An overview of lurbinectedin as a new second-line treatment option for small cell lung cancer

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***Abstract*:** Small cell lung cancer (SCLC) is a highly proliferative, aggressive form of lung cancer that carries a poor prognosis. Recent approvals with new therapeutic options represent the first in more than a decade for SCLC. Lurbinectedin, a newly approved second-line option, is a synthetic alkaloid that covalently binds DNA, generating double-strand breaks, and disrupts DNA-protein interactions and RNA transcription. Lurbinectedin may also modulate the tumor microenvironment by inducing apoptosis of peripheral blood monocytes and tumor associated macrophages, decreasing expression of the inflammatory chemokine (C-C motif) ligand 2 (CCL2) and reducing tumor angiogenesis. A single-arm, open-label, basket trial included 105 patients with SCLC that had received one prior line of therapy. Patients received lurbinectedin 3.2 mg/m^2 as an intravenous infusion every 3 weeks, resulting in a response rate of 35.2% and a disease control rate of 68.6%. The response rate was 45% among those with >90 days chemotherapy free interval (CTFI) and 22% in the resistant group (CTFI < 90 days). The median overall survival was 9.3 months. Myelosuppression is the most frequent clinically significant adverse event, particularly neutropenia; however, neutropenic fever occurred in only 5% of those in the SCLC cohort of the basket trial. Nausea and fatigue were also noted. The side effect profile compares favorably to topotecan, while a direct comparison of tolerability can be made between lurbinectedin *versus* topotecan or pegylated-liposomal doxorubicin from CORAIL, a randomized study for platinum-resistant/refractory ovarian cancer. A press release has reported the ongoing clinical trial for SCLC including combination lurbinectedin and doxorubicin *versus* topotecan or cyclophosphamide, doxorubicin, and vinblastine to be negative. The details may provide more insight at publication, and future trials will be important to further define the clinical utility of lurbinectedin. Lurbinectedin represents a new option in second-line SCLC.

Keywords: doxorubicin, lung cancer, lurbinectedin, small cell lung cancer, topotecan

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Overview

Small cell lung cancer (SCLC) accounts for 13% of all lung cancer diagnoses and is a high-grade neuroendocrine malignancy that carries a poor prognosis.[1,2] An initial response to platinum-based chemotherapy is seen in more than 60% of patients treated with first-line chemotherapy and can be dramatic with rapid clearing of disease. Unfortunately, disease progression is commonly seen within months, and, prior to recent first-line advances, the median overall survival (OS) has been less than 11 months.[3,4]

SCLC has a high mitotic rate and tumor mutational burden (TMB), which is associated with an aggressive clinical course in most cases.[5] While genomic analysis of SCLC has not identified recurrent targetable alterations, recent epigenetic and gene expression studies have suggested the existence of distinct molecular

subtypes defined by transcriptional regulators.[6] Loss-of-function alterations in the tumor suppressors P53 and retinoblastoma protein (RB1) are seen in up to 90% of SCLC tumors, preventing the arrest of cell cycle to allow for DNA repair, leading to tumorigenesis.[7–10] MYC family proteins activate gene expression programs that promote proliferation, with MYC amplification seen in about 20% of SCLC.[11,12] These genomic alterations contribute to the aggressive nature of SCLC and poor prognosis. A small molecule screen demonstrated that SCLC is particularly sensitive to compounds that downregulate transcription, which decrease expression of key super-enhancer associated transcription factors such as *MYC* family genes.[13]

Recent U.S. Food and Drug Administration (FDA)-approvals represent the first advances in decades for this challenging and aggressive disease. In the first-line setting, platinum (carboplatin or cisplatin), etoposide, and checkpoint inhibitors (atezolizumab or durvalumab) are now the standard of care, after demonstrating improvement in OS with the inclusion of a checkpoint inhibitor.[14,15] Although the median improvement was limited, the durability of disease control was more significant in the chemotherapy plus checkpoint inhibitor groups, leading to an impressive 12-month progression-free survival (PFS) improvement and an ongoing separation of OS curves.

In the second-line setting, topotecan has been the only FDA-approved option, but its use is limited by concerns about toxicity and only modest efficacy.[16–18] Despite these challenges, multiple head-to-head comparison studies using topotecan as the control arm have been negative, highlighting the resistant disease state.[19,20] National Comprehensive Cancer Network (NCCN) guidelines list multiple recommended regimens to consider in the 2nd-line setting and beyond.[21] It is notable that clinical trial is listed as one of the three preferred regimens, highlighting the limited efficacy of available treatment options. Along with topotecan, the other preferred regimen in the NCCN guidelines, lurbinectedin, is also the newest approval in SCLC and the only FDA-approved option in platinum-resistant SCLC with a chemotherapy-free interval less than 45 days. Lurbinectedin was granted accelerated approval by the FDA for metastatic SCLC on June 15, 2020.

Mechanism of action

Lurbinectedin, or PM01183, is a synthetic alkaloid that is structurally related to trabectedin, a member of the ecteinascidin family originally derived from the marine tunicate Ecteinascidia turbinate. Lurbinectedin covalently binds guanine residues in the minor groove of DNA, forming adducts that can generate double-strand DNA breaks, disrupting DNA-protein interactions and RNA transcription.[22,23] Cancer cell lines treated with lurbinectedin accumulate in S-phase and ultimately undergo apoptosis, with cytotoxicity observed in a broad panel of human cancer cell lines and xenografts.[22] In addition, xenograft studies demonstrated that exposure to lurbinectedin rapidly decreases proliferation and increases apoptosis in both platinum-sensitive and resistant epithelial ovarian cancer models.[24] By specifically targeting CG-rich DNA sequences present in the promoter regions of protein-coding genes, lurbinectedin also exerts its anti-tumor activity by impairing RNA transcription and promoting the degradation of elongating RNA polymerase II.[23] This mechanism of action may be particularly relevant for SCLC, given previous drug screens in SCLC cell lines demonstrating sensitivity to transcriptional inhibitors.[13] Both trabectedin and lurbinectedin also impair nucleotide excision repair. Cancer cells with defects in homologous recombination are significantly more sensitive to treatment with these agents.[25,26]

In addition to these direct effects on tumor cells, preclinical evidence also suggests that lurbinectedin may modulate the tumor microenvironment to favor anti-tumor immune responses. Trabectedin was found to selectively decrease peripheral blood monocytes and tumor associated macrophages (TAMs) in immunocompetent mouse models and tumor specimens from patients with soft tissue sarcoma.[27] Treatment with trabectedin induced apoptosis of monocytes and decreased the expression of the inflammatory chemokine CCL2. *In vitro* studies with purified human monocytes have shown that lurbinectedin also reduces viability, CCL2 expression, and migration.[28] Similarly, in mouse tumor models lurbinectedin treatment reduced intratumoral macrophages and tumor angiogenesis. Lurbinectedin has also been proposed to induce 'immunogenic cell death', a mode of cancer cell death that favors the generation of anti-tumor immune responses by release of danger associated molecular patters (DAMPs).[29] Consistent with this, in immunocompetent fibrosarcoma and breast

cancer mouse models, treatment with lurbinectedin synergized with anti- cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) and anti-programmed cell death 1 ligand (anti-PD-1) blockade to eradicate tumors in a CD4/CD8 T-cell dependent manner. In addition, limited anti-tumor activity was observed with lurbinectedin treatment in tumors grown in immunodeficient mice. Collectively, these studies highlight that lurbinectedin may exert its therapeutic activity through multiple mechanisms, which could be exploited as treatment combinations are considered.

Efficacy

The safety and efficacy of lurbinectedin was first examined in a phase I trial in patients with advanced solid tumors, using an accelerated titration design.[30] The recommended phase II dose established by this study was 4.0 mg/m^2, or an equivalent flat dose of 7.0 mg administered every 3 weeks, given that no relationship between body surface area (BSA) and plasma clearance was observed. Twenty-eight patients were evaluable for efficacy per RECIST criteria, with one confirmed partial response in a patient with pancreatic cancer treated at the recommended phase II dose. An additional nine patients (29%) had disease stabilization.

A single-arm, open-label, multinational phase II basket trial was performed to assess the activity of lurbinectedin in nine different tumor types. The SCLC cohort included patients without known brain metastases, treated with one previous chemotherapy-containing regimen (prior immunotherapy either with chemotherapy or alone was allowed).[31] Patients were treated with 3.2 mg/m^2 of lurbinectedin administered as an intravenous (IV) infusion once every 3 weeks. The 3.2 mg/m^2 dose was chosen based on further safety analysis, which demonstrated significant reductions in febrile neutropenia and thrombocytopenia at this dose relative to the recommended phase II dose of 4.0 mg/m^2. A total of 105 patients were enrolled, treated with lurbinectedin, and included in the primary analysis. The majority of patients were male (60%), had an Eastern Cooperative Oncology Group (ECOG) Performance Score of one (56%), extensive stage at diagnosis (70%), and had greater than three tumor sites at baseline. The median age of patients enrolled was 60 years. With 17.1 months median follow-up, the investigator-assessed response (IAR) overall response rate (ORR) was 35.2% [95% confidence interval (CI) 26.2–45.2%], while the disease control rate was 68.6%. The median duration of response (DOR) was 5.3 months (95% CI 4.1–6.4). Response rates and DOR varied by chemotherapy-free interval (CTFI); see Table 1. Patients with sensitive disease (CTFI $\geq$ 90 days) had response rates of 45% with 6.2 month duration of response, while patients with resistant disease (CTFI $<$ 90 days) had a 22% response rate and 4.7 month duration of response. The median OS for the study population was 9.3 months.

Interestingly, a relatively small fraction of patients who discontinued lurbinectedin had disease progression with new brain lesions (8/94 patients, 9%). In the subgroup of patients with a CTFI of greater than 180 days ($n = 20$), the response rate was 60% with a median OS of 16.2 months.[32] Notably, the majority of patients in this subgroup had limited stage disease at the time of initial diagnosis.

Post hoc analysis of patients in the phase II study who achieved a confirmed response by investigator assessment demonstrated that the median time to first response was 5.4 weeks (95% CI 5.0–11.7 weeks), irrespective of sensitivity to prior platinum-based chemotherapy.[33] Similar response rates were seen across the baseline characteristics that were assessed, including age, sex, prior lines of therapy, and BSA.[34] The median OS for responders was 12.6 months, with encouraging 12-month survival rates varying by CTFI (40% for CTFI $<$ 90 days, 60% for CTFI $\geq$ 90 days, and 71% for CTFI $\geq$ 180 days). Multivariable cox regression analysis indicated ECOG performance status 0-1, prior immunotherapy, limited stage disease at diagnosis, CTFI $\geq$ 90 days, and lactate dehydrogenase $\leq$ upper limit of normal were associated with improved OS. While the number of patients who had received prior immunotherapy was small ($n = 8$), it was encouraging that lurbinectedin was active in this population given that chemotherapy plus PD-L1 blockade is a standard-of-care for extensive stage SCLC in the first-line setting.[14,15] Five of these eight patients (63%) achieved durable responses with lurbinectedin. No treatment emergent adverse events (TEAE) resulted in death and only one patient had to discontinue therapy due to a TEAE.

The combination of lurbinectedin with doxorubicin has also been investigated in a phase I study, based on preclinical data demonstrating synergy.[35] Treatment consisted of a fixed dose of

Table 1. Efficacy of lurbinectedin for the second-line treatment of SCLC.[30,31].

	All patients ($n=105$)	CTFI <90 days ($n=45$)	CTFI ≥ 90 days ($n=60$)	CTFI ≥ 180 days ($n=20$)
IAR				
CR	0	0	0	0
PR	37 (35%)	10 (22%)	27 (45%)	12 (60%)
SD	35 (33%)	13 (29%)	22 (37%)	7 (35%)
PD	28 (27%)	18 (40%)	10 (17%)	1 (5%)
DOR				
Median, months	5.3 (4.1–6.4)	4.7 (2.6–5.6)	6.2 (3.5–7.3)	5.5 (2.9–11.2)
PFS				
Median, months	3.5 (2.6–4.3)	2.6 (1.3–3.9)	4.6 (2.8–6.5)	4.6 (2.6–7.3)
OS				
Median, months	9.3 (6.3–11.8)	5.0 (4.1–6.3)	11.9 (9.7–16.2)	16.2 (9.6–nr)

CR, complete response; CTFI, chemotherapy-free interval; DOR, duration of response; IAR, investigator-assessed response; OS, overall survival; PD, progressive disease; PR, partial response; PRS, progression-free survival; SCLC, small-cell lung cancer; SD, stable disease

doxorubicin 50 mg/m^2 with escalating doses of lurbinectedin, following a standard 3+3 design.

Seventy-four patients were included in dose escalation, with SCLC being the most common tumor type. The recommended dose of lurbinectedin was a fixed dose of 4.0 mg. Among the 26 patients that were evaluable for efficacy, the ORR was 57.7% (95% CI 36.9–76.6%), the median PFS was 4.1 months (95% CI 1.4–5.8 months), and the median DOR was 4.5 months (95% CI 2.3–7.8 months). In the second-line setting, the response rate was 91.7% ($n=11/12$, 95% CI 61.5–99.8%) for the 12 patients with sensitive disease (defined as platinum free interval $\geq$90 days) and 33.3% ($n=3/9$, 7.5–70.1%) for resistant disease. A response rate of 20% was seen in the five patients treated as third-line. The efficacy of this combination is being compared with topotecan or cyclophosphamide/doxorubicin/vincristine (CAV) in patients who have failed one prior line of platinum-containing therapy in the ongoing, phase III ATLANTIS study.[36]

Side-effect profile

Myelosuppression has been the most frequent clinically-significant adverse reaction observed for lurbinectedin. Of the 31 patients in the phase I study, 15 were treated at the recommended phase II dose.[30] Most adverse events at this dose were grade 1 or 2, including nausea/vomiting, diarrhea, and fatigue. As suggested by preclinical toxicology studies, myelosuppression was the primary toxicity including anemia (93% of patients, grade 3: 27%, no grade 4 events), neutropenia (73%, grade 3/4: 53%), and thrombocytopenia (67%, no grade 3, grade 4: 7%). The nadir for neutropenia occurred on day 11, with a median duration of 3 days. In the phase I study in combination with doxorubicin, the most common non-hematologic toxicities were fatigue, nausea/vomiting, decreased appetite, and mucositis.[35] Hematologic toxicity was more common and severe with the combination, with anemia (grade 3: 47%), febrile neutropenia (grade 3: 21%, grade 4: 5%), neutropenia (grade 3: 16%, grade 4: 79%) and thrombocytopenia (grade 3: 11%, grade 4: 16%) seen. The dose of doxorubicin (40 mg/m^2) and lurbinectedin (2.0 mg/m^2) were both reduced to improve the safety profile for the phase III study.[36]

A phase II randomized study of a flat dose of lurbinectedin (7.0 mg) in patients with platinum-resistant/refractory ovarian cancer provides a direct comparison to the toxicity profile of topotecan (standard 1.5–0.75 mg/m^2 days 1–5 every three weeks, or weekly 4.0–2.4 mg/m^2).[37] Significantly

more myelosuppression was seen in patients treated with lurbinectedin, with 85% grade 3–4 neutropenia, 33% grade 3–4 thrombocytopenia, and 21% with febrile neutropenia. While this study demonstrated encouraging anti-tumor activity, the higher rate of hematologic toxicity prompted reconsideration of the dosing strategy. A lower dose and BSA-based dosing were recommended, based on further pharmacokinetic analysis. The 3.2 mg/m^2 every 3 weeks dose was further explored in ovarian cancer in the phase III CORAIL study, comparing lurbinectedin to investigator's choice of pegylated-liposomal doxorubicin (PLD) or topotecan.[38] While this study did not reach its primary endpoint of improvement in PFS, it does provide further data on the toxicity profile of lurbinectedin. The overall rate of grade 3 or greater adverse events was 48% in patients treated with lurbinectedin, relative to 64% for treatment with topotecan or PLD. The topotecan/PLD arm also had more treatment-related dose reductions, delays, and discontinuation suggesting lower, BSA-based dosing improves tolerability of lurbinectedin.

Similarly, a single-arm study in patients with metastatic breast cancer also demonstrated improved tolerability with lower, BSA-based dosing. Cruz *et al.*[39] initially treated 35 germline BRCA1/2 mutated patients with the 7.0 mg flat dose of lurbinectedin every 3 weeks. The study was subsequently amended based on toxicity data, and an additional 19 patients were treated at 3.5 mg/m^2. The incidence of severe hematologic toxicity notably decreased with the dose adjustment, with the rate of a grade 3–4 anemia improving from 26% to 5%, neutropenia from 71% to 57%, and thrombocytopenia from 29% to 5%. Nausea/vomiting and fatigue were the other most frequent adverse events.

Accordingly, the basket study (Study B-005) utilized a lower 3.2 mg/m^2 dose administered by IV infusion every 3 weeks. Primary prophylaxis with granulocyte colony-stimulating factors (G-CSFs) was not allowed, but secondary prophylaxis for neutropenia was permitted and an anti-emetic regimen consisting of a corticosteroid and serotonin antagonist could be administered. Among the 554 patients who received lurbinectedin in Study B-005, grade 3 or 4 neutropenia was seen in 41% with febrile neutropenia in 7%.[40] Sepsis was reported in 2% of patients, including a 1% fatality rate (no cases in SCLC). In addition, grade 3 or 4 thrombocytopenia or anemia were seen in 10% and 17% of patients, respectively. Abnormalities in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were seen in 3–6% (grade 3) and 0.4–0.5% (grade 4) of patients. In the cohort of patients with SCLC, a similar profile of treatment related adverse events was observed (Table 2).

Discussion

Second-line SCLC is a challenging clinical scenario with a poor prognosis and until recently, a single FDA-approved therapeutic option. Lurbinectedin was approved based on data from a basket trial that included 105 patients with SCLC. Although substantial enough to demonstrate efficacy, there is likely more to understand about lurbinectedin as increasing populations of patients are treated. Cross-trial comparisons are fraught with limitations but also necessary when comparing potential treatment options. Lurbinectedin compares favorably to other drugs on the list of NCCN guideline-recommended options and has demonstrated numerically better efficacy than topotecan along with a more favorable side effect profile. Primary G-CSF prophylaxis was not allowed in the basket trial, but significant numbers of grade 3/4 neutropenia led to 23 (22%) patients developing G-CSF as secondary prophylaxis. Neutropenia was the most significant adverse event, but febrile neutropenia occurred in only 5% of participants. These numbers may increase as patients are treated with this new standard of care regimen, including some patients with less robust marrow recovery and borderline functional status. At the same time, the Basket Trial included 8 (8%) participants with ECOG two functional status. As expected, increasing CTFI improves prognosis and is associated with increasing median PFS with lurbinectedin. Although the overall trial results appear less impressive with the inclusion of platinum-resistant participants, the demonstration of responses and disease control among this particularly challenging setting is meaningful, and lurbinectedin is the only approved treatment option for individuals with a CTFI of $<$45 days.

A review of treatment options suggested in NCCN guidelines offers greater context for lurbinectedin within the landscape. Irinotecan, a topoisomerase I inhibitor, led to a 47% response rate in a very limited data set of 15 patients with a median CTFI of 7.3 months, indicating the majority enrolled had platinum-sensitive disease.[41] The median duration of response was

Table 2. Toxicity profile of lurbinectedin monotherapy (SCLC cohort).[30].

	Lurbinectedin (*n* = 105)	
	Grade 1–2 (%)	**Grade 3–4 (%)**
TRAEs		
Fatigue	51	7
Nausea	32	0
Vomiting	18	0
Diarrhea	14	1
Decreased appetite	21	0
Febrile neutropenia	0	5
Laboratory abnormalities		
Hematologic		
Anemia	87	9
Leukopenia	50	29
Neutropenia	26	46
Thrombocytopenia	37	7
Chemistries		
Increased creatinine	83	0
Increased ALT	67	5
Increased AST	43	2
Increased ALP	30	3
Increased GGT	50	15

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; TRAE; treatment-related adverse events

58 days and the median OS was 187 days. Cytopenia made up the majority of grade 3/4 adverse events. Paclitaxel has been reported in two studies with different dosing schedules, each limited to only 21 patients with a response rate of approximately 25%.[42,43] Dosing schedules include 175 mg/m^2 every 3 weeks or the more commonly utilized 80 mg/m^2 weekly for 6 weeks in 8-week cycles. The weekly dosing schedule has a limited toxicity profile with the majority of grade 3/4 adverse events described as leukopenia and/or neutropenia. Grade 3 neuropathy was noted in two of the 21 participants. Temozolomide is a prodrug that rapidly converts to an active metabolite and has the particular benefit of penetrating the blood-brain barrier, providing central nervous system (CNS) activity. Temozolomide has demonstrated a response rate of 23% among 48 patients with platinum-sensitive disease and 13% among 16 patients with platinum-refractory disease (defined as CTFI of less than or equal to 2 months). The median OS in both groups was limited to 6 months.[44] An alternative dosing schedule for temozolomide has demonstrated better tolerability. Although grade 3/4 toxicity was reported in 5 (20%), no treatment-limiting cytopenia occurred. This dosing resulted in a response rate of 12%.[45]

Cross-trial comparisons of these various regimens to a single-arm trial of lurbinectedin is fraught with complexity, but the available data provides an important background for contextualizing the value of lurbinectedin as a treatment option. At the same time, cross-trial comparison is something inherent to providing care, as it is necessary when deciding which treatment option is preferred for each individual patient. It is important to first highlight that the trials differ in the number of patients with platinum-resistant *versus* platinum-sensitive disease, which significantly affects prognosis. There is also variation in platinum-resistant being categorized as a CTFI of less than 60 or 90 days, but the topotecan studies included only those with a CTFI $>$ 45 days or $>$60 days depending on the study. Lurbinectedin did not include a specific CTFI requirement for enrollment, and 45 patients (43%) had a CTFI of $<$90 days. Despite this, the median OS of the total lurbinectedin cohort was 9.3 months, while the topotecan studies demonstrated a median OS of about 6 months.[17,18] The lurbinectedin cohort, with a CTFI of $>$90 days, yielded an impressive median OS of 12 months. The median PFS is similar between the studies, but response rates and the DOR are more meaningful in the lurbinectedin cohort. While lurbinectedin demonstrated multiple efficacy endpoints that compare well to topotecan, the side effect profile also shows lower rates of discontinuation secondary to toxicity. Although cytopenia is a common treatment-related toxicity associated with lurbinectedin or topotecan, anemia and thrombocytopenia were overwhelmingly grade 1–2 when present in the lurbinectedin study. Neutropenia was more significant, with grade 3 and 4 in 21% and 25% respectively, but febrile neutropenia was noted in only 5% of subjects. An important distinction relative to most topotecan studies is that the lurbinectedin cohort was not permitted primary G-CSF prophylaxis. Topotecan

studies have shown much higher incidence of grade 3–4 anemia and thrombocytopenia as well as neutropenia despite including primary G-CSF prophylaxis.[17,46]

Although the 105 patients enrolled to the basket trial provides a reasonably sized cohort to evaluate efficacy, particularly in comparison to the other data sets discussed, there is likely more to learn as many more patients are treated. The side effect profile has been consistent across trials enrolling more than just SCLC, but a randomized study has the potential to provide more direct evidence. For example, grade 3 fatigue was noted in seven patients (7%) in the lurbinectedin cohort. This was substantially higher than other non-lab TRAEs. Although this was considered treatment related, that can sometimes be difficult to differentiate from the disease itself. Topotecan has shown similar grade 3 fatigue, but a randomized study provides greater opportunity for direct comparison.[18]

A randomized study including combination lurbinectedin and doxorubicin has been reported in press-release to be a negative trial, not having met the primary endpoint for superiority. The combination regimen utilized a lower dose of lurbinectedin than in the single-agent basket trial, representing one potential reason for less efficacy than hypothesized.[36] In addition, the control arm allowed for investigator choice of either topotecan or CAV. CAV was a regimen previously under investigation as a first-line option before platinum-etoposide became the established first-line standard of care.[47] CAV was then often used in the second-line after platinum and etoposide with response rates of up to 28%.[48] Publication of the results is still pending at this time.

Although the trial is reportedly negative, the efficacy and tolerability data will be of interest when published as compared with those of CAV or topotecan in the control arm. Lurbinectedin has demonstrated impressive results as a single agent in second-line SCLC, representing the first progress in this setting in more than a decade, and the only new FDA-approval for SCLC other than immunotherapy. Lurbinectedin represents a new treatment option in second-line SCLC after approval in the US. Randomized trials will further define optimal use and the potential for international drug approvals.

Conflict of interest statement

Dr. Sands reports receiving personal fees for scientific advisory board/consulting from Abbvie, AstraZeneca, Blueprint Medicines, Medtronic, Eli Lilly and Company, Boehringer Ingelheim, Loxo, Genentech, Foundation Medicine, Guardant, Pharma Mar, Takeda, Jazz Pharmaceuticals, and personal fees and non-financial support from Merck, outside of the submitted work. Dr. Patel reports research funding to institution from AstraZeneca, Shattuck Labs, and Dracen Pharmaceuticals. Dr. Petty reports receiving personal fees for scientific advisory board from Jazz Pharmaceuticals

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