LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

Section Editor: Edward S. Kim, MD, MBA

Updates in the Management of Small Cell Lung Cancer

Jyoti Malhotra, MD, MPH
Associate Professor
Department of Medical Oncology & Therapeutics Research
Director, Thoracic Medical Oncology
City of Hope Orange County
Irvine, California

H&O How common is small cell lung cancer (SCLC), and what are the characteristics of this subtype of lung cancer?

JM SCLC accounts for up to 15% of all lung cancers that are diagnosed. It is the most aggressive type of lung cancer and has a worse prognosis than non–small cell lung cancer. Its likelihood of metastasizing is very high, with poor patient outcomes. SCLC usually responds well to initial treatment with chemoimmunotherapy, but most patients experience recurrence or relapse of the disease within a few months to a year.

More than 90% of patients with SCLC have a history of tobacco use, so we need to continue our efforts to reduce the rate of smoking. We also need to educate people about the need for screening eligible patients and fully investigating the symptoms of those who may have lung cancer.

H&O What are the most important recent advances in the treatment of SCLC?

JM We have seen several advances over the last 6 to 7 years. The first has been the use of programmed death ligand 1 (PD-L1) immunotherapy as a standard of care. Both atezolizumab (Tecentriq, Genentech) and durvalumab (Imfinzi, AstraZeneca) are now approved for the treatment of extensive-stage SCLC in the first-line setting in combination with platinum-based doublet chemotherapy (since 2019 and 2020, respectively).

Durvalumab also received approval in 2024 for use after chemotherapy and radiation for patients with newly diagnosed, limited-stage SCLC, on the basis of results from the ADRIATIC trial.[1] Immunotherapy is now the standard of care for all patients, regardless of stage.

Another advance is the approval of the bispecific antibody tarlatamab (Imdelltra, Amgen), on the basis of the DeLLphi-301 and DeLLphi-304 trials.[2,3] Tarlatamab, which targets both CD3 and DLL3, received accelerated approval in 2024 and full approval in 2025 for patients with extensive-stage SCLC that has progressed on prior chemoimmunotherapy. It has become an excellent option for patients in the second-line setting and beyond.

Another important agent is the oncogenic transcription inhibitor lurbinectedin (Zepzelca, Jazz/PharmaMar), which first received approval in 2020 for the treatment of patients with metastatic disease after platinum-based chemotherapy. Approval was based on results from a phase 2 trial called Study B-005.[4] In 2025, lurbinectedin received an additional indication as a first-line maintenance treatment in combination with atezolizumab or atezolizumab/hyaluronidase (Tecentriq Hybreza, Genentech) for patients with extensive-stage SCLC that has not progressed after completion of initial induction chemoimmunotherapy. This new indication is based on results from the phase 3 IMforte trial.[5]

H&O How effective are our current treatments for the first-line management of extensive-stage SCLC?

JM The addition of immunotherapy has helped improve

patient outcomes. Both the IMpower133[6] and CASPIAN[7] trials, which led to the approval of immunotherapy in the first line, showed a significant survival benefit in comparison with chemotherapy alone. In IMpower133, the use of atezolizumab vs placebo for the first-line treatment of extensive-stage disease improved median overall survival (OS) from 10.3 to 12.3 months and improved median progression-free survival (PFS) from 4.3 to 5.2 months. In CASPIAN, the addition of durvalumab to platinum/etoposide improved median OS from 10.3 to 13.0 months. So, we do hope that this addition will help patients live longer.

H&O How effective are treatments for the second-line management of extensive-stage SCLC?

JM The phase 2 DeLLphi-301 trial showed an objective response rate of 40% with tarlatamab and a median duration of response of 9.7 months among patients with SCLC previously treated with 2 or more lines of therapy.[2] These are excellent numbers to see in the second-line setting of extensive-stage disease.

Study B-005 found that lurbinectedin had a good overall response when used as second-line therapy for SCLC, and it had an acceptable and manageable safety profile.[4] In the maintenance setting, the IMforte trial showed that adding lurbinectedin to atezolizumab reduced the risk of disease progression or death by 46% and the risk of death by 27% in comparison with atezolizumab alone.[5] The median OS was 13.2 months for lurbinectedin plus atezolizumab vs 10.6 months for atezolizumab alone. Lurbinectedin is a chemotherapy agent that comes with side effects, so the decision to use maintenance therapy with lurbinectedin needs to be made very carefully, with consideration of the patient's performance status and the goals of treatment.

H&O How effective are treatments for limited-stage SCLC?

JM The results from the ADRIATIC trial showed that the use of durvalumab after platinum-based chemotherapy—cisplatin or carboplatin in combination with etoposide—and radiation therapy significantly improved median OS, from 33.4 months with placebo to 55.9 months with durvalumab.[1] As a result, maintenance therapy with durvalumab is now the standard of care for treating these patients after chemoradiotherapy, and it should be offered to all patients unless a contraindication is present. We are making a big difference in terms of OS benefits for patients with limited-stage disease.

H&O What is the role of thoracic radiation in extensive-stage disease?

JM The role of thoracic radiation in extensive-stage disease is an evolving question. NRG Oncology is running a trial called RAPTOR to investigate whether adding thoracic radiation after an initial response to induction chemoimmunotherapy can improve clinical outcomes (NCT04402788). Until we have answers from RAPTOR, the decision depends on the patient's degree of response and preference, in addition to the judgment of the treating physician. This is an area in which we need more data.

> We have made more advances in SCLC in the last 6 or 7 years than we made in the previous 30 years.

H&O Where does prophylactic cranial irradiation (PCI) stand at this point?

JM The use of PCI for SCLC is decreasing, but it is still considered for patients with limited-stage SCLC as well as for those with extensive-stage SCLC who have had a very good response to initial chemoimmunotherapy. A subgroup analysis of the ADRIATIC trial found that PCI improved outcomes, but this was a retrospective ad hoc analysis.[1] The ongoing phase 3 MAVERICK trial from the SWOG Cancer Research Network is looking at whether PCI or close surveillance with magnetic resonance imagining (MRI) is associated with better clinical outcomes (NCT04155034). This trial is enrolling patients with both limited- and extensive-stage SCLC.

H&O How are antibody-drug conjugates (ADCs) reshaping second-line treatment options?

JM ADCs are a very promising class of drugs for the treatment of SCLC, especially because SCLC tumors express certain proteins that can be good targets for ADCs. For example, several ADCs have been developed to target B7H3, which is an immunomodulatory surface protein. One such drug with promising data is ifinatamab deruxtecan (I-DXd), which has received breakthrough therapy designation based on promising data from the phase 2 IDeate-Lung01 trial.[8] The phase 3 IDeate-Lung02

trial is currently enrolling patients with relapsed SCLC (NCT06203210).

Another target of interest is DLL3. The first ADC developed against DLL3 was rovalpituzumab tesirine (Rova-T), which caused significant toxicity but laid the path for the further development of better drugs to target DLL3. Other ADCs being developed include ABBV-706, which targets SEZ6, and sacituzumab govitecan (Trodelvy, Gilead), which targets TROP2. SEZ6 is another protein expressed by SCLC cells, and a phase 1 trial has shown some encouraging data.[9] And then we have data for sacituzumab govitecan, which needs to be further evaluated.

H&O Are any promising biomarkers on the horizon for SCLC?

JM Yes. More recently we have learned that the expression of certain transcriptional regulators, including NEUROD1, ASCL1, and POU2F3, can affect the sensitivity to certain drugs. The SWOG group recently launched the phase 2 PRISM trial, in which biomarker tests are being used to select and test new treatments for extensive-stage SCLC (NCT06769126).

H&O What other relevant trials are ongoing?

JM The phase 3 DeLLphi-306 trial is looking at the use of maintenance tarlatamab after initial chemoimmunotherapy for extensive-stage SCLC (NCT06117774). We are hoping that this trial will significantly improve patient outcomes.

H&O What do you see happening in the next few years regarding treatments for SCLC?

JM We have made more advances in SCLC in the last 6 or 7 years than we made in the previous 30 years. The pace of the discovery and development of new drugs for SCLC has noticeably accelerated, and we have some additional promising drugs as well as pathways that we are trying to target. I hope that we can significantly improve patient outcomes in the future and be able to either cure or achieve durable control of the disease of most of our patients. The agents that appear to be closest to becoming clinically available are tarlatamab in the first-line setting of extensive-stage disease and I-DXd in the relapsed/refractory setting.

Disclosures

Dr Malhotra has served as an advisor or consultant for AstraZeneca, Takeda, Bristol Myers Squibb, Pfizer, Fate Therapeutics, Johnson & Johnson, and Daiichi Sankyo.

References

1. Cheng Y, Spigel DR, Cho BC, et al; ADRIATIC Investigators. Durvalumab after chemoradiotherapy in limited-stage small-cell lung cancer. *N Engl J Med*. 2024;391(14):1313-1327.
2. Mountzios G, Sun L, Cho BC, et al; DeLLphi-304 Investigators. Tarlatamab in small-cell lung cancer after platinum-based chemotherapy. *N Engl J Med*. 2025;393(4):349-361.
3. Rudin CM, Johnson ML, Paz-Ares L, et al. Ifinatamab deruxtecan in patients with extensive-stage small cell lung cancer: primary analysis of the phase II IDeate-Lung01 trial. *J Clin Oncol*. 2026;44(4):261-273.
4. Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. *Lancet Oncol*. 2020;21(5):645-654.
5. Paz-Ares L, Borghaei H, Liu SV, et al; IMforte investigators. Efficacy and safety of first-line maintenance therapy with lurbinectedin plus atezolizumab in extensive-stage small-cell lung cancer (IMforte): a randomised, multicentre, open-label, phase 3 trial. *Lancet*. 2025;405(10495):2129-2143.
6. Horn L, Mansfield AS, Szczęsna A, et al; IMpower133 Study Group. IMpower133 Study Group. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379(23):2220-2229.
7. Paz-Ares L, Dvorkin M, Chen Y, et al; CASPIAN investigators. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2019;394(10212):1929-1939.
8. Ahn MJ, Cho BC, Felip E, et al; DeLLphi-301 Investigators. Tarlatamab for patients with previously treated small-cell lung cancer. *N Engl J Med*. 2023;389(22):2063-2075.
9. Chandana SR, Choudhury NJ, Dowlati A, et al. First-in-human study of ABBV-706, a seizure-related homolog protein 6 (SEZ6)–targeting antibody-drug conjugate (ADC), in patients (pts) with advanced solid tumors [ASCO abstract 3001]. *J Clin Oncol*. 2024;42(16)(suppl).