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Antitumor activity of lurbinectedin in second-line small cell lung cancer patients who are candidates for re-challenge with the first-line treatment

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ABSTRACT

Introduction: The National Comprehensive Cancer Network guidelines recommend re-challenge with the first-line treatment for relapsed small cell lung cancer (SCLC) with chemotherapy-free interval (CTFI)≥180 days. A phase II study (NCT02454972) showed remarkable antitumor activity in SCLC patients treated with lurbinectedin 3.2 mg/m^2 1 -h intravenous infusion every 3 weeks as second-line therapy. We report results for the pre-planned subset of patients with CTFI ≥ 180 days.

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Material and Methods: Twenty patients aged ≥18 years with pathologically proven SCLC diagnosis, pretreated with only one prior platinum-containing line, no CNS metastases, and with CTFI ≥ 180 days were evaluated. The primary efficacy endpoint was the overall response rate (ORR) assessed by the Investigators according to RECIST v1.1.

Results: ORR was 60.0 % (95 %CI, 36.1−86.9), with a median duration of response of 5.5 months (95 %CI, 2.9−11.2) and disease control rate of 95.0 % (95 %CI, 75.1−99.9). Median progression-free survival was 4.6 months (95 %CI, 2.6−7.3). With a censoring of 55.0 %, the median overall survival was 16.2 months (95 %CI, 9.6-upper level not reached). Of note, 60.9 % and 27.1 % of patients were alive at 1 and 2 years, respectively. The most common grade 3/4 adverse events and laboratory abnormalities were hematological disorders (neutropenia, 55.0 %; anemia; 10.0 % thrombocytopenia, 10.0 %), fatigue (10.0 %) and increased liver function tests (GGT, 10 %; ALT and AP, 5.0 % each). No febrile neutropenia was reported.

Conclusion: Lurbinectedin is an effective treatment for platinum-sensitive relapsed SCLC, especially in patients with CTFI ≥ 180 days, with acceptable safety and tolerability. These encouraging results suggest that lurbinectedin can be another valuable therapeutic option rather than platinum re-challenge.

1. Introduction

Standard first-line chemotherapy for patients with small cell lung cancer (SCLC) consists of a platinum salt (carboplatin or cisplatin) in combination with etoposide [1,2]. Recently, atezolizumab [3] or durvalumab [4] plus carboplatin/etoposide showed improved survival compared to chemotherapy alone, and both have been approved by the US FDA as first-line therapy. However, therapeutic options are limited once patients with SCLC have relapsed disease. The National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) guidelines recommend re-challenge with the first-line regimen in relapsed SCLC patients with sensitive disease, defined as patients with a chemotherapy-free interval (CTFI) ≥90 days in the ESMO guidelines and patients with a CTFI ≥ 180 days in the NCCN guidelines [1,2].

During the last decade, few studies have published data on re-challenge with platinum-based therapy after failure of the first-line treatment in SCLC patients with sensitive disease [5–12]. Most of these studies are small retrospective analyses, usually including patients with CTFI ≥ 90 days, and mostly include Japanese patients [6,7,9–11]. In the largest retrospective analysis conducted to date (n = 112 patients), Genestreti et al. [8] showed an overall response rate (ORR) of 45 % and median overall survival (OS) of 7.9 months. More recently, Monnet et al. [12] reported data of 81 patients from the GFPC 13−01 randomized phase III trial evaluating platinum re-challenge *versus* topotecan: ORR was 49 % with re-challenge *vs.* 25 % with topotecan, median progression-free survival (PFS) was 4.7 months *vs.* 2.7 months, and median OS was 7.5 months *vs.* 7.4 months.

Limited information is available on platinum re-challenge in relapsed SCLC patients with CTFI ≥ 180 days. A phase II randomized study evaluating amrubicin *versus* platinum re-challenge included 18 of 30 patients (60.0 %) with relapse after CTFI ≥ 180 days: ORR with re-challenge was 43 % and median OS was 14.3 months [6]. Only one small retrospective study (n = 11 Japanese patients) included data exclusively obtained from patients with CTFI ≥ 180 days: ORR was 46 % and median OS was 15.7 months [7].

SCLC is a difficult-to-treat disease addicted to transcription [13], without actionable targets being identified. Four molecular SCLC subtypes recently have been described, defined by differential expression of four key transcription regulators [14]. Lurbinectedin (ZEPZELCA™, PharmaMar, Madrid, Spain) is a selective inhibitor of oncogenic transcription that binds preferentially to guanines located in the GC-rich regulatory areas of DNA gene promoters [15,16]. By preventing binding of transcription factors to their recognition sequences, the drug inhibits oncogenic transcription and leads to tumor cell apoptosis [17]. Lurbinectedin also affects the tumor microenvironment landscape by inhibiting activated transcription in tumor-associated macrophages [18].

Recently, in June 2020, the US FDA granted accelerated approval to lurbinectedin for adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy based on results from a phase II study (study B-005; NCT02454972). This pivotal study showed remarkable antitumor activity in 60 SCLC patients with CTFI ≥ 90 days treated with lurbinectedin as second-line: ORR of 45.0 %, median duration of response of 6.2 months and median OS of 11.9 months [19]. The NCCN guidelines updated on 7 July 2020 have added lurbinectedin as a preferred treatment for patients with relapsed SCLC and CTFI ≤ 180 days, and as a recommended regimen other than re-challenge with the initial therapy for patients with CTFI > 180 days [2]. We show here results for the subset of patients in this phase II study who are candidates for platinum re-challenge according to the NCCN guidelines (patients with CTFI ≥ 180 days).

2. Methods

2.1. Patients

In this phase II study, 105 SCLC patients were treated between October 2015 and January 2019 in 26 hospitals from 6 European countries and the USA [19]. Patients were ≥ 18 years old with pathologically proven SCLC diagnosis; pretreated with one prior platinum-containing line; with measurable disease as per the Response Criteria in Solid Tumors (RECIST) v.1.1 [20] and Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2; and adequate bone marrow, renal, and liver function. Patients were excluded if they had: previously received lurbinectedin or trabectedin; prior or concurrent malignant disease unless in complete remission for more than 5 years; central nervous system involvement; concomitant unstable or serious medical condition (history or presence of unstable angina, myocardial infarction, congestive heart failure, valvular heart disease, arrhythmia, severe dyspnea, or active infection), or impending need for radiotherapy.

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulations for clinical trials. The study protocol was approved by the Independent Local Ethics Committee of each participating center. Signed informed consent was obtained from all patients prior to any study-specific procedure.

2.2. Study treatment

Patients received lurbinectedin 3.2 mg/m^2 administered as a 1 -h intravenous (i.v.) infusion every 3 weeks (q3wk) until disease progression or unacceptable toxicity. All patients received antiemetic prophylaxis. Primary prophylaxis with granulocyte colony-stimulating factors (G-CSFs) was not allowed. Up to 2 dose reductions were allowed, from 3.2 to 2.6 and then to 2.0 mg/m^2.

2.3. Outcomes

Subgroup analyses by CTFI were pre-planned in this study. The primary endpoint was the ORR according to RECIST v1.1, supported by duration of response (DoR; defined as the date of first response to the date of disease progression, relapse or death due to any cause) as secondary endpoint, both assessed by the Investigators. Blinded image review was conducted by an Independent Review Committee to confirm radiological results. Secondary endpoints included disease control rate (defined as objective response plus stable disease as best response); PFS (defined as the time from the date of first infusion to the date of disease progression, death of any cause, or last tumor evaluation); OS (defined as the time from the date of first infusion to the date of death or last contact in case of patients lost to follow-up or alive at the clinical cut-off), and safety.

2.4. Assessments

Radiological assessments were done every 6 weeks until cycle 6, and every 9 weeks thereafter. Responses were confirmed at least 4 weeks later. Safety was evaluated in all patients who received at least one lurbinectedin infusion, complete or incomplete, by assessment of adverse events (AEs), clinical laboratory tests, physical examinations and vital signs. Safety was monitored throughout the treatment and up to 30 days after last lurbinectedin infusion, or until the patient started a new antitumor therapy or until the date of death, whichever occurred first. All patients were followed until recovery from any lurbinectedin-related AE.

2.5. Statistical analysis

This exploratory assessment is based on a pre-planned analysis by CTFI. Descriptive statistics were used. Non-continuous variables are described in frequency tables using counts and percentages. Continuous variables are described by median, minimum and maximum. Binomial exact estimates and its 95 % confidence interval were calculated for the evaluation of the main endpoint (ORR). The Kaplan-Meier method was used to analyze DoR, PFS and OS. AEs were recorded and coded with the Medical Dictionary for Regulatory Activities (MedDRA), v.21.0. AEs and laboratory values were graded per the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE), v.4.0. SAS software (v. 9.4) was used to generate statistical outputs.

3. Results

Twenty patients treated with lurbinectedin in this phase II study had CTFI ≥ 180 days and form the basis for this analysis. Their baseline characteristics are shown in Table 1. Patients were mostly males (60.0 %), had ECOG PS 0–1 (95.0 %), and had a median age of 57 years (range, 49–75 years). Extensive stage disease at initial diagnosis was present in 7 patients (35.0 %). All 20 patients had received prior platinum/etoposide, with no prior immunotherapy. An objective response to first-line therapy was observed in 85 % of the patients. Median CTFI was 7.5 months (range, 6.0–16.1).

ORR assessed by the Investigators was 60.0 % (12/20 patients) (95 % CI, 36.1–86.9) (Table 2), with a median DoR of 5.5 months (95 %CI, 2.9–11.2) and disease control rate of 95.0 % (95 %CI, 75.1–99.9). ORR assessed by independent review was 50.0 % (95 %CI, 27.2–72.8), with a median DoR of 5.5 months (95 %CI, 2.8–8.5) and disease control rate of 80 % (95 %CI, 56.3–94.3).

The median PFS was 4.6 months (95 %CI, 2.6–7.3). Eleven patients (55.0 %) were censored for survival analysis: eight patients were on follow-up after disease progression, two patients were ongoing lurbinectedin treatment, and one patient had treatment discontinuation because of a treatment-related adverse event (this patient had a partial response but, after 6 cycles, grade 1 peripheral neuropathy present at study entry worsened to grade 2). With a median follow-up of 15.6 months, the median OS was 16.2 months (95 %CI, 9.6-upper level not reached). Of note, 60.9 % and 27.1 % of patients were alive at 1 and 2 years, respectively (Table 2).

Table 1
Baseline characteristics in SCLC patients with CTFI ≥ 180 days (n = 20).

	n	%
Gender		
Male	12	60·0
Female	8	40·0
Age. median (range), years	57 (49–75)	
ECOG PS status		
0	10	50.0
1	9	45.0
2	1	5.0
Abnormal LDH (>ULN)	5	25.0
Smoker status		
Former/current	18	90.0
Never	2	10.0
Stage at diagnosis		
Limited	13	65.0
Extended	7	35.0
No. of sites at baseline, median (range)	3 (1–5)	
Most common sites other than lung		
Lymph nodes	16	80.0
Adrenal	5	25.0
Liver	4	20.0
Bulky disease (one lesion >50 mm)	4	20.0
CNS involvement	2 [a]	10.0
Paraneoplastic syndrome	1	5.0
Prophylactic cranial irradiation	15	75.0
No. of prior lines. median (range)	1 (1–2)	
1 line	19	95.0
2 lines	1 [b]	5.0
Prior agents		
Platinum compounds	20	100.0
Etoposide	20	100.0
Immunotherapy	0	0.0
Best response to prior platinum		
CR	7	35.0
PR	10	50.0
SD	3	15.0
CTFI, median (range), months	7.5 (6.0–16.1)	

Data shown are n (%) of patients except for median (range).
CR, complete response; CTFI, chemotherapy-free interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; PR, partial response; SD, stable disease; ULN, upper limit of normal.
[a] One patient had CNS metastases at baseline (protocol deviation) an other CNS history prior to study entry.
[b] One patient was treated with a second line consisting of an investigational drug (GSK52572).

All 20 patients were evaluable for safety (Table 3). The median number of lurbinectedin cycles administered per patient was 6 (range, 2–24) for a total of 159 cycles. The most common grade 3/4 AEs and laboratory abnormalities were hematological disorders, including neutropenia (55.0 %), anemia (10.0 %) and thrombocytopenia (10.0 %), as well as fatigue (10.0 %) and increased liver function tests (GGT, 10 %; ALT and AP, 5.0 % each). Of note, no cases of febrile neutropenia were observed in this subset of patients.

Treatment delay and dose reduction because of treatment-related events was required in 8 (5.8 %) and 9 cycles (9.5 %), respectively, mainly because of transient neutropenia.

No treatment-related deaths occurred: 9 patients (45.0 %) died during the study period due to disease progression.

4. Discussion

The NCCN guidelines [2] state re-challenge with the original first-line treatment as a preferred treatment and lurbinectedin as other recommended regimen in SCLC patients with relapse and CTFI ≥ 180 days. Evidence on re-challenge effects was obtained from small clinical

Table 2
Efficacy data in SCLC patients treated with lurbinectedin and chemotherapy-free interval ≥180 days (n = 20).

	Investigator	Independent review
ORR [a], n (%) (95 %CI)	12 (60.0) (36.1–86.9)	10 (50.0) (27.2–72.8)
Best overall response, n, (%)		
PR	12 (60.0)	10 (50.0)
SD	7 (35.0)	6 (30.0)
PD	1 (5.0)	4 (20.0)
Disease control rate (ORR + SD), n (%) (95 %CI)	19 (95.0) (75.1–99.9)	16 (80.0) (56.3–94.3)
Median DoR, months (95 %CI)	5.5 (2.9–11.2)	5.5 (2.8–8.5)
Median PFS, months (95 %CI)	4.6 (2.6–7.3)	4.6 (2.3–7.6)
Median OS, months [b] (95 %CI),	16.2 (9.6-nr)	
OS at 12 months, % (95 %CI)	60.9 (35.7–86.2)	

CI, confidence interval; CTFI, chemotherapy-free interval; nr, not reached; ORR: overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; OS, overall survival; SD, stable disease.

[a] Confirmed responses.

[b] Eleven patients (55.0 %) were censored for survival analysis: eight were on follow-up after disease progression, two were ongoing lurbinectedin treatment, and one had treatment discontinuation because of a treatment-related adverse event (worsening of prior peripheral neuropathy). Median follow-up was 15.6 months.

Table 3
Most common treatment-related adverse events and laboratory abnormalities (>10 % of patients or grade≥3) in SCLC patients treated with lurbinectedin and chemotherapy-free interval ≥180 days (n = 20).

	NCI-CTCAE grade		
	Grade 1–2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Treatment-related adverse events			
Fatigue	11 (55.0)	2 (10.0)	..
Diarrhea	4 (20.0)	..	..
Constipation	3 (15.0)	..	..
Decreased appetite	3 (15.0)	..	..
Nausea	3 (15.0)	..	..
Hematological abnormalities (regardless of relationship)			
Anemia	17 (85.0)	2 (10.0)	–
Neutropenia	5 (25.0)	2 (10.0)	9 (45.0)
Thrombocytopenia	4 (20.0)	–	2 (10.0)
Biochemical abnormalities (regardless of relationship)			
Creatinine increased [a]	16 (80.0)	..	..
ALT increased	14 (70.0)	1 (5.0)	..
GGT increased	12 (60.0)	1 (5.0)	1 (5.0)
AST increased	6 (30.0)	..	..
AP increased	5 (25.0)	1 (5.0)	..

AP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events v·4.

[a] Version 4·0 of NCI-CTCAE grades creatinine increases from baseline, even if creatinine values remain normal.

trials conducted in the 1980s [21,22]. Some of these old trials did not use platinum-based therapy as the first-line treatment and, therefore, the NCCN recommendation is to re-treat with the initial treatment, and not specifically with platinum-based therapy. Re-challenge with the initial first-line regimen is also stated in the ESMO guidelines as follows: *Only patients with sensitive disease derive benefit from re-challenge with first-line therapy (usually platinum-etoposide) [V.C]* [1]. Nevertheless, "V" level evidence comes from studies without control group, case reports and experts opinion. The "C" recommendation stated in ESMO guidelines, therefore, indicates insufficient evidence for efficacy or that the benefit does not outweigh the risk or the disadvantages (adverse events, costs), and is considered optional. Although the level of evidence is low, re-challenge seems to be widely used in daily clinical practice.

Table 4 shows the outcomes observed in the most recent studies on platinum re-challenge compared to those observed with lurbinectedin in patients with CTFI ≥ 90 days and CTFI ≥ 180 days. Acknowledging the inherent limitations of cross-trial comparison, the small patient populations evaluated, the specific characteristics of Japanese patients in terms of benefit/risk profile compared to white patients, and the limitations of the study B-005 (single-arm design with no control group and exclusion of patients with brain metastases), the results reported here in the subset of patients recommended by the NCCN guidelines (patients with CTFI ≥ 180 days) show remarkable ORR (60 %) and median OS (16.2 months) when compared with previous studies on platinum re-challenge [6,7], where ORR was 43–46 % and median OS was 14.3–15.7 months (Table 4). The efficacy outcomes previously reported with lurbinectedin in the CTFI ≥ 90 days subset [19] showed similar ORR but longer OS (11.9 months *vs.* 7.5–7.9 months) when compared with the largest studies [8,12]. This is a relevant finding because, since 1997, no chemotherapy regimens have demonstrated improvement in survival in second-line and beyond SCLC [23]. There is a desperate need for new approaches in this setting. An additional benefit of lurbinectedin as second-line therapy in patients with sensitive SCLC is prolongation of the platinum-free interval, which may further re-sensitize tumors to the original therapy for a third-line therapy [24]. After lurbinectedin, 7 of 20 patients (35 %) received further platinum.

The decision-making patterns in Europe for second-line treatment in real world practice were recently analyzed [25]. The two criteria most relevant to decision-making were performance status and the interval to recurrence since first-line treatment. In agreement with the clinical guidelines, consensus for platinum re-challenge as the preferred treatment for SCLC patients with CTFI ≥ 180 days was agreed by 92 % of the European experts consulted (no consensus was observed on the second-line therapy with a CTFI between 90 and 180 days). A study evaluating real-world treatment patterns of patients with SCLC in the EU, US and Japan showed that approximately half of patients with sensitive disease were not re-challenged with platinum-based therapy across all regions [26]. Although these two real-world analyses [25,26] did not include results of efficacy, real-world efficacy data are available from the prospective clinical cohort German study TLK [27]. Subset analysis of 31 patients undergoing second-line re-treatment with a platinum-based regimen after a median CTFI of 6.6 months, including 55 % with CTFI ≥ 90 days, demonstrated an ORR of 38.7 % and median OS of 8.0 months (95 %CI, 6.8–16.5 months). A systematic literature review on real-world effectiveness and tolerability of SCLC treatments showed a median OS of 6.3 months for patients with sensitive disease treated with chemotherapy as second-line [28]. Overall, lurbinectedin data compares favorably with respect to these real-world figures.

Lurbinectedin survival in the subset of CTFI ≥ 180 days also compares favorably to outcomes on topotecan (median survival of 8.2 months; 1-year survival rate of 32.3 %) per a pooled analysis from six studies with intravenous topotecan in 200 SCLC patients with CTFI of 180 days [29].

Lurbinectedin 3.2 mg/m^2 1 -h q3wk regimen has an acceptable and manageable safety profile, with the main toxicity being reversible myelosuppression. Primary G-CSF prophylaxis is not required [19]. In this subset of 20 patients treated with lurbinectedin, grade 3/4 neutropenia was reported in 45 % of patients, with no cases of febrile neutropenia, and grade 3/4 thrombocytopenia was reported in 10 %. Febrile neutropenia occurred in 5% of the overall SCLC population receiving lurbinectedin [19]. Limited information is available on adverse events with platinum re-challenge in SCLC relapsed patients. Although it is known that, apart from myelotoxicity, platinum re-challenge affects renal function and is associated to neuropathy and ototoxicity, until now there was not alternative option beyond topotecan. Recently, Monnet et al. [12] reported grade 3/4 neutropenia in 23 % of patients with re-challenge *vs.* 36 % with topotecan; febrile neutropenia in 6% *vs.* 10 % (primary G-CSF allowed), grade 3/4 anemia in 30 % *vs.* 22 %, and grade 3/4 thrombocytopenia in 41 % *vs.* 38 %.

Table 4
Main efficacy and safety outcomes in patients with sensitive SCLC (CTFI ≥ 90 and ≥180 days): platinum re-challenge and lurbinectedin.

	CTFI ≥ 90 days									CTFI ≥ 180 days	
	Platinum re-challenge								Lurbinectedin	Platinum re-challenge	Lurbinectedin
Reference	Korkmaz (2013) [5]	Inoue (2015) [6]	Wakuda (2015) [7]	Genestreti (2015) [8]	Shiozawa (2018) [9]	Naito (2018) [10]	Wakuda (2019) [11]	Monnet (2019) [12]	Trigo (2020) [19]	Wakuda (2015) [7]	Current analysis
STUDY DESIGN	Retrospective	Phase II randomized	Retrospective	Retrospective	Retrospective	Retrospective analysis	Retrospective	Phase III	Phase II	Retrospective	Phase II
(n)	analysis (n = 33)	(n = 30)	analysis (n = 19)	analysis (n = 112)	analysis (n = 20)	(n = 67)	analysis (n = 27)	randomized (n = 81)	single-arm (n = 60)	analysis (n = 11)	single-arm (n = 20)
Median CTFI (range)	NA	60 % CTFI >180 days	7.1 (3.1–39.2)	7.9 (3.0–39.5)	3.8 (3.0–13.2)	5.9 (3.1–50.0)	6.6 (3.1–38.7)	5.3 (4.7–5.8)	4.8 (3.0–16.1)	8.8 (6.0–38.7)	7.5 (6.0–16.1)
Age (years), median (range)	58 (NA)	67 (45–80)	69 (51–83)	64 (40–83)	65 (52–84)	NA	66 (51–73)	64 (NA)	59 (44–79)	69 (52–79)	57 (49–75)
Response first line %	NA	NA	95 %	98 %	NA	NA	98 %	NA	85 %	100 %	85 %
Limited disease, %	39 %	60 %	63 %	44 %	55 %	49 %	44 %	NA	42 %	73 %	65 %
ECOG PS 0–1, %	82 %	93 %	95 %	87 %	90 %	85 %	89 %	94 %	95 %	91 %	95 %
EFFICACY OUTCOMES											
ORR, % (95 %CI)	55 (NA)	43 (28–58)	37 (19–59)	45 (NA)	50 (NA)	52 (NA)	48 (NA)	49 (NA)	45 (32–58)	46 (21–72)	60 (36–87)
Disease control rate, % (95 %CI)	NA	80 (68–92)	84 (NA)	64 (NA)	80 (NA)	82 (NA)	74 (NA)	86 (NA)	82 (70–91)	73 (NA)	95 (75–100)
PFS (months), median (95 %CI)	6.2 (NA)	5.1 (NA)	5.6 (NA)	5.5 (4.4–6.3)	4.5 (3.5–5.4)	5.1 (4.3–5.4)	5.5 (3.4–6.1)	4.7 (3.9–5.5)	4·6 (2.8–6.5)	7.8 (NA)	4.6 (2.6–7.3)
OS (months), median (95 %CI)	11.4 (NA)	14.3 (NA)	14.4 (NA)	7.9 (6.9–9.7)	10.5 (7.9–13.0)	10.8 (8.7–14.5)	14.2 (6.4–25.6)	7.5 (5.4–9.5)	11.9 (9.7–16.2)	15.7 (NA)	16.2 (9.6-nr)
SAFETY OUTCOMES											
Primary G-CSF use	NA	No	NA	NA	NA	NA	NA	Yes	No	NA	No
Grade 3/4 neutropenia, %	NA	73 %	94 %	NA	65 %	NA	85 %	23 %	46 %	NA	45 %
Febrile neutropenia, %	NA	0%	16 %	NA	15 %	NA	19 %	6%	5%	NA	0%
Grade 3/4 thrombocytopenia, %	NA	27 %	26 %	NA	10 %	NA	37 %	41 %	7%	NA	10 %
Grade 3/4 fatigue, %	NA	3%	0%	NA	0%	NA	11 %	7%	7%	NA	10 %

CI, confidence interval; CTFI, chemotherapy-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival; NA, not available; nr, not reached (upper level); ORR, overall response rate; OS, overall survival.

Studies in Japanese patients treated with platinum re-challenge have shown grade 3/4 neutropenia in 65–94 % of patients, febrile neutropenia in 15–19 %, and grade 3/4 thrombocytopenia in 27–37 % (Table 4). Grade 3/4 fatigue, the other common adverse event with lurbinectedin, is similar than that reported with re-challenge (10 % *vs.* 3–11 %).

In conclusion, lurbinectedin is an effective treatment for platinum-sensitive relapsed SCLC, with remarkable activity in patients with CTFI $\geq$ 180 days. In addition, this drug has acceptable safety and tolerability, which is particularly favorable in terms of hematological toxicity compared to platinum re-challenge. These results suggest that lurbinectedin could be a valuable therapeutic alternative to re-treatment with the first-line therapy. Further research on larger populations is required to confirm this finding.

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CRediT authorship contribution statement

Vivek Subbiah: Investigation, Resources, Writing - original draft, Writing - review & editing. **Luis Paz-Ares:** Investigation, Resources, Writing - review & editing. **Benjamin Besse:** Investigation, Resources, Writing - review & editing. **Victor Moreno:** Investigation, Resources, Writing - review & editing. **Solange Peters:** Investigation, Resources, Writing - review & editing. **María Angeles Sala:** Investigation, Resources, Writing - review & editing. **José Antonio López-Vilariño:** Methodology, Writing - review & editing. **Cristian Fernández:** Methodology, Writing - review & editing, Supervision. **Carmen Kahatt:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Vicente Alfaro:** Methodology, Writing - original draft, Writing - review & editing. **Mariano Siguero:** Methodology, Formal analysis, Writing - review & editing. **Ali Zeaiter:** Methodology, Writing - review & editing, Supervision. **Khalil Zaman:** Investigation, Resources, Writing - review & editing. **Rafael López:** Investigation, Resources, Writing - review & editing. **Santiago Ponce:** Investigation, Resources, Writing - review & editing. **Valentina Boni:** Investigation, Resources, Writing - review & editing. **Jennifer Arrondeau:** Investigation, Resources, Writing - review & editing. **Jean-Pierre Delord:** Investigation, Resources, Writing - review & editing. **Maite Martínez:** Investigation, Resources, Writing - review & editing. **Luciano Wannesson:** Investigation, Resources, Writing - review & editing. **Antonio Antón:** Investigation, Resources, Writing - review & editing. **Javier Valdivia:** Investigation, Resources, Writing - review & editing. **Ahmad Awada:** Investigation, Resources, Writing - review & editing. **Rebecca Kristeleit:** Investigation, Resources, Writing - review & editing. **Maria Eugenia Olmedo:** Investigation, Resources, Writing - review & editing. **María Jesús Rubio:** Investigation, Resources, Writing - review & editing. **John Sarantopoulos:** Investigation, Resources, Writing - review & editing. **Sant P. Chawla:** Investigation, Resources, Writing - review & editing. **Joaquín Mosquera-Martinez:** Investigation, Resources, Writing - review & editing. **Manolo D' Arcangelo:** Investigation, Resources, Writing - review & editing. **Armando Santoro:** Investigation, Resources, Writing - review & editing. **Victor M. Villalobos:** Investigation, Resources, Writing - review & editing. **Jacob Sands:** Investigation, Resources, Writing - review & editing. **José Trigo:** Investigation, Resources, Writing - review & editing.

Declaration of Competing Interest

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