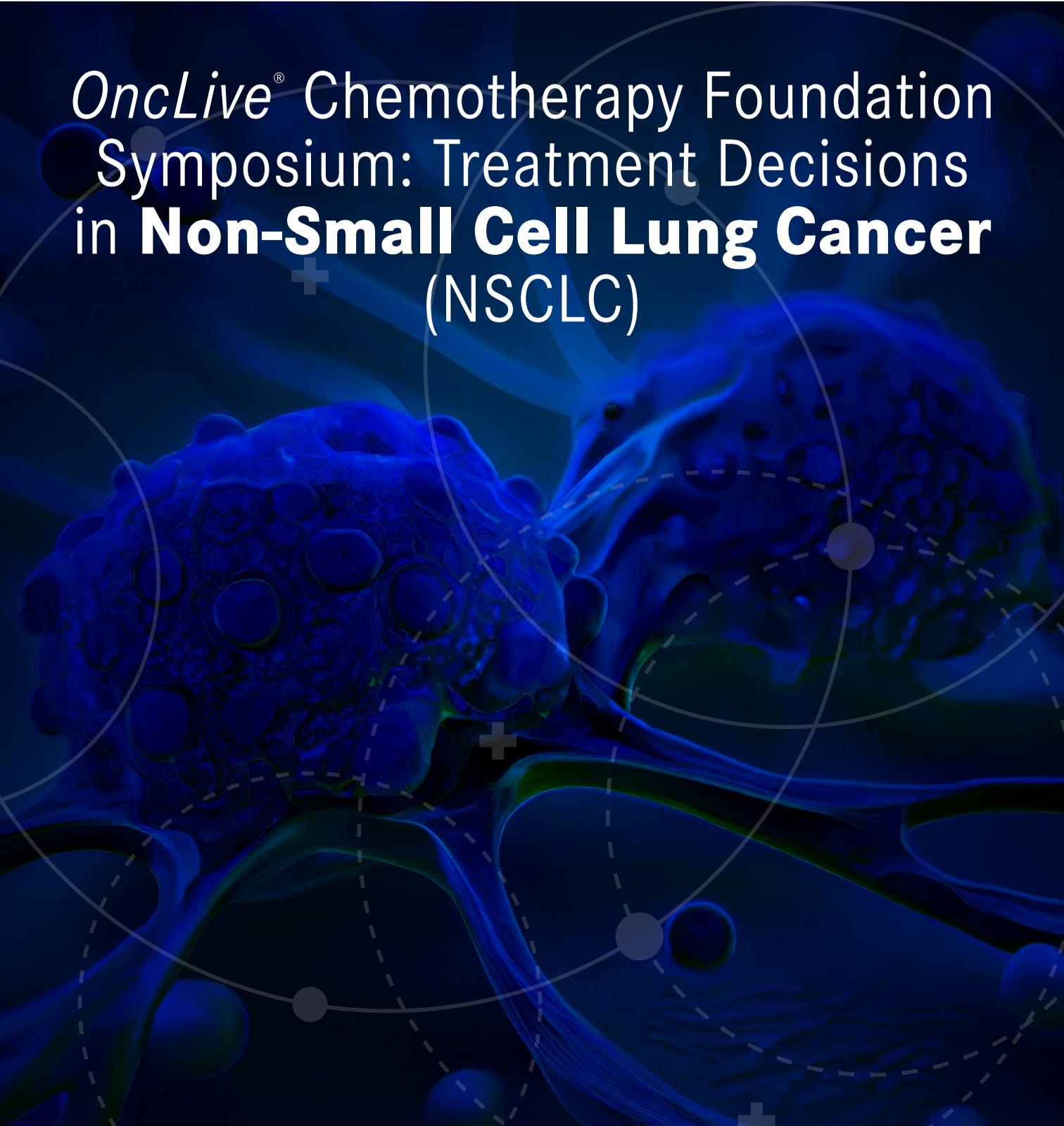


*OncLive*<sup>®</sup>

NON-SMALL CELL LUNG CANCER  
NOVEMBER 11, 2022  
VIRTUAL WORKSHOP

# SCIENTIFIC INTERCHANGE & WORKSHOP

*OncLive*<sup>®</sup> Chemotherapy Foundation  
Symposium: Treatment Decisions  
in **Non-Small Cell Lung Cancer**  
(NSCLC)

The background of the lower half of the image is a dark blue, abstract graphic. It features several large, textured, spherical shapes that resemble cells or molecular structures, rendered in shades of blue and green. These shapes are interconnected by thin, white lines and dotted paths, creating a network-like pattern. There are also several small, white plus signs scattered throughout the design, suggesting a scientific or medical theme.

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## NSCLC



# OncLive® Chemotherapy Foundation Symposium: Treatment Decisions in Non-Small Cell Lung Cancer (NSCLC)

### MODERATOR



**Joshua K. Sabari, MD**  
Assistant Professor  
of Medicine  
Department of Oncology  
NYU Langone Hospitals  
New York, NY

**ON NOVEMBER 11, 2022**, the *OncLive®*

Chemotherapy Foundation Symposium: Treatment Decisions in Non-Small Cell Lung Cancer (NSCLC) featured a panel of oncologists who specialize in lung cancer. Moderated by **Joshua K. Sabari, MD**, assistant professor of Medicine in the department of Oncology at NYU Langone Hospitals, New York, New York, the goals of the discussion were to review clinical scenarios to gain expert insight on the management of NSCLC with immunotherapy (IO)-based regimens, to discuss factors impacting therapeutic selection and sequencing strategies, and to evaluate the evolving landscape pertaining to IO-based therapeutic approaches.

## FACULTY



**Harvey I. Pass, MD**  
Stephen E. Banner Professor  
of Thoracic Oncology  
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**Kathryn C. Arbour, MD**  
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**Haiying Cheng, MD, PhD**  
Associate Professor of  
Medicine and Oncology  
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### CLINICAL SCENARIO 1: NEOADJUVANT IMMUNOTHERAPY IN A PATIENT WITH STAGE III NSCLC AND HIV

**Harvey I. Pass, MD**, presented the clinical scenario of an HIV-positive man, aged 70 years, who presents with abnormal chest imaging that reveals a right hilar opacity (TABLE 1). He has a 2-year history of dyspnea and cough and history of cigarette smoking; he currently smokes marijuana and cigars daily. There is no family history of lung cancer. Past medical history includes psoriatic arthritis, which has been successfully treated with occasional flare-ups. There is a remote history of intravenous drug abuse. The patient is currently receiving treatment for HIV infection; he had a previous case of hepatitis C infection, which was successfully treated. MRI of the brain was unremarkable. Needle and transbronchial biopsy performed via robotic bronchoscopy revealed adenocarcinoma in the upper right lobe, and further needle (4R and 11R) biopsies of the lymph nodes revealed metastatic disease. Cancer staging determined that the patient had a malignant neoplasm of the hilus of the right lung, clinically defined as stage IIIB NSCLC. Molecular testing was negative for PD-L1 expression, although a *KRAS G12C* mutation and *FGFR1* amplification were noted. After initial consultation, the patient received 3 cycles of carboplatin/pemetrexed/nivolumab. The only adverse event (AE) reported was dry eyes. Following treatment, surgery via robotic resection was performed.

### ROLE OF MOLECULAR TESTING AND TUMOR RESECTABILITY IN GUIDING TREATMENT IN NEWLY DIAGNOSED NSCLC

**Sabari** queried faculty regarding their approach to molecular testing in newly diagnosed NSCLC. **Kathryn C. Arbour, MD**, emphasized the

**TABLE 1.**  
CLINICAL SCENARIO 1: NEOADJUVANT IMMUNOTHERAPY  
IN A PATIENT WITH STAGE III NSCLC AND HIV

Presented by Harvey I. Pass, MD

Patient profile	<ul style="list-style-type: none"> <li>70-year-old man</li> <li>HIV positive</li> </ul>
Clinical presentation	<ul style="list-style-type: none"> <li>Abnormal chest imaging</li> <li>Right hilar opacity</li> </ul>
Medical history	<ul style="list-style-type: none"> <li>Patient has 2-year history of DOE and cough.</li> <li>Patient had 30 pack-year smoking history (cigarettes); now, he smokes daily marijuana and cigars.</li> <li>No family history of lung cancer was noted.</li> <li>Remote history of IV drug abuse was noted.</li> <li>Psoriatic arthritis</li> <li>He was treated with sulfasalazine and hydroxychloroquine.</li> <li>HIV infection</li> <li>He receives treatment with dolutegravir/rilpivirine.</li> <li>Hepatitis C</li> <li>He was treated successfully with ledipasvir/sofosbuvir in 2015.</li> </ul>
Evaluation	<ul style="list-style-type: none"> <li>PFTs:                             <ul style="list-style-type: none"> <li>His FEV<sub>1</sub> was 96%; his DL<sub>CO</sub> was 89%.</li> </ul> </li> <li>Brain MRI: negative</li> <li>Robotic bronchoscopy                             <ul style="list-style-type: none"> <li>Needle biopsy of the right upper lobe of the lung showed adenocarcinoma.</li> <li>Transbronchial biopsy of the right upper lobe of the lung showed adenocarcinoma.</li> <li>Needle biopsy of the lymph node (11R) showed metastatic adenocarcinoma.</li> </ul> </li> <li>Cancer staging                             <ul style="list-style-type: none"> <li>Malignant neoplasm of the hilus of right lung was reported.</li> <li>Staging: stage IIIB (cT3 cN2 cM0).</li> </ul> </li> <li>Molecular testing                             <ul style="list-style-type: none"> <li>EGFR, negative (IHC; L858R and exon 19 deletion); ALK, negative (IHC); PD-L1, negative (IHC)</li> <li><i>KRAS</i> mutation (c.34G&gt;T)</li> <li><i>FGFR1</i> amplification</li> </ul> </li> </ul>
Treatment	<ul style="list-style-type: none"> <li>3 cycles of carboplatin/pemetrexed/nivolumab were given.</li> <li>AE event of dry eyes only was reported.</li> <li>Surgery was performed via robotic resection.</li> </ul>

AJCC, American Joint Committee on Cancer; DL<sub>CO</sub>, diffusing capacity of the lungs for carbon monoxide; DOE, dyspnea on exertion; FEV<sub>1</sub>, forced expiratory volume in 1 sec; IHC, immunohistochemistry; PD-L1-, PD-L1 negative; PFTs, pulmonary function tests.

importance of conducting EGFR testing up front, especially when using IO as induction therapy. **Haiying Cheng, MD, PhD**, expressed that, at minimum, EGFR molecular testing is performed for all newly diagnosed NSCLC at her practice site. She highlighted the importance of assessing PD-L1 expression to guide the approach to treatment. If tumor PD-L1 expression is negative, then the patient may not benefit from IO in the adjuvant

setting. If *EGFR* mutations are present, the patient may benefit from future treatment with adjuvant osimertinib. At some practice sites, PD-L1 expression is reassessed after surgery to validate prior testing and identify potential tumor heterogeneity.

**Arbour** expressed that obtaining a surgery consult regarding tumor resectability may also be helpful in guiding treatment decisions. If the tumor is unresectable or

unlikely unresectable, then it may require treatment with such other options as definitive concurrent chemoradiation therapy and IO. She further noted that anticipated survival data from the correlative analyses of CheckMate 816 (NCT02998528) and other neoadjuvant IO studies will be incredibly important in helping to drive treatment decisions and provide insight regarding therapeutic strategies in the neoadjuvant setting and interpretation of the surgical results.

The phase 3 CheckMate 816 study evaluated neoadjuvant therapy with either platinum-doublet chemotherapy alone or in combination with nivolumab prior to tumor resection.<sup>1</sup> At a minimum follow-up of 21 months, median event-free survival (EFS) with nivolumab vs chemotherapy alone was 31.6 vs 20.8 months (HR, 0.63;  $P = .005$ ), and the percentage of patients with a pathological complete response (pCR) was 24.0% vs 2.2% (odds ratio [OR], 13.9;  $P < .001$ ).<sup>1</sup> Data are not yet mature, but the trend across most subgroups was toward improved survival with nivolumab vs chemotherapy alone.

The faculty agreed that borderline resectable patients pose a challenge for clinicians. **Arbour** suggested 2 options for patients with advanced disease: neoadjuvant therapy followed by attempted resection or definitive concurrent chemoradiotherapy followed by IO. **Arbour** was concerned about patients who are not resectable receiving chemotherapy-IO upfront. **Pass** recommended a surgical option if the mass is bulky and there is a chance of removing it and clearing the disease. Surgical expertise is important in this setting.

### IMMUNOTHERAPY-BASED STRATEGIES IN HIV-POSITIVE PATIENTS WITH NSCLC

Due to the presence of HIV infection and psoriatic arthritis in this patient, there was some initial hesitancy in using an IO-based treatment

approach. **Pass** noted the need for a multidisciplinary approach in this setting with consults from rheumatology and HIV disease specialists. Although literature is relatively limited, case reports have demonstrated safe and potentially effective use of pembrolizumab and nivolumab in patients living with HIV (PLWH) with NSCLC.<sup>2</sup> **Pass** presented several small studies that provide further insight regarding the use of IO in this treatment setting.

The phase 2 IFCT-1602 CHIVA2 study (EudraCT: 2016-003796-22) evaluated nivolumab following initial chemotherapy in PLWH with stage IIIB or IV NSCLC.<sup>3</sup> All patients ( $N = 16$ ) were smokers, and 63% had adenocarcinoma; PD-L1 expression was positive in 36% of tumors. The reported disease control rate was 62.5%, and median progression-free survival (PFS) and overall survival (OS) were 3.4 months and 10.9 months, respectively. Treatment-related AEs occurred in 75% of patients, and they were primarily grade 1 and 2. Investigators concluded that nivolumab following chemotherapy was beneficial and well-tolerated in PLWH with NSCLC.

A systematic review, including 21 PLWH with nonsquamous or squamous NSCLC who received IO (nivolumab, 76.8%; pembrolizumab, 21.4%; atezolizumab, 1.8%), demonstrated overall response rates similar to those observed in the general population (PLWH, 25.9%; nonsquamous, 19.0%; squamous, 20.0%), with the majority of AEs reported as grade 1 or 2.<sup>4</sup> Investigators concluded that IO appears to be feasible in PLWH and that it offers safety and efficacy that are comparable to those noted in the general population of patients with advanced cancers.

**Arbour** noted, “[These] highlight the need for clinical trials to be actively enrolling patients with HIV who are well-controlled.” **Sabari** suggested that the use of CTLA-4 inhibitors may

be a potential option in this treatment setting and should be explored in future clinical studies.

### CLINICAL SCENARIO 2: METASTATIC PD-L1-NEGATIVE NSCLC

**Cheng** presented the case of a 72-year-old man who was a smoker; he had multiple comorbidities and a history of resected right lower lobe lung adenocarcinoma (**TABLE 2**). In October 2020, the patient was found to have fluorodeoxyglucose (FDG)-avid right lower mass without FDG-avid mediastinal or hilar lymphadenopathy. A bronchoscopy with biopsy showed no adenocarcinoma, a PD-L1 tumor proportion score (TPS) of 0%, and no actionable alterations. Surgical staging revealed a positive subcarinal lymph node, resulting in the decision to delay the surgical resection for the T3N2, stage IIIB disease.

The patient was enrolled in a clinical trial. He received 1 cycle of neoadjuvant cisplatin, pemetrexed, and pembrolizumab; however, due to a persistent, stage G1 decreased creatinine clearance, as well as grade 3 neutropenia and gastrointestinal bleeding, treatment was discontinued. A right lower lobe lobectomy and mediastinal lymph node dissection were performed, revealing persistent stage IIIB disease with positive lymph node at stations 11R and 7. Adjuvant monotherapy with pembrolizumab was believed to be insufficient, and baseline neuropathy and decreased creatinine clearance ( $< 45$  mL/min) excluded chemotherapy options. Therefore, the tumor board recommended that proton beam radiotherapy be given. After 3 months, the patient presented with bone pain, and results of PET/CT scans suggested recurrent metastatic disease with new intensity on FDG-avid soft density surrounding the right middle lobe bronchus and FDG-avid bony lesions. Biopsy of the lesion and subcarinal lymph node revealed adenocarcinoma.

**TABLE 2.**  
CLINICAL SCENARIO 2: METASTATIC PD-L1-NEGATIVE NSCLC

Presented by Haiying Cheng, MD, PhD

Patient profile	<ul style="list-style-type: none"> <li>72-year-old man</li> </ul>
Clinical presentation	<ul style="list-style-type: none"> <li>Bone pain</li> </ul>
Medical history	<ul style="list-style-type: none"> <li>Significant comorbidities included CAD, COPD, DM, HTN, and HLD.</li> <li>Patient underwent resection of right lower lobe lung adenocarcinoma.</li> <li>An FDG-avid right lower mass without FDG-avid mediastinal or hilar lymphadenopathy was noted.</li> <li>Smoker (50 pack-year history)</li> </ul>
Evaluation	<ul style="list-style-type: none"> <li>PET/CT scans revealed recurrent metastatic disease.                             <ul style="list-style-type: none"> <li>New intensity was noted on FDG-avid soft density surrounding the right middle lobe bronchus and FDG-avid bony lesions.</li> </ul> </li> <li>Biopsy of the lesion and lymph node revealed adenocarcinoma.</li> <li>PD-L1 TPS was 0%.</li> <li>NGS is pending.</li> </ul>
Treatment	<ul style="list-style-type: none"> <li>Clinical trial (≈ 3 months prior) involved 1 cycle of neoadjuvant cisplatin, pemetrexed, and pembrolizumab.</li> <li>Proton beam RT was given 3 months prior.</li> <li>Docetaxel has been given weekly while NGS results are expected.</li> </ul>

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; FDG, fluorodeoxyglucose; HTN, hypertension; HLD, hyperlipidemia; NGS, next-generation sequencing; RT, radiation therapy; TPS, tumor proportion score.

### TREATMENT APPROACHES FOR RECURRENT, PD-L1-NEGATIVE NSCLC

With next-generation sequencing (NGS) results pending, faculty were asked to comment on potential treatment options. **Cheng** discussed potential study regimens briefly and reviewed key trial data. In the PD-L1-negative subgroup of the KEYNOTE-189 trial (NCT02578680), first-line pembrolizumab plus standard-of-care platinum-doublet chemotherapy (cisplatin or carboplatin plus pemetrexed) followed by pembrolizumab and pemetrexed maintenance for up to 2 years resulted in an objective response rate (ORR) of 33% vs 14% in the chemotherapy group (median OS, 17.2 vs 10.2 months, respectively).<sup>5,6</sup>

If a paclitaxel-containing platinum-doublet is preferred, the IMpower130 study (NCT02367781) regimen (atezolizumab plus carboplatin and nab-paclitaxel) has elicited favorable

outcomes in patients with PD-L1-negative NSCLC, and it may be an option.<sup>5,7</sup> In squamous NSCLC, pembrolizumab plus carboplatin and nab-paclitaxel is also associated with a favorable OS outcome in patients having PD-L1 TPS less than 1%, as revealed in the KEYNOTE-407 trial (NCT02775435).<sup>5,8</sup>

Nivolumab plus ipilimumab is not an approved regimen in this case, but it may be a potential option, based on data from the PD-L1-negative cohort of the CheckMate-227 trial (NCT02477826).<sup>5,9</sup> Similarly, the CheckMate-9LA (NCT03215706) regimen, nivolumab and ipilimumab plus chemotherapy has demonstrated favorable OS in the subgroup having PD-L1 TPS less than 1%, and it is approved for the treatment of both squamous and nonsquamous NSCLC.<sup>5,10</sup>

Given the complications noted with use of the trial regimen and persisting concerns involving kidney function, **Arbour** expressed that the

patient would have difficulty with most regimens that included chemotherapy. However, she noted that in patients with PD-L1-negative NSCLC, she typically opts for the KEYNOTE-189 regimen. **Cheng** agreed with this approach for treating nonsquamous disease, with the KEYNOTE-407 regimen preferred in patients with squamous disease. **Arbour** further expressed that because taxanes are generally challenging to tolerate for most patients with potential for early development of neuropathy, she would be hesitant with use a taxane-containing regimen.

Some participants expressed that, in practice, they have had disappointing results with nivolumab and ipilimumab combination regimens. **Arbour** added that the chemotherapy associated with Checkmate-227 and -9LA regimens can be difficult for patients to tolerate. Considering the longer follow-up data from KEYNOTE-189 that demonstrates a continued OS benefit among patients with PD-L1 negative NSCLC, as well as a more favorable tolerability with pemetrexed maintenance therapy, the faculty agreed that an approach using carboplatin, pemetrexed, and pembrolizumab would be most appropriate.

### CLINICAL SCENARIO 3: METASTATIC NSCLC WITH PD-L1 TPS OF 1-49%

**Sabari** presented the case of a 59-year-old man; he is a smoker with a history of hypertension and asthma (**TABLE 3**). He presents with worsening upper left back and chest pain accompanied by a productive cough. He lost 5 to 10 pounds over 9 months. PET and CT imaging show high FDG uptake in a left upper lung mass that extended into the mediastinum with involvement of the pleura and third left rib. Biopsy demonstrated the majority of tumor cells to be TTF1-positive and napsin-A-negative, with some focally positive for P40. Pathology testing was negative for *EGFR*

and *ALK* mutations with low PD-L1 expression (1%-4%).

### IMMUNOTHERAPY-BASED TREATMENT APPROACHES IN PD-L1-LOW NSCLC

**Arbour** discussed the differences in treating patients with low PD-L1 expression (1%-4%) compared with those on the higher end of the spectrum (25%-49%). In patients with a PD-L1 TPS of 40% who develop toxicities to chemotherapy while receiving a combination regimen of carboplatin, pemetrexed, and pembrolizumab, the clinician should consider stopping maintenance pemetrexed and using pembrolizumab as monotherapy. However, for a patient with a PD-L1 TPS of 1%, she

recommends continuing chemotherapy plus IO and implementing dose reductions and schedule modifications to manage the chemotherapy-based toxicities, as administration of IO alone may not be sufficient in this patient population.

**Cheng** recommended chemotherapy-IO based on the KEYNOTE-189 regimen for patients with PD-L1 expression of 1% to 49%. If the patient is frail with a performance status of 2 or higher, IO monotherapy should be considered.

The randomized, double-blind, phase 3 KEYNOTE-189 study evaluated pemetrexed-platinum chemotherapy given alone or in combination with pembrolizumab in patients with metastatic NSCLC without sensitizing *EGFR* or *ALK* alterations.<sup>11</sup> Patients

were stratified according to PD-L1 TPS (< 1%, 1%-49%, and ≥ 50%), with roughly one-third of patients having a PD-L1 TPS below 1%.<sup>11</sup> The projected 24-month OS and PFS rates were higher in the pembrolizumab group vs the placebo group (OS, 45.5% vs 29.9%, respectively; PFS, 20.5% vs 1.5%), as were the median OS (22.0 vs 10.7 months) and PFS (9.0 vs 4.9 months).<sup>11</sup> Any-cause AEs were reported in the majority of patients in both the pembrolizumab and placebo arms (99.8% vs 99.0%), with a greater number of grade 3 or greater AEs observed in patients receiving combination therapy (71.9% vs 66.8%).<sup>11</sup>

**Arbour** and **Sabari** agreed that pemetrexed maintenance therapy is important for this patient. However, **Arbour** noted that, in practice, she often receives second opinion referrals for patients who are receiving IO alone in the maintenance setting and are not being continued on maintenance pemetrexed. According to **Sabari**, the only reasons that he would typically discontinue pemetrexed in the maintenance setting is for renal toxicity or if the patient had a complete response and is really doing well.

### APPROACHES TO FOLLOW-UP MONITORING WITH IMMUNOTHERAPY IN THE MAINTENANCE TREATMENT SETTING

Faculty discussed the importance of when to perform follow-up imaging patient for patients receiving IO. **Sabari** expressed that the presence of symptoms plays a significant role here. Nine- or 12-week scans with IO are sensible and common. The worry for clinicians is whether they are prematurely discontinuing a particular therapeutic agent. Six-week scans are sometimes performed in the community, although this is not recommended. **Arbour** pointed out that progression observed at 9 or 12 weeks is less likely to be pseudo-progression. If a patient is feeling well on IO at 9 weeks and has

**TABLE 3.**  
CLINICAL SCENARIO 3: METASTATIC NSCLC WITH PD-L1 TPS OF 1%-49%

*Presented by Joshua K. Sabari, MD*

Patient profile	<ul style="list-style-type: none"> <li>59-year-old man</li> </ul>
Clinical presentation	<ul style="list-style-type: none"> <li>Upper left back and left-sided chest pain were experienced for the past 9 mo), worsening over the past 2 weeks.</li> <li>Patient was unable to sleep at night due to pain and pressure on left upper back.</li> <li>Over the past 9 months, the patient experienced productive cough and weight loss of 5-10 pounds.</li> </ul>
Medical history	<ul style="list-style-type: none"> <li>Hypertension</li> <li>Asthma</li> <li>Over 35 years of smoking history</li> </ul>
Evaluation	<ul style="list-style-type: none"> <li>PET/CT scan                             <ul style="list-style-type: none"> <li>High FDG uptake in the left upper lobe mass extended into the mediastinum and involved the pleura and third left rib.</li> <li>Few foci of increased uptake were found in the ribs.</li> </ul> </li> <li>Biopsy                             <ul style="list-style-type: none"> <li>Most tumor cells were positive for TTF1; some were focally positive for P40.</li> <li>Results were negative for napsin-A.</li> <li>Results favored adenocarcinoma of lung origin.</li> </ul> </li> <li>Pathology testing                             <ul style="list-style-type: none"> <li>EGFR-L858R (IHC; point mutation in exon 21): negative</li> <li>EGFR-E746_A750del (IHC; 15 base pair deletion in exon 19): negative</li> <li>ALK (IHC; clone D5F3): negative</li> <li>PD-L1 (clone 22C3) TPS was 1%-4% (low expression).</li> </ul> </li> </ul>
Treatment	<ul style="list-style-type: none"> <li>2 cycles of pemetrexed/carboplatin/pembrolizumab were given, followed by palliative chemotherapy/RT to the mass.</li> <li>Patient had been on maintenance pemetrexed/pembrolizumab for 11 cycles.</li> </ul>

FDG, fluorodeoxyglucose; IHC, immunohistochemistry; RT, radiotherapy.

mild progression, continuing the IO for a short while may be a sensible approach. However, if progression is rapid with disease advancements observed at 9 weeks, **Sabari** recommended discontinuing IO and initiating an alternative treatment regimen.

### CLINICAL SCENARIO 4: METASTATIC NSCLC WITH HIGH PD-L1 EXPRESSION

**Arbour** presented the case of a 78-year-old man with a history of non-Hodgkin lymphoma. He has no abnormalities detected; he was treated about 5 or 6 years ago, and his lymphoma was cured. The patient has a history of smoking, chronic urticaria, and coronary artery disease. He presented with worsening abdominal pain and chest wall pain. Initially, it was suspected that his lymphoma recurred, even though he had completed therapy about 5 years ago. Routine monitoring with CT scans performed every 6 months were negative until the most recent scan, which showed the sudden emergence of a 4.8-cm tumor. PET scan revealed hypermetabolic left upper lobe lesion pleural thickening and loculated pleural effusion. MRI was negative for metastatic disease. Biopsy of the left upper lobe lesion showed non-small cell adenocarcinoma with pleomorphic features. His PD-L1 score was 80%. The focus was systemic therapy. NGS testing revealed he had a *KRAS G12C* mutation but no alterations in *TP53*, *STK11*, or *KEAP1*.

### FIRST-LINE TREATMENT STRATEGIES FOR PD-L1 HIGH NSCLC WITH AUTOIMMUNE COMORBIDITIES

Given the patient's PD-L1 TPS of 80%, faculty discussed *KRAS G12C*-mutant NSCLC and potential treatment options, including IO with pembrolizumab, *KRAS G12C* inhibitors, and chemotherapy. Safety is a key consideration in IO treatment selection in the NSCLC population with comorbid autoimmune disease

**TABLE 4.**  
CLINICAL SCENARIO 4: METASTATIC NSCLC WITH HIGH PD-L1 EXPRESSION

Presented by Kathryn C. Arbour, MD

Patient profile	<ul style="list-style-type: none"> <li>78-year-old man</li> </ul>
Clinical presentation	<ul style="list-style-type: none"> <li>Worsening abdominal pain</li> <li>Chest wall pain</li> </ul>
Medical history	<ul style="list-style-type: none"> <li>Non-Hodgkin lymphoma treated and cured 5-6 years prior.</li> <li>Chronic urticaria (controlled with dupilumab injections)</li> <li>CAD</li> <li>Former smoker (70 pack-year history)</li> </ul>
Evaluation	<ul style="list-style-type: none"> <li>Routine CT scans revealed a 4.8-cm tumor.</li> <li>PET scan showed hypermetabolic left upper lobe lesion, pleural thickening, and loculated pleural effusion.</li> <li>MRI was negative for metastatic disease.</li> <li>Biopsy of the left upper lobe revealed non-small cell adenocarcinoma.</li> <li>PD-L1 TPS was 80%.</li> <li>NGS testing revealed a <i>KRAS G12C</i> mutation but no alterations in <i>TP53</i>, <i>STK11</i>, or <i>KEAP1</i>.</li> </ul>
Treatment	<p>Carboplatin/pemetrexed Opted for second-line pembrolizumab (restaging scans are pending).</p>

CAD, coronary artery disease; NGS, next-generation sequencing.

(AID).<sup>12,13</sup> Due to the widespread use of PD-L1 inhibitors and the incidence of AID (including dermatological conditions) in the NSCLC patient population, a large study assessed the toxicity profile of anti-PD-L1 therapies in this patient population. Results showed that 55% of patients experienced a worsening of their conditions, but most symptoms were manageable; only 14% of patients had their IO permanently discontinued.<sup>12</sup> **Arbour** noted that AID was well-controlled in the majority of patients who participated in these trials; they were not receiving chronic therapy with immunosuppressive agents. The faculty pointed out the importance of considering factors, such as the type of AID, the associated treatment, and the status of disease control. **Cheng** expressed successful use of IO in patients with well-controlled AID (eg, rheumatoid arthritis, inflammatory bowel disease) who were not receiving clinically significant disease-modifying agents. However,

faculty agreed that conditions such as ILD require greater caution when considering IO, noting the potential for significant irreparable harm that could negatively affect patient quality of life.

Direct *KRAS* inhibitors produce responses in approximately 35% to 45% of patients with *KRAS G12C* mutations.<sup>14</sup> Although a *KRAS G12C* inhibitor could be used before IO in this patient, **Arbour** was concerned about getting the patient into a trial with such an aggressive tumor.<sup>14</sup>

Because the patient was receiving treatment for chronic urticaria with the IO agent dupilumab, there was some concern about a blunted initial response to IO. The patient was ineligible to participate in ongoing *KRAS* inhibitor trials due to the *STK11*-negative and PD-L1-high tumor status. Therefore, **Arbour** opted to initiate the patient on a chemotherapy regimen including carboplatin and pemetrexed. Initial scans after 2 cycles showed a response to therapy. However, the patient subsequently developed renal

insufficiency, fatigue, and cytopenia and required dose reductions; follow-up CT imaging revealed further disease progression. KRAS inhibitors have provided less durable responses compared with IO. Therefore, second-line treatment was initiated with 2 cycles of IO and sotorasib was reserved for third-line treatment. Following completion of the second cycle, scans showed a 40% reduction in tumor size. Dupilumab was continued, and the patient is currently receiving routine monitoring.

**Arbour** expressed that her general approach to the treatment of patients with nonaggressive, PD-L1–high NSCLC is typically single-agent IO, whereas a combination approach with chemotherapy is preferred in patients with aggressive disease. **Cheng** also opts for a combination approach using pembrolizumab plus chemotherapy in patients with squamous NSCLC. **Sabari** agreed but advised caution when using combination regimens in older patients or those with significant comorbidities or smoking history. Because disease progression can occur in some patients receiving single-agent IO, **Arbour** noted the importance of closely monitoring for clinical symptoms following treatment initiation and performing reimaging after 2 cycles.

## LOOKING AHEAD

Faculty concluded by outlining some important lessons learned and things to keep in mind for many distinct patient subgroups with NSCLC. The importance of early EGFR and PD-L1 testing to guide treatment in the neoadjuvant setting was emphasized. The faculty acknowledged that data are still inadequate for some other clinical scenarios and stressed that patient

enrollment in clinical trials is crucial for bridging knowledge gaps in the therapeutic landscape. ■

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