Background

Small cell lung cancer (SCLC), an aggressive neuroendocrine malignancy, shows a dismal prognosis with the current pharmacopoeia. LSD1 is overexpressed in primary SCLC (1). Notch-1 signaling is involved in the development of a subset of patients with SCLC and has shown the potential to identify promising therapeutic targets (2). We have identified biomarkers in SCLC cell lines that are differential in cells highly responsive to iadademstat versus those less responsive (3). Positive Controls (C+), obtained by staining of a double positive reference tumor sample for either X1 or X2; and the Negative Control (C-), obtained by staining the same sample without primary antibody, were used for relative quantification.

CLEPSIDRA: a pilot, biomarker-guided study to assess safety, tolerability, dose finding and efficacy of iadademstat in combination with platinum-etoposide in patients with relapsed, extensive-stage small cell lung cancer

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Highlights

**Clinical trial dosing regimen**

1. **Table shows number of patients treated with the combination of iadademstat with platinum-etoposide in relapsed ED-SCLC patients.**

2. **Highlights:**

   - **iadademstat alone in ED-SCLC patients is safe and shows no hematological, general or neuronal toxicity.**

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Conclusions

- **iadademstat is a potential personalized therapeutic epigenetic drug for relapsed ED-SCLC patients.**

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**SAFETY**

In the current preliminary report, only the number of initial observed responses (ORs) has been calculated with 95% confidence interval (CI); other measures such as overall response rate (ORR) may be calculated in the future. For the currently evaluable patients for efficacy (8 at the moment this poster is written), there have not been documented so far 4 PR and 3 SD of the 50 lasting more than 4 months (Fig. 4). In the PRs, one (patient #1) is a long-lasting response, and in the remaining 7 patients this response occurred initially 78.7% of tumor reduction after 6 cycles of treatments. Since then, and upon monotherapy with iadademstat, patient is still in remission after 9 months (Cycle 12) with 86.3% of tumor reduction and with all minor lesions still progressively being reduced by the 3 CT-Scans done since Cycle 6. This patient illustrates how iadademstat alone produces a continuous clinical benefit even after 6 cycles since the doublet was stopped. Among the other PRs, one patient (#2) showed an intense response in the first CT-scan (69.7% of tumor reduction) but unfortunately died from an unrelated medical event when PR is, another is currently in cycle 2 and another progressed. For the 3 SD patients, two are currently ongoing, while the third withdrew consent. Finally, one patient progressed in cycle 2. It is worth to note that both DPs have occurred in patients where treatment was skipped at investigator’s decision to manage hematotoxicity, leaving patients for more than 50% of days without any treatment.

**EFFICACY**

In a First in Man Phase I study in acute leukemia, iadademstat was safe and well tolerated, supporting it as a meaningful candidate for combination therapy with other agents. Therefore, we launched CLEPSIDRA, to assess safety, tolerability and clinical response to iadademstat combined with platinum-etoposide in relapsed extensive disease (ED) SCLC patients who are positive for these candidate predictive biomarkers.

**Results and Discussion**

**Trial Design and Biomarkers**

CLEPSIDRA (EudraCT no 2018 000469 35) is an open label, single arm, multicenter Phase II study to assess the safety, tolerability, dose finding and efficacy of iadademstat in combination with platinum-etoposide in relapsed ED-SCLC patients. Patients will receive 4-6 cycles of the combination, at investigator’s criteria, and thereafter treatment may continue with iadademstat in monotherapy. It is planned to enroll up to 36 patients. Clinical activity is assessed by RECIST v.1 criteria, including tumor response, time to and duration of response, and overall survival.

Preclinical work showed that SCLC PDX responses to iadademstat were either strong and long-lasting or more modest. Two biomarkers, X1 and X2, have been identified, which are expected to distinguish LSD1-highly responsive SCLC tumors from the rest (Fig 1A). They have been introduced as patient inclusion criteria to increase likeliness of response to iadademstat.

**Figures**

1. **Fig. 1. Candidate duo biomarker panel for selection of SCLC patients likely to respond to iadademstat.** A: LHD: dose intensity of iadademstat by qRT-PCR. B: X1 and X2 in IHC cell line and their sensitivity to iadademstat. Green: sensitive; yellow: partially; red: resistant, as assessed by inhibition of cell proliferation. Right, analysis of hematotoxic revealed that i) patients treated with iadademstat alone following completion of the triplet cycles as per original study dosing regimen is 9 months in total. T1 and T2 principal lesions are followed in all images, as well as the secondary lesions (indicated by arrows). Both principal lesions in the first CT-scan (69.7% of tumor reduction) but unfortunately died from an unrelated medical event when PR is, another is currently in cycle 2 and another progressed. For the 3 SD patients, two are currently ongoing, while the third withdrew consent. Finally, one patient progressed in cycle 2. It is worth to note that both DPs have occurred in patients where treatment was skipped at investigator’s decision to manage hematotoxicity, leaving patients for more than 50% of days without any treatment.

2. **Table shows number of patients treated with the combination of iadademstat with platinum-etoposide in relapsed ED-SCLC patients.**

3. **Histological impact of treatment.** Table shows number of patients treated with iadademstat in combination with platinum-etoposide in relapsed ED-SCLC patients. (Grade III/IV) and the corresponding percentage referred to number of events (nº of patients). This study was sponsored by ORYZON GENOMICS S.A. and partially funded by the RETOS-COLABORACION Program from the Spanish Government (RTC-2017-6407.1).

4. **Fig. 4. Efficacy is assessed by CT-Scan and RECIST 1.1 criteria every 6 weeks.** Top, graph showing the best observed response (OR), by RECIST criteria, as percentage of patients achieving the outcome (Complete Response, CR; Partial Response, PR; Stable Disease, SD; or Progressive Disease, PD). Bottom, CT-Scans of patient #1 in different cycles of treatment with iadademstat monotherapy and cycle 12, after 6 additional cycles of combination therapy. Treatment was stopped due to exacerbated toxicity, leaving patients for more than 50% of days without any treatment.

5. **Fig. 2. Design and demographics.** Original study dosing regimen is shown (platinum-etoposide at recommended doses in second line and iadademstat at 20mg/m²/dose as defined in original trial, not shown here). This study was sponsored by ORYZON GENOMICS S.A. and partially funded by the RETOS-COLABORACION Program from the Spanish Government (RTC-2017-6407.1).

6. **Fig. 3. Hematological impact of treatment.** Table shows number of patients treated with iadademstat in combination with platinum-etoposide in relapsed ED-SCLC patients. (Grade III/IV) and the corresponding percentage referred to number of events (nº of patients). This study was sponsored by ORYZON GENOMICS S.A. and partially funded by the RETOS-COLABORACION Program from the Spanish Government (RTC-2017-6407.1).

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8. **Fig. 5. Conclusions.** This study was sponsored by ORYZON GENOMICS S.A. and partially funded by the RETOS-COLABORACION Program from the Spanish Government (RTC-2017-6407.1).

CONFLICT OF INTERESTS: All authors except Dr. November are employees of ORYZON GENOMICS S.A. Celltech Bios is Chief Executive Officer and Senior Treatment. This study was sponsored by ORYZON GENOMICS S.A. and partially funded by the RETOS-COLABORACION Program from the Spanish Government (RTC-2017-6407.1).