



REVIEW

Advances in Treatment of Recurrent Small Cell Lung Cancer (SCLC): Insights for Optimizing Patient Outcomes from an Expert Roundtable Discussion

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ABSTRACT

Second-line treatment options for patients with relapsed, extensive-stage small cell lung cancer (ES-SCLC) are limited, and even with currently available treatments, prognosis remains poor. Until recently, topotecan (a topoisomerase I inhibitor) was the only drug approved by the

United States (US) Food and Drug Administration (FDA) for the management of ES-SCLC following progression after first-line treatment with etoposide plus a platinum derivative (EP; carboplatin preferred). With the most recent approval of EP plus a programmed death ligand 1 (PD-L1) inhibitor, there are now more therapeutic options for managing ES-SCLC. A number of novel agents have emerging data for activity in relapsed ES-SCLC, and single-agent lurbinectedin (an alkylating drug and selective inhibitor of oncogenic transcription and DNA repair machinery in tumor cells) has conditional FDA approval for use in this patient population. Trilaciclib, a short-acting cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor, has also been recently approved as a supportive intervention for use prior to an EP or a topotecan-containing regimen to diminish the incidence of chemotherapy-induced myelosuppression. The current review is based on a recent expert roundtable discussion and summarizes current therapeutic agents and emerging data on newer agents and biomarkers. It also provides evidence-based clinical considerations and a treatment decision tool for oncologists treating patients with relapsed ES-SCLC. This paper discusses the importance of various factors to consider when selecting a second-line treatment option, including prior first-line treatment, available second-line treatment options, tumor platinum sensitivity, and patient characteristics (such as performance

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status, comorbidities, and patient-expressed and perceived values).

Keywords: Atezolizumab; Biomarkers; Durvalumab; Etoposide/platinum; Extensive-stage; Immunotherapy; Lurbinectedin; Relapsed; Small cell lung cancer; Topotecan

Key Summary Points

Despite recent therapeutic advances, extensive-stage small cell lung cancer (ES-SCLC) remains an extremely aggressive and difficult-to-treat disease.

The recent approvals of programmed death ligand 1 (PD-L1) immunotherapies for use in combination with etoposide plus a platinum derivative (EP) chemotherapy have introduced a new first-line standard of care for patients with ES-SCLC.

On the basis of currently available data in the immunotherapy era, the best second-line therapy after combination of chemo-immunotherapy is not well defined, as many second-line therapies have been studied only after the use of EP. Lurbinectedin and topotecan are reasonable second-line treatment options for relapsed ES-SCLC; however, second-line treatment options for patients with relapsed ES-SCLC are limited and include the reintroduction of EP (with or without immunotherapy).

Supportive care remains an integral part of the treatment course for ES-SCLC.

It is important to have a shared-decision process with the patient, including a discussion of the risks and benefits of available treatment options, clinical trials, and hospice.

INTRODUCTION

Lung cancer remains the leading cause of cancer-related deaths in the USA, accounting for approximately one-quarter of estimated cancer-related deaths in 2020, which is more than the total number of deaths resulting from breast, prostate, and colorectal cancers [1]. Small cell lung cancer (SCLC) comprises approximately 13–15% of all lung cancers, with 30,000–35,000 new cases diagnosed in the USA per year [2–4]. SCLC is a poorly differentiated neuroendocrine tumor that is strongly associated with smoking and is characterized by its aggressive nature, with a rapid doubling time, high growth fraction, and early development of metastases [4–6]. The most common sites of metastasis include the brain, liver, and bone [6].

SCLC has known pathologic, clinical, and molecular characteristics [7]. Prognosis remains poor, and without active treatment, median survival is 2–4 months; even with treatment, less than 5% of patients survive for 5 years [8]. At the time of diagnosis, up to 70% of patients with SCLC have extensive-stage (ES) disease, which has a worse prognosis compared with limited-stage (LS) disease [6, 9]. However, even in LS-SCLC, median overall survival (OS) is less than 2 years due to the high risk of disease recurrence and progression, with only 15% of patients experiencing long-term survival. Almost all patients with ES-SCLC who respond to first-line systemic treatment will eventually develop disease progression [6, 9].

A major challenge in the management of recurrent disease is the lack of effective treatment options to induce durable disease control. Despite few therapeutic successes in SCLC over the last 3 decades, increased research interest and the recent approval of new drugs are translating into changes in clinical practice and an improvement in outcomes for patients with ES-SCLC. Furthermore, a better understanding of the pathologic and molecular characteristics of SCLC may lead to the identification of biomarkers that will aid in drug development and/or better match patients' tumor subtypes with available treatment options.

The objectives of this review are to evaluate second-line treatment options for patients with relapsed ES-SCLC, including discussions of how greater use of immunotherapies as first-line therapy may affect patient outcomes and the choice of second-line strategies; to develop a practical decision tool for the management of relapsed ES-SCLC based on patient characteristics and real-world experience; and to put into clinical context novel biomarkers and their potential association with experimental therapies and implications for the future outlook of ES-SCLC treatment.

METHODS

A literature search of the PubMed database was conducted for English language articles (research articles, systematic reviews, and meta-analyses) published between January 1, 1998 and December 15, 2020. Search categories and terms included disease: “extensive-stage,” “small cell lung cancer (SCLC),” “relapsed disease”; immunotherapy: “atezolizumab,” “CASPARIAN,” “checkpoint inhibitors,” “durvalumab,” “immunotherapy,” “Impower133,” “ipilimumab,” “nivolumab,” “pembrolizumab,” “RRx-001”; chemotherapy: “etoposide,” “etoposide-platinum,” “platinum,” “irinotecan,” “lurbinectedin,” “temozolomide,” “topotecan”; targeted therapy: “cyclin-dependent kinase 4/6 (CDK 4/6),” “delta-like ligand 3 (DLL-3),” “PARP,” “trilaciclib”; biomarkers: “biomarkers,” “Schlafen 11 (SLEN11)”; other: “current,” “epidemiology,” “guidelines,” “real-world,” “second-line treatment,” “treatments.”

The results of this literature search were reviewed by the authors, who are researchers and clinicians experienced in the treatment of SCLC, and the evidence was discussed and consensus points developed during two virtual meetings. The proceedings from these meetings, supplemented by published literature and the clinical experience of the authors, are presented in this review.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

CURRENT STANDARD OF CARE: ES-SCLC

Patients with SCLC often have a variety of comorbidities associated with tobacco smoking, such as chronic obstructive pulmonary disease and cardiovascular disease, and these can be associated with poor performance status [10]. Negative prognostic factors for OS identified in patients with SCLC include history of smoking, poor performance status, male sex, and older age (≥ 70 years), along with social factors, such as being unmarried and low socioeconomic status [11, 12]. At the time of diagnosis, the majority of patients with SCLC present with extensive-stage disease [7].

First-Line Treatment Options

First-line treatment of ES-SCLC with etoposide plus a platinum derivative (EP) chemotherapy has been a standard therapy for more than 30 years, with a general preference for carboplatin over cisplatin owing to a more tolerable toxicity profile and comparable efficacy [6, 13]. However, despite high initial response rates to first-line EP therapy in patients with ES-SCLC, relapse rates are high and overall prognosis of relapsed disease is poor—most likely because of rapid development of drug resistance [14]. In response to this challenge, a number of trials have explored the use of alkylating agents (e.g., ifosfamide), anthracyclines (e.g., epirubicin, amrubicin), antifolates (e.g., pemetrexed), camptothecins (e.g., irinotecan, topotecan), or taxanes (e.g., paclitaxel) in combination with platinum drugs as first-line treatment for ES-SCLC (Table 1) [14–18]. However, none of these regimens have proven superiority over EP, which had remained the standard-of-care frontline treatment regimen until the advent of programmed death ligand 1 (PD-L1) immune-checkpoint therapy [6, 14].

New First-Line Immunotherapy Treatment Options

More recently, improved OS was demonstrated in randomized phase 3 clinical trials of PD-L1

Table 1 First-line platinum-based combination chemotherapy phase 3 trials in ES-SCLC [14–18]

	Year	Subjects, <i>n</i>	Response, %		Survival		Toxicity CTC 3/4, %				
			OR	CR	Median months	1-year (%)	NP	Anemia	TP	Other	
Cisplatin-etoposide	1985	20	88	29	9.1	30	18				
Cisplatin-etoposide	1992	159	61	10	8.6	30	70	35	13	6 ^a	
Cisplatin-etoposide- ifosfamide	1995	171	73	21	9.0	36	52	52	35		
Cisplatin-etoposide- cyclophosphamide-epirubicin	2001	226	76	21	10.5	40	99	51	78	22 ^b	
Cisplatin-irinotecan (JCOG 9511)	2002	154	84	3	12.8	58	65	27	5	16 ^c	
Cisplatin-epirubicin	2004	195	74		10.9		42				
Cisplatin-etoposide-paclitaxel	2005	587	75	16	10.6	38	44	19	22		
Cisplatin-irinotecan	2006	331	48		9.3	35	36	5	4	21 ^c	
Cisplatin-topotecan (oral)	2006	784	63	6	10.0	31	59	38	38		
Carboplatin-irinotecan	2008	209		17	8.5	34	33	5	15	11 ^c	
Cisplatin-irinotecan (S0124)	2008	671	59	4	9.7	39	33	6	4	19 ^c	
Cisplatin-topotecan (intravenous)	2008	795	55	10	10.3	40	36	12	19		
Carboplatin-pemetrexed	2008	733	25		7.3		9	10	10		
Cisplatin-irinotecan	2010	405	39.1	4	10.2	41.9	38.1	6.9	5.4	17.3 ^c	
Carboplatin-irinotecan	2011	216	62.3	4	10.0	37.1		17	23	14 ^c	
Cisplatin-irinotecan	2019	362	62.4	1.2	10.9		62.3	27.0	12.6	20.4 ^b	10.2 ^c

Adapted with permission from Demedts et al. [14]

CR complete response, CTC common toxicity criteria, ES-SCLC extensive-stage small cell lung cancer, JCOG Japanese Clinical Oncology Group, NP neutropenia, OR overall response, TP thrombocytopenia

^a Nausea/vomiting

^b Infections

^c Diarrhea

immunotherapies combined with EP regimens as first-line treatment for ES-SCLC [19, 20]. This development represents a paradigm shift and the most significant move forward in this setting in the last 3 decades [6, 21–23].

Durvalumab is a PD-L1 immunotherapy that was evaluated in the randomized, controlled, open-label, phase 3 CASPIAN trial that compared durvalumab (with or without

tremelimumab, a cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4] inhibitor) in combination with EP (with either cisplatin or carboplatin) versus EP alone in treatment-naïve patients with ES-SCLC and a World Health Organization (WHO) performance status of 0 or 1 [20]. Patients were randomly assigned to durvalumab plus EP, durvalumab plus tremelimumab plus EP, or EP alone. Treatment

consisted of up to four cycles of durvalumab plus EP with or without tremelimumab every 3 weeks followed by maintenance treatment with durvalumab (with or without tremelimumab) every 4 weeks in the immunotherapy groups and up to six cycles of EP every 3 weeks in the EP-alone group. Durvalumab (without tremelimumab) plus EP significantly reduced the risk of death at the planned interim analysis (18 months) by 27% compared with EP alone (hazard ratio [HR] 0.73 [95% confidence interval (CI) 0.59, 0.91]; $P = 0.0047$) [20].

Updated results after a median follow-up of 25.1 month (IQR 22.3–27.9) showed that durvalumab (without tremelimumab) plus EP produced a sustained improvement in OS versus EP alone (HR 0.75 [95% CI 0.62, 0.91]; nominal $P = 0.0032$); median OS was 12.9 months (95% CI 11.3, 14.7) versus 10.5 months (95% CI 9.3, 11.2) [24]. Importantly, the addition of tremelimumab to durvalumab plus EP did not improve OS compared with EP alone, suggesting that the combination immunotherapeutic approach has no added benefit in this setting [24]. The lack of benefit with CTLA-4 inhibition was also shown with ipilimumab in combination with EP, which failed to prolong OS compared with EP alone in patients with newly diagnosed ES-SCLC [25].

Atezolizumab, another PD-L1 monoclonal antibody, has also demonstrated effectiveness when used in combination with EP as first-line treatment for ES-SCLC [19]. In the IMpower133 double-blind, placebo-controlled, phase 3 trial, treatment-naïve patients with ES-SCLC and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were randomized to receive EP (with carboplatin) with either atezolizumab or placebo for four 21-day cycles (induction phase) followed by a maintenance phase during which they received either atezolizumab or placebo [19]. Both primary endpoints of OS and investigator-assessed progression-free survival (PFS) were significantly improved when atezolizumab was added to EP as first-line therapy in patients with ES-SCLC compared with EP alone [19]. A follow-up analysis showed that atezolizumab plus EP had a comparable safety profile to placebo plus EP and did not have a negative impact on health-

related quality of life [26]. In an updated OS analysis with a median follow-up of 22.9 months, median OS was 12.3 months (95% CI 10.8, 15.8) with atezolizumab plus EP versus 10.3 months (95% CI 9.3, 11.3) with placebo plus EP (HR 0.76 [95% CI 0.60, 0.95]; descriptive $P = 0.0154$) in patients with ES-SCLC [27]. At 18 months, 34% and 21% of patients were alive in the atezolizumab plus EP and placebo plus EP groups, respectively [27].

It is worth noting that in both the CASPIAN and IMpower133 trials, the Kaplan–Meier curves for OS and PFS did not diverge until about 6 months, suggesting that only a subset of patients benefited from the addition of immunotherapy to EP and that the impact was somewhat delayed even in patients who derived benefit [19, 20]. There are differences in the inclusion criteria regarding brain metastases between the studies, which is worth highlighting since patients with asymptomatic and untreated brain metastases were allowed in CASPIAN whereas they were excluded from IMpower133 [19, 20]. Currently, no biomarkers exist to differentiate between patient subsets who may benefit from the addition of a PD-L1 inhibitor to standard EP chemotherapy and those who may not. Notably, patients derived similar benefit from the addition of atezolizumab to EP in IMpower133 independent of PD-L1 immunohistochemistry or blood-based tumor mutational burden (bTMB) status [27]; however, the bTMB biomarker needs further refinement and validation as there are variable gene panel sizes, algorithms, and cutoffs that may vary on the basis of the tumor type such that a bTMB cutoff of 16 mutations per megabase may be sufficiently high for non-small cell lung cancer (NSCLC) but not for SCLC [28, 29].

In a meta-analysis of four immune-checkpoint-inhibitor trials, including two with PD-L1 inhibitors that are currently approved by the FDA for the first-line treatment of patients with ES-SCLC (CASPIAN [durvalumab] and IMpower133 [atezolizumab]) and two with programmed death 1 (PD-1) inhibitors that are not currently approved by the FDA (KEYNOTE-604 [pembrolizumab] and ECOG-ACRIN EA5161 [nivolumab]), a pooled analysis of all four of these trials showed that frontline immune-

Table 2 Select topotecan trials in relapsed SCLC [35, 40–48]

Author (year)	Patients, n (R or S) ^a	Treatment arms	ORR, %	Median PFS, time	Median OS, time	Grade 3 + toxicities, %	
						NP	TP
von Pawel et al. (1999) [40]	211 (S)	IV topotecan versus CAV	24	13 weeks	25 weeks	89	58
von Pawel et al. (2001) [41]	106 (S)	Oral topotecan versus IV topotecan	18	12 weeks	25 weeks	87	15
O'Brien et al. (2006) [42]	141 (76 R; 65 S)	BSC versus oral topotecan + BSC	23	15 weeks	32 weeks	57	53
			15	13 weeks	25 weeks	94	49
			NR	NR	14 weeks	NR	NR
			O: 7	16 weeks	26 weeks	61	38
			R: 10				25
			S: 3				
Shah et al. (2007) [43]	22 (S)	Weekly IV topotecan + chemotherapy	0	6 weeks	20 weeks	0	9
Eckardt et al. (2007) [44]	309 (S) ^b	Oral topotecan versus IV topotecan	18	12 weeks	33 weeks	71	48
			22	15 weeks	35 weeks	86	43
Spigel et al. (2011) [45]	38 (R or S)	Weekly IV topotecan	O: 8	R: 1.5 months	R: 3.7 months	53	37
			R: 0	S: 2.5 months	S: 8.6 months		
			S:16				
von Pawel et al. (2014) [46]	637 (R or S) ^c	IV amrubicin versus IV topotecan	31	O: 4.1 months	O: 7.5 months	41	21
				R: 2.8 months	R: 6.2 months		
				S: 5.5 months	S: 9.2 months		
			17	O: 3.5 months	O: 7.8 months	54	54
				R: 2.6 months	R: 5.7 months		
				S: 4.3 months	S: 9.9 months		
Goto et al. (2016) [47]	180 (S)	IV topotecan versus IV cisplatin + etoposide + irinotecan	27	3.6 months	12.5 months	86	28
			84	5.7 months	18.2 months	83	41
						84	84

Table 2 continued

Author (year)	Patients, n (R or S) ^a	Treatment arms	ORR, %	Median PFS, time	Median OS, time	Grade 3 + toxicities, %
						NP TP Anemia
Baize et al. (2020) [48]	164 (S) ^d	IV carboplatin + etoposide versus oral topotecan	49	4.7 months	7.5 months	14 31 25
			25	2.7 months	7.4 months	25 36 21

Adapted from Farid et al. [35]. Formatting changes only. This table is available under the following Creative Commons license: CC BY-NC-ND 4.0
BSC best supportive care, *CAV* cyclophosphamide plus doxorubicin plus vincristine, *IV* intravenous, *NP* neutropenia, *NR* not reported, *O* overall, *ORR* overall response rate, *OS* overall survival, *PFS* progressive-free survival, *R* resistant, *S* sensitive, *TP* thrombocytopenia

^a Cutoffs after first-line treatment: von Pawel 1999: $S \geq 60$ days; von Pawel 2001: $S \geq 90$ days; Shah 2007: $S \geq 90$ days; O'Brien 2006: $R \leq 90$ days; $S \geq 90$ days; Eckhardt 2007: $S \geq 90$ days; Spigel 2011: $R \leq 90$ days and refractory, $S \geq 90$ days; von Pawel 2014: $R \leq 90$ days, $S \geq 90$ days; Goto 2016: $S \geq 90$ days; Baize 2020: $S \geq 90$ days

^b Of the randomized patients, 304 were assessed for efficacy and safety

^c Of the randomized patients, 605 were assessed for safety

^d Of the randomized patients, 162 received treatment and were included in the analysis

checkpoint inhibitors provide significant survival benefits when combined with EP chemotherapy in patients with ES-SCLC [30]. Further, in the pooled analysis of all four trials, the addition of a PD-1/PD-L1 inhibitor to EP chemotherapy led to a significant benefit in OS (HR 0.76 [95% CI 0.68, 0.85]; $P < 0.00001$), PFS (HR 0.75 [95% CI 0.68, 0.84]; $P < 0.00001$), and objective response rate (ORR; odds ratio 1.28 [95% CI 1.04, 1.57]; $P = 0.02$) compared with EP chemotherapy alone [30]. Despite the promising results noted in the phase III KEYNOTE-604 trial, it should be noted that the P value did not meet the required significance threshold in the planned hierarchical OS analysis, and pembrolizumab is not currently FDA approved as a frontline option in patients with ES-SCLC [30, 31].

In summary, on the basis of the results from the CASPIAN and IMpower133 trials, the FDA approved either durvalumab or atezolizumab in combination with EP as first-line treatment of patients with ES-SCLC [32, 33], introducing a treatment paradigm shift in frontline therapy. However, even with these advances, almost all patients with ES-SCLC who respond to first-line systemic treatment will eventually develop progressive disease and require second-line therapy, with very few patients achieving long-term response to maintenance PD-L1 therapy [6, 13]. For these patients with disease progression, therapeutic options are limited, long-term survival is often less than 10 months [13, 34], and the general goal of systemic therapy is to palliate symptoms and prolong quality of life [6].

Second-Line Treatment Options

Two time-based criteria (i.e., 90 days or 180 days) are most commonly used to characterize relapsed ES-SCLC according to the duration of treatment-free interval since the last platinum dose given as part of frontline treatment. Thus, a tumor with durable tumor response lasting longer than 90 days from the last dose of frontline platinum doublet is termed “platinum sensitive,” while recurrence within 90 days of chemotherapy is termed

Table 3 Lurbinectedin overall efficacy [57]. Reproduced with permission of the © ERS 2021: European Respiratory Journal Jan 2010, 35 (1) 202-215. <https://doi.org/10.1183/09031936.00105009>

Outcome (95% CI)	Chemotherapy-free interval \geq 90 days ($n = 60$)	Chemotherapy-free interval $<$ 90 days ($n = 45$)	All patients ($N = 105$)
Overall response, %	45.0 (32.1, 58.4)	22.2 (11.2, 37.1)	35.2 (26.2, 45.2)
Median duration of response, months	6.2 (3.5, 7.3)	4.7 (2.6, 5.6)	5.3 (4.1, 6.4)
Patients responding at 6 months, %	55.3 (34.5, 76.0)	11.7 (0.0, 33.1)	43.0 (25.6, 60.5)
Median overall survival, months	11.9 (9.7, 16.2)	5.0 (4.1, 6.3)	9.3 (6.3, 11.8)

Adapted with permission from Trigo et al. [57]
CI confidence interval

“platinum resistant.” A “refractory” case is one in which the patient’s tumors either never responded or progressed within 45 days of treatment [4]. These are not definitive cutoffs as other studies have used various thresholds (e.g., 60 days) for classifying a relapsed SCLC as chemotherapy sensitive [35]. In general, a prolonged treatment-free interval beyond 6 months typically leads to the consideration of platinum-doublet re-treatment at the time of relapse.

Prognosis for patients who relapse or progress after first-line chemotherapy is poor: a median survival of 2–3 months was observed in patients who did not receive second-line therapy and typically 6 months or less in those who did receive second-line therapy [36]. Hence, second- or third-line treatment for ES-SCLC is primarily considered palliative, with a focus on maintaining or improving quality of life to the extent possible. Treatment options, and the likelihood of their success, may vary depending on whether the initial tumor response was considered platinum sensitive, resistant, or refractory [36]. A systematic analysis of second-line chemotherapy efficacy in sensitive and refractory SCLC determined that patients with SCLC whose tumors were platinum-sensitive ($>$ 90 days’ relapse-free interval after first-line therapy) derived greater benefit compared with those whose tumors were platinum-resistant

($<$ 90 days’ relapse-free interval after first-line therapy) [37].

Because of first-line use of immunotherapy (durvalumab or atezolizumab) plus EP, the treatment landscape for second-line therapy is rapidly evolving, albeit with limited long-term data. Most of what is currently known about second-line therapy outcomes involves patients treated only with first-line EP chemotherapy without a PD-L1 inhibitor. Moreover, whether it is beneficial to continue immunotherapy into the second-line setting for patients progressing while on maintenance immunotherapy administered as part of frontline treatment remains to be determined.

Topotecan

Since its initial approval in 1996 and until recently, topotecan has been the only FDA-approved agent as a second-line treatment option for patients with SCLC and is only approved for those with chemotherapy-sensitive, relapsed SCLC [38, 39]. Topotecan is a topoisomerase I inhibitor with cytotoxic effects [38] that has demonstrated efficacy in several second-line therapy trials of patients with relapsed SCLC, with ORRs ranging from 8% to 27% and a median OS ranging from 3.7 to 12.5 months, although the efficacy reported is largely limited to chemotherapy-sensitive disease (Table 2) [35, 40–48]. Topoisomerase I expression, as evaluated by immunohistochemistry, has been

shown to be highly prevalent in patients with SCLC and has been shown to be associated with increased disease control in patients with platinum-sensitive, relapsed SCLC who received topotecan as second-line therapy [49]. Topotecan is available for injection or oral administration [38, 39], with similar efficacy and tolerability between the two formulations (Table 2) [44].

In patients with platinum-sensitive, platinum-resistant, or platinum-refractory relapsed SCLC, the main adverse event with topotecan infusions is myelosuppression [40, 41, 44–47]. The standard intravenous (IV) dosing of topotecan is 1.5 mg/m² daily on days 1–5 of a 21-day cycle [39]. A less burdensome schedule of a higher weekly dose of topotecan (6 mg/m² IV for 6 weeks) in 38 patients with relapsed SCLC yielded no responses in those with refractory tumors and three responses (all partial, none complete) in those with sensitive tumors, which was offset by even higher levels of hematologic toxicity [45]. Irinotecan, another topoisomerase I inhibitor, is sometimes used as an alternative to topotecan in the second-line setting owing to its less frequent dosing (i.e., weekly) and lower probability of myelosuppressive adverse events [50].

Re-treatment with Platinum Chemotherapy for Platinum-Sensitive Relapse

Until recently, in both the USA and Europe, topotecan has been the go-to second-line therapy for patients with platinum-sensitive, relapsed SCLC. However, in platinum-sensitive patients (relapse \geq 90 days) with ECOG performance status 0–2, a recent study has shown platinum-based chemotherapy rechallenge to be superior to topotecan. This multicenter, open-label, randomized, phase 3 trial conducted in Japan (JCOG0605) compared topotecan alone with combination chemotherapy consisting of EP (with cisplatin) plus irinotecan [47]. OS was significantly longer in the combined chemotherapy arm versus the topotecan arm (median 18.2 months vs 12.5 months; HR 0.67 [90% CI 0.51, 0.88]; $P = 0.0079$), as was PFS (median 5.7 months vs 3.6 months; HR 0.50 [95% CI 0.37, 0.68]; $P < 0.0001$). However, grade 3 or 4 febrile neutropenia,

thrombocytopenia, and anemia were more common in the combination chemotherapy arm [47]. Given the unfavorable toxicity profile of this triplet regimen, it is unlikely to be widely adopted.

Similar results were shown for PFS in a randomized, open-label, phase 3 French study that compared orally administered topotecan with EP in patients with platinum-sensitive, relapsed SCLC [48]. Although median PFS was significantly longer in the combination EP chemotherapy arm compared with the topotecan arm (4.7 months [90% CI 3.9, 5.5] vs 2.7 months [90% CI 2.3, 3.2; HR 0.57 [90% CI 0.41, 0.73]; $P = 0.0041$), there were no significant differences between the treatment arms for median OS. Unlike the JCOG0605 triplet regimen, there were no major differences between the platinum-doublet chemotherapy and topotecan treatment arms with respect to percentages of grade 3 or 4 neutropenia, thrombocytopenia, anemia, or febrile neutropenia in this study [48]. Given the importance of platinum-based chemotherapy in SCLC—including platinum-sensitive, relapsed disease—there are agents being developed to induce or re-induce platinum sensitivity [51].

Lurbinectedin

Lurbinectedin is an alkylating drug and selective inhibitor of oncogenic transcription and DNA repair machinery in tumor cells, triggering tumor cell apoptosis and altering the inflammatory tumor microenvironment [52–54]. Lurbinectedin received an orphan drug designation in 2018 [55], and on the basis of the results of a phase 2 basket trial, received an accelerated approval in June 2020 as a second-line treatment option in patients with ES-SCLC who develop disease progression on or after platinum-based chemotherapy [52, 56].

The phase 2 basket trial was a single-arm, open-label study of lurbinectedin 3.2 mg/m² every 21 days as second-line treatment for patients with relapsed SCLC and documented progression after treatment with only one prior chemotherapy (prior immunotherapy was allowed but only 8% of patients received prior immunotherapy) [57]. All patients in the study had an ECOG performance status of 2 or better.

At data cutoff, with a median follow-up of 17.1 months, responses were observed in 37 of 105 study participants, for an ORR of 35.2% (95% CI 26.2, 45.2) (Table 3) [57]. The ORR was higher for patients with platinum-sensitive tumors (45.0%) compared with those with platinum-resistant tumors (22.2%). Moreover, 43% of all patients with a response had a durable response of 6 months or longer. The median OS was 11.9 months for patients with platinum-sensitive tumors versus 5.0 months for those with platinum-resistant tumors, and the median OS of the entire cohort was 9.3 months [57]. The most common grade 3 or 4 adverse events were neutropenia (46%), leukopenia (29%), abnormal γ -glutamyl transferase (15%), anemia (9%), fatigue (7%), and thrombocytopenia (7%) [57].

The phase 3 ATLANTIS open-label, randomized, multicenter trial examined lurbinectedin in patients with ES-SCLC but did not include an investigational treatment arm of lurbinectedin alone. The trial treatment arms compared the combination of lurbinectedin plus doxorubicin with standard of care (investigator's choice of topotecan or cyclophosphamide/doxorubicin/vincristine [CAV]) in 613 patients with SCLC, disease progression after one prior platinum-containing chemotherapy regimen, and a chemotherapy-free interval of 30 days or more [58, 59]. In December 2020, a press release reported that the trial did not meet the primary endpoint of OS for significance in the intent-to-treat patient population. The safety and tolerability data of ATLANTIS were consistent with the known safety profile of lurbinectedin, and there were no new safety signals in the lurbinectedin treatment arm [59]. The ATLANTIS trial has not yet been published since the press release, and without the full study outcomes, a full understanding of the implications of the results is not possible. On the basis of the limited information currently available, it is hypothesized that the lower lurbinectedin dose used in the phase 3 trial (2.0 mg/m² every 21 days) compared with the phase 2 trial (3.2 mg/m² every 21 days) may have affected the outcomes [57–59]. This hypothesis is in line with an exposure–response analysis of lurbinectedin dosage in SCLC that determined the

3.2 mg/m² dose every 21 days (same dose as used in the phase 2 trial and FDA approved) provided the most benefit in patients with SCLC who had disease progression on or after platinum-based chemotherapy and had a manageable risk of grade 4 neutropenia [60]. Given that the single-arm, open-label, phase 2 study in 105 patients resulted in conditional accelerated approval of lurbinectedin by the FDA on the basis of ORR and duration of response, “continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials” [61].

There was also preliminary data from the phase 1b/2 study of lurbinectedin in combination with irinotecan among 21 patients with SCLC with disease progression after no more than two prior therapies which reported an ORR of 62% and a median PFS of 6.2 months (95% CI 4.3, 8.5) [62, 63], suggesting that additional combination studies may be warranted. Given the limited treatment options in the second-line setting and the lethality of previously treated ES-SCLC, in spite of the phase 3 lurbinectedin plus doxorubicin combination failing to meet the primary endpoint with the caveats mentioned above, lurbinectedin monotherapy offers preliminary efficacy with a favorable safety profile, a facile dosing schedule, and is a reasonable second-line treatment option for patients with relapsed SCLC.

Immunotherapies

SCLC has long been considered an immunogenic disease because of high tumor mutational burden secondary to tobacco exposure related to tumor development and the occurrence of paraneoplastic disorders in 15–20% of newly diagnosed cases, providing a rational basis for consideration of immunotherapies in the treatment of SCLC [64–66]. As previously discussed, the immune-checkpoint inhibitors durvalumab and atezolizumab have an established efficacy as part of frontline therapy for ES-SCLC in combination with EP [19, 20]. Although pembrolizumab and nivolumab, both PD-1 monoclonal antibodies, had received accelerated FDA approval for patients with relapsed SCLC who had received two prior lines of treatment (including platinum-based

chemotherapy), both applications have been recently withdrawn [67–69]. Pembrolizumab initially received accelerated approval based on the pooled data from two basket trials (KEYNOTE-028 and KEYNOTE-158) [68, 70, 71]. In a pooled analysis of SCLC cohorts ($N = 83$) from KEYNOTE-028 (enrolled patients with PD-L1-positive tumors) and KEYNOTE-158 (enrolled patients irrespective of PD-L1 status of tumors), the ORR was 19.3% (95% CI 11.4, 29.4) [68]. The confirmatory phase 3 KEYNOTE-604 trial, however, did not reach statistical significance for the primary endpoint of OS, leading to voluntary withdrawal by the manufacturer of the US SCLC indication for pembrolizumab in March 2021 [31, 72].

Nivolumab was initially studied alone or in combination with ipilimumab in patients with relapsed ES-SCLC in the Checkmate-032 phase 1/2 trial. Although the study treatments were not initially designed to be compared with one another, the ORRs of nivolumab monotherapy versus nivolumab plus ipilimumab in patients with relapsed SCLC were 11.6% and 21.9%, respectively. Median OS was 5.7 months with nivolumab monotherapy versus 4.7 months with nivolumab plus ipilimumab combination therapy. Not surprisingly,

combining ipilimumab with nivolumab increased grade 3–4 toxicity from 12.9% with nivolumab monotherapy to 37.5% with nivolumab plus ipilimumab [73]. In the confirmatory phase III trial comparing nivolumab with chemotherapy (topotecan or amrubicin) in patients with relapsed SCLC, Checkmate 331, the primary endpoint of superior OS was not met [74, 75]. In addition, examination of immunotherapy maintenance strategies after first-line chemotherapy of nivolumab plus ipilimumab or nivolumab monotherapy in patients with ES-SCLC in the randomized, phase III Checkmate 451 study did not result in a prolongation of OS versus placebo [74]. On the basis of these results, the nivolumab indication for relapsed ES-SCLC was withdrawn in January 2021 from the USA by its manufacturer [69].

Since no immune-checkpoint inhibitors are FDA approved in relapsed SCLC and the current use of PD-L1 inhibitors is in the frontline setting in combination with EP and as continuation maintenance therapy, there is very limited use for immunotherapies in the standard-of-care second-line setting despite some preliminary efficacy results.

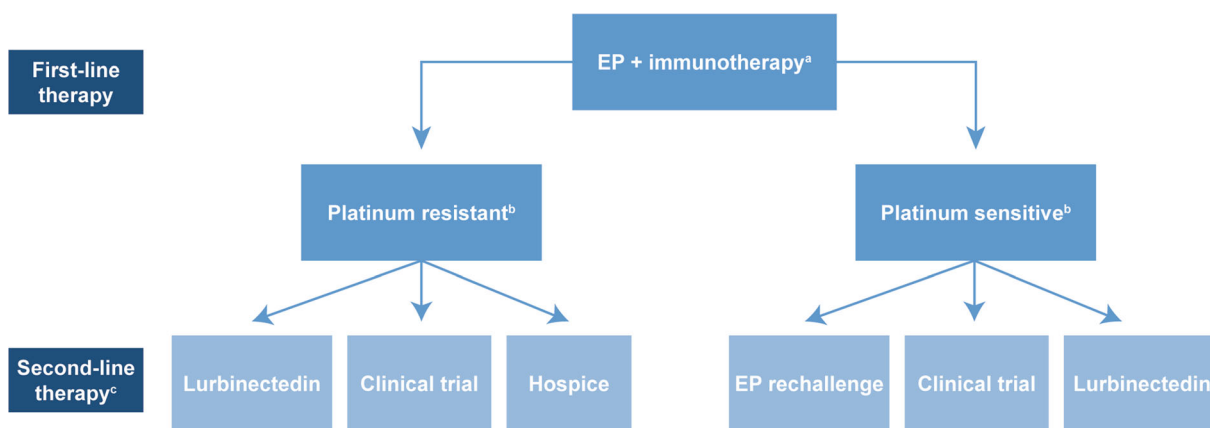


Fig. 1 A practical management guide for ES-SCLC. ^aEP + immunotherapy is the preferred first-line standard of care for all patients with extensive-stage-small-cell lung cancer (ES-SCLC). In the case of a patient who previously received EP alone and remains platinum sensitive, EP rechallenge with immunotherapy may be considered.

^bPlatinum-sensitive is defined as either chemotherapy naive or relapse > 90 days after cessation of prior chemotherapy and platinum-resistant as relapse ≤ 90 days after prior chemotherapy. ^cTopotecan and irinotecan remain possible second-line options

MANAGEMENT CONSIDERATIONS

A number of factors, including available treatments, efficacy and safety profiles, prior treatment history, disease characteristics (chemotherapy-sensitive or chemotherapy-resistant disease), and patient characteristics (performance status, comorbidities, and values) need to be taken into account when considering treatment recommendations for patients with relapsed SCLC. A balance between the benefits and risks of therapy versus those associated with untreated disease is often dependent on a joint decision between the physician and the patient. Patients with SCLC commonly present with shortness of breath or chest pain that often rapidly improve following initial chemotherapy administration. However, the probability of controlling SCLC with available systemic treatments decreases in the relapsed setting, particularly in those patients with platinum-resistant disease. Hence, quality of life is frequently an important goal of care along with the expectation of increased duration of life. These perceived conflicting value propositions sometimes still lead to aggressive therapy when the suffering from the cancer exceeds the suffering expected with side effects of treatment.

Performance Status

Poor performance status (3–4) is commonly recognized as a negative prognostic factor for outcome in patients with ES-SCLC [6, 11] and is a consideration when choosing a second-line treatment option in this patient population [76]. Patients with poor performance status may be unable to undergo a chemotherapy regimen because of its toxicity [77], especially when the probability of response, and therefore improvement in performance status, is also lower in the second-line setting compared with the first-line setting for patients with ES-SCLC [6, 65, 66, 77]. Most of the clinical trials evaluating treatments in this setting restrict patient enrollment to those with a performance status of 2 or better.

Patient Values

The importance of patient values in the decision to continue with a second-line treatment plan for relapsed ES-SCLC is critical and is recognized by many institutions and reflected in their treatment protocols. For example, ethicists at Emory University in the USA developed a “patient value tool” called Patient Preference Assessment Tool (PPAT) based on a small study of phase I clinical trial participants that ranked what was most important to patients, which included “spend more time with family,” “travel concerns,” “avoidance of side effects,” “living longer,” and may differ from what the physician considers most important [78, 79]. Therefore, consideration of the most important factors to the patient is as critical as the information about the pros and cons associated with various therapies in the shared-decision plan. Some patients may choose hospice care as their preferred option, wishing to avoid hospitalization at all costs, especially when family members may be restricted from visiting (as has been experienced during the coronavirus disease 2019 [COVID-19] pandemic), while others may choose an experimental therapy on a clinical trial.

A TREATMENT DECISION TREE

Several clinical practice guidelines are available for consultation when deciding management strategies for patients with ES-SCLC in the second-line setting [80–84]. Clinical practice frequently varies from guideline recommendations, reflecting regional, institutional, and patient factors, as well as because of convenience and cost considerations [9, 76, 80]. This review incorporates the most current evidence and the clinical experience of the authors to provide practical guidance.

The roundtable panel’s recommendations (Fig. 1) are largely consistent with published guidelines [6, 80], recent decision-making analyses [76], and real-world practices [85–87]. For first-line therapy, current data and clinical experience suggest that all patients who are able to tolerate treatment should be treated with EP

in combination with a PD-L1 inhibitor (i.e., atezolizumab, durvalumab) when there is no contraindication to the use of immunotherapy (e.g., severe autoimmune disease) [6]. In patients with platinum-sensitive, relapsed SCLC—especially if the treatment-free interval has been greater than 180 days—reintroduction of EP may be a consideration [6, 80]. Patients with platinum-sensitive, relapsed SCLC whose initial therapy did not include immunotherapy (e.g., relapse after chemoradiotherapy for LS disease) may be offered EP rechallenge with the addition of a PD-L1 inhibitor (i.e., durvalumab or atezolizumab). For patients with relapse, regardless of platinum sensitivity and/or whether they received frontline immunotherapy, a clinical trial, lurbinectedin, and topoisomerase I inhibitors are all reasonable second-line therapeutic options [6, 80].

Several guidelines vary on their preferred treatment option for relapsed SCLC on the basis of tumor sensitivity at the time of relapse and performance status. The National Comprehensive Cancer Network (NCCN) guidelines recommend (category 2A) the use of the preferred regimens of topotecan, lurbinectedin, or a clinical trial for patients with SCLC who have relapsed 6 months or less after first-line therapy [6]. Likewise, the Spanish Society of Medical Oncology (SEOM) guidelines recommend a clinical trial (preferred) as well as topotecan for patients with a relapse 3 months or less from their last platinum dose [80]. In 2020, European SCLC expert analysis identified CAV as the preferred option in fit patients with a relapse less than 3 months from the last platinum dose and a preference for topotecan in unfit patients with a relapse less than 3 months after the last platinum dose [76]. However, on the basis of the review of the most current evidence along with the clinical concerns for using topotecan (schedule, limited efficacy, and myelosuppressive toxicity), the authors do not frequently use topotecan as second-line treatment for patients with relapsed SCLC, although it is still approved on the basis of evidence from randomized phase 3 data and is used in this setting both in the USA and elsewhere. Irinotecan remains an alternative topoisomerase I inhibitor option in this setting. In the absence of head-to-head

comparative data, given the more favorable risk–benefit profile with regards to myelosuppression, and given the less frequent dosing schedule, lurbinectedin monotherapy may be considered as the preferred agent over topotecan as a second-line treatment option in patients with chemotherapy-sensitive and chemotherapy-resistant relapsed ES-SCLC. However, the one major limitation is that lurbinectedin is under conditional accelerated approval based only on data from a phase 2, open-label, single-arm trial in 105 patients and the phase 3 randomized study of combination lurbinectedin and doxorubicin that failed to show OS benefit, without a full publication available to examine the implications of this result. For many patients with relapsed ES-SCLC, a clinical trial with a novel investigational agent may be the preferred approach, while transition to hospice care remains an option for those with poor performance status (i.e., 3–4) and/or those who wish to focus on comfort.

BIOMARKERS AND EXPERIMENTAL THERAPIES: FUTURE OUTLOOK

Presently, there are no biomarkers with sufficient evidence to guide second-line treatment choices for patients with relapsed SCLC, although some potential biomarkers and investigational targeted therapies offer future promise [22, 33, 88–91]. Ongoing clinical trials aim to explore potential biomarkers to predict responsiveness to certain agents, which—it is hoped—will allow for greater advances in the field.

Biomarkers in Development and Therapeutic Targets

Delta-Like Ligand 3 (DLL-3)

DLL-3 has been postulated as a biomarker with prognostic implications in SCLC. DLL-3 is a protein that is expressed at a high level in SCLC tumor cells and at low-to-minimal levels in normal tissues [33, 92]. A 2017 phase 1 study suggested that DLL-3 expression may have

prognostic significance in SCLC [93], while three other studies indicated that it did not [94–96]. Rovalpituzumab tesirine (Rova-T), the first DLL-3-targeted antibody–drug conjugate, initially showed promise as a treatment in SCLC [97], but later failed to demonstrate superiority in a randomized phase 3 trial when compared with topotecan, with inferior OS, PFS, and ORR seen in patients receiving Rova-T. Additionally, Rova-T was noted to have a challenging toxicity profile of significant cutaneous reactions and fluid accumulation [98]. Other DLL-3 inhibitors are currently being investigated in clinical trials of SCLC, most notably, bispecific T cell engagers and chimeric antigen receptor T cells (CAR-T) [99].

Poly (ADP-Ribose) Polymerase (PARP) and Promising Biomarker Schlafen 11 (SLFN11)

PARPs are a family of enzymes that play a key role in repairing damaged DNA, including that caused by chemotherapeutic agents, by detecting and mending single-stranded DNA breaks [22, 35]. PARP inhibitors may enhance DNA-damaging or cytotoxic effects when co-administered with other chemotherapeutic agents [35, 100]. PARP is highly expressed in SCLC tissue and has become a target for therapeutic drug development [22, 35]. PARP inhibitors currently being investigated in SCLC clinical trials include veliparib (NCT02289690, NCT01642251, NCT01638546, and NCT03227016), olaparib (NCT04728230, NCT03923270, and NCT02446704), and niraparib (NCT04701307, NCT03830918, and NCT04592237).

SLFN11, a DNA/RNA helicase that irreversibly induces a block of replication and leads to cell death, is emerging as a biomarker of response for PARP inhibitors [101]. SLFN11 has also been purported to predict sensitivity to cytotoxic or DNA-damaging chemotherapies, such as topoisomerase I inhibitors (i.e., topotecan, irinotecan) and topoisomerase II inhibitors (i.e., etoposide), as well as DNA cross-linkers and alkylating agents (e.g., cisplatin) [97]. A recent study reported that PARP activity correlates with SLFN11 expression in SCLC cell lines and patient-derived xenograft models [102].

These findings suggest that SLFN11 may be a relevant predictive biomarker of sensitivity to PARP inhibitors, which are currently being explored in clinical trials in SCLC.

For example, in a phase 2 study of temozolomide plus veliparib or placebo in patients with relapsed SCLC, PFS and OS did not differ significantly between the two treatment arms. However, SLFN11 expression was associated with a significant improvement in PFS and OS in patients receiving temozolomide plus veliparib compared with those receiving temozolomide plus placebo, suggesting that SLFN11 is a promising biomarker of PARP-inhibitor sensitivity that may identify patients who benefit from this therapy [100]. An ongoing phase II study (NCT04334941) in the frontline setting of maintenance atezolizumab versus atezolizumab in combination with talazoparib in patients with SLFN11-positive ES-SCLC will examine the value of the SLFN11 biomarker in a prospective manner.

Cyclin-Dependent Kinase 4/6 (CDK 4/6)

Trilaciclib is a short-acting CDK 4/6 inhibitor designed to arrest bone marrow progenitors in the G1 phase of the cycle during cytotoxic chemotherapy with the goal of preventing myelosuppression. On the basis of three successful randomized phase 2 studies (NCT03041311, NCT02499770, and NCT02514447), trilaciclib was FDA approved in February 2021 to decrease the incidence of chemotherapy-induced myelosuppression when administered prior to an EP-containing regimen or a topotecan-containing regimen for ES-SCLC [103, 104]. The myeloprotective effects of trilaciclib have been shown when combined with EP in patients with treatment-naïve ES-SCLC [105], in previously treated patients with ES-SCLC before beginning topotecan treatment [106], and when administered prior to EP plus atezolizumab in patients with treatment-naïve ES-SCLC [107]. Although no significant differences in efficacy were observed in the pooled analysis from three phase 2 studies that resulted in the approval of trilaciclib, the addition of trilaciclib prior to chemotherapy resulted in clinically meaningful reduction in chemotherapy-induced myelosuppression [108].

Moreover, in preclinical models, it was noted that the addition of trilaciclib to combination chemotherapy/immune-checkpoint inhibitor enhanced antitumor responses compared with combination chemotherapy/immune-checkpoint alone [109]. Furthermore, peripheral lymphocyte counts increased and T cell activation was enhanced following transient exposure of patients with SCLC to trilaciclib during chemotherapy, suggesting that trilaciclib may also enhance immune function when coadministered with chemotherapy [109]. There is an ongoing phase 2 study (NCT03041311) of trilaciclib with EP and atezolizumab in the frontline setting for ES-SCLC.

CONCLUSIONS

Prognosis for patients with ES-SCLC remains poor, even with treatment. EP has been the standard-of-care, first-line treatment option for nearly 30 years. Only recently have PD-L1 immunotherapies (atezolizumab and durvalumab) begun to enter the therapeutic armamentarium, with standard use in combination with EP. The best second-line therapy after combination of chemo-immunotherapy is not well defined, as many second-line therapies were studied only after use of EP. However, second-line treatment options for patients with relapsed ES-SCLC are limited and include reintroduction of EP (with or without an immunotherapy), lurbinectedin, and topotecan. For many patients, participation in a clinical trial and transition to hospice care are preferred options. Research efforts continue in the identification of biomarkers with potential prognostic significance and predictive value with certain therapeutics. Better understanding of the molecular characteristics of SCLC and the development of biomarkers will lead to more rapid advances and better guide treatment decisions in the future.

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