PF277 ALICE: AN AML STUDY WITH LSD1i IN COMBINATION WITH AZACITIDINE IN THE ELDERLY

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Introduction

Acute Myeloid Leukemia (AML) is primarily a disease of older people. Outcomes for the elderly remain poor, with less than 20% 5-year overall survival rates. Azacitidine (Aza) is approved for AML with 20-30% blasts. Lysine-specific demethylase (LSD1) has been shown to be a partner in some gene transformations in AML and contributes to sustain the oncogenic process. Iadademstat is a highly potent and selective LSD1 inhibitor that has been shown to be effective in preclinical models (both alone or in combination with other compounds, including Aza). A Phase I FiM study supported that it is remarkably safe, and demonstrated preliminary anti-leukemic activity as monotherapy. Thus, iadademstat in combination with Aza may offer a novel treatment option for a patient group with limited therapeutic options.

Study design and objectives

ALICE is a Phase IIa, multicenter, open label clinical trial assessing the safety, tolerability and dose finding (DF) of iadademstat in combination with Aza, as well as clinical activity such as time to response (TTR), duration of response (DOR) and objective response (OR) in older AML patients ineligible for intensive chemotherapy. Other assessments include determination of specific biomarkers, morphological differentiation in blasts, determination of minimal residual disease (MRD) and PK/PD measures.

ALICE is a two-stage trial. The dose finding (DF) stage will dose 12-18 patients with a starting dose of iadademstat of 90 µg/m^2/d in combination with Aza. Depending on the dose limiting toxicities (DLTs), iadademstat may be escalated or de-escalated. Once the Recommended Phase II Dose (RP2D) is identified, an expansion cohort of 18 patients will be enrolled and treated with iadademstat in combination with Aza in this second stage. ALICE is including subjects with ≥ 60 years of age with AML according to WHO classification, ineligible for intensive chemotherapy regimen at that time, or who refused standard chemotherapy, and have not received prior treatment for AML other than hydroxyurea.

Results

Six subjects have been recruited as per May cut-off into the DF stage. All of them have been treated with iadademstat at 90 µg/m^2/d, a dose able to saturate LSD1 target engagement in PBMCs after 5 days of treatment. Only one of the six patients experienced a DLT at cycle 1 (C1) due to a differentiation syndrome (the sole SAE reported due to the treatment). In all other participants, iadademstat treatment in combination with Aza was well tolerated and a total of 11 cycles have been completed so far, with 79 AEs reported with a possible causality related to the treatment. One patient died from a subdural hemorrhage in C1 considered non-treatment related. One patient withdrew consent due to disease progression. Based on these data, the Safety Monitoring Committee at end of May has established 90 µg/m^2/d as the RP2D.

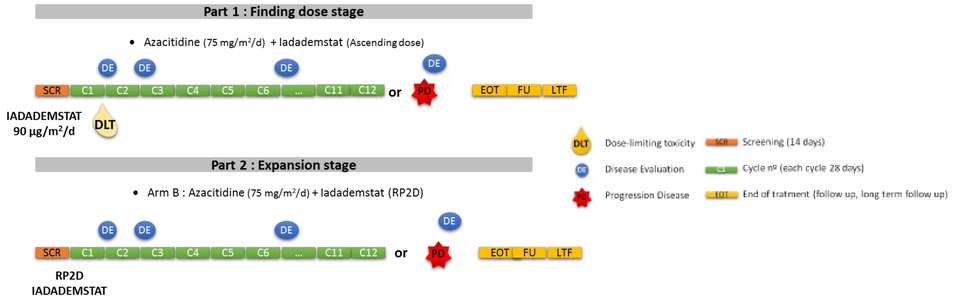
Selected iadademstat differentiation-related biomarkers show a profile similar to that described in the Phase I trial, demonstrating no impact of Aza in iadademstat-induced biomarker modulation.

Preliminary efficacy supported an Objective Response in 4 of 5 evaluable patients (80%), including three CRi and one PR. One patient has decreased his dependence on transfusions.

Highlights

- Combination of iadademstat and azacitidine shows a good safety profile in elderly AML patients
- Preliminary signals of clinical efficacy are encouraging, with 80% of ORs (4 out of 5: 3 CRi and 1 PR)
- Rapid clinical responses (median time to first response 1.5 months)
- Recommended Phase II dose (90 µg/m^2/d) established for the expansion stage of the trial

Study design



Demographics: Enrolled patients

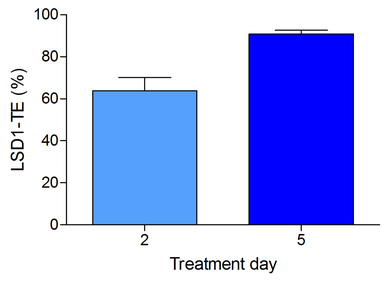
Demographic data		
nº of patients		6
Sex	Male	3 (50%)
	Female	3 (50%)
Age	Median	78.50
	(Min , Max)	(74 . 83)
Race	Caucasian	6 (100 %)
Weight(Kg)	Median	70.60
	(Min , Max)	(54.5/104)
Height (cm)	Median	159.50
	(Min , Max)	(151/171)
BMI	Median	27.53
	(Min , Max)	(20.2/35.57)

AML diagnosis		
nº of patients		6
AML subtype (WHO)	1-AML with recurrent genetic abnormalities	2 (33.3%)
	2- AML with multilineage dysplasia	0 (0 %)
	3-AML and MDS, therapy-related	3 (50 %)
	4-AML not otherwise categorized	1 (16.6%)

Preliminary Results: Safety and Tolerability

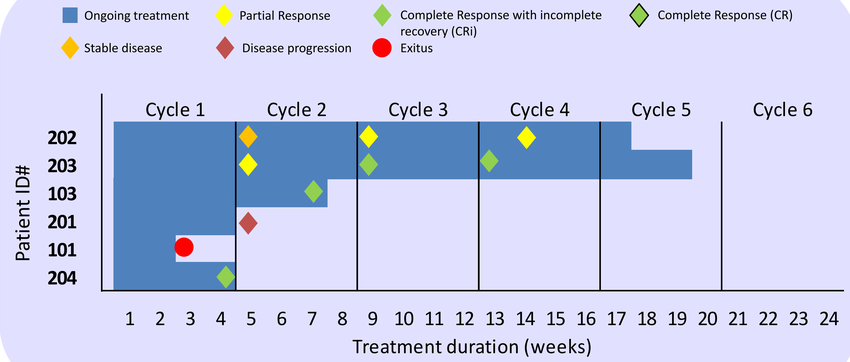
Study-drug related TEAEs (ADRs) by SOC and PT (n= 6)				
Number of Patients (%) Event Count				
System Organ Class Preferred Term (SOC) / Preferred Term(PT)	Grade 1	Grade 2	Grade 3	Grade 4
Blood and lymphatic system disorders				
Anaemia	2(33.3)5	2(33.3)7	3(50.0)8	0(0.0)0
Neutropenia	2(33.3)2	3(50.0)5	4(66.7)5	3(50.0)5
Thrombocytopenia	0(0.0)0	1(16.6)3	3(50.0)5	3(50.0)9
Gastrointestinal disorders				
Constipation	0(0.0)0	1(16.6)1	0(0.0)0	0(0.0)0
Vomiting	1(16.6)1	0(0.0)0	0(0.0)0	0(0.0)0
Gingival bleeding	0(0.0)0	1(16.6)1	0(0.0)0	0(0.0)0
General disorders and administration site conditions				
Asthenia	1(16.6)3	1(16.6)2	1(16.6)1	0(0.0)0
Hepatobiliary disorders				
Hyperbilirubinaemia	1(16.6)	1(16.6)	0(0.0)0	0(0.0)0
Investigations				
Platelet count decreased	0(0.0)0	0(0.0)0	0(0.0)0	1(16.6)1
Metabolism and nutrition disorders				
Decreased appetite	2(33.3)3	0(0.0)0	0(0.0)0	0(0.0)0
Hypomagnesaemia	1(16.6)1	0(0.0)0	0(0.0)0	0(0.0)0
Hyponatraemia	2(33.3)2	0(0.0)0	0(0.0)0	0(0.0)0
Nervous system disorders				
Dysgeusia	2(33.3)4	0(0.0)0	1(16.6)1	0(0.0)0
Respiratory, thoracic and mediastinal disorders				
Dyspnea	0(0.0)0	1(16.6)1	0(0.0)0	0(0.0)0

Preliminary Results: Pharmacodynamics



Blood samples were collected at baseline and days 2 and 5 of treatment (C1) and centrifuged to separate plasma for PK (data will be analyzed at the end of the trial; not shown). Blood cells were suspended in PBS and stabilized in PAXgene tubes for RNA isolation and subsequent gene expression analysis. PBMCs were additionally obtained for analysis of LSD1 target engagement (LSD1-TE) using a proprietary ELISA-based methodology.

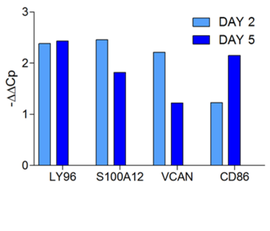
Preliminary Results: Efficacy

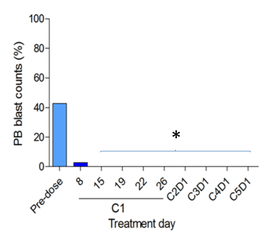


Blood samples were used to assess treatment-induced cell differentiation. Cellular smears were visualized through optical microscopy after HE staining. RNA was extracted from peripheral blood cells and analyzed by qRT-PCR. -ΔΔCp values were calculated relative to the pre-dose sample and to the endogenous control gene HPRT1. PD biomarkers assayed include LY96, S100A12, VCAN, CD86, among others.

Peripheral differentiation

Data from patient #203





* Values correspond to 0% Blasts

Preliminary Conclusions

This Phase II study aims to explore the safety and efficacy of iadademstat in combination in elderly AML patients as a first line treatment, as a prelude of 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 in this and future leukemia studies. Added toxicity appears to be manageable. Based on safety data and TE evaluation, a RP2D has been selected.

Preliminary efficacy data in this limited sample is encouraging, with 80% of OR (of which 75% CRi, 25% PR), and short time to responses. These preliminary results will be expanded in the coming months with additional patients and longer clinical observation times to better assess the frequency, consolidation and duration of the responses. LSD1 has a mechanistic role that been extensively characterized in MLL-r leukemia and erythroleukemia subtypes. However, these data support that the therapeutic applicability of LSD1 inhibition, alone or in combo, extends beyond these leukemia niches.

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