintroduced into the patient.[16] This led to a phase II/III trial testing maintenance vaccination versus observation after effective first-line chemotherapy (NCT03610360).

Targeted Therapy

Mesothelin is a tumor antigen that is highly expressed in epithelioid MPM, which makes it an interesting target for therapies. Anetumab ravtansine is an antibody drug conjugate that is bound and internalized by mesothelin-expressing tumor cells. Unfortunately, compared to vinorelbine, it failed to improve progression-free survival. [17] A trial with pembrolizumab combined with anetumab ravtansine is recruiting patients in the United States (NCT03126630). Amatuximab is a chimeric monoclonal immunoglobulin antibody targeting mesothelin. In a multicenter phase II study, amatuximab in combination with pemetrexed and cisplatin was well tolerated and resulted in a disease control rate of 90%. However, the primary endpoint, 3-month improvement in progression-free survival, was not significant.[18]

Argininosuccinate synthase 1 is absent in up to 63% of MPM, making these cells dependent on systemic arginine. When cells are depleted of arginine, they go into apoptosis. Pegylated arginine deiminase (ADI-PEG) depletes systemic arginine. Single-agent ADI-PEG in 68 patients with ASS1-deficient MPM (out of 201 screened patients) resulted in a small progression-free-survival benefit and no overall survival benefit.[19] The ongoing ATOMIC-Meso phase II/III trial randomly assigns patients with mixed-type and sarcomatoid MPM to pemetrexed and cisplatin plus either ADI-PEG or placebo (NCT02709512).

BRCA-associated protein 1 (BAP1) is one of the most common somatic mutations in MPM. This tumor suppressor is critical in repairing double-strand DNA breaks. Olaparib, an inhibitor of poly ADP ribose polymerase (PARP), an enzyme involved in DNA repair, will be tested in 40 patients with MPM (NCT03531840).

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Table 1. Results from MPM Studies

MOA	Agent	Phase of Study	Number of Patients and Indication	Overall Response Rate (%)	Progression-Free Survival (months)	Overall Survival (months)
Immuno-oncology						
	Monotherapy PD-(L)1 (Pembrolizumab, nivolumab, avelumab)[5-9,11]	II	Total >150 MPM, > 1 line	9-26	2.6-5.4	10.7-18.0
	PD-(L)1 plus CTLA-4 (Nivolumab ± ipilimumab, durvalumab + tremelimumab)[13-15]	II	Total 221 MPM, > 1 line	25-38	4.3 - 6.1	11.8 – not reached
	Monotherapy CTLA-4 (Tremelimumab vs. BSC) 12	II/III	571, MPM, > 1 line	Trem, 4.5; BSC, 1.1	Trem, 2.8; BSC 2.7. (n.s.)	Trem, 7.7 BSC, 7.3 (n.s.)
Arginine depletion						
	ADI-PEG20 vs. BSC[19]	II	68, MPM, ASS1-deficient	A, 0; BSC, 0	A, 3.2; BSC, 2.0 (p = 0.03)	A, 11.5; BSC 11.1
Angiogenesis inhibition						
	Pemetrexed/cisplatin + nintedanib or placebo[3]	III, c	458 MPM, first line	NR	Nin, 6.8; placebo, 7.0 ; p = 0.91	Nin,14.4; placebo, 16.1 , p = 0.54
	Pemetrexed/cisplatin + bevacizumab or placebo[2]	III	448 MPM, first line	NR	Beva 9.2; placebo 7.3; p = 0.0001	Beva 18.8; placebo 16.1; p = 0.02
Mesothelin						
	Amatuximab[18]	II	89 first line	40	6.1	14.8
	Anetumab ravtansine vs. vinorelbine[17]	II	166 MPM, > 1 line, mesothelin positive	AR: 8.4, vin,: 6.1	AR: 4.3; vin, 4.5s; p = 0.859	AR: 10.1; vin, 11.6 months; p = 0.721

Abbreviations: A, ADI-PEG20; ADI-PEG20, arginine-lowering agent pegylated arginine deiminase; AR, Anetumab ravtansine; Beva, bevacizumab; BSC, best supportive care; NA, not applicable; NR, not reported; n.s. not significant; V, vinorelbine; MOA, Mechanism of action.

Table 2. Ongoing Studies for Which Data Are Awaited

Target	Agent	Phase of Study	Number of Intended Patients and Indication	Estimated Primary Completion Date
Immuno-oncology				
	Nivolumab plus ipilimumab vs. PP (NCT02899299)	III, accrual completed	600 MPM, first line	Q3 2020
	Nivolumab vs. BSC (NCT03063450)	III	300 MM, > 2 line systemic therapy	Q2 2021
	Pembrolizumab vs. chemotherapy (gemcitabine or vinorelbine) (NCT02991482)	III	144, MPM, > 1 line systemic therapy	Q4 2019
	MesoPher vs. BSC (NCT03610360)	II/III	230, MPM, maintenance after first line chemotherapy	Q1 2021
	DCBI after HIPEC (NTR7060)	II	20 MPerM	Q3 2020
Chemotherapy				
	Gemcitabine vs. BSC (NTR4132)	II, accrual completed	124 MM, maintenance after first-line chemotherapy	Q2 2019
	Vinorelbine vs. BSC (NCT02139904)	II	200 MPM, progression after PP	Q4 2018
Angiogenesis inhibition				
	Bevacizumab-atezolizumab-PP vs. PP-bevacizumab (NCT03762018)	III	320 MPM, first line	Q3 2024
Arginine depletion				
	PP + ADI-PEG 20 or placebo (NCT02709512)	II/III	386, MPM, non-epithelioid, ASS1-deficient	Q3 2020
Mesothelin				
	PP + amatuximab or placebo (NCT02357147)	II	Originally 610, now 108	Q4 2018
BAP1				
	Olaparib (NCT03531840)	II	40 MM, progression after PP	Q4 2020
Surgery				
	P/D with (neo)adjuvant PP (NCT02436733)	II	64 early-stage MPM	Q4 2019
	PP+ (E)PD or BSC (NCT02040272)	-	328 early-stage MPM	Q3 2022

Abbreviations: ASS1, argininosuccinate synthetase 1; BSC, best supportive care; (E)PD, (extended) pleurectomy decortication; MM, malignant mesothelioma; MPerM, malignant peritoneal mesothelioma; MPM, malignant pleural mesothelioma; MesoPher, autologous dendritic cells loaded with allogeneic tumor cell lysate; P/D, pleurectomy/decortication; PP, platinum-pemetrexed.

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Another strategy to target DNA repair is to block enhancer of zeste-homolog 2 (EZH2), which is often upregulated when BAP1 is mutated. EZH2 regulates differentiation of stem and progenitor cells. Preliminary results with tazemetostat, an EZH2 inhibitor, demonstrated a disease control rate of 51% at 12 weeks; 15 patients (25%) sustained disease control at 24 weeks, 5 of whom continue to have ongoing disease control.[20] ✦

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MEETING PREVIEW

IASLC 2019 Mesothelioma Meeting Offers Innovative Approach for Rapid Learning

Mesothelioma is a rare tumor with limited treatment options. The upcoming IASLC 2019 Mesothelioma Meeting (July 10-12) in New York City—a first of its kind for this disease site—promises to provide the latest clinical trial and emerging therapy information in the field. Preclinical and early clinical trial data will be presented for experimental and approved agents, and early predictive biomarkers also will be discussed. This meeting is a unique resource for clinical investigators and clinical care providers alike from around the globe. ✦

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This meeting is unique, as it takes a different format than other meetings. This is rapid-fire learning, with debates on controversial concepts in genetic profiling and biomarker standards.

The combination and pipeline immunotherapy agents section will definitely be a highlight at this meeting. Because we are only at the beginning of our understanding about mesothelioma immunogenicity, research strategies to augment and sustain the immune response against mesothelioma are critical to prolong survival. The meeting offers discussion about combination and pipeline immunotherapy agents that promises to be thought provoking.

–Dr. Anne S. Tsao, meeting co-chair

EVOLVING STANDARDS OF CARE

2019 IASLC Best of the World Lung Cancer Conference Results in New Virtual Collaboration

In March 2019, another successful Best of the World Lung Cancer Conference (BWLCC) was held in Lima, Peru. This was the fourth year in a row that the IASLC-LATAM (Latin American) Group organized a BWLCC in Lima. More than 160 attendees were provided with the most scientifically important presentations from the IASLC 2018 World Conference on Lung Cancer by a world-renowned faculty of IASLC members including Drs. Hossein Borghaei, Luis E. Raez, Claudio Martin, Luis A. Corrales, Andrés Cardona, Edgardo Santos, Francisco Tarrazzi, and Ana Botero. The meeting also featured IASLC-member faculty based in Latin America, including Drs. Luis A. Mas, Carlos Carracedo, Carlos Vallejos, Edgar Amorin, and Carlos Aliaga.

Dr. Luis Raez presented to more than 160 attendees at BWLCC in Peru.

BWLCC encourages audience participation through numerous case presentations and roundtable discussions. The highlight this year was the creation of an IASLC-Lung Study Group in Peru, which comprises 30 early-career oncologists and residents who are recent IASLC members. This group will meet virtually every month with Dr. Luis E. Raez, the IASLC-LATAM chair, to discuss the latest developments in lung cancer.

The conference was organized by Drs. Denisse Bretel, Luis A. Mas, and Luis E. Raez, with the support of local and international industry. ✦

Dr. Nasser H. Hanna from page 1

For both squamous and nonsquamous histologies, some patients will still be treated with gemcitabine, and other patients will go on clinical trials. There will be some patients who have very slow minimal progression who will continue to receive pembrolizumab for a bit longer in the first-line setting, and some patients with oligometastatic progression may receive local therapy and continue on first-line therapy.

The question that I think a lot of people want to know the answer to is, if a patient receives chemotherapy plus a CPI in the first-line setting, is there any value in continuing the CPI at the time of progression? In those patients who have slow progression, there may be some value in continuing the CPI. Response data has shown that there are clear times of tumor growth and shrinkage. Based on this, I tend to continue the CPI if the patient is doing clinically well, even if there is some temporary disease progression. There are a number of ongoing trials examining the mechanism of resistance to CPIs and the potential benefit of CPIs in combination with chemotherapy.

Fortunately, toxicities usually present themselves early in treatment; typically, the patients who get beyond 3 or 4 months of treatment with a CPI tend not to have any major toxicities thereafter. I would not anticipate that re-challenging someone with a CPI or switching to a different CPI is likely to cause any change in that side-effect profile.

Q: Does this reinvigorate the role of combination docetaxel and ramucirumab in this setting?

A: Docetaxel plus ramucirumab has demonstrated a survival advantage over docetaxel alone, which is not a small bar to eclipse. I think this combination is a very reasonable and acceptable option for many patients in the second-line setting who have already received a CPI with chemotherapy in the first-line setting regardless of histology (squamous and nonsquamous) and even for those patients who had previously received a taxane in the first-line setting. Previous to the CPIs moving into the first-line setting, the standard was typically chemotherapy in the first-line setting and single-agent CPI in the second-line setting, and then docetaxel with or without ramucirumab in the third-line. As you go from first to second line and second to third line, fewer and fewer patients are likely to get those treatments for a variety of reasons; therefore, anytime a therapy moves from the third to the second line it means, by definition, that more patients are likely to be getting that regimen.

Q: With respect to patients who have been on chemotherapy/CPI combinations front line, do you think there is a role for platinum re-challenge in patient who have stabilized or responded to prior platinum regimen(s) and who experience disease progression on CPI alone or on pembrolizumab/pemetrexed?

A: I think that in a data-free zone, we use the principles from other settings and we extrapolate information. Generally speaking, if patients have responded to prior platinum-based chemotherapy and it has been more than 6 months—certainly more than 1 year—since they have been exposed to a platinum agent and the patient continues to have a good performance status and is appropriate for combination therapy, I think it is very reasonable to add a platinum agent back. I do not think it makes any sense to do so for a patient with a poor performance status or for a patient who did not seem to have a long duration of benefit from a platinum-based therapy in the initial setting. This is a general principle that we have used for years, particularly for patients with SCLC who have been off a platinum regimen for more than 6 months and then experience disease progression.

Q: In a patient with nonsquamous NSCLC, would you consider resuming carboplatin, substituting a taxane for pemetrexed, and switching the CPI for an angiogenesis inhibitor? Why or why not?

A: That's a clinical judgement. There are now data from IMpower 150, which is a randomized phase III trial in the first-line setting of patients with nonsquamous NSCLC who were randomly assigned to receive carboplatin plus paclitaxel plus atezolizumab plus bevacizumab versus a comparator arm of carboplatin plus paclitaxel plus bevicizumab.[2] This study demonstrated improved PFS and OS for the four-drug regimen (HR = 0.775; 95% CI: 0.619-0.970; p = 0.0262), which proved both statistically and clinically significant. This regimen was approved by the U.S. Food and Drug Administration on December 6, 2018.

This really does address several questions: whether we can go back to a platinum-based regimen for patients who have been off of platinum-based chemotherapy for a while, if administering a taxane to a patient in the second-line setting who previously benefited from pemetrexed is worthwhile, and if adding an angiogenesis inhibitor in the second-line setting like we do with ramucirumab is worthwhile. I think those individual answers are all potentially "yes"; now, whether collectively they are appropriate for patients really remains to be seen and requires a great deal of clinical judgment. Again the individual principles hold up: re-challenge with a platinum, switch to a taxane, and add an angiogenesis inhibitor.

Q: What role is there for adding new immunotherapeutic agents (e.g., vaccines and CTLA-4 inhibitors) to front-line CPIs in those with "smoldering progression"?

A: This presumes that a patient received either single-agent pembrolizumab or chemotherapy plus pembrolizumab and then experiences disease progression. What is the value of maintaining that and simply adding on some other immunotherapy strategy, whether a vaccine or new class of immunotherapy, such as a CTLA-4 inhibitor? I think at this point, we have to just sit back and wait for the results of clinical trials. I do not know that there are any early data that are overly promising for that strategy with our current drugs. Vaccines are still significantly behind other immuno-oncology drugs with respect to lung cancer. I think that some patients will begin to receive combination immunotherapy in the first-line setting. There are data from the CheckMate 227 trial regarding nivolumab plus ipilimumab in comparison with chemotherapy, single-agent CPI, or chemotherapy/immunotherapy for patients with high tumor mutation burden (TMB), and it does appear that the duration of response and the PFS may be better with that combination in the first-line setting.[3] Now whether adding ipilimumab, tremelimumab, or some other CTLA-4 inhibitor to a CPI after the patient has already experienced disease progression on the CPI has any benefit is purely speculative; we really must await results of clinical trials.

Q: How do you handle "oligo-progression," where most sites are stable or responding but one or more are growing? Do you pursue locally ablative therapy and continue the original CPI? Or do you switch regimens?

A: This is a wonderful question because we have come to understand that different metastatic sites have different biologic, make-up and that in turn can explain why disease can be responsive in

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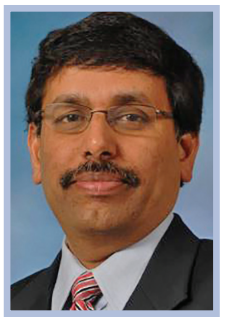
EVOLVING STANDARDS OF CARE

Q&A with Lead ALCHEMIST Investigator, Dr. Ramaswamy Govindan

ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial) is a large umbrella trial evaluating patients with early-stage NSCLC who have undergone complete tumor resection. As a whole, the trial will examine the role of erlotinib for those patients with *EGFR* mutations, crizotinib for those patients who have *ALK* rearrangements, and nivolumab for patients with no *EGFR* mutations or *ALK* rearrangements. Ramaswamy Govindan, MD, Anheuser Busch Endowed Chair in Medical Oncology, professor of medicine in the Division of Oncology, and director of the Section of Medical Oncology at Washington University School of Medicine, spoke with the *IASLC Lung Cancer News* regarding ALCHEMIST's trial design in comparison with other, similar trials in Asia, as well as the optimal duration of therapy in this setting. Dr. Govindan, who is the lead investigator of the *EGFR* portion of ALCHEMIST, highlights unanswered questions and controversies, as well as recent accrual statistics.

Q: SELECT—part of the rationale for ALCHEMIST—showed promising PFS, but a sharp drop-off after 2 years when the study drug was stopped. The same was true in a RADIANT subset analysis of patients with *EGFR* mutations and in a Canadian trial evaluating gefitinib in the adjuvant setting. This all leads to the question of whether 2 years of a TKI is sufficient in the adjuvant setting. Your thoughts?

A: That's a great question. The problem is that compliance is always a challenging issue in patients who have undergone a major surgery like thoracotomy. These patients go through not only surgery but also, most of the time, receive adjuvant chemotherapy with or without radiation. We feel that the longer duration of therapy would result in poor compliance. At some point, we have to just pick a duration; I think 2 years is a reasonable starting point. Much like what happened with endocrine therapy in breast cancer, no one knows what the optimal duration is at this point. In reality, however, these therapies have long-term side effects, such as malaise and dermatologic toxicities. If you can get patients to take 2 years of therapy, I think it's a good place to start. Future studies may have to address the question of the optimal duration of therapy. Let us crawl before we can walk. ALCHEMIST will be the first randomized trial to really look at the role of EGFR TKIs following standard therapy.



Dr. Ramaswamy Govindan

Q: Are EGFR TKIs effective when there is disease relapse, particularly after prior exposure in the adjuvant or neoadjuvant setting?

A: I think that we know, to some extent, that if patients relapse after adjuvant therapy, they may still benefit from EGFR TKIs based on the limited data we have. But post-ALCHEMIST, we will probably know a lot more about this. I suspect that (the potential benefit) will have to a lot to do with the interval time off therapy and what resistance mechanisms exist. For example, if a patient has a *EGFR* T790 mutation at the time of relapse, he or she will not respond well to erlotinib; if no *EGFR* T790 mutation is present, patients may respond well.

Q: In ALCHEMIST, is a tissue or liquid biopsy performed at the time of relapse and, if so, what molecular events are being examined?

A: We are collecting those specimens whenever possible, but we cannot mandate them for various reasons. At the time of disease progression, we encourage physicians to get tissue biopsies. If there is a sufficient amount of tissue in a specimen, we can do a comprehensive unbiased whole-exome analysis. When patients experience disease progression, they come off the study, so there is no way to mandate their cooperation regarding biopsies and lab results unless there is a follow-up study on which the patient can enroll.

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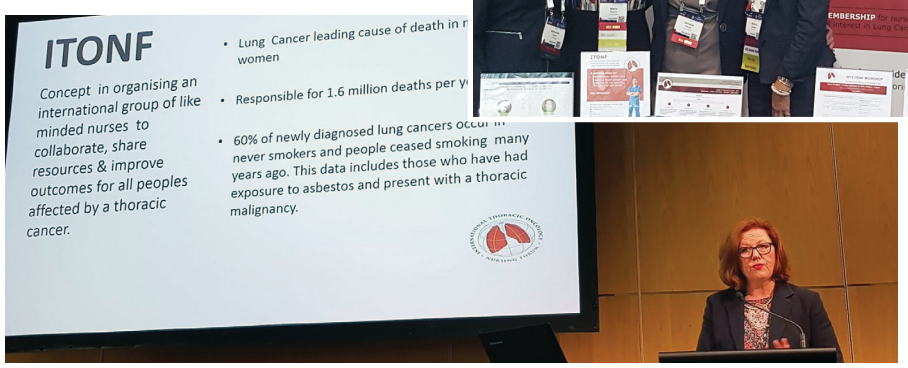
NURSES & ALLIED HEALTH PROFESSIONALS

The IASLC and the International Thoracic Oncology Nursing Forum: Celebrating Collaboration

By Marianne Davies, DNP, RN, ACNP

The International Thoracic Oncology Nursing Forum (ITONF) is an independent organization to support nurses who work in lung cancer and mesothelioma care. The organization started with a collaboration between nurse representatives from the National Lung Cancer Forum for Nurses, in the United Kingdom, and the Australia and New Zealand Lung Cancer Nurses Forum. The inaugural meeting was held at the 13th World Conference on Lung Cancer (WCLC) in San Francisco in 2009. There were more than 60 international nurses who attended. ITONF was officially launched in 2011, holding its first satellite workshop the following year at WCLC in Amsterdam. ITONF representatives have supported the local organizing committees for WCLC, assisting to develop the first Nursing and Allied Health Track within the scientific program in 2013 and, subsequently, the development of the IASLC Nurses and Allied Health Professionals Committee. ITONF holds its yearly workshop at the WCLC. ITONF representatives work closely with the IASLC Nurses and Allied Health Professionals Committee to support the WCLC.



The ITONF satellite symposium at WCLC 2019 will feature new international data about mesothelioma, as well as updates in surgery and radiation therapy.

ITONF Membership has continued to grow with members from Australia, Belgium, Canada, Denmark, Greece, Ireland, Israel, Japan, Nepal, the Netherlands, New Zealand, Norway, Sweden, Taiwan, the United Kingdom, and the United States. Speakers and delegates represent more than 20 countries. The mission of ITONF is to provide leadership with a unique forum to network internationally to support patient care, research, and education. ITONF has developed online educational materials for nurses around the world, including videos from some of the workshops with translation. ITONF is currently planning its next workshop for WCLC in Barcelona, which will feature surgical and radiation updates, information about emerging therapies, global nursing perspectives, new international data about mesothelioma, and education about evidence-based practice initiatives.

ITONF attendees enjoy international networking and online educational materials.

To register for the ITONF workshop, visit wclc2019.iaslc.org/registration/ and select the workshop from the preconference offerings. ITONF members also receive an IASLC member dues rate of only $30/year. ✦

About the Author: Ms. Davies is an assistant professor at Yale University, Smilow Cancer Hospital at Yale Comprehensive Cancer Center.

NOW ENROLLING: *MET* Amplified, Advanced/Metastatic NSCLC Patients Relapsed On Prior EGFR TKI Therapy

INSIGHT 2: A Phase 2, Single-Arm Clinical Trial for Tepotinib Combined With Osimertinib

Tepotinib is under clinical investigation and has not been proven to be safe and effective. There is no guarantee tepotinib will be approved in the sought-after indication by any health authority worldwide.

Description

INSIGHT 2 is a single-arm phase 2 trial investigating the safety and efficacy of tepotinib, an investigational oral and once-daily MET inhibitor, in combination with osimertinib in patients with *MET* amplified advanced/metastatic non–small cell lung cancer (NSCLC) harboring activating *EGFR* mutations and acquired resistance to prior 1st, 2nd or 3rd generation EGFR TKIs.

Study Design

- Locally advanced/ metastatic EGFR+ NSCLC
- *MET* amplification
- Acquired resistance to prior EGFR-TKI therapy
- N = 90

Tepotinib 500 mg QD
+
Osimertinib 80 mg QD
(21-day cycles until PD)

Select Endpoints

Primary endpoints
- Objective response rate by independent review
- Dose limiting toxicity (safety run-in only)

Secondary endpoints
- Safety
- Objective response rate by investigator assessment
- Duration of response
- Progression-free survival
- Overall survival
- Disease control
- Health-related quality of life
- Pharmacokinetics

Key Inclusion Criteria

- Histologically confirmed locally advanced or metastatic NSCLC with documented, activating *EGFR* mutation
- *MET* amplification
- Acquired resistance on previous EGFR TKI therapy
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1

Key Exclusion Criteria

- Inadequate hematological, liver, renal, or cardiac function, or hypertension uncontrolled by standard therapies
- Spinal cord compression or brain metastasis unless asymptomatic, stable or not requiring steroids for at least 2 weeks prior to start of study
- Any unresolved Grade 2 or higher toxicity from previous therapies

This information is current as of May 2019

Merck KGaA
Darmstadt · Germany

May 2019 US/TEP/0419/0003

To learn more about INSIGHT 2, please visit ClinicalTrials.gov (NCT03940703)

For more information, contact EMD Serono, Inc. at +1 888 275 7376

NOW ENROLLING: Advanced/Metastatic NSCLC Patients With *MET*ex14 Skipping Mutations or *MET* Amplification

VISION: A Phase 2, Single-Arm Clinical Trial for Tepotinib

Tepotinib is under clinical investigation and has not been proven to be safe and effective. There is no guarantee tepotinib will be approved in the sought-after indication by any health authority worldwide.

Description

VISION is a global phase 2 single-arm trial investigating the safety and efficacy of tepotinib, an investigational oral and once-daily MET inhibitor, in patients with advanced/metastatic non–small cell lung cancer (NSCLC) harboring *MET*exon14 (*MET*ex14) skipping mutations or *MET* amplification.

Study Design

- Stage IIIB/IV NSCLC
  - All histologies
- Tissue- or blood-based *MET* alterations
- 0 to 2 prior lines of therapy
- N = up to 120
- Regions: EU, US, Japan

Cohort A
***MET*ex14 skipping mutation**

Cohort B
***MET* amplification**

Tepotinib 500 mg QD
(21-day cycles until PD)

Select Endpoints

Primary endpoint
- Objective response rate by independent review

Secondary endpoints
- Objective response rate by investigator assessment
- Safety
- Duration of response
- Progression-free survival
- Overall survival
- Objective disease control
- Health-related quality of life
- Pharmacokinetics

Key Inclusion Criteria

- Patients ≥18 years of age with histologically confirmed advanced (stage IIIB/IV) NSCLC (all histologies including squamous and sarcomatoid)
- *MET*ex14 skipping mutations or *MET* amplification (plasma and/or tumor biopsy sample)
- Treatment-naive or pre-treated with no more than 2 lines of prior therapy
  - Prior therapy with a checkpoint inhibitor is permitted
- Measurable disease in accordance with RECIST version 1.1
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1

Key Exclusion Criteria

- EGFR activating mutations or ALK rearrangements that predict response to anti-EGFR or anti-ALK therapy, respectively
- Active brain metastases
- Prior treatment with other agents targeting the MET pathway

This information is current as of March 2019

Merck KGaA
Darmstadt · Germany

May 2019 US/TEP/0319/0002a

To learn more about VISION, please visit ClinicalTrials.gov (NCT02864992)

For more information, Contact EMD Serono, Inc. call +1 888 275 7376

Dr. Nasser H. Hanna from page 5

one area and progress in another area. There are a number of studies in lung and other cancers in which biopsies of different metastatic sites or a biopsy of a single metastatic site are compared with the primary site, demonstrating a different molecular biology for each site. We do this with patients who have oncogenic-driven cancers, such as *EGFR*, where patients can continue to have excellent therapeutic responses generally but experience disease progression in a few areas. We have tended to treat those areas locally and maintain the TKI, but I think a similar strategy can be looked at with the CPIs. One cautionary note about overinterpreting progression with CPIs is that sometimes patients do experience psuedoprogression, and sometimes patient responses wax and wane. We see this in the spider plots, which show from cycle to cycle how much the disease burden has increased or decreased; and we know that there is some fluctuation with immunotherapy. For many patients, treatment continues as long as they are clinically well. If it is clear that disease has progressed at a few sites but the patient is doing well otherwise and the majority of the disease burden is well controlled, I use stereotactic radiation to treat the local progression.

Q: How long are you treating patients with CPI in the second line? Does it differ based on drug?

A: I am treating patients until disease is clearly progressing or until the patient has a toxicity that requires them to discontinue treatment. We are awaiting the results of clinical trials to understand the optimal duration of therapy. With the original study of nivolumab, patients were randomly assigned after 1 year of therapy if they did not have disease progression; this was generally with nivolumab given in the second-, third-, and fourth-line setting—not in the first-line setting.[4] After 1 year, that study demonstrated that the patients who stopped the nivolumab had more rapid disease progression; PFS favored those who continued. Although a study like this was not designed or powered to show OS, the trend did favor continuation of the nivolumab. This was true for patients who had a partial or complete response to nivolumab, as well as for patients whose best response was stable disease. The studies with pembrolizumab, generally in the second-line setting, allowed for up to 2 years of therapy.[5] There are trials that are ongoing, particularly in Europe, that are looking at increasing the interval between treatments once you get to 1 or 2 years out, so patients might be randomly assigned to receive a drug every 3 weeks versus every 2.[6] Clinical trials are going to try to address this, but with the current data that we have, we do continue to treat as long as the patient appears to be clinically benefitting without experiencing a toxicity that requires discontinuation.

Q: Do some biomarkers (TMB for example) influence your choices to (re) use immunotherapy based on a patient's PD-L1 expression level?

A: The issue of biomarker development for immuno-oncology is critically important. It will help us identify patients who are destined not to benefit, as well as patients who are more likely to benefit from maybe more aggressive approaches such as combination therapy. Ultimately, our patients do want to be those 3-, 4-, and 5-year survivors and beyond, so we do want to optimize treatment; biomarkers have gone a long way in helping us do that. In fact, I would argue that we have better biomarkers for immuno-oncology than we ever had for chemotherapy. Some of those biomarkers include: PD-L1 expression; TMB; single mutations (such as *STK11* mutations, which seem to confer potential resistance); other parameters, such as neutrophil-to-lymphocyte ratios; presence of tumor-infiltrating lymphocytes; CD4 to CD8 ratios; and understanding the polymorphisms of the T cell receptor. There are a collection of clinical and biologic biomarkers that I think are all very interesting and which we are already beginning to use to some extent. In terms of PD-L1 expression specifically driving a decision in the second-line setting, I do not really think that is the case. I think it may play a larger role in something like whether we give nivolumab and ipilimumab without chemotherapy in the first-line setting rather than something like single-agent pembrolizumab or chemotherapy plus pembrolizumab. I think this will all be much clearer in the next year or two.

Q: Are you involved in any ongoing research regarding immunotherapy?

A: We have two studies that we are conducting in the Hoosier Oncology Group, both of which are investigator-initiated trials. One of these studies is in the so-called "immunoresistant" population and one is in the so-called "immunosensitive" population. We have defined "immunoresistant" patients as those who had prior platinum-based chemotherapy and a CPI but have experienced disease progression within three treatments of the CPI (NCT 02343952). These patients are being randomly assigned to single-agent chemotherapy versus chemotherapy/CPI as a way to determine whether there is any value of CPIs for patients who did not seem to benefit from CPIs in the first-line, but who perhaps could be re-sensitized or sensitized in the first place to the CPI simply by adding a different chemotherapy agent to it. "Immunosensitive" patients are those who have responded for a minimum of 3 months to a previous CPI (NCT 03083808). Our trial continues the CPI and adds a different chemotherapy agent to it at the time of progression. Again, this trial is really addressing the same question but in a different patient population. The idea behind this is that chemotherapy plus a CPI may be more effective than the CPI alone because the chemotherapy can cause some cellular kill and can introduce new neoantigens into the tumor microenvironment, thereby making that microenvironment more hospitable to the immune system, with improved capacity to recognize cancer antigens and mount a more robust response. One of our studies is approximately halfway complete, but it will take a couple of years.

The positive aspect to remember about the immunosensitive population is that when a patient responds to a single-agent CPI, the duration of response tends to be quite long—it is not usually measured in months but in years. This, however, requires a longer trial-recruitment period. For the immunoresistant population, these patients also tend to be chemotherapy resistant, so there are a number of complicating issues with trial enrollment. These trials are challenging to conduct. In theory, it is wonderful to just write down on a notepad these different trial designs, but in reality it is challenging to keep track, and it takes a considerable amount of time. ✦

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INDUSTRY AND REGULATORY NEWS

First New Treatment for SCLC in 20 Years

On March 19, 2019, the U.S. Food and Drug Administration approved atezolizumab for the first-line treatment of patients with previously untreated extensive-stage small cell lung cancer. The approval was based on data from the global, randomized, double-blind, placebo-controlled, phase III IMpower133 trial, which was presented at the IASLC 2018 World Conference on Lung Cancer. Data showed that the addition of concurrent and maintenance atezolizumab to first-line carboplatin and etoposide resulted in a significant overall survival benefit. Median OS was 12.3 months with atezolizumab versus 10.3 months in the control arm (hazard ratio [HR] for death 0.70 [0.54, 0.91]). In addition, the 1-year overall survival rate was 51.7% in the atezolizumab group and 38.2% in the placebo group. The objective response rates were 60% and 64%, respectively. ✦

(For more on the clinical and research implications resulting from IMpower133, read the ILCN article by the study author, Dr. Stephen V. Liu, at lungcancernews.org.)

EVOLVING STANDARDS OF CARE

Lorlatinib's Role in ROS1-Positive Lung Cancer

By Alice Shaw, MD, PhD

On November 2, 2018, lorlatinib, a potent and central nervous system (CNS)–penetrant next-generation ALK/ROS1 inhibitor, was granted accelerated approval by the U.S. Food and Drug Administration for the treatment of advanced ALK-positive lung cancer. The approval represents a significant advance for patients with ALK-positive lung cancer. Given lorlatinib's dual inhibition of both ALK and ROS1, the approval also raises several important questions regarding its role in ROS1-positive lung cancer.

Clinical Activity in ROS1-Positive Lung Cancer

The phase I dose-escalation study of lorlatinib enrolled 54 patients, 12 of whom had ROS1-positive lung cancer.[1] Among the 12 patients with ROS1-positive cancer, seven had received prior crizotinib. Objective responses were seen in six patients, yielding an objective response rate (ORR) of 50%; median progression-free survival (PFS) was 7 months. In the phase II study, 47 patients with ROS1-positive disease were enrolled into an expansion cohort and treated with standard-dose lorlatinib.[2] Among the patients who were crizotinib naive, overall efficacy was robust with an ORR of 62% and a median PFS of 21 months. Clinical activity was also documented in the crizotinib-refractory setting for which chemotherapy is the current standard of care, with an ORR of 27% and a median PFS of 9 months, suggesting some ability to overcome resistance to crizotinib. Of particular importance, lorlatinib demonstrated marked intracranial activity regardless of prior crizotinib exposure, with more than half the patients exhibiting a significant and durable intracranial response to lorlatinib.

Off-Label Use for Patients with ROS1-Positive Disease

Since its approval 3 months ago, lorlatinib has been prescribed for many patients in the United States with ROS1-positive disease. However, the process is not straightforward, and in many cases, the initial request was denied, most often due to the apparent lack of indication. Letters of medical necessity summarizing the patient's treatment course and citing the publicly available efficacy data (detailed previously) can often be successful in overturning a denial. In addition, referencing national guidelines such as National Comprehensive Cancer Network (NCCN) guidelines also carries significant weight, and the latest NCCN guidelines (version 3.2019) do recommend lorlatinib as a treatment option for patients with ROS1-positive disease that has progressed on crizotinib. In cases in which multiple appeals to the insurance company have failed, patients have applied successfully to the drug manufacturer (Pfizer) for free drug.

Dr. Alice Shaw

Patient Selection

Several next-generation ROS1 inhibitors are in clinical trials for patients

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INDUSTRY AND REGULATORY NEWS

Expanded Indication for Pembrolizumab

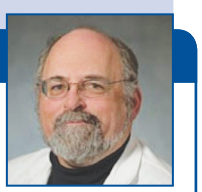
April 11, 2019—The U.S. Food and Drug Administration (FDA) expanded the approval of pembrolizumab in the first-line setting to patients with PD-L1 expression of ≥ 1% (tumor proportion score [TPS]), as determined by an FDA-approved assay. This includes patients with unresectable stage III NSCLC who are not candidates for definitive chemoradiation as well as patients with metastatic NSCLC. This indication excludes *EGFR*/*ALK* positive NSCLC.

Pembrolizumab is already approved as a single agent for the first-line treatment of patients with metastatic NSCLC and PD-L1 expression ≥ 50% (TPS) and as combined with platinum-based doublet (carboplatin and pemetrexed) regardless of PD-L1 expression. Recent approval was based on KEYNOTE-042, a randomized, multicenter, open-label, active-controlled trial conducted in 1,274 patients with stage III or IV NSCLC. Chemotherapy-naive patients with PD-L1 expression of > 1% (TPS) received either 200 mg IV of pembrolizumab every 3 weeks or investigator's choice of a carboplatin-containing regimen with either pemetrexed or paclitaxel. Patients were stratified by ECOG performance status, geographic region, histology, and PD-L1 expression (TPS > 50% or TPS 1%-49%).

Median OS was 16.7 vs 12.1 months for pembrolizumab vs chemotherapy, respectively, in those patients with PD-L1 expression > 1% (HR 0.81; 95% CI: 0.71, 0.93; p = 0.0036). For those patients with PD-L1 expression ≥ 20%, the median OS was 17.7 months and 13.0 months, respectively (HR 0.77; 95% CI: 0.64, 0.92; p = 0.004). The estimated median OS was 20 months vs 12.2 months, respectively, for patients with PD-L1 expression > 50% (HR 0.69; 95% CI: 0.56, 0.85; p = 0.0006).

However, in an exploratory analysis, in the cohort of patients with PD-L1 expression of 1%-49%, the median OS was 13.4 months for pembrolizumab versus 12.1 months for chemotherapy (HR 0.92; 95% CI: 0.77, 1.11). Hence, the positivity of this trial was driven by the results observed in patients with tumor PD-L1 expression levels of 50% or higher. ✦

EDITOR'S NOTE



The approval of single-agent pembrolizumab in patients with NSCLC with tumor PD-L1 expression levels of 1% to 49% remains controversial. As delineated by the exploratory analysis presented by Gilberto Lopes at the 2018 American Society of Clinical Oncology Annual Meeting, pembrolizumab did not result in an obvious survival advantage in this cohort compared to conventional platinum-based chemotherapy in treatment-naive patients. For now, based on the survival results of KEYNOTE-189 and KEYNOTE-407, pembrolizumab in combination with histology-appropriate chemotherapy remains the standard of comparison in this population. The National Clinical Trials Network in the United States is about to launch a phase III trial directly comparing single-agent pembrolizumab to combination pemetrexed/carboplatin and pembrolizumab in patients with advanced nonsquamous NSCLC with any degree of PD-L1 expression.

–Corey Langer, MD, Editor

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IASLC MISSION

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

MEETING HIGHLIGHTS

IASLC Targeted Therapies of Lung Cancer Meeting Draws Record Abstract Submissions, Attendance

By Paul A. Bunn, Jr., MD, FASCO

The 19th annual IASLC Targeted Therapies of Lung Cancer Meeting was held in Santa Monica, California, from February 20 to 23, 2019. The meeting chairs, Roy S. Herbst MD, PhD; Leora Horn, MD, MSc; Suresh S. Ramalingam, MD; and I created a program to be proud of and are happy to consider any feedback on the meeting for future improvements. Records were set for the number of abstracts submitted, the number of fellows and junior faculty who attended, and for the overall attendance.

The meeting started with remembrances of Adi Gazdar, MD, and Waun Ki Hong, MD, presented by Dr. Herbst; John Minna, MD; Tetsuya Mitsudomi, MD; and Giorgio Scagliotti, MD, PhD. These two lung cancer luminaries passed away shortly before the meeting and had contributed greatly to the meeting and to the thoracic oncology landscape over the years. The keynote speaker was Dr. Minna, who presented information about identification and targeting of lung cancer vulnerabilities that could lead to new therapeutic strategies and drugs. The faculty dinner speaker was Joan Schiller, MD, who gave a highly personal talk on our therapeutic progress in lung cancer as seen through her eyes over the years.

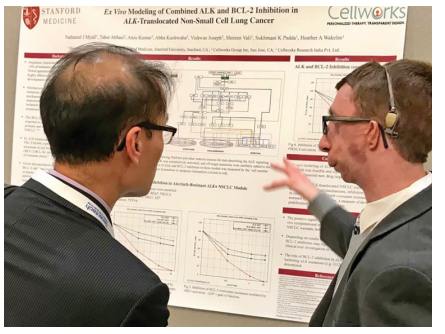
Debate Sparks Consensus

The program format was changed slightly from previous meetings to allow presentations on future directions at the end of each target session. Debates on critical issues were instructive, as well as engaging. It was clear from the presentations that both immunotherapies and molecularly defined tyrosine kinase inhibitors (TKIs) have dramatically changed the way lung cancer is evaluated and treated. All patients with advanced-stage lung cancer require molecular and immunologic biomarker testing before therapy is instituted. There was considerable debate about the optimal biomarkers and the most rapid and cost-effective way to achieve the biomarker testing, but PD-L1 scoring and next-generation sequencing have emerged as the current standard. The sessions on *ALK*, *ROS1*, *TRK*, and *RET* fusions made it clear that initial therapy for patients with these drivers should be an approved TKI; and it was equally clear that new TKIs that cross the blood–brain barrier and can target resistance mutations are emerging. Mutations in exon 20 of *EGFR* and *HER* and splicing mutations in *MET* have been challenging targets, but new agents are being investigated that may prove to be sufficiently effective for first-line use.

In addition, new strategies for immune therapy have emerged including personalized approaches and vaccines, as well as agents targeting the tumor microenvironment or other costimulatory or inhibitory targets. These treatments are being studied alone and with approved checkpoint inhibitors.

New Targets, New Hope

The standard therapy for patients with advanced SCLC has finally changed, based on recent data showing a survival advantage for the addition of atezolizumab to etoposide/platinum doublet chemotherapy. Agents targeting a number of important new targets are emerging and provide hope that continued advances will emerge. New EGFR and AXL TKIs are providing hope for future combinations and effective treatment with the development of resistance. Antibody–drug combinations and CAR-T cells are also proving effective in patients with specific targets. Developing new agents for the treatment of pleural mesothelioma has also been challenging, but there are new areas of research, including immunotherapies, antibody drug conjugates, and vaccines.



The new agents and strategies featured at the meeting provide clear evidence that outcomes in lung cancer are likely to continue to improve over time.

Although these new targeted therapies and immunotherapeutic approaches were initially developed in stage IV disease, exciting data on their use in stage III NSCLC combined with chemotherapy and radiotherapy, as well as in stages IB-IIIA combined with surgery and chemotherapy, show promise with the prospect of heightened cure rates in patients with earlier-stage disease.

Agents targeting other emerging targets such as FGFR/PDGFR and VEGFR inhibitors; PI3K, MTOR, and DNA repair inhibitors; CDK4/6 inhibitors; bromodomain inhibitors; aurora kinase inhibitors; and other miscellaneous targets are proving safe but remain in early development.

Overall, there have been a record number of recent drug approvals in lung cancer; in aggregate, these agents have transformed the therapeutic landscape and have improved outcomes for many of our patients. The new agents and strategies featured at the meeting provide clear evidence that our outcomes in lung cancer are likely to continue to improve over time. ✦


Attendees of the IASLC Targeted Therapies of Lung Cancer Meeting this past year participated in and learned from debate regarding optimal biomarkers and the most rapid and cost-effective way to perform biomarker testing.

About the Author: Dr. Bunn is distinguished professor of Medicine and the James Dudley Endowed Professor of Lung Cancer at the University of Colorado School of Medicine. Dr. Bunn is a prior IASLC President and was CEO of the IASLC from 2003-2013.

ROS1-Positive Lung Cancer

from page 9

with ROS1-positive disease. As ROS1 rearrangement is found in only 1% of NSCLC, encouraging clinical trial participation, when appropriate, is critically important to evaluating these new therapies and advancing the field. However, if clinical trials are not available or appropriate for a given patient, then prescribing lorlatinib may be a reasonable option, especially if standard treatments (eg, crizotinib, platinum-pemetrexed chemotherapy) have failed. Lorlatinib should be considered for all patients with ROS1-positive disease that is resistant or intolerant of crizotinib. Given its potent intracranial activity, lorlatinib may be particularly helpful for patients who develop CNS metastases on crizotinib. For those patients with ROS1-positive disease who have CNS metastases at the time of diagnosis, the risk of CNS progression on crizotinib is extraordinarily high, so it may be reasonable to consider off-label lorlatinib as first-line therapy in such patients to better treat and potentially prevent CNS metastases.

Whether lorlatinib will eventually gain regulatory approval for ROS1 is unknown, but in the meantime, off-label use can be an important and in some cases life-saving option for our patients with ROS1-positive NSCLC. ✦

EDITOR'S NOTE

"In The ROS1ders patient–caregiver group, we have seen many patients with ROS1-translocated NSCLC develop brain metastasis or other forms of disease progression during therapy with crizotinib. We are glad to have a second-line TKI as a treatment option, and we appreciate those providers who are willing to tackle extra paperwork to help us access it."

–Janet Freeman Daily, ILCN Associate Editor, Patient Advocacy

About the Author: Dr. Shaw is director of Thoracic Oncology, Paula O'Keeffe Endowed Chair in Thoracic Oncology, and professor of Medicine at Harvard Medical School.

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intrafusp alfa

INTR@PID CLINICAL TRIALS

Investigating the potential concomitant inhibition of TGF-β and PD-L1 with bintrafusp alfa (proposed INN for M7824) in multiple tumor types.

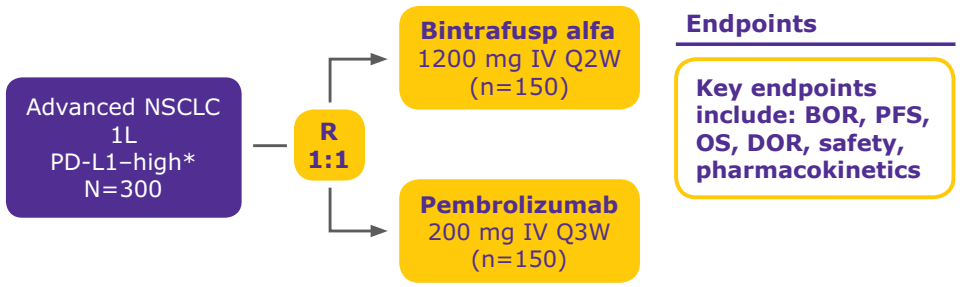
Bintrafusp alfa is under clinical investigation and has not been proven to be safe and effective. There is no guarantee that bintrafusp alfa will be approved in the sought-after indication by any health authority worldwide.

INTR@PID LUNG 0037 — Now Enrolling

LUNG 0037 | R RANDOMIZED | 1 MONOTHERAPY | STAGE IV

INTR@PID LUNG 0037 (NCT03631706) is a phase 2, randomized, multicenter, open-label study comparing bintrafusp alfa vs pembrolizumab in the first-line treatment of patients with advanced NSCLC with high PD-L1* expression levels.

Study Design | Global



Key eligibility criteria†

- Participants must have histologically confirmed advanced NSCLC with PD-L1–high* tumor expression

Key exclusion criteria†

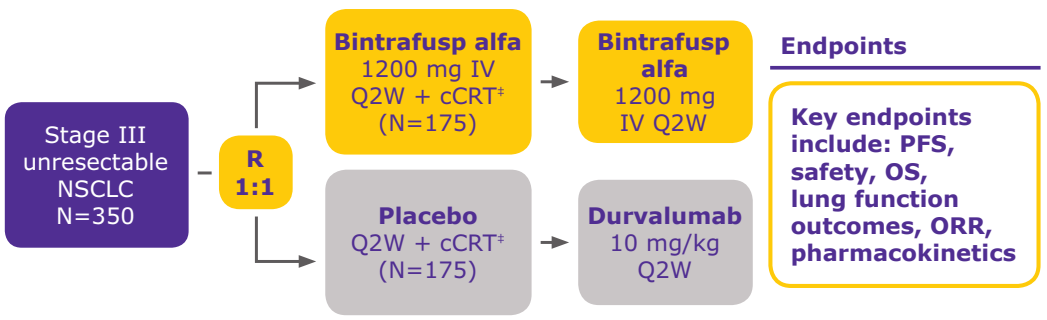
- Participants must not have received prior systemic therapy for advanced NSCLC and must not have *EGFR*-sensitizing (activating) mutations, *ALK* translocation, *ROS1* rearrangement, or *BRAF* V600E mutation

INTR@PID LUNG 0005 — Now Enrolling

LUNG 0005 | R RANDOMIZED | 1 2 COMBINATION THERAPY | STAGE III

INTR@PID LUNG 0005 (NCT03840902) is a phase 2, multicenter, double blind, randomized, controlled study evaluating bintrafusp alfa with concurrent chemoradiation followed by bintrafusp alfa versus concurrent chemoradiation plus placebo followed by durvalumab in patients with unresectable stage III NSCLC.

Study Design | North and South America, Europe, Australia, and Asia



Key eligibility criteria†

- Participants must have histologically confirmed stage III locally advanced, unresectable NSCLC, ECOG PS of 0 or 1 and adequate pulmonary function

Key exclusion criteria†

- Participants must not have mixed small cell and NSCLC histology or received prior systemic therapy for NSCLC

* PD-L1–high status as determined by central PD-L1 test or by prior testing using PD-L1 IHC 22C3 pharmDx assay.
† For a full list of all inclusion and exclusion criteria, please visit www.clinicaltrials.gov.
‡ cCRT consists of 60 Gy of radiation therapy in combination with standard chemotherapy (cisplatin/etoposide, cisplatin/pemetrexed or carboplatin/paclitaxel).

1L, first line; ALK, ALK receptor tyrosine kinase; BOR, best overall response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; IV, intravenous; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death 1 ligand 1; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks; R, randomized; TGF-β, transforming growth factor-β.

Are your patients eligible?

For more information, visit **www.clinicaltrials.gov**

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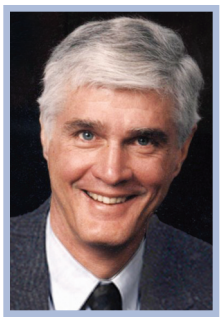
US/ONC/0519/0039 May 2019

EVOLVING STANDARDS OF CARE

The Peaks and Valleys in Lung Cancer Therapeutics Research

By Paul A. Bunn Jr., MD

It is indeed an exciting time in lung cancer therapeutics, and we have reasons to be optimistic. To put these advances in context, I remember the early days (1970s) of lung cancer research at the National Cancer Institute, when we conducted 12 consecutive phase II trials without a single response. The chemotherapeutic survival improvements were not documented until the 1980s. With as much improvement as we have seen, we still must put this recent excitement in the context of both our goals and those of our patients. The ultimate goal is to cure patients with as little toxicity as possible. Improving survival and lessening toxicity are valuable goals, but they are not the end goal. So where does that put us regarding success of molecular and immunotherapies?



Dr. Paul A. Bunn Jr.

Molecular Therapies

There is no question that patients with advanced NSCLC should undergo next-generation sequencing (NGS) panel testing for driver alterations that include at least *EGFR, ALK, ROS1, BRAF,* and *TRK* and that additional alterations may be actionable in the near future, including *RET* fusions, *MET* mutations, and *HER2* mutations. Testing for *KRAS* mutations, the most common mutation, is not useful at present, but it may be in the future.

What is the long-term outcome of patients with NSCLC with driver alterations who are treated with the appropriate TKIs? It is clear from the early Lung Cancer Mutation Consortium study and many phase II trials that objective response rates exceed 50%, progression-free survival may be as long as 3 years, and overall median survival may exceed 6 years for patients with some alterations, such as *ALK*.[1,2] This is unprecedented. In addition, patients may be spared the horrors of central nervous system and leptomeningeal metastases. This is marked progress indeed.

Despite much progress, these patients still are not cured, rarely have complete remissions, and virtually always experience relapse. Therefore, we must urgently understand the biology of disease persistence and the mechanisms of resistance, and we must develop rational drug combinations. We must understand the nature of the drivers in the other 75% of lung cancers. What about patients with early-stage disease? Could these therapies be added to standard surgery, radiation therapy, and chemotherapy to improve cure rates? The answers are unknown, but we eagerly await the results of ongoing adjuvant and neoadjuvant studies.

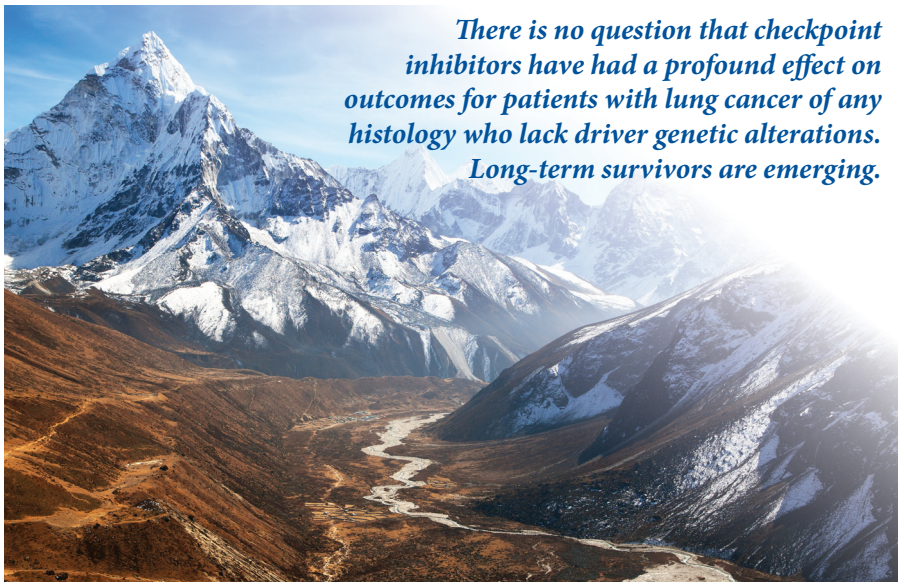
Immunotherapies

There is no question that checkpoint inhibitors have had a profound effect on outcomes for patients with lung cancer of any histology who lack driver genetic alterations. Long-term survivors are emerging. Nonetheless, only a minority of patients have disease that responds, predictive biomarkers are not fully defined, and cure remains elusive. On the positive side, assessment of PD-L1 expression is useful, at least in NSCLC histologies. Thus, all patients with advanced NSCLC should have PD-L1 testing prior to initiation of therapy. Fortunately, this immunohistochemistry testing requires only two unstained slides.

Patients with either squamous or non-squamous histology whose tumors express PD-L1 on more than 50% of cells have improved survival with single-agent pembrolizumab compared to platinum-based chemotherapy (KEYNOTE-042 and KEYNOTE-024).[3,4] This, too, is unprecedented. Never before has any therapy supplanted our standard platinum-based chemotherapy in advanced NSCLC. Despite the fact that a minority of patients have disease that responds, 2- and 3-year survival rates are quite impressive. Other studies have compared chemotherapy alone to chemotherapy plus checkpoint inhibitors in patients whose tumors have greater than 50% PD-L1 expression, and the combinations with immunotherapy have proven superior (KEYNOTE-189, KEYNOTE-407, IMpower131, and IMpower150) with respect to overall survival.[5-9] Unfortunately, there are no randomized trials directly comparing checkpoint inhibitors alone to chemotherapy plus checkpoint inhibitors. Although cross-trial comparisons are fraught with issues, the objective response rates and toxicity rates are higher with the combination, whereas long-term survival rates seem somewhat comparable. Thus, at present, it may be reasonable to treat the majority of patients whose tumors have greater than 50% PD-L1 expression and who have slowly progressive and non–life threatening cancers with immunotherapy alone, and reserve the combination for those patients who are highly symptomatic and who require an immediate response.

For patients with either squamous (KEYNOTE-407 and IMpower131) or non-squamous histology (KEYNOTE-021 Cohort G,[9] KEYNOTE-189, and IMpower150) and whose tumor cells express PD-L1 on less than 50% of cells, the combination of chemotherapy plus a checkpoint inhibitor (pembrolizumab or atezolizumab) has been shown to be superior to chemotherapy alone. This means that the majority of patients with advanced NSCLC (those without a driver genetic alteration) will receive either a checkpoint inhibitor alone or a checkpoint inhibitor with chemotherapy, depending on PD-L1 expression levels.

Although checkpoint inhibitors have clearly improved survival for many patients with NSCLC, they are not without expense and toxicity, they rarely produce complete responses, and they are unlikely to cure a large fraction of patients. Toxicities are common, may occur at any time during therapy, require discontinuation of treatment in as many as 10% of patients, and are more frequent when combined with chemotherapy.



There is no question that checkpoint inhibitors have had a profound effect on outcomes for patients with lung cancer of any histology who lack driver genetic alterations. Long-term survivors are emerging.

On the Horizon

Other potential predictive biomarkers such as tumor mutation burden from tissue or blood, gene expression profiles, and protein profiles are experimental and are under investigation.

With the goal of increasing the cure rate, there is evidence that administering a checkpoint inhibitor (durvalumab; PACIFIC trial)[10] after chemotherapy and radiation therapy will improve survival in patients with unresectable stage III NSCLC. We still await 5-year survival rates from this and other trials in stage III disease. For surgically resectable disease, there are preliminary data that the addition of either neoadjuvant or adjuvant checkpoint inhibitors to surgery with or without chemotherapy may improve survival. These studies suggest that the neoadjuvant use of checkpoint inhibitors alone or with chemotherapy prior to surgical resection produce much higher pathologic complete response rates compared to chemotherapy alone. The results of ongoing randomized trials are eagerly awaited.

SCLC

There are far fewer trials of immunotherapy in SCLC, and there are no established biomarkers for immunotherapy in this histology. Nevertheless, one published trial (IMpower133)[11] demonstrated that the addition of atezolizumab to etoposide/platinum-based chemotherapy in the first-line setting improved survival compared to chemotherapy alone. Although there have been some negative randomized trials in the second-line and maintenance settings, other first-line trials in extensive-stage disease, as well as combination trials in limited-stage disease, are ongoing.

In summary, we are only beginning to scratch the surface with immunotherapy. The available immunotherapies have improved survival in advanced disease, albeit with considerable expense and toxicity and with marginally effective predictive biomarkers. There is much to learn about the immune system and cancer therapy, and many new approaches are under investigation, including new immunotherapies, T-cell and vaccine therapies, and molecular targeted therapies for *KRAS, HER2*, *RET* and *MET*. Thus, in 2019, there are new, improved therapies for all lung cancer histologies, and biomarkers are required for all patients with advanced-stage disease

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Peaks and Valleys from page 12

before initiating therapy. Progress is definite, and, in the past decade, the pace of progress has expanded radically, but we must be realistic. We must continue to better understand the underlying biology before we can reach that elusive goal of cure for most patients. ✦

About the Author: Dr. Bunn is distinguished professor of medicine and the James Dudley Endowed Professor of Lung Cancer at the University of Colorado School of Medicine. Dr. Bunn is a prior IASLC President and was CEO of the IASLC from 2003-2013.

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Ki-67 in Pulmonary Neuroendocrine Tumors: Where Do We Stand?

By Anja C. Roden, MD, and Natasha Rekhtman, MD, PhD

Pulmonary neuroendocrine tumors are classified according to the World Health Organization into typical and atypical carcinoid tumors, small cell lung cancer (SCLC), and large cell neuroendocrine carcinomas (LCNEC).[1] Whereas typical and atypical carcinoid tumors are considered to be of low and intermediate grade, respectively, SCLC and LCNEC are high-grade carcinomas with poorer prognosis. This classification is solely based on morphologic features including cytologic characteristics, mitotic activity, and necrosis. The classification correlates well with outcome, with typical carcinoids having the highest 5-year survival rates, and LCNEC and SCLC having the lowest, with significant differences in survival between typical and atypical carcinoids and atypical carcinoids and LCNEC or SCLC independent of stage.[2] Reproducibility of this classification is substantial among experienced lung pathologists.[3]

Dr. Anja C. Roden

Dr. Natasha Rekhtman

Ki-67 labeling index (LI) does not play a role in the classification of resected lung neuroendocrine tumors, which contrasts with its status as a key parameter in the classification of gastrointestinal and pancreatic neuroendocrine tumors. In nonresection samples, expression of Ki-67 may be useful in the distinction of carcinoids from SCLC or LCNEC, specifically in small and/or crushed biopsies or cytology specimens. This application is supported by the experience of thoracic pathologists, as well as by current literature summarized in the "Best Practices Recommendations for Diagnostic Immunohistochemistry in Lung Cancer," which were recently published by members of the Pathology Committee of the IASLC.[4] In these recommendations, we emphasized that, at this time, there is no role for this marker to distinguish typical from atypical carcinoid tumors. Many studies have shown that Ki-67 LI is higher in atypical carcinoids than in typical carcinoids, but there is some overlap between these two groups.[5] Furthermore, several studies show that Ki-67 LI is associated with the risk for postsurgical recurrence of typical and atypical carcinoids; however, more data are needed to establish the added value of Ki-67 and to determine a possible cutoff.[6, 7]

There is no standardized Ki-67 scoring method for pulmonary neuroendocrine tumors.[8] Scoring of Ki-67 LI ranges from "eyeballing" the entire specimen to evaluating LI in hot spots either by manual count or digital analysis. Furthermore, reproducibility studies for the evaluation of Ki-67 LI are lacking. In metastatic gastrointestinal and pancreatic neuroendocrine tumors, Ki-67 is considered a key parameter in guiding systemic therapy. As a result, some clinical guidelines and recommendations[9, 10] have incorporated Ki-67 for clinical management of pulmonary neuroendocrine tumors, analogous to the approach used for gastroenteropancreatic tumors. However, the validity of Ki-67 LI for assessing prognosis and guiding therapy in metastatic pulmonary carcinoids still requires clinical validation. There are recent data on escalation of Ki-67 (and mitotic rate) during metastatic progression of lung carcinoids.[11] The clinical implications of this phenomenon also awaits further clinical investigation.

We recently formed a neuroendocrine working group within the Pathology Committee of the IASLC. The working group will explore practice patterns and new data in pulmonary neuroendocrine tumors that have recently emerged and how those could be incorporated into diagnosis, prognosis, and treatment of patients with these tumors. ✦

About the Authors: Dr. Roden is professor of Pathology and a thoracic and surgical pathologist in the Department of Laboratory Medicine and Pathology at Mayo Clinic. Dr. Rekhtman is a thoracic pathologist and cytopathologist in the Department of Pathology at Memorial Sloan Kettering Cancer Center.

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A DEEPER DIVE

PCI Decreases the Risk of Brain Metastases in Patients with Locally Advanced NSCLC

IN REFERENCE TO:

De Ruysscher D, Dingemans AC, Praag J, et al. Prophylactic cranial irradiation versus observation in radically treated stage III non-small-cell lung cancer: A randomized phase III NVALT-11DLCRG-02 study. *J Clin Oncol*. 2018;36(23):2366-2377.

By Elizabeth Gore, MD

Dr. De Ruysscher et al. are commended for completing a well-designed phase III trial of prophylactic cranial irradiation (PCI) in patients with radically treated stage III NSCLC.[1] The primary endpoint was incidence of symptomatic brain metastases at 2 years. The vast majority of patients were treated to 30 Gy in 10 or 12 fractions.

The incidence of brain metastases at 2 years was 7% with PCI and 27.2% with observation (p = 0.001), consistent with the findings in RTOG 0214, another contemporary phase III study comparing PCI and observation in patients with stage III NSCLC.[2] RTOG 0214 demonstrated a 1-year incidence of brain metastases of 7% with PCI versus 18% with observation (p = 0.004). Many other trials have consistently shown a decrease in brain metastases with PCI for NSCLC, although none have demonstrated improvement in overall survival. Completing a trial adequately powered to show a survival advantage has proven to be challenging for many reasons including imperfect selection criteria, physician bias, PCI toxicity, and patient reluctance to undergo randomization.

Prevention by some clinicians is viewed as less relevant now with the availability of MRI surveillance and early detection of brain metastases with effective and potentially curative treatment(s) now available. Aggressive treatment has changed the previously accepted perception of short survival once brain metastases are diagnosed. Also, trials with newer systemic therapies demonstrate blood–brain barrier penetration with decrease in the incidence of brain metastases; they can also effectively treat known metastases with the expectation of less central nervous system toxicity than PCI.

Dr. Elizabeth Gore

Mitigating Even the Acceptable Adverse Events from PCI

An interesting and important finding in this trial is the difference in physician- and patient-reported adverse events (AEs). Except for vomiting, all AEs were under reported by physicians relative to patients. Interestingly, fatigue and memory loss were more likely to be underreported by physicians for patients in the observation arm, emphasizing the need for patient-reported outcomes and pointing to a possible physician bias favoring observation. It has been suggested that even without improvement in survival, delay or prevention of brain metastases is clinically meaningful due to the deleterious effect of brain metastases on quality of life. In this trial, quality of life was worse at 3 months in the PCI arm and then returned to the same level as the observation arm thereafter. This occurred despite the significantly higher rate of symptomatic brain metastases in the observation arm, although it is unclear if AEs of brain metastases were captured in this analysis.

Although trials have consistently demonstrated that the toxicity of PCI is acceptable,[3] toxicity remains a primary concern and limitation to the acceptance of PCI. Measures, such as use of pharmacologic agents and radiation therapy techniques that may mitigate or minimize the side effect of PCI, should be undertaken. Hippocampal avoidance (HA) whole-brain radiation therapy may play an important role based on the encouraging results of NRG CC001, which evaluated HA whole-brain radiation therapy for documented brain metastases,[4] and the anticipated outcomes of a similar trial, NRG CC003 (NCT02635009), which is evaluating HA with PCI for small cell lung cancer. Additionally, careful selection of patients for PCI should incorporate known, pre-existing toxicity risks including established microvascular disease, impaired baseline neurologic function, and residual side effects from primary therapy, particularly fatigue and memory impairment.

In this study, treating approximately five patients with PCI prevented one case of symptomatic brain metastases. Many more patients would need to be treated to result in cure or increased survival of even one patient. Better understanding of tumor and host factors that increase risk of brain failures will improve this ratio and perhaps identify a cohort of patients with locally advanced disease and perhaps a subset of patients with early-stage disease who are at high risk for brain metastases and for whom brain-directed therapy is clearly indicated.

PCI is effective, but there is no proven benefit in terms of overall survival, and therefore it is not currently considered standard of care. As stated by the authors, the pros and cons of PCI necessitate a shared-decision process between patients and physicians. ✦

About the Author: Dr. Gore is a professor and medical director of Radiation Oncology, Zablocki VA Medical Center, Medical College of Wisconsin.

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INDUSTRY AND REGULATORY NEWS

European Commission Approval of Atezolizumab in Combination with Bevacizumab and Chemotherapy

On March 8, 2019, the European Commission approved the combination of atezolizumab, bevacizumab, and chemotherapy for first-line treatment of patients with metastatic non-squamous NSCLC. The approval was based on the significant survival benefit seen in the phase III IMpower150 trial for the combination of atezolizumab, bevacizumab, paclitaxel, and carboplatin (ABPC) compared with BPC alone (median overall survival [OS] = 19.8 vs 14.9 months; hazard ratio [HR] = 0.76; 95% CI: 0.63–0.96; p = 0.006). The combination has already been FDA approved in the United States. ✦

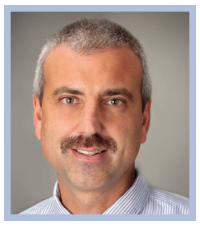
(For more a nuanced perspective on the FDA's approval, read the jointly authored perspective by the ILCN Editorial Group, "Thoughts on IMpower 150: Latest FDA Approval for Atezolizumab Misses the Mark" at lungcancernews.org.)

Names and News

FDA's New Acting Commissioner

After Scott Gottlieb's resignation as commissioner of the U.S. Food and Drug Administration (FDA) in early March, the Secretary of Health and Human Services Alex M. Azar II appointed **Norman E. Sharpless, MD,** as acting commissioner. Dr. Sharpless, a physician–scientist, is currently the director of the National Cancer Institute.

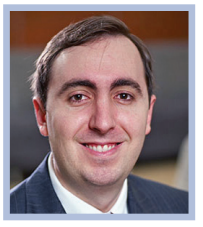
In a statement, Mr. Azar said that the FDA will not relent in its current efforts regarding drug approvals and combating both the opioid epidemic and the dramatically increasing e-cigarette youth-use rates.



Scott Antonia, MD, PhD, was appointed director of the newly formed DCI Center for Cancer Immunotherapy at Duke Cancer Institute. In addition to his leadership role, Dr. Antonia will also serve as professor of medical oncology.

In his previous roles at H. Lee Moffitt Cancer Center, he built an active lung cancer clinical research program and was recognized as Physician of the Year (2005), Mentor of the Year (2008), and Researcher of the Year (2018). Dr. Antonia was the global principal investigator for the practice-changing PACIFIC study. *(For a post-PACIFIC perspective on barriers in patient care in Europe, read the article by Mirjana Rajer, MD, on lungcancernews.org.)* He was also the lead investigator of trials that established the clinical activity of immunotherapy for SCLC, which resulted in updated National Comprehensive Cancer Network guidelines.

Howard (Jack) West, MD, has moved from the Swedish Cancer Institute in Seattle, where he directed the medical oncology component of thoracic oncology program, to City of Hope, Duarte, Calif, in March 2019. Dr. West, an associate clinical professor of medical oncology and executive director of Employer Services, made the move to build programs to export subspecialty insights to patients across a broader geography. Dr. West is also founder and president and CEO of the patient education nonprofit Global Resource for Advancing Cancer Education (GRACE).



Charles B. Simone, II, MD, has joined the New York Proton Center, which is opening this spring, as its chief medical officer. In his previous position, Dr. Simone was the medical director of the Maryland Proton Treatment Center and an associate professor of radiation oncology at the University of Maryland School of Medicine, where he also served as the director of the Stereotactic Radiation Therapy Program and the fellowship director for the Department of Radiation Oncology. Prior to his stint at University of Maryland, he was the director of Thoracic Radiation Oncology at the University of Pennsylvania. The New York Proton Center is the first and only facility for proton therapy in New York State, and it has partnered with several academic medical centers in New York—Memorial Sloan-Kettering Cancer Center, Montefiore Medical Center, and Mount Sinai Health System. ✦

Dr. Ramaswamy Govindan from page 6

Q: No study to date of an EGFR TKI in the adjuvant setting has demonstrated an OS advantage. Investigators in Japan and China are conducting several trials, but they are substituting TKIs for chemotherapy, which may be a misguided approach. Is there really a role for TKIs in the adjuvant setting, or are we studying them correctly?

A: In my opinion, the studies are somewhat overlapping and provide useful information at different levels. In general, the studies out of Asia have randomized patients after surgery to chemotherapy or EGFR TKI, whereas in ALCHEMIST we are building on our previous (modest) success with chemotherapy. I think there are two different models to test: one asks what EGFR TKIs can add on top of the proven adjuvant, chemotherapy; the other model asks whether TKIs can replace chemotherapy. I'm actually somewhat agnostic as to what is the best approach. We may also learn a lot about the side effects of EGFR TKI, tolerance, and compliance in these two different populations.

Q: As part of ALCHEMIST, the TKI components of the trial are accruing slowly, so its feasibility is in question. In stark contrast, ANVIL, which is also part of ALCHEMIST and which compares nivolumab to observation in *EGFR* wild-type NSCLC, is accruing "like gangbusters." Your thoughts?

A: A patient cannot go on the ANVIL study if they have *EGFR* mutation or *ALK* rearrangement. It is important to keep in mind that there are many more patients who do not have *EGFR* mutations or *ALK* rearrangements in early-stage NSCLC. As of January 4, 2019, the number of patients registered to the ALCHEMIST screening trial was 4,092; the number of patients registered to the *EGFR* portion was 248. *ALK* registration included 79 patients. This study has been open at more than 1,000 centers in the United States, and I am incredibly impressed and grateful to the leadership at the National Cancer Institute for supporting this study even when accrual was going slowly. We recently crossed the halfway mark for enrollment and are very encouraged by the pace of enrollment now.

Q: Finally, ALCHEMIST uses "yesterday's" drugs; if we had started the trial today, we'd have used osimertinib in lieu of erlotinib and alectinib in lieu of crizotinib. So, even if the trial demonstrates positive results, one wonders how relevant they are; if the results are negative, might we have done better with newer, more effective, less toxic agents. Comments?

A: This is the reality of drug development and clinical trials. ALCHEMIST trial was conceived nearly 10 years ago. At that time, erlotinib was the only approved drug for *EGFR*-mutated lung cancer. It took some years to get the trial approved through various agencies, during which time newer drugs came along. We debated a few times whether we should continue the current strategy or change the study drug. We decided, I think correctly, that we will complete the study based on the original design. The same applies for the *ALK* study as well. There will be industry-led studies looking at osimertinib in the adjuvant setting. In addition, we are conducting a number of scientific studies—for example, the whole-genome and whole-exome analyses of the resected specimens as part of the ALCHEMIST screening—and we will learn quite a bit from those as well. ✦

The IASLC Is on the Air—with Its First-Ever Podcast 'Lung Cancer Considered'

Those interested in lung cancer research and recent clinical developments can now tune in to "Lung Cancer Considered" twice each month for the latest news on the study of lung cancer. "Lung Cancer Considered" will feature researchers, healthcare professionals, patients, and advocates who are working to improve patient care around the globe.

The IASLC chose noted oncologist H. Jack West, MD, director of medical oncology and operations at City of Hope, to launch the podcast program as the host. Dr. West has extensive experience podcasting and creating audio content on lung cancer for his own website, West Wind Podcast and Beacon Medical Interchange, as well as for other organizations.

"I've always respected the IASLC, its mission, and the way the organization presents content to the oncology profession. I'm excited to work with [the association] on the 'Lung Cancer Considered' podcast," said Dr. West.

Future episodes of "Lung Cancer Considered" focus on research at IASLC meetings, including the World Conference on Lung Cancer in Barcelona this September, as well as current and breaking news on topics related to lung cancer research. The first topic is the evolution of SCLC.

Listeners can tune in on SoundCloud.com or on the news page of IASLC.org. ✦

FIGHTING CANCER AT 150,000 CYCLES PER SECOND

Novocure® is conducting clinical trials using TTFields (alternating electric fields) to selectively kill cancer cells in solid tumors.[1]

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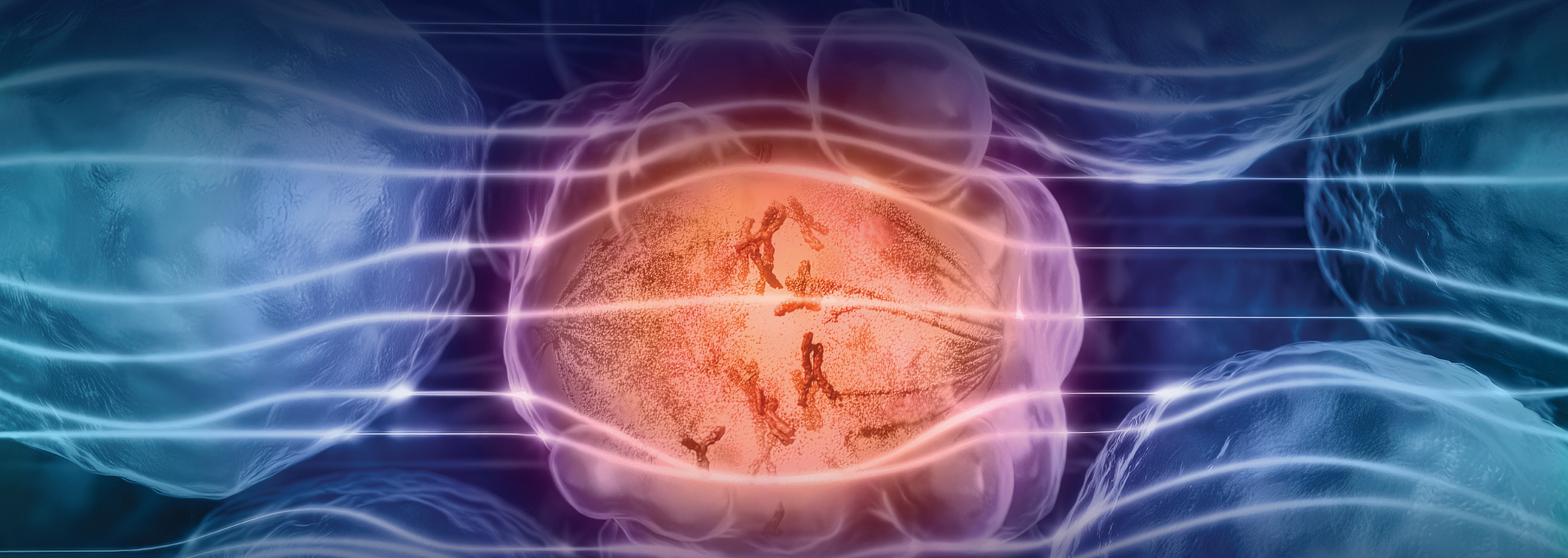

The METIS trial for patients with 1-10 newly diagnosed brain metastases as a result of non-small cell lung cancer (NSCLC) is now enrolling.[1]

This phase III trial is studying the efficacy and safety of TTFields at 150 kHz + the best lung cancer standard of care (including chemotherapy) following standard stereotactic radiosurgery (SRS).[1,5]

Eligible patients should be ≥18 years of age and newly diagnosed with 1 inoperable brain metastasis, or 2-10 previously untreated brain metastases from NSCLC, and with brain metastases that are amenable to SRS.[1,5]

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References: 1. ClinicalTrials.gov. Bethesda (MD): U.S. National Library of Medicine. Effect of TTFields (150 kHz) in non-small cell lung cancer (NSCLC) patients with 1-10 brain metastases following radiosurgery (METIS). NCT02831959. https://clinicaltrials.gov/ct2/show/NCT02831959. Updated January 15, 2019. Accessed January 23, 2019. **2.** Gutin PH, Wong ET. Noninvasive application of alternating electric fields in glioblastoma: a fourth cancer treatment modality. *Am Soc Clin Oncol Educ Book*. 2012:126-131. **3.** Kirson ED, Dbalý V, Tovarys F, et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. *Proc Natl Acad Sci USA*. 2007:104(24):10152-10157. **4.** Gera N, Yang A, Holtzman TS, Lee SX, Wong ET, Swanson KD. Tumor treating fields perturb the localization of septins and cause aberrant mitotic exit. *PLOS ONE*. 2015.10(5):e0125269. doi:10.1371/journal.pone.0125269. **5.** Novocure Data on File. NovocureTrial.com. METIS. 2018.

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