ATLANTIS: Global, Randomized Phase III Study of Lubinectedin (L) with Doxorubicin (DOX) vs. CAV or Topotecan (T) in Small-cell Lung Cancer After Platinum Therapy

Anna Farago1, Luis Paz-Ares2, Tudor-Eladie Ciuleanu3, Andrea Fülop4, Alejandro Navarro5, Laura Bonanno6, José Antonio López-Vilarino7, Rafael Núñez7, Carmen Kahatt8, Gabor Kos9, Arturo Soto Matos-Pita10

1 Massachusetts General Hospital, Massachusetts/United States of America, 2 Hospital Universitario 12 de Octubre, Madrid/Spain, 3 Prof. Dr. I. Chiricuta Institute of Oncology, Cluj County, Romania, 4 Orszagos Koranyi TBC es Pulmonologial Intezett, Budapest/Hungary, 5 Vall d’Hebron University Hospital, Barcelona, Spain, 6 Istituto Oncologico Veneto IOV IRCCS, Padova, Italy, 7 PharmaMar, Colmenar Viejo, Madrid/Spain, 8 Synexus Health

Background

Lubinectedin (Depcyt®, PMI183, L) is a new investigational drug that is thought to block transcription-activated transcription, induces DNA double-strand breaks and modulates the tumor microenvironment.

Inhibition of active transcription
- Binding of lubinectedin to the DNA (Cytosine Guanine-rich motif)
- Phosphorylation of Pol II
- Stalling of elongating Pol II
- Recruitment of the ubiquitin proteasome machinery
- RNA Pol II degradation
- Recruitment of NPF and Histones

Generation of DNA breaks
- VI-Induction of apoptosis

Tumor Microenvironment Effect
- Inhibition of tumor-associated Macrophages (TAM)
- AT: Grade 4 neutropenia 80%; Grade 4 thrombocytopenia 19%; FN 29%; Associated neutropenic infectious 10%.
- Cohort B: The study was amended to reduce the DOX dose by 20% (i.e., to 40 mg/m²) and the lubinectedin 4.0 mg/dose was transformed to 2.0 mg/m²/dose.
- Reversible myelosuppression was the most frequent adverse event observed (Grade 4 neutropenia 64%; Grade 4 thrombocytopenia 6%; FN 12%)

Study design

Randomized Dose Escalation 40 mg/m² D1 q3wk
- Lubinectedin 2 mg/m² D1 q3wk

600 patients
1:1 randomization

Key Inclusion/Exclusion Criteria

Inclusion criteria:
1. Adult patients aged ≥18 years.
2. Histologically or cytologically confirmed diagnosis of limited or extensive stage SCLC which failed one prior platinum-containing regimen. Patients who had received prior checkpoint inhibitors are allowed to participate.
3. ECOG PS ≤1
4. Adequate renal, hematologic, and metabolic function in an assessment performed within 7 days (+3 day window) of randomization.
5. At least three weeks since last prior anticancer treatment.
6. At least four weeks since completion of whole-brain RT (50-55), or at least two weeks since completion of prophylactic cranial irradiation (PCI), and at any other site not previously specified.

Exclusion criteria:
1. More than one prior CT-containing regimen (including patients re-challenged with same regimen).
2. Patients who never received any platinum-containing regimen for SCLC.
3. Prior treatment with Topotecan, etoposide or others.
4. Limited-stage patients who are candidates for local or regional therapy.
5. Symptom score needing to progress CNS disease involvement during at least four weeks prior to randomization (asymptomatic, non-progressing patients taking steroids in the process of already being tapered within two weeks prior to randomization are allowed).

Study Objectives

Multicenter, open-label, randomized, controlled phase II clinical trial to evaluate and compare the efficacy and safety of an experimental arm consisting of PMI183/DOX combination followed by PMI183 alone, or best-investigator’s choice between cyclophosphamide, doxorubicin and vincristine (CAV) or topotecan as a control arm in SCLC patients who failed one prior platinum – containing line therapy.

Primary objective:
- To determine a difference in progression-free survival (PFS) by an Independent Investigator Committee between PMI183/DOX and CAV or Topotecan as treatment in 2nd line SCLC patients.

Secondary objectives:
- Overall survival (OS) and relapsed and/or recurrent survival (OS and 24 months).
- Efficacy and safety profiles (Broad analysis in CAV and in topotecan).
- Antitumor activity according to RECIST v1.1
- Patients’ quality of life (QOL)
- Pharmacokinetics (PK) of the combination in patients treated with Lubinectedin/DOX.
- Pharmacodynamics of known polymorphisms in patients treated with lubinectedin/DOX.

Analyses plan

Key analyses will be performed in accordance with the protocol. In addition, a pre-specified interim analysis was also conducted with no modifications recommended by the IDMC.

Trial status

Trial enrollment started in September 16.
- The enrollment Target is approximately 600 patients with SCLC, randomized at a 1:1 ratio, in 154 sites in USA, Canada, Israel, and Europe.
- Trial recruitment is expected to be completed at 2Q 2018.
- Two ad-interim safety analyses, requested by the IDMC, have been conducted on the first 50 and the final 100 patients randomized and treated with 2 cycles. Both resulted in the recommendation to continue the trial unmodified.
- The pre-specified interim analyses was also conducted with no modifications recommended by the IDMC.

Intensive Safety Analysis
- First patient randomized
- 180 patients (10 per arm)

Primary Endpoint Analysis
- 420 PDs events
- 18 months after last patient randomization

Trial timeline

Overall Survival Analysis

Inclusion/Exclusion
- 1:1 Randomization
- Interim Safety Analysis
- 6 month and 1 year interim safety analysis

Follow-up
- 18 months after last patient randomization
- 3 years after last patient randomization

Post-study follow-up
- 5 years after last patient randomization

Informed consent
- Information of patients about the study is to be obtained at hospital admission.

Preclinical

Lubinectedin has cytotoxic activity against a number of platinum resistant cell lines in vitro and in xenograft animal models. An improved (additive or synergistic) in vivo antitumor activity was found after the treatment with lubinectedin plus docetaxel of mice bearing hepatic metastases. B16 melanoma.

Clinical

All院-3+ dose escalation followed by dose expansion at 80 in selected diseases, including SCLC.

Less than 3 prior chemotherapy lines for advanced disease

Treatment Schedule

Cohort A: D1: 40 mg/m² L + 40 mg/m² Doxorubicin (DOX) on D1, q3wk for 4 consecutive cycles continued with Lubinectedin 7 mg/m²/week after D8 Q3W cumulative dose of 450 mg/m²
- RD dosismin 50 mg/m² ≤ Lubinectedin 3.5 mg/m² Fat dose (FD) D1 3 x FD and continue with Lubinectedin 7 mg/m² after D8 Q3W cumulative dose of 450 mg/m².
- RD dose > 50 mg/m² ≤ Lubinectedin 2.6 mg/m² q3wk
- RD dose > 50 mg/m² ≤ Lubinectedin 2.6 mg/m² q3wk
- RD dose > 50 mg/m² ≤ Lubinectedin 2.6 mg/m² D1 1 x FD and continue with Lubinectedin 4 mg/m² after D8 Q3W cumulative dose of 450 mg/m².
- Lubinectedin dose was dose limiting (DLT) regardless of colony stimulating factor (CSF) prophylaxis.
- Activity in cohort A and B is shown in the table.

Reviews

Copy of this poster holder is obtained for public use only and may not be reproduced without permission from ASCO® and the author of this poster.