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EVOLVING STANDARDS OF CARE

Liquid Biopsy for Assessing Response or Progression in Advanced NSCLC

LIQUID BIOPSY / EXPERT VOICES

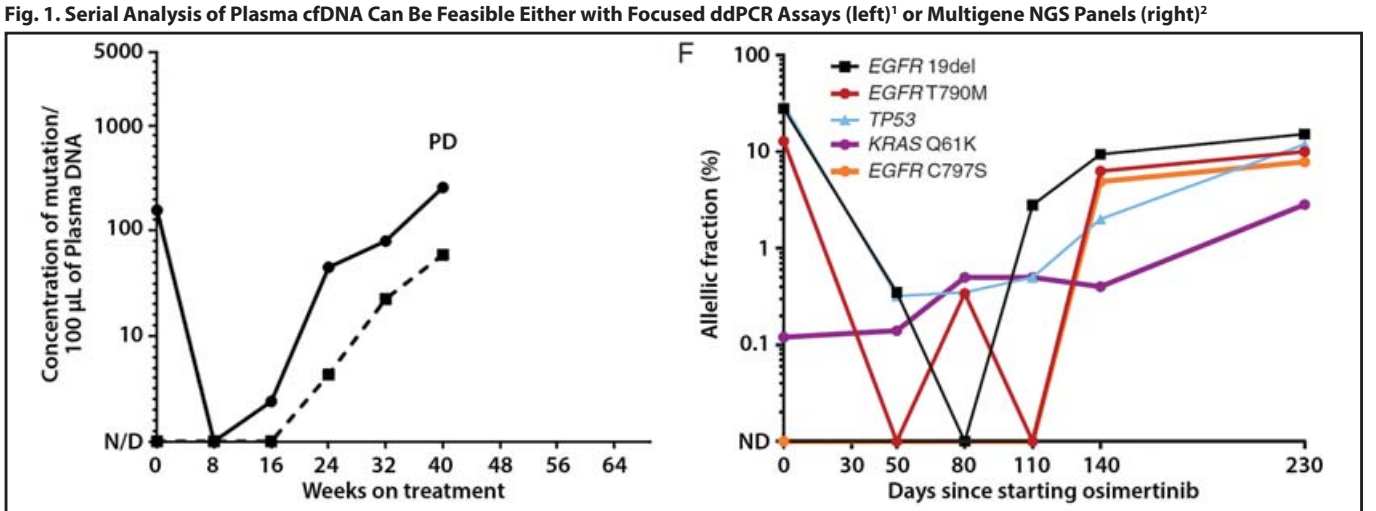
By Geoffrey R. Oxnard, MD

Genomic analysis of plasma cell free DNA (cfDNA) has been adopted widely in academic cancer centers (but not necessarily in community settings) for convenient genotyping of advanced NSCLC. Indeed, the rapid uptake of this novel diagnostic as part of the standard of care reflects the compelling nature of such a convenient molecular assay. Intuitively, many are now asking how these blood tests can be used for guiding cancer care once a treatment decision has been made.

For example, it would be valuable if we could use these blood tests to monitor treatment outcomes in the same way that serum tumor markers (e.g., CEA, CA19-9, and CA125) are used for some cancer types. In contrast to proteins found in

continued on page 3

Fig. 1. Serial Analysis of Plasma cfDNA Can Be Feasible Either with Focused ddPCR Assays (left)[1] or Multigene NGS Panels (right)[2]



Abbreviations: cfDNA, cell free DNA; ddPCR, droplet digital polymerase chain reaction; NGS, next-generation sequencing; PD, progressive disease.

EVOLVING STANDARDS OF CARE

Antibody–Drug Conjugates in NSCLC: Complexities, Challenges, and Potential

By David E. Gerber, MD

The underlying concept for antibody–drug conjugates (ADCs) is relatively straightforward: capitalize on the highly specific targeting of monoclonal antibodies to convey a lethal payload to cancer cells while minimizing exposure of normal tissues. However, after more than 20 years of clinical development, ADCs have not achieved their potential. Only recently have ADCs for NSCLC demonstrated promising effects in clinical trials, although none is yet approved for this malignancy.

Mechanism and Characteristics

To understand the challenges facing ADC development in NSCLC and other malignancies, it is worth reviewing their complex, multistep mechanism of action (Fig. 1). In an optimal scenario, ADCs extend the therapeutic window. Compared to conventional chemotherapy, they are designed to both increase efficacy and decrease toxicity. Specifically, targeted delivery of drugs to cancer cells results in increased drug doses in the tumor microenvironment, thereby lowering the minimum effective dose. Conversely, fewer drug molecules within normal, nontarget tissues lead to an increased maximum tolerated dose.[1] Both tumor and ADC characteristics affect efficacy and toxicity. Ideal tumor characteristics include: high expression of the target antigen on the tumor surface, limited expression of the target antigen in healthy tissues, no shedding of the target antigen at high levels of expression, and a target antigen–ADC complex that is internalized upon binding. Desired ADC characteristics include: an antibody that has high affinity and avidity for the target antigen, a linking protein, and a payload (i.e., a highly potent drug) that is stable

Dr. David E. Gerber

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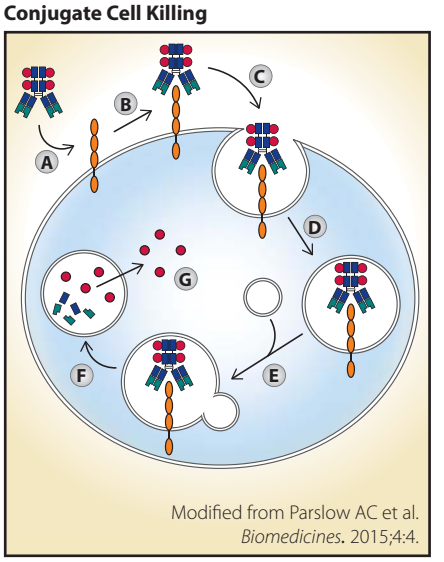
Fig. 1. Mechanism of Antibody-Drug Conjugate Cell Killing



Modified from Parslow AC et al. *Biomedicines*. 2015;4:4.

(A) Antibody-drug conjugate (ADC) accesses antigen via circulation; (B) ADC binds to antigen; (C) ADC-antigen complex is internalized; (D) ADC-antigen complex is incorporated into endosomal vesicles; (E) ADC-antigen complex is processed along the endosomal-lysosomal pathway; (F) ADC is degraded in an acidic and proteolytic rich environment; (G) Cytotoxic payload is released intracellularly.

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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Liquid Biopsy in Advanced NSCLC

from page 1

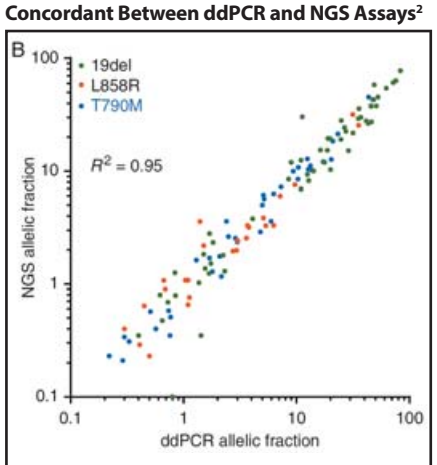
serum, plasma cfDNA has a short half-life; therefore, levels can change quickly. We and others have shown that mutation levels in plasma cfDNA can decrease dramatically during treatment and can increase in advance of disease progression.[1,2] These dynamics can be detected either with focused assays like droplet digital polymerase chain reaction (ddPCR) or with multigene assays like next-generation sequencing (NGS; Fig. 1, see page 1).

Despite these observations, some major challenges remain before treatment monitoring using plasma cfDNA can be adopted clinically.

How Best to Quantify Mutation Levels

Early assays measured the absolute concentration of mutant DNA in plasma, quantified as copies/mL.[1] With the emergence of NGS assays, it is now more common to quantify the relative prevalence of any given mutation compared with all mutant and wild-type sequencing reads, quantified as the allelic fraction (AF), a scale that most assays can use. AF calculations are highly correlated between NGS and ddPCR assays (Fig. 2),[2] but it is unknown whether benign processes could spontaneously alter the calculation of AF. For example, it is possible that a change in the levels of wild-type DNA (for example, an acute infection leading to white blood cell degranulation) could result in fluctuations in mutation AF without any corresponding change in tumor burden.

Fig. 2. Calculated Allelic Fraction is Highly Concordant Between ddPCR and NGS Assays[2]



Abbreviations: ddPCR, droplet digital polymerase chain reaction; NGS, next-generation sequencing.

Dr. Geoffrey R. Oxnard

How to Track Multiple Variants

Earlier assays like ddPCR follow the single key driver mutation in plasma, whereas many newer assays use NGS, which can detect multiple mutations. Some of these mutations are cancer drivers, and some are subclonal mutations or resistance mutations. Furthermore, some mutations in cfDNA are germline; others are somatic mutations derived from clonal hematopoiesis and not from the tumor.[3,4] How are these multiple variants best handled? Some investigators have tracked just the highest AF variant, although it may not be the driver mutation. Others have averaged the level of all variants at each timepoint. No consensus has been clearly established.

How Much Change Is Meaningful?

We know that complete clearance of mutations from plasma cfDNA is a good prognostic sign,[5] but it is unclear what lesser magnitude of response is the best marker of treatment effect. There are decades of historical precedent supporting specific objective criteria for response and progression on tumor imaging.[6] No such literature exists yet for response in plasma cfDNA. Some degree of change is likely due to random variation, unrelated to treatment effect. This must be robustly quantified so that clinicians can know what degree of change instead might be clinically meaningful. It would be unfortunate to change therapy based on variations in a blood test that are, in fact, due to assay artifact or extrinsic, nonmalignant conditions.

What Turnaround Time Is Needed?

Many have shown that plasma cfDNA analysis is much faster than getting a biopsy[7]; however, cfDNA testing remains slower than imaging or serum tumor markers. These tests involve multiple steps—spinning the plasma, extracting DNA, genomic analysis, and test interpretation—which can take days to weeks depending on the assay. This may be too slow for routine use because decisions about whether to continue treatment or to switch to a different regimen are usually made in a day or two based on imaging studies. Faster assays for cfDNA analysis are needed and are in development. In the meantime, turnaround time must be considered when building this testing into clinical decision making.

What Cost Will Be Scalable

Genomic analysis of plasma cfDNA can cost hundreds or thousands of dollars per specimen. This is likely too expensive for routine use every few months during therapy, unless clear clinical utility is established. For this reason, development of the cfDNA analysis as a monitoring assay should focus on key decision points where the cost–benefit ratio is more favorable. Of course, if cost decreases, it could be possible to run these tests more routinely.

Conclusions

Cancer monitoring using plasma cfDNA is compelling, but there is much work to be done. I currently do not use plasma cfDNA analysis on its own to assess response or progression, but at times I will use it in combination with imaging and clinical evaluation to help understand if a treatment is failing. Indeed, this also is how serum tumor markers are used—not on their own, but as a complement to imaging to understand the clinical picture. If scans seem mostly stable without response but symptoms are worsening, I might send plasma genotyping to assess for resistance. If I see high levels of the driver mutation, this is concerning because progression is likely brewing and makes me favor a change in treatment. However, if scans and symptoms are stable, a blood test on its own, especially one showing low AF mutations, is not enough to divert me from a treatment that is otherwise effective in the palliation of metastatic cancer. ✦

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About the Author: Dr. Oxnard is a physician with the Lowe Center for Thoracic Oncology Dana-Farber Cancer Institute and an associate professor of medicine at Harvard Medical School.

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INDUSTRY AND REGULATORY NEWS

Entrectinib Wins Approval for *ROS1*-Positive NSCLC

August 15, 2019—The U.S. Food and Drug Administration (FDA) granted approval for entrectinib for the treatment of adults with *ROS1*-positive metastatic NSCLC and accelerated approval for treatment of both pediatric patients older than age 12 and adults with solid tumors that harbor an *NTRK* fusion. The latter indication is tumor-agnostic because *NTRK* fusions are found in more than 25 different histologies, including NSCLC, although its incidence in advanced NSCLC is quite low (<1%).

The approvals were based on data from the phase II STARTRK-2, phase I STARTRK-1, and the phase I ALKA-372-001 trials, which included 51 patients with *ROS1*-positive metastatic NSCLC. Multiple doses and schedules were examined in the three trials, but 90% of patients received 600 mg of oral entrectinib once daily, the recommended dose. Pooled data from these ongoing trials showed a 78% ORR (95% CI: 65, 89); 55% achieved responses for 12 months or more (median, 24.6 months; 1.8-36.8 months).

The most serious adverse reactions, regardless of causality, included congestive heart failure, CNS effects, skeletal fractures, hepatotoxicity, hyperuricemia, QT interval prolongation, and vision disorders. The most common adverse reactions of any grade occurring in at least 20% of patients included, but were not limited to, fatigue, constipation, dysgeusia, edema, dizziness, and diarrhea. ✦

Antibody–Drug Conjugates from page 1

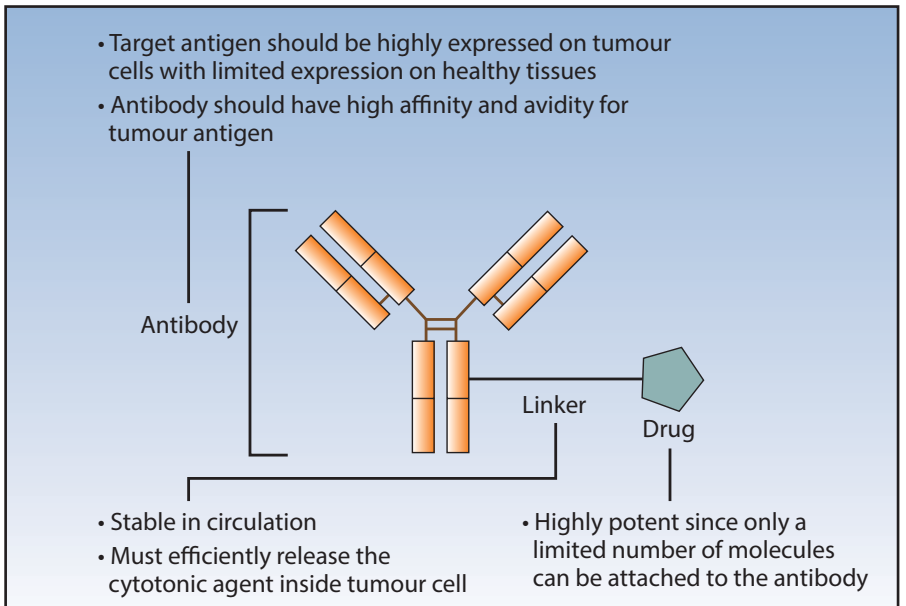
in circulation but is efficiently released inside of the tumor cells.[2]

Design and Components

ADCs are composed of a monoclonal antibody, a linker, and a cytotoxic payload (drug; Fig. 2). Optimal linkers for ADC have a suitable site for attachment to the antibody, a complementary attachment site to achieve the rate of desired drug loading per antibody molecule, stability to process chemistry and product storage, and stability in circulation. They should also be cleavable after cellular internalization.[3] ADC linkers may be cleaved through lysosomal proteases, which recognize and cleave a dipeptide bond to release free drug from conjugate, (e.g., valine-citrulline linker) or through pH-dependent hydrolysis, whereby acid labile groups within the linker are cleaved in the acidic environment of the lysosome (e.g., hydrazine linker). Alternatively, non-cleavable linkers remain attached to the ADC payload but depend on complete antibody degradation after ADC internalization. In general, non-cleavable linkers have greater stability in circulation and slower drug deconjugation than do cleavable linkers.[2]

The optimal payload has high potency to prove efficacious at achievable intracellular concentrations, selectivity in killing target cells, low immunogenic potential, compatibility with the conjugation process, chemical stability in circulation, and either activity in linked form (for non-cleavable linker systems) or in free form (for cleavable linker systems).[3] Drugs employed as toxic payloads in ADCs generally fall into two categories: microtubule inhibitors (i.e., auristatins and maytansines) or DNA-damaging agents (i.e., calicheamicins, duocarmycins, pyrrolobenzodiazepine dimers, indolinone benzodiazepines, anthracyclines, and topoisomerase inhibitors). The majority of ADCs currently in development incorporate maytansine derivatives (DM1, DM4) or auristatins (MMAE, MMAF) as the chemotherapeutic component (Table).

Fig. 2. Antibody–Drug Conjugate Components and Characteristics



Thomas A et al. ***Lancet Oncol.*** 2016;17:e264. Reprinted with permission.

The desired drug–antibody (DAR) is generally 2:1 to 4:1, with higher ratios resulting in diminished stability and lower ratios resulting in reduced potency.

Resistance and Toxicity

Resistance to ADCs can arise from decreased antigen expression on the targeted cell surface due to either decreased target gene expression or increased mutations. Resistance can also be caused by decreased ADC internalization (due to decreased cell-surface trafficking or recycling), or multidrug resistance (MDR) transporter efflux out of the targeted cell. MDR transporter efflux can also exacerbate killing effects on bystander cells in the vicinity of the targeted cell, thereby potentially enhancing toxicity. Other potential reasons for ADC toxicities include target-dependent uptake and catabolism of the ADC, or release of free drug by deconjugation of circulating ADCs.

Toxicities from target-dependent ADC uptake occur when the target antigen is expressed in healthy tissues. Although not the dominant mechanism of toxicity, when related adverse events do occur, they may be profound. In some instances, previously unrecognized target-antigen expression on healthy tissues has led to major toxicities. Due to target-antigen expression on normal gastric mucosa, an ADC directed against the Lewis^Y antigen resulted in hemorrhagic gastritis. Similarly, expression of CD446v6 in the deep layers of the skin led to fatal exfoliation from a CD446v6-directed ADC, and CA9 expression in intestinal mucosa resulted in fatal gastrointestinal toxicity from a CA9-directed ADC. Why might such surprises occur? Preclinical models may not adequately predict clinical activity and tolerability. Specifically, in some models the target antigen may not be expressed in host tissues, resulting in misleadingly favorable activity. Less severe but more common, antigen-independent toxicities reflect the inherent adverse effects of the payload, such as myelosuppression and neuropathy for microtubule inhibitors.

Clinical Development

As of March 2019, the U.S. Food and Drug Administration has approved three ADCs for the treatment of other malignancies: gemtuzumab ozogamicin (anti-CD33 antibody conjugated to calicheamicin) in acute myeloid leukemia, ado-trastuzumab emtansine in HER2-positive breast cancer, and brentuximab vedotin (anti-CD30 antibody conjugated to MMAE) in lymphoma. Ado-trastuzumab provides an example of the therapeutic benefit of ADCs, as it has demonstrated superior efficacy compared to the unconjugated anti-HER2 antibody trastuzumab. Trials are now evaluating this agent in *HER2*-mutated NSCLC.

For the treatment of thoracic malignancies, perhaps the best-known ADC is rovalpituzumab tesirine (Rova-T; SC16LD6.5). Rova-T targets delta-like ligand 3, which is expressed in more than 80% of SCLC. Although Rova-T had demonstrated highly promising results in earlier single-arm trials,[4] the phase III MERU trial was recently closed because it did not meet its primary endpoint of survival benefit for Rova-T compared with placebo.

The Table provides a listing of selected ADCs under development in NSCLC. The diversity of targeted antigens is readily apparent, as is the overwhelming use of maytansine derivatives or auristatins as toxic payloads. As is the case for other molecularly targeted therapies (e.g., small molecule inhibitors and unconjugated monoclonal antibodies), development of biomarkers for the identification of patients most likely to benefit represents a key consideration. Furthermore, with a distinct mechanism of action, ADCs may benefit a slightly different population than do other therapies with the same molecular target. For instance, small molecules targeting MET have clinical benefit largely limited to those NSCLC cases harboring *MET* exon 14 skipping mutations (< 5% of NSCLC cases). By contrast, the anti-MET ADC ABBV-399 has demonstrated responses in c-Met–positive NSCLC defined by immunohistochemical expression (up to > 50% of NSCLC cases depending on cutoff). For MET and other molecular targets, non-ADC therapies require the alteration to represent a true oncogenic driver for efficacy. However, because the primary mechanism of ADC killing is delivery of a cytotoxic payload rather than pathway

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Table. Selected Antibody-Drug Conjugates Under Clinical Development in NSCLC

Target antigen	Name	Toxic payload
AXL	Enapotamab vedotin (HuMax-AXL)	MMAE
AXL	BA3011	MMAE
CD71	CX-2029	MMAE
CD166	CX2009	DM4
CEACAM5	SAR408701	DM4
FRα	Mirvetuximab soravtansine (IMGN-853)	DM4
gpNMB	Glembatumumab vedotin	MMAE
Guanyl cyclase C	Industuzumab vedotin (MLN-0264, TAK-264)	MMAE
HER2	Ado-trastuzumab emtansine (T-DM1)	DM1
HER3	U3-1402	DC 8951 (camptothecin derivative, topoisomerase 1 inhibitor)
Ly6E	RG-7841 (Anti-Ly6E/DLYE5953A)	MMAE
Mesothelin	Anetumab ravtansine (BAY 94-9343)	DM4
MET	Telisotuzumab vedotin (ABBV-399)	MMAE
NaPi2b	Lifastuzumab vedotin (RG-7599/DNIB0600A)	MMAE
NaPi2b	XMT-1536	AF-HPA
Nectin-4	Enfortumab vedotin (ASG-22ME, ASG-22MSE)	MMAE
TF	EDO-B278	
TF	Tisotumab vedotin (HuMax-TF-ADC)	MMAE
Trop-2	Sacituzumab govitecan (IMMU-132)	SN-38 (irinotecan active metabolite)
5T4	ZV05-ADC (5T4-MMAF ADC)	MMAF
5T4	PF 06263507 (A1-mcMMAF; anti-5T4 mAb)	MMAF

Abbreviations: AF-HPA, auristatin F-hydroxypropylamide; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; FRα, folate receptor α; HER2, human epidermal growth factor receptor 2 (ErbB2); HER3, human epidermal growth factor receptor 3 (ErbB3); Ly6E, lymphocyte antigen 6 complex, locus E; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; NaPi2b, sodium-dependent phosphate transport protein 2b; TF, tissue factor (thromboplastin; CD142); Trop-2, tumor-associated calcium signal transducer 2.

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MEETING NEWS

2019 IASLC World Conference on Lung Cancer Updates

More than 7,700 delegates from around the world attended the IASLC 2019 World Conference on Lung Cancer (WCLC). With sessions and workshops on every aspect of thoracic oncology patient care, the conference offered attendees from all specialties an opportunity to learn about novel research and hear from the field's top experts. The summaries offered throughout this issue of ILCN represent just a few topics presented at the meeting. Become an IASLC member (IASLC.org/Membership) to access the full Virtual Library content for this and other live meetings.

LIBRETTO-001 Shows LOXO-292 Successfully Targets *RET* Fusion NSCLC

There are currently no approved agents to treat *RET* fusion–positive NSCLC, but that will likely change after the presentation of interim data from the LIBRETTO-001 trial. Selpercatinib, an investigational agent better known as LOXO-292, showed an objective response rate of 68% in previously treated patients and 85% in treatment-naive patients, according to a primary analysis set of 105 patients enrolled on the trial.

The sponsor plans to file a New Drug Application for the agent with the U.S. Food and Drug Administration before the end of 2019, said presenter Alexander Drilon, MD.

"The first *RET* fusion was discovered in 1985, yet we still have no regulatory approval for the treatment of *RET*-dependent cancers," Dr. Drilon said. "*RET* fusions are bona fide lung cancer drivers, and we have shown they are bona fide druggable targets."

Dr. Alexander Drilon

Multikinase inhibitors tested in the past exhibited modest clinical activity in *RET* fusion–positive NSCLC but induced significant toxicity. PD-1 and PD-L1 inhibitors appear to be less effective in driver-positive NSCLC, including *RET* fusions.

Dr. Drilon noted that *RET* fusions drive 2% of NSCLC, up to 20% of thyroid cancers, and lesser numbers of other solid tumors. Up to half of the patients with advanced disease have brain metastases.

LIBRETTO-001 is an open-label phase I/II trial that includes patients with *RET* fusion–positive NSCLC, thyroid cancer and other cancers. The interim data presented in Barcelona included a primary analysis set of the first 105 consecutive patients with NSCLC enrolled in trial.

Of 105 patients whose disease had progressed on prior chemotherapy, checkpoint inhibitors, multikinase inhibitors, or combination treatments, 68% realized an objective response.

There were two complete responders at data cutoff for the analysis and two more apparent complete responders awaiting confirmation. Among patients with brain metastases, 91% had an objective response. In a smaller group of 34 treatment-naive patients, 85% achieved an objective response.

Median duration of response to date in the primary analysis was 20.3 months, and median progression-free survival (PFS) was 18.4 months. The problem, Dr. Drilon noted, is that the medians are not statistically stable because there has been such a low number of events in the study population.

The durability of response is even murkier in the treatment-naive population. Neither the median duration of response nor PFS can be determined because there have been so few events.

"A large number of patients remain on treatment and have not [had disease progression]," Dr. Drilon indicated. "These patients have not yet reached the endpoint."

The reported safety profile of selpercatinib includes all 531 patients and is extremely good, according to Dr. Drilon. The most common treatment-emergent adverse event is dry mouth, reported in 32% of patients, followed by diarrhea (31%), hypertension (29%), and increased AST (28%) and ALT (26%) levels.

Most adverse events were judged as not treatment-related, Dr. Drilon said. There were relatively few serious adverse events, and only nine patients (1.7%) discontinued treatment due to treatment-related adverse events.

"We have been trying to target *RET* fusion for some time now with only modest results," said discussant Robert C. Doebele, MD, PhD, University of Colorado.

"Selpercatinib succeeded where other agents have not. We are very likely to have some very good options for our patients with *RET* fusion–positive NSCLC" in the near future, Dr. Doebele said. ✦

Results From First-In-Human Trial for *KRAS G12C* Treatment Reported

An abstract presented during an Oral Abstract Session dedicated to new approaches and targets in NSCLC suggests that new, more highly targeted therapies may improve outcomes for patients with molecular variants that cannot currently be treated effectively.

The most common undruggable NSCLC mutation is *KRAS G12C*, found in 11% of patients with NSCLC and about 14% of all lung adenocarcinomas. There is no approved target-specific treatment for *KRAS G12C*–mutant tumors, which are also seen in up to 3% of other solid tumors.

One of the new potential treatments for *KRAS G12C* is AMG 510, a novel small-molecule oral agent that selectively targets *KRAS G12C* and irreversibly locks it into an inactive GDP-bound state.

Ramaswamy Govindan, MD, Alvin J. Siteman Cancer Center of Washington University School of Medicine, presented results of the first-in-human trial with AMG 510. The trial has enrolled 34 patients with NSCLC to date, with 23 evaluable based on the timing of their enrollment and treatment status. Another 42 patients with other *KRAS G12C*–positive tumors were accrued but not included in the analysis presented during WCLC.

The primary endpoints for the open-label dose-escalation study were dose-limiting toxicities and safety. Key secondary endpoints included pharmacokinetics, objective response rate, duration of response, disease control rate, progression-free survival, and duration of stable disease.

Dr. Ramaswamy Govindan

Dosing in the trial included 180 mg, 360 mg, 720 mg, and 960 mg. All doses were given orally once daily.

"Because AMG 510 is so highly selective, we expected to see relatively few adverse events," Dr. Govindan said. "We were not disappointed in the safety profile."

The cohort is fairly typical of advanced NSCLC: 83% of patients enrolled had received two or more previous lines of therapy. All patients had confirmed *KRAS G12C* mutation by molecular testing of tumor biopsies, and none had active brain metastases. Median age was 67 years, 18% were female, and 94.1% had an ECOG performance score of one or two.

"As expected, we did not see many toxicities," Dr. Govindan reported. "A third of patients had treatment-related toxicities, mostly grade 1 or 2, no grade 4. There were no dose-limiting toxicities, no serious adverse events related to treatment, and no adverse events that led to discontinuation of treatment."

There were four deaths not related to treatment, and eight serious adverse events also not related to treatment.

The maximum-tested dose, 960 mg daily, yielded the best tumor response and change in tumor burden from baseline. All patients on the 960 mg dose exhibited disease control, with 54% having a partial response.

The first response to treatment came quickly, after approximately 5 weeks, and that response is ongoing, Dr. Govindan said. The mean duration of treatment when data were censored for the report was 15 weeks, with some patients on treatment for more than 42 weeks. Pharmacokinetics for the 960 mg daily dose were good, he continued.

Half-life of the drug is 5.5 hours. Therapeutic concentrations were seen on 2-hour assays for 24 hours.

"There is no need to go to twice-daily dosing because we have full *KRAS G12C* inhibition over 24 hours," Dr. Govindan said in response to a question. "And because inhibition is complete with this agent, there is no advantage to giving more drug."

A phase II monotherapy trial and phase I combination therapy trial are now enrolling patients. ✦

CheckMate 817 Trial Demonstrates Safety of Nivolumab Plus Ipilimumab in Advanced NSCLC

The most recent CheckMate 817 trial results have shown that first-line flat-dose nivolumab plus weight-based ipilimumab exhibited a consistent and reasonable safety profile in special populations with advanced NSCLC, including those with an ECOG performance status (PS) score of 2. Additionally, patients with either high tumor mutational burden (TMB) or higher tumor PD-L1 expression appeared to exhibit improved efficacy (ORR, PFS).

"In this trial, we wanted to see how the combination of ipilimumab and nivolumab performed in patients with advanced NSCLC, particularly in a population with other comorbidities, such as impaired performance status, asymptomatic untreated brain metastases, hepatic or renal impairment, or HIV, who are frequently excluded from registration trials," said Fabrice Barlesi, MD, PhD, associate editor of the *IASLC Lung Cancer News* and abstract presenter.


Dr. Fabrice Barlesi

The trial population included two cohorts of patients diagnosed with treatment-naive, advanced NSCLC. Cohort A included patients with an ECOG PS of 0-1, while cohort A1 included 198 patients who had an ECOG PS of 2 or of 0–1 with one of the aforementioned comorbidities. Cohort A1 patients were grouped as ECOG PS 2 (n = 139) and all other special populations (AOSP; n = 59). Patients with known *EGFR* mutations or *ALK* translocations sensitive to available targeted therapy were excluded from either cohort.

In both cohorts, nivolumab 240 mg Q2W plus ipilimumab 1 mg/kg Q6W was administered for 2 years or until disease progression/unacceptable toxicity. Safety and efficacy endpoints were assessed; cohort A1 analyses were exploratory.

"Overall, we found that the rate of treatment-related adverse events (TRAEs), including TRAEs leading to discontinuation or fatal events, were comparable in the two cohorts," Dr. Barlesi indicated. "Additionally, median PFS, duration of response and PFS by TMB showed encouraging results. Results of an updated analysis are pending."

Specifically, within cohort A1, grade 3-4 TRAEs were numerically higher in the AOSP subgroup versus the subgroup with an ECOG PS of 2; TRAEs leading to discontinuation were similar across populations. Overall response rate (ORR) was 25% in cohort A1 (patients with an ECOG PS of 2, 19%; AOSP, 36%) and 36% in cohort A. PFS was numerically shorter in cohort A1, as would be expected in this frail population, compared to cohort A; high TMB (≥10 mut/Mb) and higher PD-L1 expression (≥ 1% or ≥ 50%) were associated with numerically longer PFS in both cohorts.

> ***These findings are significant, as they are the first to demonstrate the activity of this combination outside of a strict phase III clinical trial.***
>
> –Dr. Fabrice Barlesi

"These findings are significant, as they are the first to demonstrate the activity of this combination outside of a strict phase III clinical trial. Finding that tolerability of combination nivolumab and ipilimumab in a frail population, with a PS of 2 or associated comorbidities, is comparable to patients with a PS of 0-1 is very interesting," Dr. Barlesi said. ✦

Three Studies Show Lack of Correlation Between TMB and Outcomes

A post hoc study of the phase I/II KEYNOTE-021 study—the first to demonstrate the safety and efficacy of combination chemotherapy/PD-1 inhibitor for patients with locally advanced or metastatic NSCLC—included a total of 70 patients with tumor tissue available for tumor mutational burden (TMB) analysis. Corey Langer, MD, editor of the *IASLC Lung Cancer News*, and his colleagues aimed to determine whether TMB was associated with outcomes for patients treated with chemotherapy alone or in combination with pembrolizumab. Response to combination therapy was assessed according to TMB-high and TMB-low tumor types in a separate analysis.

> ***Although I still think TMB has a potential role, … it certainly shouldn't be used—at least, not yet—in therapeutic decision-making.***
>
> –Dr. Corey Langer

No association between TMB and the combination's efficacy was found for either objective response (p = 0.180), PFS (p = 0.187), or OS (p = 0.081). This was also true for the TMB analysis of 26 patients treated with chemotherapy alone (p = 0.861 to p = 0.763). In addition, no association between TMB and PD-L1 expression was found.

"Although I still think TMB has a potential role, … it certainly shouldn't be used—at least, not yet—in therapeutic decision-making," Dr. Langer said.

Chemotherapy With or Without Pembrolizumab

Similarly, OS, PFS, and response rates were similar in the TMB-evaluable and total patient population of KEYNOTE-189, which compared pembrolizumab plus pemetrexed-platinum chemotherapy with the same chemotherapy alone for patients with metastatic nonsquamous NSCLC. Of the 616 patients enrolled on the trial, 293 were TMB evaluable; of these, 207 were treated with combination therapy and 86 were treated with chemotherapy alone.

TMB status did not have a significant association with OS (p = 0.174), PFS (p = 0.075), or response (p = 0.072) for patients in the combination group. Respective p values for the chemotherapy subgroup were 0.856, 0.055, and 0.434.

As with the secondary analysis of KEYNOTE 021-C and G, investigators also found no association between TMB and PD-L1 expression in the combination arm (p = 0.27) or the chemotherapy subgroup (p = 0.92).

Nivolumab With or Without Ipilimumab

Results of the phase III S1400I trial of nivolumab plus ipilimumab versus nivolumab alone for previously treated stage IV squamous-cell lung cancer were presented earlier this year at the 2019 American Society of Clinical Oncology Annual Meeting. Although an exploratory analysis previously suggested an OS benefit with the combination for patients with TMB > 10 mut/mb and PD-L1 expression of ≤ 5%, a new analysis has contradicted those findings.

The updated analysis evaluated whether TMB predicted improved OS for those patients with PD-L1 expression values from 0% to ≥ 50% who were treated with the combination. The analysis included 231 patients evaluable for TMB, 161 evaluable for PD-L1 expression, and 149 for both biomarkers. Investigators chose a cutoff of TMB ≥ 10 mut/mb for the analysis.

Analysis of TMB across the range of PD-L1 expression levels failed to identify improved OS for any specific subgroup, and neither biomarker was associated with improved OS for the combination. There was a trend toward interaction between TMB and PD-L1 (p = 0.06) favoring the combination, but an analysis of TMB < 10 mut/mb favored nivolumab monotherapy. ✦

Immunotherapy Plus Chemotherapy Improves Results in Extensive-Stage SCLC

The benefit of adding checkpoint inhibition to the current standard chemotherapy in extensive-stage SCLC capped the Presidential Plenary.

The data were part of a planned interim analysis of CASPIAN, a global, randomized, open label study comparing overall survival (OS) with durvalumab plus platinum-etoposide (EP) versus EP alone as first-line treatment for extensive-stage (ES) SCLC. Adding durvalumab to platinum-etoposide reduced the likelihood of death by 27% compared to chemotherapy alone.

"Extensive-stage NCLC is an aggressive disease with limited treatment alternatives," said presenter Luis Paz-Ares, MD. "Patients treated with etoposide and platinum (EP) may have high early response rates, but responses are not durable. We have already seen good clinical activity with checkpoint blockade, especially as first-line treatment, so it made sense to try the combination."

Until very recently, EP had been the standard first-line treatment for ES-SCLC for more than 30 years.

Patients on the durvalumab + EP arm received up to four cycles of chemotherapy combined with durvalumab with durvalumab continued as maintenance therapy until disease progression or unacceptable toxicity. EP-only patients could receive up to six cycles of treatment and prophylactic cranial irradiation at the investigator's discretion. The primary endpoint was OS. Secondary endpoints included progression-free survival, response rates, safety, tolerability, and health-related quality of life.

The trial had a third arm comparing

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ADVOCACY AND SURVIVORSHIP

Building PDX Models for *EGFR*-Mutant Lung Cancer: The Power of Partnerships

By Amy C. Moore, PhD

Globally, approximately 140,000 patients per year diagnosed with NSCLC harbor a mutation in the epidermal growth factor receptor (*EGFR*) gene.[1] In the United States, approximately 15% of patients with NSCLC have *EGFR* mutations, whereas the likelihood is even higher in patients residing in Asia.

The challenge in treating patients with *EGFR*-mutant lung cancer is that most individuals ultimately develop resistance to tyrosine kinase inhibitors (TKIs), which remain the standard of care. Further, for patients with *EGFR* or *HER2* exon 20 insertions, commercially available TKIs simply fail to work at all. Thus, understanding mechanisms of resistance and developing better therapies is key to improving outcomes for these patients.

Dr. Amy C. Moore

Creating a Model

Based on the success of the ROS1ders lung cancer patient group in launching a project to create cancer models, in early 2018, the EGFR Resisters (a patient advocacy group consisting of more than 1,000 patients in 29 countries) approached the Bonnie J. Addario Lung Cancer Foundation—which has since partnered with the Lung Cancer Alliance to become the GO_2 Foundation for Lung Cancer—to explore ways in which the two organizations could accelerate research and improve outcomes for patients with *EGFR*-mutant lung cancer. Based on these discussions, the two organizations partnered with internationally renowned lung cancer expert Pasi Jänne, MD, PhD, from Dana-Farber Cancer Institute; Champions Oncology; and the Addario Lung Cancer Medical Institute (ALCMI, an international research consortium dedicated to catalyzing and accelerating the discovery, development, and delivery of new and more effective treatment options for patients with lung cancer) to create a panel of mouse models to propel research. The resulting collaboration, "A Prospective Biospecimen Collection Study from Patients with *EGFR* Mutant Tumors," will establish PDX models for patients with *EGFR* mutations who have acquired resistance to osimertinib or other third-generation TKIs or who harbor *EGFR* or *HER2* exon 20 insertion mutations (NCT03872440).

For more information on the study and to determine eligibility, please call 1-888-403-EGFR or visit alcmi.net/research/egfr-pdx-study.

The study is open in the United States and Canada and uses ALCMI's remote study capabilities, meaning patients do not have to travel to another institution to participate. Patients with *EGFR*-positive disease who require a biopsy or surgery for medical reasons can donate a small portion of their tumor or pleural effusion fluid for the study. Champions Oncology will then establish PDX models using the donated specimens.

"We know that we need more and better models if we are to fully understand what causes resistance in patients with *EGFR*-mutant lung cancer," said Dr. Jänne, the lead investigator. "This study will help us determine how resistance occurs and will also enable us to design more effective treatments going forward."

This study provides physicians and patients in the lung cancer community with an opportunity to actively participate in research that will accelerate understanding of resistance mechanisms and help drive the development of new therapies for *EGFR*-mutant lung cancer. These models will be shared openly with research partners in academia so that patient care can be improved more quickly and successfully. ✦

About the Author: Dr. Moore is the director of Science and Research, GO2 Foundation for Lung Cancer.

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EVOLVING STANDARDS OF CARE

Key Findings from the CAR T-Cell Study Presented at the 2019 AACR Annual Meeting

By Prasad S. Adusumilli, MD, FACS, FCCP

My colleagues and I conducted a phase I clinical trial of mesothelin-targeted chimeric antigen receptor (CAR) T-cell therapy in patients with malignant pleural disease from mesothelioma and metastatic lung or breast cancer, and we presented the findings at the 2019 American Association for Cancer Research Annual Meeting.[1] Following cyclophosphamide preconditioning, patients were administered a single, escalating dose of mesothelin-targeted CAR T cells intrapleurally via catheter or by interventional radiologic procedures. The primary observation was that this therapy is safe and effective, especially when combined with anti–PD-1 agents following CAR T-cell administration.

IcasM28z CAR T cells were administered directly into the pleural cavity in 21 patients with malignant pleural disease (19 with malignant pleural mesothelioma, one with metastatic lung cancer, and one with metastatic breast cancer). These T cells included *Icaspase-9,* a safety gene that can be switched on in case of an unexpected toxicity.

During the follow-up period, the IcasM28z CAR T cells were found to be persistent in the peripheral blood of patients, which was associated with reduction in the levels of serum mesothelin–related peptide levels and evidence of tumor regression on imaging studies. On the basis of the rationale from our preclinical studies, 14 patients went on to receive anti–PD-1 checkpoint blockade agents. Among 11 patients who had at least 3 months of follow-up, 2 patients had complete metabolic response on PET scans at 60 and 32 weeks, respectively, and one response ongoing at the time of reporting; 5 patients had partial response, and 4 had stable disease.

Study Rationale and Future Directions

In our initial explorations for a cancer-associated antigen with high expression in solid tumors and very low expression in normal tissues, we observed that mesothelin is expressed in a majority of solid tumors—approximately 2 million tumors in the United States per year. The very low expression of mesothelin in normal tissues compared with cancer tissue, indicated the safety margin of targeting mesothelin. Our investigations in thoracic tumors and in preclinical mouse models showed that mesothelin overexpression affects tumor aggressiveness. This suggested that cancer cells are unlikely to shed mesothelin as an antigen immune-escape mechanism. These characteristics—relatively higher expression in cancer than in normal tissue, expression in a large number of patients with solid tumors, and evidence that cancer cells need mesothelin expression for their aggressiveness—rationalized the selection of mesothelin as an antigen target.

Dr. Prasad S. Adusumilli

Because solid tumors notoriously inactivate tumor-infiltrating lymphocytes and further render infiltrating lymphocytes ineffective by immunosuppressive mechanisms such as the PD-L1/PD-1 pathway, our strategies were designed to counteract these known factors. We studied and published findings on the tumor immune microenvironments of more than 2,000 solid tumors in patients with thoracic cancer, primarily mesothelioma and metastatic lung and breast cancers. Understanding the tumor microenvironment helped us design effective CAR T cells by use of genetic engineering. We designed the CAR to be effective against cancer cells but to spare normal cells, and we armored the CAR with potent CD28 costimulation without the need for help from other immune cells. Our CAR is the first in the world to be developed from all human genetic components so that a patient's immune system will not reject the CAR T cells in the long term, and we were able to help overcome tumor-induced immunosuppression by administering checkpoint blockade agents following CAR T cells.

More importantly, because our clinically relevant mouse models showed

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durvalumab plus tremelimumab plus EP against EP alone. This arm will continue to the final analysis and was not reported at the 2019 WCLC.

In CASPIAN, 265 patients received durvalumab + EP; 266 received EP alone. With regard to baseline demographics, both cohorts were similar; about 70% male, with similar median age (62-63 years) and stage, smoking status, and similar baseline incidence of brain or CNS metastases. Median follow-up at the time of the analysis was 14.2 months.

The median survival for the durvalumab + EP arm was 13.0 months vs. 10.3 months for EP alone. At 12 months, 53.7% of patients who received the combination were alive vs. 39.8% of patients who received EP. At 18 months, survival had dropped to 33.9% for patients who received the combination and 24.7% for EP alone. The hazard ratio favoring the combination was 0.73 (p = 0.0047).


Dr. Luis Paz-Ares

"Survival benefit was very consistent across all subgroups, including those with brain metastases," Dr. Pas-Araz said. "We saw no major differences in safety or adverse events between the two arms."

The CASPIAN results are very similar to the earlier IMpower133 trial of atezolizumab plus etoposide and carboplatin (EC) versus EC alone, where the addition of a PD-L1 inhibitor to standard chemotherapy led to a significant improvement in survival, noted discussant Myung-Ju Ahn, MD, Samsung Medical Center, Seoul Korea.

"Durvalumab plus EP is a new standard in extensive-stage SCLC," Dr. Ahn said. "CASPIAN confirmed the role of checkpoint inhibition in extensive-stage SCLC." ✦

INDUSTRY AND REGULATORY NEWS

CheckMate-227: Nivolumab/Ipilimumab Superior to Chemo in First-Line NSCLC with PD-L1 Expression > 1%

September 28, 2019—Part 1a of the phase III CheckMate-227 trial was successfully completed, with nivolumab plus low-dose ipilimumab yielding superior OS (median 17.1 months) compared to chemotherapy (14.9 months) for patients with NSCLC and PD-L1 expression of > 1% (HR 0.79; 97.72% CI: 0.65-0.96; p = 0.007). OS was also improved for patients with PD-L1 < 1% who received the combination therapy and in the study population overall. The safety profile for the combination was similar to previous findings published in the *The New England Journal of Medicine*.[1]

A prior report of this study[1] showed superior overall response and PFS for ipilimumab/nivolumab in patients with high TMB compared to standard platinum-based chemotherapy, independent of PD-L1 status, but high TMB did not translate into an OS benefit. ✦

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Antibody–Drug Conjugates from page 4

interruption, target expression may suffice for efficacy. Although broader biomarker-defined subsets may expand the pool of eligible patients, efficacy may not reach that of targeted therapies for truly oncogene-addicted tumors. Conversely, it has been suggested that, even for ADCs, the presence of cellular signal dependence (e.g., *HER2* mutations rather than HER2 expression) could enhance antitumor response, in this case through preferential ADC binding and internalization.[5]

Comparing ADC effects across tumor types provides insight into the importance of sensitivity to the cytotoxic payload. In HER2-positive (IHC 2+ or 3+) breast cancer, trastuzumab emtansine (T-DM1) had a response rate of 44% and a median progression-free survival (PFS) of 9.6 months.[6] In NSCLC, when HER2 status is assessed by IHC, responses to T-DM1 were observed only in those with 3+ expression, where the response rate was 20% and median PFS was 2.7 months.[7] Even in the more restricted—and potentially more sensitive—population of *HER2*-mutant NSCLC, median PFS was 5 months.[5] Unfortunately, multiple ADCs have demonstrated similar effects in NSCLC clinical trials, with 17% response rate for the anti-Trop2 ADC sacituzumab govitecan,[8] and a 19% response rate for the anti-MET ADC telisotuzumab vedotin in MET-positive cases.[9] These relatively disappointing results could reflect the limits of cytotoxic therapies as NSCLC treatment, particularly after exposure to multiple prior lines of therapy, as is the case for most ADC clinical trial populations.

Future Directions

Newer-generation ADCs offer improved stability in circulation and favorable payload release kinetics intracellularly. They also benefit from improved characterization of the optimal patient population through biomarker development. A growing number of clinical trials are capitalizing on the favorable toxicity profiles of some ADCs and evaluating them in combination with other therapies. Another potential area of future growth is consideration of alternative payloads beyond cytotoxic drugs. To date, however, results with existing ADCs have been relatively disappointing, and no ADC has yet been approved in advanced lung cancer. ✦

About the Author: Dr. Gerber is Professor of Internal Medicine and Population & Data Sciences at the University of Texas Southwestern Medical Center. Within the Harold C. Simmons Comprehensive Cancer at UT Southwestern, he serves as Associate Director for Clinical Research and as Co-leader of the Experimental Therapeutics Program.

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

EVOLVING STANDARDS OF CARE

Concurrent Chemoradiation Followed by Consolidation Therapy: Questions Remain Despite Transformational Data

Q&A

Now that data from the PACIFIC trial have been incorporated into daily practice, similar trials are validating the results or taking PACIFIC data in new directions. Greg Durm, MD, is a medical oncologist at the Indiana University Simon Cancer Center and principal investigator of a phase II trial examining concurrent chemoradiation with consolidation pembrolizumab in patients with unresectable stage III NSCLC. In the following interview, Dr. Durm discusses consolidation therapy with immunotherapy or checkpoint inhibitors (CPIs) following chemoradiation.

Q: In the setting of locally advanced NSCLC, do you think consolidation therapy with immunotherapy or CPIs post-chemoradiation is now an established standard?

A: For those patients with unresectable stage III disease, I really do think that consolidation therapy with CPIs post-chemoradiation is the standard of care. I realize that there are some patients who will not be candidates for this approach because of concomitant autoimmune problems or other issues. But, for the most part, the bulk of these patients will be able to tolerate these therapies, which are now a key component of therapy after chemoradiation. In patients with resectable disease, the question really becomes whether surgery or consolidation is better. We do not know the answer to that just yet because those trials were done in different eras, and the different modalities certainly have not been compared head to head.

Q: Besides being a straight phase II trial, in what ways did your study of pembrolizumab in this setting differ from the PACIFIC trial?

A: PACIFIC was a randomized trial with a control arm, which did not include any immunotherapy. Ours was a single-arm trial, so all of the patients received pembrolizumab in the consolidation setting. PACIFIC allowed a number of different chemotherapy backbones (with chemotherapy and radiation); ours was more specific in choosing three well-established chemotherapy backbones: carboplatin and paclitaxel, cisplatin and pemetrexed, and cisplatin and etoposide. Lastly, PACIFIC allowed patients to go on consolidation to durvalumab as soon as their physicians felt that they were well enough to do so after concurrent radiation, but our trial required that patients be off therapy for at least 4 weeks. After repeat imaging, patients were able to start consolidation pembrolizumab 4 to 8 weeks after completion of chemoradiation. Other than those few differences, the trials were almost identical.

Dr. Greg Durm

Q: Do you think there are any fundamental differences between durvalumab and pembrolizumab in the treatment of locally advanced NSCLC?

A: Aside from the obvious difference that one is a PD-1 inhibitor and one is a PD-L1 inhibitor, I think that, based on what we have seen in the metastatic setting both for lung cancer and other tumor types, these behave similarly in terms of efficacy and toxicity. The durvalumab data are just more robust in the stage III setting, given the larger randomized trial.

Q: Are there selection factors (e.g., age and comorbidity status) that influence your decision to adopt this approach?

A: I think the only selection factors that I really take into account are the presence or absence of interstitial lung disease or autoimmune illness, such as rheumatoid arthritis or lupus, or if the patient is on an immunosuppressive agent that I think would lessen the efficacy of the consolidation immunotherapy. I have very successfully treated patients in their late 70s and early 80s, which is a testament to how tolerable these agents are. Otherwise, I consider each patient individually, and I think that most patients—even those with a number of comorbidities—have a really good chance at doing well on these therapies.

Q: Does radiation therapy dose make a difference? What about protons vs photons in this setting?

A: In our trial the patients received definitive-dose chemoradiation, which is typically right around 60 to 66 Gy, which was the same dose range used in the PACIFIC trial. So we know that in the standard definitive-dose range, these medications work. What we do not know is if dose reduction while maintaining efficacy is possible. A number of studies

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MEETING NEWS

IASLC's Inaugural Mesothelioma Meeting Sets Baseline for Strategic Approach to Patient Care

As a rare orphan disease, mesothelioma research has been slowed by a lack of eligible patients for trials and by a dearth of resources. Because of these hurdles, agreement among oncologists and researchers in the field regarding strategic priorities is necessary. The IASLC 2018 Mesothelioma Meeting held this past July in New York City laid the groundwork for a more strategic approach to this disease by bringing together the world's experts as well as motivated early-career researchers to discuss novel data and bridge gaps in collaborative research

Anne Tsao, MD, a co-chair of the meeting, noted that the success of this first meeting could be deduced by the engagement of experts from most major centers throughout the world.

"It was so inspiring to see the number of highly committed and enthusiastic investigators who participated in the meeting to help further mesothelioma research," she said. "I think we hit the mark by establishing international collaborations and by our agreeing on which trials would likely have the biggest impact for our patients."

Just as with other solid tumor types, immunotherapies are of great interest in mesothelioma research. The immune-refractory space is also an area of extensive discussion and focus, as is the natural biology of this disease. Because chromothripsis—a clustered presence of a high number of chromosomal rearrangements—is often present in mesothelioma, the genetics of this disease are totally unique.

This inaugural meeting discussed novel research in all of these areas including the collection of biomarkers through "window of opportunity" neoadjuvant trials in the early-stage setting as well as early data on the efficacy of specific immunotherapeutic agents in combination with chemotherapy for unresectable disease in the first-line setting. Strategic frameworks were also laid regarding approaches to antiangiogenic therapies, some of which, such as VEGF-R TKIs have not been proven efficacious in phase III trials, and some of which, such as bevacizumab, should not be ruled out.

The way to generate progress is to personalize the disease.

–Dr. Anne Tsao

"The way to generate progress is to personalize the disease," Dr. Tsao told Jack West, MD, in the IASLC Podcast "Lung Cancer Considered." "Because of the rapid pace of science and technology, I'm hoping that we will be seeing new treatments based on improved understanding of the biology of this disease and will not be treating patients according to an algorithm."

For more about the state of mesothelioma patient care, listen to the full Lung Cancer Considered podcast at IASLC.org/About-IASLC/Newsroom/Lung-Cancer-Considered. ✦

Exploring Possibilities in Mesothelioma

As Dr. Tsao mentioned, little is known about the biology and mechanisms of action of mesothelioma. For an expert perspective on the role of chromothripsis in the angiogenesis of this tumor type, read the online editorial in the *Journal of Thoracic Oncology* (JTO.org) by Dr. Michele Carbone and colleagues: Does Chromothripsis Make Mesothelioma an Immunogenic Cancer?

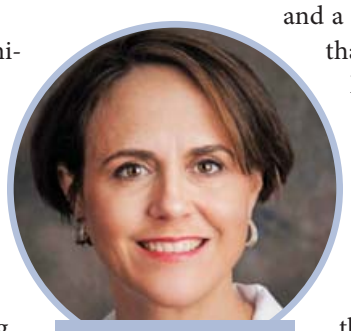
SMOKING CESSATION AND TOBACCO CONTROL

Smoking Cessation Prior to Lung Cancer Surgery

By Jessica Donington, MD, MSCR

Approximately 80% to 85% of patients undergoing lung cancer resections have a smoking history, and 20% are active smokers. Never smokers have improved short- and long-term outcomes following lung resection compared to those who have smoked. The value of smoking cessation prior to or at the time of lung cancer diagnosis is significant.[1]

The recent National Lung Screening Trial provided a unique cohort to study the effects of active tobacco use on early-stage lung cancer survival. The trial was limited to individuals with more than a 30 pack-year smoking history and included 24,190 current smoker and 26,073 former smokers. Lung cancer–specific mortality was higher in current compared to former smokers (HR 1.69) and lowest in those with the greatest number of years without smoking. Each additional year of smoking cessation resulted in a 6% decrease risk for lung cancer death.[2]



Dr. Jessica Donington

Depending on the definitions used and the extent of resection, the risk of complication following lung cancer surgery ranges from 6% to 50%. Many risk factors for operative morbidity are not modifiable including age, sex, and cancer stage, but smoking is a modifiable risk. Smoking is associated with increased hospital death and complications following lung cancer resections. The risk for respiratory complications is two times higher for active smokers compared to never smokers.

Defining Benefit

Smoking cessation improves pulmonary function over time. There is some uncertainty as to whether operative risk related to smoking can be mitigated in the timeframe needed to initiate therapy for a newly diagnosed cancer. Whereas enhancements in spirometry, ciliary clearance, and immune function occur over months and years, sputum production decreases in the initial weeks after resection. There is a similar time-related decrease in risk for postoperative respiratory complications. A recent meta-analysis of 25 trials noted a 23% reduction in postoperative respiratory complications with just 4 weeks of smoking cessation and a 47% decrease with more than 8 weeks of cessation.[3] Evidence for decreased operative complications after less than 4 weeks of smoking cessation is less clear, but there is also little evidence supporting the concept that short-term abstinence leads to acute withdrawal, with increased sympathetic activity and cardiovascular complications. The lack of significant perioperative benefit to smoking cessation within 4 weeks of surgery should not deter clinicians from strongly encouraging thoracic surgery patients to stop smoking. There are significant long-term benefits to cessation, and the perioperative period is an incredibly "teachable moment."

There are important long-term oncologic benefits to smoking cessation at the time of lung cancer diagnosis. The carcinogens in tobacco act as both a genetic inducer of malignancy and a promoter of tumor progression. Those with early-stage lung cancer who continue to smoke have a higher risk of recurrence, second primaries, and all-cause mortality compared to those who stop smoking at diagnosis.[4] Life table modeling suggests that most of the mortality benefit is due to cancer progression rather than cardiovascular causes.

Smoking cessation at any time is meaningful for all patients, but especially for those diagnosed with lung cancer. In patients with early-stage disease, smoking cessation improves short- and long-term outcomes. Tobacco cessation programs are an essential component of any lung cancer treatment team. ✦

About the Author: Dr. Donington is a professor and chief of Thoracic Surgery, University of Chicago Medicine and Biologic Sciences.

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Concurrent Chemoradiation

from page 10

have looked at different doses of chemoradiation, and we know that higher doses above a specific threshold do not work and cause more toxicity. We also know that the 60 to 66 Gy range is effective in treating these patients, even without the addition of CPIs. I think we will likely see the standard of care stay in that dose range, but the answer to whether different doses in conjunction with CPIs work better is largely unknown. The role of proton therapy in lung cancer is still evolving, but there are studies suggesting that it may reduce radiation dose to critical structures. This allows for decreased toxicity but also may improve efficacy by providing safer delivery of dose-escalated therapy to tumor sites and improving the safety and feasibility of multimodality therapy.

Q: Did all patients in the Hoosier Oncology Group trial undergo PET imaging prior to chemoradiation? Is PET prior to chemoradiation routine at this point?

A: Much like the PACIFIC trial, patients in our trial were actually treated with concurrent chemoradiation by their local physicians. Approximately one-third of the patients were treated at Indiana University (IU). The patients did not enroll until after they completed their concurrent chemoradiation and obtained follow-up imaging so we do not have PET data for all 93 patients. PET is routine prior to chemoradiation, which is why I suspect that the vast majority did undergo a PET scan prior to treatment. Before putting someone through chemoradiation and then ultimately a full year of immunotherapy, you really do need to stage them appropriately and ensure that there is no distant disease. In my practice and those of my colleagues here at IU, PET prior to chemoradiation is routine, but I do not repeat PET at 3 months. After I treat patients with concurrent radiation and put them on immunotherapy, I actually just use CT scans to follow them. Of course, if there are questions about whether what we are seeing on the CTs represents actual progression, then we will often order a PET/CT to answer that question. There are emerging data looking at mid-treatment and post-treatment PET/CTs, but I do not think that this information is ready for general practice yet.

Q: Based on your experience, what percentage of patients with locally advanced NSCLC who go through chemoradiation are ultimately eligible for consolidation immunotherapy?

A: Based on my experience, the vast majority are eligible for consolidation immunotherapy. It's very tolerable, and the baseline rates of autoimmunity in this population are reasonably low. If a patient is healthy enough to undergo concurrent chemoradiation, that patient is likely healthy enough to get systemic therapy with a single-agent immunotherapy. I would say that the vast majority of patients who go through chemoradiation are eligible for that treatment.

Q: Were there differences in outcome in your trial based on PD-L1 status?

A: Keep in mind that our trial was smaller and did not measure the PD-L1 expression levels for every patient—some of them just did not have enough tissue left over to do that analysis. In our analysis of the HOG trial, the PD-L1 expression level was not correlated with patient benefit from pembrolizumab therapy. PACIFIC offers a much larger dataset, but it is a post hoc analysis. At this point, PD-L1 status is not a factor when I decide to put my patients on consolidation immunotherapy. We know from the metastatic setting that PD-L1 is not the best biomarker. I have personally had a number of patients who had very low PD-L1 expression in the metastatic setting who have responded beautifully to CPIs. I would hate to deprive a patient of the very clear benefit seen in the PACIFIC trial and our trial by relying solely on PD-L1 as the basis for making that decision.

Q: Why do you think previous strategies failed?

A: There is certainly no shortage of trials looking at other strategies. We have tried induction chemotherapy, and all of those studies have failed to improve overall survival (OS). In regard to consolidation therapy, there was a pooled analysis of 41 separate trials, which clearly showed no significant benefit for the addition of consolidation chemotherapy after definitive chemotherapy and XRT. We actually ran our own HOG trial here, with consolidation docetaxel in this setting, and those patients actually did worse numerically with consolidation. We have looked at higher doses of radiation, EGFR inhibitors (both cetuximab and gefitinib), and we have looked at anti-VEGF therapies—all of which have either been proven unsafe (specifically in regard to some of the VEGF inhibitors) or have failed to improve OS in this setting. Why all of those failed when immunotherapy has very clearly succeeded is hard to say. One theory would be that during chemoradiation, patients are receiving chemotherapy, so you probably are selecting out a group of cells that are inherently resistant to those types of treatment. By employing immunotherapy afterward, we not only attack the remaining cancer cells with a different type of strategy, but we also do so at a time when the body is primed to achieve that type of response. As we know from a number of preclinical models and now from clinical trials, radiotherapy seems to sensitize the body to immunotherapy. It increases release of neoantigens, it increases tumor immune cells at or around the tumor bed, and it decreases some of the immunosuppressive effects of the tumor microenvironment. So there are a lot of reasons why immunotherapy may be successful in this setting. It may be that we have found the appropriate timing for these or that we have found a different modality that works in a different way than chemotherapy. Either way, I do not know that there is a clear answer to that question, but these are my theories.

> ***We have looked at higher doses of radiation, EGFR inhibitors (both cetuximab and gefitinib), and we have looked at anti-VEGF therapies—all of which have either been proven unsafe (specifically in regards to some of the VEGF inhibitors) or have failed to improve OS in this setting.***
>
> –Dr. Greg Durm

Q: What fundamental questions regarding CPIs in this setting remain?

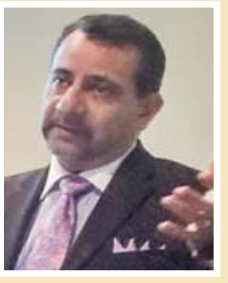
A: *What is the proper timing?* In PACIFIC, the patients were able to go on immunotherapy directly after chemoradiation therapy was completed. Some of those patients started treatment in the first couple of weeks; in our trial they were enrolled a little bit later, as was previously mentioned. Both obviously showed improvements in progression-free survival (PFS). PACIFIC showed improved OS; there also was a post-hoc analysis examining earlier vs later start for immunotherapy and suggested that those patients who started earlier may have done a bit better. In our trial, we did a similar analysis, again with a smaller number of patients, and we did not see much of a difference for those patients who started earlier in the course (Weeks 4 to 6) versus later in the course (Weeks 6 to 8). I think the danger of making that assumption is that patients who start early obviously did very well with chemoradiation; these patients may be a different patient population, however, compared to those who might have struggled through treatment. Attributing all of the benefit to the early administration of immunotherapy is a little bit difficult.

What is the proper duration? PACIFIC chose 12 months of immunotherapy; our trial also chose 12 months of pembrolizumab. Is 12 months enough treatment? Clearly there was benefit, but would 24 months show more? Or would 6 months perhaps be enough? These drugs are typically well tolerated but can demonstrate significant toxicities as well. We did see some increase in immune-related toxicities in both our trial and in the PACIFIC trial. We also know that these drugs are costly, so I think that future trials need to address whether shorter periods are just as effective, or if 12 months is the optimal duration for these patients.

Would combination therapies improve results? Using a PD-1/PD-L1 inhibitor in combination with a CTLA4 inhibitor is one strategy, and there are a number of other CPIs in development at the current time. Furthermore, there are ongoing trials looking at the addition of immunotherapy in combination with chemoradiation, which is another interesting strategy.

What role does surgery play in all of this? We do know that both our trial and PACIFIC were conducted in patients with unresectable disease, but approximately 20% of our patients have resectable stage III disease. Whether it is more beneficial for them to undergo surgery after chemoradiation or to begin consolidation immunotherapy is largely unanswered. Perhaps, in the future, it will be some combination of those two strategies, and there is at least one ongoing trial looking at incorporating both strategies. ✦

Names and News



Luis E. Raez, MD, has been elected 2019-2021 President of the Florida Society of Clinical Oncology (FLASCO). With more than 3,500 members, FLASCO plays a very important role in relationships with industry, payors, and education for oncology providers and advocacy for their patients. Dr. Raez hopes to increase rates of lung cancer screening and molecular testing in the state of Florida during his presidency.

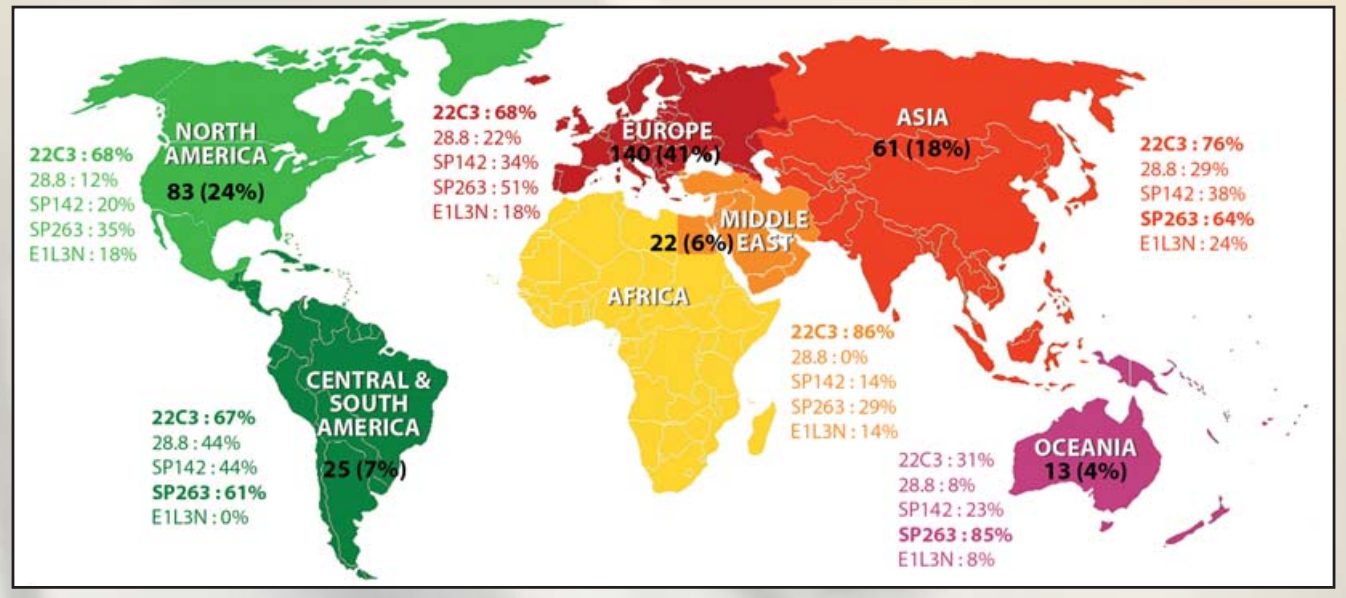
Dr. Raez is currently chief scientific officer and medical director at Memorial Cancer Institute at Memorial Health Care System, the third largest public health care system in the country. He is also clinical professor of Medicine at the Herbert Wertheim College of Medicine, Florida International University.

He serves as chairman of the IASLC Latin American Group and he is the former chair of the IASLC membership committee. ✦

Global Survey for Pathologists on PD-L1 Testing: Moving Toward Standardization

By Mari Mino-Kenudson, MD, and Sylvie Lantuejoul, MD, PhD

Fig. Global Participants and PD-L1 Antibody in the Immune Biomarker Working Group Survey



Determination of PD-L1 expression by immunohistochemistry (IHC) has been widely evaluated in clinical trials as a predictive biomarker for patients with advanced NSCLC and is routinely performed to determine eligibility for pembrolizumab therapy, either as monotherapy or in combination with chemotherapy or, in Europe, for durvalumab therapy after chemoradiation for patients with unresectable stage III NSCLC. Four PD-L1 commercial assays validated in clinical trials have been approved by the U.S. Food and Drug Administration or the European Medicines Agency or are used as in vitro diagnostic tests in multiple countries; costs have limited their use, however, leading to the use of laboratory-developed tests (LDTs). Overall, PD-L1 testing is not uniformly implemented across different geographic regions and across different laboratories. Although PD-L1 expression determined by IHC is not a perfect biomarker, implementation of uniform standards to improve its predictive performance is warranted.

With this background, the Immune Biomarker Working Group of the IASLC Pathology Committee conducted an international online survey between February 1 and May 31, 2019 on PD-L1 IHC testing for patients with NSCLC. The goals of the survey were to assess the prevalence of and process for PD-L1 testing and to identify issues to improve the practice globally. The survey included more than 20 questions on pre-analytical, analytical, and post-analytical aspects of PD-L1 IHC testing, including the availability/type of PD-L1 IHC assay(s), participation in a quality-assurance (QA) program, and completion of training.

Illuminating Global Inconsistencies

A total of 344 pathologists from 310 institutions in 64 countries participated in the survey: 140 (41%) from Europe, 83 (24%) from North America, 61 (18%) from Asia, 25 (7%) from the Central/South America, 22 (6%) from the Middle East/Africa, and 13 (4%) from Oceania (Figure). Of these, 32% primarily practice thoracic pathology, 30% practice both thoracic pathology and cytology, 6% practice primarily cytology, and 29% practice general pathology (3% defined their primary practice as "other"). Of note, a small fraction of participants (2.9% from nine countries) do not perform PD-L1 IHC, and another 9.9% send out samples to other laboratories—in particular, 25% of respondents from North America and 15% from Central/South America outsource their samples. Regarding the specimen type, although cytology specimens have not been validated in trials as samples for PD-L1 testing and the PD-L1 IHC scores on cytology samples are particularly subject to interobserver variability,[1] cell blocks and cytology smears are used by 72% and 10% of all participants, respectively, along with biopsies and surgical resections (94% and 89%, respectively). Among PD-L1 antibody clones, 22C3 is most frequently used of 69% of all respondents with the clinical-trial validated, commercial assay in 60% of the laboratories conducting 22C3 PD-L1 IHC. The SP263 assay was used by 51% of respondents; 28.8 and SP142 assays are used by only 21% and 31% of respondents, respectively (Figure). The numbers appear to reflect the regulatory approval status of PD-1 and PD-L1 agents for various indications and the subsequent requirement of use of a PD-L1 IHC assay for each indication. In Central/South America, Europe, Asia, and Oceania, the majority of laboratories run SP263 IHC (61%-85%) commonly with the commercial assay, likely reflecting the fact that > 70% of the laboratories are equipped with Ventana automation in those regions. Conversely, the SP263 clone is used only in about one-third of the laboratories in North America and in the Middle East/Africa.

The vast majority of laboratories have external QA measures in place, but 18% report a lack of QA. However, only 63% of respondent laboratories participate in a formal QA program; this is a more frequent practice in Europe (72%) and Oceania (77%). PD-L1 testing guidelines are applied in the vast majority of laboratories (96%), but national or local guidelines are used only by 62%—mainly in North America (73%), Europe (68%), Asia (61%), and Oceania (54%). Conversely, the *IASLC Atlas of PD-L1 Testing in Lung Cancer* is the only "guideline" referenced in 76% (Central/South America) and 55% (the Middle East/Africa) of laboratories. It has been reported that interobserver variability may be higher than interassay viability.[2] Thus, training for scoring of PD-L1 IHC appears to be very important to improve interobserver concordance. Although 84% of all respondents have undergone some training, the rate is lower in the North America (69%), Central/South America (64%), and in the Middle East/Africa (67%).

The median turn-around-time (TAT) for results is 1-2 days in North America, Europe, and Oceania, 2-3 days in Asia and Central/South America, and 3-4 days in the Middle East/Africa. TAT is the shortest in Europe. In North America, laboratories that outsource PD-L1 testing report longer TAT.

Although the majority of respondents noted that they use a standardized report with no significant difference between regions, 14% of laboratories report the results of PD-L1 IHC with a free text.

There is heterogeneity in PD-L1 testing practice across regions, as well as across individual laboratories. The regional differences appear significant in PD-L1 testing status, PD-L1 antibody clones/assays used, training, the availability of local or national guidelines, and TAT. In addition, a significant minority of respondents reported a lack of QA, in particular, formal QA, formal training, and/or a standardized reporting system. New actions encouraging formal QA participation, application of standardized reporting, and implementation of regional training (particularly on cytologic samples) are expected, and harmonization of LDTs must be achieved at a global level. The IASLC Pathology Committee members encourage that laboratories offering PD-L1 testing to participate in formal QA, apply a standardized reporting format, and attend regional training. ✦

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Acknowledgement: The authors thank Dr. Nolwenn Le Stang from the Biopathology Department of Centre Léon Bérard, Lyon France for her statistical assistance and contribution of the figure.

EVOLVING STANDARDS OF CARE

Adjuvant EGFR-TKI for Resected NSCLC: Who, When, and Where?

By Si-Yang Liu, MD, and Yi-Long Wu, MD

In the twentieth century, adjuvant chemotherapy became the standard of care for resected NSCLC based on several clinical trials including IALT, JBR.10, ANITA, and a meta-analysis of individual patient data from the LACE trial. Adjuvant chemotherapy increased overall survival (OS) by 5% at 5 years, and resected NSCLC was considered a "curable disease." The question raised was whether these patients with resected NSCLC could really be cured. According to the Eighth Edition Lung Cancer Stage Classification, 5-year OS in resected NSCLC ranged from 90% for stage IA disease down to 41% for pathologic stage IIIA disease.[1] As for patients with stage II to IIIA disease with lymph node metastasis, 5-year OS was only 40% to 50%, implying that more than half of these patients could not be cured.[1] This is a very important point, in that the survival of those with so-called "curable disease" is heterogeneous. There is a huge medical need to improve the long-term survival of patients whose cancers are destined to recur after surgery.

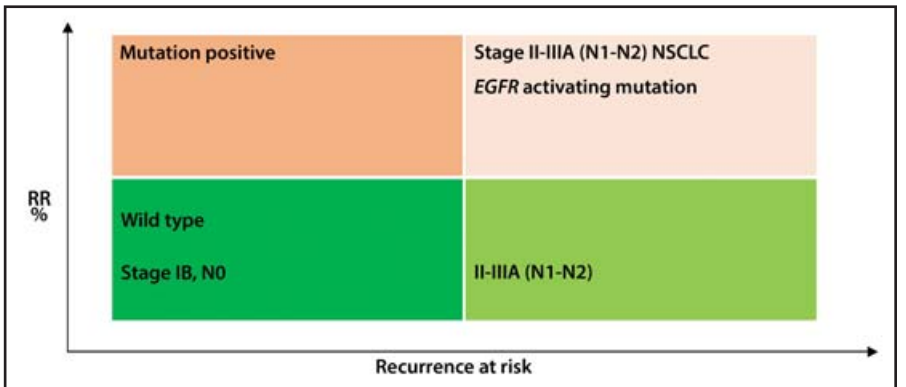
Dr. Si-Yang Liu

Dr. Yi-Long Wu

Patient Selection for Adjuvant EGFR TKIs

In the adjuvant chemotherapy era, NSCLC was considered a single disease, so most trials were designed for all comers. BR.19, the first trial to evaluate an EGFR TKI (gefitinib) in the adjuvant setting, and the subsequent RADIANT trial, which compared erlotinib to placebo, were not designed specifically for patients with *EGFR* mutations. Thus, it is no surprise that these two adjuvant TKIs failed to show meaningful benefits.[2,3] Since the publication of the phase III randomized controlled trial IPASS in 2009, NSCLC, particularly in East Asia, has been classified as *EGFR* mutant and *EGFR* wild type. Along with the use of small-molecule TKIs, significantly superior survival benefits have been achieved in select patients, with advanced *EGFR*-mutated NSCLC.[4,5] As a result, EGFR TKIs have successfully established their first-line treatment position in this subgroup, replacing chemotherapy upfront.[6] Extrapolating our knowledge from advanced NSCLC to so-called curable NSCLC, we know that N1 to N2 NSCLCs have the highest risk of recurrence and are more likely to respond to EGFR TKIs in patients harboring an *EGFR* mutation (Figure). As a result, we hypothesized that EGFR TKIs might play an important role in the adjuvant setting in such patients. One of the most important points is that the patients with stage I disease had lower recurrence rates and higher 5-year survival (~80%). So it was rational to exclude patients with resected stage IB NSCLC from automatic enrollment onto adjuvant clinical trials. (Figure)

Fig. Patients With Lymph Node Metastasis Would Benefit Most From Adjuvant Therapy, and TKIs Provide a More Appropriate Choice for Patients with EGFR-mutant Disease



Patients with lymph node metastasis would benefit most from adjuvant therapy, and TKIs provide a more appropriate choice for the *EGFR* mutant group.

Given these facts, we conducted an ADJUVANT phase III clinical trial for patients with actionable *EGFR* mutations, which only targeted N1 and N2 disease.

Dose and Schedule

The distinguishing design feature of the ADJUVANT trial was a direct comparison of adjuvant TKIs with vinorelbine plus cisplatin instead of comparing TKIs with placebo after chemotherapy, as evaluated in the BR.19 and RADIANT trials. Unsurprisingly, compliance with adjuvant TKIs (95.5%) was better than that with chemotherapy (78.4%) in our ADJUVANT trial. This means that patients receiving adjuvant TKIs were more likely to complete treatment than patients receiving standard chemotherapy. Another issue was how long to treat these patients. In addition, we raised the question of whether disease-free survival (DFS) would be a reasonable endpoint. Would it be a surrogate for OS?

Based on the data from TNM staging, the median DFS for patients with N1- to N2-positive disease ranged between 9.0 and 21.0 months, so the duration of EGFR-TKIs was set up as 24 months to best reduce recurrence.[7] However, based on observations from the SELECT study, future research directions should include a straight phase II trial evaluating erlotinib in the adjuvant setting, the length of therapy's effect on outcomes, and optimal duration. Trials testing longer treatment durations, such as ADAURA (adjuvant osimertinib vs placebo after chemotherapy), are underway.[8,9]

Cure Versus Extended Response

Because OS has been always considered the primary endpoint for most clinical trials, researchers may question whether adjuvant TKIs are able to improve cure rates or whether they just delay recurrence. The design of ADJUVANT is different from RADIANT, and the hypothesis of the two trials designs is different. The ADJUVANT study was created to test whether an EGFR TKI might be a viable treatment alternative to chemotherapy in the adjuvant setting, specifi-

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CAR T-Cell Study from page 8

that CAR T cells infused through blood are sequestered in the lungs for a few days and are not able to enter the tumor efficiently, we investigated and translated the previously mentioned strategy of directly injecting CAR T cells intrapleurally, thereby avoiding toxicity and increasing efficacy by several fold. This approach is the first in the world of its kind.

We plan to continue combination therapy with mesothelin-targeted CAR T cells and anti–PD-1 agents with dose escalation and administration of anti–PD-1 agents 4 weeks after CAR T cells. To further make the above strategy tumor specific, we designed a "decoy receptor": a PD-1 dominant negative receptor (DNR) that is combined with mesothelin-targeted CAR. We are now conducting Investigational New Drug studies to translate mesothelin PD DNR CAR into a clinical trial by early 2020.

In our publication, we have shown that at least 2 million patients with solid tumors in the United States alone are eligible for this therapy. Among solid tumors, the mesothelin antigen that we are targeting is expressed in mesothelioma (90%), lung cancer (60%), triple-negative breast cancer (35%), pancreatic cancer (70%), and ovarian cancer (60%), as well as stomach, colon, and other cancers. ✦

About the Author: Dr. Adusumilli is deputy chief and attending, Thoracic Service, Department of Surgery; Head, Solid Tumors Cell Therapy, Cellular Therapeutics Center; Director, Mesothelioma Program; and Vice Chair for Translation Research, Department of Surgery at Memorial Sloan-Kettering Cancer Center.

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INDUSTRY AND REGULATORY NEWS

The Death of MERU

August 29, 2019—AbbVie closed the phase III placebo-controlled MERU trial evaluating rovalpituzumab-tesirine, an antibody–drug conjugate targeting the delta-like ligand 3 protein, as first-line maintenance therapy for extensive-stage SCLC in patients with stable disease or response to first-line etoposide and platinum. No survival benefit was seen vs placebo at a pre-planned interim analysis. The MERU data will be published in the future. ✦

INDUSTRY AND REGULATORY NEWS

Osimertinib Performs as Expected for Previously Untreated Patients with NSCLC

September 29, 2019—The final OS results from an analysis conducted from the phase III FLAURA trial demonstrated significantly improved OS for osimertinib compared with gefitinib or erlotinib for previously untreated patients with locally advanced or metastatic NSCLC and with *EGFR* exon 19 or L858R mutations. Median OS for osimertinib was 38.6 months vs 31.8 months for erlotinib or gefitinib (HR 0.799; 95.05% CI, 0.641-0.997; p = 0.0462), even with crossover allowed for first-generation–treated patients who developed the T790M resistance mutation. OS rates for osimertinib at 1, 2, and 3 years were 89%, 74%, and 54% vs 83%, 59%, and 44%, respectively. Overall, the median follow-up for patients who received osimertinib was 35.8 months vs 27.0 for the comparator, during which time 11 fewer deaths occurred in the osimertinib arm.

FLAURA discussant Pasi A. Jänne, MD, said in a press statement that the magnitude of benefit varied by subgroup, although outcomes were consistent across groups. "The study findings are practice changing; however, osimertinib is already approved for acquired resistance due to *EGFR T790M* in 87 countries worldwide and furthermore, it is approved for first-line treatment in 78 countries worldwide. But barriers to first-line use are cost and/or lack of reimbursement," said Dr. Jänne. ✦

Atezolizumab Monotherapy Improves OS in Frontline NSCLC with High PD-L1

September 27, 2019—Atezolizumab monotherapy improved OS compared with platinum-based chemotherapy for previously untreated patients with advanced NSCLC and high PD-L1 expression (> 50% on tumor cells or > 10% on tumor-infiltrating immune cells), regardless of histology. The OS findings were confined to *ALK/EGFR* wild- type tumors.

The phase III IMpower110 trial accrued 572 treatment-naive patients and reported on 555 wild type (*ALK/EGFR* mutation negative) with previously untreated advanced nonsquamous or squamous NSCLC. Patients were randomly assigned to single-agent therapy with atezolizumab or to platinum-based chemotherapy. The primary endpoint was OS by PD-L1 subgroup; secondary endpoints included PFS, ORR, and duration of response.

Median OS at 15.7 months follow-up (range 0-35) was 20.2 months for patients who received atezolizumab vs 13.1 months for those who received chemotherapy (HR = 0.59; 95% CI: 0.40-0.89; p = 0.0106). PFS was also improved with atezolizumab, with a median PFS of 8.1 months vs. 5.0 months (HR = 0.63; 95% CI: 0.45-0.88; p = 0.007) in the same population. The ORR was 38.3% vs. 28.6%, respectively, and the median DOR was not reached for atezolizumab (vs 6.7 months for chemotherapy). ✦

Adjuvant EGFR-TKI from page 14

cally in *EGFR* mutant (+) NSCLC. In this situation, we believed that using DFS as the primary endpoint was rational. The U.S. Food and Drug Administration has stated that a prolonged delay in the development of metastatic disease is an objective and a clinically relevant outcome and that agents can be approved based on metastasis-free survival (MFS) if substantial effects on this endpoint are demonstrated and the safety profile is acceptable.[10] In addition, after adjuvant gefitinib or erlotinib, patients with disease recurrence still have the opportunity to be re-challenged with TKIs. And the median duration of treatment approximates the progression-free survival in a de novo advanced *EGFR*-mutant population.[8,11] Furthermore, several novel treatments such as third-generation TKIs have the opportunity to provide survival benefits after progression. Consequently, whether OS is the most appropriate endpoint remains an open question, and DFS is considered by many a suitable surrogate endpoint.[12]

In more recent times, in advanced NSCLC, the application of EGFR-TKIs such as dacomitinib has significantly prolonged OS.[13] In fact, virtually all patients with *EGFR*-positive NSCLC live longer than they had previously, in both the early- and late-disease settings. So in the early-disease setting it is important to delay recurrence and reduce adverse events so that patients have a better quality of life. [14] This is in line with FDA guidance on MFS.

On the other hand, adjuvant trials for early-stage NSCLC take a long time to complete. The BR.19 and RADIANT trials took more than 10 years to report. The ALCHEMIST study is another ongoing adjuvant setting trial first initiated in 2014 by the National Cancer Institute and is still enrolling patients with *EGFR* mutations. Based on the trial design, the timeframe for accrual will be at least 10 years before we can assess the primary endpoint of OS.

Conclusions

The treatment paradigm for NSCLC has dramatically changed over the past 10 years. New EGFR TKIs such as dacomitinib and osimertinib have been approved. When a trial is destined to last 10 or more years, one must consider whether the results are still clinically meaningful by the time the trial has been completed.

However, we still see a substantial portion of patients in the ADJUVANT trial who experience relapse. One question is how to select populations more precisely for adjuvant treatment. Learning from the experience of minimal residual disease in leukemia, monitoring circulating tumor DNA (ctDNA) in the plasma as a treatment marker may be a potential strategy in the adjuvant setting. From the evolutionary perspective, we might monitor ctDNA dynamically so that the duration and ideal termination of adjuvant TKIs could be precisely determined. In patients with "wild-type" NSCLC, where *EGFR* mutations and other oncogenic drivers are not present, immunotherapy has become an established component of treatment in advanced disease and is being evaluated increasingly in the perioperative setting. Recently, nivolumab was approved as adjuvant treatment for resected melanoma based on the improved relapse-free survival. For personalized adjuvant treatment in the future, we need to identify patients precisely and match the appropriate treatment with the appropriate patient. ✦

For personalized adjuvant treatment in the future, we need to identify patients precisely and match the appropriate treatment with the appropriate patient.

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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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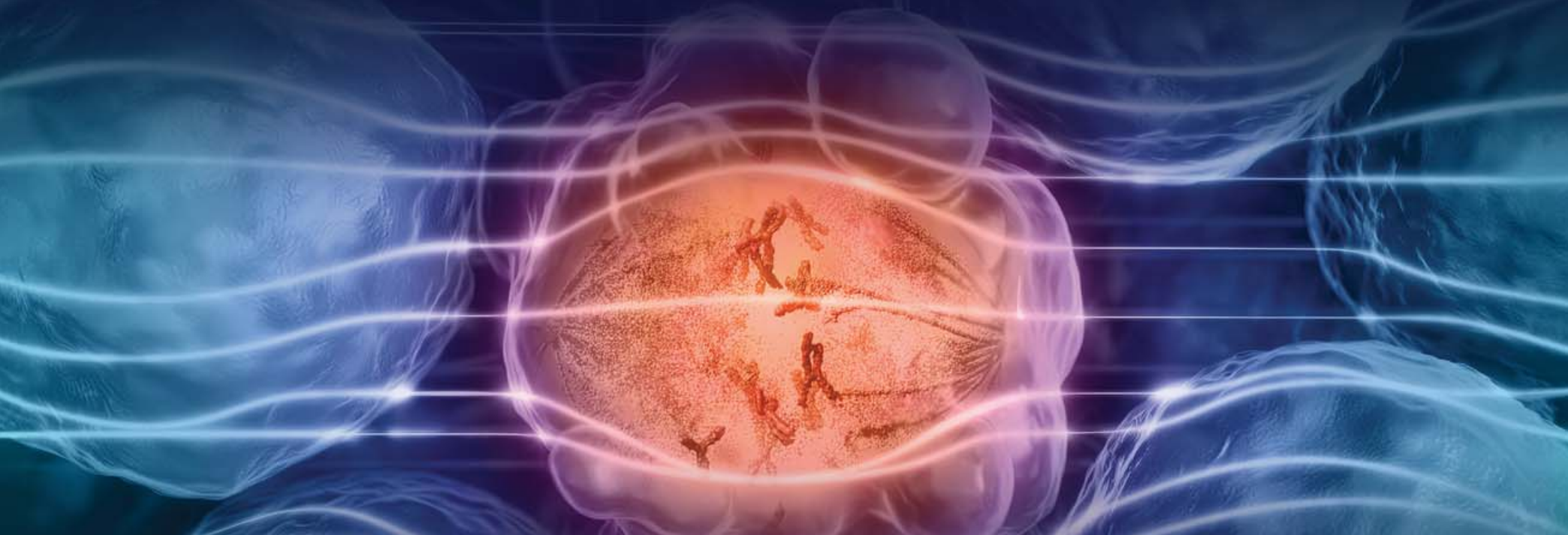

The METIS trial for patients with 1-10 newly diagnosed brain metastases as a result of non-small cell lung cancer (NSCLC) is now enrolling.[1]

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