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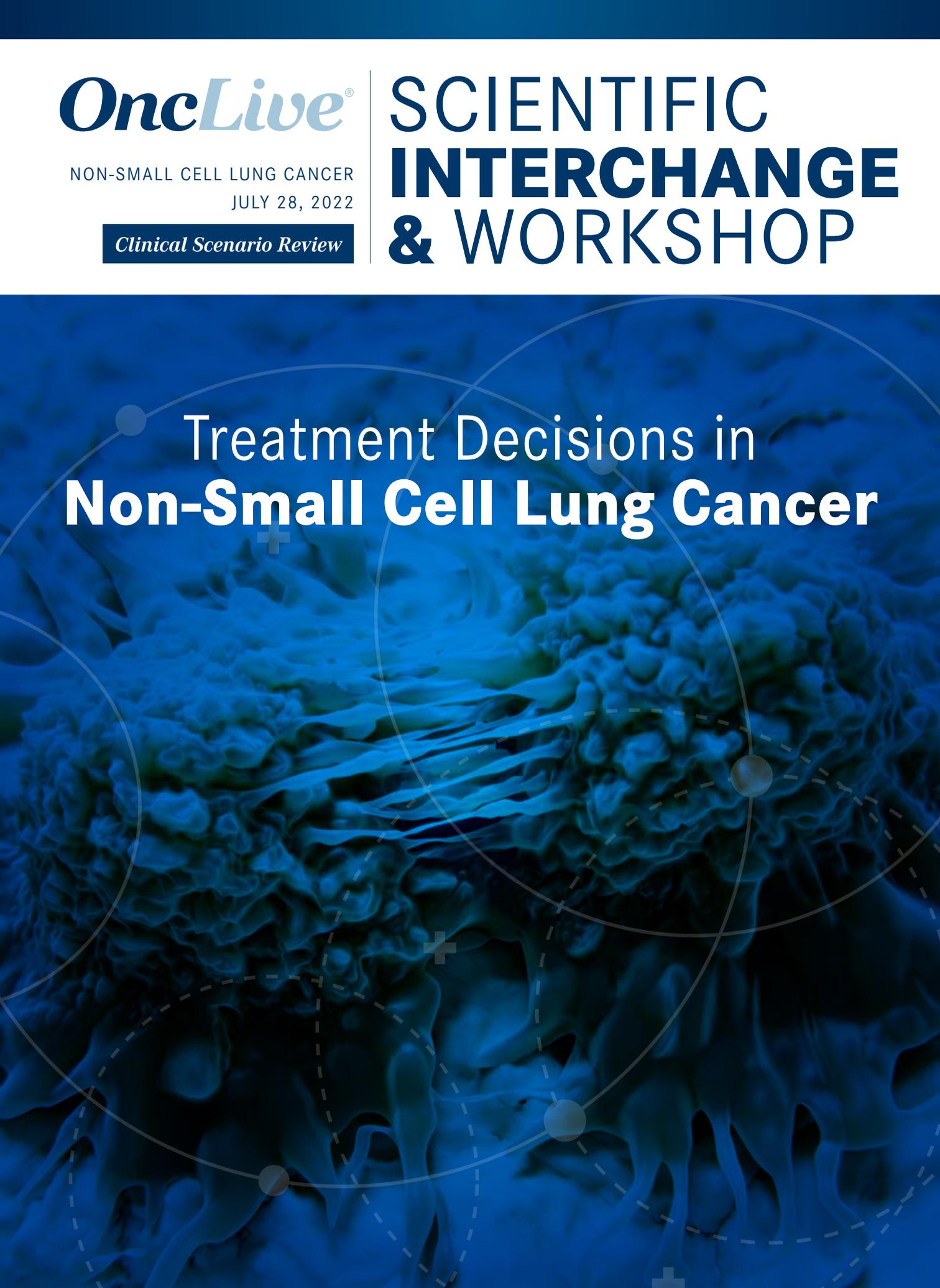
NON-SMALL CELL LUNG CANCER

JULY 28, 2022

*Clinical Scenario Review*

# SCIENTIFIC INTERCHANGE & WORKSHOP

Treatment Decisions in  
**Non-Small Cell Lung Cancer**

A microscopic view of lung tissue, showing the intricate, branching structure of the alveoli. The image is overlaid with a network of white and dashed lines, including circles and squares, suggesting a scientific or analytical theme. The overall color palette is a deep blue, with the text in white and light blue.

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## NSCLC

# Treatment Decisions in Non-Small Cell Lung Cancer

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**ON JULY 28, 2022**, the **Onclive® Scientific Interchange**: Treatment Decisions in Non-Small Cell Lung Cancer, featured a panel of thoracic oncology experts who specialize in the treatment of lung cancer. **Roy S. Herbst, MD, PhD**, director of the Center for Thoracic Cancers and professor of Medical Oncology at the Yale Cancer Center in New Haven, Connecticut, served as the moderator. The goals of the interchange were to review clinical scenarios to gain expert insight on using immunotherapy (IO) and targeted therapeutics in patients with NSCLC, to discuss factors impacting therapeutic selection and sequencing strategies in NSCLC, and to evaluate and obtain feedback on the evolving landscape of immunotherapy-based regimens in treating the disease.

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### CLINICAL SCENARIO 1: METASTATIC NSCLC WITH PD-L1 TPS OF 50% OR MORE

**Deepti Behl, MD**, presented the clinical scenario of an active and otherwise healthy woman aged 74 years with no prior smoking history who developed mid-back pain after moving an exercise bike (TABLE 1). The patient reports worsening pain following physical therapy and an unintentional weight loss of 15 lb over the last 3 months. Positron emission tomography (PET)/CT scans reveal a primary lung mass with metastatic lesions in the liver, bone, and lymph nodes. Liver biopsy confirms TTF1-positive, CK20-negative adenocarcinoma of the lung. Liquid biopsy and tissue-based next-generation sequencing (NGS) show no actionable mutations. The PD-L1 tumor proportion score (TPS) and tumor mutation burden (TMB) are both high at 50% and 14, respectively. Other nonactionable mutations identified with molecular testing include *ATRX* (7072 splice site) and *TP53* (Y239C) gene mutations.

#### First-line Treatment Approaches: The Role of IO-based Therapies

Due to the patient's nonsmoker status and PD-L1 TPS of 50%, the faculty were asked to comment on their preferred approach for first-line therapy. Given the PD-L1 TPS of 50%, **Paul Baas, MD, PhD**, expressed some hesitation in giving monotherapy with pembrolizumab, noting that he often reserves this treatment approach for cases with PD-L1 TPS above 90% and in the absence of actionable *EGFR* variants. Based on the patient's nonsmoker status, panel members agreed that monotherapy with pembrolizumab may not be sufficient; they preferred a more aggressive treatment strategy that uses IO with chemotherapy in this clinical scenario. **Corey J. Langer, MD, FACP**, suggested several combination regimens as potential treatment options, including cisplatin or carboplatin in combination

**TABLE 1.**

**CLINICAL SCENARIO 1: METASTATIC NSCLC WITH PD-L1 TPS ≥ 50%**

Presented by **Deepti Behl, MD**

<b>Patient profile</b>	<ul style="list-style-type: none"> <li>74-year-old woman</li> </ul>
<b>Clinical presentation</b>	<ul style="list-style-type: none"> <li>Presents with mid-back pain after heavy lifting</li> </ul>
<b>Medical history</b>	<ul style="list-style-type: none"> <li>Excellent health prior to diagnosis</li> <li>Unexplained weight loss &gt; 15 lb over the previous 3 months</li> <li>Smoking history: never-smoker</li> </ul>
<b>Evaluation</b>	<ul style="list-style-type: none"> <li>Chest CT: lesions in lung, lymph nodes, liver, and bone</li> <li>Brain MRI: negative</li> <li>Liver biopsy confirms TTF1+, CK20- lung adenocarcinoma</li> <li>Liquid biopsy: no actionable mutations</li> <li>RNA-based testing: no actionable mutations</li> <li>Molecular testing                             <ul style="list-style-type: none"> <li>PD-L1: TPS of 50%</li> <li>TMB: 14 (reported as 10 in first report)</li> <li>Other mutations: <i>ATRX</i> (splice site 7072); <i>TP53</i> (Y239C)</li> </ul> </li> <li>ECOG PS: 0</li> </ul>
<b>Treatment</b>	<ul style="list-style-type: none"> <li>Underwent vertebroplasty with some symptomatic relief</li> <li>Discussed single-agent IO, IO in combination with chemotherapy, and IO/IO combinations; patient wished to avoid chemotherapy.</li> <li>Started on pembrolizumab monotherapy</li> <li>Initial good clinical and radiological response</li> <li>After 8 months, disease progression mainly in the liver and lung</li> <li>Started on carboplatin/pemetrexed                             <ul style="list-style-type: none"> <li>Short-term response, progressed again in 6 months</li> <li>Started on docetaxel/ramucirumab</li> </ul> </li> <li>Worsening back pain; bony metastases worse on scan                             <ul style="list-style-type: none"> <li>Referred to palliative care for co-management of pain, but otherwise maintained excellent ECOG PS</li> </ul> </li> <li>Started on ipilimumab/nivolumab                             <ul style="list-style-type: none"> <li>Responded well initially with marked improvement in pain, but pain worsened after 4 months; radiographic progression</li> </ul> </li> <li>Started hospice</li> </ul>

CK20-, CK20-negative; ECOG, Eastern Cooperative Oncology Group; IO, immunotherapy; NSCLC, non-small cell lung cancer; PET, positron emission tomography; PS, performance status; TMB, tumor mutational burden; TPS, tumor proportion score; TTF1-, TTF1-negative.

with pemetrexed and pembrolizumab followed by pembrolizumab plus pemetrexed maintenance as used in the KEYNOTE-189 trial (NCT02578680) and pembrolizumab followed by pemetrexed plus carboplatin and pembrolizumab as used in the ongoing INSIGNA trial (NCT03793179) trial.<sup>1,2</sup>

Treatment strategies using dual immune checkpoint inhibition (ICI) (eg, pembrolizumab or nivolumab combined with ipilimumab as used in the KEYNOTE-598 trial [NCT03302234] and the CheckMate 227 trial [NCT02477826], respectively) were also discussed as potential treatment

options.<sup>3,4</sup> Long-term (4-year) follow-up data from CheckMate 227 showed clinically meaningful and sustained efficacy with nivolumab plus ipilimumab independent of PD-L1 status; however, this trial used a chemotherapy comparator arm rather than ICI monotherapy.<sup>4</sup> **Behl** emphasized that data from the KEYNOTE-598 study demonstrated that the addition of ipilimumab to pembrolizumab did not improve survival outcomes in patients with a PD-L1 TPS of at least 50%; further, because increased toxicity was noted, this strategy likely would not benefit

this patient.<sup>3</sup>

**Second-line Treatment Options Following Progression on Single-agent IO**

After 8 months of treatment with pembrolizumab monotherapy, the patient in the case scenario experienced disease progression in the lung and liver. Due to the relatively rapid progression, **Behl** explained, pembrolizumab was discontinued, and chemotherapy (pemetrexed/carboplatin) was initiated. **Jonathan Wesley Riess, MD, MS**, agreed with this approach; however, he noted that he typically continues ICI plus chemotherapy in patients who demonstrate a favorable response to the ICI initially.

**Considerations for Later Lines of Therapy**

The patient experienced further disease progression after 6 months of chemotherapy, and the faculty discussed potential next lines of treatment. **Langer** noted that several combinations, including ramucirumab

in combination with docetaxel or pembrolizumab, were used in the Lung-MAP S1800A nonmatch substudy (NCT03971474).<sup>5</sup> Given the poor response noted with prior use of pembrolizumab monotherapy, some faculty expressed a preference for the docetaxel plus ramucirumab combination. However, the results of the Lung-MAP study demonstrated that ramucirumab plus pembrolizumab was associated with improved survival outcomes compared with investigator’s choice of standard-of-care (SOC) chemotherapy, which included docetaxel plus ramucirumab.<sup>5</sup>

**CLINICAL SCENARIO 2: METASTATIC NSCLC WITH PD-L1 TPS OF 1% TO 49%**

**Paul Baas, MD, PhD**, introduced the clinical scenario of a woman aged 57 years who presented with symptoms of cough, wheezing (right side), and blood-streaked sputum that was unresponsive to antibiotic therapy (**TABLE 2**). Notable comorbidities

include hypertension and moderate rheumatoid arthritis (RA). The patient has a 24 pack-year (ongoing) history of smoking. Blood chemistry testing indicates a grade 1 elevation of liver enzymes; all other laboratory values are within normal limits. Radiologic imaging shows a central tumor mass and several irregular lesions in the liver. Biopsy of the liver mass demonstrates adenocarcinoma with a PD-L1 TPS of 25%. No actionable mutations are identified with molecular testing.

**Role of IO in TMB-high NSCLC With Autoimmune Comorbidities**

Given the presence of liver metastases and comorbid RA, participants were asked to comment on potential treatment options, including standard chemotherapy, ICI monotherapy, ICI in combination with chemotherapy, and dual ICI therapy. **Herbst** expressed a preference for ICI in combination with chemotherapy. Acknowledging the presence of mild RA, **Baas** cautioned against treatment approaches with ipilimumab, noting that he has encountered worsening of RA symptoms. **Riess** agreed, noting that the addition of chemotherapy to ICI may help to suppress a potential flare-up of worsening RA symptoms.

For clinical scenarios involving autoimmune diseases, **Behl** stated that proactive referral to the rheumatologist is standard protocol at her practice site. She further shared that in these cases, patients most often would receive ICI monotherapy accompanied by shared follow-up with the rheumatologist.

**Langer** shared his experience in using ICI in patients with various autoimmune diseases (eg, RA, polymyalgia rheumatica, Crohn disease, ulcerative colitis, and mild lupus) so long as they are not receiving immunosuppressant therapy. However, faculty agreed that treatment selection is dependent on the degree of disease severity and if the patient is receiving other immunosuppressing agents. In practice a dose of >10 mg of

**TABLE 2.**  
CLINICAL SCENARIO 2: METASTATIC NSCLC WITH PD-L1 TPS OF 1%-49%

Presented by **Paul Baas, MD, PhD**

Patient profile	<ul style="list-style-type: none"> <li>• 57-year-old woman</li> </ul>
Clinical presentation	<ul style="list-style-type: none"> <li>• Coughing</li> <li>• Blood-streaked sputum</li> </ul>
Medical history	<ul style="list-style-type: none"> <li>• Hypertension</li> <li>• Moderate rheumatoid arthritis controlled with a nonsteroidal anti-inflammatory drug</li> <li>• Recent 5% weight loss</li> <li>• Smoking history: current heavy smoker</li> </ul>
Evaluation	<ul style="list-style-type: none"> <li>• Pulmonary: wheezing, right side</li> <li>• ECOG PS : 1</li> <li>• PD-L1: TPS of 20%</li> <li>• Molecular analysis: negative</li> <li>• Renal function: liver enzymes, grade-1 elevation</li> <li>• Liver biopsy: confirmed adenocarcinoma</li> <li>• No palpable lymph nodes</li> </ul>
Treatment	<ul style="list-style-type: none"> <li>• Treated with a combination of platinum-based chemotherapy and pembrolizumab</li> <li>• Currently, after 9 months on treatment, no signs of recurrence</li> </ul>

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PS, performance status; TMB, tumor molecular burden; TPS, tumor proportion score.

prednisone per day was noted as a general threshold for ICI therapy.

Additionally, **Langer** mentioned a case of a heart transplant patient who received an ICI plus chemotherapy without major complications; however, the faculty agreed that ICIs should generally be avoided in this patient population. Moreover, panelists expressed that ICI therapy is typically used in patients with comorbidities such as HIV and hepatitis B or C without any major adverse effects (AEs). However, it was noted that specialists such as rheumatologists, endocrinologists, infectious disease specialists, and gastroenterologists should be involved when treating patients with comorbidities, including autoimmune diseases, that may be affected by ICI treatment.

### CLINICAL SCENARIO 3: METASTATIC NSCLC WITH HIGH PD-L1

**Natasha Leigh, MD, MSc, FRCPC, FASCO**, introduced the clinical scenario of a man aged 62 years with a 30 pack-year history of smoking who presented with a dominant left lower lobe lung mass, mediastinal adenopathy, and adrenal metastases (**TABLE 3**). Other notable clinical features include an ECOG performance status (PS) of 0 and comorbidities including hypertension (well-controlled) and hypercholesterolemia. Tissue biopsy revealed TTF1/CK7-positive adenocarcinoma with a PD-L1 TPS of 80% and a *KRAS* G12C mutation. The patient is diagnosed with stage IV disease and treated with single-agent ICI therapy.

#### First-line Treatment Options in PD-L1-High, KRAS-mutant NSCLC

Given the patient's PD-L1 and *KRAS* G12C mutation status, the panel discussed potential first-line treatment options. An exploratory pooled data analysis conducted by the FDA and presented at the 2022 Annual Meeting of the American Society of Clinical

**TABLE 3.**  
CLINICAL SCENARIO 3: METASTATIC NSCLC WITH HIGH PD-L1

Presented by **Natasha Leigh, MD, MSc, FRCPC, FASCO**

Patient profile	<ul style="list-style-type: none"> <li>62-year-old man</li> </ul>
Clinical presentation	<ul style="list-style-type: none"> <li>Presents with persistent cough</li> </ul>
Medical history	<ul style="list-style-type: none"> <li>Very fit</li> <li>Well-controlled hypertension</li> <li>Hypercholesterolemia</li> <li>Smoking history: heavy smoker for 30 years; quit 10 years ago</li> </ul>
Evaluation	<ul style="list-style-type: none"> <li>ECOG PS: 0</li> <li>Dominant left lower lobe lung mass with bilateral adrenal metastases</li> <li>Mediastinal adenopathy</li> <li>Biopsy reveals TTF1+, CK7+, stage IV lung adenocarcinoma</li> <li>PD-L1: TPS of 80%</li> <li>Molecular testing                             <ul style="list-style-type: none"> <li><i>KRAS</i> G12C mutation</li> <li><i>TP53</i>-</li> </ul> </li> </ul>
Treatment	<ul style="list-style-type: none"> <li>Started CHECKMATE-026 trial</li> <li>Received nivolumab for 2.5 years with complete response</li> <li>Treatment stopped when patient developed renal insufficiency and pneumonitis</li> <li>Remains in complete response (7 years post-treatment)</li> </ul>

CK7+, CK7-positive; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PS, performance status; TP53-, TP53-negative; TPS, tumor proportion score; TTF1+, TTF1-positive.

Oncology (ASCO 2022) demonstrated that patients with a current or previous smoking history and a PD-L1 TPS of at least 50% may gain little to no benefit from chemotherapy given with IO vs IO alone.<sup>6</sup> Moreover, overall survival (OS) appears to be similar between patients with *KRAS* G12C-mutant, PD-L1-high NSCLC given ICI monotherapy or chemotherapy/ICI.<sup>7</sup> In light of these data and a lack of other known co-mutations, **Leigh** explained that ICI monotherapy would be a reasonable treatment approach.

In clinical scenarios involving *STK11* or *KEAP1* mutations, **Riess** commented, that there may be a stronger case for IO in combination with chemotherapy, but noted he would not be opposed to monotherapy with pembrolizumab. **Baas** expressed a preference for a treatment approach using chemotherapy in combination with IO, emphasizing that a more aggressive therapy is needed in this scenario. Commenting further, he stated, "I've seen so many people, not long survivors, but fast progressors,

with the frustration that you start your IO therapy, and it doesn't work at all." In reference to results with the INSIGNA trial regimen, **Herbst** expressed it would also be reasonable to initiate monotherapy with pembrolizumab and then add chemotherapy later if progression occurs.<sup>2</sup>

#### Role of KRAS Inhibitors for Refractory, KRAS G12C-mutant NSCLC

Based on data from the CodeBreak100 (NCT03600883) trial, the *KRAS* inhibitor (KRASi) sotorasib has received FDA approval for the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic NSCLC who have received at least 1 prior systemic therapy.<sup>7-9</sup> The KRYSTAL-1 trial (NCT03785249) studied the investigational KRASi adagrasib in patients with *KRAS* G12C-mutated NSCLC who have received at least 1 prior systemic therapy and adagrasib is currently under review by the FDA.<sup>10,11</sup> Panelists were prompted

to comment on the potential use of a KRASi in combination with ICI in the second-line setting. Leigh cautioned that treatment with sotorasib could result in a greater inflammatory effect in the tumor. Considering the higher incidence of grade 3 or 4 treatment-related AEs reported with KRASi/ICI combination therapy vs KRASi monotherapy, Langer noted that KRASi therapy may be more appropriate; further, due to the potential differences in the incidence of AEs, adagrasib may be preferable to sotorasib.<sup>12</sup> However, all things considered, the faculty expressed a preference for treating with IO ahead of KRASis, noting that data are not that compelling. However, in the setting of a clinical trial, this may be a reasonable therapeutic approach.

#### CLINICAL SCENARIO 4: FRAIL/ELDERLY PATIENT WITH METASTATIC NSCLC WITH PD-L1 TPS OF 1% TO 49%

Corey J. Langer, MD, FACP, presented the clinical scenario of a woman aged 88 years with worsening symptoms of dyspnea on exertion (TABLE 4). The patient has a remote history of smoking (> 10 pack-years; quit > 50 years previously). Comorbidities include congestive heart failure, coronary artery disease, hyperlipidemia, and emphysema. Upon presentation, the patient's noted ECOG PS is 2, but it later improves to approximately 1. Chest CT imaging demonstrates a 4.5-cm, right lower lobe lung mass; multiple smaller, pleural-based nodules; and a large right pleural effusion. Thoracentesis reveals TTF1+ lung adenocarcinoma. Molecular testing reported a PD-L1 TPS of 20% and the presence of a KRAS G12C mutation. Other notable laboratory results include a creatinine level of 1.3 mg/dL.

#### Immunotherapy in Elderly Patients With NSCLC

Subgroup data analyses from several trials, including Checkmate 017

**TABLE 4.**  
CLINICAL SCENARIO 4: FRAIL/ELDERLY PATIENT WITH METASTATIC NSCLC AND A PD-L1 TPS OF 1%-49%

Presented by Corey J. Langer, MD, FACP

Patient profile	<ul style="list-style-type: none"> <li>88-year-old woman</li> </ul>
Clinical presentation	<ul style="list-style-type: none"> <li>Shortness of breath</li> </ul>
Medical history	<ul style="list-style-type: none"> <li>Diastolic CHF with implanted pacemaker</li> <li>CAD, HLD, and emphysema</li> <li>Smoking history: former smoker (&gt; 10 pack-years); quit more than 50 years ago</li> <li>2014: multiple, small, right-sided lung nodules; stable</li> <li>2017: increasing dyspnea on exertion; improved with pacemaker upgrade</li> <li>2019: worsening dyspnea on exertion</li> </ul>
Evaluation	<p>2019</p> <ul style="list-style-type: none"> <li>ECOG PS: 2; improved to ≈ 1 over time</li> <li>Chest CT: 4.5-cm, right lower lobe lung mass, large pleural effusion on right side</li> <li>Brain MRI: negative</li> <li>Thoracentesis: TTF1+ lung adenocarcinoma</li> <li>Creatinine: 1.3 mg/dL</li> <li>KRAS G12C mutation</li> <li>PD-L1: TPS of 20%</li> </ul>
Treatment	<ul style="list-style-type: none"> <li>2020: received 9 cycles of pembrolizumab with minor response                             <ul style="list-style-type: none"> <li>Minimal toxicity: slight fatigue</li> </ul> </li> <li>Pleural effusion controlled with drainage</li> <li>Currently alive and well                             <ul style="list-style-type: none"> <li>Off treatment for 4-5 months</li> </ul> </li> </ul>

CAD, coronary artery disease; CHF, congestive heart failure; HLD, hyperlipidemia; NSCLC, non-small cell lung cancer; PS, performance status; TPS, tumor proportion score; TTF1+, TTF1-positive.

(NCT01642004) and Checkmate 057 (NCT01673867), demonstrated that compared with younger patients, those 75 years or older did not benefit from nivolumab compared with docetaxel.<sup>13,14</sup> However, older patients usually only made up a small sample size and had a higher ECOG PS, which may have influenced the outcomes. Similarly, the KEYNOTE-010 study found that patients 65 years or older saw less benefit from pembrolizumab monotherapy than did patients younger than 65 years.<sup>15,16</sup>

Results of the KEYNOTE-189 and KEYNOTE-407 studies demonstrated that the benefit of treatment with pembrolizumab plus chemotherapy was not as robust as was treatment with chemotherapy alone in patients 65 years and older as compared with those younger than 65 years.<sup>17,18</sup> In the CheckMate 227 and CheckMate

9LA trials, patients who were at least 75 years of age did not derive benefit from the addition of nivolumab plus ipilimumab to chemotherapy.<sup>18,19</sup>

Data from the Energy-GFPC 06-2015 study (NCT03351361) presented at ASCO 2022 demonstrated deleterious effects with nivolumab plus ipilimumab combination therapy vs chemotherapy in patients at least 70 years of age who had an ECOG PS of 2; however, in patients with an ECOG PS of 0 or 1, greater benefit was noted with nivolumab plus ipilimumab.<sup>20</sup>

Given the age, ECOG PS, and PD-L1 status of this patient, Langer asked the faculty about their preferred approach to treatment. Considering her relatively fragile status, Baas expressed that the patient may not be able to tolerate chemotherapy in combination with IO. Behl further

added that given the patient’s age, her creatinine clearance may preclude use of pemetrexed. Based on the presence of a *KRAS* G12C mutation, **Langer** commented on treatment approaches using KRASi. In response, **Jänne** remarked that the patient, considering the status presented, most likely would tolerate pembrolizumab better than she would sotorasib; further, **Jänne** noted, even if the patient did respond well to sotorasib, her response likely would be short-lived. Overall, the faculty agreed that ICI monotherapy with pembrolizumab probably would be the best treatment option for this patient.

**CLINICAL SCENARIO 5: NONMETASTATIC NSCLC WITH PD-L1 TPS OF LESS THAN 1%**

**Pasi A. Jänne, MD, PhD**, introduced the clinical scenario of a woman (age, 71 years) who presented to her primary care provider with complaints of cough (TABLE 5). An initial chest x-ray demonstrates a left-sided lung mass; subsequent chest CT confirms presence of a 4.7-cm, left lower lobe lung mass with no evidence of distant/metastatic disease. A 4.8-cm, T2N0 primary tumor is removed via a left lower lobectomy. Subsequent tumor tissue sequencing reveals an *EGFR* exon 20 insertion and a PD-L1 TPS of 0%. The patient is initiated on an adjuvant regimen of cisplatin in combination with pembrolizumab; however, shortly after initiation of therapy, cisplatin is replaced with carboplatin due to intolerance. Upon follow-up, PET/CT imaging at 2 years reveals new pulmonary nodules with no signs of extra thoracic disease. Tissue biopsy confirms recurrent NSCLC with no new molecular findings (the *EGFR* exon 20 mutation remains).

**Treatment Approaches for Recurrent NSCLC Following Adjuvant Chemotherapy**

Considering the failed first-line therapy, persisting *EGFR* exon 20-variant

status, and no new molecular findings, the faculty are asked to comment on their preferred treatment approach. Given the patient’s PD-L1 status (TPS of 0%), **Behl** expressed a preference to forgo IO in this scenario. Due to the presence of an *EGFR* exon 20 mutation, **Langer** offered that amivantamab or mobocertinib may be viable treatment options. Noting the patient’s prior therapy with platinum-based chemotherapy, **Riess** agreed that this would be a reasonable treatment option in scenarios with recurrent disease within a few months of adjuvant therapy. However, since disease recurred after more than 1 year, he would opt for treatment using bevacizumab or pembrolizumab in combination with carboplatin and pemetrexed. **Riess** noted that he does not often use pembrolizumab plus chemotherapy in patients with a PD-L1 TPS of 0, but the majority of attendees said that they would use a pembrolizumab-based combination.

**Later Lines of Therapy for NSCLC With EGFR Exon 20 Mutations**

The patient was enrolled in a clinical trial to receive mobocertinib at the 160-mg dose. Due to severe diarrhea, the patient required 2 dose reductions, first to 120 mg and then to 80 mg. The patient achieved a partial response, and her disease has remained stable on treatment for 15 months. Acknowledging the high likelihood of disease progression in this clinical scenario, **Langer** noted that the IMpower150 trial (NCT02366143) of atezolizumab in combination with bevacizumab and chemotherapy (carboplatin/paclitaxel) may be a reasonable next-line option for patients who are fit and motivated.<sup>21</sup> **Jänne** emphasized the importance of repeated biopsy with disease recurrence to guide treatment selection. **Leighl** remarked that amivantamab may also be a reasonable treatment option. Because mobocertinib and possibly

**TABLE 5.**  
CLINICAL SCENARIO 5: NONMETASTATIC NSCLC WITH PD-L1 TPS < 1%

Presented by **Pasi A. Jänne, MD, PhD**

<b>Patient profile</b>	<ul style="list-style-type: none"> <li>71-year-old woman</li> </ul>
<b>Clinical presentation</b>	<ul style="list-style-type: none"> <li>Cough</li> </ul>
<b>Evaluation</b>	<ul style="list-style-type: none"> <li>Chest x-ray: left-sided lung mass</li> <li>CT: 4.7-cm, left lower lobe lung mass</li> <li>No evidence of distant disease</li> <li>Left lower lobectomy; 4.8-cm, T2N0 primary tumor</li> <li>Tumor genotyping: <i>EGFR</i> exon 20 mutation (M766_A767insASV)</li> <li>PD-L1: TPS of 0%</li> </ul>
<b>Treatment</b>	<ul style="list-style-type: none"> <li>2019: started adjuvant cisplatin/pemetrexed                             <ul style="list-style-type: none"> <li>Switched to carboplatin after first cycle due to poor tolerance</li> </ul> </li> <li>2020: new pulmonary nodule                             <ul style="list-style-type: none"> <li>PET/CT: positive</li> <li>No extrathoracic disease</li> </ul> </li> <li>Recurrent NSCLC after surgery and adjuvant chemotherapy</li> <li>Patient participated in a clinical trial of carboplatin/pemetrexed vs mobocertinib                             <ul style="list-style-type: none"> <li>Randomized to mobocertinib (160 mg/d).</li> <li>Could not tolerate full dose; reduced to 120 mg and, subsequently, to 80 mg</li> <li>Partial response continues on study after &gt; 15 months</li> </ul> </li> </ul>

NSCLC, non-small cell lung cancer; PET, positron emission tomography; TPS, tumor proportion score.

**TABLE 6.**  
CASE SCENARIO 6: METASTATIC NSCLC WITH HIGH PD-L1

Presented by **Jonathan Wesley Riess, MD, MS**

Patient profile	<ul style="list-style-type: none"> <li>65-year-old man</li> </ul>
Clinical presentation	<ul style="list-style-type: none"> <li>Worsening cough</li> <li>Shortness of breath</li> </ul>
Medical history	<ul style="list-style-type: none"> <li>Smoking history: never-smoker</li> </ul>
Evaluation	<ul style="list-style-type: none"> <li>PET-CT: left lower lobe primary with hypermetabolic lymphadenopathy in the hilum and mediastinum               <ul style="list-style-type: none"> <li>Widespread bone and liver metastases</li> </ul> </li> <li>Brain MRI: multiple, asymptomatic, subcentimeter brain metastases</li> <li>ECOG PS: 1</li> <li>Confirmed stage IVC (pT3N3M1C) NSCLC-adenocarcinoma (TTF1+)</li> <li>PD-L1: TPS of 90%</li> <li>Next-generation sequencing: <i>ERBB4</i> R842Q mutation</li> </ul>
Treatment	<ul style="list-style-type: none"> <li>Received radiation therapy for bone metastases</li> <li>Discussed KEYNOTE-189 trial, but decided against participation due to bulky disease, never-smoker status, and radiation for bone metastases</li> <li>Initiated carboplatin/pemetrexed/pembrolizumab</li> <li>Followed by pemetrexed/pembrolizumab maintenance</li> <li>Responded to treatment with controlled brain metastases; still on treatment</li> </ul>

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PET, positron emission tomography; TTF1+, TTF1-positive.

amivantamab are associated with poor penetration of the blood-brain barrier, the faculty acknowledged that these agents would not be beneficial in scenarios involving brain metastases.<sup>21-24</sup>

### CLINICAL SCENARIO 6: METASTATIC NSCLC WITH HIGH PD-L1

**Jonathan Wesley Riess, MD, MS**, introduced the clinical scenario of a man (age, 65 years) with no prior smoking history and an ECOG PS of 1 who complains of worsening cough and shortness of breath (**TABLE 6**). An initial PET/CT scan shows a primary left lower lobe lung mass with hypermetabolic lymphadenopathy in the hilum and mediastinum and widespread bone and liver metastases. Subsequent MRI reveals multiple, asymptomatic, subcentimeter brain metastases. Biopsy of the primary lung lesion confirms stage IVC, TTF1+ lung

adenocarcinoma. Molecular and NGS testing indicate presence of an *ERBB4* R842Q mutation with a PD-L1 TPS of 90%. The patient is initiated on the KEYNOTE-189 regimen (carboplatin/pemetrexed/pembrolizumab) followed by maintenance therapy that includes pemetrexed in combination with pembrolizumab.

#### *Treatment Approaches for PD-L1-High, EGFR-mutant NSCLC With Brain Metastases*

PD-L1 blockade alone is suboptimal in treating *EGFR*-mutant NSCLC, with a high frequency of reported AEs and a lack of improvement in clinical outcomes, including the objective response rate (ORR) and progression-free survival (PFS).<sup>25,26</sup> Additionally, some studies have shown a negative correlation between PD-L1 expression and *EGFR* mutations; consequently, the role of ICIs in the treatment of patients with *EGFR* mutations remains

controversial.<sup>27</sup> Moreover, published data demonstrate that PD-L1 blockade was associated with a longer OS in ever-smokers compared to never-smokers (median OS, 12.8 months vs 6.5 months; HR, 0.69; 95% CI, 0.50-0.95).<sup>28</sup>

Given the patient's PD-L1-high and *EGFR*-mutant status with no history of smoking and presence of brain metastases, the panel members were asked how they would approach treatment in this clinical scenario. In response, **Behl** expressed that in patients with no smoking history, she would typically favor a treatment approach that includes chemotherapy in combination with IO. Patients with no smoking history often present with PD-L1-low NSCLC, yet the panel acknowledged that PD-L1-high disease is also seen in this patient population.<sup>29,30</sup> **Riess** highlighted the utility of ICIs as a treatment strategy in patients with NSCLC and brain metastases, citing study data demonstrating an ICI-associated intracranial response rate of 27.3% and similar ORRs in patients with and without brain metastases (20.6% and 22.7%, respectively).<sup>31</sup> Similar results reported in a phase 2 trial of pembrolizumab (NCT02085070) in patients with PD-L1-positive NSCLC and at least 1 cerebral metastasis (size, 5-20 mm) showed a response in 29.7% of patients and a 2-year OS of 34%.<sup>32</sup> Additionally, faculty discussed data updates from the ATEZO-BRAIN trial (NCT03526900) demonstrating ORRs of 47.5% (systemic) and 40% (intracranial) with corresponding median PFS of 8.9 months and 6.9 months, respectively.<sup>33</sup>

#### *Future Directions*

As the discussion ended, the faculty acknowledged that IO has played a key role in changing the treatment landscape. Even with NSCLC, **Herbst** noted that, in some instances, patients are achieving relatively long survival times of up to 12 years with

ICI treatment. Whereas ICI-based monotherapy can be a viable option in some cases, combined use of chemotherapy and ICI generally yields better outcomes in patients with PD-L1-high NSCLC who are nonsmokers or have *EGFR*-mutant disease.<sup>25,26,28</sup>

Obtaining an initial liquid biopsy with circulating tumor DNA for a baseline can help track molecular changes within a tumor to provide insight in treatment decision-making. Among other clinical factors, deciding whether to continue ICI, add on chemotherapy, or discontinue ICI and switch to chemotherapy alone can depend upon when and how rapidly disease progression occurs. **Riess** expressed that in cases in which progression occurs more gradually, he typically adds chemotherapy to the existing ICI regimen. However, **Langer** noted that other important factors include the length of ICI therapy before progression and the type of response a patient experiences with ICI treatment. Rapid disease progression may indicate a poor tumor response to ICI treatment, and chemotherapy may be preferred in place of combination therapy with ICI.

For NSCLC with brain metastases, **Riess** commented that pemetrexed may provide benefit due to its ability to penetrate the blood-brain barrier. Additionally, data demonstrate the utility of ICIs in treating brain lesions; concordance with brain and systemic ORRs and clear intracranial responses have been observed.<sup>32</sup> Considering the favorable brain responses observed with ICI (≈ 30%), there may be a role for ICI monotherapy in some cases. Overall, the faculty anticipate the continued role of ICI in managing NSCLC and look forward to an ever-expanding number of targetable biomarkers and associated therapy options to treat patients diagnosed with the disease. ■

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