IADADEMSTAT IN COMBINATION WITH AZACITIDINE GENERATES ROBUST AND LONG LASTING RESPONSES IN AML PATIENTS (ALICE TRIAL)

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INTRODUCTION

Acute Myeloid Leukemia (AML) is an aggressive hematological malignancy. Elderly/unfit patients are treated with low dose chemotherapy (e.g. azacitidine), with best ORRs below 30% (1). A recently approved regime, venetoclax combined with azacitidine, has improved the clinical response to 64% with a median overall survival of 14.7 months. Yet, 25% of patients are refractory and 50% are estimated to early relapse (2). Therefore, the management of AML in elderly or unfit patients remains a major challenge.

Lysine-specific histone demethylase 1 (LSD1) contributes to the malignant transformation event in AML. Iadademstat (iada) selectively and potently inhibits LSD1 and has shown efficacy as monotherapy in the clinic, promoting differentiation in R/R AML. Iada has been administered to +100 oncology patients in different clinical trials, showing good safety. Given its safety profile, favorable ADME, high bioactivity and anticipated low DDI risk, iada combinations might offer additional therapeutic options for AML patients. This is a 36-month update of the ongoing Phase II ALICE clinical trial of iadademstat plus azacitidine in front-line elderly/unfit AML patients.

TRIAL DESIGN

ALICE (EudraCT 2018-000482-36) is an open-label, single arm, Phase IIa clinical trial to assess the safety, tolerability, dose finding and efficacy of iadademstat in combination with azacitidine for the treatment of adult AML patients. Patients must be ineligible for intensive chemotherapy or have refused this treatment option and have not received prior treatment other than hydroxyurea. Secondary end points of the study are ORR (CR+CRi+PR), TTR and DoR, as well as PK/PD measurements. ALICE is now fully recruited, and patients will be followed for an additional 12 months.

REFERENCES

1. Dombret, et al. Blood. 2015 Jul 16;126(3):291-9. doi: 10.1182/blood-2015-01-621664
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RESULTS
(DATA CUT-OFF OCTOBER 15TH, 2021)

The presented, unaudited data corresponds to 36 patients enrolled for safety analysis, with 34 enrolled as per protocol and 27 evaluable for efficacy (with at least 1 bone marrow disease evaluation after starting therapy). Baseline characteristics are shown in **Table 1**.

Efficacy:

Evaluable patients achieved an 78% ORR: 6 CR, 7 CRi and 8 PR (**Fig. 1**). 67% of CR/CRi patients became transfusion independent and 5 patients became MRD negative. 10 patients are still ongoing in the trial. The current median Time to Response (TTR) is 55 days. CR/CRi responses are durable: 77% higher than 6 months, extending for more than one year in six patients, and with the longest CR (MRD-) above thousand days and still ongoing. Of note, among the different subgroups in the study, 2 pts out of 2 with M5b AML and 3 pts out of 3 with TP53-mutant AML all achieved CR/CRi.

Safety:

Table 2 shows ARs reported. Two patients experienced SARs probably related to treatment: one differentiation syndrome (G3) and one intracranial hemorrhage (G5). The most frequent reported AR was platelet reduction, observed in almost half of patients (44%), although thrombocytopenia (Grade ≥3) was already present at baseline in a high proportion of patients (61%, **Table 1**). No other significant non-hematological toxicities or other organ-related toxicities were observed.

Efficacy and Exposure Relationships:

ALICE tested iada doses of 60 and 90 μg/m²/d (n=17 patients each). 90 μg/m²/d produced a higher exposure and a higher and more consistent LSD1 Target Engagement (TE) (**Fig. 2**). Preliminary data shows that there is a direct correlation between quality of clinical response and iada exposure/TE. The 90 μg/m²/d dose more consistently achieved the exposure and TE observed in CR patients as compared to the lower dose, without increasing the severity of ARs (**Fig. 3**). At 90 μg/m²/d, the iada recommended dose for future studies in combination with azacitidine, the ORR was 77%, with 80% of them CR/CRi.

Highlights

- **Enrollment completed; 27 patients evaluable as per protocol**
- **Iadademstat and azacitidine combination shows a good safety profile**
- **Signals of clinical efficacy continue to be encouraging, with 78% of ORRs**
- **90 μg/m²/d final recommended iadademstat dose for the combination**

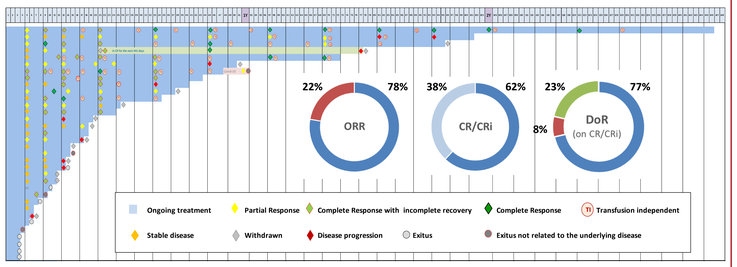
Table 1. *ALICE demographics and baseline characteristics*

Total enrolled	**36**	
Total enrolled app	**34**	
Age		
Median (range)	77	(70-83)
≥75 yr — no. (%)	21	62%
Male sex — no. (%)	16	47%
AML type		
De novo	28	82%
Secondary	7	21%
Therapy-related AML	4	57%
History of myelodysplastic syndrome or CMML	3	43%
ECOG performance-status score — no. (%)		
0-1	29	85%
2-3	5	15%
Bone marrow blast count — no. (%)		
<30%	8	24%
≥30 to <50%	16	47%
≥50%	11	32%
AML with myelodysplasia-related changes — no. (	14	41%
Cytogenetic risk category — no. (%)		
Intermediate	18	53%
Normal karyotype — no.	15	83%
Trisomy 8; +8 alone; 14 — no.	3	17%
Poor	16	47%
7 or 7q deletion — no.	7	44%
5 or 5q deletion — no.	3	19%
inv3	2	13%
complex karyotype	4	25%
Somatic mutations — no./total no. (%)		
IDH1 or IDH2	3	9%
FLT3-ITD or TKD	4	12%
NPM1	5	15%
TP53	3	9%
MLLr	1	3%
TET2	4	12%
KRAS	2	6%
IKZF1	1	3%
Baseline cytopenias grade ≥3		
Anemia — no. (%)	8	22%
Neutropenia — no./total no. (%)	24	67%
Thrombocytopenia — no. (%)	22	61%
Baseline transfusion dependence — no. (%)		
Red cells	13	38%
Platelets	11	32%
Transfusion independence	10	29%

Table 2. *Safety. Number of Adverse Reactions reported by PT and SOC. Nº Patients (%) Events*

	Adverse reactions (ARs)	Serious adverse reactions (SARs)
Blood and lymphatic system disorders	**10 (27.8) 54**	**0 (0.0) 0**
Anaemia	9 (25.0) 53	0 (0.0) 0
Leukocytosis	1 (2.8) 1	0 (0.0) 0
Congenital, familial and genetic disorders	**1 (2.8) 1**	**0 (0.0) 0**
Aplasia	1 (2.8) 1	0 (0.0) 0
Gastrointestinal disorders	**14 (38.9) 25**	**0 (0.0) 0**
Constipation	8 (22.2) 11	0 (0.0) 0
Diarrhoea	3 (8.3) 4	0 (0.0) 0
Gastrointestinal toxicity	1 (2.8) 1	0 (0.0) 0
Gingival bleeding	1 (2.8) 2	0 (0.0) 0
Nausea	4 (11.1) 6	0 (0.0) 0
Vomiting	1 (2.8) 1	0 (0.0) 0
General disorders and admin. site conditions	**8 (22.2) 13**	**0 (0.0) 0**
Asthenia	7 (19.4) 12	0 (0.0) 0
Illness	1 (2.8) 1	0 (0.0) 0
Hepatobiliary disorders	**1 (2.8) 2**	**0 (0.0) 0**
Hyperbilirubinaemia	1 (2.8) 2	0 (0.0) 0
Investigations	**20 (55.6) 219**	**0 (0.0) 0**
Blood bilirubin increased	1 (2.8) 1	0 (0.0) 0
Neutrophil count decreased	14 (38.9) 104	0 (0.0) 0
Platelet count decreased	16 (44.4) 112	0 (0.0) 0
Weight decreased	2 (5.6) 2	0 (0.0) 0
Metabolism and nutrition disorders	**5 (13.9) 8**	**0 (0.0) 0**
Decreased appetite	4 (11.1) 5	0 (0.0) 0
Hypomagnesaemia	1 (2.8) 1	0 (0.0) 0
Hyponatraemia	2 (5.6) 2	0 (0.0) 0
Neoplasms benign, malignant and unspecified	**1 (2.8) 1**	**1 (2.8) 1**
Differentiation syndrome	1 (2.8) 1	1 (2.8) 1
Nervous system disorders	**13 (36.1) 19**	**1 (2.8) 1**
Dysgeusia	12 (33.3) 18	0 (0.0) 0
Haemorrhage intracranial	1 (2.8) 1	1 (2.8) 1
Respiratory, thoracic and mediastinal disorders	**1 (2.8) 1**	**0 (0.0) 0**
Dyspnoea	1 (2.8) 1	0 (0.0) 0
Skin and subcutaneous tissue disorders	**4 (11.1) 5**	**0 (0.0) 0**
Erythema	3 (8.3) 3	0 (0.0) 0
Pruritus	1 (2.8) 1	0 (0.0) 0
Rash	2 (5.6) 3	0 (0.0) 0
Grand Total	**26 (72.2) 348**	**2 (5.6) 2**

Fig. 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. DoR: Blue, % >6 months, Green, % ongoing; Red, %<6 months)

Fig. 2. PK (Ctrough) and LSD1 target engagement (LSD1 TE) by dose level. *Iadademstat plasma trough concentrations (a) were determined by HPLC-MS/MS (LLOQ: 1pg/mL). LSD1 TE (b) was assessed in PBMC by using a proprietary chemoprobe-based sandwich enzyme-linked immunosorbent assay. Day 5 (pre-dose) levels are presented as Tukey whisker plots with outliers.*

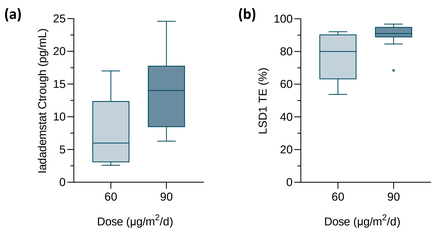
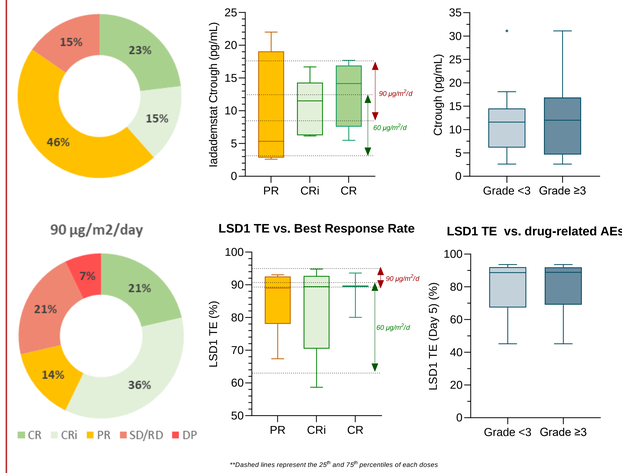


Fig. 3. Efficacy and exposure relationships.
Efficacy responses by dose level (a) and E-R relationships of iadademstat exposure (Ctrough) and LSD1 TE with efficacy (best response rate) (b) and safety (AE severity) responses (c).



**Dashed lines represent the 25th and 75th percentiles of each doses

CONCLUSIONS

Iadademstat has a good safety profile and produces robust, fast and durable responses in combination with azacitidine in elderly/unfit AML patients. Drug-related toxicity appears to be predictable, manageable, and restricted to on target hematologic events.

90 μg/m²/d is the recommended dose to be considered in further trials exploring iadademstat in combination with azacitidine. Considering iadademstat's efficacy, its manageable toxicity and low anticipated DDI interactions, combination strategies with azacitidine or other therapeutic options for AML patients in first line treatment, as well as for refractory, intolerant, or relapsed patients are warranted.

CONTACT INFORMATION

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