ATLANTIS: a Phase III study of lurbinectedin/doxorubicin versus topotecan or cyclophosphamide/doxorubicin/vincristine in patients with small-cell lung cancer who have failed one prior platinum-containing line

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Lurbinectedin is an inhibitor of active transcription of protein-coding genes, causing DNA-break accumulation, apoptosis and modulation of the tumor microenvironment. Early-phase clinical trials indicate promising activity of lurbinectedin in small-cell lung cancer. Here, we describe the rationale and design of ATLANTIS (NCT02566993), an open-label, randomized, multicenter Phase III study to compare the efficacy of lurbinectedin and doxorubicin combination with standard-of-care chemotherapy, investigator's choice of cyclophosphamide/doxorubicin/vincristine or topotecan, in patients with small-cell lung cancer that has progressed following one line of platinum-based chemotherapy. Patients are randomized in a 1:1 ratio. The primary end point is overall survival and key secondary end points include progression-free survival, best tumor response and duration of response, each assessed by independent review committee.

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Small-cell lung cancer (SCLC) is a high-grade neuroendocrine malignancy of the lung which accounts for approximately 13–15% of all lung cancers [1]. Outcomes for patients with SCLC have remained virtually unchanged for nearly 30 years, with a median overall survival (OS) of 9–11 months for patient diagnosed with metastatic disease [2–6]. A history of tobacco exposure is the most significant risk factor for developing SCLC and the vast majority of SCLCs occur in patients who are current or former smokers. The SCLC tends to present with bulky mediastinal lymph node involvement and often with distant metastases [7]. The standard-of-care, first-line therapy for metastatic SCLC is combination of platinum (carboplatin or cisplatin) with etoposide or with irinotecan [8]. Unfortunately, despite high-response rates to initial chemotherapy, ranging 50–70% in recent clinical trials [2–5], metastatic SCLC nearly always relapse.

Currently, the topoisomerase-I inhibitor topotecan is the only US FDA- and EMA-approved second-line treatment in SCLC. In recent randomized studies, the median progression-free survival (PFS) for patients treated in the topotecan control arm ranged from 3.0 to 3.5 months and the OS ranged from 7 to 8 months [9–11]. Efficacy of topotecan, as well as other agents used in the second-line setting, varies depending on the degree of platinum sensitivity of the population. Generally, 'platinum-sensitive' SCLC refers to disease that relapses >3 months after completion of the first-line therapy, and 'platinum-resistant' or 'refractory' SCLC refers to disease that relapses

≤3 months after completion of the first-line therapy, though the specific terminology and cut-offs defining these categories may vary from study to study. Across 21 studies published between 1984 and 2001, both response rates and OS were superior in platinum-sensitive patients compared with platinum-resistant patients [12]. Notably, topotecan was directly compared with cyclophosphamide/doxorubicin/vincristine (CAV) in a randomized trial of 211 patients and measures of efficacy were statistically equivalent in both groups (overall response rate [ORR] 24.3 vs 18.3%; $p = 0.285$; time-to-progression 13.1 vs 12.3 weeks; $p = 0.552$; OS 25.0 vs 24.7 weeks; $p = 0.795$ in patients treated with topotecan vs CAV, respectively) [13]. Recently, immune-checkpoint inhibitors have shown encouraging activity in SCLC [14,15], although, as of August 1 2018, are not currently FDA- or EMA-approved for use in this disease.

Despite extensive genetic characterization of SCLCs [16–19], no clear targetable alteration has emerged. The common genetic alterations in SCLC are loss of the tumor suppressor genes *TP53* and *RBI* [18]. A recent preclinical study in SCLC cell lines and genetically engineered mouse models uncovered a dependency on active transcription, with significant vulnerability to inhibition of CDK7 and subsequent reduction of RNA polymerase II-mediated gene transcription [20]. Interestingly, genes associated with highly active so-called ‘super-enhancers’ were involved in regulation of RNA polymerase II-mediated transcription and proposed proto-oncogenic transcription factors. Treatment with the CDK7 inhibitor THZ1 led to preferential down-regulation of super enhancer-associated genes in cell lines and to tumor regressions in genetically engineered mouse models [20]. Collectively, these data suggest that targeting active transcription may be an efficacious therapeutic strategy.

Lurbinectedin

Lurbinectedin (PM01183) is a synthetic analog of the natural marine-based tetrahydroisoquinoline trabectedin. It contains a pentacyclic skeleton composed of two fused tetrahydroisoquinoline rings, with an additional tetrahydro β -carboline moiety (Figure 1A) [21]. Lurbinectedin induces a specific degradation of transcribing RNA Pol II and the subsequent accumulation of DNA breaks (Figure 1B). This degradation occurs when elongating RNA polymerase II is arrested by the drug covalently bound to the CG-rich regions located within the affected gene and blocks the DNA-repair mechanism [22]. This degradation is dependent on active transcription, the presence of functional proteasome machinery and transcription-coupled nucleotide excision repair [22]. Furthermore, in transcriptionally addicted tumor cells (e.g., SCLC), lurbinectedin could cause a detachment of transcription factors (e.g., ASCL1, NeuroD1 and NFIB in SCLC) from their target promoters, inducing the block of its transactivating activity (Figure 1B). Lurbinectedin may also influence the tumor microenvironment via suppression of tumor proliferation, matrix remodeling, angiogenesis and immune suppression (Figure 1C) [23–25]. Lurbinectedin activity on SCLC cell lines was demonstrated *in vitro* and *in vivo* [26].

The ATLANTIS study

Here, we describe the design and rationale for the ATLANTIS study (NCT02566993), an open-label, randomized Phase III trial to evaluate efficacy and safety of lurbinectedin and doxorubicin combination versus investigator’s choice chemotherapy, either topotecan or CAV, in patients with SCLC who have failed one prior platinum-containing line. The study is funded by Pharma Mar SA, Madrid, Spain.

Background & rationale

In preclinical cell line and xenograft models, lurbinectedin showed activity both alone and in combination with doxorubicin. In xenografted SCLC tumors, the combination demonstrated substantial antitumor activity which appeared to be synergistic [26]. Clinical development of lurbinectedin was started in March 2009. The first-in-human single-agent lurbinectedin study established a recommended Phase II dose of 4.0 mg/m² or 7.0 mg flat dose (FD) given intravenously, every 21 days [27].

A Phase Ib study assessed the safety and efficacy of lurbinectedin combined with doxorubicin in patients with solid tumors [28]. The primary objective was to determine the recommended dose (RD) for further studies with this combination, and secondary objectives included assessing safety, analyzing possible pharmacokinetic drug–drug interactions and assessing antitumor activity. In the initial cohort (cohort A), doxorubicin was given at a dose of 50 mg/m² and lurbinectedin was given as 3–5 mg FD, both on day 1 of each 21-day cycle, with continuation of lurbinectedin at a FD of 7 mg after the cumulative dose of doxorubicin reached 450 mg/m². In this cohort, dose-limiting toxicities of febrile neutropenia were observed in one of ten patients treated without primary granulocyte colony-stimulating factors (G-CSF) prophylaxis. As a result, lurbinectedin 4.0 mg FD and doxorubicin

Figure 1. Chemical structure and schematized actions of lurbinectedin. (A) Chemical structure of lurbinectedin. **(B)** Schematic representation of lurbinectedin mechanism of action for binding DNA, inhibiting active transcription and inducing DNA breaks. **(C)** Schematic representation of lurbinectedin interactions with the tumor microenvironment. Lurb: Lurbinectedin.

50 mg/m² was defined as the RD for the combination and additional patients were enrolled in an expansion cohort treated at the RD. Reversible myelosuppression was the most common toxicity with the lurbinectedin and doxorubicin combination. Episodes of severe neutropenia, thrombocytopenia and febrile neutropenia were transient and successfully managed with cycle delays, dose reductions and G-CSF [28].

The combination-associated myelosuppression raised the question of whether the RD defined in this cohort would be safe and tolerable in a less selected/restricted Phase III population. In addition, the doxorubicin dose used in SCLC patients is usually less than 50 mg/m² per cycle (either 45 mg/m² with G-CSF support or 40 mg/m² without it), as several tobacco-related comorbidities and prior mediastinal irradiation are highly prevalent. As a result, the Phase Ib study was amended to reduce in a second cohort (cohort B) the doxorubicin RD dose by 20% (to 40 mg/m²) to limit the potentially severe myelosuppression and to explore the feasibility of this dose in less selected patients (ECOG PS score = 2 and without any age restriction). This protocol amendment also adjusted the doxorubicin dose to one that is more commonly used in these patients. The lurbinectedin dose was also adapted to a body surface (BSA)-based dose of 2.0 mg/m². The rationale for this change came from the results of a logistic regression analysis of pooled data from Phase II clinical trials with single-agent lurbinectedin in several solid tumors, which suggested that patients with the lowest BSA values could have a greater possibility of developing grade 3/4

Figure 2. Study design.

[†]Maximum 10 cycles, lurbinectedin to be continued at 3.2 mg/m².

CNS: Central nervous system; CT: Computerized tomography; CTFI: Chemotherapy-free interval; ECOG: Eastern Cooperative Oncology Group; N: No; OR: Overall response; SCLC: Small-cell lung cancer; Y: Yes.

thrombocytopenia and/or neutropenia. Hence, the lurbinectedin 4.0 mg FD was transformed to 2.0 mg/m² every 21 days, with the dose being capped at a BSA of 2.0 m² to prevent patients from receiving more lurbinectedin than 4.0 mg FD every 21 days, previously defined as the RD.

Ultimately, 48 patients with SCLC were enrolled into this Phase I study: 21 in the initial cohort (cohort A) and 27 in the second cohort (cohort B). The median age of these patients was 62 and 64, respectively and all had Eastern Cooperative Oncology Group (ECOG) performance status 1–2. In cohorts A and B, 43 and 54% of patients had received prior prophylactic cranial irradiation and the proportions of patients with known brain metastases were 33 and 4%, respectively. The proportion of patients with ‘platinum-sensitive’ disease, defined as a chemotherapy-free interval (CTFI) from completion of the first-line therapy to start of the second-line therapy of more than 90 days, was 52% in cohort A and 64% in cohort B. The proportion of patients with CTFI >30 days was 76 and 78% in cohorts A and B, respectively.

Clinical activity of lurbinectedin and doxorubicin was seen among patients with SCLC in both cohorts. In cohort A, there were two complete responses and 12 partial responses (PRs; ORR = 67%). In cohort B, there was one complete response and nine PRs (ORR = 37%). The disease control rate was 81 and 70% and the median duration of response was 4.5 months and 5.2 months in cohorts A and B, respectively. The median PFS was 4.7 months and 5.3 months among patients with CTFI >30 days and 5.8 months and 6.2 months among patients with platinum-sensitive disease (CTFI >90 days) in cohorts A and B, respectively.

In addition to the lurbinectedin/doxorubicin combination Phase Ib data, data are available from seven SCLC patients treated with lurbinectedin and paclitaxel combination in the third-line setting in a separate Phase Ib study. To date, five of these seven patients had responded to treatment (ORR = 71%) [29].

A multicenter Phase II basket trial to assess the efficacy and safety of single-agent lurbinectedin in several advanced solid tumors, including SCLC, is ongoing. In the SCLC cohort, 50 patients were treated and were evaluable for efficacy. Median age was 60 years and 29 (58%) were males; 45 patients (80%) had an ECOG PS of 0/1, 25 patients (50%) had CTFI ≥90 days. Nineteen patients (38%) had a PR; 52% (13/25) of patients with CTFI ≥90 days had a PR. Twenty patients (40%) had disease stabilization, six of them for >4 months. Median duration of response was 5.3 months and median PFS was 4.2 months (4.7 months for patients with CTFI ≥90 days) [30].

Design

Study design

The ATLANTIS study consists of a screening period, a treatment period and a follow-up period (Figure 2). During the screening period, patients provide written informed consent and screening assessments are performed,

including medical history and clinical examination, laboratory tests, measurement of left ventricular ejection fraction by echocardiogram or multiple-gated acquisition scan, pregnancy test (for women of childbearing age), electrocardiogram clinical and radiological tumor assessment, CNS tumor assessment, patient-reported outcomes using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTC QLQ-LC13 questionnaires and adverse-event reporting with grading per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4. Investigators will specify the chemotherapy selected in the control arm prior to randomization. Eligible patients are randomized in a 1:1 ratio using central randomization into one of the following two arms:

- Experimental arm: lurbinectedin and doxorubicin;
- Control arm: investigator's choice chemotherapy (topotecan or CAV).

Stratification is performed according to the ECOG PS (0 vs 1–2), CTFI after the first-line therapy (≥ 180 days vs 90–179 days vs < 90 days), baseline CNS involvement (yes vs no), prior immunotherapy against either PD-1 or PD-L1 therapy (yes vs no) and investigator's preference (best investigator's choice prior to randomization) between topotecan and CAV.

Day 0 is defined as the day of randomization and treatment (cycle 1 day 1) must start within 72 h after randomization. The treatment phase extends from randomization to disease progression, investigator's decision, unacceptable toxicity or withdrawal of consent. During treatment, evaluations include: clinical examination on day 1 of cycle 2 and subsequent cycles; laboratory tests on days 1 and 10 of cycles 1 and 2 and day 1 of subsequent cycles; measurement of left ventricular ejection fraction before cycles 3, 6, 9 and 11 (for experimental and CAV arms and as clinically indicated for topotecan arm); pregnancy test each cycle (for woman of childbearing age); ECG before cycles 6 and 11 (for experimental and CAV arms and as clinically indicated for topotecan arm); pharmacokinetics (for patients in experimental arm only); pharmacogenetics for patients who provide specific written informed consent; clinical and radiological tumor assessment every 6 weeks and CNS radiological assessment as clinically indicated; patient-reported outcomes; survival information and adverse events as per NCI-CTCAE v.4.

An end-of-treatment visit will occur within 30 days of the last treatment infusion or immediately prior to the start of a new therapy, whichever is sooner. After treatment, patients who have withdrawn from the study without progressive disease will continue tumor assessment every 6 weeks until progressive disease (PD), start of a new therapy, death or date of study termination (clinical cut-off), whichever occurs first. After PD is documented or a new antitumor therapy is started, patients will be followed for survival every 3 months during the first 18 months after randomization, and then once every 6 months until death or date of study termination, whichever occurs first.

Primary, secondary & tertiary objectives

The primary objective of the study is to determine whether there is a difference in OS between the lurbinectedin/doxorubicin arm and control arm. Secondary objectives include analyzing difference in OS between the lurbinectedin/doxorubicin and CAV arms, in patients with CAV as best investigator's choice; assessing OS/PFS in patients with and without baseline CNS involvement and subgroup analyses in platinum-sensitive and -resistant populations; assessing PFS by an independent review committee (IRC); assessing antitumor activity by IRC according to RECIST v.1.1 and assessing safety profile. Key tertiary objectives include assessing landmark analyses of OS at 12, 18 and 24 months; safety and efficacy subgroup analyses; PFS, best antitumor response and duration of response by investigator assessment; patient-reported outcomes and pharmacokinetics and pharmacogenetics.

Key eligibility criteria

Key eligibility criteria include age ≥ 18 years, ECOG performance status ≤ 2 and histologically or cytologically confirmed diagnosis of limited or extensive stage SCLC which failed one prior platinum-containing regimen. Patients who had received prior-intervening immune checkpoint inhibitor therapy are eligible. Patients must have adequate hematological, renal, metabolic and hepatic function and a washout of at least 3 weeks since last prior anticancer treatment, at least 4 weeks since completion of whole brain radiation therapy and at least 2 weeks since completion of prophylactic cranial irradiation or palliative radiation. Key exclusion criteria include patients who received more than one prior chemotherapy-containing regimen (including patients re-challenged with the same initial regimen); patients who never received any platinum-containing regimen for SCLC; prior treatment with lurbinectedin, topotecan or anthracyclines; limited-stage patients who are candidates for local or regional

therapy and symptomatic or steroid-requiring or progressive CNS disease involvement for at least 4 weeks prior to randomization.

Planned sample size

ATLANTIS is a global Phase III trial, with 154 sites in the USA, Canada, Latin America and Europe. Trial enrollment started in September 2016. The prospective assumptions are a one-sided 2.5% significance level with at least 90% power to detect a 25% decrease in the risk of death to be achieved with the experimental arm (HR: 0.75). The OS with either CAV or topotecan is expected to be 7.5 months [10]. To obtain the required 508 death events, approximately 600 patients with SCLC who failed one prior platinum-containing chemotherapy line will be stratified and randomized at a 1:1 ratio. The study reached its target enrollment of 600 randomized patients on 30 July 2018.

Of note, the study had initially been designed to cap the control arm treatments (investigator's choice of topotecan or CAV) each to a maximum of 55% of expected patients, to ensure a sufficiently large number of patients in the CAV group to provide a well-powered doxorubicin-based comparator with the experimental arm. However, as the study has proceeded, the more common investigators' preference is CAV: as of 24 April 2018, 57% of the patients within the control arm were receiving CAV and 43% were receiving topotecan. Based on this trend, the initially planned percentage of patients treated with CAV would have been capped soon thereafter and the restriction to topotecan may have negatively impacted recruitment and extend the duration of the study. Therefore, the requirement to cap recruitment in the control arm when one of the treatment options reaches 55% of the required number of recruited patients was removed in a protocol amendment dated 3 May 2018.

Dose & schedule of therapy

Patients in the experimental arm are treated with doxorubicin 40.0 mg/m² on day 1, followed by lurbinectedin 2.0 mg/m² on day 1 of each 21-day cycle. Patients receiving topotecan in the control arm are treated with topotecan at 1.5 mg/m² daily on days 1–5 of each 21-day cycle, with dose reductions specified for patients with creatinine clearance less than 60 ml/min. Patients receiving CAV in the control arm are treated with cyclophosphamide 1000 mg/m² on day 1, doxorubicin 45.0 mg/m² on day 1 and vincristine 2.0 mg total FD on day 1 of each 21-day cycle. In both arms, up to a maximum of ten cycles of doxorubicin-containing regimens are allowed. Then, if applicable, doxorubicin will be discontinued and for patients in the experimental arm, lurbinectedin will be continued as maintenance therapy at a dose of 3.2 mg/m² (or 2.6 mg/m² if more than one dose reduction was applied while on combination therapy) on day 1 of each 21-day cycle. All patients in all treatment arms will receive primary G-CSF prophylaxis, with type, dose and scheme according to institutional standard practices and guidelines.

Efficacy evaluations

Antitumor activity will be assessed using RECIST v.1.1 using the appropriate imaging modality (CT or MRI) at baseline and every 6 weeks after randomization until evidence of PD. Imaging studies will be reviewed by an IRC.

Safety evaluations

Patients will be evaluable for safety, if they have received any partial or complete treatment infusion. All adverse events will be graded according to the NCI-CTCAE v.4. Treatment delays, dose omissions, dose reductions and reason for treatment discontinuation will be monitored throughout the study.

An Independent Data Monitoring Committee (IDMC) is overseeing the conduct of the study. Two ad-hoc interim safety analyses, required by the IDMC, have been conducted on the first 50 and 100 patients randomized and treated with two cycles. Both evaluations resulted in the recommendation to continue the trial without modification. The prespecified interim safety analysis, conducted after 150 patients were recruited into each arm (Figure 3), was also conducted with no modifications recommended by the IDMC.

Statistical analyses

Time-to-event variables (OS, PFS and duration of response) and their set time estimates (such as landmark OS analyses) will be analyzed according to the Kaplan–Meier method. The stratified log-rank test (primary analysis) and the unstratified log-rank test on the intention to treat population will be used to compare the time-to-event variables. Cox regression will be used to calculate the risk reduction (OS, PFS and duration of response) and to evaluate

Figure 3. Analysis plan.
OS: Overall survival.

the influence of the stratification variables and other potential prognostic factors on the time-to-event efficacy endpoints. Continuous variables that would have been categorized as discrete variables will also be investigated in the continuum range and if the adjustment is better, then the continuous variable will be kept in the regression model. Counts and percentages, with their corresponding exact 95% confidence intervals, will be calculated for the binomial end points (e.g., response rate). The Fisher's exact test (univariate analyses) and logistic regressions will be used to compare the rates of the experimental arm and the control arm. Waterfall plots will be used to describe the best variation of the sum of target lesions during the treatment.

Conclusion

Lurbinectedin is a novel antitumor agent with encouraging efficacy signals in Phase I studies. The ATLANTIS trial seeks to determine whether the lurbinectedin and doxorubicin combination leads to improved OS compared with standard-of-care chemotherapy in the second-line setting in patients with SCLC. The results of this study will help define the role of lurbinectedin/doxorubicin in SCLC and has potential to redefine standard-of-care therapy in this difficult-to-treat cancer.

Executive summary

Background

- Small-cell lung cancer (SCLC) is a highly recalcitrant cancer for which standard-of-care therapies have remained virtually unchanged for over 20 years.
- Topotecan is the only US FDA- and EMA-approved second line therapy, though outcomes are poor.

Lurbinectedin

- Lurbinectedin is a novel anticancer marine derivative agent which inhibits active transcription of protein-coding genes and impacts the tumor microenvironment.
- Preclinical and early phase studies indicate promising antitumor activity of lurbinectedin both alone and in combination with chemotherapy.

ATLANTIS study

- This is an open-label, randomized phase III trial to compare the efficacy and safety of combination lurbinectedin and doxorubicin versus investigator's choice of chemotherapy (topotecan or cyclophosphamide/doxorubicin/vincristine) in patients with SCLC that has progressed following one prior platinum-containing line of therapy.
- The study has completed enrollment as of 30 July 2018 and the initial primary end point analysis is anticipated 18 months later.

Conclusion

- The results of this pivotal trial will help define the optimal second-line therapy for patients with SCLC following progression after initial platinum-based chemotherapy.

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