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PRELIMINARY RESULTS OF THE FRIDA STUDY: IADADEMSTAT AND GILTERITINIB IN FLT3-MUTATED R/R AML

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ORYZON

INTRODUCTION

- 50% of Acute Myeloid Leukemia (AML) patients relapse after first-line treatments, and 30-40% of AML patients harbor mutations in the fms-like tyrosine kinase 3 (FLT3) gene, which increases the risk of relapse.
- Gilteritinib, a FLT3 inhibitor (FLT3i), improved outcomes in relapsed/refractory (R/R) FLT3-mut+ AML patients, but the remission rate was low and the EFS brief (ADMIRAL Ph3 study reported 26% CR/CRh rate and 2.8 mos EFS[1])
- Iadademstat (iada) is an oral, potent and selective inhibitor of the Lysine-Specific Demethylase 1 (LSD1) enzyme. In myeloid cells, LSD1 provides a scaffold for the assembly of the GFI1/CoREST transcriptional repressor complex, which regulates hematopoietic differentiation.[2,3]
- In the clinic, iada showed activity in a Ph1 study[4] in R/R AML and in a Ph2 study[5] in unfit first line AML in combination with azacitidine.
- Preclinically, iada shows marked synergy with gilteritinib, in FLT3 wt and FLT3 mut+ AML cells and in derived cell lines resistant to venetoclax, azacitidine or other FLT3is.

OBJECTIVES

- The FRIDA Ph1 study (NCT05546580) is an escalation/expansion, open label, multicenter study of iadademstat and gilteritinib in patients with FLT3 Mut+ R/R AML, to establish the safety, tolerability, and the RP2D of this combination.

METHODS

Main eligibility criteria:
- Adult patients with FLT3 mut+ R/R AML
- ≤ 2 prior lines of therapy (including venetoclax, 7+3, midostaurin, sorafenib, and also quizartinib and gilteritinib if not refractory)
- ECOG 0-2
- Normal liver and renal function

Primary endpoints: Safety (Treatment Emergent Adverse Events (TEAEs) and Recommended Phase 2 Dose (RP2D))
Secondary endpoints: Efficacy (Complete Remission (CR)/CR with partial hematologic recovery (CRh)) rate, Overall response rate (ORR), Duration of response (DoR), Overall survival (OS), Event-free survival (EFS), transfusion rates)
Correlatives: Measurable residual disease (MRD), Mutational profile, Biomarkers of activity/resistance)

FRIDA SCHEMA

ESCALATION: (up to ~6 pts/ dose level)

28 d cycle	Iada PO, 5dON-2dOFF	Gilteritinib PO, QD
DL +1	150 µg, 4 wks	120 mg
Starting dose	100 µg, 4 wks	120 mg
DL -1	75 µg, 4 wks	120 mg
DL-2	75 µg, 3 wks	120 mg
DL -3	50 µg, 3 wks	120 mg
DL -3b	50 µg 4 wks	120 mg

3+3 design

Pharmacologically active dose/s

EXPANSION Up to ~ 14 pts/dose cohort

Dose 1: Iada + Gilteritinib

Dose 2: Iada + Gilteritinib

Safety & Efficacy Bayesian Monitoring

CONCLUSIONS

- The combination of iada and gilteritinib appears safe and well tolerated, with no DLTs reported in the 28d DLT evaluation period in the initial cohort (n=6 iada 100 µg) and DL-1 (n=7 iada 75 µg) in combination with gilteritinib. Two additional patients enrolled in DL-2 have not reported DLTs to date. No unexpected safety events reported.
- PK data support no DDI between iada and gilteritinib.
- Encouraging antileukemic activity is shown, with 5 out of 13 patients (38%) achieving CR/CRh/CRi and 9 out of 13 patients (69%) achieving BM blast clearance in the first cycle, with all but 2 patients having been refractory to prior standard regimens including venetoclax, 7+3 and midostaurin. 2 patients underwent HSCT.
- Platelet count recovery has been slow in most patients, limiting achievement of CR/CRh
- Both flat doses evaluated (starting dose and DL-1) showed maximal LSD1 target engagement (≈90%), therefore lower doses are being investigated.
- FRIDA is currently accruing patients to the DL-2 cohort (3 weeks iada treatment per cycle) aiming to maintain efficacy and to improve platelet recovery.
- As of May 20 2024, three patients are on treatment (1 in DL-1 (cycle 5) and 2 in DL-2).

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RESULTS

Demographics

Table 1. Demographics

Total enrolled	15	
Total enrolled app		
Age median (range)	69	
≥75 yr — no. (%)	4	27%
Female gender — no. (%)	6	40%
AML type — no./total no. (%)		
AML TP53 mutated	1	7%
AML with myelodysplasia-related changes	3	20%
AML with recurrent genetic abnormalities	5	33%
AML with myelodysplasia-related genes	1	7%
Undifferentiated AML (M0)	1	7%
AML, NOS	2	13%
Acute monoblastic/monocytic leukemia (M5)	1	7%
AML without mutation	1	7%
ECOG performance-status score — no. (%)		
0-1	13	87%
2	2	13%
Bone marrow blast count — no. (%)		
<30%	8	53%
≥30 to <50%	2	13%
≥50%	5	33%
Cytogenetic risk category — no. (%)		
Intermediate	9	60%
Adverse	6	40%
FLT3 mutations — total no. (%)		
ITD	13	87%
TKD (D835)	4	27%
TKD (I836)	0	0%
Baseline cytopenias grade ≥3		
Anemia — no. (%)	6	40%
Neutropenia — no./total no. (%)	8	53%
Thrombocytopenia — no. (%)	9	60%
Baseline transfusion dependence — no. (%)		
	13	87%

Table 2. Subject Disposition

Number of Patients (%) on treatment or reason for treatment discontinuation	Starting dose n=6	DL-1 n=7	DL-2 n=2	Overall n=15
Progression disease	3 (50)	4 (57.1)	-	7 (40)
Treatment toxicity	1 (16.7)	-	-	1 (6.7)
Death	1 (16.7)	1 (14.3)	-	2 (13.3)
HSCT	1 (16.7)	1 (14.3)	-	2 (13.3)
Ongoing	-	1 (14.3)	2 (100)	3 (20)

Efficacy

Table 3. Preliminary responses

Best responses	Starting dose (n=6)	DL-1 (n=7)
CR	-	1 (1 HSCT)
CRh	-	1
CRi	2	1
MLFS	3 (1 HSCT)	1
NR	1	3
ORR	5 out of 6 83%	4 out of 7 57%
% CR/CRh/CRi	33%	43%

Safety

- No DLTs observed in the 15 patients enrolled in the study (6 at starting dose, 7 at DL-1 and 2 at DL-2) during the DLT period (28 first days under treatment). One DLT in the starting cohort was called retrospectively due to prolonged cytopenia in the absence of AML
- All pts entering the study with G3-4 thrombocytopenia, continued to experience thrombocytopenia.
- Two pts (one in starting cohort and one in DL-1 cohort) proceeded to HSCT.
- No unexpected Treatment Emergent Adverse Events (TEAEs) have been observed.

Table 4. Related TEAEs (n=14)

Preferred term	TEAEs in ≥2 pts: Related to Iada	TEAEs in ≥2 pts: Related to Gilte	All G≥3 TEAEs: Related to Iada	All G≥3 TEAEs: Related to Gilte
INVESTIGATIONS				
Aspartate aminotransferase increased	3 (20%)	3 (20%)	-	-
Alanine aminotransferase increased	3 (20%)	2 (13%)	-	-
Blood alkaline phosphatase increased	2 (13%)	4 (27%)	-	-
Blood bilirubin increased	1 (7%)	1 (7%)	1 (7%)	1 (7%)
Platelet count decreased	1 (7%)	1 (7%)	1 (7%)	1 (7%)
Neutrophil count decreased	1 (7%)	1 (7%)	1 (7%)	1 (7%)
OTHERS				
Pneumonia	1 (7%)	-	1* (7%)	-
Dysgeusia	2 (13%)	2 (13%)	-	-
Constipation	2 (13%)	1 (7%)	-	-
Diarrhea	2 (13%)	2 (13%)	-	-
Oedema peripheral	-	1 (7%)	-	1 (7%)
Acute febrile neutrophilic dermatosis	-	1 (7%)	-	1* (7%)
Febrile neutropenia	1 (7%)	-	1* (7%)	-

* SAEs

PK/PD

- Iada flat doses (starting dose of 100 µg and DL-1 (75 µg)) on a 5 days ON-2 days OFF schedule resulted on median C_{trough} of 7.58 and 6.00 pg/mL, respectively, on cycle1 day 25 (C1D25)
- Both doses of iada reached ≈90% LSD1-TE at C1D25

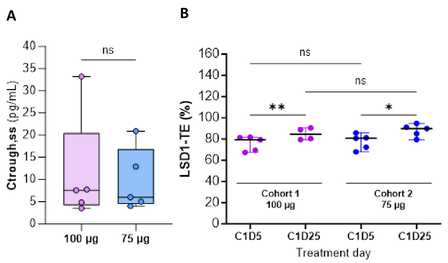

Figure 1: Iada exposure and LSD1 target engagement (TE)
A) Iada exposure (C_{trough}) at C1D25 per assigned dose in available samples. B) LSD1 TE achieved on C1D5 and C1D25. TE was measured as previously described[6]. Intra-cohort statistics (paired t-test); inter-cohort statistics (Mann-Whitney test).