

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

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In 2023, an evidence-based guideline on the systemic therapy for small cell lung cancer (SCLC) was published by ASCO and Ontario Health (Cancer Care Ontario).¹ Recently, an amendment to the guideline was published (Figs 1 and 2),² on the basis of the results of the phase III ADRIATIC trial evaluating the efficacy of consolidation immunotherapy after chemoradiotherapy in patients with limited-stage (LS) SCLC³ and the phase II DeLLphi-301 trial evaluating tarlatamab in relapsed SCLC.⁴ This companion article addresses several questions that clinicians may encounter when following the updated guideline recommendations.

WHICH PATIENTS WITH LS-SCLC SHOULD BE CONSIDERED FOR CONSOLIDATION THERAPY WITH DURVALUMAB?

On the basis of the published data from the ADRIATIC trial,³ durvalumab consolidation for up to 2 years is recommended for patients with LS-SCLC who have not had progression of disease after completion of curative-intent chemoradiotherapy. Eligibility criteria included: completion of three to four cycles of chemotherapy with cisplatin or carboplatin plus etoposide along with concurrent definitive thoracic radiotherapy; achievement of treatment response or stable disease; WHO performance status (PS) 0-1 after chemoradiotherapy; no active or prior autoimmune disease; no history of pneumonitis of grade ≥ 2 ; and resolution of toxicity from prior chemoradiotherapy to grade ≤ 1 . Prophylactic cranial irradiation (PCI) was allowed after completion of chemoradiotherapy and before the start of consolidation therapy.

To assess the appropriateness of consolidation durvalumab for an individual patient, it is necessary to understand both the benefits and risks of treatment. Patients were randomly assigned after completion of chemoradiotherapy to receive either durvalumab 1,500 mg once every 4 weeks ($n = 264$) or placebo ($n = 266$) for up to 2 years, with treatment starting within 42 days of the completion of chemoradiotherapy. With a median follow-up of 37.2 months, the median overall survival (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 36 months were 56.5% versus 47.6% for durvalumab versus placebo, respectively. The median progression-free survival (PFS) was 16.6 months for durvalumab and 9.2 months for placebo (HR, 0.76 [97.2% CI, 0.59 to 0.98]; $P = .02$). The PFS rates at 24 months were 46.2% versus 34.2% for durvalumab versus placebo, respectively. Overall, these data suggest that about 10% of patients will have a long-term survival benefit with durvalumab.

All-cause grade 3-4 adverse events (AEs) occurred in 24.4% of patients receiving durvalumab and 24.2% receiving placebo. Treatment-related grade 3-4 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% receiving placebo. Pneumonitis (of any cause) of any grade (38.2% v 30.2%) and grade 3-4 (3.1% v 2.6%) also occurred more frequently with durvalumab.

Most patients with LS-SCLC treated with definitive chemoradiotherapy have dramatic improvement in their tumor burden and cancer-associated symptoms. Although side effects of treatment, such as fatigue, myelosuppression, and esophagitis, are common, they usually improve within 6 weeks of completion of chemoradiotherapy. Therefore, most patients with LS-SCLC will be candidates for consolidation durvalumab. Although ADRIATIC was limited to

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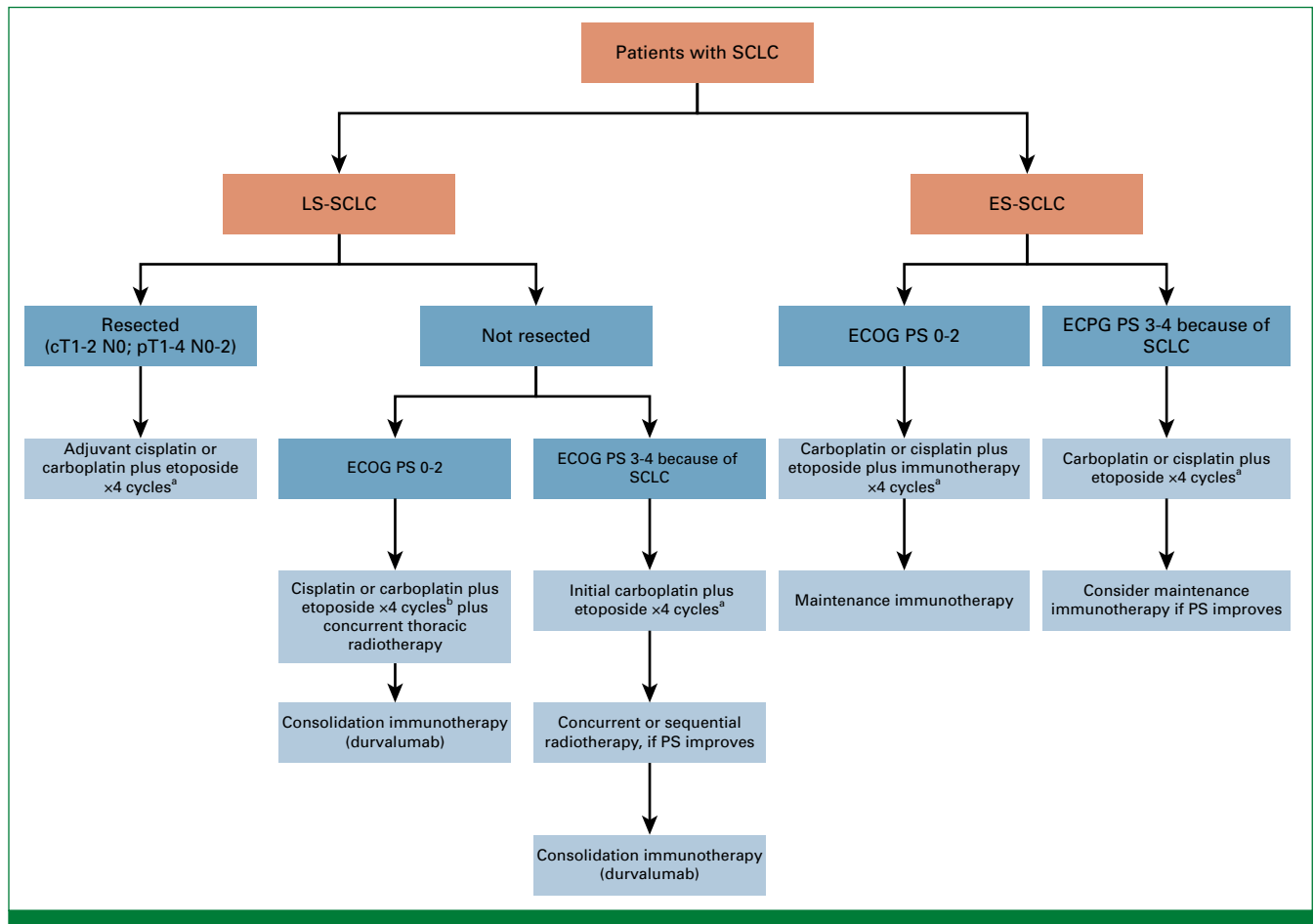


FIG 1. Algorithm. ^aMay use trilaciclib or G-CSF if clinically indicated. ^bMay use G-CSF if clinically indicated. cT, clinical TNM classification; ECOG, Eastern Cooperative Oncology Group; ES, extensive stage; G-CSF, granulocyte colony-stimulating factor; LS, limited status; PS, performance status; pT, pathologic TNM classification; SCLC, small cell lung cancer.

patients with PS 0–1, it is reasonable to include those with PS 2 as potential candidates for durvalumab. Patients with poor PS (3–4) at presentation who demonstrate substantial improvement in PS during initial therapy also may be candidates for consolidation durvalumab. However, it seems unwise to treat those with persistently poor PS (3–4) after chemoradiotherapy. Patients with poor recovery from initial therapy, such as those with persistent esophagitis or the early development of radiation pneumonitis, would also not be good candidates for consolidation therapy. While the ADRIATIC trial required patients to have had concurrent chemoradiotherapy, patients who may have received sequential chemotherapy followed by definitive thoracic radiation could be considered for durvalumab if they have an adequate PS after completion of initial therapy.

The ADRIATIC trial excluded patients with autoimmune diseases or organ transplantation, as these are both standard contraindications to the use of immune checkpoint inhibitors (ICIs). In determining eligibility for an individual patient, the type and activity of the autoimmune disease must be considered. For example, it would be reasonable to treat patients with mild rheumatoid arthritis which does

not require immunosuppressive therapy. By contrast, the presence of a paraneoplastic or preexisting autoimmune neurologic disorder is a strict contraindication to the use of ICIs.

ARE THERE MOLECULARLY DEFINED SUBSETS OF PATIENTS WITH LS-SCLC WHO WILL BENEFIT MOST FROM CONSOLIDATION IMMUNOTHERAPY?

Most SCLCs are immunologically cold, with only modest clinical improvement observed with ICI therapy.⁵ Recently, molecular classification of SCLC tumors revealed four subtypes based on gene expression profiles: SCLC-A (ASCL1-positive), SCLC-N (NEURO-D1-positive), SCLC-P (POU2F3-positive), and SCLC-I (inflamed phenotype), each with potential discrete therapeutic vulnerabilities.^{6,7} A subgroup analysis of the IMpower133 trial reported that patients with SCLC-I subtype tumors appeared to benefit most from the addition of atezolizumab to chemotherapy for extensive-stage (ES) SCLC.^{5,8} Thus far, however, there are no data available on whether patients with SCLC-I subtype tumors would be more likely to benefit from durvalumab consolidation.

Recommendation	Evidence Quality	Strength
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.	M	S
5.3.1. Patients with LS-SCLC and ECOG PS 3-4 because of 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.	L	C
4.1. In patients with relapsed SCLC with a chemotherapy-free interval of less than 90 days, single-agent systemic therapy may be offered. Preferred agents are topotecan, lurbinectedin, or tarlatamab.	M	S
<i>Qualifying statement for Recommendation 4.1: Single-agent chemotherapy is preferred over multiagent chemotherapy due to concerns regarding the balance of risks versus benefits.</i>		
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.	M	S

FIG 2. Updated Recommendations. C, conditional; ECOG, Eastern Cooperative Oncology Group; L, low; LS, limited-stage; M, moderate; PS, performance status; S, strong; SCLC, small cell lung cancer.

Currently, molecular testing to subtype SCLC is not standard of care. Clinical trials are currently being designed to determine the potential predictive therapeutic vulnerabilities of each SCLC subtype (eg, SWOG 2409 PRISM), and the Panel highly recommends enrollment on such trials.

IF CONSOLIDATION DURVALUMAB IS CONSIDERED, WHAT IS THE ROLE OF PCI IN LS-SCLC?

PCI remains a standard option for patients with LS-SCLC who have a good response to initial chemoradiotherapy and no contraindications to brain irradiation.⁹ The ongoing SWOG-NRG MAVERICK trial (ClinicalTrials.gov identifier: [NCT04155034](https://clinicaltrials.gov/ct2/show/study/NCT04155034)) is comparing PCI with magnetic resonance imaging brain surveillance in patients with LS-SCLC. Until results from this trial are available, patients should discuss the benefits and risks of PCI with their care team to make a shared decision based on their individual situation. In the ADRIATIC trial, PCI was permitted before the initiation of consolidation durvalumab, within 42 days after completing chemoradiotherapy. For patients opting to receive PCI, it is recommended to complete the 2-week course of PCI well within this timeframe.

Although early clinical trials of ICIs in patients with metastatic non-small cell lung cancer indicated the potential for intracranial activity, reports have been mixed, and trials are ongoing to more accurately define the efficacy of ICIs in treating brain metastases. Of concern, a secondary analysis of the CASPIAN trial found that the addition of durvalumab to chemotherapy did not significantly reduce the incidence of new brain metastases in patients with ES-SCLC.¹⁰ There are

currently no clinical data to support the concurrent administration of ICIs and PCI.

WHAT IS THE ROLE OF TARLATAMAB IN THE TREATMENT OF RELAPSED SCLC?

In May 2024, the US Food and Drug Administration granted accelerated approval for tarlatamab, a bispecific T-cell engager (BiTE) that targets delta-like ligand 3 (DLL3) and CD3, for patients with SCLC who had disease progression after platinum-based chemotherapy with or without immunotherapy. The recommended tarlatamab regimen is an initial dose of 1 mg IV on cycle 1 day 1, followed by 10 mg on cycle 1 day 8 and day 15, and then 10 mg once every 2 weeks until disease progression or unacceptable toxicity.

This approval was based on the phase II DeLLphi-301 study that evaluated the activity and safety of tarlatamab in patients with SCLC who had previously been treated with two or more lines of therapy, one of which must have been a platinum-based regimen.⁴ Patients with symptomatic or untreated brain metastases, interstitial lung disease, or a history of grade 2 pneumonitis or severe immune-mediated toxicity were excluded from the study.

Among the 100 patients in the study who received the recommended 10 mg dose of tarlatamab, 73% had prior immunotherapy and 23% had stable, previously treated brain metastases. The objective response rate was 40%, and 58% had a duration of response ≥ 6 months. The median OS was 14.3 months, and the OS rate at 9 months was 68%. The most common AE was cytokine release syndrome (CRS), which occurred in 51% of patients. Most cases of CRS occurred

during cycle 1 and grade 3 CRS occurred in only 1% of patients in the 10 mg group. Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 8% of patients in the 10 mg group, all were grade 1 or 2.

The relatively high response rate and long duration of response in this heavily pretreated population, including those previously treated with ICIs, has generated considerable hope for improving outcomes in relapsed SCLC. In addition, tarlatamab demonstrated activity regardless of platinum sensitivity and in patients with stable, treated brain metastases, although intracranial response is not evaluable from this study.¹¹ Given the limitations of a single-arm, phase II trial and cross-trial comparisons, the efficacy of tarlatamab compares favorably with the two other approved agents for relapsed SCLC, topotecan^{12,13}

and lurbinectedin.¹⁴ Therefore, tarlatamab is a reasonable second- or third-line option for eligible patients with relapsed SCLC, especially in those with a short chemotherapy-free interval. The results of the DeLLphi-304 trial comparing tarlatamab with standard second-line chemotherapy may help determine the appropriate sequencing of the available treatment options.

Operational barriers may hamper widespread patient access to tarlatamab because of the recommendation for inpatient observation for 24 hours to monitor for CRS and ICANS after the first two doses on days 1 and 8 of cycle 1. Each institution will need to develop and refine standard operating procedures to accommodate this requirement, which may necessitate additional training for health care staff and strain hospital resources.

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DISCLAIMER

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