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Iadademstat Shows Efficacy in Elderly AML Patients in Combination with Azacitidine. ALICE Trial

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Introduction

Acute Myeloid Leukemia (AML) is predominantly a disease of the elderly with an increasing incidence in the past decades. The probability of achieving complete remission and survival rates decrease with age, and there is rather limited treatment success with standard (chemo)therapy, leading to 5-year survival rates of 20% or lower. It has been shown that Lysine-specific demethylase 1 (LSD1) adds to malignant transformation in AML. Iadademstat is a potent and selective LSD1 inhibitor that has shown to be effective in preclinical models, both alone and in combination with other compounds, including azacitidine (Aza). A Phase I FiM study in AML showed that iadademstat exhibits a good safety profile and preliminary anti-leukemic activity as monotherapy. Iadademstat in combination with Aza may thus offer an alternative option for elderly AML patients, a population with limited therapeutic options.

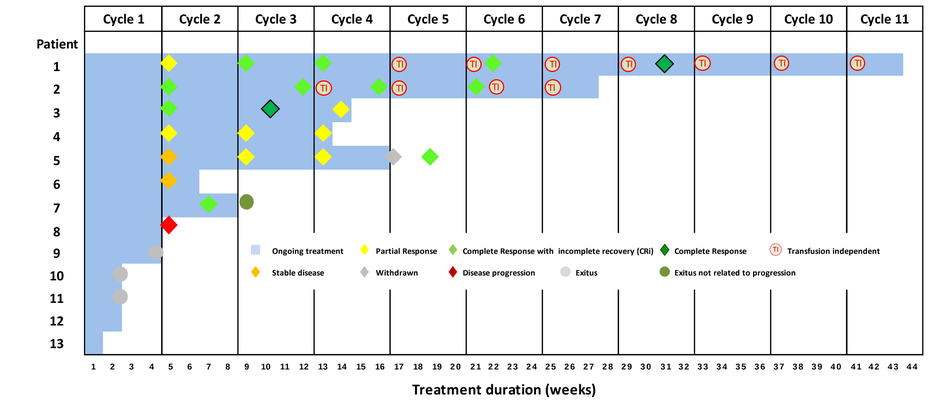
Methods

ALICE is a Phase IIa clinical trial to assess the safety, tolerability and recommended dose of iadademstat in combination with Aza, and also to measure the clinical activity of the combination, including objective responses (OR) assessed by BM aspirates, along with PK/PD measures (including a set of 6 blood biomarkers).

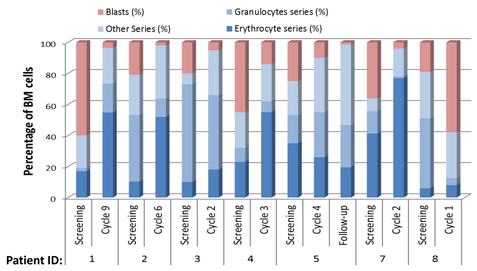
In the dose finding Part (Part 1) of the trial a maximum of 18 patients were to be treated with a starting dose of iadademstat of 90 µg/m^2/d in combination with Aza at 75 mg/m^2. Iadademstat could be escalated or de-escalated depending on the observed dose limiting toxicities. After definition of the Recommended Dose (RD) in Part 1, an expansion cohort of 18 patients will be enrolled (Part 2). AML patients ≥ 60 years of age (diagnosis according to WHO classification), considered to be ineligible for intensive chemotherapy without prior treatment for AML other than hydroxyurea, can be enrolled. Later on, the study protocol was amended to allow dosing variations of Aza and iadademstat to manage possible hematological events, as well as to contemplate the opportunity to re-escalate the dose of iadademstat (to 90 µg/m^2/d) in case of good tolerability but where no CR/CRi had been achieved.

Highlights

- Combination of iadademstat and azacitidine shows a good safety profile in elderly AML patients
- Preliminary signals of clinical efficacy are encouraging, with 75% of ORs (6 out of 8: 2 CR, 3 CRi and 1 PR)
- Rapid clinical responses (mean time to first response is currently 32 days)
- Preliminary rate of conversion to red cell Transfusion Independence (40%) is also encouraging



BM and peripheral blood analysis



Patient code	Visit	Erythrocytes (10^12/L) (% change from baseline)	Platelets (10^9/L) (% change from baseline)	Neutrophils (10^9/L) (% change from baseline)	Monocytes (10^9/L) (% change from baseline)	
1	Screening	2,91	47	0,1	0,2	
	Cycle 10	3,25 (+11,68)	79 (+68,09)	1,4 (+1300)	0,3 (+50)	TI
2	Screening	2,3	21	0,8	0,7	
	Cycle 7	3,61 (+56,96)	60 (+185,71)	1,5 (+87,5)	0,3 (-57,14)	
3	Screening	2,16	44	0,51	0,08	
	Cycle 3	2,62 (+21,3)	53 (+20,45)	1,62 (+217,65)	0,31 (+287,5)	
4	Screening	2,75	77	0,5	0,1	
	Cycle 4	2,86 (+4)	21 (-72,73)	0,2 (-60)	0 (-100)	
5	Screening	2,8	49,0	1,1	0,0	
	Cycle 4	2,65 (-6,03)	20 (-59,18)	1 (-9,09)	0 (0)	
	Followup	3,13 (+10,99)	99 (+102,04)	1,7 (+54,55)	0 (0)	
6	Screening	3,01	122	0,2	0	
	Cycle 1	2,63 (-12,62)	54 (-55,74)	0,1 (-50)	0 (0)	
7	Screening	3,08	67	1,31	0,05	
	Cycle 2	3,07 (-0,32)	2 (-97,01)	0,3 (-77,1)	0,01 (-80)	
8	Screening	2,63	90	3,4	0,5	
	Cycle 1	3,19 (+21,29)	5 (-94,44)	0,8 (-76,47)	0,9 (+80)	

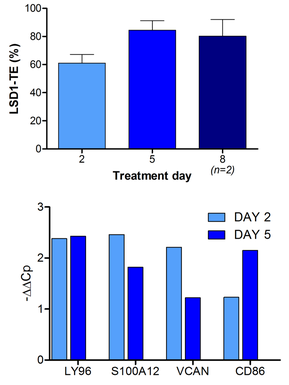
BM (left) and peripheral blood (right) analysis of evaluable patients is shown. Counts after treatment correspond to the available data at the latest cycle time-point under treatment. Detailed BM data not yet available for Patient #6. For Patient #5, follow-up data between withdrawal and CRi observation is also shown.

Demographics

Demographic data		
nº of patients		12
Sex	Male	5 (41.66%)
	Female	7 (58.33 %)
Age	Mean	78
	Median	78
	(Min , Max)	(71/83)
Race	Caucasian	100%
Weight(Kg)	Mean	73.44
	Median	71.00
	(Min , Max)	(54.50/104)
Height (cm)	Mean	158
	Median	155.5
	(Min , Max)	(151/174)
BMI	Mean	29,18
	Median	29.94
	(Min , Max)	(20.02/36.14)

AML diagnosis		
nº of patients		12
AML subtype (WHO)	AML with recurrent genetic abnormalities	2 (16.66 %)
	AML with multilineage dysplasia	0 (0.0 %)
	AML and MDS, therapy-related	6 (50 %)
	AML not otherwise categorized	4 (33.33%)

Pharmacodynamics



Blood samples were used to assess LSD1 target engagement (TE) and treatment-induced cell differentiation, analyzed by a proprietary ELISA-based methodology (LSD1 TE) and qRT-PCR, respectively. In 2 of 11 patients blood samples were collected on day 8 instead of day 5; LSD1-TE analysis in these patients demonstrated that LSD1 TE values were maintained 48 hours after the last iadademstat administration. Moreover, one patient treated with 60 µg/m^2/d (instead of 90) showed similar LSD1-TE levels. Expression PD biomarkers assayed include LY96, S100A12, VCAN, CD86, among others. Induction of differentiation genes was observed from the first treatment days. This is in line with iadademstat's previous Phase I data and confirms Aza co-treatment has no impact on the GE response pattern. Figure shows data from Patient #1 as an example.

Preliminary Safety and Tolerability

Study-drug related TEAEs (ADRs) by SOC and PT (n= 12)					
Number of Patients (%) Event Count					
System Organ Class Preferred Term (SOC) Preferred Term(PT)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders					
Anaemia	3(25.0)12	3(25)11	4(33.3)10	0(0.0)0	0(0.0)0
Leukocytosis	1(8.33)11	0(0.0)0	0(0.0)0	0(0.0)0	0(0.0)0
Neutropenia	4(33.3)6	4(33.3)7	5(41.6)13	4(33.3)10	0(0.0)0
Thrombocytopenia	3(25.0)6	3(25)10	4(33.3)10	6(50.0)14	0(0.0)0
Ear and labyrinth disorders					
Hypoacusis	1(8.33)1	0(0.0)0	0(0.0)0	0(0.0)0	0(0.0)0
Gastrointestinal disorders					
Nauseas	1(8.33)1	2(16.66)2	0(0.0)0	0(0.0)0	0(0.0)0
Constipation	1(8.33)1	1(8.33)1	0(0.0)0	0(0.0)0	0(0.0)0
Vomiting	1(8.33)1	0(0.0)0	0(0.0)0	0(0.0)0	0(0.0)0
Gingival bleeding	1(8.33)1	1(8.33)1	0(0.0)0	0(0.0)0	0(0.0)0
General disorders and administration site conditions					
Asthenia	4(33.3)6	1(8.33)2	1(8.33)1	0(0.0)0	0(0.0)0
Pyrexia	1(8.33)1	0(0.0)0	0(0.0)0	0(0.0)0	0(0.0)0
Hepatobiliary disorders					
Hyperbilirubinaemia	1(8.33)1	1(8.33)1	0(0.0)0	0(0.0)0	0(0.0)0
Investigations					
Blood bilirubin increased	0(0.0)0	1(8.33)1	0(0.0)0	0(0.0)0	0(0.0)0
Platelet count decreased	0(0.0)0	0(0.0)0	0(0.0)0	1(8.33)1	0(0.0)0
Metabolism and nutrition disorders					
Decreased appetite	2(16.66)3	0(0.0)0	0(0.0)0	0(0.0)0	0(0.0)0
Hypomagnesaemia	1(8.33)1	0(0.0)0	0(0.0)0	0(0.0)0	0(0.0)0
Hyponatraemia	2(16.66)2	0(0.0)0	0(0.0)0	0(0.0)0	0(0.0)0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Differentiation syndrome	0(0.0)0	0(0.0)0	1(8.33)1	0(0.0)0	0(0.0)0
Nervous system disorders					
Dysgeusia	3(25.0)6	0(0.0)0	1(8.33)1	0(0.0)0	0(0.0)0
Haemorrhage intracranial	0(0.0)0	0(0.0)0	0(0.0)0	0(0.0)0	1(8.33)1
Respiratory, thoracic and mediastinal disorders					
Dyspnoea	0(0.0)0	1(8.33)1	0(0.0)0	0(0.0)0	0(0.0)0
Skin and subcutaneous tissue disorders					
Rash	3(25.0)3	0(0.0)0	0(0.0)0	0(0.0)0	0(0.0)0

Results and Discussion

SAFETY: The Safety Monitoring Committee (SMC) of the study initially selected a RD of iadademstat of 90 µg/m^2/d in combination with Aza 75 mg/m^2. This decision was made based on data from the first 6 subjects, where this dose was well tolerated and only 1 DLT (differentiation syndrome; Patient #10) was observed, and based on the fact that the selected dose: i) was able to saturate LSD1 target engagement in PBMCs after 5 days of treatment; ii) was well tolerated (11 treatment cycles were completed at the moment of decision) and iii) demonstrated initial signs of efficacy. After recruitment of additional patients at the same dose, there was one patient who withdrew consent after experiencing severe fatigue (Patient #5; C4D28), and another patient (Patient #11) died due to an intracranial hemorrhage on C1D15. The SMC then decided to reduce the dose of iadademstat to 60 µg/m^2/d, a dose level also able to saturate LSD1 target engagement and with a clear biomarker effect, but with a potential better tolerability and therefore a better adherence to treatment schedule. Besides the reported hematological events, the combination appears to be safe and well tolerated and, up to date, no clinically relevant non-hematological adverse events have been reported.

EFFICACY: At the date of writing, 13 patients have been enrolled in ALICE: 8 have had ≥ 1 BM evaluation (evaluable patients as per protocol), 3 died before their first BM evaluation (one of them by an accidental fall not related to disease progression (Patient #9)), and 2 were just starting treatment (cycle 1) at the time of data cut. The mean follow up time amongst the evaluable patients was 20 weeks, with a mean Time to Response (TTR) of only 32 days (in those patients who respond). Six of the 8 evaluable patients (75 %) achieved OR responses: 2 CR, 3 CRi and 1 PR. Two of the 5 patients (40%) that have received more than 3 cycles of treatment have also become transfusion independent (not requiring subsequent red cell transfusions). Excluding patient #9, who died from a domestic accident without BM assessment, and not considering patients #12 and #13 still in C1, the OR rate in Intention-to-treat patients was 60% (6 out of 10 patients).

Conclusions

The objectives of this Phase II study include safety and efficacy of iadademstat when given in combination with Aza in elderly AML patients (first line treatment), as a prelude to a broader application in other leukemia patients. Data to-date support that iadademstat has a good safety profile compared with other anti-leukemic or epigenetic agents and is a meaningful candidate for selective combinations with other agents. Toxicity appears to be predictable, manageable and primarily hematologic events.

With historical response rates of 27% in this population when treated with azacitidine alone, the current results are supportive for a significant synergistic effect from iadademstat. BM and hematological response rates compare well with the current standard of care combination therapies for this type of elderly AML patient. These results will be expanded in the coming months with additional patients and extended clinical observation times to better assess the frequency, consolidation and duration of the responses. This additional efficacy data will be presented in future conferences, but it appears that these efficacy outcomes reported in this growing cohort of AML patients may warrant further trials with this combination therapy in a confirmatory study setting.

LSD1 has a mechanistic role that has been extensively characterized in MLL-r leukemia and erythroleukemia subtypes. However, these data clearly support that the therapeutic applicability of LSD1 inhibition, alone or in combination, extends beyond these leukemia niches.

Acknowledgements

We thank the investigators and teams and, most importantly, the patients who participate in the study and their families. This study is partially funded thanks to the Retos program RTC-2017-6407-1

DISCLOSURES: *Tim Somervaille: Novartis: consultancy; Imago Bioscience: research funding. Mabel Arévalo, Sonia Gutiérrez, Jordi Xaus, Roger Bullock, and Carlos Buesa are employees of Oryzon Genomics S.A. Carlos Buesa is the Chief Executive Officer and holds equity of Oryzon Genomics S.A. Oryzon Genomics S.A. sponsors the ALICE clinical trial.*