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NIHMS1895213 NIHPA1895213 1 Article Small Cell Lung Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology Ganti Apar Kishor P. MD 1 * Loo Billy W. Jr. MD, PhD 2 * Bassetti Michael MD 3 Blakely Collin MD, PhD 4 Chiang Anne MD, PhD 5 D'Amico Thomas A. MD 6 D'Avella Christopher MD 7 Dowlati Afshin MD 8 Downey Robert J. MD 9 Edelman Martin MD 10 Florsheim Charles 11 Gold Kathryn A. MD 12 Goldman Jonathan W. MD 13 Grecula John C. MD 14 Hann Christine MD, PhD 15 Iams Wade MD 16 Iyengar Puneeth MD, PhD 17 Kelly Karen MD 18 Khalil Maya MD 19 Koczywas Marianna MD 20 Merritt Robert E. MD 14 Mohindra Nisha MD 21 Molina Julian MD, PhD 22 Moran Cesar MD 23 Pokharel Saraswati MD 24 Puri Sonam MD 25 Qin Angel MD 26 Rusthoven Chad MD 27 Sands Jacob MD 28 Santana-Davila Rafael MD 29 Shafique Michael MD 30 Waqar Saiama N. MBBS, MSCI 31 Gregory Kristina M. RN, MSN, OCN 32 Hughes Miranda PhD 32 1 Fred & Pamela Buffett Cancer Center 2 Stanford Cancer Institute 3 University of Wisconsin Carbone Cancer Center 4 UCSF Helen Diller Family Comprehensive Cancer Center 5 Yale Cancer Center/Smilow Cancer Hospital 6 Duke Cancer Institute 7 Abramson Cancer Center at the University of Pennsylvania 8 Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute 9 Memorial Sloan Kettering Cancer Center 10 Fox Chase Cancer Center 11 Patient Advocate 12 UC San Diego Moores Cancer Center 13 UCLA Jonsson Comprehensive Cancer Center 14 The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute 15 The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins 16 Vanderbilt-Ingram Cancer Center 17 UT Southwestern Simmons Comprehensive Cancer Center 18 UC Davis Comprehensive Cancer Center 19 O'Neal Comprehensive Cancer Center at UAB 20 City of Hope National Medical Center 21 Robert H. Lurie Comprehensive Cancer Center of Northwestern University 22 Mayo Clinic Cancer Center 23 The University of Texas MD Anderson Cancer Center 24 Roswell Park Comprehensive Cancer Center 25 Huntsman Cancer Institute at the University of Utah 26 University of Michigan Rogel Cancer Center 27 University of Colorado Cancer Center 28 Dana Farber/Brigham and Women's Cancer Center 29 Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance 30 Moffitt Cancer Center 31 Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine 32 National Comprehensive Cancer Network. * Discussion Writing Committee member.

12 2021 19 12 436342 1441 1464 07 05 2023 23 05 2023 23 05 2023 15 06 2024 This file is available for text mining. It may also be used consistent with the principles of fair use under the copyright law. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Small Cell Lung Cancer (SCLC) provide recommended management for patients with SCLC, including diagnosis, primary treatment, surveillance for relapse, and subsequent treatment. This selection for the journal focuses on metastatic (known as extensive-stage) SCLC, which is more common than

limited-stage SCLC. Systemic therapy alone can palliate symptoms and prolong survival in most patients with extensive-stage disease. Smoking cessation counseling and intervention should be strongly promoted in patients with SCLC and other high-grade neuroendocrine carcinomas. The “Summary of the Guidelines Updates” section in the SCLC algorithm outlines the most recent revisions for the 2022 update, which are described in greater detail in this revised Discussion text.

Neuroendocrine tumors account for approximately 20% of lung cancers; most (approximately 14%) are small cell lung cancer (SCLC).^{1, 2} In 2021, an estimated 33,000 new cases of SCLC will occur in the United States.^{1, 3} During the COVID pandemic, the diagnosis and treatment of lung cancer have been hampered; however, this has not been reflected in the 2021 estimates for incidence and mortality because of the typical delays in collecting, calculating, and reporting the data.³ Nearly all cases of SCLC are attributable to cigarette smoking.⁴ Although the incidence of SCLC has been decreasing, the incidence in women is increasing and the male-to-female incidence ratio is now 1:1.^{1, 2} Recommended management of SCLC is described in the complete version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Small Cell Lung Cancer (available at [NCCN.org](https://www.nccn.org)). This shorter selection for JNCCN has been condensed to focus on metastatic (known as extensive-stage) SCLC, which is more common than limited-stage SCLC. Management of other lung neuroendocrine tumors is described in a different guideline (see “Lung Neuroendocrine Tumors” in the NCCN Guidelines for Neuroendocrine and Adrenal Tumors, available at [NCCN.org](https://www.nccn.org)).

SCLC is characterized by a rapid doubling time, high growth fraction, and early development of widespread metastases. Most patients with SCLC present with hematogenous metastases; approximately one third present with limited disease confined to the chest. SCLC is highly sensitive to initial chemotherapy and radiotherapy; however, most patients eventually die of recurrent disease.⁵ In patients with limited-stage SCLC, the goal of treatment is cure using chemotherapy plus thoracic radiotherapy; some patients are eligible for curative surgery followed by systemic therapy with or without mediastinal radiotherapy (see the complete version of the NCCN Guidelines for SCLC, available at [NCCN.org](https://www.nccn.org)).^{6, 7} In patients with extensive-stage disease, systemic therapy alone can palliate symptoms and prolong survival in most patients; however, long-term survival is rare.⁸ Note that the definitions for limited-stage and extensive-stage SCLC incorporate TNM staging (see “Staging,” page 1447 and [NCCN.org](https://www.nccn.org)). Surgery is only recommended for certain patients with surgically resectable stage I to IIA SCLC; stereotactic ablative radiotherapy is an option for certain patients with medically inoperable stage I to IIA SCLC (see the complete version of these guidelines at [NCCN.org](https://www.nccn.org)).^{9 - 12} Clinical trials generally represent state-of-the-art treatment for patients with SCLC. Despite recent advances, the recommended therapy for SCLC as outlined in the NCCN Guidelines still needs to be improved. Thus, participation in clinical trials should be strongly encouraged.

Smoking cessation counseling and intervention should be strongly promoted in patients with SCLC and other high-grade neuroendocrine carcinomas (see the NCCN Guidelines for Smoking Cessation, available at [NCCN.org](https://www.nccn.org)).¹³ Former smokers should be strongly encouraged to remain abstinent. Patients with SCLC who continue to smoke have increased toxicity during treatment and shorter survival.¹⁴ Programs using behavioral counseling combined with FDA-approved medications that promote smoking cessation can be very useful.

The NCCN Guidelines for SCLC were originally published 20 years ago and have been subsequently updated at least once every year.¹⁵ The “Guidelines Updates” section in the SCLC algorithm (at [NCCN.org](https://www.nccn.org)) outlines the most recent revisions for the 2022 update, which are described in greater detail in this revised Discussion text; recent references have been added (see “Summary,” page 1458, and the complete version of the NCCN Guidelines for SCLC, [NCCN.org](https://www.nccn.org)). For example, new subsequent therapy options have been added for patients with SCLC. Additional supplemental material in the SCLC algorithm includes “Signs and Symptoms of Small Cell Lung Cancer,” “Principles of Pathologic Review,” “Principles of Surgical Resection,” “Principles of Supportive Care,” “Principles of Systemic Therapy,” “Principles of Radiation Therapy,” and staging tables (see the complete guidelines at [NCCN.org](https://www.nccn.org)).

An electronic search of the PubMed database was performed to obtain key literature in SCLC using the following search term: small cell lung cancer . The PubMed database was chosen because it is the most widely used resource for medical literature and indexes peer-reviewed biomedical literature. The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: clinical trial, phase 1; clinical trial, phase 2; clinical trial, phase 3; clinical trial, phase 4; guideline; randomized controlled trial; meta-analysis; systematic reviews; and validation studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these NCCN Guidelines and discussed by the NCCN SCLC Panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion. The complete details of the development and update of the NCCN Guidelines are available at NCCN.org .

Ideally, a screening test should detect disease at an early stage when it is still curable. Currently, no effective screening test is available to detect early-stage SCLC; the disease is typically diagnosed when patients present with symptoms indicative of advanced-stage disease (see SCL-A , page 1446). 16 The National Lung Screening Trial reported that screening with annual, low-dose, spiral CT scans decreased lung cancer-specific mortality in asymptomatic high-risk individuals (see the NCCN Guidelines for Lung Cancer Screening, NCCN.org). 17 Although low-dose CT screening can detect early-stage non-small cell lung cancer (NSCLC), it does not seem to be useful for detecting early-stage SCLC. 16 - 19 Low-dose CT screening is probably not useful for SCLC because of the aggressiveness of the disease, which results in the development of symptomatic disease between annual scans, thereby limiting the potential effect on mortality. 16

SCLC typically presents as a large hilar mass and bulky mediastinal lymphadenopathy that cause cough and dyspnea. 20 Frequently, patients present with symptoms of widespread metastatic disease, such as weight loss, debility, bone pain, and neurologic compromise. The algorithm includes a section describing signs and symptoms of SCLC based on the tumor location and type of metastases (see SCL-A , page 1446). It is uncommon for patients to present with a solitary peripheral nodule without central adenopathy. In this situation, fine-needle aspiration may not adequately differentiate small cell carcinoma (which is a high-grade neuroendocrine carcinoma) from low-grade (typical carcinoid), intermediate-grade (atypical carcinoid), or large-cell neuroendocrine carcinoma (LCNEC) (which is also a high-grade neuroendocrine carcinoma) (see "Lung Neuroendocrine Tumors" in the NCCN Guidelines for Neuroendocrine and Adrenal Tumors, at NCCN.org). 21 , 22

Many neurologic and endocrine paraneoplastic syndromes are associated with SCLC. 23 - 25 Neurologic syndromes include Lambert-Eaton myasthenic syndrome, encephalomyelitis, and sensory neuropathy. Patients with the Lambert-Eaton myasthenic syndrome present with proximal leg weakness that is caused by antibodies directed against the voltage-gated calcium channels. 26 , 27 Paraneoplastic encephalomyelitis and sensory neuropathy are caused by the production of an antibody (anti Hu) that cross-reacts with both small cell carcinoma antigens and human neuronal RNA-binding proteins resulting in multiple neurologic deficits; paraneoplastic encephalomyelitis may precede the diagnosis of a tumor. 28 The NCCN SCLC Panel recommends that if neurologic paraneoplastic syndrome is suspected, then obtaining a comprehensive paraneoplastic antibody panel should be considered.

SCLC cells sometimes produce polypeptide hormones, including vasopressin (antidiuretic hormone [ADH]) and adrenocorticotrophic hormone (ACTH), which cause hyponatremia of malignancy (ie, syndrome of inappropriate ADH secretion [SIADH]) and Cushing syndrome, respectively. 29 , 30 In patients with SCLC, SIADH occurs more frequently than Cushing syndrome. Cancer treatment and/or supportive care may also cause hyponatremia (eg, cisplatin, opiates). 31 Primary treatment of SIADH includes fluid restriction (which is difficult for patients because of increased thirst) and

demeclocycline; vasopressin receptor inhibitors (ie, conivaptan, tolvaptan) can be used for refractory hyponatremia (see SCL-D , page 1449). 31 - 33 Hyponatremia usually improves after successful treatment of SCLC.

The NCCN Guidelines for SCLC include a section on pathology (see SCL-B , page 1448). The WHO classification system is used to classify lung tumors. 34 - 39 SCLC is a poorly differentiated malignant epithelial tumor that is categorized as a high-grade neuroendocrine carcinoma. 21 , 40 The classic and distinctive histology on hematoxylin and eosin may be sufficient for identifying SCLC in good-quality histologic samples, including small blue cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli. 21 , 41 The cells are round, oval, or spindle-shaped; nuclear molding is prominent. 42 The mitotic count is high in SCLC compared with the count in atypical and typical carcinoids. However, it can be difficult to count mitotic figures in small biopsy samples with crushed or necrotic cells; immunohistochemistry is useful in this setting (see next paragraph). 43 Up to 30% of specimens from patients with SCLC reveal areas of NSCLC differentiation (mainly large cell carcinoma) 42 ; this finding is more commonly detected in specimens from previously treated patients and suggests that pulmonary carcinogenesis occurs in a pluripotent stem cell capable of differentiation along divergent pathways. Although 95% of small cell carcinomas originate in the lung, they can also arise from extrapulmonary sites, including the nasopharynx, gastrointestinal tract, and genitourinary tract. 44 , 45 Both pulmonary and extrapulmonary small cell carcinomas have a similar clinical and biologic behavior, leading to a high potential for widespread metastases.

Immunohistochemistry is useful for diagnosing SCLC in limited samples and distinguishing SCLC from NSCLC or other neuroendocrine tumors . 21 , 43 , 46 - 48 Nearly all SCLCs are immunoreactive for cytokeratin (AE1/Ae3, CAM5.2); 85% to 90% of SCLCs are positive for thyroid transcription factor-1 (TTF-1). 21 , 49 - 51 Napsin A is a marker of adenocarcinoma and p40 (or p63) is a marker of squamous cell carcinoma. Napsin A and p40 (or p63) are generally negative in SCLC and, therefore, useful for distinguishing SCLC from poorly differentiated NSCLC and combined SCLC. 52 However, p40 (or p63) can be focally positive in SCLC. It is important to distinguish SCLC from other neuroendocrine tumors, especially typical and atypical carcinoids, because treatment differs for these tumors (see “Lung Neuroendocrine Tumors” in the NCCN Guidelines for Neuroendocrine and Adrenal Tumors). 37 , 43 Most SCLCs also stain positively for markers of neuroendocrine differentiation, including insulinoma-associated protein 1 (INSM1), chromogranin A, neuron-specific enolase, neural cell adhesion molecule (NCAM; CD56), and synaptophysin. 21 , 53 , 54 Fewer than 5% of SCLCs are negative for all neuroendocrine markers. However, these markers alone cannot be used to distinguish SCLC from NSCLC, because approximately 10% of NSCLCs will be immunoreactive for at least one of these neuroendocrine markers. 55 Ki-67 immunostaining is useful for distinguishing SCLC from carcinoid tumors. 37 , 43 , 56 , 57

The 2015 WHO classification recognizes 2 types of SCLC: SCLC and combined SCLC. 34 , 37 , 39 Combined SCLC consists of both SCLC histology and NSCLC histology (squamous cell, adenocarcinoma, spindle/pleomorphic, and/or large cell carcinoma). 34 , 37 , 38 No minimal percentage of NSCLC histologic elements is required for a classification of combined SCLC; if any elements are present along with SCLC, then this can be classified as combined SCLC. The exception is when SCLC is combined with LCNEC. At least 10% of the tumor should show LCNEC morphology to be classified as combined SCLC and LCNEC. 42 , 58 Patients with combined SCLC are treated using regimens for SCLC, because it is the more aggressive cancer. 58 Combined SCLC is more frequent in patients with limited-stage SCLC. Studies have shown that patients with NSCLC can undergo transformation to SCLC after treatment with EGFR tyrosine kinase inhibitors or immune checkpoint inhibitors. 59 , 60 Molecular profiling may be considered for patients with extensive-stage SCLC who have never smoked to help clarify the diagnosis and to evaluate for potential targeted treatment options. 34 , 61 - 64

The NCCN SCLC Panel adopted a combined approach for staging SCLC using both the AJCC TNM staging system and the older Veterans Administration (VA) scheme for SCLC. 5 , 65 The VA

Lung Study Group's 2-stage classification scheme has historically been used to define the extent of disease in patients with SCLC: (1) limited-stage disease is disease confined to the ipsilateral hemithorax, which can be safely encompassed within a radiation field; and (2) extensive-stage disease is disease beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion or hematogenous metastases. 66 Contralateral mediastinal and ipsilateral supraclavicular lymphadenopathy are generally classified as limited-stage disease, whereas the classification of contralateral hilar and supraclavicular lymphadenopathy is more controversial and treatment is individualized. 5 , 65 , 67 Approximately 66% of patients present with overt hematogenous metastases, which commonly involve the contralateral lung, liver, adrenal glands, brain, bones, and/or bone marrow. The AJCC revised the TNM staging system (8th edition) for lung cancer in 2018 (see the complete version of the NCCN Guidelines for SCLC, NCCN.org). 68 , 69

The NCCN SCLC Panel will continue to use both the VA and the TNM systems for staging SCLC. In applying the TNM classifications to the VA system, limited-stage SCLC is defined as stage I to III (T any, N any, M0) that can be safely treated with definitive radiation therapy, excluding T3–4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan (see the complete version of the NCCN Guidelines for SCLC, NCCN.org). Extensive-stage SCLC is defined as stage IV (T any, N any, M1a/b/c) or T3–4 due to multiple lung nodules as previously described. Because most of the literature on SCLC classifies patients based on the VA's definitions of limited-stage or extensive-stage disease, these definitions are often used for clinical decision-making. However, the TNM system is useful for selecting patients with T1-2, N0 disease who are eligible for surgery and for radiation treatment planning. 65 Clinical research studies should begin to include use of the TNM system, because it will allow for more precise assessments of prognosis and specific therapy in the future. 68

All patients with SCLC, even those with radiographically limited-stage disease, require systemic therapy either as primary or adjuvant therapy. Staging provides a therapeutic guideline for thoracic radiotherapy, which is indicated primarily for patients with limited-stage disease. Full staging includes a history and physical examination; CT scan with intravenous contrast of the chest/abdomen/pelvis; and brain imaging using MRI (preferred) or CT scan with intravenous contrast (see SCL-1 , page 1442). 67 , 70 However, once a patient has been found to have extensive-stage disease, further staging is not required, except for brain imaging. 5 Unilateral bone marrow aspirates and biopsies may be indicated in select patients with nucleated red blood cells on peripheral blood smear, neutropenia, or thrombocytopenia suggestive of bone marrow infiltration and with no other evidence of metastatic disease. Bone marrow involvement as the only site of extensive-stage disease occurs in fewer than 5% of patients. If limited-stage disease is suspected, a PET/CT scan (skull base to midhigh) can be considered to assess for distant metastases. 5 , 65 A bone scan can be performed if PET/CT is equivocal or not available; bone biopsy can be considered if bone imaging is equivocal.

PET scans can increase staging accuracy in patients with SCLC, because SCLC is a highly metabolic disease. 71 - 73 PET/CT is superior to PET alone. 73 Approximately 19% of patients who undergo PET are upstaged from limited-stage to extensive-stage disease, whereas only 8% are downstaged from extensive-stage to limited-stage disease. 67 For most metastatic sites, PET/CT is superior to CT imaging; however, PET/CT is inferior to MRI or CT for the detection of brain metastases (see the NCCN Guidelines for Central Nervous System Cancers at NCCN.org). 74 Changes in management based on PET staging were reported in approximately 27% of patients, mainly because of alterations in the planned radiation field as a result of improved detection of intrathoracic sites of disease. 67 , 72 , 75 Although PET/CT seems to improve staging accuracy in SCLC, pathologic confirmation is still required for PET/CT-detected lesions that would alter the stage.

Before surgical resection, pathologic mediastinal staging is required to confirm PET/CT scan results in patients with clinical stage I to IIA SCLC (T1–2,N0,M0) to rule out occult nodal disease. 5 However, mediastinal staging is not required if the patient is not a candidate for surgical resection or if nonsurgical treatment is planned. Invasive mediastinal staging can be performed either by

conventional mediastinoscopy or by minimally invasive techniques such as transesophageal endoscopic ultrasound-guided fine-needle aspiration, endobronchial ultrasound-guided transbronchial needle aspiration, or video-assisted thoracic surgery. 76 , 77

Thoracentesis with cytologic analysis is recommended if a pleural effusion is large enough to be safely accessed via ultrasound guidance. If thoracentesis does not show malignant cells, then thoracoscopy can be considered to document pleural involvement, which would indicate extensive-stage disease. The effusion should be excluded as a staging element if: (1) multiple cytopathologic examinations of the pleural fluid are negative for cancer; (2) the fluid is not bloody and not an exudate; and (3) clinical judgment suggests that the effusion is not directly related to the cancer. Pericardial effusions are classified using the same criteria.

Staging should not focus only on sites of symptomatic disease or on sites suggested by laboratory tests. Bone scans are positive in up to 30% of patients without bone pain or without an abnormal alkaline phosphatase level. Bone imaging with radiographs or MRI may be appropriate if PET/CT is equivocal. Brain imaging (MRI preferred or CT with contrast) can identify central nervous system metastases in 10%–15% of patients at diagnosis, of which approximately 30% are asymptomatic. Early treatment of brain metastases results in less chronic neurologic morbidity, arguing for the usefulness of early diagnosis in asymptomatic patients. Because of the aggressive nature of SCLC, staging should not delay the onset of treatment for more than 1 week; otherwise, many patients may become more seriously ill in the interval, with a significant decline in their performance status (PS).

Poor PS (3–4), extensive-stage disease, weight loss, and markers associated with excessive bulk of disease (such as lactate dehydrogenase [LDH]) are the most important adverse prognostic factors. Female gender, age younger than 70 years, normal LDH, and stage I disease are associated with a more favorable prognosis in patients with limited-stage disease. Younger age, good PS, normal creatinine level, normal LDH, and a single metastatic site are favorable prognostic factors in patients with extensive-stage disease. 78 , 79

For all patients with SCLC, systemic therapy is an essential component of appropriate treatment (see SCL-E 1 , page 1450). Many single-agent and combination systemic therapy regimens have been shown to be active in SCLC. The NCCN SCLC Panel has preference stratified all of the adjuvant, first-line, and subsequent therapy options for patients with SCLC. Certain regimens are recommended as “preferred” interventions, whereas others are designated as either “other recommended interventions” or “useful under certain circumstances.” For patients with extensive-stage disease, systemic therapy alone is recommended (see “ Extensive-Stage SCLC ,” page 1451). However, radiotherapy may be used in select patients for palliation of symptoms (see NCCN Guidelines for Palliative Care, available at NCCN.org).

In clinical practice, carboplatin is frequently substituted for cisplatin to reduce the risk of emesis, neuropathy, and nephropathy. 80 However, the use of carboplatin carries a greater risk of myelosuppression. 81 Small randomized trials in patients with SCLC have suggested similar efficacy of cisplatin and carboplatin regimens, as did a retrospective analysis in patients with extensive-stage disease. 80 , 82 , 83 A meta-analysis of individual patient data from 4 randomized studies compared cisplatin-based versus carboplatin-based regimens in patients with SCLC. 84 Of 663 patients included in this meta-analysis, 32% had limited-stage disease and 68% had extensive-stage disease. No significant difference was observed in response rate (67% vs 66%), progression-free survival (PFS) (5.5 vs 5.3 months), or overall survival (OS) (9.6 vs 9.4 months) in patients receiving cisplatin-containing versus carboplatin-containing regimens, suggesting equivalent efficacy in patients with SCLC.

The NCCN SCLC Panel recommends certain combination chemotherapy plus immunotherapy regimens as preferred options for patients with extensive-stage SCLC (see SCL-E 1 , page 1450). 85 - 87 In patients with extensive-stage disease and brain metastases, systemic therapy can be given either before or after brain radiotherapy depending on whether the patient has neurologic

symptoms (see SCL-5 , page 1443). 8 , 88 If systemic therapy is given first, brain radiotherapy is administered after completion of systemic therapy.

For many years, platinum plus etoposide had been recommended for patients with extensive-stage SCLC, with a preference for carboplatin over cisplatin due to its equivalent efficacy and more tolerable toxicity profile. However, the preferred regimens for extensive-stage SCLC now include the PD-L1–targeted immune checkpoint inhibitors, atezolizumab or durvalumab, plus platinum plus etoposide (see SCL-E 1 , page 1450). Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents. Atezolizumab or durvalumab may cause unique immune-mediated adverse events that are not seen with traditional cytotoxic chemotherapy; therefore, healthcare providers should be aware of the spectrum of potential immune-mediated adverse events, know how to manage these adverse events, and educate their patients about possible side effects. High-dose corticosteroids are generally recommended for immune-mediated adverse events based on the severity of the reaction. In addition, atezolizumab or durvalumab should be withheld or discontinued for severe or life-threatening immune mediated adverse events when indicated (see prescribing information; see also the NCCN Guidelines for Management of Immunotherapy-Related Toxicities, available at NCCN.org).

During systemic therapy for patients with extensive-stage disease, response assessment using CT with contrast of the chest/abdomen/pelvis should occur after every 2 to 3 cycles of systemic therapy and again at completion of therapy (see SCL-E 3 , this page). Serial brain imaging is also recommended in patients with extensive-stage disease who have asymptomatic brain metastases and are receiving systemic therapy before brain radiotherapy; brain MRI (preferred) or brain CT with contrast is recommended after every 2 cycles of systemic therapy and again at completion of therapy.

IMpower133, a phase 3 randomized trial, assessed the addition of atezolizumab to carboplatin plus etoposide in 403 patients with previously untreated extensive-stage SCLC. 87 In this trial, carboplatin plus etoposide was compared with the same chemotherapy plus atezolizumab followed by maintenance atezolizumab in 403 patients with previously untreated extensive-stage SCLC. Updated data show the median OS was 12.3 months (95% CI, 10.8–15.8) with the addition of atezolizumab versus 10.3 months (95% CI, 9.3–11.3) with chemotherapy alone (hazard ratio [HR], 0.76; 95% CI, 0.6–0.95; $P = .0154$). 85 Similarly, the 1-year OS rate was 51.9% for the atezolizumab regimen versus 39.0% for chemotherapy alone. Response rates were similar in both arms (60% with chemotherapy plus atezolizumab vs 64% with chemotherapy alone). The rate of grade 3 or 4 adverse events was similar in both groups (67.7% for the atezolizumab regimen vs 63.3% for chemotherapy alone). There were 4 deaths (2%) in the atezolizumab group versus 11 deaths (5.6%) in the chemotherapy alone group. The FDA recently approved different doses for atezolizumab when combined with carboplatin and etoposide for patients with extensive-stage SCLC.

The NCCN SCLC Panel recommends (category 1) carboplatin plus etoposide plus atezolizumab as a preferred first-line systemic therapy option followed by maintenance atezolizumab for patients with extensive-stage SCLC based on clinical trial data and the FDA approval (see SCL-E 1 , page 1450). 85 , 87 For this update, the NCCN Panel now recommends 2 different carboplatin/etoposide/atezolizumab regimens with slightly different doses for the maintenance atezolizumab; either 1,200 or 1,680 mg of maintenance atezolizumab is recommended. However, the category 1 recommendation is only for the regimen with 1,200 mg of maintenance atezolizumab because that dose was used in the clinical trial. 85 , 87

CASPIAN, a phase 3 randomized trial, assessed adding durvalumab to etoposide and either carboplatin or cisplatin followed by maintenance durvalumab in 537 patients with previously untreated extensive-stage SCLC. 86 , 89 In this trial, carboplatin (or cisplatin) plus etoposide was compared with the same chemotherapy plus durvalumab followed by maintenance durvalumab. Most patients received the carboplatin regimen (78%). Updated data from a 3-year analysis showed

that the median OS was 13.0 months (95% CI, 11.5–14.8) in the durvalumab plus chemotherapy group and 10.3 months (95% CI, 9.3–11.2) in the chemotherapy alone group (HR, 0.73; 95% CI, 0.59–0.91; $P = .0047$).⁹⁰ Similarly, the 1-year OS rate was 52.8% for the durvalumab regimen versus 39.3% for chemotherapy alone. The rate of serious adverse events was similar in both groups (32% vs 36%). The death rate from adverse events was also similar (2% vs 1%). In this trial, adding tremelimumab to durvalumab/etoposide carboplatin (or cisplatin) did not improve OS compared with platinum/etoposide (10.4 vs 10.5 months; HR, 0.82; 95% CI, 0.68–1.0). The NCCN SCLC Panel recommends (category 1) durvalumab plus etoposide plus (carboplatin or cisplatin) as a preferred first-line systemic therapy option followed by maintenance durvalumab for patients with extensive-stage SCLC based on clinical trial data and the FDA approval (see SCL-E 1 , page 1450).^{86 , 89 - 91}

Other recommended regimens for extensive-stage SCLC include etoposide with either cisplatin or carboplatin (see SCL-E 1 , page 1450). Before the recent favorable data on immunotherapy, many other chemotherapy combination regimens had been evaluated in patients with extensive-stage disease with little consistent evidence of benefit compared with EP. For example, the combination of irinotecan and cisplatin initially appeared to be better than EP. A small phase 3 Japanese trial reported that patients with extensive-stage SCLC who were treated with irinotecan plus cisplatin had a median survival of 12.8 months compared with 9.4 months for patients treated with EP ($P = .002$).⁹² In addition, the 2-year survival was 19.5% in the irinotecan plus cisplatin group versus 5.2% in the EP group.⁹² However, 2 subsequent large phase III trials performed in the United States comparing irinotecan plus cisplatin with EP failed to show a significant difference in response rate or OS between the regimens.^{93 , 94} A phase III randomized trial of 220 patients with extensive-stage SCLC found that median OS was slightly improved with irinotecan and carboplatin compared with carboplatin and oral etoposide (8.5 vs 7.1 months, $P = .04$).⁹⁵ Based on these studies, the cisplatin or carboplatin plus irinotecan regimens are included as options in the NCCN Guidelines for patients with extensive-stage disease. In addition, a meta-analysis suggested an improvement in PFS and OS with irinotecan plus platinum regimens compared with etoposide plus platinum regimens.⁹⁶ However, the relatively small absolute survival benefit needs to be balanced against the toxicity profile of irinotecan-based regimens. Therefore, the NCCN SCLC Panel recommends the irinotecan-based regimens as useful in certain circumstances for patients with extensive-stage SCLC (see SCL-E 1 , page 1450).

Many other strategies have been evaluated in an effort to improve on the recommended treatment for extensive-stage SCLC, including the addition of a third agent. As previously mentioned, the addition of atezolizumab or durvalumab does improve OS compared with chemotherapy alone.^{85 - 87 , 89 , 90} Despite the recent success with atezolizumab/chemotherapy or durvalumab/chemotherapy regimens, other immunotherapy-based strategies have not been as favorable. A phase 3 randomized trial in patients with extensive-stage SCLC reported that the addition of ipilimumab to etoposide with either cisplatin or carboplatin as first-line therapy did not improve either OS or PFS compared with chemotherapy alone.⁹⁷ Likewise, another phase III randomized trial reported that first-line therapy with pembrolizumab plus etoposide and either carboplatin or cisplatin followed by maintenance pembrolizumab did not improve OS compared with chemotherapy alone in patients with extensive-stage SCLC.³⁴

The benefits of antiangiogenic therapy have been evaluated in SCLC. In patients with limited-stage SCLC, a phase II study of irinotecan, carboplatin, and bevacizumab with concurrent radiotherapy followed by maintenance bevacizumab was terminated early because of an unacceptable incidence of tracheoesophageal fistulae. In extensive-stage SCLC, phase II trials of platinum-based chemotherapy plus bevacizumab have yielded promising response and survival data.^{98 - 101} However, at least 2 randomized trials have demonstrated no survival benefit for the addition of bevacizumab to standard chemotherapy.^{102 , 103} Currently, the NCCN SCLC Panel does not recommend use of bevacizumab in patients with SCLC. Overall, attempts to improve long-term survival rates in patients with SCLC through the addition of more agents or the use of dose-intense chemotherapy regimens, maintenance therapy, or alternating non-cross-resistant chemotherapy regimens have failed to yield significant advantages when compared with recommended

approaches.

In 2 trials, the addition of ifosfamide (or cyclophosphamide plus an anthracycline) to EP showed a modest survival advantage. 104 , 105 However, these findings have not been uniformly observed, and the addition of an alkylating agent, with or without an anthracycline, significantly increases hematologic toxicity when compared with EP alone. 106 Two phase III randomized trials have confirmed the lack of improvement in survival with 3-drug chemotherapy regimens compared with platinum plus etoposide in patients with extensive-stage SCLC. One of these studies assessed the combination of ifosfamide, etoposide, and epirubicin versus EP, whereas the other evaluated carboplatin plus etoposide with or without palifosfamide. 107 , 108 Similarly, the addition of paclitaxel to either cisplatin or carboplatin plus etoposide yielded promising results in phase 2 trials, but did not improve survival and was associated with unacceptable toxicity in a phase III study. 109 The use of maintenance or consolidation chemotherapy beyond 4 to 6 cycles of recommended treatment produces a minor prolongation of duration of response without improving survival and carries a greater risk of cumulative toxicity. 110 A meta-analysis reported that maintenance chemotherapy did not prolong OS. 111 The inability to destroy residual cells, despite the initial chemosensitivity of SCLC, suggests the existence of cancer stem cells that are relatively resistant to cytotoxic therapy. To overcome drug resistance, alternating or sequential combination therapies have been designed to expose the tumor to as many active cytotoxic agents as possible during initial treatment. 112 However, randomized trials have failed to show improved PFS or OS with this approach. 113 , 114 The NCCN SCLC Panel recommends 4 cycles of systemic therapy for patients with extensive-stage disease; however, some patients may receive up to 6 cycles based on the response and tolerability after 4 cycles.

Multidrug cyclic weekly chemotherapy was designed to increase dose intensity. Early phase II results of this approach were promising, although favorable patient selection was of some concern. 115 , 116 Nevertheless, no survival benefits were documented in randomized trials, and excessive treatment-related mortality was noted with multidrug cyclic weekly chemotherapy regimens. 117 - 120 The role of higher-dose chemotherapy for patients with SCLC remains controversial. Higher complete and partial response rates, and modestly longer median survival times, have been observed in patients receiving high chemotherapy doses compared with those given conventional doses of the same agents. 121 In general, however, randomized trials comparing conventional chemotherapy doses to an incrementally increased dose intensity up to 2 times the conventional dose have not consistently shown an increase in response rate or survival. 122 - 125 In addition, a meta-analysis of trials that compared recommended versus dose-intense variations of the cyclophosphamide, doxorubicin, and vincristine (CAV) and EP regimens found that increased relative dose intensity resulted in only a small, clinically insignificant enhancement of median survival in patients with extensive-stage disease. 126

Currently available cytokines (eg, granulocyte-macrophage colony-stimulating factor [GM-CSF], G-CSF) can ameliorate chemotherapy-induced myelosuppression and reduce the incidence of febrile neutropenia, but cumulative thrombocytopenia remains dose-limiting. Although trials involving patients with SCLC were instrumental in obtaining FDA approval for the clinical use of cytokines, 127 maintenance of dose intensity with growth factors does not prolong disease-free survival or OS. 128 , 129 Thus, the routine use of growth factors at the start of systemic therapy/radiation therapy is not recommended for patients with limited-stage SCLC. Trilaciclib or G-CSF may be used as prophylactic options to decrease the incidence of chemotherapy-induced myelosuppression when administering certain regimens for patients with extensive-stage SCLC (see SCL-D , page 1449). 130 - 133

The incidence of SCLC increases with age. Although the median age at diagnosis is older than 70 years, older patients are underrepresented in clinical trials. 134 Although advanced chronologic age does adversely affect tolerance to treatment, the functional status of an individual patient is much more useful than age in guiding clinical decision-making (see the NCCN Guidelines for Older Adult Oncology, available at NCCN.org). Older patients who are able to perform activities of daily living should be treated with combination systemic therapy (and radiotherapy, if indicated). 135 - 137 For

example, a subgroup analysis of the CONVERT trial suggests that concurrent chemoradiation yields equivalent median survival in older versus younger patients with limited-stage SCLC (29 vs 30 months; $P = .38$). 135 However, myelosuppression, fatigue, and lower organ reserves are encountered more frequently in older patients; therefore, they must be watched carefully during treatment to avoid excessive risk. 135 Greater attention to the needs and support systems of older patients is recommended to provide optimal care. Overall, older patients have a similar prognosis as stage-matched younger patients.

Randomized trials have indicated that less-intensive treatment (eg, single-agent etoposide) is inferior to combination chemotherapy (eg, platinum plus etoposide) in older patients with good PS (0–2). 138 , 139 A retrospective analysis in 8,637 older patients with limited-stage disease reported that chemoradiation increased survival compared with chemotherapy alone. 136 Several other strategies have been evaluated in older patients with SCLC. 83 , 140 - 142 The use of 4 cycles of carboplatin plus etoposide seems to yield favorable results, because the area-under-the-curve dosing of carboplatin takes into account the declining renal function of the aging patient. 142 However, targeting carboplatin to an area-under-the-curve of 5, rather than 6, is more reasonable in this population. 143 The usefulness of short-course, full-intensity chemotherapy has also been explored in older or infirm patients, and the results with only 2 cycles of chemotherapy seem to be acceptable, although this approach has not been directly compared with 4 to 6 cycles of therapy. 144 Prophylactic cranial irradiation (PCI) should be used with caution in older patients. Older patients (≥ 60 years) are at increased risk for cognitive decline after PCI; therefore, the risks and benefits of PCI versus close surveillance need to be discussed in detail with older patients. 145 - 148 A Dutch analysis in more than 5,000 patients suggests that median survival is decreased in older patients treated with PCI compared with younger patients regardless of stage. 149

Although SCLC is very responsive to initial treatment, most patients relapse with relatively resistant disease (see also “Surveillance,” page 1444). 150 , 151 The surveillance recommendations to assess for relapse in patients with SCLC are outlined in the algorithm (see SCL-6 , page 1444). For the current update, the algorithm now states that most NCCN Member Institutions use CT of the chest (plus/minus abdomen/pelvis) every 2 to 6 months (more frequently in years 1 to 2 and less frequently thereafter). The frequency of surveillance decreases during subsequent years because of the declining risk of recurrence. 152 If a new pulmonary nodule develops, it should prompt evaluation for a new primary lung cancer, because second primary tumors are a frequent occurrence in patients who are cured of SCLC. 153 , 154 It is important to monitor for brain metastases, which allows for early treatment before the development of potentially debilitating neurologic symptoms. The NCCN SCLC Panel recommends brain MRI (preferred) or brain CT with contrast every 3 to 4 months during year 1 for all patients and then every 6 months during year 2, regardless of the PCI status. Brain MRI is more sensitive than CT for identifying brain metastases and, therefore, is preferred over CT. PET/CT is not recommended for routine follow-up. Smoking cessation intervention is recommended for all patients with SCLC, because second primary tumors occur less commonly in patients who quit smoking (see the NCCN Guidelines for Smoking Cessation available at NCCN.org). 155 - 157 Former smokers should be encouraged to remain abstinent. The NCCN SCLC Panel also recommends the survivorship guidelines for appropriate patients (see the NCCN Guidelines for Survivorship).

Patients who experience relapse or those with primary progressive disease may be treated with subsequent systemic therapy regimens. These patients have a median survival of only 4 to 5 months when treated with older regimens; some of the newer regimens are associated with longer survival. Subsequent systemic therapy provides significant palliation in many patients, although the likelihood of response is highly dependent on the time from initial therapy to relapse. 158 If this interval is 6 months or less (refractory or resistant disease), response to most agents or regimens is poor ($\leq 10\%$). If more than 6 months have elapsed (sensitive disease), expected response rates are approximately 25%. Note that the ESMO Guidelines use cutoffs of 3 months or more for sensitive SCLC and less than 3 months for resistant SCLC. 159 Response rates are higher with newer agents such as lurbinectedin. For patients on subsequent systemic therapy, response assessment should occur after every 2 to 3 cycles using CT with contrast of the chest/abdomen/pelvis (see

SCL-E 3 , page 1452). Dose reduction or growth factor support should be considered for patients with a PS of 2 who are receiving subsequent systemic therapy. Recommended subsequent systemic therapy options for patients who have relapsed are listed in the algorithm and described here, including the clinical trial data supporting the recommendations (see SCL-E 2 , page 1451). 160 - 165

Lurbinectedin inhibits oncogenic transcription, leading to tumor cell apoptosis. A phase 2 basket trial assessed lurbinectedin as second-line therapy in 105 patients with SCLC who had received first-line platinum/etoposide; only 8% of patients had received immunotherapy. 160 Most patients (57%) had not received chemotherapy for 3 months or more. The overall response rate was 35% (95% CI, 26.2%–45.2%). The response rate was 22% (95% CI, 11.2%–37.1%) if the chemotherapy-free interval was less than 90 days. The response rate was 45% (95% CI, 32.1%–58.4%) if the chemotherapy-free interval was 90 days or more. Common grade 3 to 4 adverse events included anemia, leucopenia, neutropenia, and thrombocytopenia. There were no reported treatment-related deaths. The NCCN SCLC Panel recommends lurbinectedin as a preferred subsequent therapy option for patients with SCLC who have relapsed 6 months or less after therapy based on this trial and the FDA approval (see SCL-E 2 , page 1451). 160

In a subset analysis of the phase 2 trial previously discussed, lurbinectedin was assessed as second-line therapy in 20 patients with SCLC who had received first-line platinum/etoposide more than 6 months ago. 161 The overall response rate was 60% (95% CI, 36.1%–86.9%). The median OS was 16.2 months (95% CI, 9.6–upper level not reached). After 1 year, 60.9% of patients were alive; after 2 years, 27.1% were alive. Common grade 3 to 4 adverse events included neutropenia, anemia, thrombocytopenia, fatigue, and increased liver function tests. The NCCN SCLC Panel recommends lurbinectedin as a subsequent therapy option (one of many other recommended regimens) for patients with SCLC who have relapsed more than 6 months after therapy based on this study and the FDA approval (see SCL-E 2 , page 1451). 161

A randomized phase 3 trial compared single-agent intravenous topotecan with the combination regimen CAV as subsequent therapy for patients with SCLC who had relapsed at least 60 days after therapy. 166 Both arms had similar response rates (topotecan: 24.3% [26/107]; CAV: 18.3% [19/104]) and survival (25.0 vs 24.7 weeks), but intravenous topotecan caused less grade 4 neutropenia (37.8% vs 51.4%; $P < .001$). Compared with CAV, topotecan also improved symptoms of dyspnea, anorexia, hoarseness, and fatigue. In another phase 3 trial, oral topotecan improved OS compared with best supportive care (26 vs 14 weeks). 167 Single-agent topotecan is approved by the FDA as subsequent therapy for patients with SCLC who relapse after initial response to systemic therapy. Either oral or intravenous topotecan may be used, because efficacy and toxicity seem to be similar with either route. 167 , 168 Many practicing oncologists have noted excessive toxicity when using 1.5 mg/m² of intravenous topotecan for 5 days, and studies suggest that an attenuated dose may be equally efficacious with lower toxicity. 169 Published studies have yielded conflicting data regarding the usefulness of weekly topotecan in patients with relapsed SCLC. 170 , 171 The NCCN SCLC Panel recommends topotecan as a preferred subsequent therapy option for patients with SCLC who have relapsed 6 months or less after therapy based on these trials and the FDA approval (see SCL-E 2 , page 1451). 166 , 167

Immune checkpoint inhibitors have been evaluated in patients with relapsed SCLC. 172 - 175 CheckMate 032, a phase I–II trial, assessed nivolumab alone ($n = 147$) or various doses of nivolumab plus ipilimumab ($n=96$) for relapsed SCLC. 172 , 173 Updated data showed response rates were 11.6% for nivolumab and 21.9% for nivolumab plus ipilimumab. The 12- and 24-month OS rates were similar (nivolumab, 30.5% and 17.9%; nivolumab plus ipilimumab, 30.2% and 16.9%, respectively). Grade 3 to 4 adverse events were 12.9% (19/147) for nivolumab alone and 37.5% (36/96) for nivolumab plus ipilimumab. In patients receiving nivolumab alone, the most common grade 3 or 4 treatment-related adverse events were increased levels of lipase and aspartate aminotransferase and pneumonitis.

CheckMate 331, a randomized phase III trial, assessed nivolumab monotherapy versus topotecan or amrubicin in 569 patients with relapsed SCLC. 176 , 177 Data show that OS was 7.5 months in patients receiving nivolumab versus 8.4 months in those receiving chemotherapy (HR, 0.86; 95% CI, 0.72–1.04; P =.11). 176 OS was similar regardless of PD-L1 levels. Response rates were 13.7% for nivolumab compared with 16.5% for chemotherapy. Treatment-related deaths occurred in 2 patients receiving nivolumab and in 3 patients receiving chemotherapy. Fewer grade 3 to 4 adverse events occurred in patients receiving nivolumab compared with chemotherapy (14% vs 73%, respectively). A recent comparative effectiveness study reported that third-line therapy with nivolumab was associated with longer survival (5.7 months; 95% CI, 3.5–8.0) compared with other treatments such as paclitaxel or topotecan (3.8 months; 95% CI, 2.8–4.9; HR, 0.63; 95% CI, 0.44–0.90). 178 The 1-year OS rate was 28% with nivolumab versus 4% with the other treatments.

The NCCN SCLC Panel recommends nivolumab as a subsequent therapy option (other recommended) for patients who have relapsed 6 months or less after primary therapy based on clinical trial data, although the FDA has withdrawn the indication (see next paragraph). 172 , 173 , 176 , 177 , 179 However, the use of nivolumab is discouraged in patients whose disease progresses while on maintenance atezolizumab or durvalumab as part of first-line therapy. There are no data to suggest that if patients have progressed on immune checkpoint inhibitors, then giving them as subsequent therapy will be effective. Previously, the panel had recommended nivolumab plus ipilimumab as an option; however, this regimen was removed for Version 1.2021, because the combined regimen is more toxic and the OS is the same.

A combined analysis of 2 studies, one phase Ib (KEYNOTE-028) and one phase 2 (KEYNOTE-158), evaluated the activity of pembrolizumab in 83 evaluable patients with relapsed SCLC. 180 This analysis reported a response rate of 19.3% and a median OS of 7.7 months (95% CI, 5.2–10.1). Both OS and response rate were higher in those who were PD-L1 positive. Grade 3 or 4 adverse events occurred in 12% of patients and 2 patients died of treatment-related adverse events (pneumonitis and encephalitis). The NCCN SCLC Panel recommends pembrolizumab as a subsequent therapy option (other recommended) for patients with SCLC, regardless of PD-L1 levels, based on phase 1 and 2 data. 174 , 180

The FDA has withdrawn the subsequent therapy indications for nivolumab or pembrolizumab for patients with relapsed SCLC, because phase III randomized trial data did not show an improvement in OS. 176 However, the NCCN SCLC Panel still recommends nivolumab or pembrolizumab as subsequent therapy for certain patients (see SCL-E 2 , page 1451). The panel feels that nivolumab or pembrolizumab are just as effective as, and sometimes better than, the other subsequent therapy options; nivolumab or pembrolizumab are also less toxic. 176 , 178 , 181 In addition, a significant proportion of agents recommended as subsequent therapy options for patients with SCLC do not have an FDA indication in this setting but data show that they are effective (see “ Other Subsequent Therapy Options ,” next section). Patients with limited-stage SCLC who experience relapse and have not previously received immune checkpoint inhibitors may benefit from subsequent therapy with nivolumab or pembrolizumab. For the 2022 update (Version 1), the NCCN SCLC Panel revised the subsequent therapy recommendations for nivolumab or pembrolizumab to category 2A from category 3 (see SCL-E 2 , page 1451).

Immunotherapeutic agents, such as nivolumab and pembrolizumab, may cause unique immune-mediated adverse events that are not seen with traditional cytotoxic chemotherapy; therefore, healthcare providers should be aware of the spectrum of potential immune-mediated adverse events, know how to manage these adverse events, and educate their patients about possible side effects (see the NCCN Guidelines for Management of Immunotherapy-Related Toxicities, available at [NCCN.org](https://www.nccn.org)). 182 , 183 For patients with immune-mediated adverse events, high-dose corticosteroids are generally recommended based on the severity of the reaction. Nivolumab or pembrolizumab should be withheld or discontinued for severe or life-threatening immune-mediated adverse events when indicated (prescribing information is available online).

The optimal duration of subsequent systemic therapy has not been fully explored. For cytotoxic chemotherapy agents, the duration of treatment is usually short, and the cumulative toxicity is frequently limiting even in patients who experience response. For these reasons, subsequent systemic therapy should be continued until progression of disease or development of unacceptable toxicity (see SCL-7 , page 1445). Additional subsequent systemic therapy (eg, third line) can be considered if patients are still PS 0 to 2.

Paclitaxel was assessed in a phase II study in patients with refractory or relapsed SCLC; 24% of patients responded (5/21). 184 Grade 3 to 4 toxicity included neutropenia, infection, rash, neuropathy, and pulmonary toxicity. Another phase II study of paclitaxel in patients with refractory SCLC yielded a response rate of 29% (7/24; 95% CI, 12%–51%). 185 A retrospective study in 185 patients showed that third- or fourth-line therapy with paclitaxel was associated with a response rate of 17%. Toxicity was similar in patients with PS 2 compared with PS 0 to 1 (63% vs 62%). 186 Docetaxel was assessed in a phase II trial in patients with previously treated SCLC; 25% of patients responded (7/28). Reported toxicities included neutropenia and asthenia. 187 Irinotecan was assessed in a phase 2 study in patients with refractory or relapsed SCLC; 47% of patients responded (7/15; 95% CI, 21.4%–71.9%); myelosuppression, diarrhea, and pulmonary toxicity were reported. 188

Data suggest that temozolomide may be useful for patients with SCLC, especially those with brain metastases and methylated O 6 -methylguanine-DNA methyltransferase (MGMT). 163 , 189 , 190 A phase II study assessed temozolomide in patients with relapsed or refractory SCLC. In patients with sensitive SCLC, the overall response rate was 23% (95% CI, 12%–37%). The response rate was improved for patients with methylated MGMT compared with those with unmethylated MGMT (38% vs 7%; P =.08).

Another phase III randomized trial assessed carboplatin plus etoposide compared with oral topotecan in 162 patients with SCLC who had relapsed more than 3 months after therapy. 191 The median PFS was 4.7 months (90% CI, 3.9–5.5) in the chemotherapy group versus 2.7 months (90% CI, 2.3–3.2) in the oral topotecan group (HR, 0.57; 90% CI, 0.41–0.73). Grade 3 to 4 adverse events included thrombocytopenia, neutropenia, anemia, febrile neutropenia, and asthenia. In the topotecan group, 2 treatment-related deaths occurred; no deaths occurred in the chemotherapy group. The NCCN SCLC Panel recommends the original platinum regimen as preferred for patients with SCLC who have relapsed more than 6 months after therapy based on this trial. 191 The panel added a caveat that the use of immune checkpoint inhibitors is discouraged if patients have progressed on maintenance atezolizumab or durvalumab. 5 , 158 , 192 Since topotecan is also effective in this setting, it is a recommended option (other recommended regimen) based on this trial.

A phase III trial (JCOG0605) from Japan in patients with sensitive relapsed SCLC reported that the combination of cisplatin, etoposide, and irinotecan improved survival compared with topotecan (median survival, 18.2 vs 12.5 months; HR, 0.67; 90% CI, 0.51–0.88; P =.0079). However, the toxicity of this approach was significant and it is not recommended for subsequent therapy. 193 Amrubicin is an active drug in patients with relapsed or refractory SCLC. 194 - 197 However, grade 3 to 4 toxicity, primarily neutropenia, is common. 198 , 199 A phase 3 trial reported that amrubicin did not improve OS as second-line treatment of SCLC when compared with topotecan, except in a subset of patients with refractory disease. 200 Amrubicin is not approved by the FDA for patients with SCLC.

The NCCN SCLC Panel recommends the following subsequent therapies for patients with SCLC based on clinical expertise and trial data. For relapse of 6 months or less, the preferred regimens are topotecan (orally or intravenously), lurbinectedin, or a clinical trial; other recommended regimens include paclitaxel, docetaxel, irinotecan, temozolomide, CAV, oral etoposide, vinorelbine, gemcitabine, nivolumab, and pembrolizumab (category 2A for all agents). Bendamustine is also recommended (category 2B). For the 2022 update, the panel voted to recommend all of these subsequent therapy options regardless of the time since relapse. 201 Previously, these agents

were only recommended for relapse of 6 months or less. For relapse more than 6 months, the preferred regimen is the original regimen. 191 , 192 , 202 , 203 However, the NCCN SCLC Panel added a caveat that the use of immune checkpoint inhibitors is discouraged in patients who relapse after 6 months while on maintenance atezolizumab or durvalumab. 5 , 158 , 192 Other recommended options for relapse greater than 6 months now include topotecan, paclitaxel, docetaxel, irinotecan, temozolomide, CAV, oral etoposide, vinorelbine, gemcitabine, nivolumab, pembrolizumab, and lurbinectedin (category 2A for all agents). Bendamustine is also recommended (category 2B).

The “Principles of Radiation Therapy” section in the algorithm describes the radiation doses, target volumes, and normal tissue dose-volume constraints for limited-stage SCLC, and includes references to support the recommendations; PCI and treatment of brain metastases are also discussed (see the complete version of the NCCN Guidelines for SCLC). The “Principles of Radiation Therapy” section in the NSCLC algorithm (available at NCCN.org) may also be useful (eg, general principles of radiotherapy, palliative radiotherapy).

SCLC is a poorly differentiated high-grade neuroendocrine carcinoma. 21 Most cases of SCLC are caused by cigarette smoking. 4 The full NCCN Guidelines for SCLC provide recommended management for patients with SCLC, including diagnosis, primary treatment, surveillance for relapse, and subsequent treatment.. This section of the NCCN Guidelines focuses on metastatic (known as extensive-stage) SCLC, which is more common than limited-stage SCLC.

The NCCN SCLC Panel now recommends the following subsequent therapies for patients who have relapsed more than 6 months after therapy: topotecan, paclitaxel, docetaxel, irinotecan, temozolomide, CAV, oral etoposide, vinorelbine, gemcitabine, nivolumab, pembrolizumab, and lurbinectedin (category 2A for all); bendamustine is a category 2B recommendation in this setting (see SCL-E 2 , page 1451). 201 However, the original regimen is the preferred regimen for patients who have relapsed more than 6 months after therapy. 191 , 192 , 202 , 203 The FDA has removed the subsequent therapy indications for nivolumab or pembrolizumab for SCLC, because phase III randomized trial data did not show an improvement in OS. 176 However, the NCCN SCLC Panel still recommends subsequent therapy with nivolumab or pembrolizumab in certain settings. Patients with limited-stage SCLC who progress and have not previously received immune checkpoint inhibitors may benefit from subsequent therapy with nivolumab or pembrolizumab. The panel feels that nivolumab or pembrolizumab are just as effective as, and sometimes better than, and less toxic than the other subsequent therapy options. 176 , 181 For the current version, the NCCN SCLC Panel revised the subsequent therapy recommendations for nivolumab or pembrolizumab to category 2A from category 3, regardless of the time since relapse.

The FDA recently approved different doses for atezolizumab when combined with carboplatin and etoposide for patients with extensive-stage SCLC. The NCCN Panel now recommends a new carboplatin/etoposide/atezolizumab regimen with slightly different dosing for the maintenance atezolizumab; 1,680 mg of maintenance atezolizumab is recommended. However, the category 1 recommendation is only for the regimen with 1,200 mg of maintenance atezolizumab because that dose was used in the clinical trial. 85 , 87

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The NCCN Guidelines Staff have no conflicts to disclose.

The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:

Charles Florsheim, JD: GO2 Foundation for Lung Cancer

Billy W. Loo, Jr., MD, PhD: Tibaray, Inc.

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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

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