AML-606

Efficacy and Safety of Olutasidenib Monotherapy in Primary Refractory Acute Myeloid Leukemia: A Post Hoc Analysis of a Phase 2 Study

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Introduction

- Acute myeloid leukemia (AML) is characterized by mutations in isocitrate dehydrogenase 1 (*mIDH1*), which occur in approximately 7%–14% of patients[1,2]
- Olutasidenib is a potent, selective, oral inhibitor of mIDH1 approved for the treatment of relapsed or refractory m*IDH1* AML.[2,3] The phase 2 pivotal cohort (NCT02719574) demonstrated efficacy and tolerability of olutasidenib, with a complete remission (CR)/CR with partial hematologic recovery (CRh) rate of 35% and a median duration of CR/CRh of 25.3 months.[4,5]
- Primary refractory patients, defined as those who have not achieved a CR with initial or subsequent induction therapy, typically experience worse overall survival (OS) than those who relapse after first achieving remission[6]

Properties of Olutasidenib



Objective

To evaluate the efficacy and tolerability of olutasidenib monotherapy in a subset of primary refractory patients with m*IDH1* AML

Methods

- This post hoc analysis included primary refractory patients (those with no CR with initial or subsequent induction therapy), a subset of those with R/R m*IDH1* AML from the pivotal phase 2 study cohort
- Olutasidenib was administered at 150 mg twice daily in continuous 28-day cycles
- Primary and secondary efficacy endpoints included the CR/CRh rate, overall response rate (ORR), duration of response (DOR), and OS

Results

- 153 patients received olutasidenib monotherapy (safety population), 147 had centrally confirmed m*IDH1* AML (efficacy evaluable population), and 46 were primary refractory patients (**Tables 1 and 2**)

Table 1. Baseline Demographics and Clinical Characteristics

	Primary Refractory Patients (n=46)
Median age, years (range)	71 (45, 87)
Female, n (%)	21 (46)
ECOG performance status, n (%)	
0 or 1	33 (72)
2	12 (26)
3	1 (2)
Cytogenetic risk status, n (%)	
Favorable	2 (4)
Intermediate	34 (74)
Poor	7 (15)
Unknown	3 (7)

ECOG, Eastern Cooperative Oncology Group.

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Results

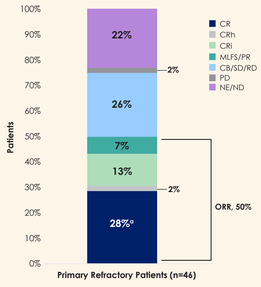
Table 2. Prior Therapies and IDH1 Mutation Type

	Primary Refractory Patients (n=46)
Number of prior regimens, n (%)	
1	28 (61)
2	13 (28)
≥3	5 (11)
Prior chemotherapy[c], n (%)	
Intensive chemotherapy	18 (39)
Non-intensive chemotherapy	25 (54)[b]
Unknown	3 (7)
Prior anticancer therapy[c], n (%)	
Cytarabine	23 (50)
Cytarabine + anthracycline	20 (43)
HMA	25 (54)
Venetoclax	3 (7)
HMA + venetoclax	2 (4)
HSCT	2 (4)[a]
IDH1 mutation type, n (%)	
R132C	29 (63)
R132H	10 (22)
R132L/G/S	7 (15)
Co-mutations, n (%)	
0	3 (7)
1-3	24 (52)
4+	9 (20)
Missing	10 (22)

[a]Latest line of therapy prior to olutasidenib. [b]3 patients received venetoclax. [c]Patients' overall prior treatment history. [d]1 patient received intensive chemotherapy and one received non-intensive chemotherapy.
HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplantation; IDH1, isocitrate dehydrogenase 1.

- The most frequently occurring co-mutations in refractory patients included: *ASXL1* (n=11), *DNMT3A* (n=9), *NPM1* (n=7), *SRSF2* (n=6), *JAK2* (n=5), *PHF6* (n=5), and *RUNX1* (n=5)

Figure 1. Best Overall Response in Patients With Primary Refractory m*IDH1* AML



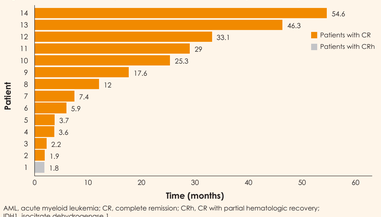
[a]Includes 1 patient with molecular CR.
AML, acute myeloid leukemia; CB, clinical benefit; CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete recovery; IDH1, isocitrate dehydrogenase 1; MLFS, morphologic leukemia-free state; ND, not determined; NE, not evaluated; ORR, overall response rate; PD, progressive disease; PR, partial remission; RD, resistant disease; SD, stable disease.

Table 3. Efficacy of Olutasidenib in Patients With Primary Refractory m*IDH1* AML

	Primary Refractory Patients (n=46)
ORR, n (%)	23 (50)
DOR, median, months (95% CI)	6.7 (3.7, 17.6)
CR[a], n (%)	13 (28)
CRh, n (%)	1 (2)
CR/CRh, n (%)	14 (30)
Duration of CR/CRh, median, months (95% CI)	17.6 (3.7, NR)
OS, median months (95% CI)	8.9 (5.4, 13.8)

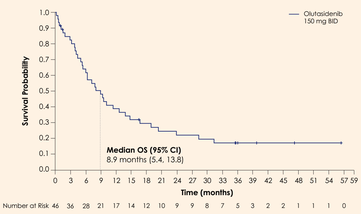
[a]Includes 1 patient with molecular CR.
AML, acute myeloid leukemia; CR, complete remission; CRh, CR with partial hematologic recovery; DOR, duration of response; IDH1, isocitrate dehydrogenase 1; NR, not reached; OS, overall survival; ORR, overall response rate.

Figure 2. Duration of CR/CRh in Patients With Primary Refractory m*IDH1* AML



AML, acute myeloid leukemia; CR, complete remission; CRh, CR with partial hematologic recovery; IDH1, isocitrate dehydrogenase 1.

Figure 3. Kaplan Meier Plot of OS



BID, twice daily; OS, overall survival.

Safety

- At least one treatment-emergent adverse event (TEAE) was reported in all patients (**Table 4**)
- 93% (43/46) of patients experienced a grade ≥3 TEAE, and 85% (39/46) experienced a serious TEAE

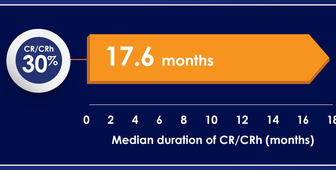
Table 4. TEAEs Reported in >20% of Patients With Primary Refractory m*IDH1* AML (n=46)

TEAEs (any grade)	Patients, n (%)
Nausea	19 (41)
Vomiting	14 (30)
White blood cell count increased	14 (30)
Pyrexia	13 (28)
Dyspnea	12 (26)
Red blood cell count decreased	12 (26)
Constipation	11 (24)
Hypokalemia	11 (24)
Platelet count decreased	11 (24)
Diarrhea	10 (22)
Differentiation syndrome	10 (22)

Reports of increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) occurred in fewer than 20% of patients. No instances of QT prolongation events ≥grade 3 were reported.
AML, acute myeloid leukemia; IDH1, isocitrate dehydrogenase 1; TEAEs, treatment-emergent adverse events.

Conclusions

- In patients with AML refractory to prior induction therapy, olutasidenib demonstrated a clinically meaningful and durable response



- No new safety signals were identified in this subset; the safety profile was consistent with previously reported findings for olutasidenib[2]

Olutasidenib monotherapy may offer an effective and tolerable treatment option for patients with primary refractory disease, a population traditionally associated with poor outcomes[6]

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