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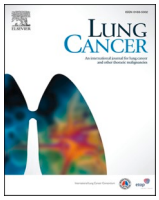

Lurbinectedin in patients with small cell lung cancer with chemotherapy-free interval ≥30 days and without central nervous metastases

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ABSTRACT

Objectives: This report focuses on lurbinectedin activity and safety in a subgroup of small cell lung cancer (SCLC) patients from a Basket phase 2 study (Trigo *et al. Lancet Oncology* 2020;21:645–654) with chemotherapy-free interval (CTFI) ≥ 30 days. This pre-planned analysis was requested for obtaining regulatory approval of lurbinectedin in Switzerland.

Materials and methods: Patients with extensive-stage SCLC, no central nervous system (CNS) metastases, and disease progression after platinum-containing therapy were included. Topotecan data from a contemporary, randomized, controlled phase 3 study (ATLANTIS) were used as indirect external control in a matched patient population (n = 98 patients).

Results: Lurbinectedin showed a statistically significant higher overall response rate (ORR) by investigator assessment (IA) compared to topotecan subgroup (41.0 % *vs.* 25.5 %; p = 0.0382); higher ORR by Independent Review Committee (IRC) (33.7 % *vs.* 25.5 %); longer median duration of response (IA: 5.3 *vs.* 3.9 months; IRC: 5.1 *vs.* 4.3 months), and longer median overall survival (10.2 *vs.* 7.6 months). Grade ≥ 3 hematological abnormalities were remarkably lower with lurbinectedin: anemia 12.0 % *vs.* 54.1 %; leukopenia 30.1 % *vs.* 68.4 %; neutropenia 47.0 % *vs.* 75.5 %, and thrombocytopenia 6.0 % *vs.* 52.0 %. Febrile neutropenia was observed at a higher incidence with topotecan (6.1 % *vs.* 2.4 % with lurbinectedin) despite that the use of growth-colony stimulating factors was mandatory with topotecan.

Conclusion: With the limitations of an indirect comparison, however using recent and comparable SCLC datasets, this *post hoc* analysis shows that SCLC patients with CTFI ≥ 30 days and no CNS metastases have a positive benefit/risk ratio with lurbinectedin, superior to that observed with topotecan.

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1. Introduction

Lurbinectedin was evaluated in a multicenter, open-label, Basket phase 2 study in nine cohorts of patients with different difficult-to-treat tumor types to establish the proof of concept for clinical development [1–5]. Based on the results observed in a cohort of 105 patients with pretreated small cell lung cancer (SCLC) [1], lurbinectedin was approved first in the United States [6] and later in several other countries worldwide. Furthermore, and based on these same results, the European Society of Medical Oncology (ESMO) and the US National Comprehensive Cancer Network (NCCN) guidelines incorporated lurbinectedin as an option for the second-line treatment of SCLC patients [7,8].

Topotecan was, until the approval of lurbinectedin, the only approved agent in the last two decades for the second-line treatment of metastatic SCLC. In ESMO guidelines [7], either oral or intravenous topotecan is recommended for patients with platinum-resistant or platinum-sensitive relapse. The NCCN SCLC panel recommends either oral or intravenous topotecan as a recommended regimen for patients with relapsed SCLC [8]. However, topotecan use is challenging because of the associated hematological toxicity along with the modest clinical benefit.

One of the most recent lurbinectedin approvals (Switzerland, March 2023) was granted for the treatment of patients with metastatic SCLC with disease progression after platinum-containing therapy, with a CTFI $\geq$ 30 days and with no central nervous system (CNS) metastases. A previous publication showed data for the whole cohort of 105 SCLC patients [1]. This report focuses on the results used for obtaining approval in Switzerland, which were based on a pre-planned analysis in a subgroup of 83 SCLC patients. Based on the recommendations from guidelines such as ICH E10 and EMEA/759784/2010, the topotecan results from a contemporary, randomized, controlled phase 3 study (ATLANTIS) [9] were used as indirect external control in a matched patient population.

2. Material and methods

The Basket phase 2 study and the ATLANTIS phase 3 study were registered at https://www.clinicaltrials.gov (NCT02454972 and NCT02566993, respectively), and the study protocol and main results in SCLC patients have been described elsewhere [1,9]. The key design features for these two studies are summarized in Table 1. Both studies were approved by the ethical committees related to the institution in which it was performed and all patients gave their informed consent.

Briefly, in the SCLC cohort of the Basket phase 2 study, eligible subjects were adult patients with Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 2 and pathologically confirmed SCLC with relapse after only one prior platinum-containing chemotherapy line (other therapies such as immunotherapy could have been previously administered as a second line). Patients with both resistant (CTFI $<$ 90 days) or sensitive disease (CTFI $\geq$ 90 days) were treated with lurbinectedin 3.2 mg/m^2 administered as a 1-hour intravenous (i.v.) infusion every three weeks (q3wk). Primary granulocyte colony-stimulating factors (G-CSFs) prophylaxis was not allowed. The primary endpoint was confirmed overall response rate (ORR) per the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 according to the Investigator assessment (IA). An independent blinded review of tumor response by an Independent Review Committee (IRC) was added as a secondary objective to confirm the investigator's assessment as well as to minimize the data interpretation bias. Other secondary endpoints were duration of response (DoR), clinical benefit rate (objective response or stable disease [SD] $\geq$ 4 months), disease control rate (objective response or SD), progression-free survival (PFS), overall survival (OS), and evaluation of safety. Adverse events (AEs) and laboratory values were graded according to the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE), v. 4.0.

Table 1
Key design features of the basket study and ATLANTIS.

Design feature	Basket study	ATLANTIS
Study design	Multicenter, open-label, uncontrolled, Basket phase 2 study	Multicenter, open label, randomized, controlled, phase 3 study
Patient population	Patients with SCLC previously treated with one prior chemotherapy-containing line of therapy	Patients with SCLC who failed one prior platinum-containing regimen
Number of patients	SCLC cohort: n = 105	Topotecan subgroup: n = 122
Patient population selected for cross-trial comparison (i.e., matched population)	CTFI $\geq$ 30 days and no CNS metastases: n = 83	CTFI $\geq$ 30 days and no CNS metastases Topotecan: n = 98
Treatment regimen	**Lurbinectedin** i.v. 3.2 mg/m^2 on Day 1 q3wk	**Topotecan** i.v. daily on Days 1–5 q3wk (according to local label), at the following doses: – 1.50 mg/m^2 daily for patients with calculated CrCL $\geq$ 60 mL/min. – 1.25 mg/m^2 daily for patients with calculated CrCL between 40 and 59 mL/min. – 0.75 mg/m^2 daily for patients with calculated CrCL between 30 and 39 mL/min.
Dose reductions	Two dose reductions permitted for grade 3 or 4 toxicities	Two dose reductions permitted for grade 3 or 4 toxicities
Dose delays	Dose delays $\leq$ 3 weeks permitted to allow recovery from treatment-associated toxicities	Dose delays $\leq$ 3 weeks permitted to allow recovery from treatment-associated toxicities
Primary prophylaxis	Antiemetics	Antiemetics; G-CSF
Primary endpoint	ORR by investigator assessment according to RECIST v1.1 (confirmed responses)	OS
Secondary endpoints	DoR, PFS, OS, and ORR by IRC	OS/PFS per RECIST v.1.1 in patients with and without CNS involvement at baseline PFS by IRC ORR by IRC DoR by IRC
Key inclusion criteria for SCLC patients	Pathologically proven diagnosis of SCLC	Histologically or cytologically confirmed diagnosis of limited or extensive stage SCLC
	Documented progression after first-line platinum-based chemotherapy with disease measurable by RECIST v1.1	Failure of one prior platinum-containing regimen and with a CTFI $\geq$ 30 days.
	ECOG PS 0 to 2	ECOG PS 0 to 2
	Adequate organ function	Adequate organ function
	Age $\geq$ 18 years	Age $\geq$ 18 years
Key exclusion criteria for SCLC patients	Prior lurbinectedin or trabectedin treatment	Prior treatment with lurbinectedin, topotecan, or anthracyclines. More than one prior chemotherapy-containing regimen. Patients who never received any platinum-containing regimen for SCLC treatment.
	Known CNS involvement, with brain imaging at baseline	Limited-stage patients who were candidates for local or regional therapy, including PCI, thoracic radiotherapy

(*continued on next page*)

Table 1 (*continued*)

Design feature	Basket study	ATLANTIS
		or both, had to have been offered that option and completed treatment or refused it prior to randomization. Symptomatic, or steroid-requiring, or progressing CNS disease involvement during at least four weeks prior to randomization.
	Radiotherapy (>30 Gy) ≤ 28 days before treatment. Palliative radiotherapy (≤30 Gy total dose) ≤ 14 days before treatment. Last chemotherapy ≤ 21 days before treatment.	Impending need for palliative radiotherapy or surgery for pathological fractures and/or for medullary compression within four weeks prior to randomization.
Patient accrual period	16 October 2015 – 15 October 2018	25 August 2016 – 30 July 2018
Safety monitoring	AEs, graded by NCI-CTCAE v4.0 Hematology and blood chemistry (Day 1,8 and 15 in Cycles 1 and 2; thereafter, Day 1). Urinalysis, vital signs, and physical exam each cycle	AEs, graded by NCI-CTCAE v4.0 Hematology and blood chemistry (Day 1 and 10 in Cycles 1 and 2; thereafter, Day 1). Urinalysis, vital signs, and physical exam each cycle

Abbreviations: AEs, adverse events; CNS, central nervous system; CrCL; creatinine clearance; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; G-CSF, growth colony-stimulating factors; Gy, greys; i.v., intravenous (ly); NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

ATLANTIS was a randomized, controlled, phase 3 clinical trial comparing lurbinectedin plus doxorubicin *versus* physician's choice of control therapy (cyclophosphamide, doxorubicin and vincristine [CAV] or topotecan). Adult patients were eligible to participate if they had ECOG performance status ≤ 2, pathologically confirmed SCLC with relapse after one prior platinum-containing chemotherapy regimen, and CTFI ≥ 30 days. This phase 3 study did not provide a direct comparison of lurbinectedin monotherapy *versus* topotecan, as the experimental arm was a combination of lurbinectedin at a reduced dose (2.0 mg/m^2) and doxorubicin 40 mg/m^2. Topotecan was administered in the control arm as 1.5 mg/m^2 daily on Days 1 to 5 q3wk with dose reductions for patients with creatinine clearance < 60 mL/min. The primary endpoint was OS. Secondary endpoints included PFS by IRC, and ORR and DoR according to RECIST v.1.1 by IRC, and safety (AEs and laboratory values were graded according to the NCI-CTCAE, v. 4.0).

Inclusion criteria in the Basket study had no restriction with respect to CTFI, and patients with known CNS involvement were excluded (screening of CNS metastases at baseline was mandatory). Inclusion criteria in ATLANTIS study stated that all patients had to have CTFI ≥ 30 days and symptomatic, or steroid-requiring, or progressive CNS disease involvement for ≥ 4 weeks before randomization were excluded (asymptomatic, non-progressing patients taking steroids in the process of already being tapered within two weeks before randomization were allowed). Therefore, to allow comparability, from all patients treated with lurbinectedin in the SCLC cohort in the Basket study (n = 105) and from all patients treated with topotecan in ATLANTIS trial (n = 122), a matched cohort was generated (n = 83 and n = 98, respectively) based on selecting those patients with CTFI ≥ 30 days and without CNS metastases.

Twenty-one SCLC patients from Basket study had CTFI < 30 days, and one patient was included and treated with CNS metastases present at baseline (protocol deviation); these 22 patients were excluded in this *post hoc* analysis (Fig. 1).

Twenty-two SCLC patients from ATLANTIS topotecan subgroup had CNS metastases (one of them with CTFI < 30 days, protocol deviation), one patient had CTFI < 30 days (protocol deviation), and one patient was randomized to receive topotecan but was finally treated with lurbinectedin plus doxorubicin (this was a major protocol deviation that resulted in the patient discontinuing treatment after Cycle 1). These 24 patients were excluded in this *post hoc* analysis (Fig. 1).

3. Results

The Basket study was conducted between October 2015 and November 2020, and the ATLANTIS study was conducted between August 2016 and February 2020. The choice of the matching factors (CTFI ≥ 30 days and no CNS metastases) was based on reasons related to protocol differences, but both studies were contemporaneous and the overall information on baseline characteristics collected was very similar and included a comprehensive number of prognostic and demographic characteristics well described in the literature. The lurbinectedin and topotecan matched populations had similar median age (60 *vs.* 63 years, respectively), time from diagnosis to study entry (8.5 *vs.* 9.1 months), disease control rates (response plus stable disease) on first-line chemotherapy (97.6 % *vs.* 88.7 %), median CTFI following first-line chemotherapy (3.9 *vs.* 4.2 months), and percentage of patients with resistant disease (CTFI 30–90 days; 28.9 % *vs.* 29.6 %) (Table 2). Other prognostic factors, such as lactate dehydrogenase (LDH), ECOG performance status or liver metastases before treatment, were similar in both populations. The evaluated data were from two independent studies and, therefore. the full balance expected from a head-to-head, randomized comparison was not possible. Some baseline factors, such as bulky disease or prior response to platinum, could favor the lurbinectedin data. However, other factors were not in favor of lurbinectedin: for instance, more patients with ECOG PS 2 treated with lurbinectedin; all patients had extensive disease while 12.2 % of patients treated with topotecan had limited disease; more patients with paraneoplastic syndrome treated with lurbinectedin; more patients treated with two prior lines; or shorter CTFI and less patients with CTFI ≥ 180 days.

Efficacy outcomes for lurbinectedin and topotecan for second-line treatment of SCLC in patients with CTFI ≥ 30 days and no CNS metastases, based on results from the matched population in Basket and ATLANTIS studies, are summarized in Table 3. In this population, lurbinectedin showed at the nominal significance level of 0.05 (two-sided) a statistically significant higher ORR by IA compared to topotecan (41.0 % *vs.* 25.5 %; p = 0.0382 in Fisher's exact test); higher ORR by IRC (33.7 % *vs.* 25.5 %; p = 0.2533); longer median DoR (IA: 5.3 *vs.* 3.9 months, log-rank p = 0.7323; IRC: 5.1 *vs.* 4.3 months, p = 0.6102), and longer median OS n (10.2 *vs.* 7.6 months; log-rank p = 0.3037).

Table 4 summarizes the occurrence of AEs in the matched patient population in each study. Lurbinectedin had a notably lower incidence with respect to topotecan in terms of grade ≥ 3 AEs (55.4 % *vs.* 90.8 % regardless of relationship; 41.0 % *vs.* 82.7 % related to treatment); AEs leading to dose reduction (24.1 % *vs.* 49.0 %; 24.1 % *vs.* 48.0 % related to treatment), AEs leading to treatment discontinuation (3.6 % *vs.* 18.4 %; 0 % *vs.* 15.3 % related to treatment), and AEs leading to death (1.2 % *vs.* 8.2 %; 0 % *vs.* 4.1 % related to treatment).

The AE profile observed mostly consisted of fatigue and gastrointestinal events, although the incidence of grade ≥ 3 AEs was higher in the ATLANTIS topotecan subgroup, particularly for fatigue (Table 4). Febrile neutropenia was observed at a higher incidence with topotecan (6.1 % *vs.* 2.4 % with lurbinectedin) despite that the use of growth-colony stimulating factors (G-CSF) was mandatory in ATLANTIS (Table 4). Alopecia was observed only with topotecan.

The incidence for most of the grade ≥ 3 hematological abnormalities was remarkably lower with lurbinectedin in the Basket study when compared to topotecan ATLANTIS subgroup: anemia 12.0 % *vs.* 54.1 %; leukopenia 30.1 % *vs.* 68.4 %; neutropenia 47.0 % *vs.* 75.5 %, and

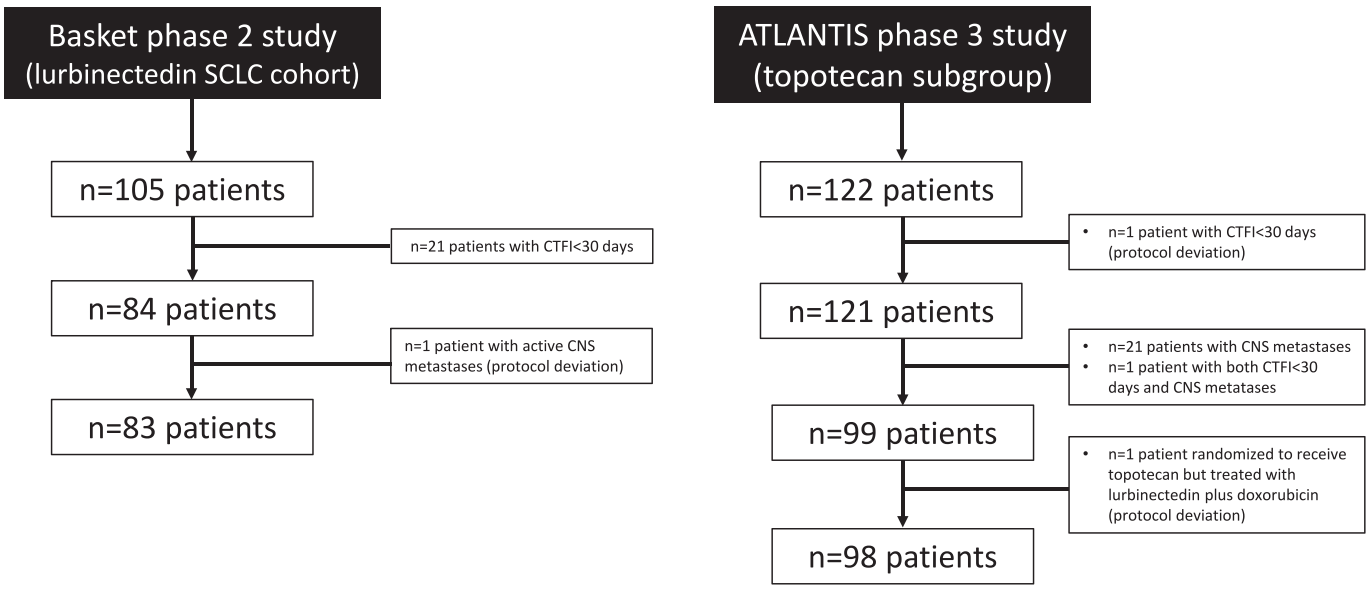

Fig. 1. Flow chart for the selection of the matched population: patients with chemotherapy-free interval ≥ 30 days and without central nervous system metastases treated with lurbinectedin in the Basket phase 2 study (small cell lung cancer cohort) and treated with topotecan in the ATLANTIS phase 3 study.

thrombocytopenia 6.0 % *vs.* 52.0 % (Table 4). In agreement with these findings, less patients in the Basket study required G-CSF therapeutic support (13.3 % *vs.* 22.4 %), red blood cell transfusions (10.8 % *vs.* 46.9 %), platelets transfusions (2.4 % *vs.* 16.3 %) and erythropoietin support (2.4 % *vs.* 12.2 %) compared to topotecan in ATLANTIS (Table 4).

No relevant differences were observed in biochemical abnormalities (Table 4).

4. Discussion

Most second-line treatment datasets available in SCLC might be considered as obsolete in terms of SCLC management in general [10,11]. In this analysis, the results with lurbinectedin reported in the SCLC cohort of a phase 2 Basket trial were compared to data obtained with topotecan in SCLC patients from a contemporary randomized phase 3 trial in a matched population, which was defined as patients with CTFI ≥ 30 days and without CNS metastases. With the inherent limitations of an indirect comparison, ATLANTIS can be considered an appropriate external control for efficacy and safety of topotecan in the selected patient population, based on the recommendations in the guidelines ICH E10 and EMEA/759784/2010. An indirect comparison of clinical trial efficacy data with historical data from confirmatory trials of the reference treatment might only be considered an adequate alternative to a direct comparison under certain conditions (EMEA/759784/2010). Namely, the selected historical/external trial is a randomized, controlled clinical trial that was planned, conducted, and reported to high standards with methods of data collection, synthesis and analysis, for efficacy and for safety data. ATLANTIS was planned, conducted, and reported by the same Sponsor than the Basket study using similar case report forms and the same clinical data management system (i.e., Medidata Rave). The Sponsor therefore had full oversight of all clinical trial operations, and both studies were conducted using the same high standards. Furthermore, the Sponsor had access to the full study dataset, which is preferable to reference to published data in the public domain. The ATLANTIS study was run in parallel with the Basket trial and several factors did not differ to an important degree: e.g., the region of trial sites (both were conducted in the European Union and United States), main characteristics of patient population, background standard of care/concomitant medication or endpoints, or the frequency of tumor evaluations. Additionally, the ESMO Clinical Practice recommendations for second-line treatment of SCLC did not change between the start of Basket study and the start of the ATLANTIS study, indicating no changes in standard of care/background therapy between the two studies. Data were very mature, with long follow-up and number of events close to 90 %.

This *post hoc* analysis shows overall higher activity for lurbinectedin, with an ORR by IA of 41.0 %, which almost doubled that of topotecan of 25.5 %. Interestingly, the ATLANTIS efficacy results observed for topotecan were comparable to the previously published data [12–15]. For instance, von Pawel *et al.,* [14] conducted a randomized phase 3 trial comparing i.v. topotecan to CAV in relapsed SCLC with CTFI at least higher than 60 days and found an ORR for topotecan of 24.3 %. Eckardt *et al.* [13] performed a randomized phase 3 clinical trial to compare oral and i.v. topotecan in relapsed SCLC (8.6 % of patients had CTFI < 90 days) and found and ORR for i.v. topotecan of 21.9 %. It is noted that studies reporting ORR for topotecan in SCLC included mainly populations with sensitive disease, and results are variable depending on the CTFI and the criteria used to evaluate antitumour activity [10,11,13,14,16–21]. The most recent phase 3 trials reported an ORR of 16–21 % for topotecan alone or for chemotherapy groups including topotecan in the second-line setting [10,18–21]. A systematic review and meta-analysis of 1347 SCLC patients showed for patients with sensitive disease (CTFI > 60 days) a response rate of 17 % (95 % CI, 11–23 %) [12].

All extensive stage SCLC treated patients eventually show disease relapse, and the majority of them is eligible for second-line therapy. Selection of second-line chemotherapy depends on the CTFI after the first line. The disease is usually theoretically considered platinum sensitive if CTFI ≥ 90 days; resistant if CTFI < 90 days, and refractory if the patient does not respond on first-line chemotherapy (CTFI < 30 days) [22,23]. CTFI is a continuous measure, and the cut-off of 90 days is arbitrary and does not have a clear biological support at the individual level. However, the length of response to initial treatment influences the likelihood of response to subsequent cytotoxic treatment. If the disease free-interval is less than 90 days from the last day of initial treatment (resistant relapse) or there was no initial response (refractory disease), most agents or regimens demonstrate low response rates (<10 percent) [8]. In particular, patients with SCLC and CTFI < 30 days are considered to have refractory disease and have the worst prognosis. Twenty-one of 105 SCLC patients treated in the Basket study had CTFI < 30 days and, as expected, results were the poorest: ORR by IA and IRC of 14.3 % and 9.5 %, respectively, and median OS of 4.7 months. On the contrary, data

Table 2
Key population characteristics in the indirect comparison of lurbinectedin (Basket phase 2 study, small cell lung cancer cohort) and topotecan (ATLANTIS phase 3 study) in a matched population: patients with chemotherapy-free interval ≥ 30 days and without central nervous system metastases.

		Basket phase 2 study SCLC cohort Lurbinectedin (n = 83)	ATLANTIS phase 3 study Topotecan subgroup (n = 98)
Age (years)	**Median (range)**	60 (41–83)	63 (37–77)
	<65 years	57 (68.7 %)	61 (62.2 %)
	≥65 years	26 (31.3 %)	37 (37.8 %)
Gender	**Male**	48 (57.8 %)	60 (61.2 %)
	Female	35 (42.2 %)	38 (38.8 %)
Race	**White**	66 (79.5 %)	88 (89.8 %)
	Non-white	2 (2.4 %)	2 (2.0 %)
	UK/NA	15 (18.1 %)	8 (8.2 %)
ECOG PS	**0/1**	80 (96.4 %)	97 (99.0 %)
	2	3 (3.6 %)	1 (1.0 %)
BSA (m^2)	**Median (range)**	1.8 (1.4–2.6)	1.8 (1.5–2.6)
Smoke status	**Current/ Former**	76 (91.6 %)	92 (93.9 %)
	Never	7 (8.4 %)	6 (6.1 %)
Stage at study entry	**Limited**	0 (0.0 %)	12 (12.2 %)
	Extensive	83 (100.0 %)	86 (87.8 %)
Number of sites	**Median (range)**	3 (1–6)	4 (2–11)
	Liver	31 (37.3 %)	37 (37.8 %)
	Lymph nodes	67 (80.7 %)	69 (70.4 %)
	Adrenal	20 (24.1 %)	23 (23.5 %)
Paraneoplastic syndrome		8 (9.6 %)	4 (4.1 %)
Bulky disease (one lesion > 50 mm)		23 (27.7 %)	36 (36.7 %)
LDH (x ULN)	**Median (range)**	0.9 (0.2–6.2)	1 (0.4–6.3)
	≤ ULN	48 (58.5 %)	52 (53.6 %)
	> ULN	34 (41.5 %)	45 (46.4 %)
Albumin (g/dL)	**Median (range)**	4.1 (2.9–5.1)	4.2 (3–5.1)
Prior systemic lines of chemotherapy	**Median (range)**	1 (1–2)	1 (1–1)
	1	77 (92.8 %)	98 (100.0 %)
	2	6 (7.2 %)	–
Response to prior platinum-based therapy	**CR**	8 (9.6 %)	2 (2.0 %)
	PR	61 (73.5 %)	64 (65.3 %)
	SD	12 (14.5 %)	21 (21.4 %)
	PD	–	5 (5.1 %)
	UK	2 (2.4 %)	6 (6.1 %)
CTFI (months)	**Median (range)**	3.9 (1.1–16.1)	4.2 (1–24.2)
	CTFI 30–90 days	24 (28.9 %)	29 (29.6 %)
	CTFI ≥ 90 days	59 (71.1 %)	69 (70.4 %)
	≥180 days	19 (22.9 %)	28 (28.6 %)
Prior radiotherapy	**PCI**	58 (69.9 %)	50 (51.0 %)
Prior immunotherapy		7 (8.4 %)	4 (4.1 %)
Time from diagnosis to registration/ randomization (months)	**Median (range)**	8.5 (4.6–20)	9.1 (3.5–29.7)

Abbreviations: BSA, body surface area; CR, complete response; CTFI, chemotherapy-fee interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; NA, not available; PCI, prophylactic cranial irradiation; PD, disease progression; PR, partial response; SCLC, small cell lung cancer; SD; stable disease; UK, unknown; ULN, upper limit of normal.

from a pre-planned subset of SCLC patients with CTFI ≥ 180 days from the Basket trial showed and ORR of 60.0 % (95 %CI, 36.1–86.9 %) [24]. Nevertheless, as around 10 % of patients with refractory disease achieved response to lurbinectedin, there can be an advantage in terms of safety for lurbinectedin in comparison with topotecan.

Table 3
Efficacy outcomes in the indirect comparison of lurbinectedin (Basket phase 2 study, small cell lung cancer cohort) and topotecan (ATLANTIS phase 3 study) in a matched population: patients with chemotherapy-free interval ≥ 30 days and without central nervous system metastases.

	Basket phase 2 study SCLC cohort Lurbinectedin (n = 83)		ATLANTIS phase 3 study Topotecan subgroup (n = 98)	
	IA	**IRC**	**IA**	**IRC**
ORR, % (95 % CI)	41.0 (30.3–52.3)	33.7 (23.7–44.9)	25.5 (17.2–35.3)	25.5 (17.2–35.3)
DoR (months), median (95 % CI)	5.3 (3.5–5.9)	5.1 (4.8–5.9)	3.9 (3.0–5.7)	4.3 (3.0–5.6)
PFS (months), median (95 % CI)	4.0 (2.6–4.7)	3.7 (2.6–4.6)	4.2 (3.0–4.8)	4.1 (2.9–4.7)
OS (months), median (95 % CI)	10.2 (7.6–12.0)		7.6 (6.1–10.3)	
% events	74 (89.2 %)		80 (81.6 %)	
Censored	9 (10.8 %)		18 (18.4 %)	

Abbreviations: CI, confidence interval; DoR, duration of response; IA, investigator assessment; IRC, Independent Review Committee; ORR, overall response rate; PFS, progression free survival; OS, overall survival.

Recently published pooled safety data from 554 patients (335 from all nine tumor-specific cohorts of the phase 2 Basket trial and 219 from the phase 3 CORAIL trial in ovarian cancer) [25] confirmed that single-agent lurbinectedin 3.2 mg/m^2 on Day 1 q3wk has a manageable safety profile in patients with advanced solid tumors, with the most common severe toxicity being transient and reversible myelosuppression: grade ≥ 3 neutropenia (41 %), grade ≥ 3 anemia (17 %) and grade ≥ 3 thrombocytopenia (10 %). Consistency was observed between the safety profile of lurbinectedin in this pooled population and the profiles previously reported in single cohorts from the phase 2 Basket trial in patients with relapsed SCLC [1], Ewing sarcoma [2], breast cancer [4], neuroendocrine tumors [3], endometrial cancer [5], and in the phase 3 trial in patients with relapsed ovarian cancer [26].

A favorable safety profile was observed in this *post hoc* analysis for lurbinectedin compared to topotecan, especially for hematological toxicities. In addition, direct comparison with topotecan is available from a randomized phase 3 trial (CORAIL) in patients with platinum-resistant ovarian cancer: grade 3 anemia, grade ≥ 3 neutropenia and grade 3 thrombocytopenia were statistically less frequent with lurbinectedin ($p < 0.0001$) [26]. Severe hematological abnormalities more common with topotecan involves requirement of more frequent use of supportive care (G-CSF support, erythropoietin support, RBC transfusions and platelets transfusions) compared to lurbinectedin. This advantageous safety profile of lurbinectedin may help to counteract the significant health resources consumption observed in patients with relapsed SCLC treated with topotecan. In accordance, a recent study done in the United States has shown lurbinectedin as a cost-effective second-line treatment for patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy, with the acquisition cost partially offset by the lower myelosuppression prophylaxis cost [27]. Reinforcing this concept, results from phase 2 Basket, and ATLANTIS and CORAIL phase 3 studies consistently showed a low number of hospitalizations due to serious adverse events in patients treated with lurbinectedin compared to patients treated with topotecan (Table 5).

5. Conclusion

Based on the efficacy and safety outcomes shown in this *post hoc* analysis, patients with CTFI ≥ 30 days and no CNS metastases have a positive benefit/risk ratio with lurbinectedin, superior to that reported with topotecan. Lurbinectedin is more active, as measured by all usual outcomes metrics, and is clearly less toxic and better tolerated than topotecan. An ongoing confirmatory phase 3 trial (LAGOON, registered

Table 4
Overview of adverse events, support for hematological toxicities, most common treatment-related adverse events (≥5% of patients) and laboratory abnormalities regardless of their relationship in the indirect comparison of lurbinectedin (Basket phase 2 study, small cell lung cancer cohort) and topotecan (ATLANTIS phase 3 study) in a matched population: patients with chemotherapy-free interval ≥ 30 days and without central nervous system metastases.

Patients with:	Basket phase 2 study SCLC cohort Lurbinectedin (n = 83)		ATLANTIS phase 3 study Topotecan subgroup (n = 98)	
	n	%	n	%
Adverse events				
Regardless of relationship, any grade	81	97.6	97	99.0
Regardless of relationship, grade ≥ 3	46	55.4	89	90.8
Treatment-related (or with unknown relationship), any grade	73	88.0	92	93.9
Treatment-related (or with unknown relationship), grade ≥ 3	34	41.0	81	82.7
Adverse events leading to dose reduction	20	24.1	48	49.0
Treatment-related (or with unknown relationship), any grade	20	24.1	47	48.0
Adverse events leading to treatment discontinuation	3	3.6	18	18.4
Treatment-related (or with unknown relationship), any grade	.	.	15	15.3
Adverse events leading to death	1	1.2	8	8.2
Treatment-related (or with unknown relationship), any grade	.	.	4	4.1
Support for hematological toxicities				
G-CSF				
Primary prophylactic	.	.	98 [a]	100.0
Therapeutic	11	13.3	22	22.4
Transfusions				
Red blood cell	9	10.8	46	46.9
Platelets	2	2.4	16	16.3
Erythropoietin	2	2.4	12	12.2

	NCI-CTCAE grade ≥1		NCI-CTCAE grade ≥3		NCI-CTCAE grade ≥1		NCI-CTCAE grade ≥3	
	n	%	n	%	n	%	n	%
Treatment-related adverse events (>5% of patients)								
Fatigue	49	59.0	7	8.4	46	46.9	12	12.2
Nausea	28	33.7	–	–	26	26.5	1	1.1
Decreased appetite	19	22.9	–	–	11	11.2	4	4.1
Vomiting	14	16.9	–	–	8	8.2	–	–
Diarrhea	13	15.7	1	1.2	13	13.3	2	2.0
Constipation	10	12.0	–	–	9	9.2	–	–
Febrile neutropenia	2	2.4	2	2.4	6	6.1	6	6.1
Alopecia	–	–	–	–	6	6.1	–	–
Hematological laboratory abnormalities (regardless of relationship)								
Anemia	79	95.2	10	12.0	95	96.9	53	54.1
Lymphopenia	72	86.7	38	45.8	84	85.7	43	43.9
Leukopenia	70	84.3	25	30.1	90	91.8	67	68.4
Neutropenia	61	73.5	39	47.0	84	85.7	74	75.5
Thrombocytopenia	38	45.8	5	6.0	91	92.9	51	52.0
Biochemical laboratory abnormalities (regardless of relationship)								
Creatinine increased [b]	70	85.4	–	–	80	81.6	–	–
ALT increased	61	74.4	4	4.9	41	41.8	2	2.0
AST increased	30	36.6	1	1.2	25	25.5	1	1.0
AP increased	25	30.5	2	2.4	42	42.9	1	1.0
Total bilirubin increased	8	9.8	–	–	16	16.3	2	2.0
CPK increased	5	6.1	–	–	8	8.2	–	–

[a] Primary G-CSF prophylaxis was mandatory in ATLANTIS.
[b] Most of these were non-clinically significant creatinine increases. Creatinine values were within normal range and grade 1 was due to creatinine increase > 1–1.5 x baseline according to the NCI-CTCAE v.4 severity calculation.
Abbreviations: AP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; G-CSF, growth colony-stimulating factors; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events v.4; SCLC, small cell lung cancer.

at https://www.clinicaltrials.gov as NCT05153239) is evaluating lurbinectedin as single agent or in combination with irinotecan *versus* topotecan or irinotecan in the population of adult SCLC patients who have failed one prior platinum-containing line with CTFI ≥ 30 days and controlled asymptomatic CNS metastases.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Table 5
Patients with hospitalizations due to serious adverse events in Basket phase 2 study, ATLANTIS phase 3 study and CORAIL phase 3 study.

Hospitalization rates due to:	Basket phase 2 study SCLC cohort Lurbinectedin (n = 105)		ATLANTIS phase 3 study Topotecan subgroup (n = 121)		CORAIL phase 3 study			
					Lurbinectedin (n = 219)		Topotecan (n = 87)	
	n	%	n	%	n	%	n	%
SAEs regardless of relationship	36	34.3	60	49.6	86	39.3	44	50.6
SAEs treatment-related	11	10.5	39	32.2	40	18.3	26	29.9

SAEs, serious adverse events.

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References

[1] J. Trigo, V. Subbiah, B. Besse, V. Moreno, R. López, M.A. Sala, S. Peters, S. Ponce, C. Fernández, V. Alfaro, J. Gómez, C. Kahatt, A. Zeaiter, K. Zaman, V. Boni, J. Arrondeau, M. Martínez, J.-P. Delord, A. Awada, R. Kristeleit, M.E. Olmedo, L. Wannesson, J. Valdivia, M.J. Rubio, A. Anton, J. Sarantopoulos, S.P. Chawla, J. Mosquera-Martinez, M. D'Arcangelo, A. Santoro, V.M. Villalobos, J. Sands, L. Paz-Ares, Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial, Lancet Oncol. 21 (5) (2020) 645–654.

[2] V. Subbiah, I. Brana, A. Longhi, V. Boni, J.P. Delord, A. Awada, P. Boudou-Rouquette, J. Sarantopoulos, G.I. Shapiro, A. Elias, R. Ratan, C. Fernandez, C. Kahatt, M. Cullell-Young, M. Siguero, A. Zeaiter, S.P. Chawla, Antitumor activity of lurbinectedin, a selective inhibitor of oncogene transcription, patients with relapsed ewing sarcoma: results of a basket phase II study, Clin. Cancer Res. 28 (13) (2022) 2762–2770.

[3] F. Longo-Muñoz, D. Castellano, J. Alexandre, S.P. Chawla, C. Fernández, C. Kahatt, V. Alfaro, M. Siguero, A. Zeaiter, V. Moreno, E. Sanz-García, A. Awada, A. Santaballa, V. Subbiah, Lurbinectedin in patients with pretreated neuroendocrine tumours: results from a phase II basket study, Eur. J. Cancer 172 (2022) 340–348.

[4] V. Boni, B. Pistilli, I. Braña, G.I. Shapiro, J. Trigo, V. Moreno, D. Castellano, C. Fernández, C. Kahatt, V. Alfaro, M. Siguero, A. Zeaiter, F. Longo, K. Zaman, A. Antón, A. Paredes, G. Huidobro, V. Subbiah, Lurbinectedin, a selective inhibitor of oncogenic transcription, in patients with pretreated germline BRCA1/2 metastatic breast cancer: results from a phase II basket study, ESMO Open 7 (5) (2022) 100571.

[5] R. Kristeleit, A. Leary, J. Delord, V. Moreno, A. Oaknin, D. Castellano, G.I. Shappiro, C. Fernández, C. Kahatt, V. Alfaro, M. Siguero, D. Rueda, A. Zeaiter, A. Awada, A. Santaballa, K. Zaman, J. Sehouli, V. Subbiah, Lurbinectedin in patients with pretreated endometrial cancer: results from a phase 2 basket clinical trial and exploratory translational study, Invest New Drugs (2023 (in press)).

[6] S. Singh, A.A. Jaigirdar, F. Mulkey, J. Cheng, S.S. Hamed, Y. Li, J. Liu, H. Zhao, A. Goheer, W.S. Helms, X. Wang, R. Agarwal, R. Pragani, K. Korsah, S. Tang, J. Leighton, A. Rahman, J.A. Beaver, R. Pazdur, M.R. Theoret, H. Singh, FDA approval summary: lurbinectedin for the treatment of metastatic small cell lung cancer, Clin. Cancer Res. 27 (9) (2021) 2378–2382.

[7] A.C. Dingemans, M. Fruh, A. Ardizzoni, B. Besse, C. Faivre-Finn, L.E. Hendriks, S. Lantuejoul, S. Peters, N. Reguart, C.M. Rudin, D. De Ruysscher, P.E. Van Schil, J. Vansteenkiste, M. Reck, Small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 32 (7) (2021) 839–853.

[8] NCCN Clinical Practice Guidelines in Oncology. Small Cell Lung Cancer. Version 3.2023 -December 21, 2022. https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf.

[9] S.P. Aix, T.E. Ciuleanu, A. Navarro, S. Cousin, L. Bonanno, E.F. Smit, A. Chiappori, M.E. Olmedo, I. Horvath, C. Grohe, A.F. Farago, J.A. Lopez-Vilarino, M. Cullell-Young, A. Nieto, N. Vasco, J. Gomez, C. Kahatt, A. Zeaiter, E. Carcereny, J. Roubec, K. Syrigos, G. Lo, I. Barneto, A. Pope, A. Sanchez, J. Kattan, K. Zarogoulidis, C. F. Waller, H. Bischoff, O. Juan-Vidal, N. Reinmuth, M. Domine, L. Paz-Ares, Combination lurbinectedin and doxorubicin versus physician's choice of chemotherapy in patients with relapsed small-cell lung cancer (ATLANTIS): a multicentre, randomised, open-label, phase 3 trial, Lancet Respir. Med. 11 (1) (2023) 74–86.

[10] J. von Pawel, R. Jotte, D.R. Spigel, M.E. O'Brien, M.A. Socinski, J. Mezger, M. Steins, L. Bosquee, J. Bubis, K. Nackaerts, J.M. Trigo, P. Clingan, W. Schutte, P. Lorigan, M. Reck, M. Domine, F.A. Shepherd, S. Li, M.F. Renschler, Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer, J. Clin. Oncol. 32 (35) (2014) 4012–4019.

[11] M.E. O' Brien, T.E. Ciuleanu, H. Tsekov, Y. Shparyk, B. Cucevia, G. Juhasz, N. Thatcher, G.A. Ross, G.C. Dane, T. Crofts, Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer, J Clin Oncol 24(34) (2006) 5441-7.

[12] N. Horita, M. Yamamoto, T. Sato, T. Tsukahara, H. Nagakura, K. Tashiro, Y. Shibata, H. Watanabe, K. Nagai, M. Inoue, K. Nakashima, R. Ushio, M. Shinkai, M. Kudo, T. Kaneko, Topotecan for relapsed small-cell lung cancer: systematic review and meta-analysis of 1347 patients, Sci. Rep. 5 (2015) 15437.

[13] J.R. Eckardt, J. von Pawel, J.L. Pujol, Z. Papai, E. Quoix, A. Ardizzoni, R. Poulin, A. J. Preston, G. Dane, G. Ross, Phase III study of oral compared with intravenous

topotecan as second-line therapy in small-cell lung cancer, J. Clin. Oncol. 25 (15) (2007) 2086–2092.
[14] J. von Pawel, J.H. Schiller, F.A. Shepherd, S.Z. Fields, J.P. Kleisbauer, N. G. Chrysson, D.J. Stewart, P.I. Clark, M.C. Palmer, A. Depierre, J. Carmichael, J. B. Krebs, G. Ross, S.R. Lane, R. Gralla, Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer, J. Clin. Oncol. 17 (2) (1999) 658–667.
[15] A. Ardizzoni, H. Hansen, P. Dombernowsky, T. Gamucci, S. Kaplan, P. Postmus, G. Giaccone, B. Schaefer, J. Wanders, J. Verweij, Topotecan, a new active drug in the second-line treatment of small-cell lung cancer: a phase II study in patients with refractory and sensitive disease. The european organization for research and treatment of cancer early clinical studies group and new drug development office, and the lung cancer cooperative group, J. Clin. Oncol. 15 (5) (1997) 2090–2096.
[16] J. von Pawel, U. Gatzemeier, J.L. Pujol, L. Moreau, S. Bildat, M. Ranson, G. Richardson, C. Steppert, A. Riviere, I. Camlett, S. Lane, G. Ross, Phase II comparator study of oral versus intravenous topotecan in patients with chemosensitive small-cell lung cancer, J. Clin. Oncol. 19 (6) (2001) 1743–1749.
[17] T.L. Evans, B.C. Cho, K. Udud, J.R. Fischer, F.A. Shepherd, P. Martinez, R. Ramlau, K.N. Syrigos, L. Shen, M. Chadjaa, M. Wolf, Cabazitaxel versus topotecan in patients with small-cell lung cancer with progressive disease during or after first-line platinum-based chemotherapy, J. Thorac. Oncol. 10 (8) (2015) 1221–1228.
[18] M. Reck, D. Vicente, T. Ciuleanu, S. Gettinger, S. Peters, Efficacy and safety of nivolumab (nivo) monotherapy versus chemotherapy (chemo) in recurrent small cell lung cancer (SCLC): Results from CheckMate 331, Ann. Oncol. 29 (Suppl 10) (2018) x39–x43, https://doi.org/10.1093/annonc/mdy511.
[19] M.J. Edelman, M. Dvorkin, K. Laktionov, A. Navarro, O. Juan-Vidal, V. Kozlov, G. Golden, O. Jordan, C.Q. Deng, D. Bentsion, C. Chouaid, H. Dechev, A. Dowlati, N. Fernandez Nunez, O. Ivashchuk, I. Kiladze, T. Kortua, N. Leighl, A. Luft, T. Makharadze, Y. Min, X. Quantin, Randomized phase 3 study of the anti-disialoganglioside antibody dinutuximab and irinotecan vs irinotecan or topotecan for second-line treatment of small cell lung cancer, Lung Cancer 166 (2022) 135–142.
[20] F. Blackhall, K. Jao, L. Greillier, B.C. Cho, K. Penkov, N. Reguart, M. Majem, K. Nackaerts, K. Syrigos, K. Hansen, W. Schuette, J. Cetnar, F. Cappuzzo, I. Okamoto, M. Erman, S.W. Langer, T. Kato, H. Groen, Z. Sun, Y. Luo, P. Tanwani, L. Caffrey, P. Komarnitsky, N. Reinmuth, Efficacy and safety of rovalpituzumab tesirine compared with topotecan as second-line therapy in DLL3-high SCLC: results from the phase 3 TAHOE study, J. Thorac. Oncol. 6 (9) (2021) 1547–1558.
[21] D.R. Spigel, D. Vicente, T.E. Ciuleanu, S. Gettinger, S. Peters, L. Horn, C. Audigier-Valette, N. Pardo Aranda, O. Juan-Vidal, Y. Cheng, H. Zhang, M. Shi, A. Luft, J. Wolf, S. Antonia, K. Nakagawa, J. Fairchild, C. Baudelet, D. Pandya, P. Doshi, H. Chang, M. Reck, Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331, Ann. Oncol. 32 (5) (2021) 631–641.
[22] J.L. Hurwitz, F. McCoy, P. Scullin, D.A. Fennell, New advances in the second-line treatment of small cell lung cancer, Oncologist 14 (10) (2009) 986–994.
[23] B. Fischer, A. Arcaro, Current status of clinical trials for small cell lung cancer, Rev. Recent Clin. Trials 3 (1) (2008) 40–61.
[24] V. Subbiah, L. Paz-Ares, B. Besse, V. Moreno, S. Peters, M.A. Sala, J.A. Lopez-Vilarino, C. Fernandez, C. Kahatt, V. Alfaro, M. Siguero, A. Zeaiter, K. Zaman, R. Lopez, S. Ponce, V. Boni, J. Arrondeau, J.P. Delord, M. Martinez, L. Wannesson, A. Anton, J. Valdivia, A. Awada, R. Kristeleit, M.E. Olmedo, M.J. Rubio, J. Sarantopoulos, S.P. Chawla, J. Mosquera-Martinez, Antitumor activity of lurbinectedin in second-line small cell lung cancer patients who are candidates for re-challenge with the first-line treatment, Lung Cancer 150 (2020) 90–96.
[25] A. Leary, A. Oaknin, J.M. Trigo, V. Moreno, J.P. Delord, V. Boni, I. Brana, C. Fernandez, C. Kahatt, A. Nieto, M. Cullell-Young, A. Zeaiter, V. Subbiah, Pooled safety analysis of single-agent lurbinectedin in patients with advanced solid tumours, Eur. J. Cancer 192 (2023) 113259.
[26] S. Gaillard, A. Oaknin, I. Ray-Coquard, I. Vergote, G. Scambia, N. Colombo, C. Fernandez, V. Alfaro, C. Kahatt, A. Nieto, A. Zeaiter, M. Aracil, L. Vidal, B. Pardo-Burdalo, Z. Papai, R. Kristeleit, D.M. O'Malley, I. Benjamin, P. Pautier, D. Lorusso, Lurbinectedin versus pegylated liposomal doxorubicin or topotecan in patients with platinum-resistant ovarian cancer: a multicenter, randomized, controlled, open-label phase 3 study (CORAIL), Gynecol. Oncol. 163 (2) (2021) 237–245.
[27] W. Su, B. Rengarajan, D. Profant, K. Mayo, M. Groff, G. Tremblay, EE152 Cost-effectiveness modeling of lurbinectedin as a second-line therapy in patients with small cell lung cancer (SCLC), Value Health 26 (6, Supplement) (2023) S87.