EVIDENCE REVIEW

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Lurbinectedin: Small Cell Lung Cancer Subsequent Therapy

Overview: It can be difficult in the oncology space to keep up with the slew of new medications, many of which receive accelerated approvals. One such example is lurbinectedin (Zepzelca™), which received accelerated approval in 2020 based on overall response rate and duration of response for adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). Recent data, which shows that the drug's initial promise may have been too optimistic, reaffirms Evolent's preference for other regimens on its preferred clinical pathway for this disease state.

Key findings

1. The phase 3 ATLANTIS trial failed to meet its primary endpoint of lurbinectedin improving overall survival (OS) when compared to the control arm.
2. Despite a more favorable side-effect profile than current standard of care, lurbinectedin comes at the risk of financial toxicity.
3. More data is required to determine the true benefit for patients treated with lurbinectedin.
4. For patients with a chemotherapy-free interval (CTFI) of less than 6 months, Evolent's preferred pathway agents are tarlatamab (NCCN Category 1), topotecan and irinotecan; selected for either superior efficacy (tarlatamab) or comparable efficacy to lurbinectedin at significantly lower cost (irinotecan, topotecan). For patients with a CTFI greater than 6 months, Evolent recommends rechallenging with a platinum-based doublet prior to considering subsequent therapy options.

Clinical trial evidence

Phase 2 basket trial (Study B-005)

Lurbinectedin's approval was based on the results of a single-arm, open-label, phase 2 basket trial (Study B-005). A basket trial incorporates patients from different subgroups into one group based on the presence of a specific factor; this trial used several disease criteria (not SCLC-specific) for patient inclusion. The trial's primary endpoint of overall response rate (ORR) showed 35% of patients had a response, all of which were partial responses. An independent review committee found that the response rate was even lower at 30%.[1]

Phase 3 ATLANTIS trial

These results prompted the follow-up phase 3 ATLANTIS trial, which evaluated the efficacy of lurbinectedin versus established standards of care. Lurbinectedin and doxorubicin were compared against either topotecan or cyclophosphamide, doxorubicin and vincristine (CAV).[2] This combination utilized a lower dose of lurbinectedin and was selected based on preclinical evidence suggesting synergy with doxorubicin. The ATLANTIS trial failed to meet its primary endpoint of improving overall survival (OS) with a median OS of 8.6 months for the lurbinectedin and doxorubicin group vs. 7.6 months in the control group. The difference in OS was not statistically significant, and this lack of

survival benefit was seen across all subgroups analyzed. Median PFS, as assessed by an independent review committee, was the same in both arms at 4 months. The lurbinectedin arm had a lower incidence of adverse events ≥ grade 3 than the control arm (66% vs 86.5% in the control group) along with lower rates of treatment discontinuation due to adverse events (9% vs 16%). Grade 3 or worse hematologic adverse events were also less frequent with the lurbinectedin arm than in the control group: anemia (19% vs. 38%), neutropenia (37% vs. 69%), and thrombocytopenia (14% vs. 31%).[3]

Patient population limitations

It is notable that patients with central nervous system (CNS) disease and cardiac comorbidities were excluded from both lurbinectedin trials. These are significant challenges for this patient population, with 50% of SCLC patients expected to develop CNS metastasis[4] and a cardiovascular disease prevalence of approximately 35%.[5] For CNS progression, NCCN recommends consideration of irinotecan along with radiotherapy.[6] Additionally, both trials primarily enrolled patients with ECOG performance status 0-1, which does not fully reflect the broader SCLC population, where many patients present with ECOG 2 or higher due to disease burden and comorbidities. This discrepancy underscores the importance of tailoring therapy to functional status and integrating supportive and palliative care early in the treatment continuum. Evidence suggests that early palliative care in advanced lung cancer improves quality of life and may even extend survival, making it a critical component of comprehensive care planning.[7,8]

Comparative outcomes

Table 1 demonstrates the data from the ATLANTIS trial and its comparison to other drugs/regimens existing in today's market.

Table 1

	Topotecan (Hycamtin)	Irinotecan (Camptosar)	Tarlatamab-dlle* (Imdelltra)	Lurbinectedin (Zepzelca)
Trial	ATLANTIS Topotecan vs. CAV	NCT03098030	DeLLphi-301 DeLLphi-304	Study B-005
N	107 (All patients evaluated were platinum-sensitive[a])	190 (126 Platinum-resistant 64 Platinum sensitive)	254 (DeLLphi-304) 99 (DeLLphi-301) (27 Platinum-resistant 42 Platinum-sensitive)	105 (45 Platinum-resistant 60 Platinum sensitive)
Median Age	---	61.5	65 (DeLLphi-304) 64 (DeLLphi-301)	60
Overall Response Rate % (95% CI)				
All Patients	Not reported	18.9 (13.6 – 25.3)	40 (31,51)[#]	35 (26, 45)
Platinum-resistant	Not reported	Not reported	52 (32, 71)[#]	22 (11, 37)
Platinum-sensitive[a]	24 (15, 32)	Not reported	31 (18, 47)[#]	45 (32, 58)
Complete Response, All Patients, %	0	2.6	2	0
Partial Response, All Patients, %	24	22.1	38	35

Median DOR, months	3.6	--	9.7	5.1
Median OS, months	6.3	7	13.6	9.3
Median PFS, months	3.3	3	4.2	3.5
Dose	1.5 mg/m^2 days 1-5 every 3 weeks	350 mg/m^2 every 3 weeks	1 mg on Cycle 1 Day 1 followed by 10 mg on Days 8, 15 and every 2 weeks thereafter*	3.2 mg/m^2 every 3 weeks
Adverse Events: **All Grades (Grade ≥ 3), %**				
Discontinuation due to AE (%)	--	--	6	1.9
Dose interruption due to AE (%)	--	--	38	30.5
Cytokine Release Syndrome	--	--	56 (1.2*)	--
Fatigue	5	25.7 (9.1)	39 (6*)	77 (12)
Lymphocytopenia	--	11.8 (3.7)	65 (27*)	79 (43)
Anemia	42	29.4 (9.6)	51 (4.5*)	74 (10)
Neutropenia	70	25.1 (16.6)	15 (10*)	71 (46)
Thrombocytopenia	29	7 (0)	25 (0.4*)	37 (7)

** Toxicity, overall and progression free survival data and dosing are derived from the DeLLphi-304 trial; all other data reflect findings from DeLLphi-301.*
[a] Platinum-sensitive defined as ≥ 60 days or ≥ 90 days chemotherapy-free interval, dependent on trial definitions
[#] In DeLLphi-301,69 patients had available platinum-sensitivity data, ORRs are reflective of this cohort
┼ pulled from package insert for LexiComp

Real-world evidence

The results of these trials underscore the need for continued research in treating patients with SCLC who progress after first-line therapy. Early response rates and survival data indicate that tarlatamab offers a notable advantage over other available options. However, this comes with serious toxicity concerns typically present with bispecific antibody therapies. While lurbinectedin remains an alternative for this population, current evidence does not demonstrate a meaningful improvement in survival outcomes in comparison to topotecan or irinotecan. Real-world data further support this modest benefit: A retrospective study within the Mayo Clinic Health System reported a median overall survival of just 5.1 months among 50 patients receiving lurbinectedin in the second-line setting.[10]

Toxicity comparison

Table 2 provides a comparative overview of toxicity profiles across these agents. Irinotecan is associated with the greatest gastrointestinal burden, topotecan with the highest hematologic risk, and lurbinectedin with notable hepatic toxicity. Neurotoxicity and cytokine release syndrome (CRS) remain unique adverse effects linked to tarlatamab in the subsequent therapy setting.

Table 2

Adverse effects (%)	Topotecan	Irinotecan	Tarlatamab-dlle	Lurbinectedin
Nausea	27-33%	70-86%	24%	37%
Vomiting	19-21%	62-67%	--	22%
Anemia (grades 3/4)	94% (37-42%)	60-97% (5-7%)	33%	>10% (17%)
Febrile neutropenia	23-28%	1-10%	<1%	7%
Thrombocytopenia (grades 3/4)	81% (27-29%)	96% (1-4%)	36%	1-10% (10%)
Increased alanine aminotransferase (ALT)	≤ 4%	-	42%	66%
Increased serum aspartate aminotransferase (AST)	≤ 4%	10%	44%	26%
Diarrhea (grades 3/4)	14-22% (6%)	83-88% (14-31%)	--	20% (4%)

Source: Lexicomp. Adverse Reactions: Topotecan, Irinotecan, and Lurbinectedin.

Financial toxicity

Although lurbinectedin may be an attractive option for those that are not candidates for tarlatamab, its financial impact cannot be overlooked. Based on the latest ASP pricing, 90 days of treatment with lurbinectedin (3.2 mg/m² every 3 weeks) costs approximately $45,100, compared to just $210 for irinotecan and $5,600 for intravenous topotecan over the same period, a notable difference. Table 3 highlights the quarterly cost comparison, underscoring the significant economic considerations when selecting therapy.

Table 3

	Topotecan IV	Topotecan oral	Irinotecan	Tarlatamab-dlle	Lurbinectedin
Quarterly Cost	$5,600 *(Includes cost of pegfilgrastim)*	$43,300 *(Includes cost of pegfilgrastim)*	$210	$95,400	$45,100

Dosing based on BSA of 1.7m^2; Source: Centers for Medicare & Medicaid Services: Medicare. Medicare Part B Drug Average Sales Price. 2025 ASP Drug Pricing Files. Medispan NDC data. Updated 10/2025.

Best practices

According to NCCN guidelines, tarlatamab is the preferred Category 1 option for subsequent therapy in small cell lung cancer (SCLC), with topotecan, irinotecan and lurbinectedin listed as alternative subsequent therapy regimens. The previous recommendation to rechallenge patients with a platinum-based regimen for relapse after >6 months was removed in Version 2.2026 of the guidelines and replaced with “prolonged disease-free time.” Based on clinical trial definitions for platinum sensitive/resistant disease, Evolent will continue to utilize CTFI <90-180 days. For platinum-resistant

relapse, Evolent recommends tarlatamab, restricting its use to patients with a performance status of 0 or 1 due to its toxicity profile. Tarlatamab is particularly preferred for patients with CTFI <90 days. For those with a CTFI ≥90 days, rechallenge with platinum, irinotecan (particularly for CNS involvement), or topotecan is advised. In all cases, early integration of supportive and palliative care should be emphasized to optimize quality of life and symptom management, as evidence shows this approach improves outcomes in advanced lung cancer.

When applying a value-based approach, the marginal benefit of lurbinectedin at a substantially higher cost does not justify its use over topotecan or irinotecan for most patients. While lurbinectedin introduces a novel treatment modality, its role remains uncertain and warrants further investigation in an area with historically poor outcomes. Current evidence indicates that tarlatamab offers the most significant advantage among available options, followed by irinotecan or topotecan for patients with recurrent metastatic small cell lung cancer.

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