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

O. Salamero[1], T. Somervaille[2], A. Molero[1], E. Acuña[3], A. Pérez[1], I. Cano[3], R. Rodriguez-Veira[3], M. Arévalo[4], S. Gutierrez[4], R. Bullock[4], C. Buesa[4], F. Bosch[1], P. Montesinos[3]

1. Vall d' Hebron University Hospital, Barcelona, Spain; 2. Cancer Research UK Manchester Institute, The University of Manchester, Manchester, United Kingdom; 3. Hospital Universitario La Fe, Valencia, Spain. 4. Oryzon Genomics S.A., Cornellà de Llobregat, Spain

Introduction

Acute Myeloid Leukemia (AML) in elderly patients unfit for intensive chemotherapy remains a challenge. 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. Recent combos of hypomethylating with pro-apoptotic agents showed improved therapeutic prospects in early clinical trials. Iadademstat (iada) is a differentiating drug that selectively inhibits LSD1 and has shown efficacy in preclinical models, both alone and in combination with other compounds including azacitidine (Aza) and BCL2 inhibitors. A First in Man Phase I study in acute leukemia showed a good safety profile and anti-leukemic activity for iada (manuscript submitted). Combination of iada with Aza may offer an alternative or complementary therapeutic option for this population. Herein, we report preliminary results of the ALICE study (EudraCT 2018-000482-36).

Methods

ALICE is a Phase IIa clinical trial to assess the safety, tolerability, and dose finding of iada in combination with Aza for the treatment of elderly patients with AML. The study also investigates the anti-leukemic activity of this combination, including overall response rate (ORR), time to response (TTR) and duration of response (DOR), as secondary endpoints. Additional assessments include hematological improvement and overall survival, along with PK/PD measures comprising a set of 7 blood biomarkers. ALICE includes patients older than 60 yrs, diagnosed with AML according to the WHO classification, who have not received prior treatment for AML other than hydroxyurea and are considered by the investigator as ineligible for intensive chemotherapy or refuse this treatment option. The dose finding phase was planned for a maximum of 18 patients (Part 1), followed by an expansion phase (Part 2) planned for a maximum of 18 patients to be treated with iada at the Recommended Phase II Dose (RPIID) in combination with Aza.

Results & Discussion - I

Eighteen patients (median age 77 yrs) have been enrolled up to April 30th and are reported in this communication. Recruitment rate has been temporarily reduced in the last two months due to Covid-19 pandemia. Demographic characteristics of patients are shown in **Table 1**. The current RPIID of iada in combination with Aza is 60µg/m2/d.

SAFETY: Main safety events include 96 grade 3-4 AEs in 12 patients that were considered as related to the study drugs, Aza or iada. Most of them were neutropenia and thrombocytopenia, whereas only 3 non-hematological AEs, asthenia and dysgeusia in one patient and weight reduction in another patient, were observed. Among the 38 serious adverse events reported, only 2 were considered as related to iada: 1 differentiation syndrome (grade 3) on C1D10 and 1 intracranial hemorrhage (grade 5) on C1D15. Seven deaths have been reported in the trial, 5 before first bone marrow (BM) assessment. Causes of death were: intracranial hemorrhage (2), accidental fall leading to femoral fracture and subarachnoid hemorrhage (1), respiratory infection (2), neutropenic colitis (1) and disease progression (1). Besides the expected hematological impact, the combination appears to be safe and well tolerated.

Highlights

- 18 patients enrolled up to date; 13 evaluable as per protocol
- Iadademstat and azacitidine combination shows a good safety profile in elderly AML patients
- Signals of clinical efficacy are encouraging, with 77% of ORs (10 out of 13: 6 CR/CRi and 4 PR)
- Rapid clinical responses (mean time to first response is currently 37 days). Longest response up to date 488 days
- Preliminary rate of conversion to red cell Transfusion Independence is also encouraging

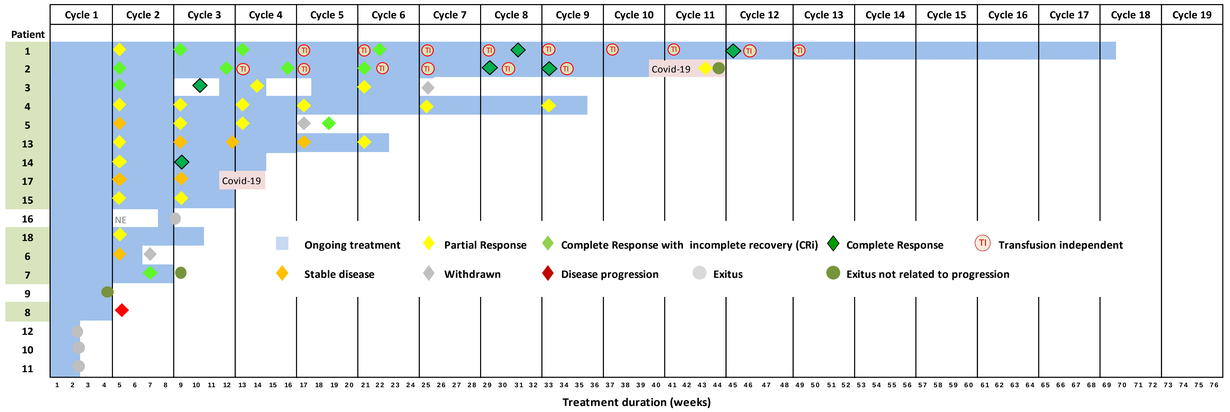

Figure 1. Efficacy response based on bone marrow cellularity in patients treated with iada in combination with Aza. Cycles correspond to 4 weeks treatment. Non-colored weeks correspond to transient treatment interruption periods due to adverse events or patient hospitalization.

Demographic data		
nº of patients		18
Sex	Male	9 (50%)
	Female	9 (50 %)
Age	Mean	76
	Median	77
	(Min , Max)	(70/83)
Race	Caucasian	100%
Weight (Kg)	Mean	72.13
	Median	70.90
	(Min , Max)	(54.50/104)
Height (cm)	Mean	161
	Median	160,00
	(Min , Max)	(150/175)
BMI	Mean	27.98
	Median	27.33
	(Min , Max)	(20.02/36.14)

AML Diagnose	
WHO (n=18)	
AML not otherwise categorized	10 (55.6 %)
AML and MDS, therapy-related	7 (38.9%)
AML with recurrent genetic abnormalities	1 (5.6 %)
FAB (n=16)	
M0 (myeloblastic, minimally differentiated)	4 (25.0 %)
M1 (myeloblastic, minimal maturation)	3 (18.8 %)
M2 (myeloblastic, with granulocytic maturation)	5 (31.3 %)
M4 (acute myelomonocytic leukemia)	3 (18.8 %)
M5a (monoblastic)	1 (6.3 %)

Table 1. Demographic and AML diagnose of the recruited patients. Two patients did not report FAB diagnose in the eCRF.

	Grade 1-3	Grade 4-5
Blood and lymphatyc system disorders	**5 (13.9 %)/ 4 (22.2 %)**	**3 (8.3 %)/ 3 (16.7 %)**
Febrile neutropenia	*5 (13.9 %)/ 4 (22.2 %)*	*3 (8.3 %)/ 3 (16.7 %)*
General disorders and administration site conditions	**3 (8.3 %)/ 3 (16.7 %)**	**1 (2.8 %)/ 1 (5.6 %)**
Death		*1 (2.8 %)/ 1 (5.6 %)*
Pyrexia	*2 (5.6 %)/ 2 (11.1 %)*	
Mucosal Inflammation	*1 (2.8 %)/ 1 (5.6 %)*	
Infections and infestations	**10 (27.8 %)/ 8 (44.4 %)**	**7 (19.4 %)/ 5 (27.8 %)**
Sepsis		*5 (13.9 %)/ 4 (22.2 %)*
Cellulitis	*3 (8.3 %)/ 3 (16.7 %)*	
Pneumonia or respiratory tract infection	*2 (5.6 %)/ 2 (11.1 %)*	*2 (5.6 %)/ 2 (11.1 %)*
Other	*5 (13.9 %)/ 3 (16.7 %)*	
Investigations	**1 (2.8 %)/ 1 (5.6 %)**	
ALT increase	*1 (2.8 %)/ 1 (5.6 %)*	
Musculoskeletal and connective tissue disorders	**2 (5.6 %)/ 1 (5.6 %)**	
Bone pain	*2 (5.6 %)/ 1 (5.6 %)*	
Nervous system disorders		**2 (5.6 %)/ 2 (11.1 %)**
Haemorrhage intracranial		*1 (2.8 %)/ 1 (5.6 %)*
Subarachnoid haemorrhage		*1 (2.8 %)/ 1 (5.6 %)*
Renal and urinary disorders	**1 (2.8 %)/ 1 (5.6 %)**	
Haematuria	*1 (2.8 %)/ 1 (5.6 %)*	
Respiratory, thoracic and mediastinal disorders	**1 (2.8 %)/ 1 (5.6 %)**	
Pneumonia aspiration	*1 (2.8 %)/ 1 (5.6 %)*	

Table 2. Distribution by severity and by System Organ Class (SOC) of the 36 Serious Adverse Events (SAEs) that have been considered as non-related to iada treatment. SAEs within each SOC class are also listed by Preferred Term (PT). Values represent "number of events" (% of total non-related SAEs) / "number of patients affected" (% of total patients).

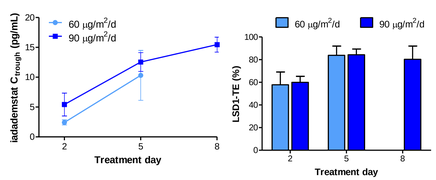

Figure 2. Iada Ctrough levels were assessed in plasma by LC-MS/MS and LSD1-TE was determined in PBMC by a proprietary ELISA-based method. In 2 out of the 10 patients dosed at 90 µg/m2/d samples were collected on day 8 instead of day 5.

		Maximum response (-ΔΔCp)						
		monocytic				erythrocytic		
Patient Id.	FAB Subtype	LY96	S100A12	VCAN	CD86	HBB	HBA1	GYPB
#1	M1	2.4	2.5	2.2	2.2	-1.3	-1.0	-1.4
#8	M4	2.6	4.5	1.9	2.5	1.0	1.4	0.6

Figure 3. Iada-induced differentiation was assessed in peripheral blood cells by analyzing gene expression changes of selected biomarkers by qRT-PCR. -ΔΔCp values >0 indicate gene up-regulation, whereas those <0 indicate down-regulation. Only patients with peripheral blast counts >30% are shown.

Results & Discussion - II

EFFICACY: Among the 18 patients reported herein, 13 have had at least 1 BM evaluation (evaluable patients as per protocol). Five patients died before their first BM evaluation (one of them by an accidental fall not related to disease progression, patient #9). One patient died at the end of C2 but was not assessed in C1. One patient in CR died of Covid-19 at cycle 10 (patient #2). The current mean duration in the study is 20 weeks, with a mean Time to Response (TTR) of only 37 days (in those patients who respond). Ten of the 13 evaluable patients (77 %) achieved an OR response: 4 CR, 2 CRi and 4 PR. So far, the longest response in CR is 488 days (patient still under treatment and in CR). Two of the 5 patients (40%) who received more than 5 cycles of treatment were transfusion independent (not requiring subsequent red cell transfusions). Excluding patient #9, who died from a domestic accident without BM assessment, the OR rate in the intention-to-treat patients was 59% (10 out of 17 patients).

PK-PD: PK analysis showed a dose-dependent increase in exposure and moderate accumulation after repeated dosing (Ctrough) in keeping with the FiM study. PD behavior in terms of LSD1 Target Engagement (TE) was comparable between doses (**Figure 2**), supporting the dose of 60 µg/m2/d as pharmacologically equivalent to the dose of 90 µg/m2/d. Modulation of gene expression (GE) levels of selected biomarkers (**Figure 3**) suggests iada-induced cell differentiation is triggered from the first days of treatment, in line with previous FiM data and confirming Aza co-treatment has no impact on the GE response pattern.

Conclusions

The objectives of this Phase II study include safety and efficacy of iada when given in combination with Aza in elderly AML patients (1L treatment), as a prelude to broader application in other leukemia settings. Data to-date support that iada 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 restricted to hematologic events. With historical response rates of 27% in this elderly AML population when treated with Aza alone, the current results are supportive of a significant synergistic effect for iadademstat. The robust BM and hematological response rates continue to compare well with the current standard of care combination therapies for this population. Considering the difference of MoA between proapoptotic BCL2 inhibitors and pro-differentiating iada, it is of great interest to increase the therapeutic options in this hard to treat population. ALICE is still recruiting patients and extended clinical observation times will allow to better assess the frequency, consolidation and duration of the responses. Additional data will be presented in future conferences, but if the current responses are maintained over time, these data 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, ALICE 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: OS*: honoraria from Celgene, Novartis, Daichii Sankyo and Jazz Pharmaceuticals; consulting or advisory role from Celgene, Novartis, Pfizer and Jazz Pharmaceuticals; and travel, accommodations or expenses from Celgene, Novartis and Daiichi Sankyo.* ***TS****: consultancy from Novartis; research funding from Imago Bioscience; and honoraria from Novartis.* ***AM****: honoraria from Abbvie and Jansen; and Travel, Accommodations, Expenses from Celgene;* ***FB****: honoraria from Roche, Celgene, Takeda, Astra-Zeneca, Novartis, AbbVie and Janssen.* ***SG****,* ***RB****, and* ***CB*** *are employees of Oryzon Genomics S.A.* ***CB*** *is the Chief Executive Officer and holds equity of Oryzon Genomics S.A. Oryzon Genomics S.A. sponsors the ALICE clinical trial.*