

NCCN Guidelines Updates: New Immunotherapy Strategies for Improving Outcomes in Non–Small Cell Lung Cancer

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ABSTRACT

For the use of immunotherapy in metastatic non–small cell lung cancer (NSCLC), the NCCN Guidelines for NSCLC reflect the importance of assessing levels of PD-L1 expression to determine the best use of PD-1/PD-L1 inhibitors, whether alone or in combination with chemotherapy. Patients who lack a driver mutation and have tumor PD-L1 expression $\geq 50\%$ are recommended to receive single-agent pembrolizumab, although combining with carboplatin/pemetrexed is also a reasonable choice, especially if there is higher burden of disease. For tumors with PD-L1 expression $< 50\%$, it is important to distinguish between nonsquamous and squamous cell carcinoma (SCC). For patients with non-SCC disease, pembrolizumab + carboplatin/pemetrexed is preferred. Alternately, a 4-drug regimen of carboplatin/paclitaxel/bevacizumab/atezolizumab is reasonable, especially for patients ineligible for pemetrexed. In patients with SCC, carboplatin + paclitaxel or nab-paclitaxel with pembrolizumab is a category 1 recommendation. Tumor mutational burden is emerging as a biomarker for efficacy but is not yet ready to be used in patient selection. Optimal management of the unique toxicities associated with immunotherapy, which can be more frequent with these combinations, is also critical for good outcomes.

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Expression of PD-L1 is the key determinant for frontline immunotherapy selection in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non–Small Cell Lung Cancer (NSCLC) because patients can benefit greatly from PD-1/PD-L1 inhibitors, according to Matthew A. Gubens, MD, MS, Associate Professor of Medicine, Division of Hematology/Oncology, University of California, San Francisco, and treating physician at UCSF Helen Diller Family Comprehensive Cancer Center. Dr. Gubens discussed updates to the NCCN Guidelines based on 2018 data from KEYNOTE-189, KEYNOTE-407, and IMpower150. In his presentation, Dr. Gubens focused on the significance of the 50% PD-L1 threshold and treatment according to histology.

Dr. Gubens was joined by Marianne Davies, DNP, CNS, ACNP-BC, AOCNP, Assistant Professor of Nursing, Yale University, and Thoracic Oncology Nurse Practitioner. Dr. Davies discussed toxicities related to immunotherapy in NSCLC, focusing on the management of pneumonitis.

PD-1/PD-L1

PD-L1 Testing for Treatment in the First Line

“PD-L1 testing is important for determining the appropriateness of single-agent immunotherapy in the first line,” Dr. Gubens said. Although not an optimal

biomarker, PD-L1 expression is currently the best one for assessing whether patients are candidates for PD-1/PD-L1 inhibitors alone versus in combination, the NCCN panel emphasized in the guidelines.

Two pivotal studies that evaluated first-line single-agent PD-1 inhibitors, both originally presented at the 2016 ESMO Congress, helped establish the PD-L1 cut point for use of single-agent immunotherapy in the first line: KEYNOTE-024 evaluated pembrolizumab in patients with PD-L1 expression $\geq 50\%$, producing positive results,¹ and CheckMate 026 evaluated nivolumab in patients with $\geq 5\%$ PD-L1 expression, with negative results.²

Use of first-line immunotherapy is restricted to patients without *EGFR* or *ALK* mutations, Dr. Gubens reminded listeners, because even with high PD-L1 expression these patients tend to have much poorer outcomes with single-agent immunotherapy.

PD-L1 Expression $\geq 50\%$

In KEYNOTE-024, pembrolizumab more than doubled median overall survival (mOS) compared with chemotherapy for patients with PD-L1 expression $\geq 50\%$, improving mOS to 30.0 from 14.2 months with chemotherapy (hazard ratio [HR], 0.63; $P = .002$).³ This finding showed PD-L1 expression $\geq 50\%$ to be a critical

cut point in selecting candidates for pembrolizumab and elevated single-agent pembrolizumab, for both adenocarcinoma and squamous cell carcinoma (SCC), as the panel's preferred first-line option (category 1) when PD-L1 expression is $\geq 50\%$.

Chemotherapy + pembrolizumab (or atezolizumab + bevacizumab) is also a category 1 recommendation suitable for select patients with high PD-L1 expression (ie, those with a high disease or symptom burden), with KEYNOTE-189 showing improved OS compared with chemotherapy alone.⁴ Although this regimen carries greater toxicity than pembrolizumab alone, clinicians and patients may consider it important to take their best shot early. "I worry that some patients may not get to the second line if I don't get chemotherapy in upfront," he said, with admittedly cross-trial comparisons suggesting a higher response rate with the combination in those with PD-L1 expression $\geq 50\%$. This option represents an addition to the NCCN Guidelines.

PD-L1 Expression <50%

At this time, single-agent pembrolizumab is *not* currently recommended in the NCCN Guidelines as frontline treatment for patients with NSCLC and PD-L1 expression <50%, although it is FDA approved in this setting based on data from the phase III KEYNOTE-042 trial.⁵

"In the subset of patients with $\geq 50\%$ expression, such as those in KEYNOTE-024, there was benefit for pembrolizumab. But, in those with 1% to 49% expression, there was no significant benefit for pembrolizumab versus chemotherapy," Dr. Gubens noted. "Even though it was a positive study overall, the panel has not adopted pembrolizumab as a recommendation for this subset of patients with PD-L1 expression of 1% to 49%."

For patients with PD-L1 expression of <50%, the panel added pembrolizumab/pemetrexed and either cisplatin or carboplatin as a preferred category 1 initial systemic therapy option. This recommendation is based on results of the phase III KEYNOTE-189 trial, in which this regimen reduced the risk of death by 51% versus chemotherapy alone.⁴ mOS was not reached in the pembrolizumab cohort compared with 11.3 months for chemotherapy ($P < .001$). Although survival was more pronounced in patients with $\geq 50\%$ PD-L1 expression, the benefit with pembrolizumab was observed across PD-L1 subgroups, including subsets with expression of <1% and 1% to 49%. These findings led to full approval of this chemotherapy and pembrolizumab regimen in this setting in August 2018.

Another key frontline immunotherapy option for patients with non-SCC NSCLC (especially those who are pemetrexed-ineligible) is the 4-drug regimen of atezolizumab/carboplatin/paclitaxel/bevacizumab (category 1). This recommendation is based on the IMpower150 trial that showed a 22% reduction in risk of death

when atezolizumab was given with chemotherapy versus chemotherapy alone ($P = .0164$).⁶ "At every level of PD-L1 expression, we saw a robust HR and a separation in the curves, which led to FDA approval in December 2018," Dr. Gubens said.

Immunotherapy Options for Patients With SCC

For patients with SCC NSCLC, the preferred category 1 recommendation for first-line treatment is pembrolizumab/carboplatin with either paclitaxel or nab-paclitaxel, a regimen that was FDA-approved in October 2018. The approval and NCCN recommendation are based on "exciting" results of the phase III KEYNOTE-407 trial.⁷ Pembrolizumab plus chemotherapy reduced the risk of death by 36% compared with chemotherapy alone, with mOS of 15.9 and 11.3 months, respectively ($P = .0017$). Benefit was observed regardless of PD-L1 expression level, choice of taxane, age, sex, or performance status.

"So, a compelling case can be made for platinum therapy plus chemotherapy along with pemetrexed and pembrolizumab in these patients," he said. "This is an important advance in the care of this patient population."

Driver Mutations and Immunotherapy

Patients with *EGFR* and other driver mutations consistently achieve minimal benefit from single-agent immunotherapies, as recently demonstrated in a 2018 meta-analysis of studies comparing PD-1/PD-L1 inhibitors versus docetaxel in *EGFR*-mutated NSCLC.⁸ Lack of response is seen even when patients with *EGFR* mutations exhibit high levels of PD-L1 expression. Some evidence shows, however, that the addition of bevacizumab to chemotherapy (carboplatin/paclitaxel) + atezolizumab, as in IMpower150, improves outcomes for patients with *EGFR/ALK*-positive disease.

"This suggests that there's some interplay between bevacizumab and immunotherapy," Dr. Gubens commented. Although he has used this 4-drug regimen in some patients with *EGFR*-positive disease, he stated that it is not yet FDA-approved for *EGFR*- and *ALK*-positive disease.

Summary of First-Line Recommendations

Summing up, Dr. Gubens emphasized that the choice of first-line treatment for metastatic NSCLC first hinges on the level of PD-L1 expression (Figure 1) and whether patients have a driver mutation, because those with the latter should always receive targeted therapy first, not immunotherapy. Patients with $\geq 50\%$ PD-L1 expression are recommended to receive pembrolizumab as a single-agent, although those with higher disease burden or symptomatic burden may benefit also from up-front combination with carboplatin/pemetrexed, which may result in higher response rates.

PD-L1 expression $\geq 50\%$	PD-L1 expression $< 50\%$
<ul style="list-style-type: none"> • Pembro preferred • Chemo + pembro also category 1, and with higher response rate –Consider for higher disease burden –Consider for higher symptom burden –?Consider for fitter patients 	<ul style="list-style-type: none"> • Nonsquamous –Carbo, pemetrexed, pembro preferred –Carbo, paclitaxel, bev, and atezolizumab also category 1, perhaps for non-pemetrexed-eligible • Squamous –Carbo, paclitaxel or nab-paclitaxel and pembro also category 1

▪**Driver mutations:** Targeted therapy, NOT immunotherapy!

Figure 1. Summary of first-line treatment recommendations. Abbreviations: bev, bevacizumab; carbo, carboplatin; chemo, chemotherapy; pembro, pembrolizumab.

For patients with PD-L1 expression $< 50\%$, it is important to distinguish non-SCC from SCC. For those with non-SCC disease, carboplatin/pemetrexed/pembrolizumab is the preferred option. “Category 1 data for this regimen are excellent, and a survival benefit has been proven across PD-L1 expression levels, including 0%,” he noted.

Carboplatin/paclitaxel/bevacizumab/atezolizumab is also reasonable, especially for patients ineligible for pemetrexed, with some evidence showing it might also be helpful in the *EGFR* and *ALK* setting after completion of appropriate targeted therapy, a population not included in the KEYNOTE trials. For patients with SCC, carboplatin + paclitaxel or nab-paclitaxel with pembrolizumab is a category 1 recommendation. These recommendations reflect the addition of 2018 data, Dr. Gubens said.

Biomarker Testing for PD-L1

Emerging biomarkers could soon join PD-L1 expression testing as a way to select patients for immunotherapies and to serially monitor patients over time. “PD-L1 testing could be archaic in 5 years,” he said. Meanwhile, PD-L1 testing remains the only validated biomarker, and one of the issues for clinicians is determining which test to use. Some wonder, he said, whether any proprietary assay can be used on any PD-1/PD-L1 inhibitor.

According to Dr. Gubens, there is good association among the current tests except for SP142 (companion diagnostic for atezolizumab; F. Hoffmann-La Roche Ltd), based on the Blueprint Project by the International Association for the Study of Lung Cancer (IASLC) that showed 3 of the 4 tests “tracked nicely,” with the outlier being SP142.⁹ “It’s reasonable to use any of the other 3 tests for patient selection,” he said.

Biomarkers Beyond PD-L1: Tumor Mutational Burden

An “up and coming” biomarker is tumor mutational burden (TMB), which reflects the accumulation of

somatic mutations. TMB corresponds with response to immunotherapy in some studies.

The 2018 CheckMate 227 study enrolled 1,739 treatment-naïve patients with metastatic NSCLC and no known driver mutations.¹⁰ There were 2 cohorts in this study, those with PD-L1 expression of $\geq 1\%$ and of $< 1\%$, and they were randomized to various immunotherapy arms. High TMB (≥ 10 mutations/Mb) was associated with significantly improved outcomes with nivolumab/ipilimumab, with 1-year progression-free survival of 43% versus 13% for chemotherapy (HR, 0.58; $P = .0002$). For patients with lower TMB, immunotherapy was not superior. Other studies have measured TMB in the blood and produced similar results for treatment with atezolizumab.¹¹

The NCCN Guidelines currently note that TMB is “an evolving biomarker that may be helpful in selecting patients for immunotherapy.” Additional factors in the tumor microenvironment that reflect its immunogenicity could also emerge as biomarkers, as well as host factors, and these might also be useful to evaluate in a serial fashion before, during, and after immunotherapy. As Dr. Gubens predicted, “That’s the future of biomarker testing, which has the potential to enable precision immuno-oncology.”

Management of Immune-Related Toxicities

The increasing use of PD-1/PD-L1 inhibitors in combination with chemotherapy portends for more immune-related adverse events (irAEs). Although these are usually low-grade irAEs, they can escalate quickly, and high-grade toxicities require prompt and appropriate management, as described in the NCCN Guidelines. The guidelines also encourage clinicians to rule out other causes of AEs and to collaborate with specialists in severe cases. “We used to consider this intuitive, but now we are calling out this point,” Dr. Davies said.

“It can be challenging to determine the causative agent, especially with combination therapy,” she explained. Clinicians should call upon their “differential skills,” looking at onset, variability, and pattern over time. For example, although low-grade nephritis is rare, when a platinum chemotherapy agent is used, the risk increases. Therefore, is the patient’s nephritis an irAE or due to the platinum? By properly deciphering this, it may be possible to eliminate the platinum but keep the patient on pemetrexed and pembrolizumab, rather than discontinue treatment altogether.

Toxicities Related to NSCLC Treatment

The predominance of each irAE varies by cancer type. In NSCLC, pneumonitis occurs more frequently and earlier than in some other diseases. Endocrinopathies, rash, and colitis also occur more frequently.

In the pivotal KEYNOTE-024 trial, grade ≥ 3 toxicities of any type were less frequent with pembrolizumab

Adverse Events	Chemotherapy	PD-1/PD-L1
Overall	86.08%	66.20%
High-grade	43.53%	14.26%
Treatment discontinuation	13.92%	5.94%
Toxic deaths	1.12%	.48%
Fatigue, all grade	30.83%	18.75%
Rash, irAE	2.76%	5.77%
Colitis, irAE	0%	0.70%
Hypothyroidism, irAE	0.23%	4.89%
Pneumonitis, irAE	0.65%	3.21%
Hepatic, irAE	0.89%	1.85%

Figure 2. Frequent toxicities experienced by patients with non-small cell lung cancer in a meta-analysis of 4,413 patients from 8 trials. Abbreviation: irAE, immune-related adverse event. Data from Luo W, Wang Z, Tian P, Li W. Safety and tolerability of PD-1/PD-L1 inhibitors in the treatment of non-small cell lung cancer: a meta-analysis of randomized controlled trials. *J Cancer Res Clin Oncol* 2018;144:1851-1859.

(26.6%) than with chemotherapy (53.3%), but severe irAEs occurred in 9.7% and 0.7% of patients, respectively.¹ Severe irAEs primarily included pneumonitis (2.6%), severe skin reaction (3.9%), and colitis (1.3%). In IMpower150,

grade 3-4 toxicities with atezolizumab and chemotherapy included rash (2.3%), transaminase elevations (4.1%), pneumonitis (1.5%), colitis (1.3%), and hypothyroidism (0.3%).⁶

In the adjuvant setting, clinicians should be aware of toxicities that can develop when durvalumab is given after chemotherapy and radiation, especially pneumonitis, which was determined to be immune-related in 12.6% of patients in the pivotal phase III PACIFIC trial.¹² Clinicians should be aware that pneumonitis needs to be deciphered from radiation-related pneumonitis, Dr. Davies advised.

An overview of frequent toxicities was recently published in a meta-analysis,¹³ which examined 8 studies of pembrolizumab (n=3), nivolumab (n=3), and atezolizumab (n=2) in NSCLC (Figure 2).

NCCN Recommendations for Managing Pneumonitis

Dr. Davies described the management of pneumonitis, which is a potentially severe irAE of particular interest in NSCLC. As with all irAEs, the key elements of management include prevention, detection (ie, ruling out other causes), monitoring, and treatment (Figure 3).

“Patients often come in with very subtle symptoms. We encourage everyone to obtain a baseline oxygen

Pulmonary Adverse Events

Prevent/Anticipate	Detect/Monitor	Treat/Management
Smoking cessation, vaccinations Dyspnea, dry cough, wheezing, tachypnea, tachycardia, hypoxia, increased oxygen requirements Chest pain Increased risk with prior chest radiation and chemotherapy	Rule out other causes: infection, disease progression, pulmonary embolism, pleural effusion, sarcoidosis, pulmonary fibrosis Pulmonary function tests	Supportive care Dyspnea management Oxygen support Nebulizer treatments

PULMONARY ADVERSE EVENT(S)	GRADING	MANAGEMENT ^a
Pneumonitis ^a	Mild (G1) ^b Asymptomatic; confined to one lobe or <25% of parenchyma	<ul style="list-style-type: none"> • Consider holding immunotherapy^f • Reassess in 1-2 weeks ▶ H&P ▶ Pulse oximetry (resting and with ambulation) • Consider chest CT with contrast^g ▶ Consider repeat chest CT in 4 weeks or as clinically indicated for worsening symptoms
	Moderate (G2) ^c New or worsening symptoms; increased oxygen requirements. 25%-50% of lung	<ul style="list-style-type: none"> • Hold immunotherapy^f • Pulmonary consultation • Consider infectious workup: <ul style="list-style-type: none"> ▶ Nasal swab for potential viral pathogens ▶ Sputum culture, blood culture, and urine culture • Consider bronchoscopy with bronchoalveolar lavage (BAL) to rule out infection and malignant lung infiltration • Consider chest CT with contrast^g ▶ Repeat chest CT in 3-4 weeks • Recommend infectious evaluation with institutional immunocompromised panel • Consider empiric antibiotics if infection has not yet been fully excluded • Prednisone/methylprednisolone 1-2 mg/kg/day^h • Monitor every 3-7 days with: <ul style="list-style-type: none"> ▶ H&P ▶ Pulse oximetry (resting and with ambulation) • If no improvement after 48-72 hours of corticosteroids, treat as grade 3
	Severe (G3-4) ^d	See ICI_PULM-2

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Management of Immune Checkpoint Inhibitor-Related Toxicities

Figure 3. Pulmonary adverse events.

saturation at rest and with ambulation. With grade 1–2 toxicity, consider withholding the checkpoint inhibitor. With worsening symptoms, withhold the checkpoint inhibitor, obtain a pulmonary consultation, rule out other infectious causes, consider a bronchoscopy to rule out infection and malignant lung infiltration, consider empiric antibiotics, and obtain a CT scan,” she advised.

The NCCN Guidelines advise that steroids at 1–2 mg/kg/d should be started for grade ≥ 2 toxicities, and patients monitored every 2 to 7 days. A more aggressive approach should be considered if no improvement is seen in 48 to 72 hours, which can include escalating the steroid dose and adding another immunosuppressant. For severe grade 3–4 pneumonitis, the NCCN Guidelines advise to permanently discontinue the immunotherapy, potentially escalate methylprednisolone, and consider adding a second immunosuppressant (ie, infliximab, mycophenolate mofetil, intravenous immunoglobulin)

if no improvement is seen in 48 hours. Dr. Davies further advised clinicians to obtain prior authorization for the additional immunosuppressant early on if patients appear destined for hospitalization, to avoid delays in treatment.

Disclosures: Dr. Gubens has disclosed that he has received consulting fees from AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim GmbH, Bristol-Myers Squibb Company, Genentech, Inc., Heron Therapeutics, Roche Laboratories, Inc., and Takeda Pharmaceuticals North America, Inc.; and has received grant/research support from Celgene Corporation, Merck & Co., Inc., Novartis Pharmaceuticals Corporation, and OncoMed Pharmaceuticals. Dr. Davies has disclosed that she serves on the Product/Speakers Bureaus for AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Genentech, Inc., and Merck & Co., Inc.

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References

1. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016;375:1823–1833.
2. Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N Engl J Med* 2017;376:2415–2426.
3. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. *J Clin Oncol* 2019;37:537–546.
4. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018;378:2078–2092.
5. Lopes G, Wu YL, Kudaba I, et al. Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) $\geq 1\%$: open-label, phase 3 KEYNOTE-042 study [abstract]. *J Clin Oncol* 2018;36(Suppl):Abstract LBA4.
6. Socinski MA, Jotte R, Cappuzzo F, et al. Overall survival analysis of IMpower150, a randomized Ph 3 study of atezolizumab chemotherapy \pm bevacizumab vs chemo + bev in 1L nonsquamous NSCLC [abstract]. *J Clin Oncol* 2018;36(Suppl):Abstract 9002.
7. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med* 2018;379:2040–2051.
8. Lee CK, Man J, Lord S, et al. Clinical and molecular characteristics associated with survival among patients treated with checkpoint inhibitors for advanced non-small cell lung carcinoma: a systematic review and meta-analysis. *JAMA Oncol* 2018;4:210–216.
9. Rimm DL, Han G, Taube JM, et al. A prospective, multi-institutional, pathologist-based assessment of 4 immunohistochemistry assays for PD-L1 expression in non-small cell lung cancer. *JAMA Oncol* 2017;3:1051–1058.
10. Hellman MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med* 2018;378:2093–2104.
11. Gandara DR, Paul SM, Kowanetz M, et al. Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab. *Nat Med* 2018;24:1441–1448.
12. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2017;377:1919–1929.
13. Luo W, Wang Z, Tian P, Li W. Safety and tolerability of PD-1/PD-L1 inhibitors in the treatment of non-small cell lung cancer: a meta-analysis of randomized controlled trials. *J Cancer Res Clin Oncol* 2018;144:1851–1859.