AML-619

Olutasidenib as Maintenance Therapy After Treatment Response in Mutated *IDH1* Acute Myeloid Leukemia

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Introduction

- Mutations in the isocitrate dehydrogenase 1 gene (*mIDH1*) occur in 7%-14% of patients with acute myeloid leukemia (AML)[1,2]
- Olutasidenib, a potent, selective, oral inhibitor of mIDH1, is FDA approved for relapsed/refractory *mIDH1* AML based on results from the pivotal cohort of a phase 2 open-label trial (NCT02719574) where olutasidenib induced complete remission (CR) or CR with partial hematologic recovery (CRh) in 35% of patients for a median duration of 25.3 months[3-5]
- Olutasidenib selectively binds and inhibits both single- and double-mutated IDH1 variants, inhibiting neomorphic activity while retaining essential wild-type IDH1 function[6,7]

Properties of Olutasidenib



Objective

To evaluate the efficacy and tolerability of olutasidenib as maintenance therapy in a separate cohort of patients with m*IDH1* AML who achieved CR or CR with incomplete blood count recovery (CRi) after prior induction therapy

Methods

- Single-agent olutasidenib was evaluated as maintenance therapy in adults with AML in morphologic CR or CRi after prior induction therapy and with minimal residual disease (MRD, defined as *IDH1* mutation detected in bone marrow) ≥0.01%
- Olutasidenib was administered at 150 mg twice daily in continuous 28-day cycles until discontinuation criteria were met (eg, relapse, unacceptable toxicity, withdrawal of consent)
- The primary efficacy endpoint was 4-month relapse-free survival (RFS) rate, defined as the proportion of patients without relapse or death by the 4-month evaluation
- Secondary endpoints included overall survival (OS) and event-free survival (EFS), which was defined as time from first dose of study drug to disease progression, relapse, death, treatment failure, or start of new therapy
- Data are presented with 95% confidence intervals unless otherwise specified
- Data cutoff was June 2023

Results

- The study cohort included 18 patients (**Table 1**)
- Median treatment duration with olutasidenib was 19.6 months (9.5, 42.3)
- Two patients with prior venetoclax therapy entered the study as CRi and improved to CRh and CR over the course of treatment (**Table 2**)
- The primary endpoint of 4-month RFS was 83% (59%, 96%), with a median RFS of 18.4 months (9.5, not reached) (**Figure 2**)
- The 12-month EFS was 71% (44%, 87%)
- Median follow-up was 36.3 months (27.3, 41.7)

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Results

Table 1. Demographics and Baseline Characteristics

	Overall (n=18)
Age, years, median (range)	68.5 (38-77)
Female, n (%)	6 (33)
ECOG performance status, n (%)	
0	8 (44)
1	10 (56)
AML type, n (%)	
Primary de novo	17 (94)
Secondary	1 (6)
IDH1 mutation type, n (%)	
R132C	10 (56)
R132H	6 (33)
R132L/G/S	2 (11)
Bone marrow blasts, %, median (range)	2 (1-5)
Number of co-mutations, median (range)	1 (1-5)
Number of co-mutations, n (%)	
1-3	9 (50)
4-7	2 (11)
Not done/unknown	7 (39)
Number of prior regimens, n (%)	
1	2 (11)
2	7 (39)
≥3	9 (50)
Prior regimens, n (%)	
Cytarabine	17 (94)
Daunorubicin/idarubicin	14 (78)
HMA	5 (28)
HSCT	2 (11)
Venetoclax	2 (11)
Olutasidenib	2 (11)[a]

[a]These patients were previously enrolled in other cohorts of the phase 2 open-label trial.

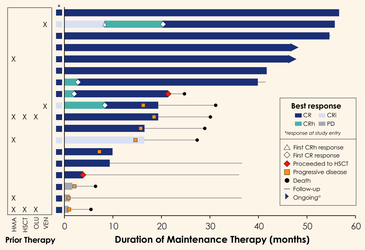
AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IDH1, isocitrate dehydrogenase 1.

Table 2. Summary of Improved Responses in Patients Receiving Prior Venetoclax

	Response, Timing in Months	
CRi at Baseline	**CRh**	**CR**
Patient 1	1	8.3
Patient 2	8.3	20.3

CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete blood count recovery.

Figure 1. Time on Treatment



Reasons for discontinuation (n=16) included: progressive disease (n=8), HSCT (n=2), investigator decision (n=1), and other reasons (n=5).

*In addition to the 2 patients who were receiving ongoing olutasidenib at the end of the study, 5 patients were receiving olutasidenib via post-trial access.

CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete blood count recovery; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; OLU, olutasidenib; PD, progressive disease; VEN, venetoclax.

Safety

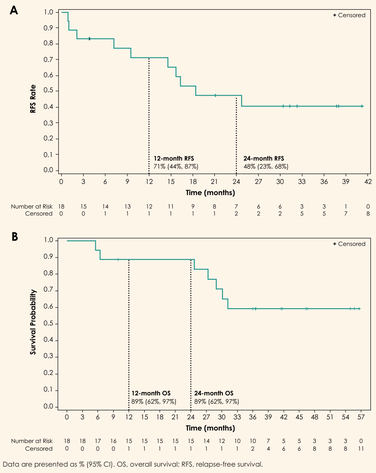
- All patients reported ≥1 treatment-emergent adverse event (TEAE) (**Table 3**)
- Serious TEAEs occurred in 33% (6/18) of patients
  - Grade 3 or 4 serious TEAEs included febrile neutropenia, diarrhea, acute hepatitis, device-related infection, fall, increased hepatic enzymes, increased lipase, and pyoderma gangrenosum, each of which occurred in 1 patient
- Grade 3 or 4 TEAEs occurred in 61% (11/18) of patients
- There were no TEAEs or serious TEAEs that led to olutasidenib discontinuation

Table 3. TEAEs Reported in >20% of Patients

TEAE (any grade), n (%)	Patients (n=18)
Fatigue	6 (33)
Headache	6 (33)
Nausea	5 (28)
Constipation	4 (22)
Neutrophil count decreased	4 (22)
Back pain	4 (22)

TEAE, treatment-emergent adverse event.

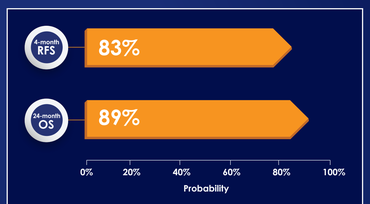
Figure 2. Kaplan-Meier Estimates of (A) RFS and (B) OS



Data are presented as % (95% CI). OS, overall survival; RFS, relapse-free survival.

Conclusions

- Olutasidenib as a single agent demonstrated clinically meaningful activity as a switch maintenance strategy in a subset of AML patients with CR/CRi and persistent MRD ≥0.01% after prior therapy



The safety profile in the maintenance cohort was consistent with other cohorts in the study, and AEs were anticipated and manageable

This analysis supports the potential benefit of switching to olutasidenib upon response to therapy, with the goal of prolonging remission

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