



Antitumor Activity of Lurbinectedin, a Selective Inhibitor of Oncogene Transcription, in Patients with Relapsed Ewing Sarcoma: Results of a Basket Phase II Study

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ABSTRACT

Purpose: Lurbinectedin suppresses the oncogenic transcription factor EWS-FLI1 through relocalization to the nucleolus, and delays tumor growth in mice bearing Ewing sarcoma xenografts. On the basis of this rationale, lurbinectedin was evaluated in patients with relapsed Ewing sarcoma.

Experimental Design: This open-label, single-arm, Basket phase II trial included a cohort of 28 treated adult patients with confirmed Ewing sarcoma, measurable disease as per Response Evaluation Criteria In Solid Tumors (RECIST) v.1.1, Eastern Cooperative Oncology Group performance status ≤ 2 , adequate organ function, no central nervous system metastasis, and pretreated with ≤ 2 chemotherapy lines for metastatic/recurrent disease. Patients received lurbinectedin 3.2 mg/m² as a 1-hour infusion every 3 weeks. Primary endpoint was overall response rate (ORR) as per RECIST v.1.1. Secondary endpoints included time-to-event parameters and safety profile.

Results: ORR was 14.3% [95% confidence interval (CI), 4.0%–32.7%], with median duration of response of 4.2 months (95% CI, 2.9–5.5 months). Median progression-free survival was 2.7 months (95% CI, 1.4–4.3 months), clinical benefit rate was 39.3%, and disease control rate was 57.1%. With 39% censoring, median overall survival was 12.0 months (95% CI, 8.5–18.5 months). Most common grade 3/4 adverse events were neutropenia (57%), anemia, thrombocytopenia, and treatment-related febrile neutropenia (14% each). No deaths or discontinuations were due to toxicity.

Conclusions: Lurbinectedin was active in the treatment of relapsed Ewing sarcoma and had a manageable safety profile. Lurbinectedin could represent a valuable addition to therapies for Ewing sarcoma, and is currently being evaluated in combination with irinotecan in advanced Ewing sarcoma in a phase Ib/II trial.

Introduction

Ewing sarcoma, formerly referred to as the Ewing family of tumors (EFT), is an aggressive form of sarcoma that comprises malignancies such as classic Ewing sarcoma, peripheral neuroectodermic tumors (PNET), and Askin tumor. Ewing sarcoma is the

second most common malignant bone tumor among children, adolescents, and young adults, striking them in the prime of their lives (1). Ewing sarcoma may also appear in soft tissue, with the most common sites being trunk and limbs (2). The average incidence of Ewing sarcoma is 2.93 cases per million per year (3), and most patients are under the age of 20 years.

The prognosis of Ewing sarcoma varies depending on primary tumor site, presence of metastases, and tumor size. First-line treatment with surgery, radiotherapy, and multi-agent chemotherapy has resulted in 5-year disease-free survival rates of 60% to 70% in patients with localized sarcoma, but less than 20% if metastases are present at diagnosis (4), with an inferior outcome being observed in patients younger than 18 years (5, 6). There is no established treatment for relapsed Ewing sarcoma. Management of relapsed disease mostly consists of different combinations of the same agents used as prior therapy (e.g., alkylators or topoisomerase inhibitors), radiotherapy of lung and bone, and surgical removal of metastases. However, failure on second-line therapy is very common, and the agents used are associated with short- and long-term toxicity (7, 8). Patients with relapsed Ewing sarcoma have a dismal prognosis, with a 5-year survival rate of 13% (9). Development of therapeutics in Ewing sarcoma is challenging due to its rarity and the absence of classic kinase targets (10). Therefore, there is an urgent need for new therapeutic agents with different mechanisms of action to manage this patient population.

Lurbinectedin (Zepzelca) is a synthetic tetrahydroisoquinoline alkaloid structurally related to trabectedin that inhibits oncogenic transcription primarily through binding to guanine-rich DNA sequences around gene promoters, thereby altering the 3D DNA

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Translational Relevance

Novel therapeutic agents are needed for patients with relapsed/refractory Ewing sarcoma who have a dismal prognosis. Lurbinectedin blocks transcription and induces DNA double-strand breaks, leading to apoptosis. In preclinical models it was shown that lurbinectedin is effective in suppressing the activity of the oncogenic transcription factor EWS-FLI1 through relocalization to the nucleolus and delayed tumor growth in mice bearing Ewing sarcoma xenografts. This Basket clinical trial demonstrated clinical antitumor activity of lurbinectedin with an objective response rate of 14.3%, clinical benefit rate (response or disease stabilization for ≥ 4 months) of 39.3%, and disease control rate (response or disease stabilization of any duration) of 57.1% in a cohort of patients with relapsed Ewing sarcoma. Lurbinectedin could represent a valuable addition to relapsed Ewing sarcoma, which constitutes a highly unmet medical need.

structure and evicting oncogenic transcription factors from their binding sites (11–13). Lurbinectedin adducts may also inhibit mRNA synthesis and induce the ubiquitination and degradation of RNA polymerase II (14), and favor the production of DNA double-strand breaks and trigger apoptotic cell death (15). Lurbinectedin has received FDA accelerated approval for treatment of patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy (16). A previous phase II study had shown efficacy for trabectedin in pretreated patients with advanced Ewing sarcoma, including 3 partial responses (PR) and 7 disease stabilizations in a cohort of 20 patients; progression-free survival (PFS) rate at 6 months was 25% (17). Preclinical studies showed that lurbinectedin is more effective than trabectedin in suppressing the activity of the oncogenic transcription factor EWS-FLI1 in mice through relocalization to the nucleolus (18, 19). *In vivo*, administration of lurbinectedin delayed tumor growth in mice bearing Ewing sarcoma xenografts (19). Lurbinectedin also showed an improved therapeutic index relative to trabectedin, with suppression of EWS-FLI1 activity observed in mice at clinically achievable concentrations (19). Compared with trabectedin, lurbinectedin had a more favorable pharmacokinetic profile, as suggested by a higher recommended dose (RD) and greater exposure values at the RD when administered as single agent every 3 weeks (20, 21).

This study evaluated the monotherapy activity of lurbinectedin in terms of response rate, PFS, clinical benefit rate (CBR), and disease control rate (DCR) in a cohort of patients with relapsed Ewing sarcoma.

Experimental Design

This single-arm, open-label, Basket phase II trial evaluated the efficacy and safety of lurbinectedin in 9 cohorts of patients with difficult-to-treat tumors. This report is focused on the cohort of patients with Ewing sarcoma (labelled as EFTs in the study protocol) treated at 11 sites in Belgium, France, Italy, Spain, and the U.S. The trial was conducted in compliance with ICH Good Clinical Practice guidelines. The protocol was approved by the centers' Research Ethics Committees. Signed written informed consent was obtained for each patient before study-specific procedures. The trial is registered at <https://www.clinicaltrials.gov> as NCT02454972.

Eligibility criteria

Eligible patients were aged ≥ 18 years, with Ewing sarcoma previously treated with ≤ 2 chemotherapy lines in the metastatic/recurrent setting, measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST) v.1.1 (22) and documented disease progression, Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2 , and adequate bone marrow, hepatic, renal, and metabolic function who had recovered from any previous toxicities.

Patients were excluded if they had been pretreated with lurbinectedin or trabectedin, had prior/concurrent malignant disease (unless in complete remission for >5 years), had impending need for radiotherapy, were pregnant or lactating women or women of childbearing potential who were not using effective contraceptives, or had central venous involvement, relevant cardiac disease, severe dyspnea or daily intermittent oxygen requirement, active infection, unhealed wounds, external drainages, immunocompromise (including human immunodeficiency virus infection), or limited ability to comply with treatment or follow-up.

Study treatment

All patients were given lurbinectedin 3.2 mg/m² as a 1-hour intravenous infusion once every 3 weeks. Treatment delays and dose reductions were allowed to manage toxicity at the investigator's discretion. Treatment was administered until disease progression, unacceptable toxicity, treatment delay >3 weeks (except if clear clinical benefit), requirement of >2 dose reductions, intercurrent illness precluding study continuation, and patient refusal and/or noncompliance with study requirements. Standard antiemetic prophylaxis was administered before each lurbinectedin infusion. Only secondary prophylaxis with granulocyte colony-stimulating factor (G-CSF) was allowed.

Study assessments

Antitumor activity was evaluated in patients who had at least one complete infusion of lurbinectedin, and who either had at least one tumor assessment (as per RECIST v.1.1) or were considered treatment failures (i.e., discontinued treatment due to toxicity/clinical disease progression or died due to the disease before the first tumor assessment). Radiologic tumor assessments (CT scans or MRI) were conducted every 6 weeks until Cycle 6, and every 9 weeks thereafter. Any patients showing a response had to have a confirmatory assessment using the same technique at least 4 weeks later.

Safety was evaluated in all patients who received at least one lurbinectedin infusion through the assessment of adverse events (AE), laboratory tests, physical examination, and vital signs. Laboratory tests were conducted weekly during Cycles 1 and 2, and on Day 1 of subsequent cycles. Safety was monitored throughout treatment and up to 30 days after the last lurbinectedin infusion, start of a new antitumor therapy, or death, whichever occurred first. Any lurbinectedin-related AE was followed until recovery. AEs and laboratory abnormalities were graded with the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4 (23), and coded using the Medical Dictionary for Regulatory Activities v.21.0.

Endpoints

All study endpoints were assessed by the investigators. The primary endpoint was the antitumor activity of lurbinectedin in terms of overall response rate [ORR; percentage of patients with complete response (CR) or PR as per RECIST v.1.1]. Secondary endpoints were duration of response (DoR; time from the date of first response to the date of first disease progression or death from any cause in patients with response), CBR (percentage of patients with response or disease stabilization for

Table 1. Baseline characteristics of patients with Ewing sarcoma.

	All treated patients (n = 28)
Gender	
Male	16 (57%)
Female	12 (43%)
Median age, years (range)	33 (18–74)
ECOG performance status	
0	11 (39%)
1	16 (57%)
2	1 (4%)
Median BSA, m ² (range)	1.9 (1.6–2.4)
Abnormal LDH (>ULN)	10 (36%)
Disease stage at diagnosis	
Early	14 (50%)
Locally advanced	5 (18%)
Metastatic	9 (32%)
Ewing sarcoma anatomical subtype ^a	
Extraosseous	15 (58%)
Osseous	11 (42%)
Median number of tumor sites at baseline (range)	2 (1–6)
≥3 sites	10 (36%)
Most common sites of disease at baseline	
Lung	18 (64%)
Bone	16 (57%)
Pleura	9 (32%)
Lymph nodes	6 (21%)
Skin	5 (18%)
Prior surgery	20 (71%)
Prior radiotherapy	20 (71%)
Median number of prior systemic therapy lines (range) ^b	2 (1–5)
Setting of prior systemic therapy	
Neoadjuvant	9 (32%)
Adjuvant	10 (36%)
Neoadjuvant + adjuvant	2 (7%)
Advanced	23 (82%)
Prior anticancer agents	
Vincristine	26 (93%)
Doxorubicin	25 (89%)
Ifosfamide	25 (89%)
Cyclophosphamide	22 (79%)
Etoposide	20 (71%)
Irinotecan	17 (61%)
Temozolomide	14 (50%)

Note: Data are n (%) of patients or median (range).

Abbreviations: BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ULN; upper limit of normal.

^aMissing data for 2 patients.

^bAll but one of these lines were chemotherapy-containing lines.

≥4 months), DCR (percentage of patients with response or disease stabilization of any duration), PFS (time from the date of first infusion to the date of disease progression, death from any cause, or last tumor evaluation), PFS at 4 and 6 months, overall survival (OS; time from the date of first infusion to the date of death or loss to follow-up), OS at 6 and 12 months, and pharmacogenomics and safety profile of lurbinectedin.

Statistical analysis

Up to 25 evaluable patients were to be enrolled to test the null hypothesis that 1% or fewer patients would achieve a response to lurbinectedin ($P \leq 0.01$) versus the alternative hypothesis that 10% or

Table 2. Overall efficacy of lurbinectedin treatment in patients with Ewing sarcoma.

	All treated patients (n = 28)
Response by RECIST	
CR	—
PR	4 (14%)
SD	12 (43%)
≥4 months ^a	7 (25%)
<4 months	5 (18%)
PD	9 (32%)
Not evaluable ^b	3 (11%)
ORR (%) (95% CI)	14.3% (4.0%–32.7%)
CBR (%) (95% CI) ^c	39.3% (21.5%–59.4%)
DCR (%) (95% CI) ^d	57.1% (37.2%–75.5%)
DoR	
Events, n/N (%)	3/4 (75%) ^e
Median DoR, months (95% CI)	4.2 (2.9–5.5)
Patients still responding at 4 months (95% CI)	50.0% (1.0%–99.0%)
PFS	
Events, n/N (%)	22/28 (79%)
Median PFS, months (95% CI)	2.7 (1.4–4.3)
4-month PFS (95% CI)	46.2% (27.0%–65.3%)
6-month PFS (95% CI)	23.1% (5.9%–40.3%)
Overall survival	
Events, n/N (%)	17/28 (61%)
Median OS, months (95% CI)	12.0 (8.5–18.5)
6-month OS (95% CI)	88.2% (75.7%–100.8%)
12-month OS (95% CI)	48.5% (27.8%–69.2%)

Abbreviations: CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; DoR, duration of response; ORR, overall response rate; OS, overall survival; PD, disease progression; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

^aIncludes 1 patient who had an unconfirmed PR.

^bThree patients were not evaluable because they had no radiologic assessments during treatment, either due to symptomatic deterioration caused by disease progression ($n = 2$) or early death from malignant disease ($n = 1$).

^cPR or stable disease for ≥4 months.

^dPR or stable disease.

^eOne patient with confirmed PR discontinued treatment after showing clinical deterioration following an episode of disease-related cognitive disorder; this was a decision by the Investigator. No radiologic disease progression was observed at the time of discontinuation, and hence the patient was censored for DoR assessment.

more patients would achieve a response to lurbinectedin ($P \geq 0.10$). The variance of the standardized test was based on the null hypothesis. The type I error (alpha) associated with this one-sided test was 0.025 and the type II error (beta) was 0.2; thus, statistical power was 80%. With these assumptions, the null hypothesis could be rejected if the number of patients who achieved a confirmed response was ≥2.

Frequency tables were prepared for categorical variables. Continuous variables were described using summary tables with the median, mean, standard deviation, minimum, and maximum for each variable. Noncontinuous variables were described using frequency tables with counts and percentages. Binomial exact estimates and 95% confidence intervals (CI) were used to evaluate the primary endpoint (ORR), CBR, and DCR. The Kaplan–Meier method was used to evaluate time-to-event endpoints. For DoR and PFS, patients who did not progress or die by data cutoff were censored at the date of their final tumor evaluation. For OS, patients who were still alive were censored at data cutoff. SAS v.9.4 was used for all statistical analyses.

Table 3. Characteristics of patients with clinical benefit (confirmed response or disease stabilization for ≥ 4 months).

Age (years)/gender/ECOG PS	Location sites	Baseline characteristics				Study treatment characteristics						
		Disease subtype	No. of prior lines	Last therapy/Best response	TTP to last prior therapy (mo)	Cycles received	Sum of target lesions at baseline (mm)	Best response	DoR (mo)	PFS (mo)	OS (mo)	
30/M/0	Lung Pleura	Extra-osseous	2	Vincristine, dactinomycin, cyclophosphamide, ifosfamide, and etoposide/SD	16.6	6	43	SD ≥ 4	—	4.2	38.1+	
58/M/0	Lung Pleura Bone	Extra-osseous	3	Irinotecan, temozolomide/UK	7.8	14	29	SD ≥ 4	—	8.2+	9.9+	
37/M/0	Lung Lymph nodes Bone	Extra-osseous	2	Vincristine, irinotecan, temozolomide/UK	3.2	14	35	PR (54% reduction)	4.2+	8.3+	9.8+	
22/M/1	Skin Subcutaneous tissue Bone	Osseous	2	Vincristine, irinotecan, temozolomide/UK	6.4	9	71	PR (75% reduction)	5.5	7.1	13.4	
24/F/0	Skin Subcutaneous tissue	Osseous	2	Vincristine, irinotecan, temozolomide/NA	22.2	9	32	SD ≥ 4	—	6.4	26.7+	
30/F/0	Lung Bone	Extra-osseous	2	Vincristine, irinotecan/SD	4.8	6	53	SD ≥ 4	—	5.1	14.9	
74/M/1	Lung Lymph nodes Pleura	Extra-osseous	2	Vincristine, irinotecan, temozolomide/SD	2.6	5	82	SD ≥ 4	—	4.0+	18.5	
37/F/0	Bone	Osseous	2	Cyclophosphamide, topotecan/CR	16.7	12	43	SD ≥ 4	—	8.8	20.1+	
30/F/1	Lymph nodes	Extra-osseous	2	Irinotecan, temozolomide/SD	24.7	6	32	SD ≥ 4	—	4.1	9.3	
49/M/1	Lymph nodes Pleura Pericardial effusion	Extra-osseous	2	Irinotecan, temozolomide/PD	2.4	6	85	PR (52% reduction)	2.9	4.1	12.0	
54/M/1	Lung Lymph nodes Pleura	Osseous	1	Vincristine, dactinomycin, ifosfamide/SD	8.4	6	76	PR (57% reduction)	2.9	4.3	19.1	

Abbreviations: CR, complete response; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; F, female; M, male; mo, months; NA, not available; OS, overall survival; PD, disease progression; PFS, progression-free survival; PR, partial response; PS, performance status; SD, stable disease; TTP, time to progression; UK, unknown.

Data sharing statement

Individual participant data are not publicly available because this requirement was not anticipated in the study protocol considering that this trial started patient enrollment in 2015. Clinical trial summary results were placed at ClinicalTrials.gov (<https://www.clinicaltrials.gov>).

Results

Characteristics of patients and treatment

A total of 29 patients with Ewing sarcoma were enrolled into the study between August 25, 2015 and November 16, 2020. Of these, 28 patients were treated with lurbinectedin and were evaluable for both safety and efficacy.

Baseline characteristics of these 28 treated patients are summarized in **Table 1**. Most patients (57%) were male, with median age 33 years (range, 18–74 years). Ewing sarcoma were mostly extraosseous (58%; PNET in 50%); the other 42% were osseous. Ten patients (36%) had ≥ 3 metastatic sites, with the most common sites being lung, bone, and pleura. All patients had received previous systemic therapy, with a median of 2 lines (range, 1–5 lines) each. The most common prior

anticancer agents were vincristine (93%), doxorubicin, ifosfamide (89% each), cyclophosphamide (79%), etoposide (71%), irinotecan (61%), and temozolomide (50%).

A total of 135 treatment cycles were administered, for a median of 4 cycles (range, 1–14 cycles) per patient. Eleven patients (39.3%) received ≥ 6 cycles each. Median relative dose intensity was 97.7% (range, 69.7%–104.5%). Treatment-related AEs resulted in dose administration delays in 7 patients (29%) and dose reduction in 6 patients (25%); all delays and reductions were due to hematologic toxicity (mostly febrile neutropenia).

Efficacy

Median follow-up was 8.3 months (95% CI, 4.0 months—upper limit not reached). PR was observed in 4 patients with extraosseous ($n = 2$) and osseous ($n = 2$) Ewing sarcoma (ORR = 14.3%; 95% CI, 4.0%–32.7%; **Table 2** and **Table 3**). Median DoR was 4.2 months (95% CI, 2.9–5.5 months). Disease stabilization was observed in 12 patients (43%), which lasted ≥ 4 months in 7 of them (25%; **Table 3**). Hence, CBR was 39.3% (95% CI, 21.5%–59.4%) and DCR was 57.1% (95% CI, 37.2%–75.5%). Median PFS was 2.7 months (95% CI,

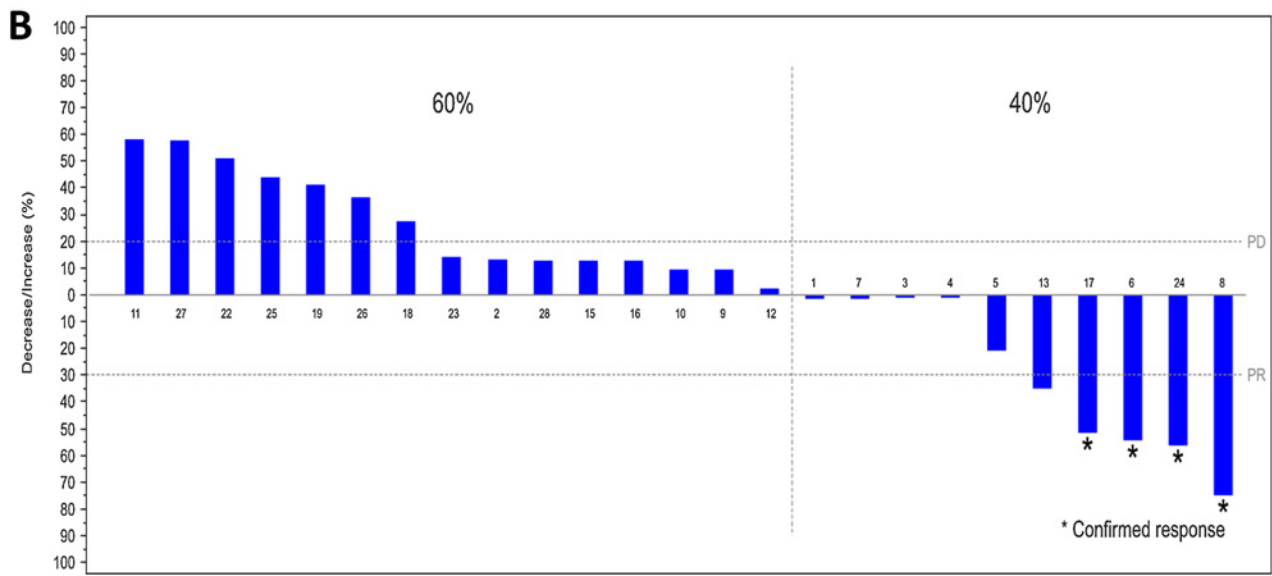
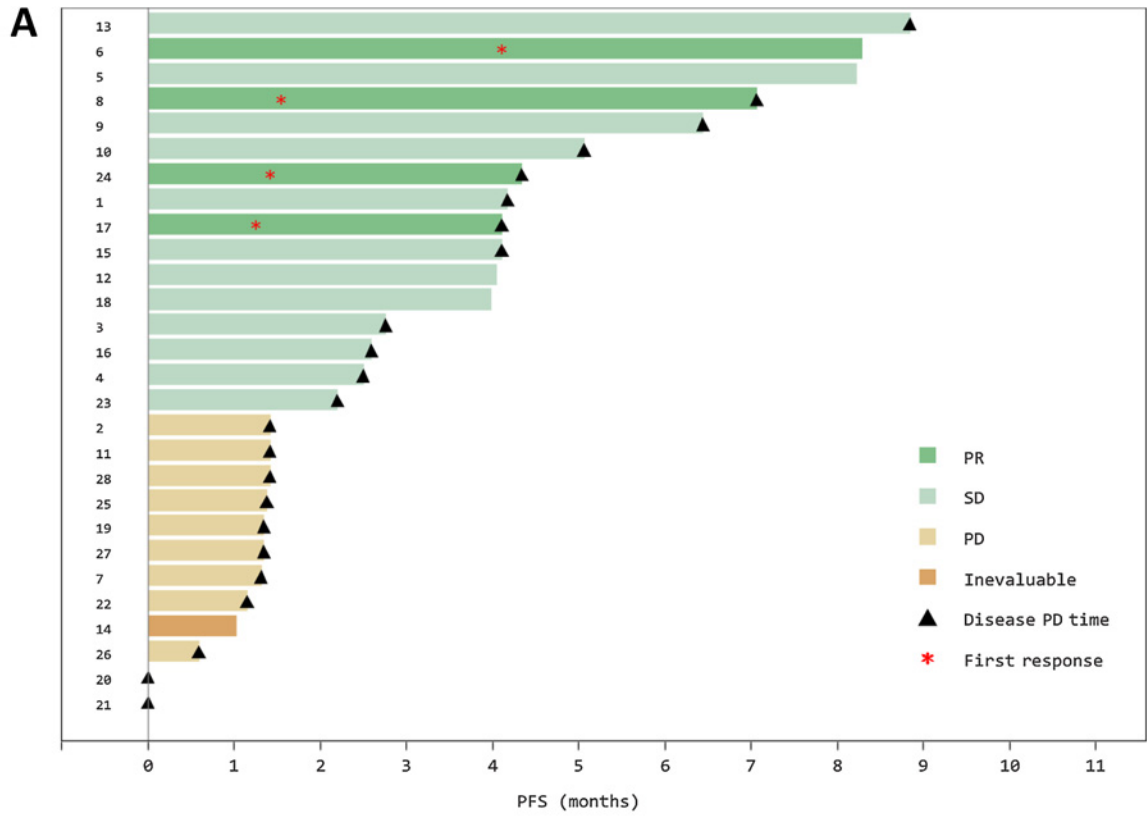


Figure 1. **A**, PFS. Each numbered bar represents a patient with Ewing sarcoma treated with lurbinectedin ($n = 28$). The times when each patient experienced disease progression as per RECIST, and response to treatment, are shown with triangles and asterisks, respectively. **B**, Maximum variation of target lesions in patients with measurable disease and at least one radiologic tumor assessment. Each patient is identified using the same number as in **A**. PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

1.4–4.3 months; **Fig. 1**). With a censoring of 39% (11 of 28 patients alive), median OS was 12.0 months (95% CI, 8.5–18.5 months; **Table 2**).

Ten patients (40%) showed objective tumor shrinkage in target lesions: 7 patients with extraosseous Ewing sarcoma, and 3 with osseous Ewing sarcoma (**Fig. 1** and **Fig. 2**).

After discontinuing lurbinectedin, 19 patients (67.9%) received further antitumor therapy (the most common drugs received were cyclophosphamide, gemcitabine, and ifosfamide). Response to first subsequent therapy was observed in 2 patients (10.5%), neither of whom had shown response to lurbinectedin.

Safety

All 28 treated patients were evaluable for safety (**Table 4**). Most treatment-related AEs and laboratory abnormalities regardless of

relationship were grade 1 or 2. The most common grade 3/4 AEs and abnormalities were hematologic disorders, including neutropenia (57% of patients; grade 4 in 43%), leukopenia (46%; grade 4 in 11%), thrombocytopenia (14%; grade 4 in 4%), grade 3 anemia (14%), and treatment-related febrile neutropenia (14%; grade 4 in 4%). Eleven patients (39.3%) required G-CSF support as secondary prophylaxis or treatment for neutropenia, 3 patients (10.7%) received red blood cell transfusions, and 1 patient (3.6%) received platelet transfusions. No treatment discontinuations or deaths were due to toxicity. Twenty-three patients (82%) discontinued lurbinectedin treatment due to disease progression as per RECIST v.1.1; the other five treatment discontinuations were due to the patient's decision to start another therapy ($n = 2$), multiple cycle delays caused by the study disease or other illnesses ($n = 1$), clinical decline unrelated to treatment ($n = 1$), or death caused by disease progression ($n = 1$).

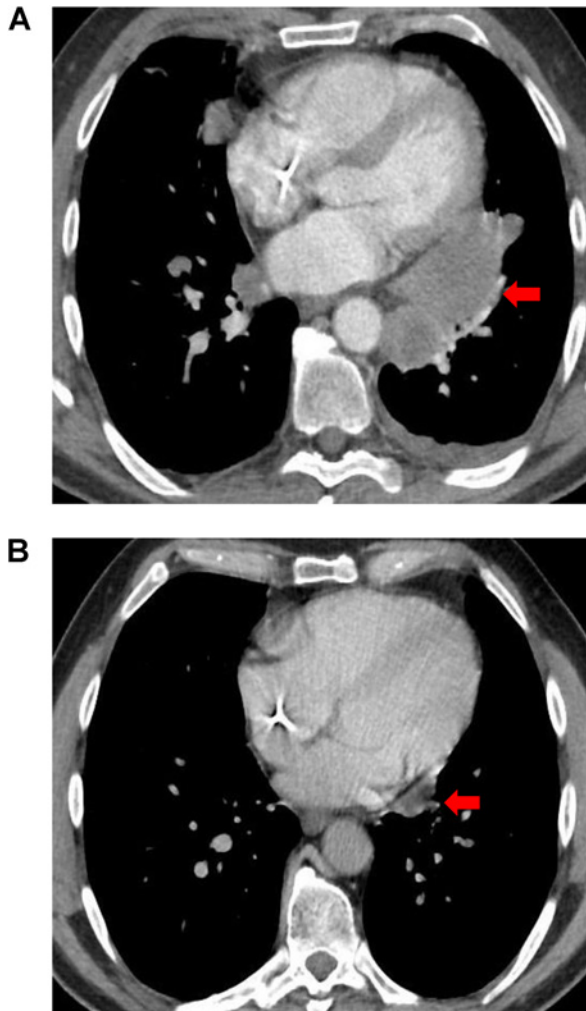


Figure 2.

A, Tumor shrinkage observed in a 54-year-old male with osseous Ewing sarcoma who achieved PR with lurbinectedin. The patient had been pretreated with two lines of chemotherapy for advanced disease. Three target lesions were present at baseline: two in the lung and one in a right hilar lymph node. **B**, After two cycles of treatment with lurbinectedin all target lesions were smaller, with the sum of longest diameters decreasing from 76 to 35 mm (i.e., a tumor shrinkage of 53.9%). In both images, the red arrow shows the location of the lesions. PR, partial response.

Discussion

A total of 28 patients with Ewing sarcoma pretreated with a median of 2 lines of systemic therapy each were treated with lurbinectedin in this Basket phase II trial. Confirmed response assessed by Investigators was observed in 4 patients (ORR = 14.3%), with a median DoR of 4.2 months. Furthermore, 39.3% of patients had clinical benefit (response or disease stabilization for ≥ 4 months) and 57.1% showed disease control (response or disease stabilization of any duration). Of note, 5 patients (18%) had disease stabilization for ≥ 6 months, including 2 patients with ongoing stabilization at 8.2+ and 8.3+ months at the time of study termination. The number of patients with confirmed response assessed by Investigators was higher than the statistical boundary of ≥ 2 responses defined per protocol. Therefore, lurbinectedin at a dose of 3.2 mg/m² given as a 1-hour intravenous infusion every 3 weeks was active in relapsed Ewing sarcoma.

Management of patients with metastatic or treatment refractory Ewing sarcoma is far from established, because robust evidence is lacking. The different polychemotherapy regimens currently used are based on small studies, and are largely dependent on institutional preferences. Patients with relapsed Ewing sarcoma are usually treated with high-dose chemotherapy combinations such as cyclophosphamide and topotecan, or irinotecan and temozolomide with or without vincristine (24–29). Agents used in these regimens have shown little activity against relapsed Ewing sarcoma when given as monotherapies, but synergistic activity when given as combination therapies. For instance, the response rate reported for topotecan in recurrent and refractory Ewing sarcoma increased from 7% as single agent (24, 30) to 32%–35% when combined with cyclophosphamide (24, 26). The current study had the limitation of not including patients aged <18 years, a population with a high incidence of Ewing sarcoma. Nevertheless, the response rate of 14.3% observed herein for single-agent lurbinectedin warrants further development of the drug in the treatment of relapsed Ewing sarcoma. Combination of lurbinectedin with irinotecan or temozolomide might improve the antitumor activity of single-agent lurbinectedin in relapsed Ewing sarcoma. An ongoing phase Ib/II trial (NCT02611024) is currently evaluating lurbinectedin in combination with irinotecan in advanced solid tumors, including Ewing sarcoma (31).

The safety profile of single-agent lurbinectedin was manageable. Reversible myelosuppression was the most common toxicity, and was managed with cycle delays, dose reductions, G-CSF support, and transfusions. Severe hematologic abnormalities were more frequent in this cohort of patients with Ewing sarcoma than in a cohort of patients with second-line SCLC in this same Basket study (32), and

Table 4. Laboratory abnormalities and treatment-related AEs in patients with Ewing sarcoma treated with lurbinectedin.

NCI-CTCAE grade	All treated patients (n = 28)			
	1-2	3	4	Total
Hematologic laboratory abnormalities				
Anemia	20 (71%)	4 (14%)	—	24 (86%)
Leukopenia	11 (39%)	10 (36%)	3 (11%)	24 (86%)
Neutropenia	3 (11%)	4 (14%)	12 (43%)	19 (68%)
Thrombocytopenia	12 (43%)	3 (11%)	1 (4%)	16 (57%)
Biochemical laboratory abnormalities				
Creatinine increased	23 (82%)	1 (4%)	—	24 (86%)
ALT increased	19 (68%)	2 (7%)	—	21 (75%)
GGT increased	17 (61%)	—	—	17 (61%)
AST increased	15 (54%)	—	—	15 (54%)
AP increased	14 (50%)	—	—	14 (50%)
Bilirubin increased	3 (11%)	—	—	3 (11%)
CPK increased	2 (7%)	1 (4%)	—	3 (11%)
Treatment-related AEs				
Fatigue	11 (39%)	—	—	11 (39%)
Nausea	8 (29%)	—	—	8 (29%)
Decreased appetite	4 (14%)	—	—	4 (14%)
Febrile neutropenia	—	3 (11%)	1 (4%)	4 (14%)
Diarrhea	3 (11%)	—	—	3 (11%)
Headache	3 (11%)	—	—	3 (11%)
Peripheral neuropathy	3 (11%)	—	—	3 (11%)
Gastroesophageal reflux disease	2 (7%)	—	—	2 (7%)
Arthralgia	1 (4%)	—	—	1 (4%)
Constipation	1 (4%)	—	—	1 (4%)
Pyrexia	1 (4%)	—	—	1 (4%)
Upper respiratory tract infection	1 (4%)	—	—	1 (4%)
Vomiting	1 (4%)	—	—	1 (4%)

Note: Data are n (%) of patients. Hematologic and biochemical abnormalities are shown regardless of relationship to treatment.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; GGT, gamma-glutamyltransferase; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

among patients with platinum-resistant ovarian cancer in a randomized phase III trial (33). Thus, higher incidences were observed in patients with Ewing sarcoma for grade 3/4 neutropenia (57% vs. 46% and 32% respectively), grade 3/4 thrombocytopenia (14% vs. 7% and 9%), and treatment-related febrile neutropenia (14% vs. 5% and 5.5%). This is likely due to a heavier pretreatment with chemotherapy in the cohort of patients with Ewing sarcoma compared to the other two populations, taking into account that current management of primary Ewing sarcoma consists of high-dose induction chemotherapy to reduce the primary tumor and target microscopic disease, followed by consolidation chemotherapy to remove any residual cells (34). Patients with relapsed Ewing sarcoma in this trial received a median of 2 prior chemotherapy-containing regimens. Overall, these results suggest that primary G-CSF prophylaxis should be given to patients with relapsed Ewing sarcoma while on treatment with lurbinectedin.

In conclusion, this single-arm phase II study showed signs of antitumor activity with lurbinectedin used as monotherapy at 3.2 mg/m² every 3 weeks in patients with relapsed Ewing sarcoma, with a manageable safety profile. Lurbinectedin could represent a valuable addition to therapies currently used in the management of these complex diseases, which constitute a highly unmet medical need.

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