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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Background

Small cell lung cancer (SCLC), an aggressive neuroendocrine malignancy, shows a dismal prognosis with the current pharmacopeia. LSD1 is overexpressed in primary SCLC (1). Notch-1 is a tumor suppressor repressed in SCLC. Iadademstat, a selective Lysine Specific Demethylase-1 (LSD1) inhibitor, 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 chemo-resistant SCLC PDX models (2). We have identified biomarkers in SCLC cell lines that are differential in cells highly responsive to LSD1i as well as in human primary tumors. Preclinical work showed strong synergy between iadademstat and etoposide-carboplatin/cisplatin or topoisomerase inhibitors. 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. For these reasons, we launched CLEPSIDRA, to assess safety, tolerability and clinical responses to iadademstat combined with platinum-etoposide in relapsed extensive disease (ED)-SCLC patients who are positive for these candidate predictive biomarkers.

Goals

This Phase IIa clinical trial, CLEPSIDRA, has three main goals. First, to assess the safety and tolerability of combining iadademstat with a rechallenge of platinum plus etoposide (PE) (doublet) in platinum-sensitive relapsed ED-SCLC patients. Second, to discern if iadademstat is adding a therapeutic benefit to the chemotherapy. And third, to explore if the biomarkers of response to iadademstat 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 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 v1.1 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 LSD1i-highly responsive SCLC tumors from the rest (Fig 1A). They have been introduced as patient inclusion criteria to increase likeliness of response to iadademstat.

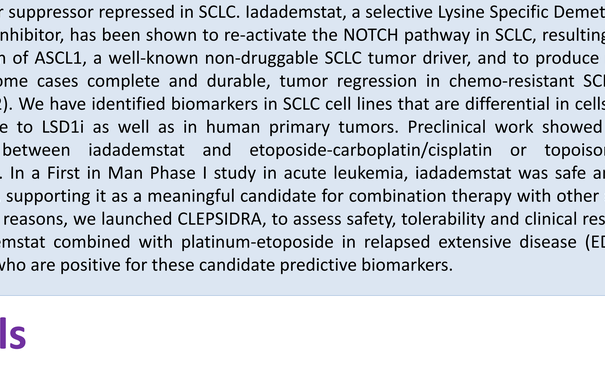
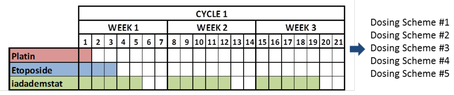


Figure 1. Candidate duo biomarker panel for selection of SCLC patients likely to respond to iadademstat. (A) Left: dot plot representing gene expression levels by qRT-PCR (absolute Cp values) of X1 and X2 in SCLC cell lines and their sensitivity to iadademstat. Green: sensitive, yellow: partially, red: resistant, as assessed by inhibition of cell proliferation. Right: analysis of corresponding X1 and X2 protein levels by IHC in SCLC cell lines #1, 2 and 5. Cell lines with high mRNA expression (Cp < 32 in qRT-PCR) of X1 and X2 show strong staining for the respective biomarkers in IHC. (B) Example of IHC staining of the tumor samples of a patient from the CLEPSIDRA trial, positive for the biomarker duo X1 and X2. 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.

Highlights

- **CLEPSIDRA is actively recruiting biomarker positive relapsed ED-SCLC patients**
- **Main toxicity observed in the combination with carboplatin plus etoposide (CbEt) is hematotoxicity**
- **Current level of observed responses (75%; 4PRs and 2 long-SD out of 8 evaluable patients) may suggest that patient selection by Biomarkers is effective to increase ratio of ORs**
- **Iadademstat alone in ED-SCLC patients is safe and shows no hematological, general or neuronal toxicity, suggesting potential for monotherapy and other combos**



Demographic data		
nº of patients		10
Sex	Male	9 (90%)
	Female	1 (10%)
Age	Median	63.2
	(Min /Max)	(52/79)
Race	Caucasian	10 (100 %)
Weight	Median(kg)	76.72
	(Min /Max)	(61/94)
Height	Median (cm)	170
	(Min /Max)	(155/184)
BMI	Median	26.64
	(Min / Max)	(21.9/31.0)

Figure 2. Design and demographics. Original study dosing regimen is shown (platinum-etoposide at recommended doses in second line and iadademstat 60 ug/m²/day). Several modifications (5, not shown) have been incorporated to adapt original scheme due to the exacerbated hematological impact observed. As per 15.09.2019, 10 patients have been included throughout the different dosing schemes, all of them treated with carboplatin-etoposide (CbEt). One patient died before first CT-Scan time-point and was considered as per protocol not evaluable for efficacy.

	CbEt+iada	Iadademstat Monotherapy
Completed cycles	29	9
Hematological toxicity*	40	0
Thrombocytopenia (≥ Grade III)	19 (65.5%)	0
Neutropenia (≥ Grade III)	11 (37.9%)	0
Anemia (≥ Grade III)	10 (34.5%)	0

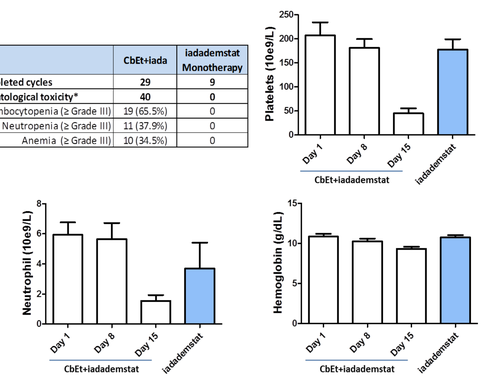


Figure 3. Hematological impact of treatment. Table shows number of completed treatment cycles and hematological toxicity for the iadademstat-CbEt combination and iadademstat monotherapy. *Hematological toxicity is considered as number of thrombocytopenia, neutropenia or anemia events (Grade III/IV) and the corresponding percentage referred to number of completed treatment cycles. Graphs represent the mean ± SEM of patient compiled values at Day 1, 8 or 15 of CbEt+iadademstat combination treatment (cycles 1 up to 6) compared to values observed once patient enters into iadademstat monotherapy.

Results and Discussion

SAFETY

In spite of the guidelines recommendations, there is very limited experience and reports on platinum-etoposide (PE) based rechallenge regimens in PE sensitive relapsed SCLC patients, since most of these patients are either being treated with topotecan or included in clinical trials. Hematological toxicity of PE-based therapy, particularly carboplatin-etoposide (CbEt), is well known and described to cause myelosuppression resulting in thrombocytopenia and neutropenia. In CLEPSIDRA, patients showed exacerbated hematological impact beyond the levels experienced in the first chemotherapy line. To manage the observed hematotoxicity and assess the tolerability of the CbEt-iadademstat combination (triplet), the original dosing regimen of the combination was adapted and several new cohorts with different combination dosing schemes are being evaluated. In a number of patients, iadademstat dose reductions by skipping days or weeks were also done at investigator's discretion. The analysis of hematotox revealed that i) patients treated with iadademstat alone following completion of the triplet cycles as per protocol quickly recovered PLT, ANC and Hb levels (Fig 3) with no additional hematological alterations; ii) patients treated with iadademstat alone before start of CbEt treatment did not show decrease on the hematological values before the administration of the doublet; iii) in patients where, by investigator's decision iadademstat was skipped, similar hematological toxicities to those of the triplet appeared when the patient was only under CbEt; and iv) in AML myelosuppressed patients, same iadademstat dose as used here is compatible with platelet and neutrophil marrow regeneration (data not shown). While these observations would suggest that observed toxicity might be mainly driven by the rechallenge with CbEt, the current rates of hematological toxicities observed in this initial part of the study seem to be higher than recent reports of CbEt alone, where thrombocytopenia events range in the 31% (3), so it may not be ruled out that some additive hematox effect is produced by the triplet. There is current work in progress to refine the combination dosing scheme to manage thrombocytopenia under triplet combo treatment. Importantly, in the 10 patients evaluated till now no signs of liver, renal or neuronal toxicity have been observed.

CONFLICT OF INTERESTS: *All authors except Dr. Navarro are employees of ORYZON GENOMICS S.A. Carlos Buesa is Chief Executive Officer and Tamara Maes Chief Scientific Officer, and both are shareholders 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).*

EFFICACY

In this preliminary report, only the number of initial observed responses (ORs) has been considered, as OS or PFS will become meaningful measures only as the trial advances. From the currently evaluable patients for efficacy (8 at the moment this poster is written), there have been documented so far as best responses 4 PR and 3 SD (2 of the SD lasting more than 4 months) (Fig 4). In the PRs, one (patient #1) is a long-lasting response, and still in response. This patient showed initially 78.7% of tumor reduction after 6 cycles of triplet. 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 or disappearing according to 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 (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 in PR, another is currently in cycle 2 and another progressed. From 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.

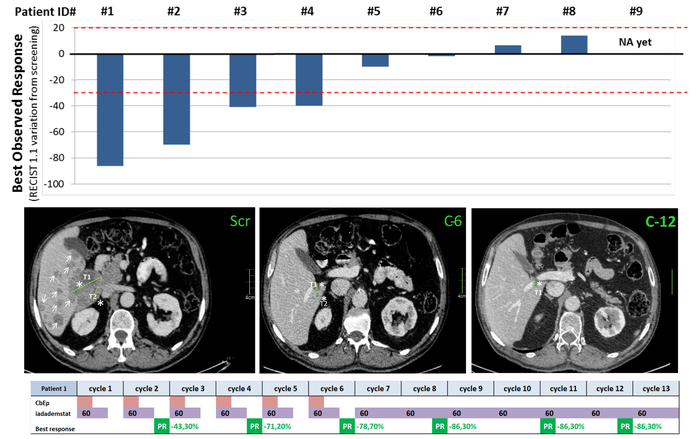


Figure 4. Efficacy is assessed by CT-Scan and RECIST 1.1 criteria every 6 weeks. Top, graph showing the best observed response (OR) (NA yet, first CT-Scan time-point not yet reached). Bottom, CT-Scan images of patient #1 at screening, cycle 6 (4.5 months of treatment with CbEt+iadademstat combination) and cycle 12, after 6 additional cycles of iadademstat monotherapy regimen (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 are progressively reduced during treatment even during iadademstat monotherapy period, and secondary lesions almost totally disappear.

Conclusions

- Iadademstat is a potential personalized therapeutic epigenetic drug for relapsed ED-SCLC patients. It has not been associated to neurological, liver or renal toxicity.
- Preliminary activity of iadademstat in combination with CbEt chemotherapy is promising (ORR=75% of evaluable patients) considering that standard of care topotecan in second line has shown limited activity (ORR range between 15-24% (4)).
- Hematological toxicity has impaired so far to establish a definitive dosing regime for the combination and thus it is still early to make a definitive assessment of its clinical benefit. Nevertheless, work is in progress to refine the dosing regime.
- Iadademstat alone is hematologically safe and provides therapeutic benefit.
- Epigenetics is growing as a new potential field of personalized medicine for several tumor types including ED-SCLC. Iadademstat has arisen as a promising drug in this area, with a favourable safety profile and demonstrated activity in PDX models. Combination of iadademstat plus other therapies for ED-SCLC represents a strategy of great interest.

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