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Final safety and efficacy data from CLEPSIDRA trial in 2L ED-SCLC

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Background and objetives

Iadademstat (iada) is a potent and selective LSD1 inhibitor. In SCLC, it re-activates the NOTCH pathway, resulting in the repression of the tumor driver ASCL1. In chemo-resistant PDX models, iada produces a robust and, in some cases, complete and durable tumor regression in some, while in others a more modest effect was observed. Based on preclinical data, a panel of two biomarkers that is expected to distinguish LSD1i-highly responsive SCLC tumors was identified, which could be useful as patient inclusion criteria to increase likeliness of response to iada in clinical trials. Moreover, in a First-in-Man Phase I study in acute leukemia, iada was safe and well tolerated, showing to be a meaningful candidate for combination therapy in oncology.

To explore the potential therapeutic benefit of iada in 2L ED-SCLC, a Phase II clinical trial (CLEPSIDRA) was designed to address three main goals: first, to assess the safety and tolerability of iada in combination with a rechallenge of platinum plus etoposide (PE); second, to assess if iada is adding a therapeutic benefit to PE chemotherapy in 2L ED-SCLC; and third, to explore if the two biomarkers used as inclusion criteria in this trial are effective to enrich the number of clinical responses in this particularly hard to treat population.

Trial Design

CLEPSIDRA (EudraCT no 2018 000469 35) was an open label, single arm, multicenter Phase II study to assess the safety, tolerability, dose finding and efficacy of iada in combination with PE in relapsed ED SCLC patients considered platinum-sensitive (relapse after 90 days of initial chemotherapy). Eligible patients had to be positive for both selection biomarkers.

Patients received 4-6 cycles, at investigator's criteria, of the combination iada plus standard regime of PE chemotherapy, and thereafter treatment could be continued with iadademstat in monotherapy.

It was planned to enroll up to 36 patients in two stages: the first one (18 patients) to define the recommended dose of iada in the combination treatment, and the second part to assess the efficacy of the iada-PE combination at the recommended dose in an additional 18 patients.

Clinical activity was assessed by RECIST v1.1 criterion, including tumor response, time to and duration of response, and overall survival.

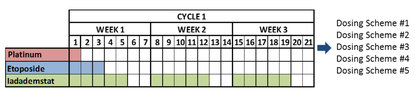


Figure 1. Original study dosing regimen is shown (PE at recommended doses in second line and iada 60 ug/m2/day). Several modifications (5, not shown) were incorporated to adapt original scheme due to the exacerbated hematological impact observed.

Demographics		
nº of patients		N=14
Sex	Male	12 (85.7 %)
	Female	2 (14.3 %)
Age	Mean	65
	(Min/Max)	(52/79)
Race	Caucasian	14 (100%)
Weight	Mean (kg)	76.5
	(Min/Max)	(61/94)
Height	Mean (cm)	169.1
	(Min/Max)	(155/184)
BMI	Mean	26.8
	(Min/Max)	(21.87/31.33)

Table 1. Demographics. CLEPSIDRA trial was terminated after the inclusion of 14 ED-SCLC patients. However, two of them (patient #203 and #401) were included with a major protocol deviation since reanalysis of the inclusion biomarkers showed negative or not evaluable expression due to poor quality of the biopsy sample. Therefore, only 12 subjects were biomarker positive and considered evaluable for efficacy.

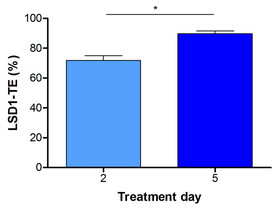


Figure 3. LSD1 Target engagement (TE) was determined in PBMCs on days 2 and 5 of the first week of iada treatment by a proprietary ELISA-based method (n=13). Almost complete LSD1-TE (>80%) was already achieved after 5 days of treatment and it was sustained, as comparable values were also observed after the 2-day washout (day 8, not shown). Iada exposure was also monitored in terms of plasma through concentrations by LC-MS/MS (not shown).

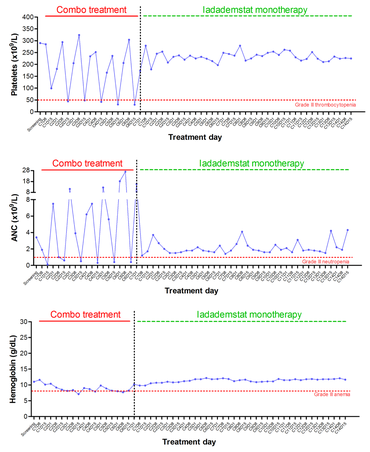
Highlights

- **The combination of platinum-etoposide with iadademstat produced hematotoxicity, suggesting this may not be a viable clinical proposition in 2L ED-SCLC**
- **When administered alone, iadademstat was well tolerated supporting potential for monotherapy and for other treatment combinations**
- **Efficacy signals were encouraging with 40% OR and mean DoR of 4.5 months, suggesting that patient selection by biomarkers may be effective to increase ratio of ORs in SCLC trials with iadademstat**
- **Patient #102 showed a sustained therapeutic benefit when treated with iadademstat alone, confirming previously reported preclinical efficacy of iadademstat monotherapy in PDX from relapsed chemo-resistant patients**

Results and Discussion

PT_NAME	SOC_NAME	CTCA grade	Relation with Iada	Outcome
Anaemia	Blood and lymphatic system disorders	Grade 4	Non related	Not recovered
Death	General disorders and administration site conditions	Grade 5	Non related	Fatal
Dyspnoea	Respiratory, thoracic and mediastinal disorders	Grade 5	Non related	Fatal
Dyspnoea	Respiratory, thoracic and mediastinal disorders	Grade 5	Non related	Fatal
Neutropenia	Blood and lymphatic system disorders	Grade 4	Unlikely	Recovered
Pancytopenia	Blood and lymphatic system disorders	Grade 3	Possible	Recovered
Pleural effusion	Respiratory, thoracic and mediastinal disorders	Grade 3	Possible	Recovered
Septic shock	Infections and infestations	Grade 5	Possible	Fatal
Thrombocytopenia	Blood and lymphatic system disorders	Grade 4	Unlikely	Recovered

Figure 2. Safety and Hematological impact of treatment. Table summarizes the 9 Serious Adverse Events (SAEs) reported in CLEPSIDRA trial, all of them during the iada-PE combo period. SAEs within each class are listed by System Organ Class (SOC) and Preferred Term (PT); potential causal relation with iada treatment is also reflected. Graphs on the right show platelet, neutrophil and hemoglobin levels throughout the clinical trial of Patient #102, as a representative patient of the cyclic hematotoxicity observed during the combined treatment with PE and iada, while normal hematological levels are recovered and maintained without any intervention or treatment adjustment during iada monotherapy period. Patient #102 was treated during 6 cycles with the iada-PE combination and 16 cycles with iada in monotherapy.



SAFETY

14 ED-SCLC relapsed patients were enrolled (Table 1). Although it was planned to present final data in this poster, the COVID-19 pandemic is delaying the monitoring and data cleaning activities of the trial, therefore the study results presented here should be considered as preliminary as the study database is not locked yet.

High hematotoxicity (mainly thrombocytopenia and neutropenia) was reported in most of the subjects (11 of 14; 78.6%) through the iada-PE treatment period despite different combination dosing schemes were evaluated, including skipping iada and/or combined treatment dose reductions in order to achieve normal platelet values at the beginning of each cycle, or the use of filgrastim to manage the reduction in neutrophils (Figure 2). From the 27 AEs (Grade 3 or higher) observed, only one was not hematology related (hypoglycemia), which was considered by the PI as non-related to iada treatment. Remarkably, no signs of liver, renal or neuronal toxicity were observed in any of the study subjects. A total of 9 SAEs were reported in 7 patients (50%), 4 of them fatal (1 death for unknown reason, 2 dyspnea and 1 septic shock) (Table in Figure 2). Remarkably, patients treated with iada alone before or after chemotherapy dosing did not show any hematotoxicity (accounting for a total number of weeks dosed with iada alone >60), confirming the excellent tolerability of iada in monotherapy (Figure 2).

Iada exposition and LSD1 target engagement observed in CLEPSIDRA patients (Figure 3) was comparable to previous Phase I FiM trial in RR leukemia patients where with equivalent iada doses antileukemic activity has been documented. With the safety data obtained in these 14 patients, the level of hematotoxicity was determined, precluding to consider this particular combination as a meaningful treatment option for 2L ED-SCLC patients, and therefore recruitment was stopped.

EFFICACY

As per protocol, 10 out the 14 patients were considered evaluable for efficacy (2 patients died before the first CT-Scan and 2 patients were considered major protocol deviations due to non-conformity with the biomarker inclusion criteria). Despite the difficulties to find a favorable iada-PE combo dosing scheme and the skipping of several doses, resulting in 30% to 60% reduction of the intended iada dose per cycle, iada-PE resulted in a relevant clinical benefit rate (40% PR and 20% long-term SD>4 months) (Figure 4), suggesting that biomarker-driven patient stratification might be a valuable tool. No PR were observed in the two biomarker negative patients, although one of these patients showed a third long-term SD. Mean study permanence was 3.9 months. Mean duration of response (DoR) in PR patients was 4.5 months (Figure 4), and in all of them PR was observed at the first CT-Scan, performed after 6 weeks of treatment. The longest Progression Free Survival (PFS) (#102) was 15.1 months, of which 10 months were as iada monotherapy, resulting in a maintained response which even improved for an additional tumor reduction of 53%, leading to a final tumor reduction of 90% in this patient (Figure 5).

Results from patient #102 are particularly encouraging, since further reduction in tumor load was observed under iada monotherapy. This is the first clinical confirmation of the preclinical evidence reported with PDX from relapsed chemo-resistant ED-SCLC patients with iada in monotherapy yielding some robust and long-lasting responses (Auger et al., 2019).

All together, these preliminary efficacy data, given this hard to treat population, are encouraging and will inform next iada trials in ED-SCLC patients.

Efficacy	
N	14
Biomarker positive (+/+)	12 (ITT)
Evaluable patients (EP)	10 (EP)
OR on EP	4 (40%)
CR	*0 (0%)*
PR	*4 (40%)*
LT-SD on EP	2 (20%)
Clinical benefit on EP (OR and LT-SD)	60%
mean DoR (months) (min, max	4.5 (0.2-14.0)
ORR on ITT	33%

Figure 4. Efficacy Figure 4. Efficacy was assessed by CT-Scan and RECIST 1.1 criteria every 6 weeks. Left, graph showing the best observed response (OR) in the evaluable patients; blue PR, grey SD (dark grey: long-term (more than 4 months) SD), red PD. Right, Table summarizing the efficacy data. EP, evaluable patients; ITT, intention to treat; OR, objective response; LT-SD, long-term stable disease; DoR, duration of response; ORR, objective response rate.

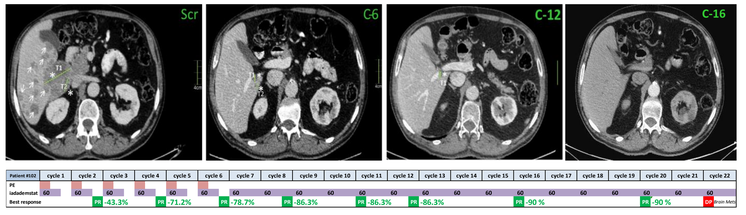


Figure 5. CT-Scan images of patient #102 at screening, cycle 6 (4.5 months of treatment with PE+iada combination), cycle 12 and 16 (after 6 and 10 additional cycles of iada monotherapy regimen, respectively). T1 and T2 principal lesions are followed in all images, as well as the secondary non-target lesions (indicated by arrows). Both target lesions were progressively reduced during treatment even during iada monotherapy period, and non-target lesions almost totally disappear.

1. Augert et al. Targeting NOTCH activation in small cell lung cancer through LSD1 inhibition. Sci Signal. 2019 Feb 5;12(567):eaau2922. doi: 10.1126/scisignal.aau2922.

Conclusions

CLEPSIDRA data suggest that LSD1 inhibition may be a relevant approach for a personalized therapy in ED-SCLC patients. Iadademstat is a promising drug, with a better safety profile than other LSD1 inhibitors, and has shown clinical benefit in SCLC, including a long-lasting therapeutic efficacy in one patient. Although combination with conventional PE chemotherapy in 2L is producing a strong hematotoxicity, the combination of iadademstat with other non- or less-hemotoxic agents in ED-SCLC emerges as an interesting option. Synergism between LSD1 inhibition and checkpoint inhibitors has been reported and this combination with I/O drugs represents a future strategy of interest.

CONFLICT OF INTERESTS: *SG, RB and CB are employees of ORYZON GENOMICS S.A. AN: consulting, advisory role or travel and accommodation by Pfizer, Roche and/or Boehringer Ingelheim. OJ: Honoraria or Advisory role at Boehringer Ingelheim, BMS, MSD, Roche/Genentech, AstraZeneca, Pfizer, Eli Lilly, Abbvie. AA: advisory role or travel and accommodation by BMS, MSD, Roche and/or Eli Lilly. LPA: consulting, advisory role or travel and accommodation by Roche, Eli Lilly, BMS, MSD, AstraZeneca, Amgen, Novartis, Pfizer, and/or Boehringer Ingelheim. AC: consulting, advisory role or travel and accommodation by AstraZeneca, Boehringer-Ingelheim, Pfizer, Roche/Genentech, Eli Lilly, Novartis, MSD, and/or BMS. CB: 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).*