Systemic Therapy for Small Cell Lung Cancer: ASCO Guideline Rapid Recommendation Update

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ASCO Rapid Recommendation Updates highlight revisions to select ASCO guideline recommendations as a response to the emergence of new and practice-changing data. The rapid updates are supported by an evidence review and follow the guideline development processes outlined in the ASCO Guideline Methodology Manual. The goal of these articles is to disseminate updated recommendations, in a timely manner, to better inform health practitioners and the public on the best available cancer care options. Guidelines and updates are not intended to substitute for independent professional judgment of the treating clinician and do not account for individual variation among patients. See appendix for disclaimers and other important information (Appendix 1 and Appendix 2, online only).

ACCOMPANYING CONTENT

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Appendix

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BACKGROUND

In 2023, ASCO published a guideline on systemic therapy for small cell lung cancer (SCLC).[1] The recently published results of the phase III ADRIATIC trial and the phase II DeLLphi-301 trial have prompted this amendment to the guideline.[2,3]

METHODS

A targeted electronic literature search to identify clinical trials in this patient population was conducted and one phase III randomized control trial and one phase II clinical trial were found. The original guideline Expert Panel was reconvened to review new evidence from the phase III ADRIATIC trial and the phase II DeLLphi-301 trial, and to review and approve the revised recommendations.

EVIDENCE REVIEW

ADRIATIC: Consolidation Durvalumab in Limited-Stage SCLC

Literature Review Update and Analysis

The results of the interim analysis of the ADRIATIC trial, a phase III, randomized, double-blind, placebo-controlled, international study evaluating the efficacy of consolidation immunotherapy after concurrent chemoradiotherapy in patients with limited-stage (LS) SCLC, were recently published.[2] Eligible patients had stage I-III (LS) SCLC with no previous therapy, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1, and no evidence of disease progression after completion of concurrent chemoradiotherapy. Prophylactic cranial irradiation was allowed before random assignment. Although the study included three arms (durvalumab 1,500 mg + placebo; durvalumab 1,500 mg + tremelimumab 75 mg; or placebo + placebo once every 4 weeks for four cycles followed by either durvalumab or placebo once every 4 weeks for up to 2 years), the only data published thus far pertain to the dual primary end points of overall survival (OS) and progression-free survival (PFS) of the durvalumab alone versus placebo arms.

Of the 730 total patients enrolled, 264 received durvalumab + placebo and 266 received placebo. The median follow-up for OS was 37.2 months and for PFS was 27.6 months. The median OS was 55.9 months for durvalumab and 33.4 months for placebo (hazard ratio [HR], 0.73 [98.3% CI, 0.54 to 0.98]; $P = .01$). The OS rates at 24 and 36 months were 68% *v* 58.5% and 56.5% *v* 47.6% for durvalumab versus placebo, respectively. The median PFS was 16.6 months for durvalumab and 9.2 months for placebo (HR, 0.76 [97.2% CI, 0.59 to

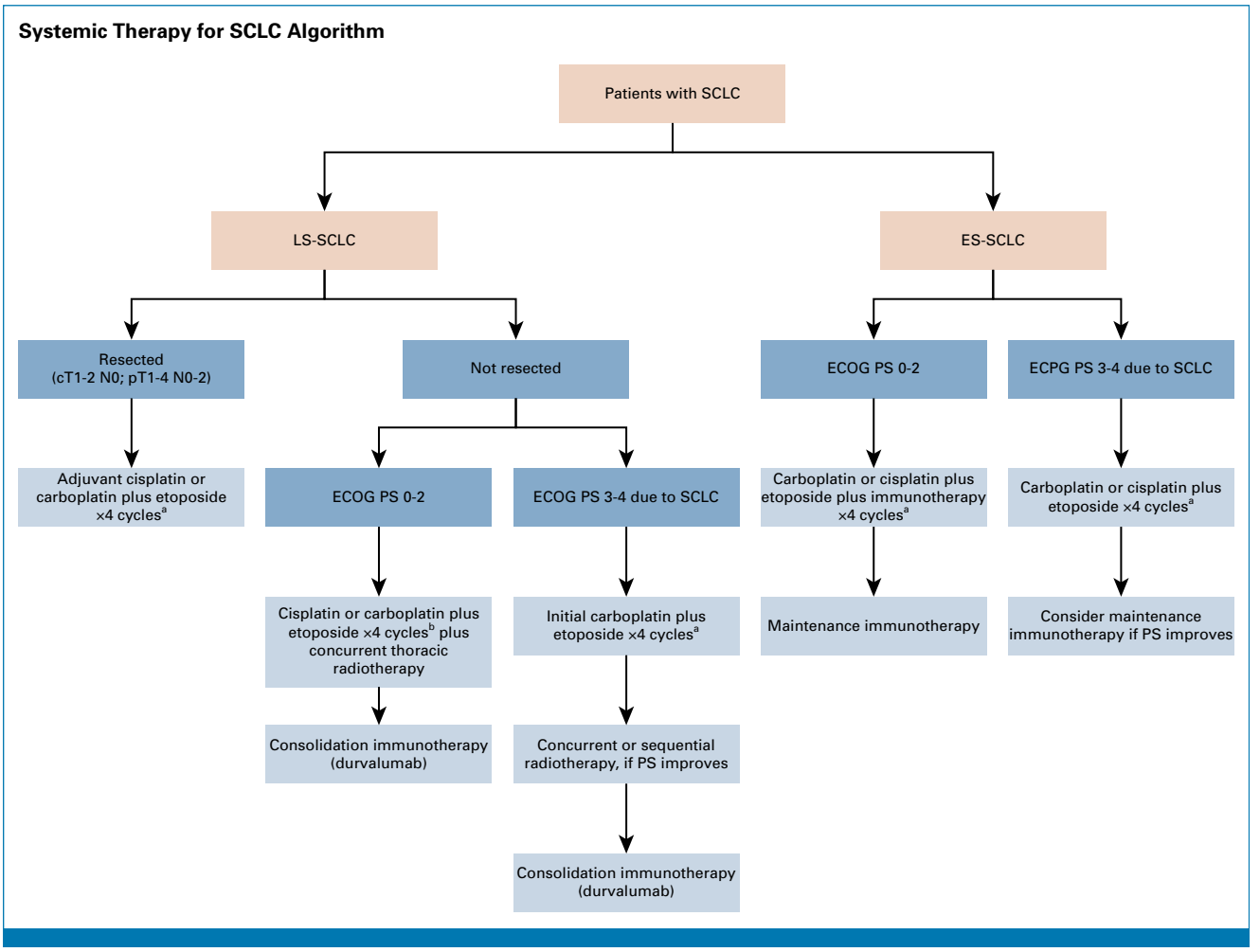

FIG 1. Systemic therapy for SCLC algorithm. This algorithm is derived from recommendations in the Guideline by Khurshid et al[1] and in this Rapid Recommendation Update. This is a tool based on an ASCO Guideline and is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients. This tool does not purport to suggest any particular course of medical treatment. Use of the guideline and this tool is voluntary. [a]May use trilaciclib or G-CSF if clinically indicated. [b]May use G-CSF if clinically indicated. cT, clinical TNM classification; ECOG PS, Eastern Cooperative Oncology Group performance status; ES, extensive-stage; G-CSF, granulocyte colony-stimulating factor; LS, limited stage; pT, pathologic TNM classification; SCLC, small cell lung cancer.

0.98]; $P = .02$). The PFS rates at 18 and 24 months were 48.8% *v* 36.1% and 46.2% *v* 34.2% for durvalumab versus placebo, respectively. The benefits for OS and PFS were observed across the predefined subgroups.

All-cause grade 3 to 4 adverse events (AEs) occurred in 24.4% of patients receiving durvalumab and 24.2% receiving placebo. Treatment-related grade 3 to 4 AEs were reported in 8.8% of patients receiving durvalumab and 6% of patients receiving placebo. Patients receiving durvalumab had higher rates of AEs, leading to drug discontinuation (16.4% *v* 10.6%) and death (2.7% *v* 1.9%). Immune-related AEs were reported in 32.1% of patients receiving durvalumab and 10.2% of those receiving placebo. Pneumonitis (of any cause) of any grade (38.2% *v* 30.2%) and grade 3 to 4 (3.1% *v* 2.6%) also occurred more frequently with durvalumab than placebo.

Clinical Interpretation

The goal of treatment for people with LS-SCLC is to achieve cure. Recent studies of concurrent chemoradiotherapy have reported 2-year and 5-year OS rates of 51%-58% and 29%-34%, respectively, with either once-daily or twice-daily radiotherapy.[4,5] The recently published data from the ADRIATIC trial are similar to the 2-year OS rate seen in these previous trials for chemoradiotherapy alone (58.5%) and suggest that the addition of consolidation durvalumab can significantly improve the 2-year OS rate by about 10%. It is imperative to continue work on identifying the subset of patients with SCLC who derive benefit from immunotherapy.[6] Although the results from other trials evaluating the role of immunotherapy in LS-SCLC (NRG-LU005 [ClinicalTrials.gov identifier: NCT03811002], KEYLYNK-013 [ClinicalTrials.gov identifier: NCT04624204], ACHILES

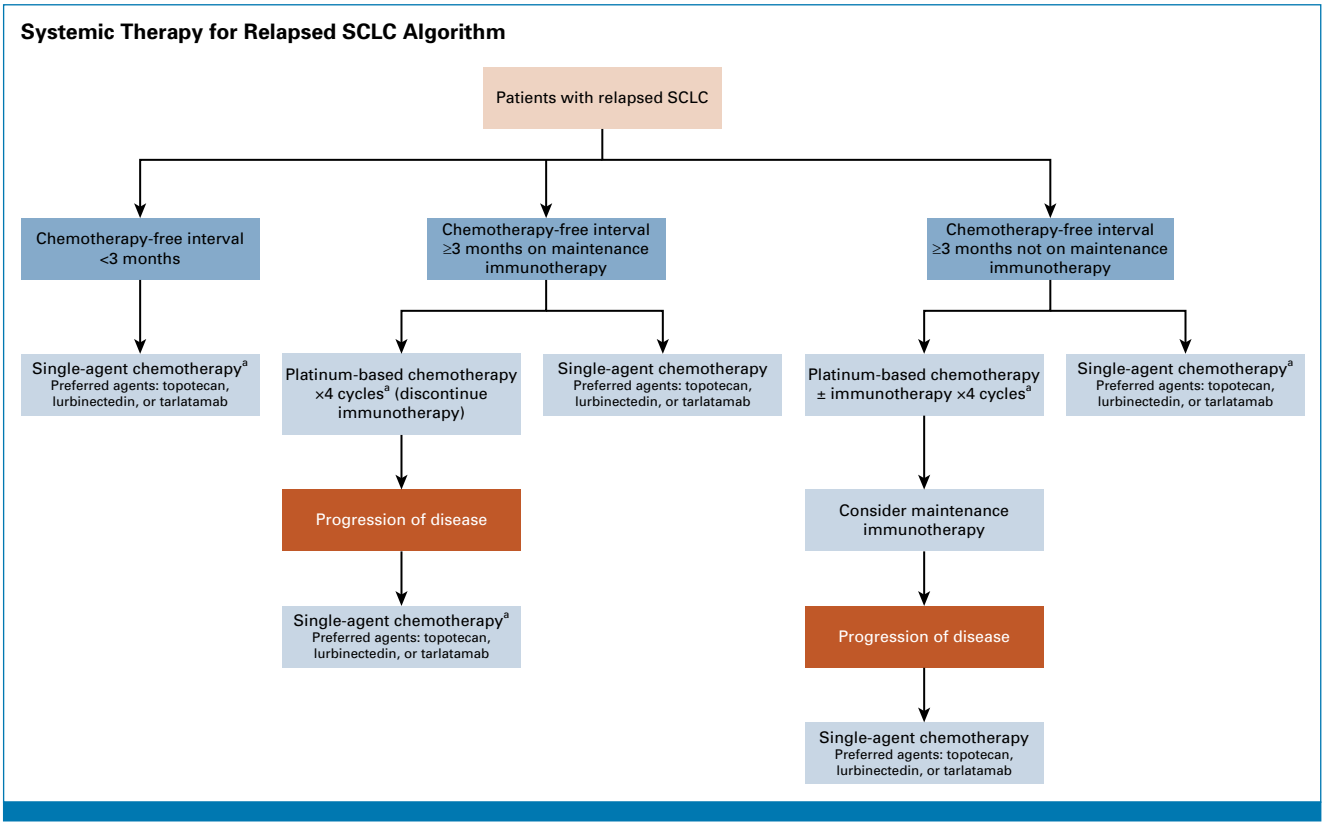

FIG 2. Systemic therapy for relapsed SCLC algorithm. This algorithm is derived from recommendations in the Guideline by Khurshid et al.[1] This is a tool based on an ASCO Guideline and is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients. This tool does not purport to suggest any particular course of medical treatment. Use of the guideline and this tool is voluntary. [a]May use trilaciclib or G-CSF if clinically indicated. SCLC, small cell lung cancer.

[ClinicalTrials.gov identifier: NCT03540420]) and long-term follow-up on OS from the ADRIATIC trial are still pending, the addition of consolidation durvalumab after chemoradiotherapy represents a new standard of care for patients with LS-SCLC.

DeLLphi-301: Tarlatamab as Subsequent Therapy for SCLC

Literature Review Update and Analysis

In May 2024, the US Food and Drug Administration (FDA) approved tarlatamab for treatment of patients with relapsed SCLC on the basis of the results of the phase II DeLLphi-301 trial.[3] Tarlatamab is a bispecific T-cell engager that targets both DLL3, which is expressed on nearly all SCLC cells, and CD3, which is expressed on T cells, to stimulate the immune-mediated killing of SCLC cells. This trial included patients with SCLC who had disease progression after at least two previous systemic regimens, one of which must have been a platinum-based regimen; 73% of patients had previous immunotherapy. All patients had PS 0-1, and patients with asymptomatic, previously treated, stable brain metastases were eligible. Exclusion criteria included interstitial lung disease, active pneumonitis, infusion reactions, severe immune-related AEs, or grade ≥2 pneumonitis due to previous immunotherapy.

Although the trial compared two doses of tarlatamab, 10 mg once every 2 weeks and 100 mg once every 2 weeks, this review focuses on those patients who received the 10 mg dose (n = 100) that is recommended by the FDA. The overall response rate was 40% with a median duration or response of 9.7 months. The response rate was 31% in patients with platinum-sensitive disease and 52% in patients with platinum-resistant disease. The median PFS was 4.9 months. The PFS and OS rates at 9 months were 28% and 68%, respectively.

Cytokine release syndrome (CRS) occurred in 51% of patients (30% grade 1, 20% grade 2, 1% grade 3). The most common symptoms of CRS were fever (97%), hypotension (20%), and hypoxia (17%). The median onset of CRS was 13 hours, and the median duration was 4 days. Nearly all CRS events occurred during the first cycle. Immune effector cell–associated neurotoxicity syndrome (ICANS) occurred in 8% of patients, all grade 1 or 2 with a median onset of 5 days, mostly during cycle 1.

Clinical Interpretation

Tarlatamab joins topotecan and lurbinectedin as the only agents approved by the FDA for patients with relapsed SCLC. Other single drugs, including paclitaxel and temozolomide, have been shown to have activity in smaller phase II trials. Cross-trial comparisons suggest that both lurbinectedin and tarlatamab are more effective than topotecan or other agents, although the duration of response of >9 months reported with tarlatamab is substantially longer than that seen with other agents. Currently there are no data reporting direct comparison of efficacy between any of these agents to determine how they should be sequenced in the setting of relapsed SCLC. The DeLLphi-304 trial comparing tarlatamab with standard of care chemotherapy in people with relapsed SCLC is ongoing to address this question.

Tarlatamab can cause the unique immune-mediated toxicities of CRS and ICANS, for which inpatient monitoring is recommended for 24 hours after the first two doses of cycle 1 (days 1 and 8). At the 10 mg dose of tarlatamab, treatment-related AEs of grade ≥3 occurred in 26% of patients, but grade ≥3 CRS and ICANS were only 1% and 0%, respectively.

The recommended tarlatamab regimen is an initial 1 mg dose intravenously on day 1 of cycle 1 followed by 10 mg once on days 8 and 15 of cycle 1, then once every 2 weeks thereafter until disease progression or unacceptable toxicity.

UPDATED RECOMMENDATIONS

Recommendation 2.4

Patients with LS-SCLC who have completed concurrent chemoradiotherapy and do not have disease progression should be offered consolidation immunotherapy (durvalumab) for up to 2 years if there are no contraindications to immunotherapy (Evidence quality: Moderate; Strength of recommendation: Strong).

Recommendation 5.3.1

Patients with LS-SCLC and ECOG PS 3-4 due to SCLC who have been treated with concurrent or sequential chemotherapy and radiotherapy may be offered consolidation immunotherapy (durvalumab) for up to 2 years if there are no contraindications to immunotherapy and there is improvement in PS (Evidence quality: Low; Strength of recommendation: Conditional).

Recommendation 4.1

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

Qualifying Statement

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

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, lurbinectedin, or tarlatamab) may be offered (Evidence quality: Moderate; Strength of recommendation: Strong).

DISCUSSION

Evidence supporting unchanged recommendations and sections on patient-clinician communication, multiple chronic conditions, cost implications, and more is found in the full guideline publication and applies to this Rapid Update.[1] Figures 1 and 2 include the updated algorithms. Additionally, for guideline tools and resources, including a complete summary table, visit www.asco.org/thoracic-cancer-guidelines.

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline Recommendation Update provides a recommendation update, with review and analysis of the relevant literature for the recommendation. Additional information, including links to patient information at www.cancer.org, is available at www.asco.org/thoracic-cancer-guidelines.

EQUAL CONTRIBUTION

G.P.K. and H.K. were Expert Panel Co-Chairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Conception and design: All authors
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REFERENCES

1. Khurshid H, Ismaila N, Bian J, et al: Systemic therapy for small-cell lung cancer: ASCO-Ontario Health (Cancer Care Ontario) guideline. J Clin Oncol 41:5448-5472, 2023
2. Cheng Y, Spigel DR, Cho BC, et al: Durvalumab after chemoradiotherapy in limited-stage small-cell lung cancer. N Engl J Med 391:1313-1327, 2024
3. Ahn MJ, Cho BC, Felip E, et al: Tarlatamab for patients with previously treated small-cell lung cancer. N Engl J Med 389:2063-2075, 2023
4. Faivre-Finn C, Snee M, Ashcroft L, et al: Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): An open-label, phase 3, randomised, superiority trial. Lancet Oncol 18:1116-1125, 2017
5. Bogart J, Wang X, Masters G, et al: High-dose once-daily thoracic radiotherapy in limited-stage small-cell lung cancer: CALGB 30610 (Alliance)/RTOG 0538. J Clin Oncol 41:2394-2402, 2023
6. Gay CM, Stewart CA, Park EM, et al: Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. Cancer Cell 39:346-360.e7, 2021

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX 3. SYSTEMIC THERAPY FOR SMALL CELL LUNG CANCER GUIDELINE PANEL

The following are members of the Systemic Therapy for Small-Cell Lung Cancer guideline panel: Humera Khurshid, MD; Nofisat Ismaila, MD; Jessica Bian, MD; Raetasha Dabney, MD; Millie Das, MD; Peter Ellis, MD; Jill Feldman, BS, MA; Christine L. Hann, MD, PhD; Swati Kulkarni, MD; Janessa Laskin, MD, PhD; Rami Manochakian, MD; Deebya Raj Mishra, MD; Isabel Preeshagul, DO; Pavan Reddy, MD; Ashish Saxena, MD, PhD; Frank Weinberg, MD, PhD; and Gregory P. Kalemkerian, MD.