



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

Vivek Subbiah<sup>a,\*</sup>, Luis Paz-Ares<sup>b</sup>, Benjamin Besse<sup>c</sup>, Victor Moreno<sup>d</sup>, Solange Peters<sup>e</sup>, María Angeles Sala<sup>f</sup>, José Antonio López-Vilariño<sup>g</sup>, Cristian Fernández<sup>g</sup>, Carmen Kahatt<sup>g</sup>, Vicente Alfaro<sup>g</sup>, Mariano Sigüero<sup>g</sup>, Ali Zeaiter<sup>g</sup>, Khalil Zaman<sup>e</sup>, Rafael López<sup>h</sup>, Santiago Ponce<sup>b</sup>, Valentina Boni<sup>i</sup>, Jennifer Arrondeau<sup>j</sup>, Jean-Pierre Delord<sup>k</sup>, Maite Martínez<sup>l</sup>, Luciano Wannesson<sup>m</sup>, Antonio Antón<sup>n</sup>, Javier Valdivia<sup>o</sup>, Ahmad Awada<sup>p</sup>, Rebecca Kristeleit<sup>q</sup>, Maria Eugenia Olmedo<sup>r</sup>, María Jesús Rubio<sup>s</sup>, John Sarantopoulos<sup>t</sup>, Sant P. Chawla<sup>u</sup>, Joaquín Mosquera-Martinez<sup>v</sup>, Manolo D' Arcangelo<sup>w</sup>, Armando Santoro<sup>x</sup>, Victor M. Villalobos<sup>y</sup>, Jacob Sands<sup>z</sup>, José Trigo<sup>A</sup>

<sup>a</sup> The University of Texas MD Anderson Cancer Center, Houston, TX, USA

<sup>b</sup> Hospital Universitario Doce de Octubre, Madrid, Spain

<sup>c</sup> Gustave Roussy Cancer Campus, Villejuif, France

<sup>d</sup> START Madrid-FJD, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain

<sup>e</sup> University Hospital CHUV, Lausanne, Switzerland

<sup>f</sup> Hospital Universitario de Basurto, Bilbao, Spain

<sup>g</sup> PharmaMar, Colmenar Viejo, Spain

<sup>h</sup> Hospital Clínico Universitario de Santiago de Compostela, Santiago De Compostela, Spain

<sup>i</sup> START Madrid-CIOCC, Hospital Universitario Sanchinarro, Madrid, Spain

<sup>j</sup> Hôpital Cochin, Paris, France

<sup>k</sup> Institut Claudius Regaud, Toulouse, France

<sup>l</sup> Complejo Hospitalario de Navarra, Pamplona, Spain

<sup>m</sup> Ospedale San Giovanni, Bellinzona, Switzerland

<sup>n</sup> Hospital Universitario Miguel Servet, Zaragoza, Spain

<sup>o</sup> Hospital Universitario Virgen de las Nieves, Granada, Spain

<sup>p</sup> Institut Jules Bordet, Université Libre De Bruxelles, Brussels, Belgium

<sup>q</sup> UCL Cancer Institute, London, United Kingdom

<sup>r</sup> Hospital Universitario Ramón y Cajal, Madrid, Spain

<sup>s</sup> Hospital Universitario Reina Sofía, Córdoba, Spain

<sup>t</sup> Institute for Drug Development, Mays Cancer Center at University of Texas Health San Antonio MD Anderson Cancer Center, San Antonio, TX, USA

<sup>u</sup> Sarcoma Oncology Center, Santa Monica, CA, USA

<sup>v</sup> Complejo Hospitalario Universitario A Coruña, A Coruña, Spain

<sup>w</sup> Ospedale Santa Maria delle Croci, Ravenna, Italy

<sup>x</sup> Istituto Clinico Humanitas, Rossano, Italy

<sup>y</sup> University of Colorado Cancer Center, Aurora, USA

<sup>z</sup> Dana-Farber Cancer Institute, Boston, MA, USA

<sup>A</sup> Hospital Universitario Virgen de la Victoria, Málaga, Spain

### ARTICLE INFO

#### Keywords:

Lurbinectedin  
Chemotherapy-free interval  
Platinum re-challenge  
NCCN guidelines

### 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)  $\geq 180$  days. A phase II study (NCT02454972) showed remarkable antitumor activity in SCLC patients treated with lurbinectedin 3.2 mg/m<sup>2</sup> 1-h intravenous infusion every 3 weeks as second-line therapy. We report results for the pre-planned subset of patients with CTFI  $\geq 180$  days.

\* Corresponding author at: Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX, 77030, USA.

E-mail address: [vsubbiah@mdanderson.org](mailto:vsubbiah@mdanderson.org) (V. Subbiah).

<https://doi.org/10.1016/j.lungcan.2020.10.003>

Received 21 August 2020; Accepted 5 October 2020

Available online 10 October 2020

0169-5002/© 2020 The Authors.

Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Material and Methods:** Twenty patients aged  $\geq 18$  years with pathologically proven SCLC diagnosis, pretreated with only one prior platinum-containing line, no CNS metastases, and with CTFI  $\geq 180$  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  $\geq 180$  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)  $\geq 90$  days in the ESMO guidelines and patients with a CTFI  $\geq 180$  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  $\geq 90$  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  $\geq 180$  days. A phase II randomized study evaluating amrubicin *versus* platinum re-challenge included 18 of 30 patients (60.0 %) with relapse after CTFI  $\geq 180$  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  $\geq 180$  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  $\geq 90$  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  $\leq 180$  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  $\geq 180$  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  $\geq 18$  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)  $\leq 2$ ; 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<sup>2</sup> 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<sup>2</sup>.

### 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  $\geq$  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

**Table 1**

Baseline characteristics in SCLC patients with CTFI  $\geq$  180 days (n = 20).

|   | n              | %     |
|---|----------------|-------|
| <b>Gender</b>                                   |                |       |
| Male  | 12             | 60.0  |
| Female  | 8              | 40.0  |
| <b>Age, median (range), years</b>               | 57 (49–75)     |       |
| <b>ECOG PS status</b>                           |                |       |
| 0   | 10             | 50.0  |
| 1   | 9              | 45.0  |
| 2   | 1              | 5.0   |
| <b>Abnormal LDH (&gt;ULN)</b>                   | 5              | 25.0  |
| <b>Smoker status</b>                            |                |       |
| Former/current                                  | 18             | 90.0  |
| Never   | 2              | 10.0  |
| <b>Stage at diagnosis</b>                       |                |       |
| Limited   | 13             | 65.0  |
| Extended  | 7              | 35.0  |
| <b>No. of sites at baseline, median (range)</b> | 3 (1–5)        |       |
| <b>Most common sites other than lung</b>        |                |       |
| Lymph nodes                                     | 16             | 80.0  |
| Adrenal   | 5              | 25.0  |
| Liver   | 4              | 20.0  |
| Bulky disease (one lesion >50 mm)               | 4              | 20.0  |
| <b>CNS involvement</b>                          | 2 <sup>a</sup> | 10.0  |
| <b>Paraneoplastic syndrome</b>                  | 1              | 5.0   |
| <b>Prophylactic cranial irradiation</b>         | 15             | 75.0  |
| <b>No. of prior lines, median (range)</b>       | 1 (1–2)        |       |
| 1 line  | 19             | 95.0  |
| 2 lines   | 1 <sup>b</sup> | 5.0   |
| <b>Prior agents</b>                             |                |       |
| Platinum compounds                              | 20             | 100.0 |
| Etoposide                                       | 20             | 100.0 |
| Immunotherapy                                   | 0              | 0.0   |
| <b>Best response to prior platinum</b>          |                |       |
| CR  | 7              | 35.0  |
| PR  | 10             | 50.0  |
| SD  | 3              | 15.0  |
| <b>CTFI, median (range), months</b>             | 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.

<sup>a</sup> One patient had CNS metastases at baseline (protocol deviation) another CNS history prior to study entry.

<sup>b</sup> One patient was treated with a second line consisting of an investigational drug (GSK52572).

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).

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  $\geq$  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  $\geq 180$  days (n = 20).

|  | Investigator                      | Independent review       |
|--|-----------------------------------|--------------------------|
| ORR <sup>a</sup> , n (%) (95 %CI)                                    | 12 (60.0)<br>(36.1–86.9)          | 10 (50.0)<br>(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)<br>(75.1–99.9)          | 16 (80.0)<br>(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 <sup>b</sup> (95 %CI), OS at 12 months, % (95 %CI) | 16.2 (9.6–nr)<br>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.

<sup>a</sup> Confirmed responses.

<sup>b</sup> 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 $\geq 3$ ) in SCLC patients treated with lurbinectedin and chemotherapy-free interval  $\geq 180$  days (n = 20).

|  | NCI-CTCAE grade    |                  |                  |
|--|--------------------|------------------|------------------|
|  | Grade 1–2<br>n (%) | Grade 3<br>n (%) | Grade 4<br>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 <sup>a</sup>                        | 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.

<sup>a</sup> 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  $\geq 90$  days and CTFI  $\geq 180$  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  $\geq 180$  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  $\geq 90$  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  $\geq 180$  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  $\geq 90$  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  $\geq 180$  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<sup>2</sup> 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  $\geq 90$  and  $\geq 180$  days): platinum re-challenge and lurbinectedin.

|                               | CTFI $\geq 90$ days   |                       |                   |                       |                     |                        |                    |                     |                     | CTFI $\geq 180$ 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, %                        | 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, %       | 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          | 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           | 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.

#### Prior presentation

Presented at the European Society of Medical Oncology Congress, Madrid, Spain, 18–22 September 2020.

#### Funding statement

The study was funded by Pharma Mar S.A, including grants from the *Centro para el Desarrollo Tecnológico Industrial (CDTI)* during the conduct of the study. One of the centers, the Institute for Drug Development, Cancer Therapy and Research Center at University of Texas Health Science Center San Antonio, San Antonio, TX, USA, received a Cancer Center Support Grant (P30CA054174).

#### 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-Vilarino:** 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

**Vivek Subbiah** received clinical trials research support from Altum, Amgen, ABBVIE, Agensys, Bayer, Berghealth, Blueprint Medicines, Boston Medical, Celgene, D3, Dragonfly therapeutics, Exelexis, Fujifilm, GSK, Idera Pharma, INCYTE, Inhibrx, LOXO Oncology, MedImmune, Multivir, Nanocarrier, Northwest Biotherapeutics, Novartis, Pfizer, Roche/Genentech, Takeda, and Vegenics, outside the submitted work. He also declares National Comprehensive Cancer Network, NCI-CTEP and UT MD Anderson Cancer Center and travel support from Novartis, Pharma Mar, ASCO, ESMO, Helsinn, and Incyte, and advisory board from Helsinn, LOXO Oncology, R-Pharma US, Incyte, and Medimmune. **Luis Paz-Ares** received personal fees for scientific advice/speaker from Adacap, Amgen, AstraZeneca (grant), Bayer, Blueprint, Boehringer Ingelheim, Bristol Myers Squibb (grant), Celgene, Incyte, Ipsen, Lilly, Merck, MSD (grant), Novartis, Pfizer (grant), Pharma Mar, Roche, Sanofi, Servier, Sysmex; from Genomica as advisory board member; and from Altum Sequencing as co-founder and board member outside the submitted work. **Benjamin Besse** received grants from Abbvie, Amgen, AstraZeneca, Biogen, Blueprint Medicines, Bristol-Myers Squibb, Celgene, Eli Lilly, GlaxoSmithkline, Ingnyta, Inivata, Ipsen, Merck, MSD Oncology, Nektar, Onxeo, Pfizer, Pharma Mar, Sanofi, Spectrum Pharmaceuticals, Takeda, and Tiziana Therapeutics, outside the submitted work. **Victor Moreno** received personal fees for advisory roles from Basilea, Bayer, BMS, Janssen, and Pieris, outside the submitted work. **Solange Peters** received personal fees for advisory board from Abbvie, Amgen, AstraZeneca, Bayer, Biocartis, Bioinvent, Boehringer-Ingelheim, Bristol-Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, Eli Lilly, F. Hoffman-La Roche, Foundation Medicine, Illumina, Janssen, Merck Sharp and Dohme, Merck Serono, Merrimack, Novartis, Pharma Mar, Pfizer, Regeneron, Sanofi, Seattle Genetics, and Takeda; as speaker for AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, F. Hoffman-La Roche, Merck Sharp and Dohme, Novartis, Pfizer, Takeda; and for investigation in trials from Amgen, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Clovis, F. Hoffman-La Roche, Illumina, Merck Sharp and Dohme, Merck Serono, Novartis, Pfizer, and Sanofi, outside the submitted work. **José Antonio López-Vilarino, Cristian Fernandez, Carmen Kahatt, Vicente Alfaro, Mariano Siguero** and **Ali Zeaiter** received personal fees for salary as full time employees and stock ownership from Pharma Mar, outside the submitted work. **Khalil Zaman** received grants from AstraZeneca, Celgene, Daiichi, Eisai, Exact Science, Genomic Health, Lilly, MSD, Mylan, Novartis, Pfizer, Pierre Fabre, and Roche for travel accommodation, advisory board, sponsoring of academic symposium, or research, outside the submitted work. **Rafael López** received grants/fees for advisory board, accommodation, lectures, research grants and travel from Bayer, BMS, Lilly, Merck, Novartis, Pfizer, Pharma Mar, Pierre Fabre, and Roche, outside the submitted work. **Javier Valdivia** received fees for accommodation from Novartis and fees for speakers bureau from BMS, outside the submitted work. **Ahmad Awada** received travel grants, advisory board, and speaker fees from BMS, Eisai, IPSEN, Leo Pharma, Lilly, Novartis, Pfizer, and Roche, outside the submitted work. **John Sarantopoulos** received a grant from the Institute for Drug Development, Cancer Therapy and Research Center at University of Texas Health Science Center San Antonio, during the conduct of the study. **Sant P. Chawla** received non-financial support from Pharma Mar (drug supply), outside the submitted work. **Armando Santoro** received fees for advisory board from Bayer, BMS, Eisai, Gilead, MSD, Pfizer and Servier; for speakers' bureau from Abbvie, Amgen, Arqule, AstraZeneca, Bayer, BMS, Celgene, Eisai, Gilead, Lilly, MSD, Novartis, Roche, Sandoz, Servier, Pfizer, and Takeda; and as consultant from Arqule and Sanofi, outside the submitted work. **Victor M. Villalobos** received fees for advisory board from Abbvie, Agios, Blueprint, Janssen, Lilly,

Nanocarrier, and Springworks, outside the submitted work. **Jacob Sands** received personal fees for consulting/advisory board from Abbvie, AstraZeneca, Boehringer Ingelheim, Celgene, Eli Lilly and Company, Foundation Medicine, Genentech, Guardant, Incyte, Jazz Pharmaceuticals, Loxo, Medtronic, Merck, Pharma Mar, and Trovogene, outside the submitted work. **José Trigo** received personal fees for scientific advice and speaker roles from Astra Zeneca, BMS, Merck Serono, Pfizer and Roche; advisory board from Boehringer and Takeda; and travel grant from BMS and MSD, outside the submitted work. The remaining authors declare no conflict of interest.

## Acknowledgements

We gratefully acknowledge the patients, their families and investigator teams.

## References

- [1] M. Fruh, D. De Ruyscher, S. Papat, L. Crino, S. Peters, E. Felip, E.G.W. Group, Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, *Ann. Oncol.* 24 (Suppl 6) (2013) vi99–105.
- [2] NCCN clinical practice guidelines in oncology, Small Cell Lung Cancer (2020). Version 4.2020 - July 7, [https://www.nccn.org/professionals/physician\\_gls/pdf/sclc.pdf](https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf).
- [3] L. Horn, A.S. Mansfield, A. Szczesna, L. Havel, M. Krzakowski, M.J. Hochmair, F. Huemer, G. Losonczy, M.L. Johnson, M. Nishio, M. Reck, T. Mok, S. Lam, D. S. Shames, J. Liu, B. Ding, A. Lopez-Chavez, F. Kabbinar, W. Lin, A. Sandler, S. V. Liu, I.M.S. Group, First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer, *N. Engl. J. Med.* 379 (23) (2018) 2220–2229.
- [4] L. Paz-Ares, M. Dvorkin, Y. Chen, N. Reinmuth, K. Hotta, D. Trukhin, G. Statsenko, M.J. Hochmair, M. Ozguroglu, J.H. Ji, O. Voitko, A. Poltoratskiy, S. Ponce, F. Verderame, L. Havel, I. Bondarenko, A. Kazarnowicz, G. Losonczy, N.V. Conev, J. Armstrong, N. Byrne, N. Shire, H. Jiang, J.W. Goldman, C. investigators, Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial, *Lancet* 394 (10212) (2019) 1929–1939.
- [5] T. Korkmaz, S. Seber, U. Kefeli, E. Sari, M. Canhoroz, B. Oven, E. Yildirim, N. Yasar, D. Aydin, O. Balvan, N. Sener, S. Yuksel, A. Mert, O. Polat, F. Yumuk, O. Kanat, M. Gumus, N.S. Turhal, Comparison of second-line treatment outcomes between sensitive and refractory small cell lung cancer patients: a retrospective analysis, *Clin. Transl. Oncol.* 15 (7) (2013) 535–540.
- [6] A. Inoue, S. Sugawara, M. Maemondo, Y. Mori, S. Oizumi, M. Harada, K. Taima, N. Morikawa, T. Ishida, I. Kinoshita, H. Watanabe, T. Suzuki, T. Nakagawa, R. Saito, T. Nukiwa, Randomized phase II trial comparing amrubicin with rechallenge of platinum doublet in patients with sensitive-relapsed small-cell lung cancer: North Japan Lung Cancer Study Group trial 0702, *Lung Cancer* 89 (1) (2015) 61–65.
- [7] K. Wakuda, H. Kenmotsu, T. Naito, H. Akamatsu, A. Ono, T. Shukuya, Y. Nakamura, A. Tsuya, H. Murakami, T. Takahashi, M. Endo, T. Nakajima, N. Yamamoto, Efficacy of rechallenge chemotherapy in patients with sensitive relapsed small cell lung cancer, *Am. J. Clin. Oncol.* 38 (1) (2015) 28–32.
- [8] G. Genestreti, M. Tiseo, H. Kenmotsu, W. Kazushige, M. Di Battista, G. Cavallo, F. Carloni, A. Bongiovanni, M.A. Burgio, C. Casanova, G. Metro, E. Scarpì, T. Korkmaz, S. Selcuk, K. Roopa, R. Califano, Outcomes of platinum-sensitive small-cell lung cancer patients treated with Platinum/Etoposide rechallenge: a multi-institutional retrospective analysis, *Clin. Lung Cancer* 16 (6) (2015) e223–8.
- [9] T. Shiozawa, I. Sekine, Y. Aida, H. Watanabe, K. Nakazawa, K. Kurishima, H. Satoh, N. Hizawa, Rechallenge with first-line platinum chemotherapy for sensitive-relapsed small-cell lung cancer, *Case Rep. Oncol.* 11 (3) (2018) 622–632.
- [10] Y. Naito, K. Yamada, Y. Imamura, H. Ishii, N. Matsuo, T. Tokito, T. Kinoshita, K. Azuma, T. Hoshino, Rechallenge treatment with a platinum-based regimen in patients with sensitive relapsed small-cell lung cancer, *Med. Oncol.* 35 (5) (2018) 61.
- [11] K. Wakuda, T. Miyawaki, E. Miyawaki, N. Mamesaya, T. Kawamura, H. Kobayashi, S. Omori, K. Nakashima, A. Ono, H. Kenmotsu, T. Naito, H. Murakami, K. Mori, M. Endo, T. Takahashi, Efficacy of second-line chemotherapy in patients with sensitive relapsed small-cell lung cancer, *In Vivo* 33 (6) (2019) 2229–2234.
- [12] I. Monnet, N. Baize, L. Greillier, M. Geier, H. Lena, H. Janicot, A. Vergne, J. Crequit, R. Lamy, J.B. Auliac, J. Le Treut, H. Le Caer, R. Gervais, E. Dansin, A. Madroszyk, P. Renault, G. Legarff, R. Schott, P. Saulnier, C. Chouaid, OA15.02 carboplatin-etoposide versus topotecan as second-line treatment for sensitive relapsed small-cell lung cancer: phase 3 trial, *J. Thorac. Oncol.* 14 (10) (2019) S246.
- [13] C.L. Christensen, N. Kwiatkowski, B.J. Abraham, J. Carretero, F. Al-Shahrouh, T. Zhang, E. Chipumuro, G.S. Herter-Sprie, E.A. Akbay, A. Altabel, J. Zhang, T. Shimamura, M. Capelletti, J.B. Reibel, J.D. Cavanaugh, P. Gao, Y. Liu, S. R. Michaelsen, H.S. Poulsen, A.R. Aref, D.A. Barbie, J.E. Bradner, R.E. George, N. S. Gray, R.A. Young, K.K. Wong, Targeting transcriptional additions in small cell lung cancer with a covalent CDK7 inhibitor, *Cancer Cell* 26 (6) (2014) 909–922.
- [14] C.M. Rudin, J.T. Poirier, L.A. Byers, C. Dive, A. Dowlati, J. George, J.V. Heymach, J.E. Johnson, J.M. Lehman, D. MacPherson, P.P. Massion, J.D. Minna, T.G. Oliver, V. Quaranta, J. Sage, R.K. Thomas, C.R. Vakoc, A.F. Gazdar, Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data, *Nat. Rev. Cancer* 19 (5) (2019) 289–297.
- [15] J.F. Leal, M. Martinez-Diez, V. Garcia-Hernandez, V. Moneo, A. Domingo, J. A. Bueren-Calabuig, A. Negri, F. Gago, M.J. Guillen-Navarro, P. Aviles, C. Cuevas, L.F. Garcia-Fernandez, C.M. Galmarini, PM01183, a new DNA minor groove covalent binder with potent in vitro and in vivo anti-tumour activity, *Br. J. Pharmacol.* 161 (5) (2010) 1099–1110.
- [16] G. Santamaria Nunez, C.M. Robles, C. Giraudon, J.F. Martinez-Leal, E. Compe, F. Coin, P. Aviles, C.M. Galmarini, J.M. Egly, Lurbinectedin specifically triggers the degradation of phosphorylated RNA polymerase II and the formation of DNA breaks in cancer cells, *Mol. Cancer Ther.* 15 (10) (2016) 1–14.
- [17] M.L. Harlow, N. Maloney, J. Roland, M.J. Guillen Navarro, M.K. Easton, S. M. Kitchen-Goosen, E.A. Boguslawski, Z.B. Madaj, B.K. Johnson, M.J. Bowman, M. D'Incalci, M.E. Winn, L. Turner, G. Hostetter, C.M. Galmarini, P.M. Aviles, P. J. Grohar, Lurbinectedin inactivates the ewing sarcoma oncoprotein EWS-FLI1 by redistributing it within the nucleus, *Cancer Res.* 76 (22) (2016) 6657–6668.
- [18] C. Belgiovine, E. Bello, M. Liguori, I. Craparotta, L. Mannarino, L. Paracchini, L. Beltrame, S. Marchini, C.M. Galmarini, A. Mantovani, R. Frapolli, P. Allavena, M. D'Incalci, Lurbinectedin reduces tumour-associated macrophages and the inflammatory tumour microenvironment in preclinical models, *Br. J. Cancer* 117 (5) (2017) 628–638.
- [19] 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.
- [20] E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancy, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij, New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), *Eur. J. Cancer* 45 (2) (2009) 228–247.
- [21] P.E. Postmus, H.H. Berendsen, N. van Zandwijk, T.A. Splinter, J.T. Burghouts, W. Bakker, Retreatment with the induction regimen in small cell lung cancer relapsing after an initial response to short term chemotherapy, *Eur. J. Cancer Clin. Oncol.* 23 (9) (1987) 1409–1411.
- [22] G. Giaccone, P. Ferrati, M. Donadio, F. Testore, A. Calciati, Reinduction chemotherapy in small cell lung cancer, *Eur. J. Cancer Clin. Oncol.* 23 (11) (1987) 1697–1699.
- [23] M. Lattuca-Truc, J.F. Timsit, M.G. Levra, S. Ruckly, J. Villa, I. Dumas, J. Pinsolle, L. Ferrer, P. Guillem, D. Moro-Sibilot, A.C. Toffart, F. Multidisciplinary Thoracic Oncology Group Grenoble University Hospital, Trends in response rate and survival in small-cell lung cancer patients between 1997 and 2017, *Lung Cancer* 131 (2019) 122–127.
- [24] A. Rossi, Relapsed small-cell lung cancer: platinum re-challenge or not, *J. Thorac. Dis.* 8 (9) (2016) 2360–2364.
- [25] M. Fruh, C.M. Panje, M. Reck, F. Blackhall, R. Califano, F. Cappuzzo, B. Besse, S. Novello, P. Garrido, E. Felip, M. O'Brien, L. Paz Ares, F. de Marinis, V. Westeel, D. De Ruyscher, P.M. Putora, Choice of second-line systemic therapy in stage IV small cell lung cancer (SCLC) - A decision-making analysis amongst European lung cancer experts, *Lung Cancer* 146 (2020) 6–11.
- [26] M.D. DiBonaventura, B. Shah-Manek, K. Higginbottom, J.R. Penrod, Y. Yuan, Adherence to recommended clinical guidelines in extensive disease small-cell lung cancer across the US, Europe, and Japan, *Ther. Clin. Risk Manag.* 15 (2019) 355–366.
- [27] C.C. Steffens, C. Elender, U. Hutzschenreuter, S. Dille, A. Binnering, L. Spring, M. Janicke, N. Marschner, T.L.K. Group, Treatment and outcome of 432 patients with extensive-stage small cell lung cancer in first, second and third line - Results from the prospective German TLK cohort study, *Lung Cancer* 130 (2019) 216–225.
- [28] M. Povicic, A. Enstone, R. Wyn, K. Kornalska, J.R. Penrod, Y. Yuan, Real-world effectiveness and tolerability of small-cell lung cancer (SCLC) treatments: a systematic literature review (SLR), *PLoS One* 14 (7) (2019), e0219622.
- [29] [https://www.ema.europa.eu/en/documents/scientific-discussion-variation/hycamintin-h-c-123-ii-0034-epar-scientific-discussion-variation\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-discussion-variation/hycamintin-h-c-123-ii-0034-epar-scientific-discussion-variation_en.pdf). (Accessed 22 June 2020).