Iadademstat shows preliminary efficacy signals in relapsed ED-SCLC patients:

A case report within CLEPSIDRA, a Phase II trial of iadademstat in combination with platinum-etoposide in biomarker-positive patients

J. Xaus,PhD[1] ; M. Fernández, MD[2]; A. Navarro, MD[3]; M. Arévalo, PhD[1]; S. Gutiérrez[1]; R. Bullock, MD[1]; C. Buesa, PhD[1].

[1]ORYZON GENOMICS S.A. Carrer Sant Ferran 74, 08940 Cornellà de Llobregat, Barcelona, Spain; [2]Insitut Oncològic Dr. Rosell, Barcelona, Spain; [3]Vall d´Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain

Background

Small cell lung cancer (SCLC), an aggressive neuroendocrine malignancy, shows a dismal prognosis with the current pharmacopeia. LSD1 is overexpressed in primary SCLC. Notch-1 is a tumor suppressor repressed in SCLC. Iadademstat is a selective Lysine Specific Demethylase-1 (LSD1) inhibitor and has been shown to re-activate the NOTCH pathway in SCLC, resulting in the repression of ASCL1, a well known non-druggable SCLC tumor driver, and to produce robust, and in some cases complete and durable, tumor regression in some chemo-resistant PDX models. We have identified biomarkers in SCLC cell lines that are differential in cells highly responsive to LSD1 as well as in human primary tumors. In a previous Phase I study in acute leukemia, iadademstat was safe and well tolerated, supporting it as a meaningful candidate for combination therapy with other agents. Preclinical work in SCLC cell lines showed strong synergy between iadademstat and etoposide-carboplatin/cisplatin or topoisomerase inhibitors. For this reason, we launched CLEPSIDRA in LSD1 responsiveness biomarker-positive, relapsed ED-SCLC patients.

Trial Design

CLEPSIDRA (EudraCT no 2018-000469-35) is a Phase II study of iadademstat as a second line treatment in combination with platinum-etoposide re-challenge chemotherapy in patients with relapsed extensive stage SCLC, which includes biopsy biomarkers expression as inclusion criteria to increase likeliness of response to iadademstat treatment. CLEPSIDRA is an open label single-arm multicenter study to assess for the first time the safety, tolerability, dose finding and efficacy of iadademstat in combination with platinum-etoposide chemotherapy in SCLC patients. Combination is administered to patients for 4 to 6 cycles, and from then on iadademstat in monotherapy.

It is planned to enroll up to 36 patients in four active sites in Spain. The study comprises a dose/regime finding part aimed at establishing the recommended dose and regime of the combination, and a second part to assess clinical activity by RECIST criteria, including objective responses, time to and duration of response, and overall survival.

Patient description

Patient 102 corresponds to a 68 year old Caucasian male diagnosed with Grade IIIb SCLC (T4N3M0) on 02/10/2017. First line treatment started on 16/10/2017 with cisplatin 80 mg/m^2/day 1 plus etoposide 100 mg/m^2/day 1 to 3 for four cycles with a partial response as the best efficacy sign. From 22/11/2017 to 05/12/2017 the patient was treated with thoracic radiotherapy 45G in 30 1.5G fractions.

In September 2018 a relapse was observed and treated with nivolumab 3 mg/Kg as second line treatment from 10/10/2018 to 11/12/2018 (5 cycles), and radiosurgery of a left cerebelosum lesion on 26/10/2018 due to disease progression.

Informed Consent to participate in CLEPSIDRA was signed on 27/12/2018 and first dosing started on 09/01/2019.

Highlights

- **CLEPSIDRA is actively recruiting biomarker-positive relapsed ED-SCLC patients**
- **We report here data from the patient with the longest treatment period in the study**
- **Iadademstat in monotherapy is safe and has no hematological toxicity (thrombocytopenia, neutropenia or anemia)**
- **The combo led to a clear clinical activity**
- **Tumor reduction continues upon iadademstat monotherapy, with 86.3% overall tumor reduction at end of cycle 8**
- **More complete safety and efficacy data of the first set of patients will be reported at ESMO-2019**

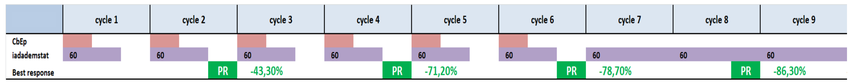

Figure 1. Dosing scheme. The initial study design proposed that iadademstat would be administered during the three weeks of each cycle, however the observed hematologic impact of the combination moved us to suspend the third week of iadademstat treatment in all cycles to let the patient recover. Despite this dose reduction, patient 102 has shown a continuous tumor reduction, which has continued even when iadademstat is administered in monotherapy (from cycle 7 onwards); % of RECIST value reduction shown in green. CbEp: carboplatin-etoposide

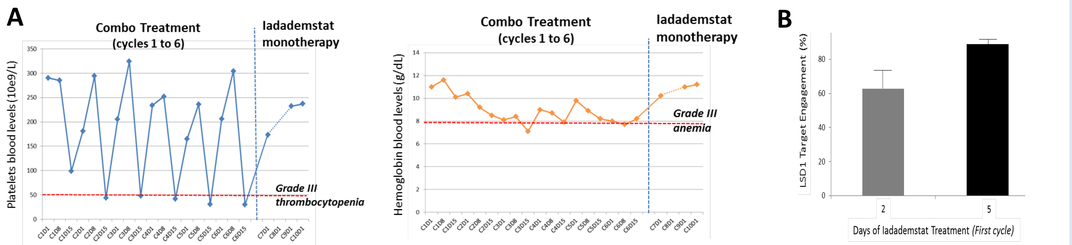

Figure 2. A) Hematological impact of treatment. Platelet blood levels were strongly impacted (Grade III thrombocytopenia) by the combination, although recovered during the third week of each cycle. Iadademstat in monotherapy resulted in a full hematological recovery within normal values. Hemoglobin blood levels were also decreased only during the combination period, and also fully recovered under iadademstat monotherapy. Red dotted line indicates threshold for grade III thrombocytopenia/anemia. **B) LSD1 target engagement** in blood PBMCs was determined after 24 hours (day 2) and 120 hours (day 5) of initial iadademstat treatment (first cycle), showing that almost full LSD1 target engagement is achieved after 5 days of treatment, in agreement with previous results from Phase I clinical trial (data not shown).

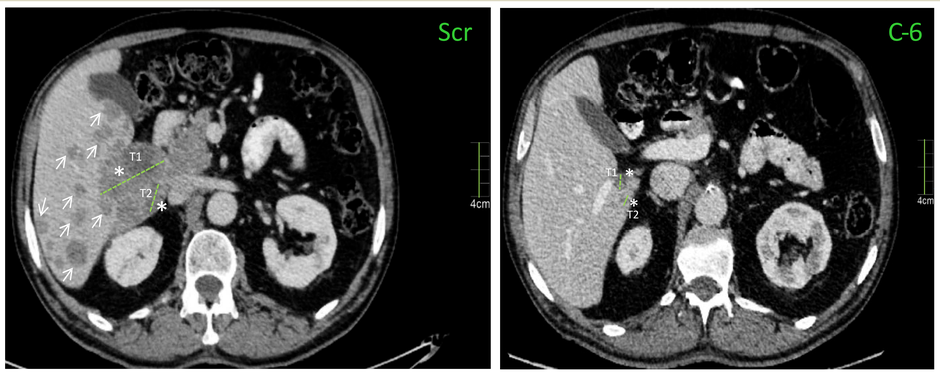

Figure 3. Efficacy. Tumor reduction in patient 102 was assessed by CT-Scan with RECIST 1.1 criteria every 6 weeks. Left, at screening; right, at cycle 6. T1 and T2 principal lesions are shown in both images, as well as the secondary lesions (indicated by arrows), which almost totally disappear after finalization of the combination treatment (end of cycle 6).

Results and Discussion

We present here initial CLEPSIDRA data, corresponding to the first and longest-term treated patient in the study (patient 102), which at the time of preparation of this poster was in cycle 11. Data reported here correspond to end of cycle 9.

SAFETY

Patient 102 has been treated during 6 cycles (21 days per cycle) with carboplatin 60 mg/m^2 i.v. on day 1 plus etoposide 100 mg/m^2 i.v. on days 1-3 and iadademstat 60 ug/m^2 p.o. on days 1-5 and 8-12 of every cycle. Starting from cycle 7, iadademstat has been administered alone (**Figure 1**).

During combination administration (cycles 1-6) grade III thrombocytopenia was observed in cycles 2 to 6, with platelets recovering normal levels in each third week of each cycle (**Figure 2A**). Strong neutropenia was also observed (day 15 of each cycle), and was managed by the administration of filgrastim, restoring neutrophil levels by the first week of each following cycle (data not shown). Progressive anemia was also observed (**Figure 2A**). After initiation of monotherapy with iadademstat (cycle 7 onwards), patient 102 showed a full recovery of platelets, ANC and hemoglobin to normal physiological values (**Figure 2A**), and with no additional hematological alterations.

In spite of the guidelines recommendations, there is limited experience and reports on platinum-etoposide-based rechallenge regimens in platinum-etoposide sensitive relapsed patients, since most of the relapsed patients are currently being treated either with topotecan or included in clinical trials. The fact that after initiation of monotherapy with iadademstat patient 102 showed a full functional marrow regeneration is suggestive that the observed hematological toxicity of the combo is mainly driven by the rechallenge with platinum-etoposide.

EFFICACY

In the first scan according to protocol (week 6), patient 102 showed a Partial Response (PR) (RECIST 80→43) with strong responses in the 2 main lesions (M1 Hepatic SVII and ADP porto-caval metastasis) and similar reduction of other non-target lesions. This PR continued improving over the following cycles (**Figure 1 and 3**), reducing the size of the tumor in each MRI.

Remarkably, after cycle 6, and with the patient being dosed only with iadademstat, the clinical response continued and RECIST was again reduced (from 17 → 11, week 24), accounting for an 86.3% overall tumor size reduction at the end of cycle 8.

CONFLICT OF INTERESTS: *All authors except Dr. Fernández and Dr. Navarro are employees of ORYZON GENOMICS S.A. Carlos Buesa is Chief Executive Officer and shareholder of ORYZON GENOMICS S.A. This study was sponsored by ORYZON GENOMICS S.A. S.A and partially funded by the RETOS-COLABORACION Program from the Spanish Government (RTC-2017-6407.1).*