Drugs in Context

drugsincontext.com

REVIEW

Place in therapy of key treatments for platinum-sensitive, relapsed, extensive-stage small cell lung cancer with a focus on lurbinectedin: a narrative review with case studies

Leonid Shunyakov[1], Firas B Badin[2], Judith Hafer[3], David König[3], Patrizia Froesch[4], Laurent Greillier[5]

[1]Oncology/Hematology, Citizens Memorial Hospital, Bolivar, MO, USA; [2]Baptist Health Medical Group, Lexington, KY, USA; [3]Department of Medical Oncology, University Hospital Basel, Basel, Switzerland; [4]Istituto Oncologico della Svizzera Italiana, Ospedale Regionale di Bellinzona e Valli, Bellinzona, Switzerland; [5]Multidisciplinary Oncology and Therapeutic Innovations Department, Aix Marseille University, Assistance Publique-Hôpitaux de Marseille, Marseille, France

Abstract

Background: Virtually all patients with extensive-stage small cell lung cancer (SCLC) develop resistance to first-line platinum-based chemoimmunotherapy and experience relapse. Second-line therapy is therefore an integral part of the treatment paradigm.

Methods: Evidence was reviewed for key second-line regimens recommended in major guidelines for treatment of patients with platinum-sensitive relapse (chemotherapy-free interval ≥90 days), focusing on recent prospective clinical trials and post hoc analyses. Case studies of second-line lurbinectedin are presented as examples of the current management approach to platinum-sensitive relapsed SCLC.

Results: Subject to the limitations of cross-trial comparisons, the evidence review allowed us to draw broad conclusions about the place in therapy of approved options for platinum-sensitive relapse. Platinum rechallenge is more effective and better tolerated than topotecan and is a reasonable second-line choice in suitable patients. Topotecan provides modest clinical benefit and has the potential to cause dose-limiting haematological toxicities. Cyclophosphamide-doxorubicin-vincristine combination therapy offers no clear advantages over topotecan. Efficacy outcomes with second-line lurbinectedin are similar or better than those reported with platinum rechallenge, and lurbinectedin has a more favourable safety profile and simpler administration schedule. Second-line lurbinectedin preserves platinum rechallenge for later use and may resensitize tumour cells to platinum with potential survival advantages. Lurbinectedin safety is not affected by advanced age (≥65 years). Case studies highlight objective and durable responses to second-line lurbinectedin, along with good tolerability and quality of life.

Conclusions: Available evidence supports second-line lurbinectedin as a useful alternative to platinum rechallenge, topotecan and cyclophosphamide-doxorubicin-vincristine in patients with platinum-sensitive relapsed SCLC.

Download the **Plain Language Summary** of this article: https://www.drugsincontext.com/wp-content/uploads/2025/10/dic.2025-7-9-PLS.pdf

Keywords: extensive-stage small cell lung cancer, lurbinectedin, platinum rechallenge, second-line chemotherapy, topotecan.

Citation

Shunyakov L, Badin FB, Hafer J, König D, Froesch P, Greillier L. Place in therapy of key treatments for platinum-sensitive, relapsed, extensive-stage small cell lung cancer with a focus on lurbinectedin: a narrative review with case studies. *Drugs Context*. 2025;14:2025-7-9. https://doi.org/10.7573/dic.2025-7-9

Introduction

Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine carcinoma characterized by rapid tumour progression, early metastatic spread and a poor prognosis.[1] Approximately two-thirds of patients with SCLC present with metastatic (extensive-stage) disease at diagnosis.[2] Despite high response rates (60-70%) to first-line platinum-based therapy, virtually all patients relapse, at least half within 6 months.[3-6] Relapse is driven primarily by the development of resistance to platinum.[7] Thorough planning of second-line therapy for qualifying patients is therefore an integral part of the treatment concept in patients with extensive-stage SCLC.

Standard first-line treatment for extensive-stage SCLC consists of platinum-based chemotherapy (platinum-etoposide) in combination with a PD-L1 inhibitor (atezolizumab or durvalumab), followed by maintenance immunotherapy.[8,9] Upon relapse, key criteria guiding treatment selection are the patient's performance status and duration of response to first-line platinum-based therapy, that is, the chemotherapy-free interval (CTFI) since the last platinum dose.[10] A longer CTFI increases the likelihood of a clinically meaningful response to second-line chemotherapy.[11] Generally, platinum-sensitive patients are those who develop recurrent disease 3–6 months or longer after completion of first-line therapy. Accordingly, important guidelines from Europe and the USA base their second-line treatment recommendations on these parameters, although with differences in terms of (approved) treatment options and the definition of CTFI.[12,13] In clinical practice, selection of second-line treatment is further influenced by quality of life considerations, patient preferences, treatment burden and the safety profiles of candidate regimens.[9,14]

Rechallenge with platinum-based therapy is currently a standard of care option for patients with platinum-sensitive relapse. European Society for Medical Oncology (ESMO) guidelines recommend rechallenge with platinum-etoposide in patients with a CTFI of ≥3 months,[12] whilst National Comprehensive Cancer Network (NCCN) guidelines position platinum rechallenge as a preferred regimen in patients with a CTFI of >6 months and as a regimen to be considered in patients with a CTFI of 3–6 months.[13] Other regimens for this setting include single-agent topotecan or lurbinectedin, combination chemotherapy with cyclophosphamide-doxorubicin-vincristine (CAV), and irinotecan and tarlatamab in the USA only (Table 1).[12,13]

In 2020, the FDA granted accelerated approval to lurbinectedin for the treatment of relapsed SCLC.[15,16] Lurbinectedin is currently approved in 18 countries and territories (Argentina, Australia, Canada, China, Ecuador, Hong Kong, Israel, Macau, Mexico, Oman, Peru, Qatar, Singapore, South Korea, Switzerland, Taiwan, United Arab Emirates, USA) for the treatment of adult patients with metastatic SCLC and disease progression on or after platinum-based chemotherapy.

To gain insight into the relative place in therapy of key regimens recommended in major guidelines to treat patients with platinum-sensitive relapsed SCLC, we examined available evidence focusing on recent prospective clinical trials and post hoc analyses. Case studies featuring the use of lurbinectedin in the second line provide examples of the current approach to treating platinum-sensitive relapsed SCLC. Note that the content of this manuscript does not address the evolution of the SCLC treatment paradigm as per clinical trial data presented at the American Society of Clinical Oncology (ASCO) 2025 meeting. New data presented at the ASCO 2025 meeting have demonstrated that the field of extensive-stage SCLC is undergoing rapid change. Results from both the phase III DeLLphi-304 study and the phase III IMforte study are promising and likely to change the therapeutic landscape. Further, whilst we acknowledge the positioning of tarlatamab and irinotecan in NCCN guidelines as recommended regimens for relapsed platinum-sensitive SCLC,[13] the data synthesis for this review excludes therapies without marketing authorization in both the USA and Europe.

Second-line treatments for platinum-sensitive relapsed SCLC

This section overviews the mechanism of action, efficacy and safety outcomes, and administration schedule of key second-line treatments for platinum-sensitive relapsed SCLC.

Platinum rechallenge

As reviewed in detail by Dómine Gómez et al.,[17] platinum compounds (e.g. cisplatin and carboplatin) act primarily by forming covalent bonds with purine bases on DNA, creating cross-links that distort its normal structure. This damage hinders DNA replication and transcription, leading to cell cycle arrest and apoptosis (programmed cell death). Platinum-induced cross-links can also overwhelm tumour cell repair mechanisms and trigger cellular stress responses that activate pro-apoptotic pathways. Mechanisms that contribute to the development of platinum resistance include alterations in uptake genes (downregulation)

Table 1. Guideline recommendations for treatment of SCLC after failure of first-line platinum-based chemoimmunotherapy.

ESMO clinical practice guidelines[12]		**NCCN guidelines[13]**	
Recurrent SCLC (second-line therapy and beyond)		**SCLC subsequent systemic therapy (PS 0–2)** **Consider dose reduction or growth factor support for patients with PS 2**	
Platinum-resistant relapse (<3 months TFI)	**Platinum-sensitive relapse (≥3 months TFI)**	**CTFI ≤6 months**	**CTFI >6 months**
Refractory and/or PS >2: • Best supportive care • Lurbinectedin PS 0–2: • Oral or IV topotecan • CAV • Lurbinectedin	• Rechallenge with platinum-etoposide • Oral or IV topotecan • CAV	Preferred regimens: • Clinical trial enrolment • Lurbinectedin • Topotecan oral or IV • Irinotecan • Retreatment with platinum-based doublet may be considered for CTFI 3–6 months Other recommended regimens • Nivolumab or pembrolizumab (if not previously treated with an ICI) • Paclitaxel • Temozolomide • CAV • Docetaxel • Gemcitabine • Oral etoposide	Preferred regimens: • Clinical trial enrolment • Retreatment with platinum-based doublet Other recommended regimens: • Lurbinectedin • Topotecan oral or IV • Irinotecan • Tarlatamab

CAV, cyclophosphamide-doxorubicin-vincristine; CTFI, chemotherapy-free interval; ESMO, European Society for Medical Oncology; ICI, immune checkpoint inhibitor; IV, intravenous; NCCN, National Comprehensive Cancer Network; PS, performance status; SCLC, small cell lung cancer; TFI, treatment-free interval.

and efflux transporters (upregulation) which result in decreased intracellular accumulation of platinum, enhancement of DNA repair pathways involving the nucleotide excision repair (NER) system and evasion of apoptosis due to changes in the expression of apoptotic regulators.[17]

A review of evidence for platinum rechallenge in patients with SCLC and a CTFI of ≥90 days supported its activity in platinum-sensitive disease, though most articles were small retrospective analyses.[18] Studies reported objective response rates (ORRs) of 37-55%, median progression-free survival (PFS) of 4.5–6.2 months and median overall survival (OS) of 7.5–14.4 months; however, in the absence of primary prophylaxis with granulocyte colony-stimulating factor (G-CSF), grade 3/4 haematological adverse events (AEs), such as neutropenia (65-94%) and febrile neutropenia (15-19%), were common. Amongst available studies, a phase III trial that compared carboplatin-etoposide (n=81) with topotecan (n=81) in the second line reported outcomes in favour of platinum rechallenge.[19] Treatment with carboplatin-etoposide was associated with a higher ORR (49% *versus* 25%; p=0.0024) and prolonged median PFS (4.7 *versus* 2.7 months, stratified HR 0.57; p=0.0041) than topotecan, though with no difference in median OS (7.5 *versus* 7.4 months, HR 1.03; p=0.94). Whereas use of filgrastim primary prophylaxis was high in both treatment groups (88% and 85%), grade 3/4 haematological AEs (neutropenia: 14% *versus* 22%; thrombocytopenia: 31% *versus* 36%; febrile neutropenia: 6% *versus* 11%) were numerically lower with platinum rechallenge than with topotecan.[19]

Platinum rechallenge is administered as an intravenous (IV) infusion of carboplatin (area under the curve 5 mg/mL per min) on day 1 plus IV etoposide (100 mg/m^2) from day 1 to day 3, every 3 weeks, for a maximum of six cycles. Prophylactic use of filgrastim is generally recommended when the risk of febrile neutropenia is ≥20%.[12,13]

Topotecan

Topotecan exerts its cytotoxic effect by inhibiting topoisomerase I, an enzyme necessary for DNA replication. Topotecan forms a stable covalent complex with the DNA/topoisomerase I aggregate, leading to breaks in the DNA strand and, ultimately, to apoptosis and cell death.[20]

Regulatory approval of topotecan for second-line treatment of SCLC (initial approval in the USA was in 1996) was supported largely by the results of two randomized phase III trials in patients with recurrent/relapsed SCLC.[21,22] In patients with a CTFI of ≥60 days, IV topotecan was at least as effective as IV CAV with respect to response rate (24.3% *versus* 18.3%; p=0.285), median time to progression (13.3 *versus* 12.3 weeks, p=0.552) and median survival (25.0 *versus* 24.7 weeks, p=0.795) and was associated with significantly greater symptom improvement and less interference with daily activity than CAV (p<0.05).[21] A phase II randomized study designed to evaluate the activity of oral topotecan in relapsed SCLC found it to be similar in efficacy to IV topotecan but with less grade 4 neutropenia and more convenient administration.[23] Proof of clinical benefit of oral topotecan was subsequently documented in a phase III trial in patients with platinum-sensitive relapse (median CTFI 87 days), in which oral topotecan prolonged survival (25.9 *versus* 13.9 weeks) and provided quality-of-life benefits and greater symptom control compared with best supportive care alone.[22]

In the above-mentioned phase III trial comparing carboplatin-etoposide rechallenge with second-line topotecan in patients with SCLC and a CTFI of ≥90 days, efficacy and safety outcomes favoured platinum rechallenge.[19] Treatment with topotecan resulted in a lower ORR (25% *versus* 49%; p=0.0024) and shorter median PFS (2.7 *versus* 4.7 months; HR 0.57; p=0.0041) compared to platinum rechallenge; and topotecan was associated with a higher frequency of haematological side-effects such as grade 3/4 neutropenia (22% *versus* 14%) and grade 3/4 febrile neutropenia (11% *versus* 6%). Two treatment-related deaths (both febrile neutropenia with sepsis) occurred in the topotecan group *versus* none in the platinum rechallenge group.[19]

Topotecan is administered IV at a dose of 1.5 mg/m^2/day on days 1–5 every 21 days,[24] or orally at a dose of 2.3 mg/m^2/day on days 1–5 every 21 days.[25] It is generally administered for four to six cycles but can be continued until progression if tolerance is favourable. The FDA's boxed warning cautions about bone marrow suppression and the need to monitor peripheral blood cell counts.[24,25] In Europe, it is standard practice to manage neutropenia by administering topotecan with other medicinal products (e.g. G-CSF) or by reducing the dose to maintain neutrophil counts.[26]

Cyclophosphamide-doxorubicin-vincristine

The CAV combination aims to target tumour cells with different mechanisms. Cyclophosphamide damages DNA, doxorubicin interferes with DNA replication and repair and vincristine disrupts microtubules, preventing cell division. All processes result in cell death.[27]

In the previously mentioned randomized phase III trial of topotecan and CAV in patients with relapsed SCLC and a CTFI of ≥60 days, efficacy outcomes between regimens were broadly similar for response rate (24.3% *versus* 18.3%; p=0.285), median time to progression (13.3 *versus* 12.3 weeks, p=0.552) and median survival (25.0 *versus* 24.7 weeks; p=0.795).[21] Grade 4 neutropenia occurred in fewer courses with topotecan than CAV (37.8% *versus* 51.4%; p<0.001), whereas incidences of grade 4 thrombocytopenia (9.8% *versus* 1.4%; p<0.001) and grade 3/4 anaemia (17.7% *versus* 7.2%; p<0.001) were significantly lower with CAV than topotecan. Dose reductions for non-haematological toxicities (mainly due to neurotoxicity) were more frequent with CAV than with topotecan (10.6% *versus* 0.9%; p=0.003).[21]

CAV is administered over approximately 2 h as IV cyclophosphamide 1000 mg/m^2, doxorubicin 45.0 mg/m^2 and vincristine 2.0 mg on day 1 of 21 day cycles. Treatment can be administered until disease progression.

Lurbinectedin

Lurbinectedin is a selective inhibitor of oncogenic transcription with several mechanisms of action.[28] Lurbinectedin binds covalently to one DNA strand and forms non-covalent bonds with the opposite strand, thus preventing strand separation and transcription. This transcriptional blockage affects genes essential for tumour survival, ultimately triggering apoptosis of tumour cells. Lurbinectedin also induces DNA damage and interferes with the NER machinery, thereby delaying the repair process. Additionally, lurbinectedin modulates the tumour microenvironment by inducing apoptosis of tumour-associated macrophages, reducing their supportive functions (secretion of growth factors, cytokines and proteases) and diminishing the immunosuppressive environment within the tumor.[28]

Lurbinectedin is approved by the FDA for treatment of adult patients with metastatic SCLC and disease progression on or after platinum-based chemotherapy.[29] ESMO guidelines recommend lurbinectedin for platinum-resistant relapse (CTFI <3 months).[12] NCCN guidelines recommend lurbinectedin as subsequent systemic therapy for patients with CTFI >180 days (Table 1).[13] In Switzerland, lurbinectedin is approved for treatment of adult patients with metastatic SCLC who have progressed after

Table 2. Outcomes according to chemotherapy-free interval in patients with relapsed extensive-stage small cell lung cancer enrolled in the phase II lurbinectedin basket study.[18,31]

Efficacy by investigator assessment	All patients (*n*=105)	CTFI ≥90 days (*n*=60)	CTFI ≥180 days (*n*=20)
ORR, % (95% CI)	35.2 (26.2–45.2)	45.0 (32.1–58.4)	60.0 (36.1–86.9)
DCR, % (95% CI)	68.6 (58.8–77.3)	81.7 (69.6–90.5)	95.0 (75.1–99.9)
Median DoR, months (95% CI)	5.3 (4.1–6.4)	6.2 (3.5–7.3)	5.5 (2.9–11.2)
Median PFS, months (95% CI)	3.5 (2.6–4.3)	4.6 (2.8–6.5)	4.6 (2.6–7.3)
Median OS, months (95% CI)	9.3 (6.3–11.8)	11.9 (9.7–16.2)	16.2 (9.6–NR)
12 month OS, % (95% CI)	34.2 (23.2–45.1)	48.3 (32.5-64.1)	60.9 (35.7–86.2)

CI, confidence interval; CTFI, chemotherapy free interval; DCR, disease control rate; DoR, duration of response; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

platinum-containing therapy with a CTFI of ≥30 days and with no central nervous system (CNS) metastases.[30]

FDA approval of single-agent lurbinectedin was supported by an open-label, multicentre, single-arm phase II basket study that included 105 patients with SCLC who were treated after failure of first-line platinum-based chemotherapy.[31] In prespecified subgroup analyses, second-line lurbinectedin demonstrated antitumour activity across all CFTI categories, particularly in platinum-sensitive relapse. In patients with a CFTI of ≥90 or ≥180 days, respective ORRs were 45.0% and 60.0%, the disease control rate was 81.7% and 95.0%, and median OS was 11.9 and 16.2 months (Table 2).[18,31] The safety profile of second-line lurbinectedin was regarded as acceptable and manageable, with reversible myelosuppression as the main toxicity.[31]

Lurbinectedin is administered as a 1-h IV infusion at a dose of 3.2 mg/m^2 every 3 weeks. Treatment can be continued until disease progression if tolerability is acceptable. Primary G-CSF prophylaxis is not required.[29,30]

Activity of lurbinectedin relative to other second-line therapies for platinum-sensitive relapsed SCLC

Efficacy

Efficacy of lurbinectedin versus platinum rechallenge

In the absence of a head-to-head comparison of lurbinectedin and platinum rechallenge, insight into their relative efficacy is derived by comparing results of the phase II lurbinectedin basket trial and phase III platinum-etoposide *versus* topotecan trial. In patients with a CTFI of ≥90 days, second-line lurbinectedin was associated with a median OS of 11.9 months and a 12 month OS rate of 48.3%;[31] corresponding outcomes with carboplatin-etoposide rechallenge in a comparable setting were 7.5 months and 25%.[19]

To determine the possible impact of second-line lurbinectedin on the efficacy of subsequent therapy for relapsed SCLC, a *post hoc* analysis of the basket trial examined data for patients with a CTFI of ≥90 days who received systemic therapy after lurbinectedin; 27 patients received platinum and 17 received no further platinum after lurbinectedin.[32] Baseline characteristics did not differ between groups and time to progression on first-line platinum-based therapy was 8.6 months in both groups. The ORR (48.1% *versus* 47.1%) was comparable in the platinum and no further platinum groups, whereas median duration of response (7.3 *versus* 5.8 months), median PFS (6.0 *versus* 4.0 months) and median OS (15.9 *versus* 11.8 months) were prolonged in the platinum group. Amongst the 17 patients who received platinum immediately after lurbinectedin, outcomes (ORR 35%, median PFS 3.4 months, median OS of 7.2 months)[32] were comparable to those achieved with second-line platinum (ORR 49%, median PFS 4.7 months, median OS 7.5 months) in the phase III platinum-etoposide *versus* topotecan study.[19]

Efficacy of lurbinectedin versus topotecan/CAV

The phase III ATLANTIS study comparing second-line lurbinectedin plus doxorubicin (*n*=307) with 'control' treatment (topotecan (*n*=127) or CAV (*n*=179)) in patients with relapsed SCLC and a CFTI of ≥30 days failed to demonstrate a statistically significant difference in the

primary endpoint of OS.[33] After a median follow-up of 24.1 months, median OS was 8.6 months and 7.6 months, respectively (HR 0.97, 95% CI 0.82–1.15; p=0.70). According to investigators, the negative result may have been due to the use of a lower dose (2.0 mg/m^2) of lurbinectedin than the approved dose (3.2 mg/m^2) and incorporation of doxorubicin into the regimen given that it has little to no single-agent activity in SCLC. Notably, exploratory subgroup analyses pointed to survival advantages for lurbinectedin plus doxorubicin over topotecan/CAV in patients older than 65 years (8.9 *versus* 5.9 months; HR 0.75, 95% CI 0.58–1.00) and in those with a CTFI of ≥180 days (12.7 *versus* 9.8 months; HR 0.85, 95% CI 0.61–1.19).[33]

A pre-planned *post hoc* analysis conducted to support regulatory approval of lurbinectedin in Switzerland examined data for a subset of patients in the phase II basket study who had a CTFI of ≥30 days and no CNS metastases (n=83).[34] Data from a matched population (n=98) of patients treated with topotecan in the phase III ATLANTIS study (n=127) served as an indirect external control. The significantly higher ORR (41.0% *versus* 25.5%; p=0.0382), longer median duration of response (5.3 *versus* 3.9 months) and longer median OS (10.2 *versus* 7.6 months) associated with lurbinectedin indicated a superior risk-to-benefit ratio relative to topotecan.[34]

Safety

Safety of lurbinectedin versus platinum rechallenge

Safety data from patients with SCLC and a CTFI of ≥90 days who were treated with lurbinectedin in the phase II basket study[31] or with carboplatin-etoposide in the phase III platinum rechallenge study[19] point to a more favourable safety profile with lurbinectedin. In the respective studies, frequencies of grade ≥3 thrombocytopenia (6.0% *versus* 31%) and anaemia (12% *versus* 24%) were lower with lurbinectedin than platinum-etoposide. Although grade ≥3 neutropenia was more frequent with lurbinectedin than with carboplatin-etoposide (47% *versus* 13%), this can be explained by protocol differences regarding use of growth factor support. Primary G-CSF prophylaxis was not required in the phase II basket study; 22% of 105 patients received secondary G-CSF prophylaxis or therapy for neutropenia.[31] Primary G-CSF prophylaxis was recommended for all patients in the phase III platinum rechallenge study; 88% of 81 patients in the carboplatin-etoposide group received filgrastim.[19] Additionally, relative to carboplatin-etoposide, lurbinectedin was associated with lower incidences of AEs leading to dose reductions (24.1% *versus* 41.0%), treatment discontinuations (0% *versus* 17%) and hospitalizations (10.5% *versus* 37%).[19,31]

Safety of lurbinectedin versus topotecan/CAV

An analysis of safety results for matched populations (CTFI ≥30 days and no CNS metastases) from the phase II basket study[31] and the phase III ATLANTIS study[33] favoured lurbinectedin over topotecan.[34] Incidences of grade ≥3 neutropenia (47.0% *versus* 75.5%), thrombocytopenia (6.0% *versus* 52.0%), leukopenia (30.1% *versus* 68.4%) and anaemia (12.0% *versus* 54.1%) reported per dataset were markedly lower with lurbinectedin than with topotecan. Lurbinectedin was also associated with fewer instances of AEs leading to dose reductions (24.2% *versus* 48.0%), treatment discontinuations (0% *versus* 15.3%) and hospitalizations (10.5% *versus* 32.2%), and with need for G-CSF primary prophylaxis (0% *versus* 100%).[34] In the ATLANTIS study, incidences of grade ≥3 anaemia (19% *versus* 26%), neutropenia (37% *versus* 66%), febrile neutropenia (4% *versus* 10%) and thrombocytopenia (14% *versus* 18%) were lower with lurbinectedin plus doxorubicin than with CAV.[33]

Special populations

As elderly patients are of special interest due to frailty and comorbidities, a *post hoc* analysis explored the efficacy and safety of second-line regimens for relapsed SCLC in patients aged ≥65 years with a CTFI of ≥30 days.[35] Data were analysed for 26 patients treated with lurbinectedin in the phase II basket study,[31] 121 patients treated with lurbinectedin plus doxorubicin in the phase III ATLANTIS study,[33] and 118 patients treated with physician's choice (topotecan or CAV) in the phase III ATLANTIS study.[33] Median age across treatment groups was around 70 years. Outcomes were generally more favourable with lurbinectedin, as a single agent or in combination with doxorubicin, compared with topotecan/CAV. Incidence rates of grade ≥3 AEs in respective studies were 69% with lurbinectedin, 73% with lurbinectedin plus doxorubicin and 94% with topotecan/CAV (Table 3).[35]

Case reports

Four case reports (two from Switzerland, two from the USA) illustrate the current approach to managing patients with platinum-sensitive relapsed SCLC featuring the use of lurbinectedin in the second line. As all cases are anonymized and contain no information enabling identification of the patients, patient consent was not required.

Case 1

A 64-year-old Swiss man (former smoker; 40 pack/years) presented to the emergency department with cough, fever, nausea and muscle pain. His medical history was notable only for arterial hypertension. His functional ability was good (Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1).

A chest computed tomography (CT) scan revealed a tumour in the right upper lobe of the lung with bronchus

Table 3. Efficacy and safety of lurbinectedin versus standard of care (physician's choice) in patients aged ≥65 years with relapsed small cell lung cancer and a chemotherapy-free interval of ≥30 days. Adapted from ref.[35]

Variable	Phase II basket trial[31]	Phase III ATLANTIS trial[33]		OR/HR (95% CI)[c]
	Lurbinectedin (*n*=26)	Lurbinectedin + doxorubicin[b] (*n*=121)	Physician's choice (topotecan/CAV)[b] (*n*=118)	
Median number of cycles	4	6	4	-
Efficacy outcomes				
ORR[a], %, (95% CI)	34.6 (17.2–55.7)	24.8 (17.4–33.5)	26.3 (18.6–35.2)	0.93 (0.50–1.73)
Median DoR[a], months, (95% CI)	5.1 (2.4–5.9)	6.9 (4.1–10.1)	4.2 (3.6–5.7)	0.48 (0.26–0.89)
Median PFS[a], months, (95% CI)	3.4 (2.6–5.1)	4.2 (3.5–4.8)	3.0 (2.8–4.0)	0.65 (0.49–0.86)
Median OS, months, (95% CI)	9.7 (6.2–14.9)	9.0 (7.8–10.8)	5.9 (5.3–7.6)	0.76 (0.56–0.99)
Safety outcomes				***p* value[c]**
Grade ≥3 AEs, %	69.2	72.7	94.1	-
Most frequent grade ≥3 AEs, regardless of relationship, %				
Anaemia	19.2	23.1	36.4	0.0333
Fatigue	15.4	13.2	15.3	0.7130
Neutropenia	65.4	43.8	73.7	<0.0001
Febrile neutropenia	3.8	5.0	9.3	0.2161
Thrombocytopenia	7.7	16.5	33.9	0.0027

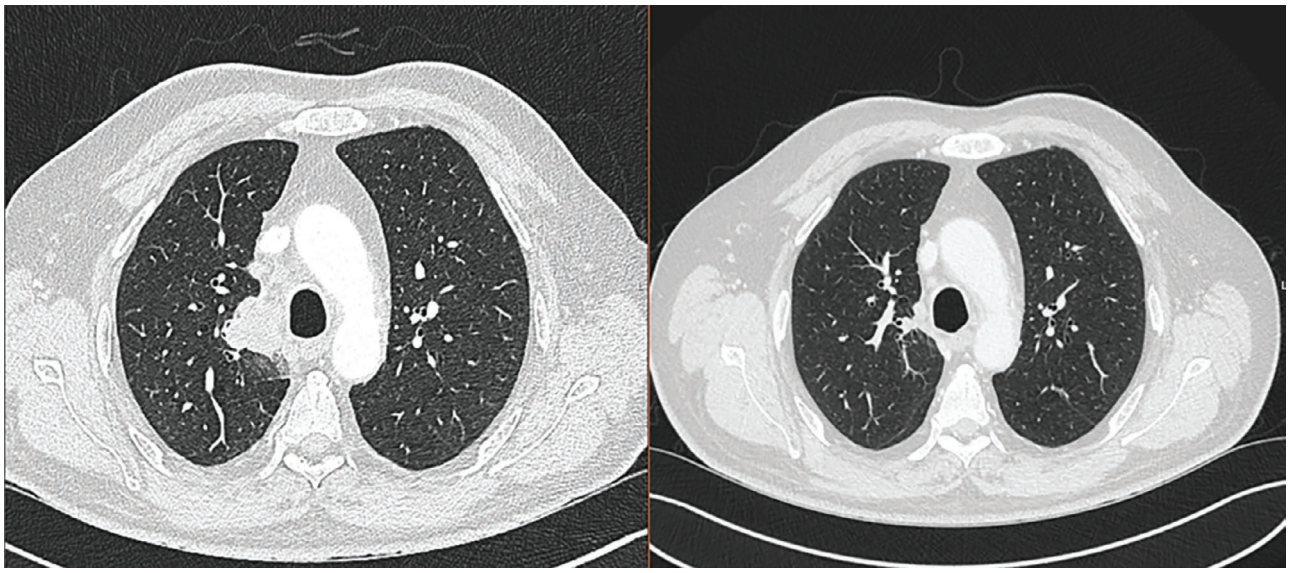
[a]Confirmed by Independent Review Committee.
[b]Primary G-CSF prophylaxis was mandatory.
[c]Nominal comparisons in ATLANTIS due to small number of patients in phase II basket trial.
AEs, adverse events; CAV, cyclophosphamide-doxorubicin-vincristine; CI, confidence interval; DoR, duration of response; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

obstruction and ipsilateral mediastinal lymphadenopathy. Bronchoscopy was performed and small cell carcinoma cells were detected by endobronchial ultrasound-guided transbronchial needle aspiration. A fluorodeoxyglucose PET–CT scan confirmed a metabolically active tumour without infiltration of the mediastinum, mediastinal, parasternal and right supraclavicular lymph node metastases, and showed metabolically active bone metastases in the pelvis. MRI was negative for brain metastases.

The diagnosis was SCLC of the right upper lobe, with a Tumor, Node, Metastasis (TNM; 8th edition) stage of cT3, cN3, cM1c, UICC stage IVB (extensive-stage SCLC). The case was presented at the multidisciplinary tumour board and palliative chemoimmunotherapy was recommended. Four cycles of carboplatin-etoposide plus atezolizumab were well tolerated and the patient's respiratory symptoms disappeared. CT staging indicated a complete response. Atezolizumab was continued as maintenance therapy.

Three months after the last platinum dose, the ipsilateral mediastinal and hilar lymphadenopathy progressed. The patient remained in good physical condition (ECOG PS 1) without symptoms. After evaluating second-line options, lurbinectedin was recommended based on the phase II lurbinectedin basket trial.[31] The decision to proceed was taken in concordance with the patient and his family. After 3 months of treatment at the approved dose of 3.2 mg/m^2 every 3 weeks, the patient achieved a partial response as the best radiological response (Figure 1). Lurbinectedin was well tolerated with grade 2 fatigue as the only side effect.

Figure 1. Response to second-line lurbinectedin after failure of first-line platinum-based chemoimmunotherapy in a patient with extensive-stage small cell lung cancer. The chemotherapy-free interval was >90 days. After 3 months of treatment, a partial response was observed; mediastinal and hilar lymph nodes are significantly reduced in size. Images courtesy of Judith Hafer and David König.



After 10 months of treatment, the patient developed nausea, vomiting and fever. Cerebral metastases were identified in the frontal lobe and cerebellum and stereotactic cerebral radiotherapy was initiated. Extracranially, progressive mediastinal and right hilar lymphadenopathy was observed.

Given the patient's continued good performance status, he proceeded to third-line treatment with CAV along with stereotactic radiotherapy of the cerebral and cerebellar metastases. After three cycles, the cerebral metastases progressed. Weekly topotecan was initiated for two cycles but was discontinued due to haematotoxicity and deterioration of performance status. No further treatment was recommended, and a best supportive care strategy was implemented.

Key message

Second-line lurbinectedin 3 months after the last dose of platinum-based first-line therapy led to a partial response lasting 10 months. Lurbinectedin was well tolerated.

Case 2

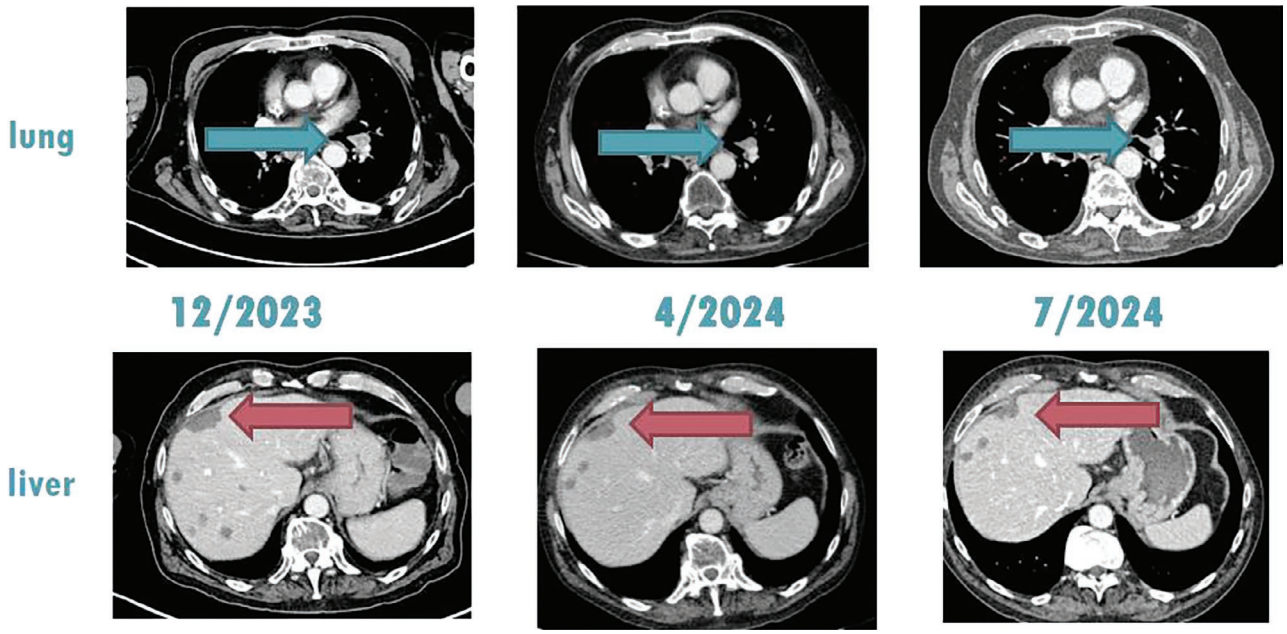
A 68-year-old Swiss male (active smoker; 50 pack/years) presented with weight loss and fatigue. Relevant comorbidities were type 2 diabetes mellitus, chronic obstructive pulmonary disease and hypertension.

A thoracoabdominal CT scan demonstrated a left hilar mass, multiple bilateral pulmonary nodules, lymphadenopathies above and below the diaphragm, and multiple hepatic lesions, the largest measuring 5.5 cm. Brain MRI showed no evidence of intracranial involvement. A PET–CT scan confirmed extensive lymph node and hepatic infiltration. Although the pulmonary nodules did not exhibit fluorodeoxyglucose uptake, they remained morphologically suspicious for metastatic disease. Liver biopsy indicated small cell cancer with neuroendocrine differentiation, compatible with SCLC metastasis. Immunohistochemistry was positive for cytokeratin 7, thyroid transcription factor 1, chromogranin A, synaptophysin and Ki-67. In March 2023, the patient was diagnosed with extensive-stage SCLC.

The patient received standard first-line treatment for stage IV SCLC consisting of four cycles of carboplatin-etoposide plus atezolizumab. A PET–CT scan performed 3 months later confirmed a partial response, with residual disease confined mainly to the mediastinal lymph nodes. Treatment was well tolerated. Maintenance therapy with atezolizumab monotherapy was continued from June to December 2023, until radiological evidence of disease progression, predominantly involving hepatic lesions. The CTFI was 6 months (≥180 days).

Based on evidence review, and the patient's physical status (ECOG PS 0–1), second-line lurbinectedin at a dose of 3.2 mg/m^2 every 3 weeks was initiated in December 2023. After 4 months, a partial response was observed (Figure 2). Lurbinectedin was generally well tolerated with only grade 1 asthenia reported. Haematological toxicity (grade 3 neutropenia) at the fifth cycle led to a delay of

Figure 2. Response to second-line lurbinectedin after failure of first-line platinum-based chemoimmunotherapy in a patient with extensive-stage small cell lung cancer. The chemotherapy-free interval was >180 days. After 4 months of treatment, a partial response was observed; lung and liver metastases are reduced in size. Images courtesy of Patrizia Frösch.



cycle 6 and dose reduction to 2.6 mg/m^2. No GSF prophylaxis was administered in the following cycles. Treatment is ongoing and radiological evaluation as of April 2025 confirmed a sustained partial response.

Key message

This case highlights an objective and durable response to lurbinectedin (>14 months) in a patient with a long CTFI (≥180 days). Tolerability issues were managed with a dose reduction that allowed prolonged treatment and sustained clinical benefit.

Case 3

A 66-year-old woman from the USA (current smoker; 1 pack/day) presented to emergency complaining of voice changes and cough. She described a recent 5 kg weight loss. Her medical history included hypertension controlled with oral angiotensin-converting enzyme inhibitors (daily), hyperlipidaemia treated with oral atorvastatin (daily), and chronic obstructive pulmonary disease treated with maintenance fluticasone furoate, umeclidinium and vilanterol inhalation (daily). Physical examination revealed a current weight of 57 kg, ECOG PS 1, and clear lungs with no wheezing.

A thoracic CT scan identified a 2.1 cm mass in the right upper lobe and bulky right mediastinal lymph nodes. An abdominal CT scan revealed liver metastases. Brain MRI was negative for metastases. Diagnostic pathology confirmed SCLC. Immunohistochemistry was positive for synaptophysin and CD56.

After reviewing therapeutic options with the patient and her family, treatment commenced with carboplatin-etoposide plus durvalumab (four cycles) followed by maintenance durvalumab. After four cycles of durvalumab (4 months since completing carboplatin-etoposide), a follow-up CT scan revealed progressive disease in the form of new right paratracheal lymphadenopathy.

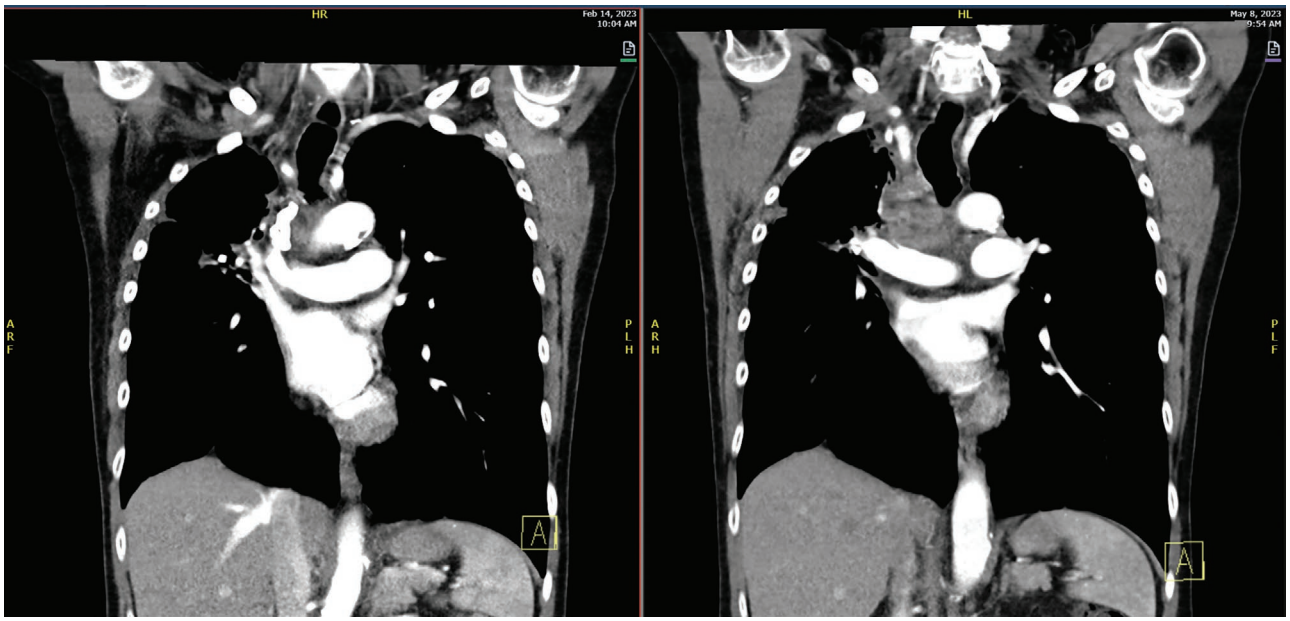
Second-line treatment consisted of lurbinectedin every 3 weeks. The patient achieved a partial response (Figure 3) and maintained a good quality of life. Treatment continued for 12 cycles (10 months) before disease progression.

Carboplatin-etoposide was administered in the third line, but the patient progressed after about 5 months. Tarlatamab was initiated and maintained for three cycles (2.5 months) until her status began to decline.

Key message

Second-line lurbinectedin led to an objective and durable response and preserved platinum for later use. As the patient enjoyed a good quality of life whilst receiving lurbinectedin, she was mentally prepared for third-line platinum rechallenge.

Figure 3. Response to second-line lurbinectedin after failure of first-line platinum-based chemoimmunotherapy in a patient with extensive-stage small cell lung cancer. The chemotherapy-free interval was >90 days. Best radiological response was a partial response; near complete resolution is observed of bulky level 4 right paratracheal lymph nodes. Image courtesy of Firas Badin.



Case 4

A 79-year-old man from the USA with an extensive history of smoking and worsening cough underwent a screening chest CT scan in January 2023, which showed multiple bilateral non-calcified nodules and a right lower pretracheal lymph node. A PET–CT scan revealed a 3.6 cm right pretracheal lymph node with a standardized uptake value of 12.3 as well as multiple bilateral pulmonary nodules, foci in the liver, and a pelvic lytic lesion, with increased metabolic activity. Brain MRI was negative. EBUS bronchoscopy indicated small cell carcinoma at lymph node stations 4R and 11R and well-differentiated squamous cell carcinoma at station 4L.

Diagnoses were made of advanced-stage SCLC and stage IIIB squamous cell lung cancer. From March to May 2023, the patient received four cycles of carboplatin-etoposide plus durvalumab (cycles 1 and 2). Durvalumab was held due to grade 3 colitis, which was successfully treated with prednisone. In March 2023, the patient also began monthly denosumab. A restaging CT scan in June 2023 showed a complete response. A circulating tumour DNA (ctDNA) small cell tumour-informed Signatera assay was negative. Maintenance durvalumab was administered until September 2023, when a restaging CT scan showed development of a pretracheal lymph node, consistent with recurrent disease.

Second-line lurbinectedin commenced in September 2023. A restaging CT scan in December 2023 showed stable disease, with a persistent 1.5 cm pretracheal lymph node. Subsequent scans showed a gradual increase in size, reaching 3.8 × 2.3 cm in June 2024. This was accompanied by an increase in ctDNA up to 115 mean tumour molecules (MTM)/mL. In July 2024, the patient received radiation therapy (XRT; 3000 cGy in 10 fractions) to the mediastinal nodes. A CT scan in August 2024 showed decreased size of the right paratracheal lymph node, now measuring 2.9 × 1.8 cm. Signatera ctDNA decreased to 52 MTM/mL, followed by an increase to 105 MTM/mL in October 2024 and to 236 MTM/mL in December 2024. A restaging CT scan showed an increase in right paratracheal lymphadenopathy to 4.5 × 4.1 cm. At this time, lurbinectedin, which had been administered for 22 cycles up to December 2024 and was tolerated with minimal side effects, was discontinued.

Tarlatamab-dlle was initiated. In March 2025, a restaging CT scan indicated a complete response accompanied by a decrease in Signatera ctDNA to 3.3 MTM/mL. At the time of the report (June 2025), treatment was ongoing.

Key message

Despite the patient's advanced age (79 years), he was able to receive 22 cycles of lurbinectedin over a 16-month period, achieving stable disease with good tolerability.

Discussion

Lurbinectedin, the first drug to be approved for use in relapsed SCLC since the approval of topotecan in 1996, has challenged long-established treatment paradigms. With the aim of informing treatment selection after failure of first-line platinum-based chemotherapy, we reviewed evidence for key guideline-recommended second-line treatments for platinum-sensitive relapsed SCLC. Subject to the usual limitations of cross-study comparisons, we have drawn some broad conclusions about the place in therapy of platinum rechallenge, topotecan, CAV and lurbinectedin.

Efficacy and safety outcomes from a phase III study comparing platinum-etoposide with topotecan as second-line treatment in patients with SCLC and a CTFI of ≥90 days support platinum rechallenge as the better option.[19] Consistent with previous studies of topotecan,[21-23,36-38] its clinical benefit was modest (response rate 25%) and haematological toxicity exceeded that of platinum rechallenge. Although CAV-specific data are limited, they suggest that the combination holds few, if any, advantages over topotecan as a second-line choice for platinum-sensitive relapsed SCLC.[21,33]

Available evidence indicates that lurbinectedin may be a useful second-line option for platinum-sensitive relapsed SCLC. A comparison of outcomes from the phase II basket study of lurbinectedin,[31] and the phase III study of platinum-etoposide *versus* topotecan,[19] suggests that, in patients with a CTFI of ≥90 days, the efficacy of lurbinectedin is at least as good or better than that of platinum rechallenge. A comparison of outcomes from the phase II basket study[19] and the phase III ATLANTIS study[33] suggests that lurbinectedin is better tolerated than platinum rechallenge and topotecan, particularly as regards haematological toxicities. As lurbinectedin-related AEs tend to be transient, reversible and non-cumulative, most patients can achieve full dose intensity.[39] Moreover, lurbinectedin is a versatile choice given that its safety profile does not appear to be affected by advanced age (≥65 years).[35] Additionally, the convenient administration schedule of lurbinectedin, especially relative to platinum rechallenge, and the lack of need for G-CSF primary prophylaxis, may lessen treatment burden for patients.

The term 'platinum-sensitive' implies that tumour cells may harbour residual sensitivity upon completion of platinum-based chemotherapy. As such, the possibility exists that using a non-platinum *versus* platinum-based regimen in the second line may resensitize tumour cells to platinum. This concept is supported at the cellular level by the complementary mechanisms of action of lurbinectedin and platinum. As reviewed by Dómine Gómez et al.,[17] SCLC cells have opposite sensitivity depending on the presence of NER machinery: NER-deficient cells are sensitive to platinum, whereas lurbinectedin is particularly effective in NER-proficient cells. Administered in the second line, lurbinectedin targets platinum-resistant cancer cells (especially NER-proficient cells) by inducing replication and transcription-coupled double-strand DNA breaks. Within the tumour microenvironment, lurbinectedin directly attacks platinum-resistant tumour cells, leading to immunogenic cell death and dismissing pro-tumorigenic macrophages and cytokines, thereby turning the tumour from 'cold' to 'hot' immunologically, which lures antitumourigenic cells (e.g. T cells or natural killer cells) that can recognize tumour antigens and kill the remaining tumour cells.[17] The exploratory analysis of the phase II basket study in patients with a CTFI of ≥90 days has provided initial evidence that intercalation with second-line lurbinectedin may restore platinum sensitivity, with potential survival benefits for patients. Outcomes (duration of response, PFS and OS) favoured the patient group treated with platinum *versus* no further platinum after second-line lurbinectedin.[32]

The case studies illustrate the use of lurbinectedin according to its approved label in routine clinical practice in Switzerland and the USA. Consistent with the known demographics of SCLC, the patients were older (age range 64–79 years) and most were men. Notably, second-line lurbinectedin produced a partial response in three of the four cases and treatment continued for more than 9 months in all four cases, including 16 months (22 cycles) in a 79-year-old man. Time on treatment can serve as a surrogate marker for acceptable tolerability and quality of life, which are both important goals in the palliative setting. Cases 2 and 3 illustrate how second-line lurbinectedin can preserve platinum for later use, thus extending the treatment pathway.

The revival of interest in relapsed SCLC over recent years has seen the introduction of newer therapies and investigation of established therapies in different settings (e.g. from second-line to first-line use or in a maintenance role) and in combination regimens. As such, the SCLC treatment paradigm is likely to undergo a number of changes in the upcoming years as accumulating evidence clarifies the place in therapy of all available options.

The review is limited by cross-study comparisons; however, in the absence of head-to-head comparative studies, this is a common method of analysis in the scientific and medical community when comparing therapeutic alternatives. Nevertheless, the results should be interpreted with caution. A further limitation is the absence of studies involving therapies (especially tarlatamab) without current marketing authorization in Europe.

Contributions: All authors contributed equally to the preparation of this manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: LS has been a speaker for Amgen, BMS and Jazz. FBB has received fees for consulting, advising and speaking fees from Amgen, BMS, Boehringer Ingelheim, Guardant, Jazz, Lilly and Merck. JH has received support for attending meetings and/or travel from Amgen. DK has received grants or contracts from Geistlich-Stucki-Stiftung; consulting fees from AstraZeneca, Impulze, Merck, Merck Sharp and Dohme (MSD), Novartis and PharmaMar; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Amgen, AstraZeneca, Bristol-Myers Squibb (BMS), Mirati, Roche, Sanofi and Swiss Oncology in Motion; support for attending meetings and/or travel from Amgen, Roche and Sanofi; participation on a Data Safety Monitoring Board or Advisory Board for AstraZeneca, BMS, Iaculis, Johnson & Johnson, Merck, Merck Sharp and Dohme and Roche. PF has provided consultancy services for AstraZeneca, BMS, Janssen, Pfizer, PharmaMar, Roche, Sanofi and Takeda. LG has received grants or contracts (paid to institution) from BMS, MSD, Takeda, Pfizer, Roche, Amgen, Sanofi, Janssen, Lilly and Novartis; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from BMS, MSD, Takeda, Pfizer, Roche, Amgen, Sanofi, Janssen, Lilly, Novartis, PharmaMar and Regeneron; support for attending meetings and/or travel from Pfizer, MSD, AstraZeneca, Takeda and Amgen; participation on a Data Safety Monitoring Board or Advisory Board for Inhatarget Therapeutics. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2025/10/dic.2025-7-9-COI.pdf

Acknowledgements: Medical writing support was provided by Kerry Dechant, ISMPP CMPP™, on behalf of Content Ed Net (Madrid, Spain), with funding from PharmaMar (Madrid, Spain).

Funding declaration: This manuscript was funded by PharmaMar (Madrid, Spain). PharmaMar reviewed the manuscript but did not influence the data or its interpretation other than to supplement the bibliography with additional relevant materials such as conference abstracts. The authors were involved in the development of this manuscript and retain final authority, including the choice of journal for publication.

Article URL: https://www.drugsincontext.com/place-in-therapy-of-key-treatments-for-platinum-sensitive-relapsed-extensive-stage-small-cell-lung-cancer-with-a-focus-on-lurbinectedin-a-narrative-review-with-case-studies

Correspondence: David König, Department of Medical Oncology, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland. Email: david.koenig@usb.ch

Provenance: Submitted; externally peer reviewed.

Submitted: 30 July 2025; **Accepted:** 26 September 2025; **Published:** 29 October 2025.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: 6 Green Lane Business Park, 238 Green Lane, New Eltham, London, SE9 3TL, UK.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

For all manuscript and submissions enquiries, contact the Editorial office editorial@drugsincontext.com

For all permissions, rights, and reprints, contact David Hughes david.hughes@bioexcelpublishing.com

References

1. Raso MG, Bota-Rabassedas N, Wistuba II. Pathology and classification of SCLC. *Cancers*. 2021;13(4):820. https://doi.org/10.3390/cancers13040820
2. Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. *Nat Rev Dis Primers*. 2021;7:3. https://doi.org/10.1038/s41572-020-00235-0
3. Paz-Ares L, Dvorkin M, Chen Y, et al. 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. https://doi.org/10.1016/S0140-6736(19)32222-6
4. Rudin CM, Awad MM, Navarro A, et al. Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: randomized, double-blind, phase III KEYNOTE-604 study. *J Clin Oncol*. 2020;38(21):2369–2379. https://doi.org/10.1200/JCO.20.00793
5. Liu SV, Reck M, Mansfield AS, et al. Updated overall survival and PD-L1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (IMpower133). *J Clin Oncol*. 2021;39(6):619–630. https://doi.org/10.1200/JCO.20.01055
6. Goldman JW, Dvorkin M, Chen Y, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(1):51–65. https://doi.org/10.1016/S1470-2045(20)30539-8
7. Zhai X, Zhang Z, Chen Y, et al. Current and future therapies for small cell lung carcinoma. *J Hematol Oncol*. 2025;18:37. https://doi.org/10.1186/s13045-025-01690-6
8. Zugazagoitia J, Paz-Ares L. Extensive-stage small-cell lung cancer: first-line and second-line treatment options. *J Clin Oncol*. 2022;40(6):671–680. https://doi.org/10.1200/JCO.21.01881
9. Badin F. Considerations for selecting second-line treatment in patients with progressive small cell lung cancer and the use of lurbinectedin in this setting. *Cancer Treat Res Commun*. 2024;39:100803. https://doi.org/10.1016/j.ctarc.2024.100803
10. Früh M, Panje CM, Reck M, et al. Choice of second-line systemic therapy in stage IV small cell lung cancer (SCLC) — a decision-making analysis amongst European lung cancer experts. *Lung Cancer*. 2020;146:6–11. https://doi.org/10.1016/j.lungcan.2020.03.024
11. Owonikoko TK, Behera M, Chen Z, et al. A systematic analysis of efficacy of second-line chemotherapy in sensitive and refractory small-cell lung cancer. *J Thorac Oncol*. 2012;7(5):866-872. https://doi.org/10.1097/JTO.0b013e31824c7f4b
12. Dingemans AC, Früh M, Ardizzoni A, et al. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(7):839-853. https://doi.org/10.1016/j.annonc.2021.03.207
13. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Small cell lung cancer, Version 4.2025. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1462. Accessed June 26, 2025.
14. Das M, Padda SK, Weiss J, Owonikoko TK. Advances in treatment of recurrent small cell lung cancer (SCLC): insights for optimizing patient outcomes from an expert roundtable discussion. *Adv Ther*. 2021;38(11):5431–5451. https://doi.org/10.1007/s12325-021-01909-1
15. Markham A. Lurbinectedin: first approval. *Drugs*. 2020;80:1345–1353. https://doi.org/10.1007/s40265-020-01374-0
16. Singh S, Jaigirdar AA, Mulkey F, et al. FDA approval summary: lurbinectedin for the treatment of metastatic small cell lung cancer. *Clin Cancer Res*. 2021;27(9):2378–2382. https://doi.org/10.1158/1078-0432.CCR-20-3901
17. Dómine Gómez M, Subbiah V, Peters S, et al. Lurbinectedin is an effective alternative to platinum rechallenge and may restore platinum sensitivity in patients with sensitive relapsed small cell lung cancer. *Expert Rev Anticancer Ther*. 2025;25(1):27–40. https://doi.org/10.1080/14737140.2024.2438067
18. Subbiah V, Paz-Ares L, Besse B, et al. Antitumor activity of lurbinectedin in second-line small cell lung cancer patients who are candidates for re-challenge with the first-line treatment. *Lung Cancer*. 2020;150:90–96. https://doi.org/10.1016/j.lungcan.2020.10.003
19. Baize N, Monnet I, Greillier L, et al. Carboplatin plus etoposide versus topotecan as second-line treatment for patients with sensitive relapsed small-cell lung cancer: an open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol*. 2020;21(9):1224–1233. https://doi.org/10.1016/S1470-2045(20)30461-7
20. Kollmannsberger C, Mross K, Jakob A, Kanz L, Bokemeyer C. Topotecan — a novel topoisomerase I inhibitor: pharmacology and clinical experience. *Oncology*. 1999;56(1):1-12. https://doi.org/10.1159/000011923
21. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol*. 1999;17:658–667. https://doi.org/10.1200/JCO.1999.17.2.658

22. O'Brien ME, Ciuleanu TE, Tsekov H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. *J Clin Oncol*. 2006;24(34):5441–5447. https://doi.org/10.1200/JCO.2006.06.5821
23. von Pawel J, Gatzemeier U, Pujol JL, et al. Phase ii comparator study of oral versus intravenous topotecan in patients with chemosensitive small-cell lung cancer. *J Clin Oncol*. 2001;19(6):1743–1749. https://doi.org/10.1200/JCO.2001.19.6.1743
24. US Food and Drug Administration. Hycamtin (topotecan injection). Highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022453s002lbl.pdf. Accessed June 26, 2025.
25. US Food and Drug Administration. Hycamtin (oral topotecan). Highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020981lbl.pdf. Accessed June 26, 2025.
26. European Medicines Agency. Hycamtin. Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/hycamtin-epar-product-information_en.pdf. Accessed June 26, 2025.
27. Zhang Y, Yang SH, Guo XL. New insights into Vinca alkaloids resistance mechanism and circumvention in lung cancer. *Biomed Pharmacother*. 2017;96:659–666. https://doi.org/10.1016/j.biopha.2017.10.041
28. Calles A, Calvo E, Santamaría Nuñez G, et al. Unveiling the mechanism of -lurbinectedin's action and its potential in combination therapies in small cell lung cancer. *Mol Cancer Ther*. 2025;24(6):828–839. https://doi.org/10.1158/1535-7163.MCT-24-0050
29. US Food and Drug Administration. Zepzelca (lurbinectedin). Highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/213702s008lbl.pdf. Accessed June 26, 2025.
30. SwissMedic. Refdata. Zepzelca. https://www.swissmedicinfo.ch/ShowText.aspx?textType=FI&lang=DE&authNr=67729. Accessed June 26, 2025.
31. 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. https://doi.org/10.1016/S1470-2045(20)30068-1
32. Trigo JM, Besse B, Zaman K, et al. P13.07-06 Efficacy of platinum given after lurbinectedin in sensitive relapsed SCLC Patients. *J Thorac Oncol* 2023;18(11 Suppl.):S708–S709. https://doi.org/10.1016/j.jtho.2023.09.1366
33. Aix SP, Ciuleanu TE, Navarro A, et al. Combination lurbinectedin and doxorubicin versus physician's choice of chemotherapy in patients with relapsed small-cell lung cancer (ATLANTIS): a multicentre, randomised, open-label, phase 3 trial. *Lancet Respir Med*. 2023;11:74–86. https://doi.org/10.1016/S2213-2600(22)00309-5
34. Peters S, Trigo J, Besse B, et al. Lurbinectedin in patients with small cell lung cancer with chemotherapy-free interval ≥30 days and without central nervous metastases. *Lung Cancer*. 2024;188:107448. https://doi.org/10.1016/j.lungcan.2023.107448
35. Cousin S, Paz-Ares LG, Fülöp A, et al. Efficacy and safety of lurbinectedin in elderly patients with relapsed SCLC. *J Clin Oncol*. 2023;41:8591–8591. https://doi.org/10.1200/JCO.2023.41.16_suppl.8591
36. Eckardt JR, von Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol*. 2007;25:2086–2092. https://doi.org/10.1200/JCO.2006.08.3998
37. von Pawel J, Jotte R, Spigel DR, et al. Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. *J Clin Oncol*. 2014;32(35):4012–4019. https://doi.org/10.1200/JCO.2013.54.5392
38. Evans TL, Cho BC, Udud K, et al. Cabazitaxel versus topotecan in patients with small-cell lung cancer with progressive disease during or after first-line platinum-based chemotherapy. *J Thorac Oncol*. 2015;10(8):1221–1228. https://doi.org/10.1097/JTO.0000000000000588
39. Leary A, Oaknin A, Trigo JM, et al. Pooled safety analysis of single-agent lurbinectedin in patients with advanced solid tumours. *Eur J Cancer*. 2023;192:113259. https://doi.org/10.1016/j.ejca.2023.113259