**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%, 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.

**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 PLCOm2012 and were provided with brief, non-judgemental smoking-cessation advice where appropriate. Participants with PLCOm2012 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 continued on page 4.
IMPORTANT DEADLINES

Abstract submission: April 10
Travel award application: April 10
Early registration: June 7
Regular registration: July 19

Abstract submission is now open!

#WCLC19
Tumor Mutation Burden in NSCLC: Not Ready for Prime Time

By Daniel Tan, BSc, MBBS, MRCP, PhD

Assessing TMB from page 1

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, 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 non-synonymous mutations, as determined by whole-exome sequencing, identified patients who were more likely to achieve durable clinical benefit with pembrolizumab. 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.

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%. 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]). 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 role of TMB 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

About the Author: Dr. Barlesi is professor of medicine at the University of Aix Marseille and head of the Multidisciplinary Oncology and Therapeutic Innovations department at Assistance Publique Hôpitaux de Marseille, France. He is associate editor for the IASLC Lung Cancer News.

References:

1. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previ-
ously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised con-
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.

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, we will have to wait and see whether this holds true in the long run.

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, which would be considered a good value. The findings from this pilot have been published in the Breathe journal.3

Continued on page 6
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%. An estimated 70,500 women in the United States alone died in 2018 due to lung cancer, 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. 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.” 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 with 2015 and ending with 2030 using a Bayesian log-linear Poisson model. The median ASMRs are projected to increase for lung cancer in 32 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.

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

References:
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 granting 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 non-competing 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.

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.

Finally, Dr. Sharpless discussed ways the NCI is planning to cope with the 7-year timeline of the funding for the Cancer Moonshot, 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.

### References

---

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

### 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, RD51 patient advocate in the Netherlands.
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. 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 oft en 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 utmost 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
A DEEPER DIVE

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

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 biologically verified quitting, resulted in superior sustained 6-month quit rates (9.4% to 16.0%) compared with usual care (6.0%).7 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).

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.2 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 incentives 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.

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;378:2302-2310.

References:


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

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.

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.
The 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. Teliso-V combines the anti-c-MET monoclonal antibody ABT-700 (telisotuzumab) with monomethyl auristatin E, a cytotoxic antimitotubule 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%), constipation (27%), decreased appetite (23%), vomiting (21%), dyspnea (21%), diarrea (19%), peripheral edema (19%), and neutropathy (17%). The most common higher-grade (≥ 3) treatment-related adverse events were fatigue, anemia, neutropenia, and hypoalumuninemia (4% each).

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 immunocomjugates. 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

References:
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. 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. 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. 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 non-infected groups. Patients in both groups responded to therapy, with response rates continued on page 13

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

References:
References:

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

©2019 Novocure. All rights reserved. Novocure is a registered trademark of Novocure. SRC-256
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 know the many pitfalls that can involve selection of antibody panels, clones, and staining patterns.

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 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 have experienced frustration with cytologic material, and often these useful specimens are left out of clinical trials. The use of cytology specimens for the diagnosis of lung cancer is not optimized. The work of the committee will be expanded under a study from 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. The article by the IASLC Pathology Committee provides guidelines and quick, useful explanations for pathologists and the lung cancer healthcare provider community concerning the best use of IHC encountered in daily routine for the diagnosis of lung carcinoma.

Table. Key Questions and Recommendations for Diagnostic Immunohistochemistry in Lung Cancer

<table>
<thead>
<tr>
<th>Key Questions</th>
<th>Short Answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What is the best combination of markers to use in daily practice?</td>
<td>When IHC is needed for the subclassification 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 preferential to p63 to identify squamous cell carcinoma.</td>
</tr>
<tr>
<td>2. What extent of TTF1- and p40-positive reactions should we consider to be positive?</td>
<td>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.</td>
</tr>
<tr>
<td>3. Are there any staining differences in lung adenocarcinoma between the TTF1 clones (SPT24, SP141, and 8G7G3/1)?</td>
<td>The performance of TTF1 varies among the clones. Among the most commonly used antibodies, 8G7G3/1 is the most specific antibody to identify lung adenocarcinoma.</td>
</tr>
<tr>
<td>4. Should an NSCLC that is diffusely positive for CK7 but negative for TTF1 and p40 be regarded as probably adenocarcinoma?</td>
<td>CK7 is not specific for adenocarcinoma; the marker can be seen in squamous cell carcinoma. The use of CK7 is discouraged for subclassification of NSCLC.</td>
</tr>
<tr>
<td>5. When should NE markers be applied to an NSCLC?</td>
<td>NE markers should be applied only in support of NE morphology.</td>
</tr>
<tr>
<td>6. What is the best antibody panel to differentiate NE tumors from other types of NSCLC, and which one is the most reliable?</td>
<td>Chromogranin A, synaptophysin, and CD56 is the best combination to identify NE tumors. 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.</td>
</tr>
<tr>
<td>7. When should a proliferation marker be used in diagnosis?</td>
<td>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.</td>
</tr>
<tr>
<td>8. Is IHC useful to render a specific diagnosis of uncommon lung cancer subtypes (sarcomatoid carcinoma, salivary gland-type tumors, and NUT carcinoma)?</td>
<td>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 them from the mimics.</td>
</tr>
<tr>
<td>9. What portion of the cytologic sample is best for immunostaining: the cell block, the air-dried smears, or the ethanol-fixed smears?</td>
<td>Can denatured smears be used adequately? All cytologic preparations, including cell blocks and ethanol-fixed and air-dried 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.</td>
</tr>
<tr>
<td>10. Which IHC panel is recommended to differentiate lung mucinous adenocarcinoma from metastatic mimics?</td>
<td>There is no useful marker to differentiate pulmonary mucinous adenocarcinoma from metastatic mimics. A clinicopathologic tumor board is crucial for this clinical context.</td>
</tr>
<tr>
<td>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, urethelial, nonpulmonary NE, prostate, and liver cancers?</td>
<td>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.</td>
</tr>
</tbody>
</table>

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.

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.

Immune Checkpoint Inhibition

from page 10

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/L-1 therapy, 88 patients received baseline steroids greater than or equal to 10 mg/day of prednisone or equivalent.3 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. *

ATTENTION PATHOLOGISTS!

We want to hear from you!

We invite pathologists to support an initiative that aims to improve PD-L1 testing in lung cancer patients throughout the world by taking this 10-minute survey.

YOUR PARTICIPATION IS VALUABLE!

Your answers will advance and promote the potential development of a validated, lower-cost testing method that is easily accessible to health care professionals worldwide.

TO TAKE THE SURVEY: IASLC.org/pathologysurvey


References:

About the Author: Dr. Naidoo is an assistant professor of oncology at Johns Hopkins University.
Understanding the Effects of Time to Surgery on Upstaging for Stage I Non-Small Cell Lung Cancer

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.4-6 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.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. Secondly, the authors failed to account for co-morbidities or patient factors such as time taken to mitigate those comorbidities, social issues, or functional impairment, thus confounding the results of the current study. 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.9,10 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.

Mr. Russell Bahar
Dr. Elliot Wakeam

In reference to:

Mr. Russell Bahar and Dr. Elliot Wakeam are a surgical fellow and a medical student in the Division of Thoracic Surgery at the Toronto General Hospital, Toronto, Ontario. About the Authors: Mr. Bahar is a third-year medical student in the School of Medicine, University of Toronto, Toronto, Ontario. Dr. Wakeam is a surgical fellow in the Division of Thoracic Surgery at the Toronto General Hospital, Toronto, Ontario.

References:
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 Gutierrez 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.

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. 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:

References:

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.
Now Calling for International Participation
Contribute data to the IASLC 9th Edition Lung Cancer Staging Project

Help change the landscape of lung cancer treatment for future patients!
• New clinical and molecular elements have been added
• International participation is crucial to the project’s success
• The 9th Edition recommendations will be developed in 2022

TIMELINE:
The study consists of lung cancer patients diagnosed between January 1, 2011 and December 31, 2019. Cases may be submitted through 2019, with follow-up for survival through 2021.

For more information: www.iaslc.org/staging