ALICE MAINTAINS HIGH CLINICAL RESPONSE RATES SUPPORTING THE EFFICACY OF IADADEMSTAT COMBINATION WITH AZACITIDINE IN AML MANAGEMENT

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Introduction

Combination of hypomethylating with pro-apoptotic agents have improved therapeutic prospects in elder AML patients. Yet, there is still a high unmet medical need due to the high relapse rate. Iadademstat (iada) is an oral differentiating drug that selectively inhibits LSD1 and has shown efficacy in preclinical models, both alone and in combination with other agents including azacitidine (Aza), BCL2 inhibitors and anti-CD47. A First in Man Phase I study in acute leukemia showed a good safety profile and anti-leukemic activity for iada (1). Combination of iada with Aza may offer an alternative or complementary therapeutic option for this AML population. Herein, we report preliminary results of the first 30 months of the ongoing 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 or unfit 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. ALICE includes patients older than 60 yrs or unfit, diagnosed with AML according to the WHO classification, who have not received prior treatment for AML. The trial aims to recruit up to 36 patients.

Results & Discussion - Safety

Twenty-seven patients (median age 77 yrs) have been enrolled up to May 24th and are reported in this communication. One patient was considered not to fulfill the inclusion criteria and has only been analyzed for safety. Eighteen were evaluable as per protocol (app) (patients with BMA at C1) and 2 were still in C1 at the cutoff date. Demographic characteristics of the enrolled patients are shown in Table 1. Fifteen patients (56%) were diagnosed as de novo AML patients and 19 (70%) presented with > 30% marrow blasts. Fourteen patients (54%) presented high cytogenetic risk and 11 (42%) intermediate risk. A significant majority of recruited patients showed at baseline severe thrombocytopenia (TCP, G≥3) (63%). Initially, 10 patients were dosed with iada at 90 µg/m2/d and 75 mg/m2 Aza. To improve tolerability iada was reduced to 60 µg/m2/d. Since then, all patients have been treated with this dose.

26 patients (96.3%) have experienced a total of 766 AEs and 48 of these in 23 patients (85.2%) were reported as SAEs (Table 2A). Within these AEs, 301 presented in 24 patients (88.9%) were considered as related to treatment (ARs) by the investigators and only 2 of them (in 2 patients; 7.4%) were deemed as serious (SARs). Most frequent ARs were: platelet count decrease: 93 events in 13 patients (48.2%), and neutrophil count decrease: 88 events in 12 patients (44.4%). Other ARs (incidence ≥ 10% per PT) were dysgeusia, anemia, asthenia, constipation, nausea and decreased appetite. The 2 SARs were 1 differentiation syndrome (G3) and 1 intracranial hemorrhage (G5). Nine deaths have been reported in the trial, 6 of them before bone marrow (BM) assessment. Two patients died from Covid-19 at C4 and C12, respectively. The remaining causes have been: 2 sepsis, 2 ICHs (both with previous significant infections), 1 lung infection, 1 domestic accident with multiple fractures and subarachnoid hemorrhage, and 1 death at home (reportedly linked to sepsis). To mitigate deaths due to infection and sepsis, a protocol amendment has been implemented to incorporate prophylactic antimicrobial agents.

Full suppression of LSD1 activity produces TCP, it seems reasonable to think that iada (and the combined aza) may trigger TCP or intensify the already occurring cytopenia in AML patients. Yet, 63% of patients already had TCP G≥3 at baseline (Table 1). It is difficult to attribute severe cytopenias only to iada as intensity and duration of TCP in the trial is variable and probably other factors may impact on the observed TCP. Patients with TCP at baseline experienced full or significant platelet recovery within the first 3 cycles or response achievement. Besides the hematological impact, the combination appears to be generally safe and well tolerated and we have not observed other significant non-hematological toxicities as it has been described with other agents in the AML treatment. These results are encouraging, and this combination may represent an alternative in AML treatment.

Highlights

- ❖ 27 patients enrolled up to date; 18 evaluable as per protocol
- ❖ Iadademstat and azacitidine combination shows a good safety profile in elderly AML patients
- ❖ Signals of clinical efficacy are encouraging, with 83% of ORs (15 out of 18: 10 CR/CRi and 5 PR)
- ❖ Rapid clinical responses (mean time to first response is 1 Cycle)
- ❖ Longest response to date 858 days (still ongoing)

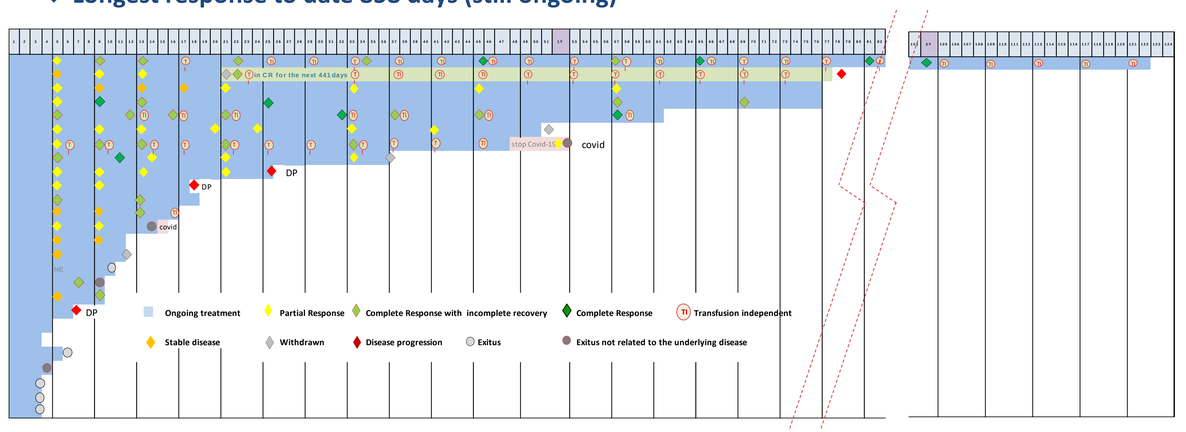

Figure 1. *Efficacy response based on bone marrow cellularity in patients treated with iada in combination with Aza. Responses are as reported preliminary by the investigators in the eCRF*

Baseline characterization		
Total enrolled	27	
Total enrolled a.p.p.	**26**	
Age		
Median (range)	**76.5**	**(70-83)**
≥75 yr — no. (%)	**15**	**55.5%**
Gender: Female/Male — no. (%)	**17/10**	**63%/37%**
AML type (n=27)		
De novo	**15**	**56%**
Secondary	**12**	**44%**
Therapy-related AML	**1**	**8%**
History of myelodysplastic syndrome or CMML	**10**	**83%**
Bone marrow blast count— no. (%)		
<30%‡	**8**	**30%**
≥30 to <50%	**15**	**55%**
≥50%	**4**	**15%**
Cytogenetic risk category (n=25) — no. (%)*		
Intermediate	**11**	**42%**
Normal karyotype — no.	**10**	
Trisomy 8; +8 alone; 14 — no.	**1**	
High	**14**	**54%**
7 or 7q deletion — no.	**6**	
5 or 5q deletion — no.	**1**	
inv3	**2**	
complex karyotype	**2**	
Baseline cytopenias grade ≥3		
Anemia — no. (%)	**4**	**15%**
Neutropenia — no./total no. (%)	**17**	**63%**
Thrombocytopenia — no. (%)	**17**	**63%**

Table 1*. Demographic and AML diagnose of the enrolled patients. *Two patient did not report cytogenetic risk in the eCRF. Baseline cytopenias were reported for all enrolled patients.*

Table 2B: *Distribution of ARs per System Organ Class (SOC) and Preferred Term (PT) with an incidence ≥ 5% per PT and all SARs (regardless incidence). Number of PT (%) Event Count*

Number of Patients (%) Event Count				
	Adverse events (AEs)	Adverse reactions (ARs)	Serious adverse events (SAEs)	Serious adverse reactions (SARs)
TOTAL	26 (96.3) 766	24 (88.9) 301	23 (85.2) 48	2 (7.4) 2

Number of Patients (%) Event Count		
System Organ Class Preferred Term	Adverse reactions (ARs)	Serious adverse reactions (SARs)
Investigations	**17 (63.0) 184**	**0 (0.0) 0**
Platelet count decreased	13 (48.2) 93	0 (0.0) 0
Neutrophil count decreased	12 (44.4) 88	0 (0.0) 0
Gastrointestinal disorders	**12 (44.4) 23**	**0 (0.0) 0**
Constipation	7 (25.9) 11	0 (0.0) 0
Nausea	4 (14.8) 6	0 (0.0) 0
Diarrhoea	2 (7.4) 3	0 (0.0) 0
Nervous system disorders	**10 (37.0) 15**	**1 (3.7) 1**
Dysgeusia	9 (33.3) 14	0 (0.0) 0
Haemorrhage intracranial	1 (3.7) 1	1 (3.7) 1
Blood and lymphatic system disorders	**9 (33.3) 46**	**0 (0.0) 0**
Anaemia	8 (29.6) 45	0 (0.0) 0
General disorders and administration site conditions	**9 (33.3) 14**	**0 (0.0) 0**
Asthenia	7 (25.9) 12	0 (0.0) 0
Metabolism and nutrition disorders	**4 (14.8) 7**	**0 (0.0) 0**
Decreased appetite	3 (11.1) 4	0 (0.0) 0
Hyponatraemia	2 (7.4) 2	0 (0.0) 0
Skin and subcutaneous tissue disorders	**4 (14.8) 5**	**0 (0.0) 0**
Rash	2 (7.4) 3	0 (0.0) 0
Neoplasms benign, malignant and unspecified	**1 (3.7) 1**	**1 (3.7) 1**
Differentiation syndrome	1 (3.7) 1	1 (3.7) 1

Table 2A: *Accumulative number of AEs/ARs /SAEs/SARs (safety cut-off date 17 May 2021). Number of Patients (%) Event Count*

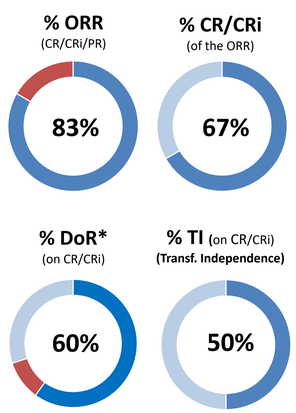

Figure 2*: Summary of efficacy responses based on bone marrow cellularity in patients treated with iada in combination with Aza. Responses are as reported preliminary by the investigators in the eCRF. *DoR represents the % of CR/CRi responses lasting for more than 6 months.*

Results & Discussion - Efficacy

As per May 24th, among the 18 evaluable patients, 15 (83.3 %) achieved an OR. Ten responses were CR/CRi; 5 of them were CRs, with 3 being MRD negative, and 5 were CRi (3 of which still evolving). Five other responses were reported as PRs. Remarkably, one of the responders is a CRi achieved in 29 days in a patient with M5b (monocytic) AML, a traditional hard-to-treat leukemia subgroup, who also had an adverse prognosis (inv(3)(q21;q26.2)).

Responses to the iada+Aza combination are observed early, with a median Time to Response (TTR) of 29 days. To date, 8 out of the 15 responding patients (53%) have had responses lasting more than 6 months. If we consider the 10 CR/CRi, 6 are long-lasting (60%), with 3 further recent responses (30%) that are maturing but still below the 6-month threshold. The longest response in CR is 858 days (ongoing, in CR and MRD negative), with other 4 patients with responses > 1yr (3 still ongoing). Five of the 10 CR/CRi (50%) have become transfusion independent.

The ORR rate in the intention-to-treat patients was an encouraging 62% (15 out of 24 patients) as per ITT.

Conclusions

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 restricted to hematologic events. With historical OR data[2] of 28% in this elderly AML population when treated with azacitidine alone, the current results are supportive of a significant synergistic effect for iadademstat. Considering the different mechanisms of action of pro-apoptotic BCL2 inhibitors and the pro-differentiating agent iadademstat, we believe that combination strategies with iadademstat might increase therapeutic options for AML patients in first line treatment, as well as for refractory, intolerant or relapsed patients. ALICE is still recruiting patients. Additional data will be presented in future conferences.

References

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2. https://ascopost.com/issues/july-25-2020/viale-a-trial-supports-survival-benefit-of-venetoclax-plus-azacitidine-in-elderly-patients-with-aml/

DISCLOSURES: *OS: honoraria from BMS-Celgene, Novartis, and Jazz Pharmaceuticals; consulting from BMS-Celgene, Novartis, Pfizer and Jazz Pharmaceuticals. TS: consultancy from Novartis; research funding from Imago Bioscience; and honoraria from Novartis. AM: honoraria from Abbvie and Jansen; and Travel, Accommodations, Expenses from BMS-Celgene; ERA: honoraria from Jazz Pharmaceuticals and Eurocept, and research funding from Pfizer; FB: honoraria from Roche, BMS-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.*

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