IADADEMSTAT COMBINATION WITH AZACITIDINE SHOWS ENCOURAGING SAFETY AND EFFICACY DATA IN ELDERLY AND UNFIT AML PATIENTS

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INTRODUCTION

Acute Myeloid Leukemia (AML) is a hematological malignancy with highest incidence and lowest survival rates in the elderly. Previously reported ORR with hypomethylating agents such as azacitidine alone is less than 30%[1]. Recently, combinations of hypomethylating agents with venetoclax have shown improved response ratios (CR+CRi 66.4%) and a median overall survival of 14.7 months. However, refractory disease (25%) or relapse (50%) continues to be a substantial challenge[2], particularly in elderly and high-risk subpopulations, and remains a considerable unmet need.

Lysine-specific histone demethylase 1 (LSD1) is an epigenetic enzyme that contributes to the malignant transformation event in AML by sustaining the oncogenic transformation, proliferation and the maintenance of the undifferentiated state in leukemia[3] through control of chromatin remodeling and regulation of transcription.

Iadademstat (iada), an oral small molecule that selectively and potently inhibits LSD1, has shown in a Phase I study a manageable safety profile and preliminary efficacy as monotherapy by promoting differentiation in R/R AML[3,4]. In addition to the safe profile, shown in more than 100 patients treated in oncological indications, iada exhibits favorable ADME properties, including high bioavailability and low anticipated DDI risk, making it a suitable drug for combinations with other antileukemic therapies for the treatment of AML patients.

We present here a 42-month update on the ongoing Phase II ALICE study of iadademstat plus azacitidine in front-line elderly/unfit AML patients (EudraCT 2018-000482-36).

OBJECTIVES

ALICE is a Phase IIa study to assess the safety, tolerability and the recommended Phase II dose (RP2D) of iada in combination with azacitidine for the treatment of adult patients newly diagnosed with AML.

ALICE STUDY DESIGN

Adult patients diagnosed with AML, as per WHO 2017 classification, who have not received prior treatment (other than hydroxyurea) and who are ineligible for or have refused intensive chemotherapy are dosed with iada (PO days 1-5 followed by 2 days off every week) in combination with azacitidine (sc, 7 days or 5-2-2) in 28-day cycles. Two doses of iada are studied in the trial: 60 and 90 µg/m²/d combined with the standard 75 mg/m² dose of azacitidine.

Secondary endpoints investigate anti-leukemic activity including overall response rate (ORR) according to ELN recommendations, time to response (TTR) and duration of responses (DoR). Additional assessments include measurable residual disease (MRD) status, overall survival (OS) and PK/PD determinations.

The trial completed accrual of 36 patients in October 2021 and is currently in follow up.

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REFERENCES

1 Dombret *et al.*, Blood.2015 Jul 16; 126(3): 291-9. doi:10.1182/blood-2015-01-6216642
2 Di Nardo *et al.*, N Engl J Med. 2020 Aug 13; 383(7): 617 doi:10.1056/ NEJMoa 2012971
3 Harris *et al.*, Cancer Cell 2012 Apr17; 21(4):473-87. doi: 10.1016/j.ccr.2012.03.014
4. Salamero *et al.*, J Clin Oncol 2020 Dec 20;38(36):4260-4273. doi: 10.1200/JCO19.03250
5. Salamero et al., Poster#3376 at ASH 2021

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RESULTS

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), with data cutoff of April 15, 2022.

Total enrolled	**36**	
Total enrolled app	**34**	**no (%)**
Age		
Median (range)	77 (70-83)	
≥75 yr	21	62%
Male gender	16	47%
AML type		
De novo	**27**	**79%**
Secondary	**7**	**21%**
Therapy-related AML	4	57%
History of MDS or CMML	3	43%
AML with MDS-related change	**14**	**41%**
ECOG performance-status score		
0-1	29	85%
2-3	5	15%
Bone marrow blast count		
<30%	8	24%
≥30 to <50%	15	44%
≥50%	11	32%
Cytogenetic risk category		
Intermediate	**18**	**53%**
Normal karyotype	15	83%
Trisomy 8; +8 alone; 14	3	17%
Poor	**16**	**47%**
7 or 7q deletion	7	44%
'5 or 5q deletion	3	19%
inv3	2	13%
complex karyotype	4	25%
Somatic mutations	30	88%
IDH1 or IDH2	4	13%
FLT3 ITD or TKD	4	13%
NPM1	5	17%
TP53	10	33%
MLLr	1	3%
TET2	8	27%
KRAS	4	13%
ASXL1	5	17%
RUNX1	3	10%
DNMT3a	4	14%
ETV6	3	10%
EZH2	3	10%
IKZF1	1	3%
Other	11	38%
Baseline cytopenias grade ≥3		
Anemia	9	25%
Neutropenia	24	67%
Thrombocytopenia	19	58%
Baseline transfusion dependence		
Red cells	14	41%
Platelets	8	24%
Transfusion independence	13	38%

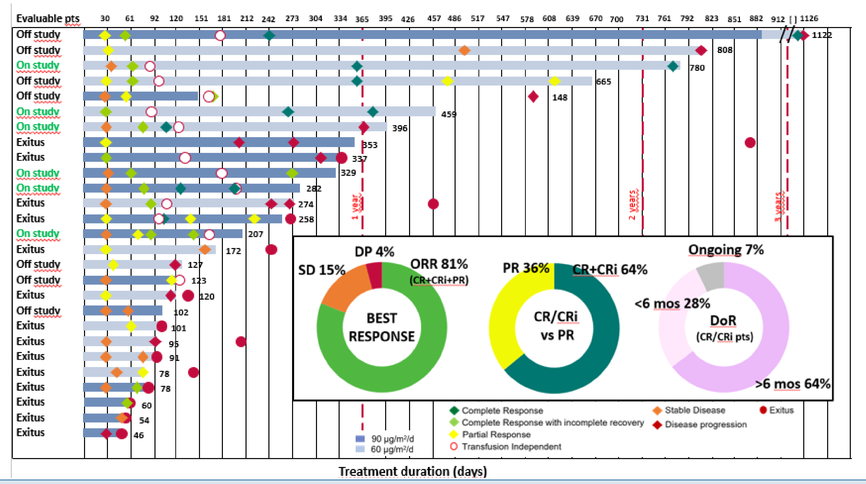
Table 1: Patient baseline characteristics

RESULTS-SAFETY

The most frequent reported AR (Adverse reaction or drug related AE with causal relationship to medication) was platelet reduction, observed in about half of patients (53%), although thrombocytopenia (Grade ≥ 3) was already present at baseline in a high proportion of patients (58%, Table1).

Serious Adverse Events (SAEs) occurring in >1 patient are shown in Table 2. Serious Adverse Reactions (SARs) occurred in 2 patients, one with differentiation syndrome (G3) and one with intracranial hemorrhage (G5). No other significant non-hematological toxicities or other organ-related toxicities were observed. There are 13 reported on-study deaths, due to infection (8), bleeding (3) or other (2).

RESULTS -EFFICACY



In the evaluable patient population:

- ✓ 81% of the patients achieved an objective response: 7 CR, 7 CRi (3 of them CRh) and 8 PR (86% of CR/CRi patients became transfusion independent: all pts with CR or CRh and 2 CRi).
- ✓ 75% CR tested samples were MRD negative by flow cytometry.
- ✓ 64% of CR/CRi responses are durable (more than 6 months).
- ✓ 91% of the patients responded by the end of cycle 2.
- ✓ 100% of the CR patients and 71% of the CRi patients reached transfusion independence for red blood cells and platelets.
- ✓ 3 patients on study for >1 year; 2 for more than 2 years and 1 for > 3 years. 6 patients still ongoing in the trial.
- ✓ Of note 3/3 evaluable patients with FLT3-ITD and 6/8 with p53 mutations responded.

Figure 1. Swimmer's plot of evaluable patients as currently reported in the eCRF. First, final and any change in BM assessments are represented with colored rhombus.

RESULTS-SAFETY

N=36 pts	n (%)	
Preferred Term	**Serious adverse events (SAEs)**	**AEs Grade 3-4**
Febrile neutropenia	13 (36.1)	16 (44.4)
Pneumonia	5 (13.9)	3 (8.3)
Pyrexia	4 (11.1)	0
Cellulitis	3 (8.3)	4 (11.1)
Sepsis	3 (8.3)	3 (8.3)
COVID-19 pneumonia	3 (8.3)	0
Respiratory tract infection	2 (5.6)	2 (5.6)
Skin infection	2 (5.6)	2 (5.6)
Urinary tract infection	2 (5.6)	2 (5.6)
Septic shock	2 (5.6)	1 (2.8)
Hemorrhage intracranial	2 (5.6)	0
Hypotension	1 (2.8)	3 (8.3)
Device related infection	1 (2.8)	2 (5.6)
Platelet count decreased	0	26 (72.2)
Neutrophil count decreased	0	20 (55.6)
Anemia	0	19 (52.8)
Asthenia	0	5 (13.9)
Hypokalemia	0	3 (8.3)
Acute kidney injury	0	2 (5.6)
Leukocytosis	0	2 (5.6)

Table 2: Preferred terms for which more than 1 patient experienced a SAEs or a ≥G3/4 AE. A patient with more than one finding in the specific PT was only counted once.

RESULTS: EFFICACY AND EXPOSURE RELATIONSHIPS

The 90 µg/m2/d dose of iada produced a higher exposure in plasma compared to the 60 µg/m2/d dose (median C_{trough} at steady-state 14 pg/mL vs 6 pg/mL; P<0.05) and higher and more consistent LSD1 Target Engagement (TE) in PBMCs at day 5 (median 91% vs 80%; P<0.05)[5]

Fig 2a shows that at the 90 µg/m2/d dose 63% of patients achieved CR/CRi versus 39% at the 60 µg/m2/d dose. Fig 2b shows that the median exposure in patients with CR/CRi is higher than in those with a PR (14 vs. 5 pg/mL), and that the median TE in all patients that responded is close to 90%.

Those levels of exposure and TE are in the PK/PD range of the RP2D (90 µg/m2/d). Fig 2c shows no significant differences in AE type or frequency between the two doses.

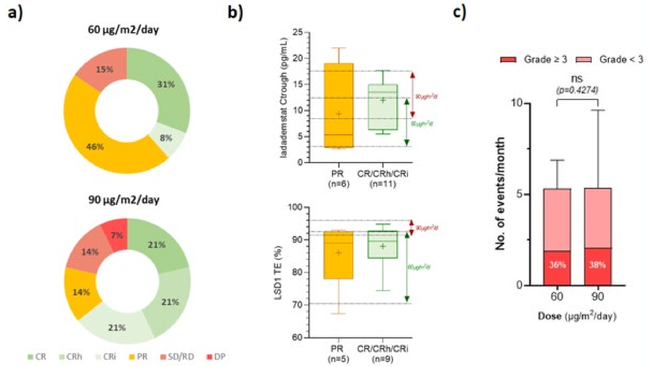


Figure 2. Exposure and PD/Dose-Response relationships and safety analysis per dose cohort. (a) Best response rate per assigned dose. (b) Relationships of iada exposure (C_{trough}) and LSD1 target engagement (TE) on day 5 with best response achieved. Dashed lines represent the 25th and 75th percentiles of the C_{trough} and LSD1 TE levels reached at each dose. (c) Adverse events (AEs) per dose cohort. Median with interquartile range of the number of events per month is represented. Percentages of Grade ≥ 3 events with respect to the total events/month are depicted. Two-tailed Mann Whitney test was used for statistical comparisons.

CONCLUSIONS

- **The combination of iadademstat with azacitidine is safe and effective for the treatment of newly diagnosed elderly/unfit AML patients.**
  - **81% of evaluable patients achieved an objective response**
  - **Responses are deep: 64% of responses were CR/CRi and 86% of those achieved transfusion independence**
  - **Responses are rapid (91% by end of 2 cycles) and durable (64% of patients with CR/CRi respond for >6 months)**
  - **Safety is manageable, with no significant non-hematological toxicity observed**
- **The RP2D of iada in combination with SoC azacitidine is 90 µg/m2/d.**
- **Responses are seen in patients with a diversity of mutations and support further research combining iada with targeted therapies for the treatment of AML subpopulations (see abstract PB1850 for the treatment of FLT3 mut+ R/R AML).**

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