Systemic Therapy for Small-Cell Lung Cancer: ASCO-Ontario Health (Cancer Care Ontario) Guideline

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ABSTRACT

PURPOSE To provide evidence-based recommendations to practicing clinicians on the management of patients with small-cell lung cancer.

METHODS An Expert Panel of medical oncology, thoracic surgery, radiation oncology, pulmonary, community oncology, research methodology, and advocacy experts were convened to conduct a literature search, which included systematic reviews, meta-analyses, and randomized controlled trials published from 1990 through 2022. Outcomes of interest included response rates, overall survival, disease-free survival or recurrence-free survival, and quality of life. Expert Panel members used available evidence and informal consensus to develop evidence-based guideline recommendations.

RESULTS The literature search identified 95 relevant studies to inform the evidence base for this guideline.

RECOMMENDATIONS Evidence-based recommendations were developed to address systemic therapy options, timing of therapy, treatment in patients who are older or with poor performance status, role of biomarkers, and use of myeloid-supporting agents in patients with small-cell lung cancer.
Additional information is available at www.asco.org/thoracic-cancer-guidelines.

ACCOMPANYING CONTENT

Appendix

Data Supplement

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INTRODUCTION

Small-cell lung cancer (SCLC) is an aggressive, poorly differentiated, neuroendocrine carcinoma with more than 150,000 people diagnosed worldwide each year.[1,2] Nearly all patients with SCLC have a history of cigarette use. In the United States, SCLC accounts for approximately 15% of all new lung cancer cases and its incidence is declining because of decreased rates of cigarette smoking.[3]

SCLC is usually staged using the Veterans Administration Lung Study Group staging system, which defines limited-stage (LS-SCLC) as disease confined to one hemithorax within a tolerable radiation field, and extensive-stage (ES-SCLC) as disease extending beyond LS-SCLC, including malignant pleural effusion, contralateral lung involvement, and hematogenous metastases.[4] Over two thirds of patients present with extensive-stage disease at diagnosis.

LS-SCLC is potentially curable when treated with concurrent chemoradiotherapy, with 5-year overall survival (OS) rates reported as up to 34%.[5] ES-SCLC remains an incurable disease with a 5-year OS rate of <5%.[2,3] Until recently, the major improvements in outcomes achieved for patients with SCLC were due to advances in radiotherapy, particularly in those with limited-stage disease.[6,7] Since the last ASCO update in SCLC management in 2015,[8] there have now been significant advances in the systemic treatment of ES-SCLC with the incorporation of immune checkpoint inhibitors (ICIs) into first-line therapy,[9,10] and additional options for subsequent treatment of recurrent disease.[11,12]

Importantly, any discussion of the management of patients with SCLC would be incomplete without a strong recommendation for smoking cessation, not only to decrease the risk of developing lung cancer, but also to improve the outcomes of people already diagnosed with lung cancer. Numerous studies have reported that smoking cessation results in superior outcomes in terms of cancer recurrence, tolerance of and response to treatment, and OS for patients with both early-stage and advanced lung cancer.[13-17] The purpose of this ASCO and Ontario Health (Cancer Care Ontario) updated guideline is to summarize recommendations for systemic therapy in the management of patients with SCLC in light of recent advances.

THE BOTTOM LINE

Systemic Therapy for Small-Cell Lung Cancer: ASCO-Ontario Health (Cancer Care Ontario) Guideline

Guideline Questions

What is the optimal systemic therapy for patients with small-cell lung cancer (SCLC)?

Target Population

Patients with SCLC.

Target Audience

Medical oncologists, radiation oncologists, thoracic surgeons, pulmonologists, pathologists, radiologists, primary care physicians, nurse practitioners, physician assistants, pharmacists, nurses, and other providers.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

Recommendation 1.1

Adjuvant chemotherapy should be offered to patients with resected limited-stage SCLC who have adequate performance status (PS) (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Strong).

Recommendation 1.2

Adjuvant chemotherapy should consist of four cycles of cisplatin (PE) or carboplatin plus etoposide (CE) (Type: Informal consensus, benefits outweigh harms; Evidence quality: Not applicable; Strength of recommendation: Weak).

Recommendation 1.3

Adjuvant chemotherapy should be initiated within 8 weeks from resection (Type: Informal consensus, benefits outweigh harms; Evidence quality: Not applicable; Strength of recommendation: Weak).

Recommendation 2.1

Cisplatin and etoposide should be administered with concurrent radiotherapy in patients with limited-stage small-cell lung cancer (LS-SCLC) (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 2.2

Carboplatin and etoposide may be offered as systemic therapy concurrent with radiation for patients with LS-SCLC and contraindications to the use of cisplatin (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Strong).

Recommendation 2.3

Chemotherapy should be commenced as soon as possible in patients with LS-SCLC and not deferred until radiation therapy can be started (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Strong).

Recommendation 3.1

First-line systemic therapy with CE or PE plus immunotherapy (atezolizumab or durvalumab) followed by maintenance immunotherapy should be offered to patients with extensive-stage small-cell lung cancer (ES-SCLC) if there are no contraindications to immunotherapy (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 4.1

In patients with relapsed SCLC with a chemotherapy-free interval of <90 days, single-agent chemotherapy may be offered. Preferred agents are topotecan or lurbinectedin (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Qualifying statement. Single-agent chemotherapy is preferred over multi-agent chemotherapy due to concerns regarding the balance of risks versus benefits.

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THE BOTTOM LINE (CONTINUED)

Recommendation 4.2

In patients with relapsed SCLC with a chemotherapy-free interval of at least 90 days, rechallenge with a platinum-based regimen or single-agent chemotherapy (preferred agents are topotecan or lurbinectedin) may be offered (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Recommendation 4.3

In patients with relapsed SCLC who had progression while on maintenance immunotherapy, there is no evidence to support continuation of immunotherapy (Type: Informal consensus, benefit to harm ratio not assessable; Evidence quality: Not applicable; Strength of recommendations: Strong).

Recommendation 4.4

In an immunotherapy-naïve patient, second-line immunotherapy alone is not recommended outside of the clinical trial setting. Participation in clinical trials to better identify predictive biomarkers is encouraged (Type: Evidence based, no net benefit; Evidence quality: Moderate; Strength of recommendation: Strong).

Recommendation 5.1

Older patients with LS-SCLC and Eastern Cooperative Oncology Group (ECOG) PS 0-1 may be offered standard treatment with concurrent chemoradiotherapy with curative intent (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Recommendation 5.2

Patients with LS-SCLC and ECOG PS 2 due to SCLC may be offered standard treatment with concurrent chemo-radiotherapy with curative intent (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 5.3

Patients with LS-SCLC and ECOG PS 3-4 due to SCLC may be offered initial chemotherapy followed by sequential radiotherapy if there is improvement in PS (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 5.4

Older patients with ES-SCLC and ECOG PS 0-1 may be offered standard treatment with carboplatin and etoposide plus immunotherapy (atezolizumab or durvalumab) followed by maintenance immunotherapy (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Recommendation 5.5

Patients with ES-SCLC and ECOG PS 2 may be offered carboplatin and etoposide plus immunotherapy (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 5.6

Patients with ES-SCLC and ECOG PS 3-4 due to SCLC may be offered chemotherapy (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 6.1

Patients with non–small-cell lung cancer (NSCLC) harboring an *EGFR* mutation that has transformed to SCLC should be managed with CE or PE (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Qualifying statement. There is insufficient evidence to support the use of immunotherapy in this setting. Clinical trial enrollment should be offered whenever possible.

Recommendation 6.2

EGFR inhibitor may be continued with chemotherapy in patients with NSCLC harboring an *EGFR* mutation that has transformed to SCLC (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

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THE BOTTOM LINE (CONTINUED)

Recommendation 7.1

There is no evidence to support the use of molecular profiling and biomarker analysis to guide standard treatment in patients with de novo SCLC (Type: Evidence based, benefit to harm ratio not assessable; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 8.1

Trilaciclib or granulocyte colony-stimulating factor (G-CSF) may be offered as a myeloid supportive agent for patients with untreated or previously treated ES-SCLC who are undergoing treatment with chemotherapy or chemoimmunotherapy (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).

Recommendation 8.2

G-CSF may be offered in patients with LS-SCLC who are undergoing chemoradiotherapy (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).

Additional Resources

Definitions for the quality of the evidence and strength of recommendation ratings are available in Appendix Table A2 (online only). More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/thoracic-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

In addition, ASCO has appraised and endorses the American Society for Radiation Oncology guidelines on radiotherapy for patients with SCLC.[18]

GUIDELINE QUESTIONS

This clinical practice guideline addresses eight overarching clinical questions: (1) What is the optimal treatment regimen for adjuvant systemic therapy in patients with resected SCLC? (2) What is the optimal systemic therapy for use with concurrent radiotherapy in patients with LS-SCLC? (3) What is the optimal first-line systemic therapy for patients with ES-SCLC? (4) What systemic therapy options are available for treating relapsed SCLC? (5) What is the best management approach for treatment-naïve patients who are older or who have poor performance status (PS)? (6) What is the optimal systemic therapy for patients with non–small-cell lung cancer (NSCLC) harboring an epidermal growth factor receptor (*EGFR*) mutation that has transformed to SCLC? (7) What is the role of biomarkers, including molecular profiling in guiding therapy for patients with SCLC? (8) Which myeloid supportive agents may be considered for use in patients with SCLC?

METHODS

Guideline Development Process

This systematic review (SR)–based joint guideline product was developed by a multidisciplinary Expert Panel with representatives from OH (CCO), a patient representative, and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1). Four full panel and several subgroup panel meetings were held and members were asked to provide ongoing input on the quality and assessment of the evidence, generation of recommendations, draft content, as well as review and approve drafts during the entire development of the guideline. ASCO staff met routinely with the expert panel co-chairs and corresponded with the panel via e-mail to coordinate the process to completion. The guideline recommendations were sent for an open comment period of 2 weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review, and submitted to the *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Evidence Based Medicine Committee (EBMC) before publication. In addition to the ASCO approval process, OH (CCO) provided approval through its Program in Evidence-Based Care approval internal and external processes. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a SR of evidence identified through online searches of PubMed (January 1990-December 2022) and Cochrane Library (January 2010-August 2022) of phase II and III randomized clinical trials (RCTs), and clinical experience. Articles were selected for inclusion in the SR based on the following criteria.

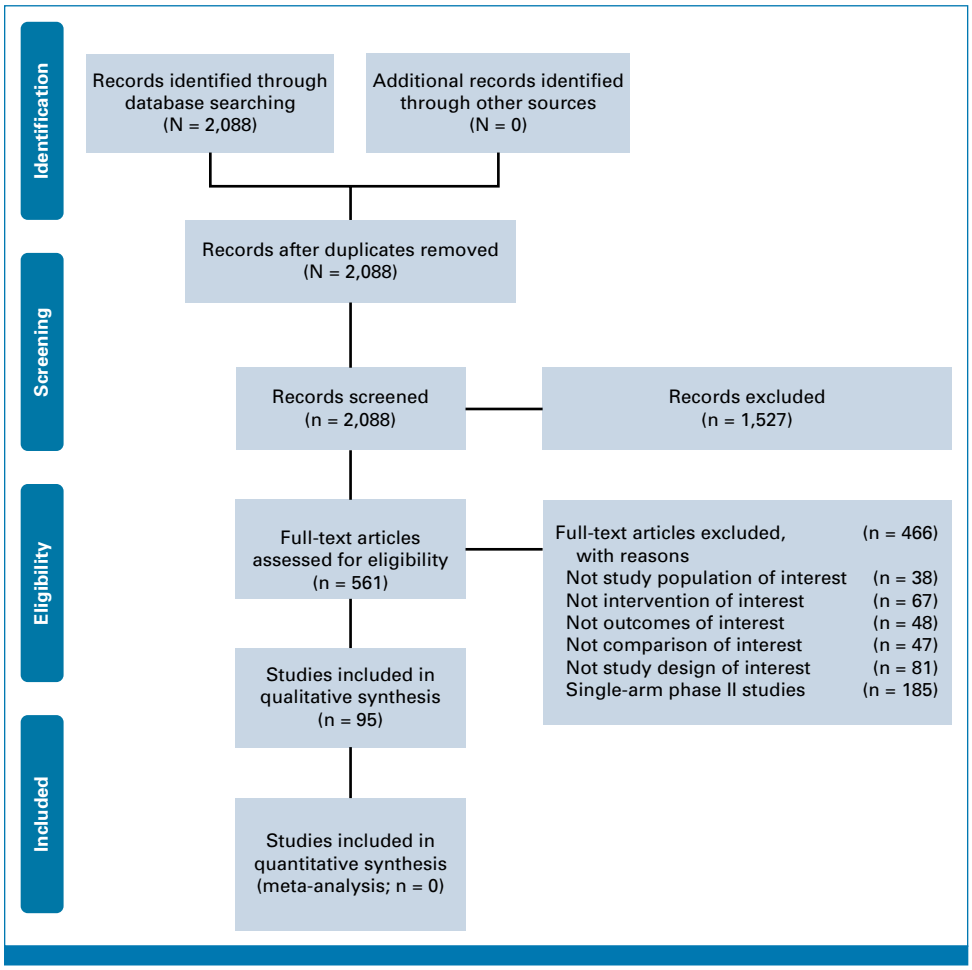

FIG 1. PRISMA flow diagram. From Moher et al.[117]

- Population: Patients with SCLC
- Interventions and comparisons: Systemic therapies, biomarkers, and myeloid supportive agents
- Outcomes: Survival, response rates (RRs), quality of life (QoL), and toxicity
- Study designs: SRs, meta-analyses (MAs), phase III RCTs, and phase II RCTs for some specific research questions.

Articles were excluded from the SR if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; and (3) published in a non-English language. The guideline recommendations are crafted, in part, using the *Guidelines Into Decision Support* (GLIDES) methodology and accompanying BRIDGE-Wiz software.[19] In addition, a guideline implementability review was conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for type and strength of the recommendation, and evidence quality are provided with each recommendation. The quality of the evidence for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process.[20,21] GRADE quality assessment labels (ie, high, moderate, low, very low) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel co-chairs and reviewed by the full Expert Panel.

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by ASCO to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The

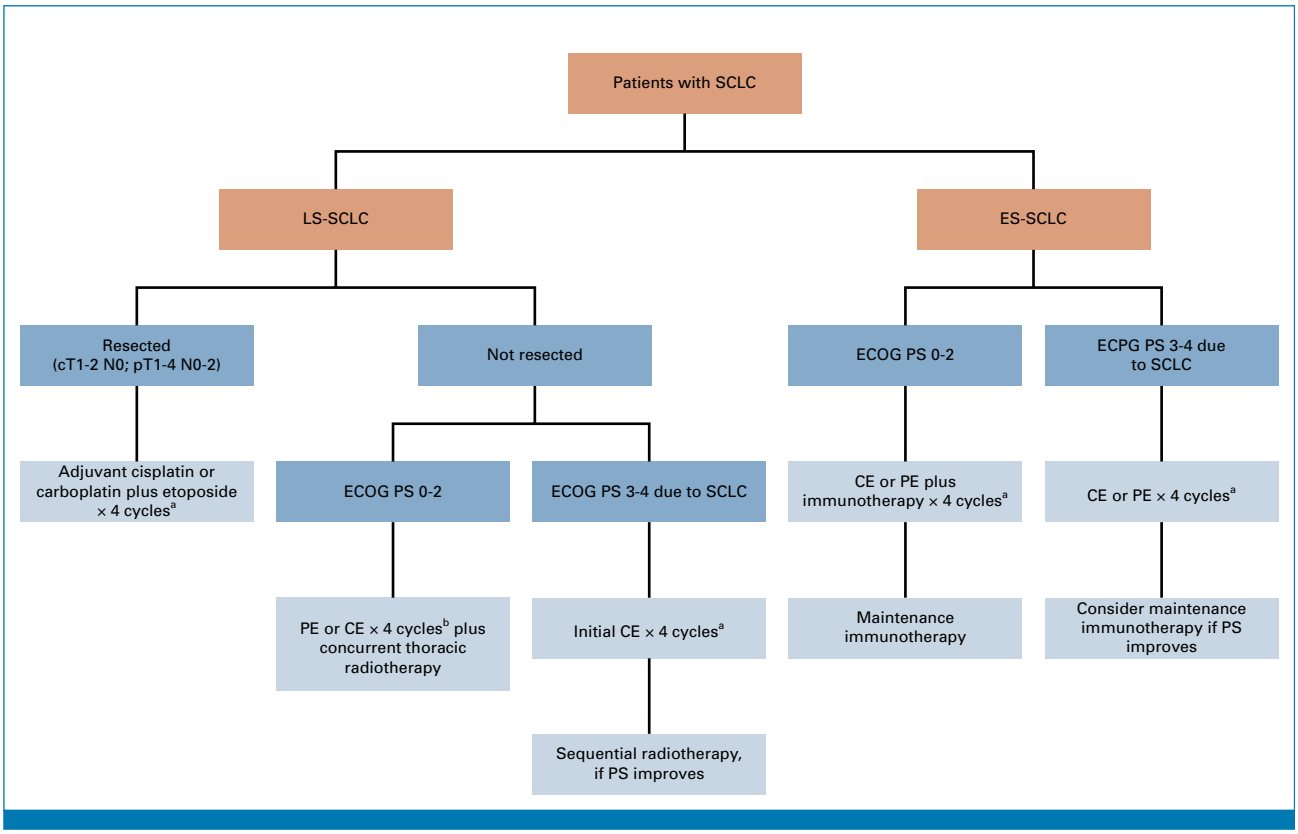

FIG 2. Systemic therapy for SCLC algorithm. [a]May use trilaciclib or G-CSF if clinically indicated. [b]May use G-CSF if clinically indicated. CE, carboplatin plus etoposide; cT, clinical TNM classification; ECOG, Eastern Cooperative Oncology Group; ES-SCLC, extensive-stage small-cell lung cancer; G-CSF, granulocyte colony-stimulating factor; LS-SCLC, limited-stage small-cell lung cancer; PE, cisplatin plus etoposide; PS, performance status; pT, pathologic TNM classification; SCLC, small-cell lung cancer.

information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations specify the level of confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO does not endorse third-party drugs, devices, services, or therapies used to diagnose, treat, monitor, manage, or alleviate health conditions. Any use of a brand or trade name is for identification purposes only. ASCO provides this information on an "as is" basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions. OH (CCO) makes no representations or guarantees of any kind whatsoever regarding the report content or its use or application and disclaims any responsibility for its use or application in any way.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at https://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of

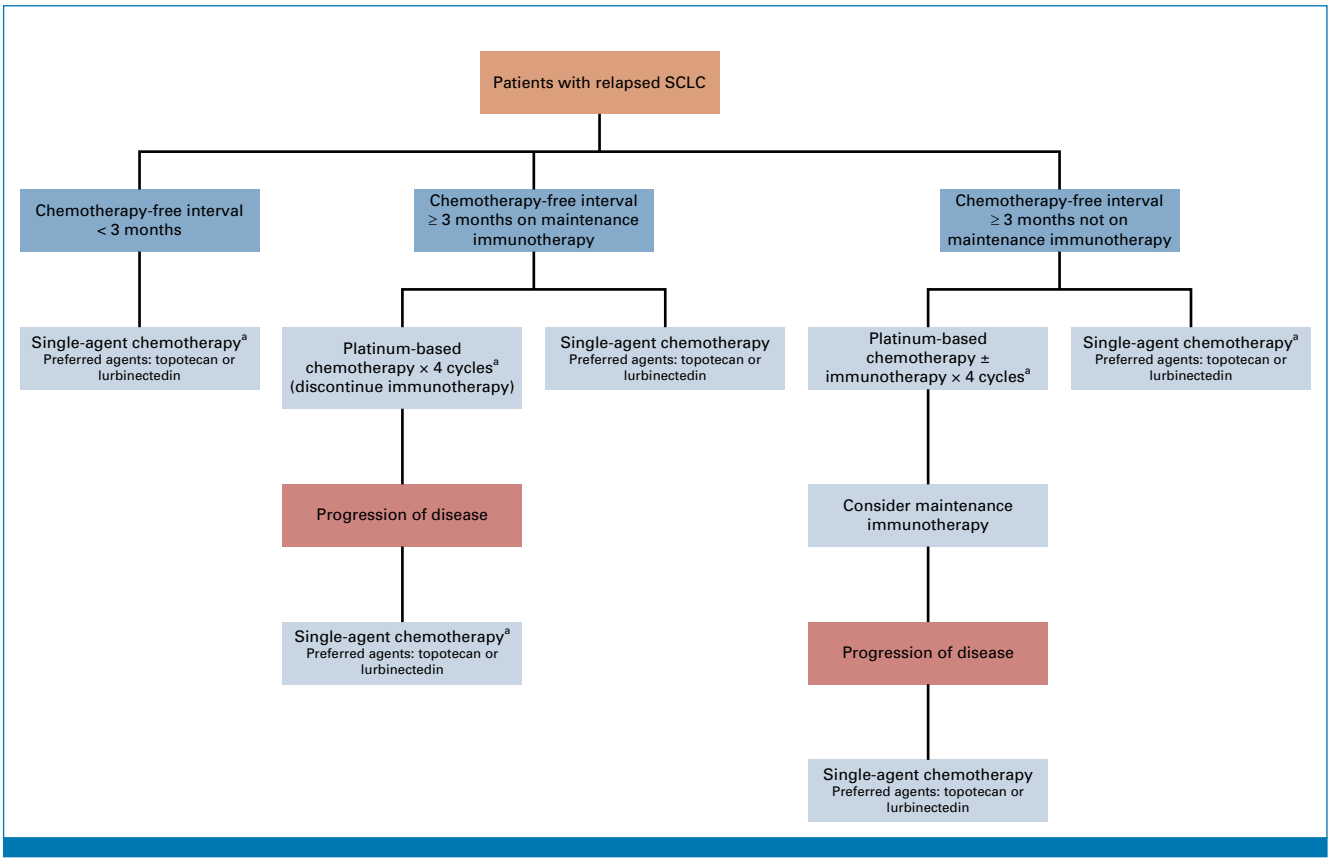

FIG 3. Systemic therapy for relapsed SCLC algorithm. [a]May use trilaciclib or granulocyte colony-stimulating factor if clinically indicated. SCLC, small-cell lung cancer.

the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Characteristics of Studies Identified in the Literature Search

A total of 2,088 articles were identified in the literature search. After applying the eligibility criteria, 95 remained, forming the evidentiary basis for the guideline recommendations. These include 19 SRs and MAs,[22-40] three pooled analyses,[41-43] 34 phase III RCTs,[44-77] 26 phase II studies,[78-103] and four prospective[104-107] and nine retrospective cohort studies.[108-116] Primary studies already included in the SRs and MA are not included in this total.

The identified trials were published between 1990 and 2022. The studies compared different systemic therapy treatments, timing of therapy, therapy in patients who are older or with poor PS, biomarker testing, and use of myeloid supportive agents. The outcomes included OS, disease-free survival, progression-free survival (PFS), RR, QoL, toxicity, and febrile neutropenia. Figure 1 presents the SR flow diagram. Evidence summary tables for all included studies are available in the Data Supplement (online only).

Evidence Quality Assessment

Study quality was formally assessed for the RCTs identified. Design aspects related to the individual study quality were assessed by the research methodologist, with factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, etc, generally indicating an unclear to high overall risk-of-bias assessment for most of the identified evidence. Details of the assessment can be found in the GRADE tables included in the Data Supplement. Refer to Methodology Manual for definitions of ratings for overall potential risk of bias.

RECOMMENDATIONS

Clinical Question 1

What is the optimal treatment regimen for adjuvant systemic therapy in patients with resected SCLC? (1) Who should be offered adjuvant systemic therapy for resected SCLC? (2) What is the optimal timing for receiving adjuvant systemic therapy?

Recommendation 1.1

Adjuvant chemotherapy should be offered to patients with resected limited-stage SCLC who have adequate PS (Type:

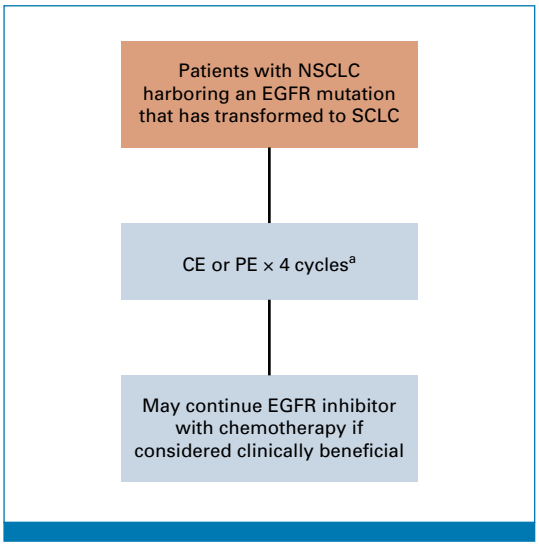

FIG 4. Systemic therapy for *EGFR*-mutant NSCLC transformed to SCLC algorithm. [a]May use trilaciclib or granulocyte colony-stimulating factor if clinically indicated. CE, carboplatin plus etoposide; NSCLC, non–small-cell lung cancer; PE, cisplatin plus etoposide; SCLC, small-cell lung cancer.

Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Strong).

Literature review and clinical interpretation. Surgery is performed in fewer than 5% of patients with SCLC, primarily in those with clinical stage I-IIA (T1a-2b N0) disease. There are no randomized trials of adjuvant systemic therapy in SCLC, so the evidence base for adjuvant therapy is of lower quality than that for NSCLC in which there are multiple randomized trials of adjuvant systemic therapy.

The literature review identified only one population-based cohort study of patients with early-stage SCLC.[114] This study includes patients from the National Cancer Database with T1-2 N0 M0 SCLC who had surgical resection from 2003 to 2011. Patients with a prior malignancy, neoadjuvant therapy, incomplete resection, missing data, or treated outside the reporting facility were excluded. Of 1,574 patients who underwent surgical resection, 954 were included in the analysis. Patients were treated with surgery alone, surgery plus chemotherapy, surgery plus chemotherapy and radiation, or radiation alone. Patients treated with surgery and chemotherapy ± radiation had a significantly longer median OS than those who had surgery alone (66 months *v* 42.1 months), with a significant improvement in 5-year OS rate (52.7% *v* 40.4%; $P < .01$). In a multivariate analysis, the use of adjuvant chemotherapy alone (hazard ratio [HR], 0.78; 95% CI, 0.63 to 0.95) and the use of adjuvant chemotherapy plus radiation to the brain (HR, 0.52; 95% CI, 0.36 to 0.75) were associated with significant improvements in OS. Interestingly, the use of chemotherapy plus radiation to the chest was not associated with a significant improvement in OS (HR, 0.88; 95% CI, 0.63 to 1.23). The design of this study is subject to potential selection bias, hence the quality of the evidence is considered low. However, the committee agreed with a strong recommendation for the use of adjuvant chemotherapy for patients who have undergone complete resection of limited-stage SCLC.

Recommendation 1.2

Adjuvant chemotherapy should consist of four cycles of cisplatin (PE) or carboplatin plus etoposide (CE) (Type: Informal consensus, benefits outweigh harms; Evidence quality: Not applicable; Strength of recommendation: Weak).

Literature review and clinical interpretation. There were no data identified comparing different types of adjuvant chemotherapy in patients with resected SCLC. The committee felt that it was reasonable to extrapolate from data in other clinical scenarios in SCLC in which platinum plus etoposide is the preferred regimen.

Recommendation 1.3

Adjuvant chemotherapy should be initiated within 8 weeks from resection (Type: Informal consensus, benefits outweigh harms; Evidence quality: Not applicable; Strength of recommendation: Weak).

Literature review and clinical interpretation. There were no data identified examining the appropriate time frame in which to initiate adjuvant chemotherapy in patients with resected SCLC. The committee felt it was reasonable to extrapolate from data in patients with NSCLC where it is recommended that adjuvant chemotherapy should ideally be initiated within 8 weeks of resection.

Clinical Question 2

What is the optimal systemic therapy for use with concurrent thoracic radiotherapy in patients with LS-SCLC? (1) What is the optimal timing for starting systemic therapy in LS-SCLC?

Recommendation 2.1

Cisplatin and etoposide should be administered with concurrent radiotherapy in patients with LS-SCLC (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

Literature review and clinical interpretation. The combination of cisplatin and etoposide has been the standard chemotherapy regimen used in the majority of trials evaluating concurrent chemoradiotherapy in patients with limited-stage SCLC.[39] Standard dosing should be used, that is, cisplatin 60-80 mg/m² once on day 1 and etoposide 100-120 mg/m² once on days 1, 2, and 3 of an every 3-week cycle with attempts to minimize dose reductions, especially during the first two cycles.[118] Given that there is no evidence

of a survival benefit for extending chemotherapy to six cycles, chemotherapy is usually limited to four cycles.[119]

The updated SR identified only one RCT where cisplatin and etoposide were compared to cisplatin and irinotecan in patients with limited-stage SCLC.[120] In this Japanese trial, patients with previously untreated limited-stage SCLC initially received one cycle of PE with concurrent radiotherapy before randomization to three more cycles of either cisplatin and etoposide or cisplatin and irinotecan. OS was not significantly different between the two arms (median, PE = 3.2 years [95% CI, 2.4 to 4.1] *v* cisplatin plus irinotecan = 2.8 years [95% CI, 2.4 to 3.6]; HR, 1.09; 95% CI, 0.80 to 1.46). Thus, PE has remained the preferred regimen.[53]

Recommendation 2.2

Carboplatin and etoposide may be offered as systemic therapy concurrent with radiation for patients with LS-SCLC and contraindications to the use of cisplatin (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Strong).

Literature review and clinical interpretation. Clinically, carboplatin is often substituted for cisplatin in patients with contraindications or intolerance to cisplatin across tumor types. The sole contraindication to cisplatin listed in its US Food and Drug Administration (FDA) label is hypersensitivity to cisplatin; however, other, often irreversible, toxicities of cisplatin, including nephrotoxicity, neuropathy, and ototoxicity, are listed as black box warnings.

One randomized trial has directly compared PE to CE in patients with both LS-SCLC (n = 82) and ES-SCLC (n = 61).[121] Patients were randomly assigned to receive six cycles of either PE or CE. Most of those with LS-SCLC also underwent concurrent thoracic radiotherapy and prophylactic cranial irradiation. For LS-SCLC, RRs were 76% for PE and 86% for CE. Comparative survival data were only reported for patients with all stages combined, with no clinically relevant differences between PE and CE: time to progression (8.4 *v* 8.6 months, respectively); OS (12.5 *v* 11.8 months, respectively). The COCIS MA of 663 patients from four trials compared cisplatin- to carboplatin-based therapy for first-line treatment of SCLC with 33% of patients having LS-SCLC.[36] Overall, there were no significant differences between cisplatin and carboplatin in any efficacy endpoint: RR (67% *v* 66%; *P* = .83), median PFS (5.5 *v* 5.3 months; *P* = .25), and median OS (9.6 *v* 9.4 months; *P* = .37). Subset analyses did not demonstrate any significant survival difference in patients with LS-SCLC. Carboplatin-based regimens resulted in more myelosuppression, while cisplatin caused more nausea, vomiting, neurotoxicity, and nephrotoxicity.

Review of the literature identified one cohort study of 4,408 patients with SCLC who were enrolled in the National Veterans Affairs Central Cancer Registry and had received either cisplatin-based or carboplatin-based chemotherapy.[122] Of these, 1,756 patients were identified with LS-SCLC treated with concurrent chemoradiotherapy: 801 received carboplatin-based therapy, 1,018 received cisplatin-based therapy, and 62 were exposed to both cisplatin and carboplatin. No significant difference was observed for the primary endpoint of OS (median, cisplatin 26.9 months *v* carboplatin 25.6 months; HR, 1.04; 95% CI, 0.94 to 1.16; *P* = .46). The quality of evidence is considered low as this was a retrospective study and 95% of the cohort was male. Based on the broad use of carboplatin in patients with lung cancer and intolerance or contraindication to cisplatin, and lack of data suggesting worse outcomes with the use of carboplatin, the panel agreed with a strong recommendation for the use of carboplatin in patients with LS-SCLC who are intolerant or have contraindications to cisplatin.

Recommendation 2.3

Chemotherapy should be commenced as soon as possible in patients with LS-SCLC and not deferred until radiation therapy (RT) can be started (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Strong).

Literature review and clinical interpretation. While there are ample data regarding the need to start radiotherapy early in the treatment course (ie, within the first two cycles of chemotherapy), there were no data identified examining the most appropriate time to start chemotherapy. The committee felt it was most reasonable to recommend initiation of chemotherapy as soon as possible, given the aggressiveness of SCLC, the usually high symptom burden caused by the disease, and the high degree of responsiveness of SCLC to chemotherapy. Frequently, the initiation of radiotherapy is delayed due to the need for complex treatment planning, whereas chemotherapy can usually be started in a more timely manner. The timing of radiation initiation with respect to chemotherapy in patients with LS-SCLC is addressed in the American Society for Radiation Oncology guidelines.[18,123]

Clinical Question 3

What is the optimal first-line systemic therapy for patients with ES-SCLC?

Recommendation 3.1

First-line systemic therapy with CE or PE plus immunotherapy (atezolizumab or durvalumab) followed by maintenance immunotherapy should be offered to patients with ES-SCLC if there are no contraindications to immunotherapy (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

Literature review and clinical interpretation. The current recommendation for first-line chemoimmunotherapy in patients with ES-SCLC is derived primarily from two,

large, randomized, phase III clinical trials, IMpower133 and CASPIAN. IMpower133 was a multinational, phase III trial in which 403 patients were randomly assigned to receive four cycles of carboplatin and etoposide with either atezolizumab or placebo followed by continuation maintenance therapy with atezolizumab or placebo.[124] While the RR was similar in both arms (60% *v* 64%), both PFS (1-year, 12.6% *v* 5.4%; HR, 0.77; $P = .02$) and OS (1-year, 52% *v* 38%; HR, 0.70; $P = .007$) were significantly improved by the addition of atezolizumab. In subset analyses, patients with brain metastases had no apparent benefit (though the analysis is limited by enrollment of only 35 patients with brain metastases) and those younger than 65 had greater benefit than older patients. An update continued to support an improvement in OS with chemoimmunotherapy (18-month, 34% *v* 21%, HR, 0.76; $P = .015$).[10] Grade 3-4 adverse events (AEs; 56.6% *v* 56.1%) and treatment-related deaths (1.5% in both arms) were similar in both arms, though immune-related AEs (39.9% *v* 24.5%) were more common with immunotherapy. Patient-reported quality-of-life outcomes were also similar in both arms.[125]

CASPIAN was an international, phase III, open-label trial in which 805 patients with previously untreated ES-SCLC were randomly assigned to one of three arms: chemotherapy alone (PE or CE × 6 cycles); chemotherapy plus durvalumab × 4 cycles followed by maintenance durvalumab; or chemotherapy plus durvalumab and tremelimumab × 4 cycles followed by maintenance durvalumab.[126] The addition of durvalumab to chemotherapy improved RR (68% *v* 58%), PFS (1-year, 18% *v* 5%, HR, 0.78), and OS (1-year, 54% *v* 40%, HR, 0.73; $P = .005$). A recent update reported 18-month OS of 32% with durvalumab plus chemotherapy and 25% with chemotherapy alone.[127] Overall toxicity was similar in both arms, with 62% of patients having grade 3-4 AEs and treatment-related mortality of 5%-6%, while immune-related AEs were more common with durvalumab (20% *v* 3%).[126] The addition of both durvalumab and tremelimumab to chemotherapy failed to significantly improve RR, PFS, or OS when compared to chemotherapy alone.[127]

ASTRUM-005 was a phase III trial performed in China in which 585 patients with untreated ES-SCLC were randomly assigned in a 2:1 manner to receive carboplatin and etoposide × 4 cycles plus either serplulimab (an anti–PD-1 monoclonal antibody) or placebo followed by maintenance with serplulimab or placebo. All efficacy endpoints favored serplulimab: RR (80.2% *v* 70.4%), PFS (median, 5.7 *v* 4.3 months; HR, 0.48, 95% CI, 0.38 to 0.59), and OS (median, 15.4 *v* 10.9 months; 1-year, 61% *v* 48%; $P < .001$).[128]

A similar phase III study, KEYNOTE-604, allocated 453 patients with previously untreated ES-SCLC to receive CE or PE plus either pembrolizumab or placebo followed by maintenance with pembrolizumab or placebo.[129] The addition of pembrolizumab significantly improved PFS (1-year, 13.6% *v* 3.1%, HR, 0.75; $P = .002$), but the improvement in OS did not reach statistical significance (2-year, 22.5% *v* 11.2%, HR, 0.80; $P = .16$). EA5161, a randomized phase II trial of chemotherapy with CE or PE alone versus chemotherapy plus nivolumab followed by maintenance nivolumab, enrolled 160 patients with previously untreated ES-SCLC, and found that both PFS and OS were significantly better in patients who received nivolumab.[130]

Several MAs have further confirmed the overall benefit of chemoimmunotherapy over chemotherapy alone for patients with ES-SCLC.[25,28-31,131] For example, the MA by Yu et al[25] included four randomized trials of chemoimmunotherapy versus chemotherapy alone (Impower133, CASPIAN, KEYNOTE-604, and EA5161) with a total of 1,553 patients, and found strong evidence for an improvement in both PFS and OS with the addition of immunotherapy, with no significant difference between anti–PD-L1 and anti–PD-1 agents. Based on the available evidence, the panel suggests that patients with ES-SCLC should be treated with first-line platinum and etoposide plus either durvalumab or atezolizumab for four cycles followed by maintenance immunotherapy.

Platinum plus etoposide is the preferred first-line chemotherapy option either in combination with immunotherapy or alone in patients with contraindications to immunotherapy. Only one trial has directly compared PE to CE, randomizing 147 patients with LS- or ES-SCLC to six cycles of PE or CE with concurrent thoracic RT for those with LS-SCLC.[121] There was no difference in RR (57% *v* 58%), time to progression (8.4 *v* 8.6 months), or OS (12.5 *v* 11.8 months) between PE and CE, respectively. The COCIS MA of 663 patients from four trials compared cisplatin- to carboplatin-based therapy for first-line treatment of SCLC with 67% of patients having extensive-stage disease, and reported no significant difference between cisplatin and carboplatin in any efficacy endpoint: RR (67% *v* 66%; $P = .83$), median PFS (5.5 *v* 5.3 months; $P = .25$), and median OS (9.6 *v* 9.4 months; $P = .37$).[36] Carboplatin-based regimens resulted in more myelosuppression, while cisplatin caused more nausea, vomiting, neurotoxicity, and nephrotoxicity. Given the available data and the palliative nature of therapy for patients with ES-SCLC, CE appears to be a favorable treatment option, though the choice of chemotherapy should be based on individual patient characteristics.

For patients who are not candidates for immunotherapy, chemotherapy with platinum plus etoposide for 4-6 cycles remains the recommended therapy, though cisplatin or carboplatin plus irinotecan is another reasonable alternative based on RCT data and MAs.[32,33,120,132-135] The optimal duration of chemotherapy for ES-SCLC is not clearly defined; however, 4-6 cycles of chemotherapy should be given based on patient tolerance and response to therapy.

Numerous chemotherapy-based strategies have been studied in randomized trials, including dose intensification,[65,66] three-drug cytotoxic regimens,[63,73,136,137] alkylator-anthracycline–based regimens,[68,69,75] platinum-based

nonetoposide regimens,[71,72,74] alternating non–cross-resistant regimens,[69,75] maintenance therapy,[61,62,87] and consolidation therapy.[76] All have failed to yield convincing improvements in survival and/or resulted in unacceptable toxicity. A wide variety of molecularly targeted agents, including anti-angiogenics and poly (ADP-ribose) polymerase (PARP) inhibitors, used either concurrently with chemotherapy[30,64,92,93,95-99] or as maintenance therapy[38,59,60,86,88-91] have also not demonstrated a significant improvement in outcomes.

Clinical Question 4

What systemic therapy options are available for treating patients with relapsed SCLC? (1) Which systemic therapy options should be given based on treatment-free interval?

Recommendation 4.1

In patients with relapsed SCLC with a chemotherapy-free interval of <90 days, single-agent chemotherapy may be offered. Preferred agents are topotecan or lurbinectedin (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Qualifying statement. Single-agent chemotherapy is preferred over multi-agent chemotherapy due to concerns regarding the balance of risks versus benefits.

Literature review and clinical interpretation. Patients who initially had either LS-SCLC or ES-SCLC and develop a recurrence of SCLC within 90 days of completion of first-line chemotherapy (ie, chemotherapy-free interval of <90 days) are generally considered to be resistant or refractory to combination, platinum-based therapy. In such patients, single-agent chemotherapy is recommended as second-line treatment, preferably with topotecan or lurbinectedin.

Data supporting topotecan come from two randomized studies that predated the use of immunotherapy in the first-line setting.[50,84] In the first trial, 211 patients with relapsed SCLC who had recurred at least 60 days after completion of first-line chemotherapy were randomly assigned to receive either topotecan or combination therapy with cyclophosphamide, doxorubicin, and vincristine (CAV).[84] While the overall response rates observed with topotecan and CAV were 24% *v* 18%, respectively ($P = .28$), there was no significant difference in OS (median, 25 *v* 24.7 weeks; $P = .79$). Patients receiving topotecan were significantly less likely to have neutropenia and more likely to have improvement in symptoms. In the second trial, 141 patients with relapsed SCLC who were not deemed to be candidates for intravenous (IV) chemotherapy were randomly assigned to receive oral topotecan versus best supportive care (BSC).[50] Despite a RR of only 7%, topotecan resulted in an improvement in OS (25.9 *v* 13.9 weeks; $P = .0104$). Topotecan also resulted in greater symptom control and slower deterioration of QoL. Other trials have reported no difference in efficacy or safety between the oral and IV formulations of topotecan.[138]

Recent data have shown that the novel transcriptional inhibitor, lurbinectedin, has substantial activity against relapsed SCLC. In a phase II study of 105 patients with relapsed SCLC and no brain metastases whose disease had progressed on or after platinum-based chemotherapy with or without immunotherapy, single-agent lurbinectedin yielded a RR of 33% with a median duration of response of 5.1 months and with 25% of patients responding for at least 6 months. Among patients with a chemotherapy-free interval of <90 days, the RR was 22%, while in those with a chemotherapy-free interval of at least 90 days, the RR was 45%.[11]

ATLANTIS, a randomized phase III trial evaluating lurbinectedin 2.0 mg/m^2 plus doxorubicin 40 mg/m^2 once on a 21 day cycle versus investigator's choice of CAV or topotecan in 613 patients with relapsed SCLC, failed to find any significant difference in efficacy between the two arms: RR (32% *v* 29%); PFS (median, 4 months in both arms); and OS (median, 8.6 *v* 7.6 months; HR, 0.97; $P = .70$).[139] Single-agent lurbinectedin remains a reasonable choice for second-line treatment of patients with relapsed SCLC with appreciable activity and tolerability.

Other options for treatment of patients with relapsed SCLC are based on phase II studies demonstrating RRs of 10%-25% and include single-agent irinotecan, paclitaxel, docetaxel, temozolomide, gemcitabine, or vinorelbine.[140-143] All subsequent treatments should be based on individual patient's PS and clinical trial eligibility.

Amrubicin is a synthetic anthracycline that is not approved for use in the United States, but is an option in Japan. A phase III trial comparing amrubicin to topotecan in 637 patients with relapsed SCLC demonstrated improved RR with amrubicin (31% *v* 17%; $P < .001$), but no difference in OS (median, 7.5 *v* 7.8 months; $P = .17$). In a subset analysis, patients with a chemotherapy-free interval of < 90 days had a significant improvement in OS with amrubicin (median, 6.2 *v* 5.7 months; $P = .047$). Amrubicin did result in higher rates of infection and febrile neutropenia, but less overall myelosuppression.[144]

Recommendation 4.2

In patients with relapsed SCLC with a chemotherapy-free interval of at least 90 days, rechallenge with a platinum-based regimen or single-agent chemotherapy (preferred agents are topotecan or lurbinectedin) may be offered (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Literature review and clinical interpretation. Two recent phase III trials have compared rechallenge with a platinum-based chemotherapy regimen to topotecan in patients with relapsed SCLC and a chemotherapy-free interval of

at least 90 days. A phase III study from France compared CE to oral topotecan in 164 patients who had previously responded to first-line platinum plus etoposide, but had disease progression at least 90 days after completion of first-line treatment.[47] Combination therapy improved both RR (49% *v* 25%; *P* = .002) and PFS (4.7 *v* 2.7 months; *P* = .004), though there was no significant difference in OS (median, 7.5 *v* 7.4 months; *P* = .94). The lack of survival benefit may be secondary to a large crossover, particularly in the topotecan group with almost 40% of patients receiving CE as third-line treatment. Toxicity favored platinum rechallenge with higher rates of grade 3-4 myelosuppression and febrile neutropenia in patients receiving topotecan. The results from this study also confirm the findings of a multi-institutional retrospective analysis that reported a median PFS of 5.5 months in patients with sensitive-relapsed SCLC who were rechallenged with platinum plus etoposide.[145]

The phase III JCOG0605 trial from Japan compared the combination of cisplatin, etoposide, and irinotecan to topotecan in 180 patients with sensitive-relapsed SCLC.[48] RR (84% *v* 27%; *P* < .0001), PFS (5.7 *v* 3.6 months; *P* < .0001), and OS (18.2 *v* 12.5 months; *P* = .008) all favored combination therapy, though combination therapy also resulted in much higher rates of myelosuppression and febrile neutropenia as well as high rates of dose reduction and delay. These data support combination platinum-based therapy as a second-line treatment option for patients with good PS and sensitive-relapsed SCLC.

In patients who were initially treated for LS-SCLC without immunotherapy and have had a chemotherapy-free interval of at least 90 days, treatment with platinum-based chemotherapy plus immunotherapy followed by maintenance immunotherapy may be offered.

Recommendation 4.3

In patients with relapsed SCLC who had progression while on maintenance immunotherapy, there is no evidence to support continuation of immunotherapy (Type: Informal consensus, benefit to harm ratio not assessable; Evidence quality: Not applicable; Strength of recommendation: Strong).

Literature review and clinical interpretation. There are no RCTs in patients who develop disease progression while on maintenance immunotherapy comparing continuation of immunotherapy in combination with second-line therapy versus second-line therapy alone. There are also no reported clinical trials evaluating switching to a different immunotherapy agent or a combination of immunotherapy agents after disease progression on maintenance immunotherapy. Due to limited data in this clinical setting and lack of oncological rationale, the general consensus is to recommend against continuing immunotherapy in patients with disease progression while on maintenance immunotherapy.

Recommendation 4.4

In an immunotherapy-naïve patient, second-line immunotherapy alone is not recommended outside of the clinical trial setting. Participation in clinical trials to better identify predictive biomarkers is encouraged (Type: Evidence based, no net benefit; Evidence quality: Moderate; Strength of recommendation: Strong).

Literature review and clinical interpretation. Promising data from early trials of immunotherapy in patients with relapsed SCLC who had not received prior immunotherapy led to the accelerated FDA approval of both single-agent nivolumab and pembrolizumab for these patients. However, the disappointing results of subsequent randomized trials led to the voluntary withdrawal of both nivolumab and pembrolizumab in the relapsed setting. In the phase III CheckMate-331 trial, nivolumab did not improve OS when compared to chemotherapy (topotecan or amrubicin) in patients with relapsed SCLC.[46] The KEYNOTE-604 phase III trial of platinum and etoposide plus either pembrolizumab or placebo as first-line treatment in untreated patients was also a negative trial as the difference in OS did not reach statistical significance.[129] Even though this study was not done in the relapsed setting, the results dimmed enthusiasm for pembrolizumab in SCLC. Finally, in the randomized phase II IFCT-1603 trial, which compared atezolizumab to chemotherapy (topotecan plus etoposide or CE) as second-line therapy in people with relapsed SCLC, both RR and PFS were better in the chemotherapy arm while OS was similar in both arms.[82] Taken together, these data do not support the use of immunotherapy alone as subsequent treatment in immunotherapy-naïve SCLC patients.

Clinical Question 5

What is the best management approach for treatment-naïve patients who are older or with poor PS?

A large proportion of people with SCLC do not fit within the standard inclusion criteria for clinical trials, specifically, those who are older and/or have a poor Eastern Cooperative Oncology Group (ECOG) PS. Historically, these two often unrelated categories of patients have frequently been combined in studies and individual trials have used varying definitions of "older patient," further complicating the development of clear guidance on how to manage and treat these challenging patients. Most studies have defined "older patient" as ≥70 years of age, but some have used ≥65 years, which aligns with the WHO definition. There is little data on which to base treatment decisions in people over 80 years of age.

Approximately 40% of patients with SCLC are older than 70 years of age. In these older patients, treatment of SCLC is more challenging, given the decline in physiological reserve, increased comorbidities, polypharmacy, cognitive

decline, and other age-related medical and social issues. Most of the data on the treatment of older patients comes from retrospective studies. However, limited prospective data are available to guide treatment decisions in this special population. Based on available data, standard approaches are feasible in carefully selected, "fit" older patients.[146]

Comprehensive geriatric assessment (CGA), which includes essential domains such as evaluations of function (Activities of Daily Living scales, Instrumental Activities of Daily Living scales), comorbidity, nutritional status, social support, medications, and psychological and cognitive status, has been shown to be a better predictor of fitness, vulnerabilities, and impairments in cancer patients over 65 years of age than routine oncologic assessment tools. While there are no published trials evaluating CGA in older patients with SCLC, studies on patients with other cancers have demonstrated that CGA-based interventions, including modification of systemic therapy and referrals to physical therapy, nutritional counseling, and psychological evaluation, result in better treatment completion, compliance, and tolerance without compromising survival.[147,148]

The Expert Panel endorses ASCO guidelines for CGA prior to systemic anticancer treatment in order to better identify "fit" older patient who may qualify for standard SCLC therapy.[149]

Recommendation 5.1

Older patients with LS-SCLC and ECOG PS 0-1 may be offered standard treatment with concurrent chemoradiotherapy with curative intent (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Literature review and clinical interpretation. Most of the data to support this recommendation come from subset analyses of trials that included patients of all ages. Schild et al[52] compared the outcomes of patients ≥70 years of age to those of their younger counterparts enrolled in a phase III trial of combined-modality therapy with hyperfractionated versus once-daily radiotherapy for LS-SCLC. All patients received six cycles of PE with radiation given concurrently during cycles 4-5. Of 263 total patients, 54 (21%) were ≥70 years of age. The older cohort did lose more weight and had a higher rate of pneumonitis (6% *v* 0%), but the rates of other common toxicities were comparable and there was no significant difference in OS (5-year, 17% *v* 22%; $P = .14$).

In a similar study, Yuen et al[112] compared the outcomes of 50 (13%) patients ≥70 years of age to younger patients enrolled in the Intergroup 0096 study, which randomly assigned patients with LS-SCLC to receive either once-daily or twice-daily radiotherapy concurrently with four cycles of PE. The older cohort had more grade 4-5 hematological toxicity (84% *v* 61%; $P < .01$), and more fatalities (10% *v* 1%; $P = .01$), but the RR was similar for both age categories. However, the 5-year OS rate did favor the younger cohort (22% *v* 16%; $P = .05$) primarily due to deaths within first 6 months, likely from treatment toxicity.

The toxicity profile of cisplatin can be a barrier to treatment in older patients and there is evidence to support the preferred use of carboplatin. Kim et al[113] reported on a large cohort of 565 people abstracted from the SEER database between 1992 and 2007 who were ≥65 years of age (median, 72 years) and received concurrent chemoradiotherapy with either PE or CE. The reported outcomes were virtually identical, with median (13.8 *v* 13.7 months) and 5-year OS (10.2% *v* 10.9%) for those receiving cisplatin versus carboplatin, respectively.

These studies echo previous findings from earlier trials of combined-modality therapy and support the recommendation that patients ≥70 years of age with good PS should be offered concurrent chemoradiation with a detailed discussion of the risks and benefits that will allow them to make rational treatment decisions, given the inherent side effects of these intensive treatment regimens.

Recommendation 5.2

Patients with LS-SCLC and ECOG PS 2 due to SCLC may be offered standard treatment with concurrent chemoradiotherapy with curative intent (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Literature review and clinical interpretation. People are often diagnosed with SCLC based on cancer-related symptoms, and an individual's medical fitness and comorbidities play a significant role in the therapeutic decision-making process. Historically, there has been reluctance to include patients with poor PS in clinical trials, because of concerns regarding tolerability and toxicity, which might dilute the potential benefit of new therapies. Many SCLC trials do include patients with ECOG PS 2, so there is sufficient data to support the recommendation for potentially curative, concurrent chemoradiotherapy for this patient subgroup. For example, in the concurrent National Cancer Institute-Canada trials (BR3 and BR6), 12%-16% of patients had ECOG PS 2-3.[150]

As PS can be subjective and multifactorial, a practical approach to inclusion of ECOG PS 2 patients has been demonstrated in recent trials, such as the CONVERT study.[5] In this multicenter randomized phase III study of concurrent chemoradiotherapy with radiotherapy given either once daily or twice daily, the inclusion criteria specified that patients with PS 2 could be included if their debility was due to disease-related symptoms and not comorbidities. Although only 3% of the 547 patients enrolled had PS 2, the wording of the inclusion criterion aligns with this panel's

recommended approach for considering more intensive treatment for this subgroup of patients.

Recommendation 5.3

Patients with LS-SCLC and ECOG PS 3-4 due to SCLC may be offered initial chemotherapy followed by sequential radiotherapy if there is improvement in PS (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Literature review and clinical interpretation. There is little published data to guide therapeutic decision-making for patients who present with LS-SCLC and very poor PS. As previously noted, although a very small number of patients with ECOG PS 3 have been included in concurrent chemoradiotherapy trials,[150] it is difficult to draw generalizable conclusions.

As with people who present with LS-SCLC and ECOG PS 2, those who are even more debilitated by symptoms that are related to their SCLC may derive benefit from an aggressive treatment approach. SCLC tends to exhibit a robust response to initial chemotherapy, so symptoms due to disease, such as pain, cough, or dyspnea may improve rapidly enough to reconsider concurrent treatment with subsequent cycles. Therefore, a step-wise approach to treatment may be considered on a case-by-case basis, starting with systemic therapy and then introducing radiotherapy, either concurrently or sequentially, for those patients who improve with initial treatment. Consideration of palliative care, including palliative radiotherapy, is also an option for this diverse patient cohort.

Recommendation 5.4

Older patients with ES-SCLC and ECOG PS 0-1 may be offered standard treatment with carboplatin and etoposide plus immunotherapy (atezolizumab or durvalumab) followed by maintenance immunotherapy (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Literature review and clinical interpretation. As yet, there are no studies that specifically address the safety and efficacy of chemoimmunotherapy in older patients with ES-SCLC. The best evidence comes from the subset analyses of older patients enrolled in the CASPIAN and IMpower133 trials (referenced previously in section 4). In the CASPIAN trial, 113 of 537 patients with ES-SCLC and ECOG PS 0-1 were defined as older, and in the IMpower133 trial, 186 of 403 patients were ≥65 years of age. Neither study was powered to evaluate the impact of age on outcomes, but there appeared to be no difference in the benefit of chemoimmunotherapy in older versus younger patients.

As real-world evidence accumulates and new trials are developed for this population, more informative data should become available. Currently, there is sufficient evidence to support the use of combination chemoimmunotherapy in carefully selected patients ≥65 years of age with ES-SCLC and ECOG PS 0-1.

Recommendation 5.5

Patients with ES-SCLC and ECOG PS 2 may be offered carboplatin and etoposide plus immunotherapy (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Literature review and clinical interpretation. Despite the fact that many patients with ES-SCLC present with ECOG PS ≥ 2, few such patients are enrolled in randomized clinical trials. As with LS-SCLC, the distinction between a poor PS driven by SCLC rather than underlying comorbidities should be the primary consideration when contemplating the addition of systemic therapy to BSC.

Support for the use of CE for patients with ECOG PS 2 can be deduced from the inclusion of such patients in prior randomized trials. For example, a MA comparing cisplatin- versus carboplatin-containing regimens for first-line treatment of SCLC included four randomized trials that included 663 patients with ECOG PS 0-2 (or 0-3 in one trial), most of whom had ES-SCLC.[36] Overall, there was no significant difference in the efficacy between cisplatin- and carboplatin-containing regimens, though there were differences in the toxicity profiles. In addition, outcomes appeared to be similar in the PS 0-1 and PS ≥ 2 cohorts.

The JOG 9702 study[151] was a randomized phase III study that compared CE to divided-dose PE in patients with PS 3 and age <70, or PS 0-2 and age 70 or older. Although there were more frequent AEs in patients with poor PS, both groups demonstrated promising OS rates. This trial provides the rationale for the JOG's ongoing phase II study of carboplatin, etoposide, and durvalumab in patients with ES-SCLC and poor PS.[152]

In 2004, Treat et al reported the results of a retrospective analysis of five topotecan registration trials in patients with relapsed SCLC. Of 480 patients, 98 had ECOG PS 2.[153] RRs were similar for those with PS 0-1 versus PS 2, but toxicity was greater and OS was shorter in the PS 2 population. PS is a strong prognostic indictor in SCLC, and the balance of treatment risks and benefits must be carefully considered for each patient.

Recommendation 5.6

Patients with ES-SCLC and ECOG PS 3-4 due to SCLC may be offered chemotherapy (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Literature review and clinical interpretation. There is a true paucity of data for patients with ES-SCLC with an ECOG PS 3-4, highlighting an area of much-needed research. There is anecdotal evidence of response and benefit for patients whose poor PS is directly due to SCLC, for example,

patients with abrupt respiratory compromise who respond quickly to chemotherapy, but this cannot be considered a general recommendation.

As noted previously, the COCIS MA did not demonstrate any significant differences in efficacy between cisplatin- versus carboplatin-containing regimens, though only one of the included studies allowed patients with PS 3.[36] Similar results have been reported in a more contemporary Japanese trial comparing carboplatin-based with cisplatin-based regimens.[143] Given the more favorable toxicity profile of carboplatin, it would appear to be more reasonable to offer carboplatin-based rather than cisplatin-based treatment for people with poor PS. As is the case for all patients with ES-SCLC, an emphasis should be placed on palliative and supportive care, which may include palliative radiotherapy.

Clinical Question 6

What is optimal systemic therapy for patients with NSCLC harboring an EGFR mutation that has transformed to SCLC?

Recommendation 6.1

Patients with NSCLC harboring an *EGFR* mutation that has transformed to SCLC should be managed with CE or PE (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Qualifying statement. There is insufficient evidence to support the use of immunotherapy in this setting. Clinical trial enrollment should be offered whenever possible.

Literature review and clinical interpretation. Transformation to SCLC has been reported to occur in 3%-14% of people with *EGFR*-mutant lung adenocarcinoma as a mechanism of resistance at the time of progression on EGFR tyrosine-kinase inhibitor (TKI) therapy. *EGFR* mutations have also rarely been identified in de novo SCLC.[154-156] Several pooled analyses and case series have reported that progression with transformed SCLC occurs after a median of 16-19 months on EGFR TKI therapy and that the OS after transformation is poor (median of 6-11 months).[154-156] Frequency of small cell transformation in *ROS1* and *ALK* fusion-positive lung cancers appears relatively low (2% and 0.8%, respectively).[157]

Thus far, there are no prospective studies evaluating the appropriate treatment of transformed SCLC. The majority of reported patients with transformed SCLC have received treatment with platinum plus etoposide. In one pooled analysis of 46 such patients treated with platinum plus etoposide, the RR was 54% and the median PFS was 3.4 months.[155] Another pooled analysis of 48 patients treated with platinum plus etoposide reported a RR of 45%.[154]

Only one case series has evaluated the efficacy of ICIs in transformed SCLC, reporting no responses in 17 patients treated with either single-agent or combination immunotherapy.[155] Thus, there is no evidence to support the use of immunotherapy in the treatment of *EGFR*-mutant, transformed SCLC.

Recommendation 6.2

EGFR inhibitor may be continued with chemotherapy in patients with NSCLC harboring an *EGFR* mutation that has transformed to SCLC (Type: Informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Literature review and clinical interpretation. Case series and pooled analyses have shown that although the majority of transformed SCLCs retain the original *EGFR* mutation, EGFR protein expression is suppressed, resulting in resistance to further EGFR TKI therapy. However, in some patients, there is co-occurring persistence of an *EGFR*-mutant adenocarcinoma component, which may retain sensitivity to an EGFR TKI, providing rationale for continuation of EGFR TKI therapy. Overall, there is inadequate data to recommend for or against continuation or reintroduction of EGFR TKI therapy and the decision should be made on an individual patient basis.

Clinical Question 7

What is the role of biomarkers, including molecular profiling in guiding therapy for patients with de novo SCLC?

Recommendation 7.1

There is no evidence to support the use of molecular profiling and biomarker analysis to guide standard treatment in patients with de novo SCLC (Type: Evidence based, benefit to harm ratio not assessable; Evidence quality: Low; Strength of recommendation: Weak).

Literature review and clinical interpretation. There are few prospective studies investigating the utility of biomarker analysis to guide therapy in patients with SCLC. In a phase II study, 14 patients with ES-SCLC expressing c-Kit were treated with imatinib maintenance therapy after four cycles of cisplatin plus irinotecan with a 4-month PFS rate of only 1.3 months (95% CI, 1 to 5.7 months) after initiation of imatinib, leading to early study closure as it did not meet the predetermined threshold.[78] A more recent phase II umbrella study enrolled 286 patients with relapsed ES-SCLC who received either biomarker-directed or non–biomarker-directed therapy. Patients with *CDKN2A* and *TP53* mutations or *MYC* amplification were treated with adavosertib, a WEE1 inhibitor, and those with *RICTOR* amplification were treated with vistusertib, a mTORC1/2 inhibitor. Patients with tumors lacking these biomarkers were randomly assigned to treatment with adavosertib or vistusertib. Neither objective response nor PFS was improved by the biomarker-driven interventions.[104] Another study of 51 patients with LS- or ES-SCLC who were receiving chemotherapy with or without radiotherapy

investigated circulating tumor cells (CTCs) as a predictive and prognostic biomarker. Patients with ≥8 CTCs detected on pretreatment samples had worse OS than those with <8 CTCs (HR, 3.5; 95% CI, 1.45 to 8.60; $P = .0014$). The worst outcomes overall were noted in patients with ≥8 CTCs on post-treatment samples or samples obtained at relapse.[105]

Most of the data on the potential clinical utility of predictive and prognostic biomarkers in SCLC comes from retrospective studies. Liu et al performed an exploratory analysis of PD-L1 expression in patients enrolled on IMpower133, the randomized, phase III study of first-line atezolizumab plus chemotherapy in patients with ES-SCLC. An OS benefit was found across all PD-L1 subgroups and PD-L1 expression did not appear to be a predictive biomarker for chemo-immunotherapy in patients with ES-SCLC. This analysis was limited, since only 34% of the study population had undergone PD-1 analysis.[10] This study also found that blood tumor mutational burden (TMB) was not predictive of benefit with chemoimmunotherapy. The lack of predictive utility for PD-L1 expression has been echoed in similar analyses of the CASPIAN and KEYNOTE 604 trials.[129,158]

Hellmann et al[106] analyzed the predictive value of TMB in a nonrandomized cohort of patients with ES-SCLC from the CheckMate 032 study, which evaluated nivolumab or nivolumab plus ipilimumab in patients with advanced solid tumors. While the efficacy of immunotherapy was better in patients in the highest tertile of TMB (≥248 total somatic missense mutations) as compared to those with medium (143-247 mutations) or low (0-143 mutations) TMB, subsequent studies have not confirmed the predictive power of TMB for immunotherapy response in SCLC. Larger, prospective studies are needed to define the potential role of TMB in treatment decision making in SCLC.

Multiple retrospective studies have focused on understanding the genomic landscape of SCLC as both a predictive and prognostic biomarker. Several studies seeking to identify genetic alterations which might serve as candidates for therapeutic intervention have found nonrandom aberrations in several key pathways, including cell cycle regulation, receptor kinase or PI3K signaling, transcriptional regulation, Notch signaling, and neuroendocrine differentiation.[159] A subsequent retrospective study of tumors from patients with SCLC found that alterations in six genes (*MCM2*, *EXH2*, *CDKN2A*, *CEMPK*, *CHEK1*, and *EXOSC2*) correlated with OS. Some of these alterations also predicted response to anti–PD-1 therapy and cisplatin.[111] In another study that assessed tumors from 231 patients with LS-SCLC who were treated with chemoradiotherapy, *CDK4* and *GATA6* expression as well as EGFR-activating mutations were prognostic for poorer OS (HR, 2.18; HR, 2.39; HR, 2.26).[160] Additionally, Zhang et al[109] created a prognostic signature based on N^6-methyladenosine (m^6A), an epigenetic modification involved in tumorigenesis and immune function. Among 265 patients with LS-SCLC, those with a high m6A score had decreased OS (HR, 5.19; 95% CI, 2.75 to 9.77; $P < .001$), a finding that was validated in two independent cohorts. In addition, a low m^6A score was predictive of benefit from chemotherapy and immunotherapy.[109]

Recently, there has been a concerted effort to differentiate the genomic landscape of SCLC by characterizing subtypes that may predict outcomes with specific therapies. Gay et al proposed four distinct subtypes of SCLC based on expression of specific transcription factors: SCLC-A (high ASCLC1), SCLC-N (high NEUROD1), SCLC-P (high POUF2F3), and SCLC-I (low ASCLC1, NEUROD1, and POUF2F3). The SCLC-I subtype appeared to be most responsive to chemo-immunotherapy.[161] Further studies are needed to fully determine whether these subtypes are predictive of benefit for rationally designed targeted therapies.[162,163] To date, there is no validated role for any predictive biomarker to guide treatment of patients with SCLC.

Clinical Question 8

Which myeloid supportive agents may be considered for use in patients with SCLC? (1) What is the role of trilaciclib or granulocyte colony-stimulating factor (G-CSF) in patients with ES-SCLC? (2) What is the role of G-CSF in patients undergoing chemoradiotherapy?

Recommendation 8.1

Trilaciclib or G-CSF may be offered as a myeloid supportive agent for patients with untreated or previously treated ES-SCLC who are undergoing treatment with chemotherapy or chemoimmunotherapy (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).

Literature review and clinical interpretation. In February 2021, the FDA approved trilaciclib, a CDK 4/6 inhibitor, to reduce the frequency of chemotherapy-induced bone marrow suppression in adults receiving certain types of chemotherapy for ES-SCLC. A phase Ib, randomized phase II trial of trilaciclib in patients with SCLC receiving first-line chemotherapy with CE showed a significant reduction of both the occurrence and duration of severe neutropenia and a reduction in the percentage of patients receiving red blood cell transfusions and the rate of transfusions.[80]

A randomized, placebo-controlled phase II trial showed that, compared with placebo, trilaciclib administered prior to first-line carboplatin, etoposide, and atezolizumab in patients with ES-SCLC resulted in significant decreases in the mean duration of severe neutropenia in cycle 1 (0 *v* 4 days; $P < .0001$) and the occurrence of severe neutropenia (1.9% *v* 49.1%; $P < .0001$), with additional improvements in red blood cell and platelet measures and health-related QoL. Patients receiving trilaciclib had fewer grade ≥3 AEs than those receiving placebo.[164]

Another randomized, placebo-controlled, phase II trial reported that the administration of trilaciclib prior to

topotecan in previously treated patients with ES-SCLC resulted in statistically significant decreases in duration of severe neutropenia in cycle 1 (mean, 2 *v* 7 days; $P < .0001$) and occurrence of severe neutropenia (40.6% *v* 75.9%; $P = .016$), with numerical improvements in red blood cell and platelet measures. Myelopreservation benefits extended to improvements in patient-reported outcomes.[79]

Two separate pooled analyses of the previously mentioned studies confirmed that trilaciclib led to a statistically significant improvement in multilineage chemotherapy-induced myelosuppression, thereby reducing the need for supportive care and improving QoL. Trilaciclib had no effect on antitumor efficacy.[41,43] Another exploratory pooled analysis assessed five major adverse hematological events, including all-cause hospitalizations, all-cause chemotherapy dose reductions, febrile neutropenia, prolonged severe neutropenia, and RBC transfusions, and demonstrated that, compared to placebo, trilaciclib resulted in statistically significant reductions in all of these endpoints except all-cause hospitalizations.

Recommendation 8.2

G-CSF may be offered in patients with LS-SCLC who are undergoing chemoradiotherapy (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).

Literature review and clinical interpretation. Historically, the use of G-CSF has been discouraged in patients with LS-SCLC undergoing chemoradiotherapy. In the early 1990s, SWOG 8812, a prospective randomized phase III study, evaluated the effect of granulocyte-macrophage colony-stimulating factor (GM-CSF) in LS-SCLC[45] in patients treated with six cycles of PE and concurrent thoracic radiotherapy of 45 Gy in 25 fractions. Patients receiving GM-CSF had a significantly increased frequency and duration of grade 3-4 thrombocytopenia, nonhematologic toxicity, and treatment-related deaths. Subsequently, ASCO guidelines for use of white blood cell growth factors in 2006 and 2015 recommended avoiding GM-CSF and G-CSF in patients receiving concurrent chemoradiotherapy, particularly involving the mediastinum.[165,166]

Two subsequent studies reported less toxicity with G-CSF administration during concurrent chemoradiotherapy in the era of modern 3D-conformal RT techniques. In a phase II study of concurrent chemotherapy and once-daily versus twice-daily thoracic radiation in LS-SCLC, 20 patients received G-CSF according to local policy for treatment of febrile neutropenia, or as primary or secondary prophylaxis.[81] This showed an increased risk of clinically significant thrombocytopenia without increased risk of pneumonitis. No episodes of bleeding were observed, and no treatment-related deaths occurred. The authors noted that G-CSF was given to patients already at elevated risk of hematologic toxicity, which may have confounded interpretation of results. This was followed by the phase III, open-label, randomized CONVERT trial evaluating once-daily versus twice-daily radiotherapy with concurrent chemotherapy in 487 patients with LS-SCLC.[44] G-CSF administration was allowed per investigator choice for primary or secondary prophylaxis. In a secondary analysis, 180 patients who received G-CSF had a higher incidence of severe thrombocytopenia and rate of blood transfusions without observed differences in RT-related toxicity, treatment-related mortality, or survival outcomes. More patients who received G-CSF achieved an optimal dose intensity of chemotherapy. The higher incidence of severe thrombocytopenia and blood transfusions was attributed to selection bias, as those patients selected for G-CSF had higher risks of myelotoxicity. However, it is worth noting this was an unplanned secondary analysis and the study lacked strict criteria for G-CSF administration.

Based on these more recent studies, the panel concludes that G-CSF may be offered in patients with LS-SCLC who undergo chemoradiotherapy if there is an appropriate clinical indication. The use of GM-CSF is not recommended. Potential higher risks of thrombocytopenia and need for blood transfusions should be noted and may reflect baseline increased hematologic risk in those patients selected for G-CSF administration during chemoradiotherapy.

Please refer to the treatment algorithm in Figures 2-4 for the visual representation of these recommendations.

DISCUSSION

It is clear to all clinicians caring for people with SCLC that all patients are not the same. Future advances will require the identification of subsets of patients with specific predictive biomarkers and molecular vulnerabilities. Along these lines, several molecular subtypes of SCLC have now been defined based on gene expression profiling[161,162] and molecular genetic analysis.[167] Current and future research now aims to identify and therapeutically target the molecular drivers of cell survival, proliferation, and metastasis that are unique to each of these SCLC subtypes.

Although ICIs are only FDA-approved as first-line therapy in combination with chemotherapy for ES-SCLC, about 10%-15% of patients with SCLC have demonstrated some benefit from ICIs regardless of clinical scenario, be it first-line therapy, maintenance therapy, or relapsed disease. Even in the negative maintenance trials of pembrolizumab[168] and nivolumab,[169] about 10% of patients had long-term disease control, and third-line pembrolizumab yielded a 2-year OS rate of 21%.[170] Recent studies have presumptively identified an inflammatory subtype in about 10% of SCLC samples that may predict response to immunotherapy.[161]

Clinically useful predictive biomarkers have not yet been defined for immunotherapy. In addition to identifying positive predictive biomarkers to select patients most likely to benefit from treatment, it is equally important to identify negative biomarkers that identify those who will not benefit in order to spare them from the potential toxicity of ICIs.

The identification of negative predictive biomarkers also may aid in the detection of potential targets for novel strategies to overcome therapeutic resistance. Due to the complexity of immunoregulatory pathways, indices incorporating multiple tumor and host characteristics, rather than a single marker, may hold the most promise as clinically useful predictive factor.

In LS-SCLC, the addition of ICIs to chemoradiotherapy, either concurrently or as consolidation therapy, may offer hope for improving long-term outcomes, as consolidation durvalumab has in stage III NSCLC, and the results from several ongoing clinical trials are eagerly awaited (ClinicalTrials.gov identifiers: NCT03811002, NCT02402920, NCT03540420 [ACHILES], NCT02046733 [STIMULI], NCT03585998).

Up to 60% of patients with SCLC develop brain metastases during the course of their disease.[171] In the IMpower133 trial, the presence of brain metastases was associated with lack of benefit from atezolizumab.[124] Studies exploring combinations of ICIs with other agents to improve CNS activity may overcome this limitation. One such trial is investigating nivolumab plus temozolomide, an oral cytotoxic agent with blood-brain barrier penetrance (ClinicalTrials.gov identifier: NCT03728361).

Many studies evaluating novel combinations of ICIs with molecularly targeted drugs or other immunomodulatory agents are underway. Combinations of ICIs with CHK1 and PARP inhibitors have reported dramatic effects in preclinical models of SCLC.[172] Thus far, clinical trials of ICIs plus PARP inhibition in SCLC have been disappointing[173,174] but have suggested potential biomarkers for enhanced patient selection.

SCLC causes substantial morbidity and debility in most patients with the disease and the restriction of clinical trials to people with good PS limits the generalizability of trial results. Expanding clinical trial eligibility to patients with marginal PS (ie, ECOG PS 2) would allow better assessment of the risk-benefit ratio for ICIs and other novel therapies in a broader range of patients.

While empiric chemotherapy and radiotherapy have had a major impact on the survival of patients with SCLC, it is doubtful that these modalities will provide further significant improvements in outcomes. The addition of ICIs to the SCLC armamentarium has offered patients new therapeutic options and hope for the first time in over 30 years, but the number of patients benefitting from treatment remains small. Recently, advances in our knowledge of SCLC biology, molecular subtypes, and therapeutic vulnerabilities have created a buzz in the field for the first time in several decades. Ongoing efforts to translate these findings to the clinic will hopefully launch a golden age of SCLC research and improvements in survival.

PATIENT AND CLINICIAN COMMUNICATION

In the era of precision medicine, the evolution of biomarkers has become an accelerating revolution in the treatment of NSCLC, but small-cell lung cancer advancements have only been incremental. There are some promising studies in the pipeline, but managing the disease continues to be complicated. Furthermore, the cancer symptoms and side effects from treatment can significantly impact a person's QoL.

At a time when patients and families are faced with making difficult treatment decisions, distress and anxiety cloud their ability to comprehend clearly, so you can expect an emotional reaction. However, it is how you communicate that will make a difference. Beyond words, the simple yet complex art of conversation is the heart of a patient's experience.

- Get to know your patients. Leave all assumptions at the door, step out of the scientific box, and ask relational, not technical, questions. Patients want to know that the doctor caring for them also cares about them.
- Treating small-cell lung cancer is more complicated than ever, and with scientific evidence often incomplete and/or conflicting, there often are no concrete rights or wrongs. The right thing is to know the medical data and apply it in the context of the patient and their family.
- OS is not the only important endpoint for patients and families. It is not enough to just survive; patients want life! What that means is unique to each patient and can only be answered by the patient and their family.
- The most important conversations with patients are not the data-driven ones. Have those difficult conversations about goals of care, what is important and meaningful in their life besides living longer, what they are afraid of, and what tradeoffs they are willing to make. These discussions need to happen before talking about treatment.
- You are the experts in the science, but patients also have their PhD—person with history of disease. Patients are the experts in the lived experience and the only reliable source for symptoms, side effects, severity, and how they impact QoL.
- Words matter. Smoking-related stigma is an important issue. Taking a person's smoking history is important for cancer treatment, but it must be addressed as an addiction, a disease, not a behavior or moral failing.
- The IASLC Language Guide was created to provide best practices when talking or writing about lung cancer. There are four main principles: person first, stigma-free, blame-free, and equitable and inclusive language. The guide is not meant to call people out but instead to call people in as an essential step in increasing respect and unity throughout the lung cancer community.
- Provide hope, with reality—hope may need to be redefined at times, but it is a vital emotion no matter where someone is in their phase of care.

Every person is different, but there is one thing we all share—a common goal of survival. How that goal is reached

will be different for each patient, but achieving that goal absolutely requires good communication: an open, honest, and respectful relationship between physicians and patients. You may not save every life, but if you help your patients find their hope, you will make a difference in their lives and their families.

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care and/or receive fragmented care. Factors such as race and ethnicity, age, socioeconomic status, sexual orientation, geographic location, and insurance access are known to affect cancer care outcomes.[175] Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial and ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[176-178] Studies have found that Black race, lack of insurance or having nonprivate insurance, lower education, and older age were factors associated with lower odds of receiving systemic treatment for ES-SCLC. In addition to racial disparities in the delivery of chemotherapy for patients with ES-SCLC, other studies have reported that Black patients are less likely to receive prophylactic cranial irradiation and effective doses of consolidative thoracic radiotherapy. Socioeconomic factors such as type of health insurance may also affect receipt of chemotherapy and survival. Higher education was associated with an increased likelihood of receiving chemotherapy. Older patients have a higher incidence of comorbidities and tend to have worse outcomes in general. The poorer OS in older patients with SCLC could be related to decreased tolerance or dose limitations of chemotherapy or RT, in addition to non–cancer-related causes of death.[179] Studies also show that older patients and non-Hispanic Black patients are less likely to receive guidelines-concordant treatment across most clinical subgroups of lung cancer.[180]

Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations. Achieving health equity requires efforts that inform, educate, and empower all individuals. Stakeholders should work toward achieving health equity by ensuring equitable access to both high-quality cancer and research, and addressing the structural barriers that preserve health inequities.[175]

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions—a situation in which the patient may have two or more such conditions, referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients in order to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

All treatment plans need to take into account the complexity and uncertainty created by the presence of MCC, and patients with MCC highlight the importance of shared decision-making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[181,182] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[183,184]

Discussion of cost can be an important part of shared decision making.[185] Clinicians should discuss with patients the use of less-expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[185]

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different

products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[185]

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effective analyses that lack contemporary cost data; agents that are not currently available in either the United States or Canada; or are industry-sponsored. Four cost-effectiveness analyses were identified to inform some of the topics discussed in this guideline.[186-189]

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from January 17 through 31, 2023. There were 15 respondents in total and were all medical oncologists. Response categories of "Agree as written," "Agree with suggested modifications" and "Disagree. See comments" were captured for every proposed recommendation with 53 written comments received. A total of 80%-92% of the responses either agreed or agreed with slight modifications to the recommendations and 8% of the responses disagreed. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated prior to EBMC review and approval.

The draft was submitted to OH external reviewers with content expertise in medical oncology. It was rated as high quality, and it was agreed it would be useful in practice. Comments were reviewed by the Expert Panel and integrated into the final manuscript before approval by the EBMC.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is not only to assess the suitability of the recommendations to implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/thoracic-cancer-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Radiation Therapy for Small Cell Lung Cancer[18] (http://ascopubs.org/doi/10.1200/JCO.20.03364)
- Integration of Palliative Care into Standard Oncology Care[190] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[191] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

GENDER-INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of individuals regardless of sexual orientation or gender identity.[192] Transgender and nonbinary people, in particular, may face multiple barriers to oncology care including stigmatization, invisibility, and exclusiveness. One way exclusiveness or lack of accessibility may be communicated is through gendered language that makes presumptive links between gender and anatomy.[193-196] With the acknowledgment that ASCO guidelines may impact the language used in clinical and research settings, ASCO is committed to creating gender-inclusive guidelines. For this reason, guideline authors use gender-inclusive language whenever possible throughout the guidelines. In instances in which the guideline draws upon data based on gendered research (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/thoracic-cancer-guidelines.

EQUAL CONTRIBUTION

H.K. and G.K. were expert panel co-chairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Systemic Therapy for Small-Cell Lung Cancer: ASCO-Ontario Health (Cancer Care Ontario) Guideline

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Systemic Therapy for Small-Cell Lung Cancer Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
Humera Khurshid, MD (Co-Chair)	Brown University, Providence, RI	Medical Oncology
Gregory P. Kalemkerian, MD (Co-Chair)	University of Michigan, Ann Arbor, MI	Medical Oncology
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Frank Weinberg, MD, PhD	University of Illinois, Chicago, IL	Medical Oncology
Nofisat Ismaila, MD	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

TABLE A2. Recommendation Rating Definitions

Term	Definitions
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects
	In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects
	All or almost all informed people would make the recommended choice for or against an intervention
Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists
	In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists
	Most informed people would choose the recommended course of action, but a substantial number would not