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**FOR THORACIC SPECIALISTS**

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## INSIDE



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POINT/COUNTERPOINT

# Why TMB Should Be Assessed in Patients with Advanced NSCLC

By Fabrice Barlesi, MD, PhD

Immune checkpoint inhibitors, especially PD-1 and PD-L1 inhibitors, have deeply changed the second-line treatment of patients with advanced NSCLC, with three newly registered drugs in only a few years. Immune checkpoint inhibitors are also changing the first-line treatment of patients with advanced and locally advanced NSCLC and will likely change the treatment of patients with extensive small cell lung cancer (SCLC) and mesothelioma. These changes are mainly supported by the long-term efficacy of immune checkpoint inhibitors, with a proportion of patients experiencing long-lasting responses and durable survival. Therefore, identifying those likely to respond while looking for alternative strategies for those who are not likely to respond or whose responses are likely to be limited is crucial.

**For an opposing perspective on use of TMB as a biomarker, see the article by Dr. Daniel Tan on page 3.**

## PD-L1: A Good Strategy

Increased PD-L1 expression is globally associated with an increased benefit of PD-L1 immune checkpoint inhibitors as monotherapy. However, a significant benefit over the standard docetaxel therapy has also been demonstrated in patients with low or no PD-L1 expression.[1] Conversely, a significant proportion of patients with high tumor PD-L1 expression (≥ 50%) experience progressive disease within 3 months on first-line pembrolizumab monotherapy.[2] Moreover, PD-L1 expression has demonstrated no impact in predicting the benefit of immune checkpoint inhibitor combinations with chemotherapy over chemotherapy alone. In summary, PD-L1 is an imperfect marker, and prediction of immune checkpoint inhibitor efficacy by PD-L1 expression remains a perfectible strategy.

## TMB: A Better Strategy

Tumor mutational burden (TMB) offers a solid biologic rationale as a better strategy. TMB is defined as the number of mutations per DNA megabases (Mb). It was first suggested that the creation of neoantigens induced by mutation acquisition would increase tumor immunogenicity and, consequently, response to immune checkpoint inhibitors. Technically, although TMB was historically assessed by tissue whole-genome sequencing or whole-exome sequencing, targeted next-generation sequencing and

Dr. Fabrice Barlesi

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LUNG CANCER SCREENING

# Bringing Lung Cancer Screening into Communities: An NHS Pilot Program's Success

By Richard Booton, MD, PhD, FRCP

The symptomatic presentation of lung cancer is typically associated with advanced disease and poor survival. Screening asymptomatic at-risk individuals using low-dose CT (LDCT) reduces lung cancer–specific mortality by 20% to 26%,[1] but challenges remain in ensuring participation of the most at-risk populations, such as current smokers or those of lower socioeconomic status. Travel to hospital sites is recognized as a key barrier to access; screening among this at-risk population and reducing these barriers are critical to the successful implementation of LDCT screening.

Dr. Richard Booton

## One-Stop Shop: Cessation Advice, LDCT Scanning, and Scan Interpretation

A pragmatic, community-based pilot was designed around the concept of a one-stop lung health check, located next to local shopping centers, to minimize barriers to participation by reducing travel and increasing convenience and service accessibility (Figure, page 4). Ever-smokers aged 55 to 74 years registered by participating general practitioners were invited and assessed for symptoms, spirometry, and 6-year lung cancer risk using $PLCO_{m2012}$ and were provided with brief, non-judgemental smoking-cessation advice where appropriate. Participants with $PLCO_{m2012}$ risk score of 1.51% or greater were offered immediate LDCT scanning on a co-located scanner, and imaging was interpreted by radiologists with a specialist interest in thoracic oncology according to modified British Thoracic Society Guidelines for the Investigation and Management of Pulmonary Nodules. Scan reports were categorized as negative, indeterminate, or positive. Indeterminate results required a community-based 3-month follow-up scan, and positive scans required an immediate assessment at a lung cancer clinic within a regional cardiothoracic center. Participants eligible for LDCT scanning underwent a baseline scan (T0) and a single annual scan (T1).

Demand for the service was extremely high, with all appointments booked within a few days. Overall, 1,429 participants (56.2%) qualified for LDCT screening, and 1,384 had a LDCT scan. At T0, a negative scan was reported for 82.6%, an indeterminate scan for 12.7% (with a further 1.2% positive at 3 months), and a positive scan for 4.7%. Of the 81 participants referred for further assessment (5.9%), 42 had confirmed cancer. The false-positive rate was 48.1%, or 2.8% for all participants. There were no surgical interventions for benign disease. The prevalence of lung cancer at T0 was 3% (95% CI [2.3%, 4.1%]), 80.4% had stage I-II lung cancer, the surgical resection

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CONQUERING THORACIC CANCERS WORLDWIDE

POINT/COUNTERPOINT

# Tumor Mutation Burden in NSCLC: Not Ready for Prime Time

By Daniel Tan, BSc, MBBS, MRCP, PhD

Despite the expanding scope for the use of immune checkpoint inhibitors in NSCLC, not all patients derive clinical benefit, highlighting the need for high-precision individualized biomarkers that can improve patient selection and future combination strategies. At present, the implementation of PD-L1 expression testing and determination of cutoffs have been based on superior efficacy and quality of life, relative to standard-of-care treatment. After initial studies established the role of monotherapy PD-1/PD-L1 inhibition in the second-line setting and beyond, immuno-oncology combinations (with chemotherapy or CTLA-4 antibodies) have more recently been explored in the first-line setting. Given the variability in PD-L1 testing methodologies, as well as spatial and temporal heterogeneity,[1] additional biomarkers to further refine patient stratification, such as tumor mutational burden (TMB), have been actively explored.

The initial premise for TMB was that the number of somatic mutations would correspond to the likelihood of harboring tumor-associated neoantigens, which, in turn, would represent a surrogate indicator of immunogenicity. This hypothesis was first examined in a cohort of 34 patients with NSCLC, where a threshold of 178 nonsynonymous mutations, as determined by whole-exome sequencing, identified patients who were more likely to achieve durable clinical benefit with pembrolizumab.[2] This observation was further extended to other clinical datasets involving atezolizumab and nivolumab, independently highlighting the value of TMB across different PD-1/PD-L1 antibodies.[3]


Dr. Daniel Tan

One of the most striking results was the potential role of TMB in prediction of response to combination PD-1 and CTLA-4 antibodies for those patients with PD-L1 expression levels less than 1%.[4] This combination was examined in a large prospective phase III study that randomly assigned 1,739 patients with NSCLC to three arms based on PD-L1 status: ipilimumab/nivolumab versus nivolumab monotherapy versus chemotherapy in those with PD-L1 expression of 1% or higher or ipilimumab/nivolumab versus nivolumab/chemotherapy versus chemotherapy alone in those with no PD-L1 expression. However, after restricting the patient cohorts to those who had (1) TMB evaluated successfully and (2) patients with 10 or more mutations per megabase, only 139 patients assigned to ipilimumab/nivolumab and 160 assigned to chemotherapy were included in the efficacy analysis. Most notably in patients with PD-L1 expression levels of 1% or greater, the hazard ratio (HR) for disease progression or death was 0.62 (95% CI [0.44, 0.88]), whereas the HR was 0.48 (95% CI [0.27, 0.85]) for patients with PD-L1 expression levels less than 1%. The comparable patient cohort with TMB ≥ 10 and PD-L1 ≥ 1% showed a HR of 0.75 (95% CI [0.53, 1.07]).[4] These data suggest a role for combination ipilimumab/nivolumab in the absence of PD-L1 expression; because only selected cohorts were included in this analysis, reports on the other subgroups are eagerly awaited.

The lack of relationship between PD-L1 status and TMB has been observed in several different studies, highlighting the potential complementary role for both biomarkers. This discordance suggests that PD-L1 and TMB may reflect different processes in the development of lung cancer. In the context of exhausted T cells from chronic antigen stimulation, PD-L1 overexpression provides a measure of the extent to which immune escape might be implicated. On the other hand, TMB, derived from counting the number of coding mutations, provides a window to crudely infer the life history of a tumor. However, numerous factors can influence the final mutational load, such as DNA repair capacity and mutation rate. Because current neoantigen-predictive algorithms are imperfect, it is likely that the relationship between TMB and antigenicity is not entirely linear. Furthermore, emerging studies suggest that additional factors can affect immunogenicity, including the clonality

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**Assessing TMB** from page 1

whole-exome sequencing demonstrated a good correlation to estimate TMB.[3] Subsequently, a blood-based assay, a more convenient way to assess TMB in routine practice, has been developed with success. Finally, and more importantly, TMB has been demonstrated to be fully independent of tumor PD-L1 expression, even in the subgroup with high levels of PD-L1 expression.

TMB has demonstrated a strong predictive value for efficacy (response rate and/or progression-free survival [PFS]) of immune checkpoint inhibitors in second- and third-line monotherapy. Rizvi et al. first reported a hazard ratio (HR) below 0.20 for PFS between patients with low and high TMB who were treated with pembrolizumab (median PFS 3.4 months versus NR; HR 0.15, 95% CI [0.04, 0.59] in the validation set).[4] Kowanetz et al. showed comparable results in the FIR/BIRCH and POPLAR studies for atezolizumab alone or versus docetaxel (HR for PFS 0.49, 95% CI [0.25, 0.93] and 0.49, 95% CI [0.19, 1.3] in the ≥ 9.9/MB and ≥ 15.8/MB subgroups, respectively).[5] Gandara et al. confirmed those results in blood TMB in samples from the POPLAR and OAK studies (HR for PFS of 0.73, 0.65, and 0.61, for TMB ≥ 10/MB, ≥ 16/MB, and ≥ 20/MB, respectively).[6]

TMB has also demonstrated a predictive value for efficacy (response rate and/or PFS) of immune checkpoint inhibitors in first-line monotherapy. In CheckMate 026, Carbone et al. retrospectively showed an HR for PFS clearly favoring nivolumab over platinum-based chemotherapy in the TMB-high (243 or more mutations) subgroup (median PFS 9.7 months vs. 5.8 months; HR 0.62, 95% CI [0.38, 1.0]).[7]

Finally, TMB has demonstrated a predictive value for efficacy (response rate and/or PFS) of immune checkpoint inhibitors in the first line for combination nivolumab and ipilimumab. In the predefined high TMB (≥ 10 mut/Mb) subgroup of the CheckMate 227 study, Hellmann et al. showed a better PFS for patients treated with combination immune checkpoint inhibitors compared to platinum-based chemotherapy (median PFS 7.2 versus 5.5 months; HR 0.58, 97.5% CI [0.41, 0.81]; $p < 0.001$).[8] Moreover, when considering those patients with less than 1% PD-L1 expression in the same study, Borghaei et al. nicely showed how TMB allows the selection of patients who derive a large benefit from the combination of nivolumab and ipilimumab over platinum-based chemotherapy (1-year PFS of 45% versus 18% for TMB high vs. low, respectively). In addition, this benefit translated into long-lasting responses (with 93% of responses still maintained a year or more).[9] These results have also been confirmed in extensive SCLC.

Although preliminary, these results together highlight how TMB strongly complements PD-L1 expression assessment and will, therefore, help us treat patients with advanced NSCLC with immune checkpoint inhibitors alone or in combination. Several prospective studies are ongoing to provide clinicians with a simple, fast, reproducible, and affordable blood-based assay to assess TMB in daily practice. ✦

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**References:**

1. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet.* 2017;389(10066):255-265.
2. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med.* 2016;375(19):1823-1833.
3. Rizvi H, Sanchez-Vega F, La K, et al. Molecular Determinants of Response to Anti-Programmed Cell Death (PD)-1 and Anti-Programmed Death-Ligand 1 (PD-L1) Blockade in Patients With Non-Small-Cell Lung Cancer Profiled With Targeted Next-Generation Sequencing. *J Clin Oncol.* 2018; 36(7):633-641.
4. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science.* 2015;348(6230):124-128.
5. Kowanetz M, Zou W, Shames D, et al. Tumor Mutation Burden (TMB) is Associated with Improved Efficacy of Atezolizumab in 1L and 2L+ NSCLC Patients. *J Thorac Oncol.* 2017;12(1) S321–S322.
6. Gandara D, Kowanetz M, Mok T, et al. Blood-Based Biomarkers for Cancer Immunotherapy: Tumor Mutational Burden in Blood (bTMB) is Associated With Improved Atezolizumab (atezo) Efficacy. *Ann Oncol.* 2017:v460-v496.
7. Carbone D, Reck M, Paz-Ares L, et al. First-Line Nivolumab in Stage IV or Recurrent Non–Small-Cell Lung Cancer. *N Engl J Med.* 2017;376:2415-2426.
8. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. *N Engl J Med.* 2018;378:2093-2104.
9. Borghaei H, Hellmann MD, Paz-Ares LG, et al. Nivolumab + Ipilimumab, Nivolumab + Chemotherapy, and Chemotherapy in Chemo-Naive Patients With Advanced Non-Small Cell Lung Cancer and <1% Tumor PD-L1 Expression: Results From CheckMate 227. *J Clin Oncol.* 2018;36 (suppl; abstr 9001).
10. Hellmann MD, Callahan MK, Awad MM, et al. Tumor Mutational Burden and Efficacy of Nivolumab Monotherapy and in Combination with Ipilimumab in Small-Cell Lung Cancer. *Cancer Cell.* 2018;33(5):853-861.

IMMUNOTHERAPY

# PACIFIC Flooded Us with Optimism. Now What?

***PACIFIC data were ground-breaking, but obstacles in Europe prevent a change in the standard of care.***

By Mirjana Rajer, MD, PhD

For many years, the treatment of patients with stage III lung cancer has been a topic of intense debate among surgeons, radiation oncologists, and medical oncologists. Each discipline has eagerly expected new trials and results to make these discussions clearer and more optimistic. One of the most important trials in this arena was the PACIFIC trial, which was published in 2017.[1] Prior to the PACIFIC trial, there were no breakthroughs for many years; we treated patients with stage III inoperable NSCLC in the same way. Patients received a high dose of radiation (60 Gy-66 Gy) and usually one or two cycles of concurrent chemotherapy, with or without induction chemotherapy. Such treatment was called radical, even if we managed to cure only up to 20% of patients. We can no longer be satisfied with these results.

Dr. Mirjana Rajer

In the PACIFIC trial, patients were randomly assigned to two groups: one group received the so-called "standard treatment" (chemotherapy, irradiation, and placebo afterwards), while the other group's standard treatment was followed by immunotherapy with durvalumab for up to 1 year. The results of the trial were excellent. The median progression-free survival (PFS) from the completion of standard treatment was 16.8 months in the immunotherapy group, compared to 5.6 months in patients receiving placebo. A similar PFS was reported in a recently published article with updated results, with a PFS of 17.2 versus 5.6 months, respectively. PFS is an important endpoint, but patients are more eager to know if they will live longer with the new treatment, and PACIFIC recently gave us an answer to this question: overall survival (OS) in the durvalumab group was superior (median not reached vs. 28.7 months in the placebo group, HR 0.68).[1,2] These results, together with the lack of major toxicity differences between the two groups, have caused a flood of optimism for oncologists and their patients.

## Implications for Standard of Care in Europe

Is there something keeping us from considering this treatment strategy the absolute new standard of treatment? Of course. As with every trial, we are looking at PACIFIC with critical judgment. For example, one reservation is the possibility of long-term toxicity, with pneumonitis and lung fibrosis our main concerns. In the PACIFIC trial, the incidence of pneumonitis was not significantly higher in people treated with immunotherapy, but we will have to wait and see whether this holds true in the long run.

Unexpectedly, skepticism has emerged from another perspective. Post-hoc analysis showed that baseline PD-L1 status might play a role in outcome. Data showed a benefit in PFS but not OS in patients with less than 1% PD-L1 expression. This observation has "informed" the drug approval process. While the U.S. Food and Drug Administration (FDA) approved durvalumab for all patients,

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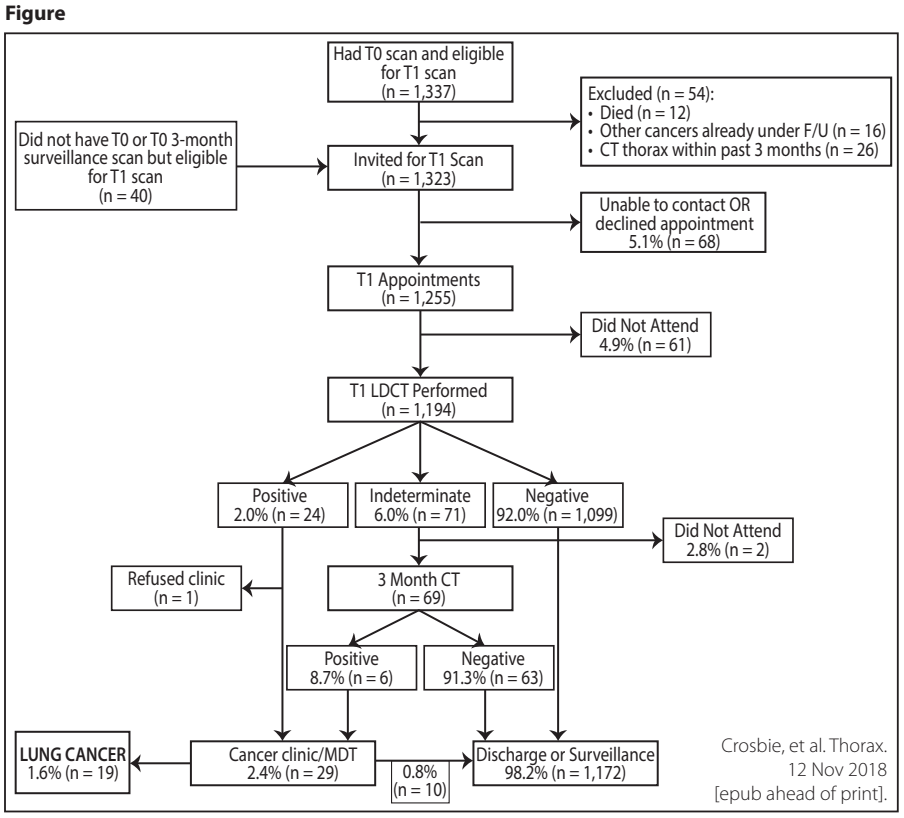
**NHS Pilot Program** from page 1

rate was 65%, and curative intent treatment rate was 89.1%. There was one death within 90 days of surgery.[2]

Between June and August 2017, 1,194 participants underwent their T1 community-based scan, confirming a 90% adherence to LDCT screening. A negative scan was identified for 92%, and a positive scan was identified for 2.5% of participants; 5.9% of participants had indeterminate scans (6 participants had positive scans at 3 months). Of 29 participants referred for further evaluation (2.4%), 19 were diagnosed with lung cancer, representing a false-positive rate of 34.5% (0.8% of all T1 participants). The incidence of lung cancer at T1 was 1.6%, 79% had stage I-II disease, and curative-intent treatment was provided in 78.9% (surgery 47%, stereotactic ablative radiotherapy 26%, and radical radiotherapy 5%). One participant received surgery for granulomatous disease; there were no deaths at 90 days. The false-negative rate for T0 was 0.4%, with a negative predictive value of 99.6%, sensitivity of 89.4%, and specificity of 97.1%. Overall (T0 + T1), the benign surgical resection rate was 2.5%.[3]

**Figure**




Crosbie, et al. Thorax. 12 Nov 2018 [epub ahead of print].


Photos used with permission from Dr. Booton.

The mobile health screening structure (above) and equipment (left). Adoption of a larger-scale program—10,000 lung health checks—begins in April 2019.

## Saving Lives, Saving Money

This pilot was undertaken in low-income areas of Manchester, United Kingdom, and it used a "Lung Health Check" design to facilitate uptake of a targeted lung cancer screening program. Attendees could be ranked according to degree of deprivation in small areas of England, using domains that included income, employment, education, health, crime, environment, and barriers to housing, from 1 (most deprived) to 32,844 (least deprived). Seventy-five percent of attendees were ranked in the lowest deprivation quintile, and screening adherence was high. Throughout both screening rounds, we identified one lung cancer for every 23 scans performed. Approximately 80% of lung cancers were identified at an early stage and underwent high rates of curative-intent surgery, with low false-positive rates and low benign surgical resection rates. An ultra-conservative cost-effectiveness analysis of the pilot suggested an incremental cost-effectiveness ratio of £10,069 per quality-adjusted life year,

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GLOBAL INITIATIVES

# Lung Cancer Global Mortality Projections Skyrocket for Women

***Largely due to tobacco use in low-income countries, female lung cancer deaths are expected to outpace those from breast cancer.***

By Joy Curzio

Lung cancer is the leading cause of cancer death among women, with the 5-year survival rate at just 21%.[1] An estimated 70,500 women in the United States alone died in 2018 due to lung cancer,[1] and a recent study analyzing data from the World Health Organization (WHO) has projected that estimated global mortality for women with lung cancer will continue to climb to as high as 43% by 2030, surpassing breast cancer mortality—a trend that has already begun in several countries.

A study by Martín-Sánchez et al.,[2] which appeared in *Cancer Research*, found that the shift is most likely due to highly effective and utilized screening tools for breast cancer, as well as an increase in tobacco use among women in many countries. Until recently, lung cancer mortality has been higher in high-income countries than in middle- and low-income countries because tobacco use has not been as widespread in the latter. However, according to a report by The International Agency for Research on Cancer (IARC), "The extent of the projected increases in lung cancer and other tobacco-related disease is, however, inextricably linked to the global tactics of tobacco companies aiming to expand their sales."[3] The report states that countries with a low Human Development Index and in economic transition, such as Bangladesh and China, are experiencing a surge in tobacco use, with women adopting the habit in geographic areas where smokers had mainly been men, and that more than 80% of all smokers reside in low- and middle-income countries.

Martín-Sánchez and colleagues used cancer mortality data from the WHO Mortality Database. Age-standardized mortality rates (ASMRs) per 100,000 were calculated for 2008 to 2014 and projected for 5-year intervals beginning with 2015 and ending with 2030 using a Bayesian log-linear Poisson model. The median ASMRs are projected to increase for lung cancer in 52 countries from 11.2 in 2015 to 16.0 in 2030. The highest rate projections are for Europe and Oceania, and the lowest rate projections are for the Americas and Asia.

PACO COMO / Shutterstock.com

Both the IARC report and the Martín-Sánchez study emphasize that tobacco control measures, such as taxes and the elimination of advertising,[3] could have the most dramatic and lasting effects on these projections. ✦

**References:**

1. American Cancer Society. *Cancer Facts & Figures 2018.* Atlanta: American Cancer Society; 2018.
2. Martín-Sánchez JC, Lunet N, González-Marrón A, et al. Projections in Breast and Lung Cancer Mortality among Women: A Bayesian Analysis of 52 Countries Worldwide. *Cancer Res.* 2018;78(15): 4436-4442.
3. International Agency for Research on Cancer. World Cancer Report 2014. api.iarc.fr/shop/5158e6975a76c427360727251e15a223565ae26fabc115991f5b43811d908110/World%20Cancer%20Report.pdf. Accessed December 4, 2018.

NCI CORNER

## NCI Director Dr. Norman E. Sharpless Discusses 2019 Budget Plans During Social Media Event

By Erik MacLaren, PhD

On January 25, 2019, the Director of the National Cancer Institute (NCI) Norman E. Sharpless, MD, participated in a live social media event to discuss the NCI's budget plans for 2019. During the hour-long discussion, Dr. Sharpless presented his assessment of the current funding situation, elaborated on his vision for the future of the NCI, and fielded questions from the other panel members—Elizabeth M. Jaffee, MD, deputy director of the Sidney Kimmel Comprehensive Cancer Center and chair of the NCI's National Cancer Advisory Board, and Dafna Bar-Sagi, PhD, senior vice president and vice dean for science, chief scientific officer, NYU Langone Health and chair of the NCI's Board of Scientific Advisors—and the online audience.

Dr. Sharpless opened the session by discussing increases in funding and knowledge that have been achieved in recent years, saying, "It's a special time in cancer research; we're making progress at a breathtaking pace." He highlighted broad bipartisan support in Congress for the NCI and increases in the NCI's budget for the past 5 years running. Dr. Sharpless also noted a striking and unexpected increase in new grant applications during this time and attributed this rise to "recent advances, Congressional support, and enthusiasm generated by the Cancer Moonshot." These new applications, he said, demonstrated the vibrancy of current cancer research but also made grant funding more competitive for cancer scientists because the number of new applications has outstripped available new funding. Noting that the overall NCI budget is set by Congress, Dr. Sharpless discussed ways to reprioritize available funds to increase the Research Project Grant (RPG) Pool, from which extramural grants are funded. These included: a 5% cut to the budget for divisions, offices, and centers within NCI; 3% cuts to noncompeting awards; and slowing the growth in funding for certain ongoing initiatives such as the National Cryo-Electron Microscopy program at the Frederick National Laboratory for Cancer Research.[1]

In response to a question from the audience about funding for lung cancer research, Dr. Sharpless first explained the difficulty in calculating detailed funding information for a specific disease site. This is because there are many areas of spending that affect more than one type of cancer, such as immunotherapeutics, or increase knowledge without immediately producing clinical benefits. "I would argue that the progress in lung cancer bears that point out," Dr. Sharpless said. "The great new therapies available in terms of immunotherapies, ALK inhibitors, EGFR inhibitors, and other targeted agents have occurred because we have really improved our understanding of the basic science of lung cancer." Additionally, Dr. Sharpless expressed his view that planned funding increases for clinical trials and the RPG Pool would benefit lung cancer research directly and that none of the budget changes being made would be detrimental with respect to funding in this area.

Dr. Norman E. Sharpless

Finally, Dr. Sharpless discussed ways the NCI is planning to cope with the 7-year timeline of the funding for the Cancer Moonshot,[2] which contributed $300 million to the NCI's budget each year in 2017 and 2018, $400 million this year, and $200 million per year through 2023. Dr. Sharpless acknowledged the difficulties that reduced funding in future years will cause by saying, "There is no doubt that the things we are building using Moonshot funding, such as the immuno-oncology networks, are going to continue to exist and will need to be funded from our general budget. Fortunately, we have plenty of time to plan for that."

The discussion was broadcast live on Facebook and Twitter, and a recording of the event is available on the NCI's YouTube channel.[3] ✦

**References:**

1. National Cryo-Electron Microscopy Facility. National Cancer Institute. cancer.gov/research/resources/cryoem. Accessed February 12, 2019.
2. Cancer Moonshot. National Cancer Institute. cancer.gov/research/key-initiatives/moonshot-cancer-initiative. Accessed February 12, 2019.
3. NCI'S 2019 Plans: Conversation with the NCI Director [Video]. YouTube. youtube.com/watch?v=eit6uuGkQ3Y&feature=youtu.be. Accessed February 12, 2019.

**PACIFIC Trial** from page 4

the European Medicines Agency (EMA) restricted its approval to patients with PD-L1 expression of greater than 1%. Of course, I cannot unilaterally oppose the decisions of any health care authorities, but as a treating oncologist in Europe, I must express at least a bit of doubt about this process. If we look at the data, we soon realize that a lot is missing and that the obvious answer may not be the right answer. In the PACIFIC trial, PD-L1 testing was not mandatory; 37% of patients were not tested, analysis according to PD-L1 expression was not pre-planned, and a benefit was observed in PFS in patients with less than 1% expression. Therefore, to get the definitive answer, we would need another trial that would prospectively assess results based on PD-L1 expression. Personally, I think that will never happen.

Another issue that deserves consideration is the PD-L1 status per se. Evidence suggests that PD-L1 can be induced with radiotherapy. The problem is how to monitor it because repeating a biopsy after chemoradiotherapy is impractical and potentially even dangerous for patients. One potential option to address this issue came from a trial conducted by Adams et al. They monitored PD-L1 in blood samples and showed that in 31% of patients whose tumors did not have PD-L1 expression before radiotherapy, PD-L1 was detected in their blood samples after the completion of radiotherapy, suggesting that radiotherapy could induce the expression of PD-L1.[3]

Currently, durvalumab is available to many European patients with PD-L1 expression of 1% or greater. In some countries the drug was made available immediately, after EMA approval (e.g., Germany), whereas in other countries, patients can get it only through so-called "early-access" programs. The exception is Switzerland, where patients get access to new drugs immediately upon European Medicines Agency approval. How many patients in other European countries will actually have access to the drug through current reimbursement paradigms is still difficult to estimate. In most European countries, negotiations with insurance companies are conducted either on a national or regional level or even with individual insurance companies; consequently, it can take many months or years, if ever, to get such agents reimbursed. This is a particularly important issue for lower-income, East European countries.

Limiting approval to patients with PD-L1 expression greater than 1% can have a positive effect regarding immunotherapy in stage III disease. It could facilitate access because there will be less financial toxicity, which often prevents payers from authorizing reimbursement. On the other hand, this is the first treatment in decades that has actually shown a benefit in stage III NSCLC. The results of the PACIFIC trial are clear and convincing; however, exclusion based on PD-L1 expression of greater than 1% is not as scientifically sound.

In summary, most patients with stage III disease will receive immunotherapy, either as primary treatment or after progression, where immunotherapy is not limited by PD-L1 status. Our biggest concern is that under current standards, some patients who could be cured by adding immunotherapy will not be able to receive this treatment. ✦

*About the Author: Asst. Prof. Rajer is radiation oncologist and resident in medical oncology at the University Clinic Golnik, Slovenia.*

**References:**

1. Antonia SJ, Villegas A, Daniel D, et.al. Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. *N Engl J Med.* 2017;377:1919-1929.
2. Antonia SJ, Villegas A, Daniel D, et.al. Overall Survival with Durvalumab after Chemoradiotherapy in stage III NSCLC. *N Engl J Med.* 2018;379:2342-2350.
3. Adams DL, Adams DK, He J, et.al. Sequential Tracking of PD-L1 Expression and RAD50 Induction in Circulating Tumor and Stromal Cells of Lung Cancer Patients Undergoing Radiotherapy. Clin Cancer Res. 2017;23:5948-5958.

### PATIENT ADVOCATE COMMENT

"If a treatment is significantly beneficial for a group of patients, they should have access to this treatment; approvals should follow proven benefit. With the developments in cancer care, the current healthcare systems in Europe must adjust. On national and international levels, all stakeholders will have to work together, with goals based on provision of best-possible patient care, not based on research cost or financial profit."

–Merel Hennick,
ROS1 patient advocate in the Netherlands

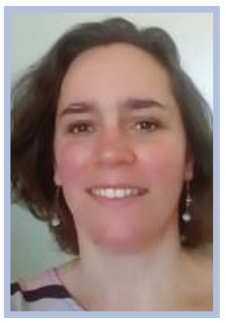
EVOLVING STANDARDS OF CARE

# ICU Care for the Patient with Lung Cancer

***Issues associated with ICU admission and lack of patient understanding or overall treatment plan can be complicating factors.***

By Anne-Claire Toffart, MD, PhD, and Jean-François Timsit, MD, PhD

Survival rates for patients with lung cancer who were admitted into the intensive care unit (ICU) have improved during the past 2 decades. In recent studies, ICU mortality for those patients admitted on an unscheduled basis was 30% to 40%.[1,2] This improved ICU survival rate is due to a better understanding of organ dysfunction and to breakthroughs in lung cancer treatment such as targeted therapies and immune checkpoints inhibitors. In addition, it is possible that earlier admission and more careful selection of patients who would benefit most from an ICU admission also have contributed to improved ICU survival rates. Nevertheless, among patients with hematologic and solid tumors, patients with lung cancer often have the poorest prognosis, which often leads to a refusal of ICU admission or stigmatization during the admittance process.



Dr. Anne-Claire Toffart

Dr. Jean-François Timsit

Although stigmatization after ICU admission was previously an issue, the past 10 years or so has shown great improvement in the understanding of ICU staff and care specialists regarding therapeutic benefits and side effects of more modern treatments. Perhaps this improved understanding is not as prevalent in other parts of the world but, in the experience of the authors, stigmatization of patients is more frequently seen (and, therefore, more important) prior to ICU admission.

Oncologists and supportive care specialists should remember the objectives of treatment for critically ill patients with cancer in the ICU: to discharge the patient from the ICU and the hospital with an acceptable quality of life and, if warranted, to provide benefit from further cancer therapy (Figure, page 10). Anticipation of issues associated with ICU admission, as well as a close alliance between the oncologist and the intensive care specialists are the two keys to the success of a patient-centered healthcare plan in life-threatening situations.

## Establishing a Patient-Centered Healthcare Plan

Each individual patient is central to the decision-making process about ICU admission. Patient wishes or advance directives are obviously extremely important to this process. In the context of intensive care, the patient and/or relatives are often unable to express coherent desires regarding his or her overall treatment goals or overall healthcare plan.[3] End-of-life (EOL) discussions between the patient and the primary oncologist are of upmost importance because the patient is not always aware of his own care plan, nor is the appointment of legal representatives for decision making and the creation of advance directives systematic. Any patient wishes expressed during the EOL discussion should be written clearly in the medical file to be easily accessible in case of emergency. In a prospective study, early EOL discussions were associated with less aggressive care and greater use of hospice at EOL.[4]

## Identifying the Necessary Level of Support, Bolstering Survival

Factors associated with survival were related to patient characteristics, cancer history, and acute disease.[5] For example, patients with a poor performance status

continued on page 10

## A DEEPER DIVE

# Financial Incentives and Free Treatment Aids for Smoking Cessation in the Workplace

**IN REFERENCE TO:**

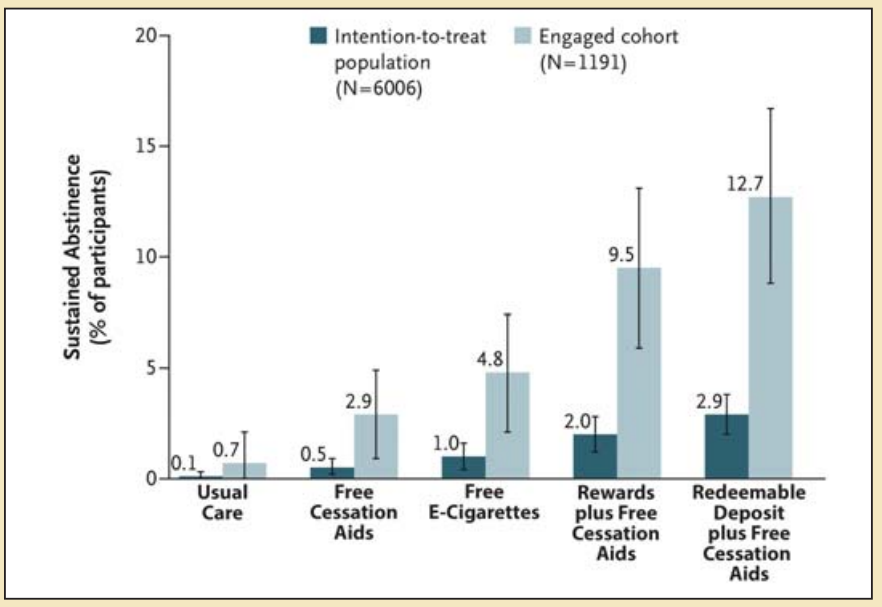
**Halpern SD, French B, Small DS, et al. Randomized trial of four financial incentive programs for smoking cessation. *N Engl J Med*. 2015;372:2108-2117.**

By Raymond Niaura, PhD

As has been true for decades, smoking remains the leading cause of preventable morbidity and mortality in the United States.[1] Smoking prevalence continues to decline, but approximately 14% of adults still smoke cigarettes regularly (34.3 million).[2] First-line, U.S. Food and Drug Administration–approved smoking cessation treatments (e.g., varenicline, bupropion, and nicotine replacement therapy [NRT]) are effective for approximately 20% of smokers after 1 year,[3] but they remain underutilized.[4] Workplace interventions can reach large numbers of smokers, and financial incentives to quit smoking, delivered via workplace smoking-cessation programs, have shown some promise.[5,6] For example, financial incentive programs (up to $800), contingent on biochemically verified quitting, resulted in superior sustained 6-month quit rates (9.4% to 16.0%) compared with usual care (6.0%).[6] These studies, however, report results only for those motivated smokers who volunteered and engaged in the programs, and they did not test the potential combined efficacy of financial incentives and other approaches (e.g., cessation aids such as NRT).

Dr. Raymond Niaura

**Fig. Sustained Smoking Abstinence at 6 Months After the Target Quit Date.**




Estimates were adjusted for the phase (1 or 2) of enrollment. The engaged cohort consists of participants who logged on to the trial website at least once. I bars indicate 95% confidence intervals.

Reproduced with permission from Halpern SD et al. *N Engl J Med*. 2018;278:2302-2310.

## Gathering Data

The most recent study by Halpern and colleagues tested the efficacy of separate and combined treatments including financial incentives and the offer of free e-cigarettes or NRT patches, gum, and lozenges.[7] The results present a mixed picture. Only 19.8% of smokers informed about the study (1,191 of 6,006) engaged in the trial, logging in at least once onto the trial website (another 125 opted out before random selection). The intent-to-treat analyses showed that sustained smoking abstinence at 6 months ranged between 0.1% for usual care and 2.9% for smokers who participated in the redeemable deposit incentive program along with access to free cessation aids (Fig.). Although smokers in the financial-incentive group were statistically significantly more likely to achieve abstinence, overall low quit rates call into question the practical significance of these findings. The pattern of findings was similar, but quit rates overall were higher when data only from smokers who engaged in treatment were analyzed.

Therefore, it seems fair to conclude that financial incentives added to free cessation aids (mostly NRT) can augment quit rates compared to free cessation aids alone. Left unanswered, however, is whether incentives can also boost quit rates when combined with free e-cigarettes. Smokers offered free e-cigarettes are more likely to quit compared to those offered NRT, although not significantly so. More important than the treatment effects, perhaps, are the overall low rates of treatment engagement (19.8%) and low rates of incentive treatment acceptance, defined as agreeing to the incentive contract (51.2%). Smokers, however, were more likely to accept the external monetary reward-based incentive programs (90.0%) than the monetary self-deposit based reward programs (13.7%). More research is required to determine why smoking cessation treatments, even those that are free, remain overwhelmingly underutilized when offered in workplace settings. ✦

*About the Author: Dr. Niaura is a professor of Social and Behavioral Sciences at New York University.*

**References:**

1. Ma J, Siegel RL, Jacobs EJ, Jemal A. Smoking-attributable Mortality by State in 2014, U.S. *Am J Prev Med*. 2018;54(5):661-670.
2. Wang TW, Asman K, Gentzke AS, et al. *MMWR Morb Mortal Wkly Rep*. 2018;67(44):1225-1232.
3. Rosen LJ, Galili T, Kott J, Goodman M, Freedman LS. Diminishing benefit of smoking cessation medications during the first year: a meta-analysis of randomized controlled trials. *Addiction*. 2018;113:805-816.
4. Rodu B, Plurphanswat N. Quit Methods Used by American Smokers, 2013-2014. *Int J Environ Res Public Health*. 2017;14(11).
5. Volpp KG, Troxel AB, Pauly MV, et al. A randomized, controlled trial of financial incentives for smoking cessation. *N Engl J Med*. 2009;360:699-709.
6. Halpern SD, French B, Small DS, et al. Randomized trial of four financial incentive programs for smoking cessation. *N Engl J Med*. 2015;372:2108-2117.
7. Halpern SD, Harhay MO, Saulsgiver K, Brophy C, Troxel AB, Volpp KG. A Pragmatic Trial of E-Cigarettes, Incentives, and Drugs for Smoking Cessation. *N Engl J Med*. 2018;378(24):2302-2310.

## INDUSTRY AND REGULATORY NEWS

### FDA Grants Priority Review to Roche's Personalized Medicine Entrectinib

February 19, 2019—The US Food and Drug Administration (FDA) accepted a New Drug Application (NDA) and granted Priority Review for entrectinib for treatment of patients with ROS-1 mutations and metastatic NSCLC. The FDA is expected to make a final decision regarding approval by mid-August 2019.

Entrectinib also has received the FDA's Breakthrough Therapy Designation, Priority Medicines designation by the European Medicines Agency (EMA), and Sakigake designation by the Japanese health authorities for the treatment of NTRK fusion-positive locally advanced or metastatic solid tumors in adult or pediatric patients who have experienced disease progression following prior therapies or have no other treatment options. ✦

## INDUSTRY AND REGULATORY NEWS

### European Medicines Agency Approves Lorlatinib

March 1, 2019—The EMA has endorsed lorlatinib for the treatment of patients with ALK-positive advanced NSCLC that has progressed during prior kinase inhibitor therapy. The Committee for Medicinal Products for Human Use recommended granting of a conditional marketing authorization. Lorlatinib is recommended as monotherapy for patients whose disease has progressed after first-line treatment with alectinib or ceritinib, or with crizotinib plus at least one other ALK-based TKI.

Lorlatinib was approved by the US Food and Drug Administration in November 2018. ✦

THOUGHT LEADER PERSPECTIVE

# c-MET Antibody–Drug Conjugates: Misconceptions Corrected, Excitement Explained—An Interview with Dr. Karen Kelly

The first in-human study evaluating telisotuzumab vedotin (Teliso-V)—a c-MET antibody–drug conjugate formerly known as ABBV-399— has shown encouraging activity for patients with c-MET–positive NSCLC.[1] Teliso-V combines the anti–c-MET monoclonal antibody ABT-700 (telisotuzumab) with monomethyl auristatin E, a cytotoxic antimicrotubule agent.

Of the 48 patients enrolled, 35.4% had NSCLC and all were heavily pretreated, receiving at least four prior therapies. Thirty nine unselected patients were in the dose-escalation phase, and nine patients with c-Met–positive NSCLC participated in the dose-expansion phase. c-Met overexpression was defined as an immunohistochemistry membrane H score of 150 or greater. Dosages ranged from 0.15 to 3.3 mg/kg and were administered intravenously every 3 weeks.

The maximum-tolerated dose was not identified, but the dose of 2.7 mg/kg was selected as the phase II dose based on overall safety and tolerability. One patient each in the 3.0 mg/kg and 3.3 mg/kg groups experienced dose-limiting toxicities. The most common adverse events (any grade) were fatigue (42%), nausea (27%), constipation (27%), decreased appetite (23%), vomiting (21%), dyspnea (21%), diarrhea (19%), peripheral edema (19%), and neuropathy (17%). The most common higher-grade (≥ 3) treatment-related adverse events were fatigue, anemia, neutropenia, and hypoalbuminemia (4% each).


Dr. Karen Kelly

Partial response was seen in three of the 16 (18.8%) patients with c-Met–positive NSCLC who received 2.4 to 3.0 mg/kg of Teliso-V (95% CI: 4.1% to 45.7%). The duration of response was 3.1, 4.8, and 11.1 months; progression-free survival was 5.7, 6.0, and 15.4 months. No other patients experienced response.

Based on these early but encouraging data, the *IASLC Lung Cancer News* spoke with Karen Kelly, MD, associate director for clinical research at the UC Davis Comprehensive Cancer Center and chair of the lung cancer committee in the SWOG Cancer Research Network, about c-Met immunoconjugates. Dr. Kelly, a long-time member of the IASLC, is a coauthor on the Teliso-V trial.

**Q: What percentage of patients with advanced NSCLC are known to be Met positive? Are there any differences based on histology?**

**A:** The exact percentage of patients with advanced NSCLC whose tumor express the MET receptor by IHC is unclear due to 1) methodology differences in the assays and their definition of positive expression, 2) the retrospective and single-institutional experience of most studies, and 3) the limited number of advanced disease specimens analyzed. In the randomized phase II study evaluating the Met antibody onartuzumab plus erlotinib versus erlotinib plus placebo, 128 patients had sufficient tissue for MET

continued on page 13

## TMB Not Ready for Prime Time

from page 3

of neoantigens and the tumor microenvironment.[5] Thus, like PD-L1 expression, there can also be reasons for varying clinical relevance of a TMB result, including clonal architecture (distinct between smokers and non-smokers)[6] and region-specific increases in mutation load, as well as technical factors such as low tumor purity. The latter is reflected, in part, by the observation that only 58% of patients in CheckMate-227 had TMB successfully evaluated using the FoundationOne panel, a commercial platform using high-depth targeted next-generation sequencing.[4]

### Panel Variance

Although it has been suggested that exome sequencing estimations of TMB and targeted panels are largely concordant, these studies have been restricted to broad robust panels such as FoundationOne and MSK-IMPACT, encompassing 315 and 468 genes, respectively.[7] Indeed, the practical issues of cost, turnaround time, and tissue attrition currently preclude such broad gene panels as a standard assay in the first-line setting for majority of patients with lung cancer. Computerized analysis further suggests that it may be feasible to estimate TMB based on smaller panels (e.g., 0.5 megabases), which result in wider confidence intervals from the true estimate.[8] One recent study further highlights the potential of curating a specific gene set (e.g., 24 genes) that correlates with TMB.[9] Nevertheless, the significant variability in tumor purities, sequencing parameters, and reference genomes, as well as the hitherto lack of concordance and cross-validation of next-generation sequencing panels, makes it challenging to implement TMB as a routine, reproducible clinical test.

Until more validation data are available from clinical trial cohorts with predefined cutoffs and the logistical challenges are addressed, TMB remains, at best, a promising exploratory biomarker. ✦

*About the Author: Dr. Tan is a senior consultant in the Division of Medical Oncology, National Cancer Centre Singapore and senior clinician-scientist at Genome Institute of Singapore. He also directs the Experimental Cancer Therapeutics Unit and is current Chair of the IASLC Education Committee.*

**References:**

1. Hirsch FR, McElhinny A, Stanforth D, et al. PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project. *J Thorac Oncol.* 2017;12(2):208-222.
2. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer Immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science.* 2015;348(6230):124-128.
3. Kowanetz M, Zou W, Shames D, et al. OA20.01 Tumor Mutation Burden (TMB) is Associated with Improved Efficacy of Atezolizumab in 1L and 2L+ NSCLC Patients. *J Thorac Oncol.* 2017;12:S321-S322.
4. Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. *Lancet Oncol.* 2017;18(1):31-41.
5. Schumacher TN, Hacohen N. Neoantigens encoded in the cancer genome. *Curr Opin Immunol.* 2016;41:98-103.
6. Nahar R, Zhai W, Zhang T, et al. Elucidating the genomic architecture of Asian EGFR-mutant lung adenocarcinoma through multi-region exome sequencing. *Nat Commun.* 2018;9(1):216.
7. Hellmann MD, Nathanson T, Rizvi H, et al. Genomic Features of Response to Combination Immunotherapy in Patients with Advanced Non-Small-Cell Lung Cancer. *Cancer Cell.* 2018;33(5):843-844.
8. Chalmers ZR, Connelly CF, Fabrizio D, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Med.* 2017;9(1):34.
9. Lyu G-Y, Yeh Y-H, Yeh Y-C, Wang Y-C. Mutation load estimation model as a predictor of the response to cancer immunotherapy. *NPJ Genom Med.* 2018;3:12.

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INTERNATIONAL EDITION



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IMMUNOTHERAPY

# Expanding Opportunities for Patients to Be Treated with Immune Checkpoint Inhibition: Autoimmune Conditions, HIV, and More

By Jarushka Naidoo, MB, BCH

The U.S. Food and Drug Administration (FDA) has approved immune checkpoint inhibitors for multiple cancer types, including stage III and IV NSCLC, and now SCLC. As approvals have expanded, so too has access to these agents for patients who would not have been eligible to receive them as part of a prospective clinical trial. Patients with active or prior autoimmune conditions, hepatitis B or C, and HIV, as well as those receiving corticosteroids at baseline, may now have access to these agents. This raises important questions regarding safety, appropriate monitoring, and the likelihood of sustaining a successful anticancer response in these patient populations. Several publications have provided guidance in these situations, and future studies are likely to address questions that remain outstanding.

## Patients with Known/Active Autoimmune Conditions

In a retrospective multicenter study of 56 patients with NSCLC with known autoimmune conditions who were treated with anti–PD-1 therapies, 26% developed a high-grade immune toxicity, and 13% had a high-grade flare of their known condition.[1] However, these patients still sustained a response to therapy comparable to those without autoimmune conditions (22%, mainly second-line NSCLC). Patients who were symptomatic from their autoimmune condition at the start of immunotherapy had a greater chance of a flare of the autoimmune condition. No extra care for these patients, such as a pre-immunotherapy consultation with an organ specialist as is done in some centers, was noted in the study.

In a similar retrospective study in patients with metastatic melanoma, 52 of 119 patients treated with an anti–PD-1 therapy had a known autoimmune condition. Thirty-eight percent had a flare of their known condition requiring immunosuppression, but only 8% overall discontinued treatment for toxicity, and 33% of those who had a known autoimmune condition sustained an antitumor response.[2] Although patients with inactive autoimmune disease at the start of treatment were less likely to have a flare than those with active disease, 30% of these patients still had an exacerbation of their underlying disease.

A prospective clinical trial by the National Cancer Institute (primary investigators: Hussein Tawbi, MD, PhD, and Elad Sharon, MD) is being planned to assess the safety of anti–PD-1 in patients with advanced-stage solid malignancies and selected autoimmune conditions, including rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, dermatomyositis, and scleroderma.

## Hepatitis B and C

In a phase I/II trial (CheckMate 040), nivolumab was administered to patients with advanced hepatocellular carcinoma with or without hepatitis B or C.[3] Patients had Child-Pugh scores of less than 7 (dose-escalation) and less than 6 (dose-expansion). Patients with hepatitis B infection were receiving antiviral therapy (viral load < 100 IU/mL). Antiviral therapy was not required for patients with hepatitis C infection. Toxicity profiles were similar and acceptable in both infected and noninfected groups. Patients in both groups responded to therapy, with response rates

continued on page 13

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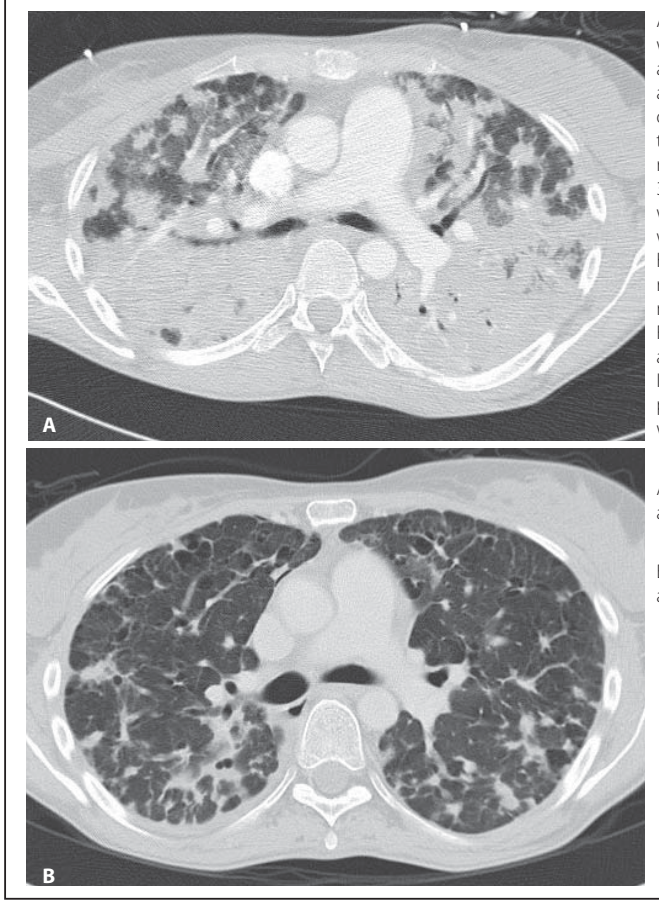
**ICU Care** from page 7

(PS score higher than 2) had poor survival. Both the overall treatment plan and treatment response are probably more important than metastatic status. This is particularly true for patients who are eligible for targeted therapy[6] or who are responding to immune checkpoint inhibitors. Finally, patients with cancer must be admitted to ICU with few organ failures. Patients with no organ dysfunction but physiologic disturbances could also be admitted in order to avoid late ICU admission (condition associated with higher mortality).[7] Uses of invasive mechanical ventilation or vasopressors are known to be associated with ICU mortality.

Clarification of a patient's code status is necessary at the time of admission.[8] In patients admitted with a full-code status, the decision-making process is similar to that of other patients in the ICU without malignancy. ICU trial consists of unlimited ICU support for a limited time period. Trials of ICU care lasting 1 to 4 days may be sufficient for patients with poor-prognosis solid tumors.[9] Limited support can also be offered at ICU admission; for example, respiratory support or hemodynamic failure support. Admission policy should be explained to the patient and/or relatives. After 3 days of ICU care, a discussion regarding the intensity of care is strongly recommended for each patient. Oncologists should continue to participate in the decision-making process during the patient's ICU stay and should be present for all patient/caregiver discussions. ✦

*About the Authors: Dr. Toffart is associate professor in the thoracic oncology unit, Grenoble Alpes Teaching Hospital, France. Dr. Timsit is professor in the Medical and Infectious Diseases ICU, Bichat-Claude Bernard Hospital, APHP, France.*

**Figure.**




A 35-year-old woman with metastatic adenocarcinoma and an exon 19 *EGFR* deletion was admitted to ICU for an acute respiratory failure after 3 weeks of treatment with erlotinib, which was continued during her ICU stay. She required invasive mechanical ventilation. Finally, she discharged alive after 1 month of ICU. At 6 months, her performance status was 1.

A: CT scan at ICU admission.

B: CT scan 2 months after ICU admission.

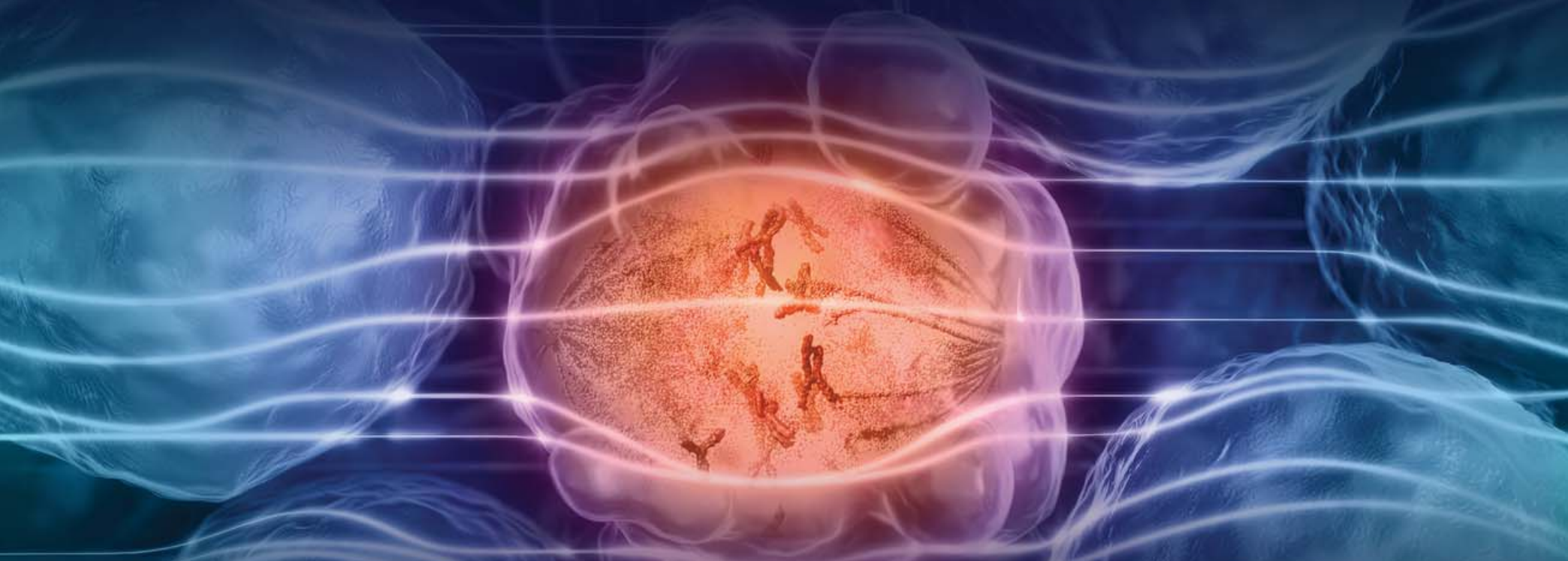
**References:**

1. Soubani AO, Ruckdeschel JC. The outcome of medical intensive care for lung cancer patients: the case for optimism. *J Thorac Oncol* 2011; 6: 633-638.
2. Ostermann M, Ferrando-Vivas P, Gore C et al. Characteristics and Outcome of Cancer Patients Admitted to the ICU in England, Wales, and Northern Ireland and National Trends Between 1997 and 2013. *Crit Care Med* 2017; 45: 1668-1676.
3. Rigaud JP, Large A, Meunier-Beillard N, et al. What are the ethical aspects surrounding intensive care unit admission in patients with cancer? *Ann Transl Med.* 2017;5(Suppl 4):S42.
4. Mack JW, Cronin A, Keating NL, et al. Associations between end-of-life discussion characteristics and care received near death: a prospective cohort study. *J Clin Oncol.* 2012;30(35):4387-4395.
5. Toffart AC, Minet C, Raynard B, et al. Use of intensive care in patients with nonresectable lung cancer. *Chest*. 2011;139(1):101-108.
6. Toffart AC, Dhalluin X, Girard N, et al. Patients with advanced lung cancer harboring oncogenic mutations should be admitted to intensive care units. *Intensive Care Med*. 2015;41(1):164-165.
7. Thiery G, Azoulay E, Darmon M, et al. Outcome of cancer patients considered for intensive care unit admission: a hospital-wide prospective study. *J Clin Oncol*. 2005;23(19):4406-4413.
8. Azoulay E, Soares M, Darmon M, et al. Intensive care of the cancer patient: recent achievements and remaining challenges. *Ann Intensive Care*. 2011;1(1):5.
9. Shrime MG, Ferket BS, Scott DJ, et al. Time-Limited Trials of Intensive Care for Critically Ill Patients With Cancer: How Long Is Long Enough? *JAMA Oncol*. 2016;2(1):76-83.

# 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]**

When delivered at 150 kHz, TTFields may relentlessly attack and selectively kill dividing cancer cells by causing a cascade of effects at multiple phases in the cell cycle, which prevents mitosis.[1-4]



**The LUNAR non-small cell lung cancer (NSCLC) trial is now enrolling.**
This phase III clinical trial is studying the efficacy and safety of TTFields at 150 kHz in combination with an immune checkpoint inhibitor or docetaxel as second-line treatment for NSCLC.[1,5]

Eligible patients are ≥22 years of age and recently diagnosed with squamous or non-squamous, unresectable, stage 4 NSCLC with radiological progression while on or after their first platinum-based systemic therapy.[1,5]

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**References: 1.** ClinicalTrials.gov. Bethesda (MD): U.S. National Library of Medicine. Effect of Tumor Treating Fields (TTFields) (150kHz) concurrent with standard of care therapies for treatment of stage 4 non-small cell lung cancer (NSCLC) following platinum failure (LUNAR). NCT02973789. https://clinicaltrials.gov/ct2/show/NCT02973789. Updated January 17, 2019. Accessed January 23, 2019. **2.** Gutin PH, Wong ET. Noninvasive application of alternating electric fields in glioblastoma: a fourth cancer treatment modality. *Am Soc Clin Oncol Educ Book*. 2012:126-131. **3.** Kirson ED, Dbalý V, Tovarys F, et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. *Proc Natl Acad Sci USA*. 2007:104(24):10152-10157. **4.** Gera N, Yang A, Holtzman TS, Lee SX, Wong ET, Swanson KD. Tumor treating fields perturb the localization of septins and cause aberrant mitotic exit. *PLOS ONE*. 2015.10(5):e0125269. doi:10.1371/journal.pone.0125269. **5.** Novocure Data on File. NovocureTrial.com. LUNAR. 2018.

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

# The IASLC Pathology Committee Recommendations for the Use of Diagnostic Immunohistochemistry in Lung Cancer

By Andre L. Moreira, MD

Most of the progress in thoracic oncology is in the treatment of patients with NSCLC. The determination of subtypes of NSCLC, namely adenocarcinoma and squamous cell carcinoma, is directly linked with chemotherapy regimens and the search for targetable molecular alterations. The 2015 World Health Organization Classification of Lung Tumors first introduced the importance of immunohistochemical (IHC) stains as an ancillary test to separate NSCLC subtypes, especially in small biopsy and cytologic samples that constitute most specimens for the diagnosis of lung cancer. One important consideration is the need to balance tissue use for diagnostic and molecular testing when more stains are added to the panels.

Although the classification of lung cancer remains based on histologic features, IHC is recommended in cases with no morphologic evidence of differentiation, thus improving diagnostic accuracy. However, interpretation of IHC can be challenging. The pathologists must be aware of the many pitfalls that can involve selection of antibody panels, clones, and staining patterns.

Dr. Andre L. Moreira

The IASLC Pathology Committee undertook a comprehensive project to provide a consensus guideline for IHC use for lung cancer classification. Members of the Committee were asked to raise questions concerning IHC use in their daily practice. The questions were not limited to the subclassification of NSCLC but rather were inclusive of all possible scenarios in which IHC should be used in lung cancer pathology, including best markers to distinguish NSCLC subtypes, use of IHC for the diagnosis of neuroendocrine tumors, uncommon subtypes, and distinction of primary pulmonary tumors from metastatic cancers to the lung.

Most clinicians experience frustration with cytologic material, and often these useful specimens are left out of clinical trials. The use of cytology specimens for IHC is addressed in this study and will be expanded under a study from the cytology working group of the IASLC Pathology Committee. Their additional observations and recommendations will be the subject of a separate publication.

The results of this project were summarized into 11 practical core questions that were then answered by literature search and consensus discussions within the group (Table). The results are now published in the *Journal of Thoracic Oncology*.[1] The article by the IASLC Pathology Committee provides guidelines and quick, useful explanations for pathologists and the larger lung cancer healthcare provider community concerning the best use of IHC encountered in daily routine for the diagnosis of lung carcinoma. ✦

*About the Author: Dr. Moreira is a professor in the Department of Pathology, director of the Cardiopulmonary Pathology Fellowship Program, director of Surgical Pathology, director of NYU Center for Biospecimen Research and Development, and director of Pulmonary Pathology at NYU Langone.*

**Reference:**

1. Yatabe Y, Dacic S, Borczuk AC, et al. Best Practices Recommendations for Diagnostic Immunohistochemistry in Lung Cancer. *J Thorac Oncol.* 2019;14(3):377-407.

**Table. Key Questions and Recommendations for Diagnostic Immunohistochemistry in Lung Cancer[1]**

| Key Questions | Short Answers |
|---|---|
| 1. What is the best combination of markers to use in daily practice? | When IHC is needed for the subtyping of NSCLC, TTF1 and p40 are the criterion standard, and these two markers are usually sufficient in clinical practice if there are no morphologic features of NE differentiation. p40 is preferable to p63 to identify squamous cell carcinoma. |
| 2. What extent of TTF1- and p40-positive reactions should we consider to be positive? | Focal positivity for TTF1 is considered a positive reaction indicating pulmonary adenocarcinoma in the proper clinical context, whereas for p40, the cutoff rate should be positivity in more than 50% of tumor nuclei. Focal or weak positivity for p40 is not diagnostic of squamous cell carcinoma. |
| 3. Are there any staining differences in lung adenocarcinoma between among TTF1 clones (SPT24, SP141, and 8G7G3/1)? | The staining performance of TTF1 varies among the clones. Among the most commonly used antibodies, 8G7G3/1 is the most specific antibody to identify lung adenocarcinoma. |
| 4. Should an NSCLC that is diffusely positive for CK7 but negative for TTF1 and p40 be regarded as probably adenocarcinoma? | CK7 is not specific for adenocarcinoma; the marker can be seen in squamous cell carcinoma. The use of CK7 is discouraged for subtyping of NSCLC. |
| 5. When should NE markers be applied to an NSCLC? | NE markers should be applied only in support of NE morphology. |
| 6. What is the best antibody panel to differentiate NE tumors from other types of NSCLC, and which one is the most reliable? | A panel of chromogranin A, synaptophysin, and CD56 is the best combination to identify NE tumors. The staining significance of each antibody varies among the sample types, histologic subtypes, and extent and/or intensity of positive reactions. |
| 7. When should a proliferation marker be used in diagnosis? | The main established role of Ki-67 in lung carcinomas is to help distinguish carcinoids from high-grade NE carcinomas (large cell NE carcinoma and small cell carcinomas), especially in small or crushed biopsy or cytologic samples. The role of Ki-67 in separating typical from atypical carcinoids is not established and needs more investigation. |
| 8. Is IHC useful to render a specific diagnosis of uncommon lung cancer subtypes (sarcomatoid carcinoma, salivary gland-type tumors, and NUT carcinoma)? | Currently, IHC and molecular testing are needed to achieve the definitive diagnoses of uncommon lung cancers such as sarcomatoid carcinoma, salivary gland-type tumors, and NUT carcinoma and to distinguish from the mimics. |
| 9. What portion of the cytologic sample is best for immunostaining: the cell block, the air-dried smears, or the ethanol-fixed smears? Can destained smears be used adequately? | All cytologic preparations, including cell blocks and ethanol-fixed and airdried slides, can principally be used for immunostaining. Formalin-fixed cell blocks are most straightforward, whereas rigorous protocol optimization, validation, and quality control are required in immunostaining in cytologic examination. |
| 10. Which IHC panel is recommended to differentiate lung mucinous adenocarcinoma from metastatic mimics? | There is no useful marker to differentiate pulmonary mucinous adenocarcinoma from metastatic mimics. A clinicopathologic tumor board is crucial for this clinical context. |
| 11. Are there any IHC or other markers to differentiate between primary lung cancers and metastases; between squamous cell carcinomas of lung primary and metastases from thymic, head and neck, endocervical, and the other cancers; and between adenocarcinomas of primary and metastases from gynecologic, mammary, uroepithelial, nonpulmonary NE, prostate, and liver cancers? | In this clinical context, morphologic comparison with prior tumor is crucial. There are no absolute IHC markers to make the differential diagnosis, and pathologists should be aware of the pitfalls of IHC. |

Abbreviations: CD56, an alias for neural cell adhesion molecule 1 (NCAM 1); CK7, cytokeratin 7; IHC, immunohistochemistry; NE, neuroendocrine; NSCC, non–small cell carcinoma; NUT, nuclear protein in testis; TTF1, thyroid transcription factor 1.

## Immune Checkpoint Inhibition

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of 20% (with HCV, 10 of 50) and 14% (with HBV, 7 of 51) respectively, which was similar to the overall response rate in the study population of 20% (42 of 214). These response rates also are comparable to those for uninfected patients who were treated with sorafenib (21%, 12 of 57), as well as for those who were sorafenib naive (23%, 12 of 56). Anti–PD-1 therapy displayed limited antiviral activity, with some changes in hepatitis C virus RNA, and no cases of hepatitis B reactivation or anti-hepatitis B seroconversion.

### HIV

It remains an open question as to whether it is safe to administer immune checkpoint blockade to patients with HIV. A prospective clinical trial in France is underway to assess this question in patients with NSCLC (NCT03304093). In addition, other trials are aimed at identifying whether HIV-related malignancies may be responsive to anti–PD-1+/–CTLA-4 (NCT02408861) therapy.

### Baseline Corticosteroids

In 640 patients with NSCLC treated with anti–PD-1/-L1 therapy, 88 patients received baseline steroids greater than or equal to 10 mg/day of prednisone or its equivalent.[4] Progression-free survival and overall survival were poorer in those receiving baseline steroids versus those receiving no steroids or less than 10 mg/day of prednisone or equivalent, although it is unclear if there may have been other confounding factors that might have contributed to poorer outcome in this population that required steroids.

These data have supported the cautious use of immune checkpoint blockade in circumstances that would have precluded inclusion into clinical trials. While we await prospective data to support these approaches, it may be clinically appropriate for patients with active autoimmune conditions to be co-treated by their relevant medical subspecialist during immunotherapy, in anticipation of a potential flare of their conditions.

In patients with hepatitis B or C, a hepatology consult prior to treatment and assessment of a Childs-Pugh score is likely to be relevant. In patients already receiving corticosteroids at a dose of 10 mg/day or more of prednisone/equivalent, it may be prudent to reduce this to less than 10 mg/day prior to treatment start, if clinically appropriate. Monitoring of these patients must also be adapted. In certain situations, the patients mentioned above or those receiving combination immune checkpoint inhibition are likely to require more frequent monitoring in an attempt to identify an immune-related adverse event early, for example, by weekly visits or provider phone calls for the first 4 to 6 weeks of therapy. The value of this approach and effects on early diagnosis of an immune-related adverse event must be prospectively assessed, with the knowledge that immune toxicities may occur at unpredictable times in a patient's treatment course. ✦

*About the Author: Dr. Naidoo is an assistant professor of oncology at Johns Hopkins University.*

**References:**

1. Leonardi GC, Gainor JF, Altan M, et al. Safety of Programmed Death-1 Pathway Inhibitors Among Patients With Non-Small-Cell Lung Cancer and Pre-existing Autoimmune Disorders. *J Clin Oncol.* 2018;36(19):1905-1912.
2. Menzies AM, Johnson DB, Ramanujam S, et al. Anti-PD-1 therapy in patients with advanced melanoma and pre-existing autoimmune disorders or major toxicity with ipilimumab. *Ann Oncol.* 2017;28(2):368-376.
3. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet.* 2017;389(10088):2492-2502.
4. Arbour KC, Mezquita L, Long N, et al. Deleterious effect of baseline corticosteroids on efficacy of PD-(L)1 blockade on patients with NSCLC. *J Clin Oncol.* 2018;36(suppl; abstr 9003).

## c-MET Antibody–Drug Conjugates

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IHC.[2] Fifty-two percent were Met positive. Only 10 patients had squamous cell histology, and the remainder had adenocarcinoma. In the subsequent phase III trial in which Met positivity was required, 1,790 patient samples were screened, but the percentage that was positive was not reported. A total of 499 (28%) patients enrolled, 58% had nonsquamous and 26% had squamous histology.[3] Overall it appears that the approximately 50% of patients with nonsquamous histology have Met expression. In squamous cell histology the percentage is unknown, but in early-stage NSCLC it has been reported to be approximately 25%.[4]

**Q: To what extent, if any, does this immunoconjugate target c-Met amplifications or exon 14 skipping mutation?**

**A:** Met receptor protein expression is required for Teliso-V activity. MET amplification or MET exon 14 skip mutations may or may not result in a concordant increase in protein expression. Data from the phase III onartuzumab trial demonstrated MET amplification in only 33% of the samples from enrolled patients. I am not aware of data analyzing patients with exon 14 skip mutations for concordance with protein expression. Testing for MET amplification or mutations cannot substitute for protein expression testing.

**Q: Could this agent be reasonably expected to have activity in patients who have *EGFR* mutations who develop c-Met amplification as a mechanism of TKI resistance?**

**A:** As just discussed, MET amplification alone is not a biomarker for Teliso-V. However, if this subgroup of patients had a corresponding increase in Met protein expression, Teliso-V should be active. I would encourage a trial to evaluate Teliso-V in this population.

**Q: Are there any major toxicity concerns?**

**A:** No, I do not have any major concerns about toxicity. Teliso-V is a well-tolerated chemotherapeutic agent as we would expect from its direct delivery to the Met-positive tumor cells. Its mild side effect profile is an attractive feature.

In closing, I know we are all excited about immunotherapy and oncogenic-driven inhibitors, but there remains a large unmet need for the majority of patients for whom these agents fail or who are not eligible to receive them. I am very excited to see this new class of agents being evaluated in lung cancer. ✦

**References:**

1. Strickler JH, Weekes CD, Nemunaitis J, et al. First-in-Human Phase I , Dose-Escalation and -Expansion Study of Telisotuzumab Vedotin, An Antibody–Drug Conjugate Targeting c-Met, in Patients With Advanced Solid Tumors. *J Clin Oncol.* 2018;36(33):3298-3306.
2. Spigel DR, Ervin TJ, Ramlau RA, et al. Randomized phase II trial of Onartuzumab in combination with erlotinib in patients with advanced non-small-cell lung cancer. *J Clin Oncol.* 2013; 31(32):4105-14.
3. Spigel DR, Edelman MJ, O'Byrne K, et al. Results From the Phase III Randomized Trial of Onartuzumab Plus Erlotinib Versus Erlotinib in Previously Treated Stage IIIB or IV Non-Small-Cell Lung Cancer; METLung. *J Clin Oncol.* 2017; 35(4):412-420.
4. Hellmann MD, Anderson TA, Eng J, et al. Clinicopathologic characteristics and prognostic impact of MET receptor overexpression in patients with stage I-IIIA squamous cell lung carcinomas (SQCLCs). *J Clin Oncol.* 2014;32(5 suppl): Abstr 7570.

## A DEEPER DIVE

# Understanding the Effects of Time to Surgery on Upstaging for Stage I Non-Small Cell Lung Cancer

**IN REFERENCE TO:**

**Serna-Gallegos DR, et al "Effects of time from completed clinical staging to surgery: Does it make a difference in stage 1 non-small cell lung cancer?" AATS 2018; Abstract 67.**

By Russell Bahar, Bsc and
Elliot Wakeam, MD, MPH

Pathologic upstaging of NSCLC occurs in an estimated 14% to 25% of patients postoperatively and is known to be significantly associated with poor patient outcomes.[2-4] Delay to surgery may be one factor that leads to greater rates of upstaging. However, the precise relationship between time to surgery and upstaging remains unknown, as does the ideal time to surgery. The National Cancer Comprehensive Network (NCCN) recommends not delaying surgical resection beyond 60 days following completion of clinical staging—a timeline comparable to previously published recommendations by the British Thoracic Society and the RAND corporation, which have advocated for 8 and 6 weeks, respectively.[5-7] However, recent work by Serna-Gallegos and colleagues argues that 8 weeks may still be too late. Their retrospective investigation of 52,406 patients from the National Cancer Database suggests that a surgical delay of as little as 2 weeks may have significant implications for rates of pathologic upstaging in patients with stage I NSCLC.

Comparing the rates of pathologic upstaging between patients with varying degrees of surgical delay, this study revealed a 4% increase in upstaging frequency for every week of delay between staging and resection. This finding is particularly worrisome given that 21% of patients in the study did not undergo resection within 8 weeks of staging completion. The authors, therefore, advocate for earlier intervention following staging completion. Although these numbers are certainly concerning, the limitations of the study should not be overlooked. First, the confidence intervals of the week-to-week data demonstrated significant overlap. For example, the odds ratios observed between 1 and 8 weeks of surgical delay were not statistically significant. Additionally, the study was retrospective and, as such, it is unclear what effect selection bias may have had on the results: Are patients who undergo delayed surgery experiencing the delay because they are sicker, or are there other oncologic or comorbidity issues that are not captured in the data? Patients with greater medical morbidity are more likely to be upstaged in general, and their increased time to surgery may have resulted from other factors such as time taken to mitigate those comorbidities, social issues, or functional impairment, thus confounding the results of the current study.

Mr. Russell Bahar

Dr. Elliot Wakeam

The study raises several important questions. The percentage of patients who failed to undergo surgical intervention following the NCCN-recommended maximum of 8 weeks was a surprising 21%. The authors identified increased medical comorbidity score as a factor, as well as African American race. This observation highlights the significance of social, as well as medical, factors as important determinants of outcomes in patients with resectable NSCLC, especially given the recently estimated 52-day median time to treatment in the United States.[8] From a healthcare-resource perspective, the argument could, therefore, be made that reducing the number of patients who wait beyond 8 weeks should be the priority, rather than prioritizing more urgent resection in all patients.

Another relevant factor in NSCLC management that this paper reinforces is the importance of adequate lymph node dissection. Patients who underwent resection at academic hospitals were more likely to be upstaged, yet they also demonstrated overall higher survival rates. The authors explained this finding with reference to the observation that academic centers sampled two lymph nodes on average more than nonacademic centers. This argument is supported by several studies demonstrating significantly increased survival associated with more systematic lymph node dissection or sampling , generally peaking between 10 and 18 nodes.[9-11]

Ultimately, this study raises several important points with regard to surgical delay and its implications for upstaging of NSCLC. Although the authors' claims of significant week-to-week variability may not be strongly supported by the data presented and may require further study, they succeed in highlighting the importance of reducing surgical delay to a maximum of 8 weeks as well as performing adequate lymph node sampling in patients with NSCLC. ✦

**Are patients who undergo delayed surgery experiencing the delay because they are sicker, or are there other oncologic or comorbidity issues that are not captured in the data?**

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**References:**

1. Serna-Gallegos DR, Mercado F, Imai T, Berz D, Soukiasin HJ. Effects of Time From Completed Clinical Staging to Surgery: Does it Make a Difference in Stage 1 Non-Small Cell Lung Cancer? Presented at: AATS 98th Annual Meeting. Los Angeles; 2018: Abstract 67.
2. López-Encuentra A, García-Luján R, Rivas JJ, et al. Comparison Between Clinical and Pathologic Staging in 2,994 Cases of Lung Cancer. *Ann Thorac Surg.* 2005;79(3):974-979; discussion 979.
3. Boffa DJ, Kosinski AS, Paul S, Mitchell JD, Onaitis M. Lymph Node Evaluation by Open or Video-Assisted Approaches in 11,500 Anatomic Lung Cancer Resections. *Ann Thorac Surg.* 2012;94(2):347-353.
4. Bott MJ, Patel AP, Crabtree TD, et al. Pathologic upstaging in patients undergoing resection for stage I non-small cell lung cancer: Are there modifiable predictors? *Ann Thorac Surg.* 2015;100(6):2048-2053.
5. Non-Small Cell Lung Cancer. *Natl Compr Cancer Netw.* 2018;1.2019.1
6. The Lung Cancer Working Party of the British Thoracic Society Standards of Care Committee. BTS recommendations to respiratory physicians for organising the care of patients with lung cancer. *Thorax.* 1998;53 Suppl 1(Suppl 1):S1-8.
7. Asch S, Kerr E, Hamilton E, Reifel J, Mcglynn EA, eds. *Quality of Care for Oncologic Conditions and HIV: A Review of the Literature and Quality Indicators.* Santa Monica, CA: RAND Corporation, 2000.
8. Vidaver RM, Shershneva MB, Hetzel SJ. Typical Time to Treatment of Patients With Lung Cancer in a Multisite, US-Based Study. *J Oncol Pract.* 2018;12(6): e643-53.
9. Ludwig MS, Goodman M, Miller DL, Johnstone PAS. Postoperative Survival and the Number of Lymph Nodes Sampled During Resection of Node-Negative Non-Small Cell Lung Cancer. *Chest.* 2005;128(3):1545-1550.
10. Varlotto JM, Recht A, Nikolov M, Flickinger JC, Decamp MM. Extent of lymphadenectomy and outcome for patients with stage i nonsmall cell lung cancer. *Cancer.* 2009;115(4):851-858.
11. Liang W, He J, Shen Y, et al. Impact of examined lymph node count on precise staging and long-term survival of resected non-small-cell lung cancer: A population study of the US SEER database and a Chinese multi-institutional registry. *J Clin Oncol.* 2017;35(11):1162-1170.

# Mentorship and Travel Awards for Nursing and Allied Health at WCLC 2018

By Erik MacLaren, PhD

In September 2018, several attendees of the 19th World Conference on Lung Cancer (WCLC) in Toronto, Canada, received Travel and Mentorship Awards from the Nursing and Allied Health Professionals (AHP) Committee of the IASLC. Nurses and AHPs comprise approximately 5% of IASLC membership according to Pippa Labuc, the chair of the Committee and a senior occupational therapist from Guy's Hospital in London, UK. "The purpose of these awards is to show that IASLC supports not only doctors, but also nurses and AHP, and that there is a role for these professionals in the society and in the management of patients with lung cancer," she told the IASLC *Lung Cancer News*. "We want to encourage more applications from the next generation of nurses and AHP, especially those early in their careers or from low-income countries." The *IASLC Lung Cancer News* spoke with the winners about the effects the IASLC award has had on their careers, as well as on their countries.

## Travel Award for AHP

The Travel Award for AHP was given to Dégi L. Csaba, PhD, MSW, who is a trained social worker, medical psychologist, and associate professor at Babes-Bolyai University, in Cluj-Napoca, Romania.

**Q: How has the Travel Award supported your work?**

**A:** This was the third time I attended the WCLC, and this conference always provides very important opportunities for continuing education and networking with social workers, psychologists, nurses, and other allied health professionals who are all part of this multidisciplinary field. Not only is the latest medical information presented at the WCLC, but there is also a lot of focus on patient advocacy issues such as awareness, prevention, detection, screening, diagnosis, and therapies. This is the only conference and professional society I know that cares so strongly about advocacy for patients with lung cancer.

**Q: What is the general state of thoracic oncology in Romania, and how do you think involvement in the IASLC will help improve it?**

**A:** It is very important to be part of this global organization because it provides tools to use in our work in Romania. I am an introvert, and it can be difficult to go out to speak to politicians and try to influence policies. The WCLC helps those of us in the field to speak up and be stronger advocates for needed changes, not just on the level of individual patients with cancer, but also on big-picture items, which we need to get right in order to be effective on the individual level.

For example, we have been successful in raising awareness regarding distress in patients with cancer in Romania, but we do not yet have the necessary resources to address it. At the moment, there are fewer than 20 clinical psychologists in the Romanian public health sector, whereas there are 100,000 new patients with cancer every year. We have not yet gotten the big picture right.

## Nursing Travel Award

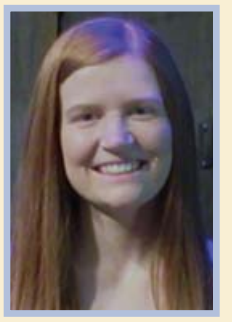
The winner of the Nursing and Allied Health Travel Award was Bárbara De Souza Gutierres Aguilar, MS, a nursing professor from the Universidade Paulista, in São Paulo, Brazil.

**Q: How has the Nursing Travel Award supported your work?**

**A:** In Brazil, researchers have no support to attend conferences, so the Travel Award made it possible for me to attend my first WCLC last year, where I had the opportunity to meet and network with health professionals from all over the world. It was great to exchange experiences and research skills with my foreign colleagues, and I am hopeful that these contacts will result in collaborative studies in the future.

Dr. Dégi L. Csaba

Ms. Bárbara De Souza Gutierres Aguilar



Ms. Brooklyn Mazure

**Q: What is the general state of thoracic oncology in Brazil, and how do you think involvement in IASLC will help improve it?**

**A:** In Brazil, immunotherapy and next-generation sequencing for lung cancer are approved by regulatory agencies; however, they are too expensive for most private health insurance companies and are not available in the public health system. The study that I presented at WCLC 2018 showed that more than 70% of trials sponsored by the pharmaceutical industry assessed innovative drugs, but only 20% assessed a biomarker.[1] I believe the IASLC can help to improve patient access to immunotherapy worldwide by encouraging the development of reliable biomarkers, perhaps by creating a task-force for the issue.

## Allied Health Professional Mentorship Award

Another first-time attendee, Brooklyn Mazure, MRT (T), a radiation therapist from the Cross Cancer Institute, in Edmonton, Canada, won this past year's Allied Health Professional Mentorship Award.

**Q: How has the Allied Health Professional Mentorship Award supported your work?**

**A:** This mentorship award provided me with an amazing opportunity to spend a week in the radiation therapy department at the Princess Margaret Hospital, in Toronto, Canada. It was a great opportunity to see varying radiation techniques for patients with lung cancer and to observe the practices and procedures of a department across the country, as well as to bring some of those ideas back to my department. The WCLC allowed me to gain a better grasp on the big picture surrounding patients with thoracic cancer, and I have now become mindful about how we can provide the patient with the best quality of life possible as a team.

**Q: What is the general state of thoracic oncology in Canada, and how do you think involvement in IASLC will help improve it?**

**A:** In Canada, the state of thoracic oncology has improved through numerous research initiatives nationally, but like many other countries across the world, patient survival remains staggeringly low. The IASLC funds research to improve outcomes in these patients, and at the WCLC, I saw amazing research that has helped find new drug and immunotherapy combinations to improve the survival of these patients. ✦

**Reference:**

1. Gutierres B, Dourado B, Alves A, et al. What is the cost of a strong evidence for the treatment of advanced non-small cell lung cancer? *J Thorac Oncol.* 2018;13:S327.

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**NHS Pilot Program** from page 4

well within current National Institute for Health and Clinical Excellence thresholds for implementation.[4]

The extraordinary performance of this pilot confirms that taking lung cancer screening into communities using a lung health check approach is effective and can engage populations in deprived communities. The model of care required careful collaboration between primary care and commissioners, with the service delivered by and assured by a specialist cardiothoracic center. The success of the pilot has resulted in an expanded program to start in April 2019, with more than 10,000 lung health checks estimated. This is projected to result in more than 5,600 LDCT scans each year and approximately 175 lung cancer resections.

More recently, the National Health Service (NHS) has committed to rolling out the Manchester pilot across the United Kingdom in the NHS Long Term Plan 2019 (available in detail at longtermplan.nhs.uk). ✦

*About the Author: Dr. Booton is programme director for the Manchester Lung Health Check Programme & clinical director for Thoracic Oncology at Manchester University NHS Trust, and honorary senior lecturer at the University of Manchester, United Kingdom.*

**References:**

1. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med.* 2011;365(5):395-409.
2. Crosbie PA, Balata H, Evison M, et al. Implementing lung cancer screening: baseline results from a community-based 'Lung Health Check' pilot in deprived areas of Manchester. *Thorax.* 2018 Feb 13. [Epub ahead of print].
3. Crosbie PA, Balata H, Evison M, et al. *Thorax.* 2018 Nov 12. [Epub ahead of print].
4. Hinde S, Crilly T, Balata H, et al. The cost-effectiveness of the Manchester 'lung health checks', a community-based lung cancer low-dose CT screening pilot. *Lung Cancer.* 2018;126:119-124.

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