NCCN: Continuing Education

Target Audience: This activity is designed to meet the educational needs of physicians, nurses, pharmacists, and other healthcare professionals who manage patients with cancer.

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Release date: December 10, 2019; Expiration date: December 10, 2020

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Non–Small Cell Lung Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Non–Small Cell Lung Cancer

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

Kerrin M. Rosenthal, MA; Kimberly Callan, MS; Genevieve Emberger Hartzman, MA; Erin Hesler; Kristina M. Gregory, RN, MSN, OCN; Rashmi Kumar, PhD; Karen Kanefield; and Kathy Smith.

Individuals Who Provided Content Development and/or Authorship Assistance:

David S. Ettinger, MD, Panel Chair, has disclosed that he is a scientific advisor for AstraZeneca Pharmaceuticals LP, and Bristol-Myers Squibb Company.

Miranda Hughes, PhD, Oncology Scientist/Senior Medical Writer, NCCN, has disclosed that she has no relevant financial relationships.

To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/disclosures/guidelinepanellisting.aspx.

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Non–Small Cell Lung Cancer, Version 1.2020

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Non–Small Cell Lung Cancer (NSCLC) address all aspects of management for NSCLC. These NCCN Guidelines Insights focus on recent updates in immunotherapy. For the 2020 update, all of the systemic therapy regimens have been categorized using a new preference stratification system; certain regimens are now recommended as "preferred interventions," whereas others are categorized as either "other recommended interventions" or "useful under certain circumstances."

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*Provided content development and/or authorship assistance.

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

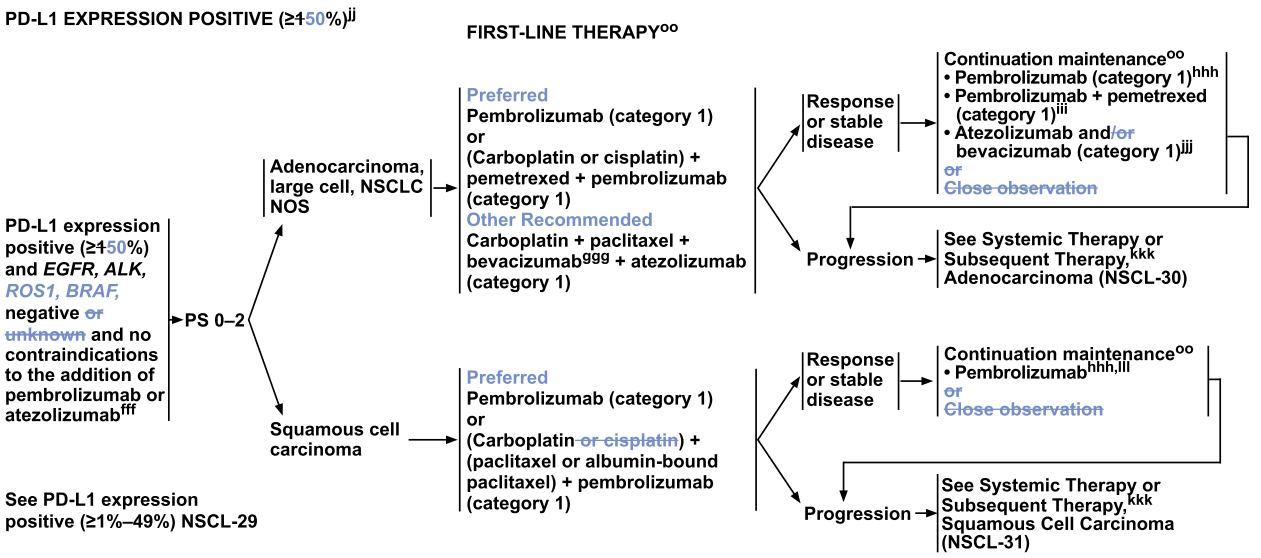
Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

The NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their application or use in any way.

The complete and most recent version of these NCCN Guidelines is available free of charge at NCCN.org.



[jj] See Principles of Molecular and Biomarker Analysis (NSCL-G).
[oo] See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[fff] Useful in Certain Circumstances: Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene, which would predict lack of benefit. If there are contraindications, refer to NSCL-30 (adenocarcinoma) or NSCL-31 (squamous cell carcinoma).
[ggg] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[hhh] If pembrolizumab monotherapy given.
[iii] If pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed given.
[jjj] If atezolizumab/carboplatin/paclitaxel/bevacizumab given.
[kkk] If patient has not received platinum-doublet chemotherapy, refer to "systemic therapy." If patient received platinum chemotherapy and anti-PD-1/PD-L1, refer to "subsequent therapy."
[lll] If pembrolizumab/carboplatin/(paclitaxel or albumin-bound paclitaxel) given.

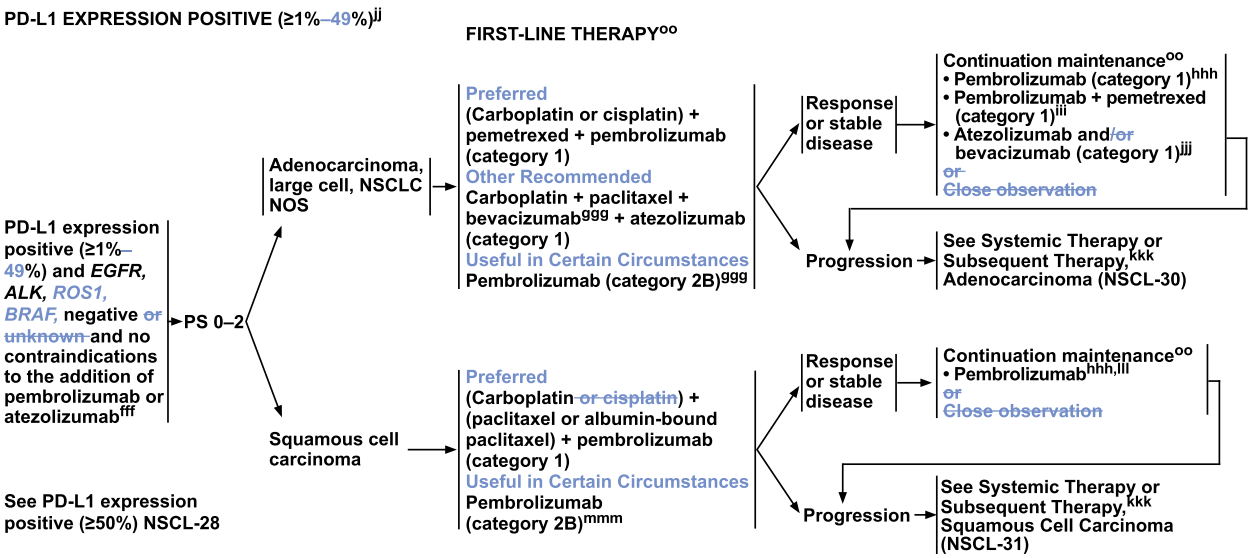
NSCL-28

Overview

Lung cancer is the leading cause of cancer death in the United States.[1] In 2019, an estimated 228,150 people in the United States will be diagnosed with lung and bronchial cancer, and 142,670 will die of the disease.[1] Only 25% of all patients with non–small cell lung cancer (NSCLC) are alive ≥5 years after diagnosis; the 5-year relative survival rate for metastatic disease is approximately 6% when patients receive historic cytotoxic chemotherapy regimens.[2] However, certain patients with metastatic NSCLC who are eligible for newer immunotherapies or targeted therapies are now surviving longer, with 5-year survival rates ranging from 15% to 50%, depending on the biomarker.[3–12] New first-line immunotherapy regimens are now recommended in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC, including pembrolizumab monotherapy, pembrolizumab/chemotherapy, and atezolizumab/bevacizumab/chemotherapy.[13–20] These NCCN Guidelines Insights focus on recent updates in immunotherapy for eligible patients with metastatic NSCLC. Furthermore, in the 2020 update to the NCCN Guidelines, all of the systemic therapy regimens have been categorized using a new preference stratification system. These NCCN Guidelines Insights explain, in greater detail than the parent NCCN Guidelines, the reasons why the NCCN NSCLC Panel revised the guidelines, and provide a valuable resource for busy healthcare providers who need to quickly learn about the recent recommendations to improve outcomes for their patients with metastatic NSCLC.

Preference Stratification

The NCCN Guidelines for NSCLC now include new categories of preference for all of the systemic therapy regimens, which are based on clinical trial data and the expertise of the NCCN NSCLC Panel (see CAT-1, page 1470).[20] The different categories of preference include "preferred," "other recommended options," and "useful under certain circumstances." However, preference stratification is not a tiered system. These new preference categories are intended to emphasize the most commonly used regimens in clinical practice, and are not intended to replace the NCCN Categories of Evidence and Consensus (eg, category 1, category 2A). Previously, several regimens were already listed as preferred in the NCCN Guidelines for NSCLC, such as first-line therapy with osimertinib for certain patients with metastatic NSCLC and *EGFR* mutations. However, the 2020 update of the guidelines has expanded the preference stratification categories to include all of the systemic therapy regimens.



[ji] See Principles of Molecular and Biomarker Analysis (NSCL-G).
[oo] See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[fff] Useful in Certain Circumstances: Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene, which would predict lack of benefit. If there are contraindications, refer to NSCL-30 (adenocarcinoma) or NSCL-31 (squamous cell carcinoma).
[ggg] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[hhh] If pembrolizumab monotherapy given.
[iii] If pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed given.
[jjj] If atezolizumab/carboplatin/paclitaxel/bevacizumab given.
[kkk] If patient has not received platinum-doublet chemotherapy, refer to "systemic therapy." If patient received platinum chemotherapy and anti-PD-1/PD-L1, refer to "subsequent therapy."
[lll] If pembrolizumab/carboplatin/(paclitaxel or albumin-bound paclitaxel) given.
[mmm] Pembrolizumab monotherapy can be considered in PD-L1 1%–49%, in patients with poor PS or other contraindications to combination chemotherapy.

NSCL-29

First-Line Immunotherapy Regimens

Pembrolizumab Monotherapy

Clinical Trial Data

A phase III randomized trial (KEYNOTE-024) compared single-agent pembrolizumab versus platinum-based chemotherapy as first-line therapy for patients with advanced squamous cell carcinoma or nonsquamous NSCLC, PD-L1 expression levels ≥50%, and wild type *EGFR* or *ALK*.[11,21] The response rate for pembrolizumab monotherapy was 44.8% (95% CI, 36.8%–53.0%) versus 27.8% (95% CI, 20.8%–35.7%) for chemotherapy alone.[21] An updated analysis of KEYNOTE-024 showed that median overall survival (OS) was longer with pembrolizumab monotherapy (30.0 months; 95% CI, 18.3–not reached [NR]) compared with chemotherapy (14.2 months [95% CI, 9.8–19.0]; hazard ratio [HR], 0.63 [95% CI, 0.47–0.86]).[11] Fewer severe treatment-related adverse events (grades 3–5) were observed in patients receiving pembrolizumab monotherapy compared with those receiving chemotherapy (31.2% vs 53.3%, respectively).[11] Treatment-related deaths occurred in 1.3% (2/154) of patients receiving pembrolizumab monotherapy versus 2% (3/150) of those receiving chemotherapy alone.[11]

Another phase III randomized trial (KEYNOTE-042) compared single-agent pembrolizumab versus platinum-based chemotherapy as first-line therapy for patients with advanced squamous cell or nonsquamous NSCLC, PD-L1 expression levels ≥1%, and wild type *EGFR* or *ALK*.[22] OS was similar in patients with PD-L1 levels of 1% to 49% who received single-agent pembrolizumab (13.4 months; 95% CI, 10.7–18.2) compared with chemotherapy (12.1 months; 95% CI, 11.0–14.0) in a subgroup analysis (HR, 0.92; 95% CI, 0.77–1.11). However, OS was longer in patients with PD-L1 levels ≥50% who received single-agent pembrolizumab (20.0 months; 95% CI, 15.4–24.9) compared with chemotherapy (12.2 months [95% CI, 10.4–14.2]; HR, 0.69 [95% CI, 0.56–0.85]; *P*=.0003). Thus, both KEYNOTE-024 and KEYNOTE-042 show that pembrolizumab monotherapy improves survival compared with platinum-based chemotherapy for patients with metastatic NSCLC, PD-L1 levels ≥50%, and negative test results for *EGFR* mutations and *ALK* rearrangements. In addition, long-term data from KEYNOTE-001 show a 5-year survival of approximately 23% for treatment-naïve patients and 15.5% for those with metastatic NSCLC previously treated with pembrolizumab monotherapy; for patients with PD-L1 levels ≥50%, 5-year OS was approximately 29.6% and 25.0%, respectively.[3] Median OS was 22.3 months (95% CI, 17.1–32.3) for treatment-naïve patients and 10.5 months (95% CI, 8.6–13.2) for those previously treated with pembrolizumab monotherapy.

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]
INITIAL SYSTEMIC THERAPY OPTIONS

Adenocarcinoma, Large Cell, NSCLC NOS (PS 0–1)
No contraindications to the addition of pembrolizumab or atezolizumab[c]
Preferred
- **Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,d]**
- **Pembrolizumab/cisplatin/pemetrexed (category 1)[2,d]**

Other Recommended
- **Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category 1)[3,d,f,g,h]**

Useful in Certain Circumstances
Contraindications to the addition of pembrolizumab or atezolizumab[c]
- **Bevacizumab[e]/carboplatin/paclitaxel (category 1)[4,f,g,h]**
- **Bevacizumab[e]/carboplatin/pemetrexed[4,5,f,g,h]**
- **Bevacizumab[e]/cisplatin/pemetrexed[6,f,g,h]**
- **Carboplatin/albumin-bound paclitaxel (category 1)[7]**
- **Carboplatin/docetaxel (category 1)[8]**
- **Carboplatin/etoposide (category 1)[9,10]**
- **Carboplatin/gemcitabine (category 1)[11]**
- **Carboplatin/paclitaxel (category 1)[12]**
- **Carboplatin/pemetrexed (category 1)[13]**
- **Cisplatin/docetaxel (category 1)[8]**
- **Cisplatin/etoposide (category 1)[14]**
- **Cisplatin/gemcitabine (category 1)[12,15]**
- **Cisplatin/paclitaxel (category 1)[16]**
- **Cisplatin/pemetrexed (category 1)[15]**
- **Gemcitabine/docetaxel (category 1)[17]**
- **Gemcitabine/vinorelbine (category 1)[18]**

Adenocarcinoma, Large Cell, NSCLC NOS (PS 2)
Preferred
- **Carboplatin/pemetrexed[13]**

Other Recommended
- **Carboplatin/albumin-bound paclitaxel[20,21]**
- **Carboplatin/docetaxel[8]**
- **Carboplatin/etoposide[9,10]**
- **Carboplatin/gemcitabine[11]**
- **Carboplatin/paclitaxel[12]**

Useful in Certain Circumstances
- **Albumin-bound paclitaxel[19]**
- **Docetaxel[22,23]**
- **Gemcitabine[24-26]**
- **Gemcitabine/docetaxel[17]**
- **Gemcitabine/vinorelbine[18]**
- **Paclitaxel[27-29]**
- **Pemetrexed[30]**

References are available online, at NCCN.org.

[a] Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) are contraindicated.
[b] Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.
[c] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene, which would predict lack of benefit.
[d] If progression on PD-1/PD-L1 inhibitor, switching to another PD-1/PD-L1 inhibitor is not ~~routinely~~ recommended.
[e] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[f] Bevacizumab should be given until progression.
[g] Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.
[h] Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.

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For patients with metastatic NSCLC receiving chemotherapy alone, 5-year OS was approximately 6%.[3]

NCCN Recommendations

The NCCN NSCLC Panel recommends single-agent pembrolizumab (category 1; preferred) as a first-line therapy option for certain patients with metastatic NSCLC and high PD-L1 expression (tumor proportion score [TPS] ≥50% by PD-L1 IHC 22C3 pharmDx [Agilent Technologies, Inc]) based on the results of KEYNOTE-024 and FDA approval (NSCL-28, page 1466).[11,20,21] Pembrolizumab monotherapy is recommended (category 1; preferred) as a first-line option for patients with metastatic nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma), squamous cell NSCLC, or NSCLC not otherwise specified (NOS); PD-L1 expression levels of ≥50%; no contraindications to immunotherapy; and nonsquamous NSCLC with negative test results for *EGFR*, *ALK*, *ROS1*, or *BRAF* genetic alterations. Contraindications to immunotherapy may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents, or an oncogene that would predict lack of benefit. Maintenance therapy with pembrolizumab is also a recommended option (category 1). The panel also recommends single-agent pembrolizumab for patients with metastatic NSCLC and PD-L1 levels of 1% to 49% but negative for *EGFR*, *ALK*, *ROS1*, or *BRAF* genetic alterations who either cannot tolerate or refuse platinum-based chemotherapy with pembrolizumab (category 2B; useful in certain circumstances) (NSCL-29, page 1467).[22] In patients with PD-L1 levels of 1% to 49%, the HR of 0.92 is not statistically or clinically significant for pembrolizumab monotherapy versus chemotherapy; therefore, pembrolizumab/chemotherapy is recommended (category 1; preferred) if patients can tolerate the therapy.

For the 2020 update, the panel again emphasized that clinicians should obtain molecular testing results for actionable biomarkers before administering first-line therapy, if clinically feasible; therefore, the panel deleted "or unknown" regarding test results for actionable biomarkers before administering immunotherapy (see NSCL-28 and NSCL-29, pages 1466 and 1467, respectively).[20] In addition, the panel added *ROS1* rearrangements and *BRAF* mutations to the list of actionable biomarkers that need to be negative before administering immunotherapy.[23] Patients with metastatic NSCLC and PD-L1 expression levels of ≥50%—but who also have a targetable driver oncogene molecular alteration (eg, *EGFR*, *ALK*, *ROS1*)—should receive first-line targeted therapy for that oncogene and not first-line pembrolizumab monotherapy, because targeted therapies

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,i]
INITIAL SYSTEMIC THERAPY OPTIONS

Squamous Cell Carcinoma (PS 0–1)

No contraindications to the addition of pembrolizumab[c]

Preferred
- **Pembrolizumab/carboplatin/paclitaxel[31,d] (category 1)**
- **Pembrolizumab/carboplatin/albumin-bound paclitaxel[31,d] (category 1)**
- ~~**Pembrolizumab/cisplatin/paclitaxel**~~
- ~~**Pembrolizumab/cisplatin/albumin-bound paclitaxel**~~

Useful in Certain Circumstances

Contraindications to the addition of pembrolizumab[c]
- **Carboplatin/albumin-bound paclitaxel (category 1)[7]**
- **Carboplatin/docetaxel (category 1)[8]**
- **Carboplatin/gemcitabine (category 1)[11]**
- **Carboplatin/paclitaxel (category 1)[12]**
- **Cisplatin/docetaxel (category 1)[8]**
- **Cisplatin/etoposide (category 1)[14]**
- **Cisplatin/gemcitabine (category 1)[12,15]**
- **Cisplatin/paclitaxel (category 1)[16]**
- **Gemcitabine/docetaxel (category 1)[17]**
- **Gemcitabine/vinorelbine (category 1)[18]**

Squamous Cell Carcinoma (PS 2)

Preferred
- **Carboplatin/albumin-bound paclitaxel[20,21]**
- **Carboplatin/gemcitabine[11]**
- **Carboplatin/paclitaxel[12]**

Other Recommended
- **Carboplatin/docetaxel[8]**
- **Carboplatin/etoposide[9,10]**

Useful in Certain Circumstances
- **Albumin-bound paclitaxel[19]**
- **Docetaxel[22,23]**
- **Gemcitabine[24-26]**
- **Gemcitabine/docetaxel[17]**
- **Gemcitabine/vinorelbine[18]**
- **Paclitaxel[27-29]**

References are available online, at NCCN.org.

[a] Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) are contraindicated.
[b] Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.
[c] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene, which would predict lack of benefit.
[d] If progression on PD-1/PD-L1 inhibitor, switching to another PD-1/PD-L1 inhibitor is not ~~routinely~~ recommended.
[i] Cisplatin/gemcitabine/necitumumab in the first-line setting and afatinib in the second-line setting are not used at NCCN Member Institutions for these indications related to the efficacy and safety of these agents compared to the efficacy and safety of other available agents.

NSCL-J
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yield higher response rates (eg, osimertinib, 80%) than pembrolizumab monotherapy (poor response rates) in the first-line setting, targeted therapy is better tolerated, and these patients have been found to be unlikely to respond to immune checkpoint inhibitors.[24–26]

Combination Immunotherapy/ Chemotherapy Regimens

Clinical Trial Data

KEYNOTE-189 was a phase III randomized trial assessing first-line therapy with pembrolizumab/carboplatin (or cisplatin)/pemetrexed versus carboplatin (or cisplatin)/pemetrexed in 616 patients with metastatic nonsquamous NSCLC and wild-type *EGFR* or *ALK*.[16] Most patients received pembrolizumab/carboplatin/pemetrexed (n=445; 72%), but some received pembrolizumab/cisplatin/pemetrexed (n=171; 28%). The estimated rate of OS at 1 year was 69.2% (95% CI, 64.1%–73.8%) in patients receiving pembrolizumab/chemotherapy versus 49.4% (95% CI, 42.1%–56.2%) for chemotherapy alone. After a median follow-up of 10.5 months, median OS was longer for pembrolizumab/chemotherapy (NR) compared with chemotherapy alone (11.3. months [95% CI, 8.7–15.1]; HR for death, 0.49 [95% CI, 0.38–0.64]; $P<.001$); OS was longer regardless of PD-L1 levels. Tumor mutational burden also did not predict for response.[27] The response rate was 47.6% (95% CI, 42.6%–52.5%) for pembrolizumab/chemotherapy versus 18.9% (95% CI, 13.8%–25.0%; $P<.001$) for chemotherapy alone; however, the response rate was higher for patients with PD-L1 levels of ≥50% (61.4% vs 22.9%, respectively). Grade ≥3 adverse events occurred at a similar rate in both arms (pembrolizumab/chemotherapy, 67.2% vs chemotherapy, 65.8%). Treatment-related deaths occurred in 6.7% (27/405) of patients receiving pembrolizumab/chemotherapy versus 5.9% (12/202) of those receiving chemotherapy alone.

IMpower150 was a phase III randomized trial assessing first-line therapy with atezolizumab combined with bevacizumab/carboplatin/paclitaxel (ABCP) versus bevacizumab/chemotherapy for patients with metastatic nonsquamous NSCLC.[17] Median OS was 19.2 months (95% CI, 17.0–23.8) in the ABCP arm compared with 14.7 months (95% CI, 13.3–16.9) for bevacizumab/carboplatin/paclitaxel (HR for death, 0.78; 95% CI, 0.64–0.96; $P=.02$). Response rates were 63.5% (224/353; 95% CI, 58.2%–68.5%) in the ABCP group versus 48.0% (159/331; 95% CI, 42.5%–53.6%) for bevacizumab/chemotherapy. Grade 3 to 4 adverse events occurred in 55.7% (219/393) of patients receiving ABCP versus 47.7% (188/394) of those on bevacizumab/chemotherapy. Treatment-related deaths were similar in both groups

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

(ABCP, 2.8% [11/393] vs bevacizumab/chemotherapy, 2.3% [9/394]). A subgroup analysis (IMpower150) reported that subsequent therapy with the ABCP regimen improved survival in 26 patients with *EGFR* mutation–positive metastatic NSCLC whose disease had progressed after first-line EGFR tyrosine kinase inhibitor (TKI) therapy compared with 32 patients treated with bevacizumab/chemotherapy alone.[28]

KEYNOTE-407 was a phase III randomized trial assessing first-line therapy with carboplatin/paclitaxel (or albumin-bound paclitaxel)/pembrolizumab versus carboplatin/paclitaxel (or albumin-bound paclitaxel) for patients with metastatic squamous cell NSCLC; 32% of patients received albumin-bound paclitaxel (also known as nab-paclitaxel).[18] Median OS was 15.9 months (95% CI, 13.2–NR) with pembrolizumab/chemotherapy versus 11.3 months (95% CI, 9.5–14.8) with chemotherapy alone (HR for death, 0.64; 95% CI, 0.49–0.85; $P<.001$). The response rate was 57.9% (95% CI, 51.9%–63.8%) for pembrolizumab/chemotherapy versus 38.4% (95% CI, 32.7%–44.4%) for chemotherapy alone. Grade ≥3 adverse events were similar in both groups (pembrolizumab/chemotherapy, 69.8% vs chemotherapy alone, 68.2%). Treatment-related deaths occurred in 8.3% (23/278) of patients receiving pembrolizumab/chemotherapy versus 6.4% (18/280) of patients receiving chemotherapy alone.

NCCN Recommendations

The NCCN NSCLC Panel recommends (category 1; preferred) pembrolizumab/carboplatin (or cisplatin)/pemetrexed as first-line therapy options for certain patients with metastatic nonsquamous NSCLC based on a phase III randomized trial (KEYNOTE-189) and on FDA approval (see NSCL-28, NSCL-29, and NSCL-J 2 of 4, pages 1466, 1467, and 1468, respectively).[16,20,29] The pembrolizumab/chemotherapy regimens are recommended (category 1; preferred) as first-line therapy options for patients with metastatic nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or NSCLC NOS; no contraindications to immunotherapy; or nonsquamous NSCLC with negative test results for *EGFR*, *ALK*, *ROS1*, or *BRAF* genetic alterations, regardless of PD-L1 expression levels (see NSCL-28, NSCL-29, and NSCL-J 2 of 4, pages 1466, 1467, and 1468, respectively). The pembrolizumab/chemotherapy regimens may be used (category 1; preferred) for patients with metastatic nonsquamous cell NSCLC and PD-L1 levels of ≥50% if they have significant disease burden, performance status 0–1, and no actionable molecular biomarkers. Maintenance therapy with pembrolizumab/pemetrexed is also a recommended option (category 1) if patients received the pembrolizumab/carboplatin (or cisplatin)/pemetrexed regimens. Patients with metastatic NSCLC and positive

PD-L1 expression levels of ≥1%—but who also have a driver oncogene molecular alteration (eg, *EGFR, ALK, ROS1*)—should receive first-line targeted therapy for that oncogene and not first-line immunotherapy regimens, because targeted therapies have higher response rates than immunotherapy regimens in the first-line setting and because targeted therapies are better tolerated.[24–26]

The panel recommends the ABCP regimen (also known as the *quadruplicate regimen*) as a first-line therapy option (category 1; other recommended) for certain patients with metastatic nonsquamous NSCLC or NSCLC NOS based on results of the IMpower150 trial and FDA approval (see NSCL-28, NSCL-29, and NSCL-J 2 of 4, pages 1466, 1467, and 1468, respectively).[17,20] First-line therapy with the ABCP regimen is recommended (category 1; other recommended) for patients with no contraindications to immunotherapy or bevacizumab and with negative test results for *EGFR*, *ALK*, *ROS1*, or *BRAF* genetic alterations, regardless of PD-L1 expression levels. The ABCP regimen is listed as an "other recommended" option, because the panel prefers the pembrolizumab/chemotherapy regimens based on tolerability and experience with these regimens. Maintenance therapy with atezolizumab and bevacizumab is also recommended for patients who received the ABCP regimen (category 1) (see "Maintenance Therapy," pages 1466 and 1467). Although not FDA-approved for patients with these genetic alterations, the IMpower150 trial did include these patients after they experienced disease progression on targeted therapy. Therefore, the ABCP regimen is also a subsequent therapy option in patients who have exhausted all TKI options and are considering a platinum-based regimen. Bevacizumab biosimilars may be used in any of the systemic therapy regimens containing bevacizumab (eg, ABCP) that are used for eligible patients with metastatic NSCLC based on clinical data and FDA approvals.[30–34] However, a specific bevacizumab biosimilar should be used for the entire regimen, including maintenance therapy, and should not be substituted in the middle of therapy.

The panel recommends (category 1; preferred) carboplatin/paclitaxel (or albumin-bound paclitaxel)/pembrolizumab as first-line therapy options for certain patients with metastatic squamous cell NSCLC based on results of KEYNOTE-407 and FDA approval (see NSCL-28, NSCL-29, NSCL-J 3 of 4, pages 1466, 1467, and 1469, respectively).[18,20,35] The carboplatin/paclitaxel (or albumin-bound paclitaxel)/pembrolizumab regimens are recommended (category 1; preferred) as first-line therapy options for patients with metastatic squamous cell NSCLC and no contraindications to immunotherapy, regardless of PD-L1 expression levels. The pembrolizumab/chemotherapy regimens may be used (category 1; preferred) for patients with metastatic squamous cell NSCLC and PD-L1 levels of ≥50% if they have significant disease burden, performance status 0–1, and no actionable molecular biomarkers. Maintenance therapy with pembrolizumab is also a recommended option (category 1) if patients received the carboplatin/paclitaxel (or albumin-bound paclitaxel)/pembrolizumab regimens.

Summary

The NCCN Guidelines for NSCLC address all aspects of disease management. For the 2020 update, all of the systemic therapy regimens have been categorized using a new preference stratification system by the NCCN NSCLC Panel; certain regimens are now recommended as preferred interventions, whereas other regimens are categorized as either other recommended interventions or useful under certain circumstances.[20] These NCCN Guidelines Insights focus on recent updates regarding immunotherapy.

The panel recommends single-agent pembrolizumab (category 1; preferred) as a first-line therapy option for certain patients with metastatic NSCLC and PD-L1 expression levels of ≥50% (NSCL-28, page 1466).[11,20,21] Pembrolizumab monotherapy is recommended (category 1; preferred) as a first-line therapy option for patients with metastatic nonsquamous NSCLC, squamous cell NSCLC, or NSCLC NOS; PD-L1 expression levels of ≥50%; no contraindications to immunotherapy; and nonsquamous NSCLC with negative test results for *EGFR*, *ALK*, *ROS1*, or *BRAF* genetic alterations. The panel also recommends single-agent pembrolizumab for patients with metastatic NSCLC and PD-L1 levels of 1% to 49% who cannot tolerate or refuse platinum-based chemotherapy (category 2B; useful in certain circumstances).[22]

Pembrolizumab/carboplatin (or cisplatin)/pemetrexed is recommended as first-line therapy (category 1; preferred) for certain patients with metastatic nonsquamous NSCLC or NSCLC NOS.[16,20,29] Pembrolizumab/chemotherapy regimens are recommended (category 1; preferred) as first-line therapy options for patients with metastatic nonsquamous NSCLC, no contraindications to immunotherapy, and negative test results for *EGFR*, *ALK*, *ROS1*, or *BRAF* genetic alterations, regardless of their PD-L1 expression levels. The panel recommends the ABCP regimen as a first-line therapy option (category 1; other recommended) for certain patients with metastatic nonsquamous NSCLC or NSCLC NOS.[17,20] The ABCP regimen is recommended (category 1; other recommended) as a first-line option for patients with metastatic nonsquamous NSCLC, no contraindications to immunotherapy or bevacizumab, and negative test results for *EGFR*, *ALK*, *ROS1*, or *BRAF* genetic alterations, regardless of PD-L1 expression levels. The ABCP regimen is listed as an "other recommended" option, because the

panel prefers the pembrolizumab/chemotherapy regimens based on tolerability and experience with these regimens.[16,18]

For certain patients with metastatic squamous cell NSCLC, carboplatin/paclitaxel (or albumin-bound paclitaxel)/pembrolizumab is recommended (category 1; preferred) as a first-line therapy option.[18,35] The carboplatin/paclitaxel (or albumin-bound paclitaxel)/pembrolizumab regimens are recommended (category 1; preferred) as first-line therapy options for patients with metastatic squamous cell NSCLC and no contraindications to immunotherapy, regardless of PD-L1 expression levels.

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