AML-629

A Phase 2 Study of Olutasidenib in Relapsed/Refractory Acute Myeloid Leukemia: Outcomes by Number of Prior Treatment Regimens

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Introduction

- A subset of patients (7%-14%) with acute myeloid leukemia (AML) have mutations in the isocitrate dehydrogenase 1 gene (*mIDH1*)[1,2]
- Olutasidenib, a selective, potent, oral inhibitor of mIDH1, is approved for treatment of relapsed/refractory (R/R) *mIDH1* AML[3]
- Results from the phase 2 pivotal cohort (NCT02719574) demonstrated clinical efficacy and tolerability of olutasidenib, with a complete remission/complete remission with partial hematological recovery (CR/CRh) rate of 35% for a median duration of 25.3 months[4,5]
- 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

1. Selective for mutant IDH1 vs. wild type
2. Low molecular weight of 355 g/mol
3. Binds and inhibits single- and double-mutant IDH1

Objective

To evaluate the efficacy and safety of olutasidenib in patients with R/R *mIDH1*-AML grouped by the number of prior regimens

Methods

- The pivotal cohort of the phase 2 study assessed olutasidenib 150 mg BID in adult patients and included efficacy endpoints of CR/CRh, overall response rate (ORR), duration of response (DOR), and overall survival (OS)
- This post hoc analysis evaluated outcomes based on when patients received olutasidenib: after 1-2 or ≥3 prior lines of therapy
- Univariate and multivariate analyses were performed using logistic regression

Results

- There were 147 patients in the efficacy population set (1 prior regimen: n=48; 2 prior regimens: n=45; ≥3 prior regimens, n=54)
- Demographics and baseline characteristics are presented in **Table 1**
- The median duration of treatment overall was 4.5 months (range: 3 days, 57.9 months). In patients with 1-2 prior regimens, the median duration of treatment was 5.2 months (range: 3 days, 57.9 months), and in those with ≥3 prior regimens, the median duration of treatment was 3.8 months (range: 8 days, 57.6 months).
- All 17 patients who had prior HSCT were in the ≥3 prior regimens group (31%)
  - The overall response rate in this subgroup was 29%

Table 1. Demographics and Baseline Characteristics

Efficacy Population (n=147)	1-2 Prior Regimens n=93	≥3 Prior Regimens n=54
Median age, years (range)	72 (45, 87)	67 (32, 81)
Female, n (%)	42 (45)	31 (57)
ECOG performance status, n (%)		
0	31 (33)	18 (33)
1	45 (48)	25 (46)
2	16 (17)	11 (20)
3	1(1)	0
AML cytogenetic risk classification, n (%)		
Favorable	3 (3)	3 (6)
Intermediate	66 (71)	41 (76)
Poor	17 (18)	8 (15)
Unknown	7 (8)	2 (4)
IDH1 mutation type, n (%)		
R132C	51 (55)	34 (63)
R132H	22 (24)	13 (24)
R132L, G, or S	20 (22)	7 (13)

Prior treatment with HMA, n (%)

1-2 prior regimens	≥3 prior regimens
40 (43)	18 (33)

Prior venetoclax therapy, n (%)

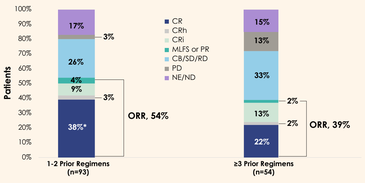
1-2 prior regimens	≥3 prior regimens
10 (11)[a]	2 (4)[b]

[a]1-2 prior regimens: 8/10 had HMA + venetoclax; [b]≥3 prior regimens: 2/2 had HMA + venetoclax.
AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplantation; IDH1, isocitrate dehydrogenase 1.

Results

- In both subgroups, median time to CR/CRh was 1.9 months:
  - 47% and 38% of patients in the 1-2 prior and ≥3 prior regimens group required at least 2 months of therapy to achieve a response
  - 11% and 15% of patients, respectively, required more than 4 months of therapy

Figure 1. Best Overall Response With Olutasidenib in Patients by Number of Prior Regimens



Percentages may not total 100% due to rounding.
*Includes 1 patient with molecular CR.
CB, clinical benefit; CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete recovery; CRm, molecular CR; 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.

- A univariate analysis for CR/CRh identified bone marrow blast percentage (*P*<0.0001), transfusion independence at study entry (*P*<0.0001), mutation in RTK pathway genes (*P*=0.0234), IDH1 mutation type (*P*=0.0305), prior HSCT (*P*=0.0347), and number of prior therapies (1-2 vs ≥3, *P*=0.0393) as significant factors
- Multivariate analysis confirmed the significant effects of bone marrow blast percentage (*P*<0.0001) and transfusion independence at study entry (*P*=0.0019) as significant factors on achievement of CR/CRh
  - Number of prior regimens (*P*=0.0526), IDH1 mutation type (*P*=0.0510) and presence of RTK pathway gene mutation (*P*=0.0830) were not significant in the multivariate analysis

Table 2. Efficacy of Olutasidenib by Number of Prior Regimens

Efficacy overall (n=147)	1-2 Prior Regimens n=93	≥3 Prior Regimens n=54
ORR, n (%); 95% CI	50 (54); 43.1, 64.2	21 (39); 25.9, 53.1
DOR, median, months (95% CI)	14.8 (7.4, 25.9)	16.6 (5.8, NR)
CR rate, n (%); 95% CI	35 (38); 27.8, 48.3	12 (22); 12.0, 35.6
DOR, median, months (95% CI)	21.3 (12.0, NR)	NR (8.7, NR)
CR/CRh rate, n (%); 95% CI	38 (41); 30.8, 51.5	13 (24); 13.5, 37.6
DOR, median, months (95% CI)	25.3 (12.0, NR)	NR (8.7, NR)

CI, confidence interval; CR, complete remission; CRh, CR with partial hematologic recovery; DOR, duration of response; NR, not reached; ORR, overall response rate.

Safety

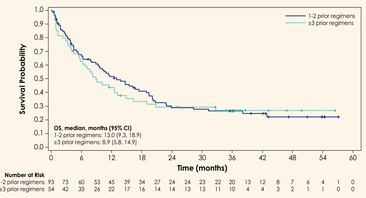
- All patients experienced ≥1 treatment-emergent adverse event (TEAE)
  - The most common TEAEs included nausea, decreased red blood cell count, and fatigue
- Serious TEAEs were reported in 73% (68/93) and 78% (42/54) of patients in the 1-2 and ≥3 prior regimens groups, respectively
  - The most common serious TEAEs were febrile neutropenia (13% [12/93] and 20% [11/54] in the 1-2 and ≥3 prior regimens groups, respectively)and differentiation syndrome (14% [13/93] and 2% [1/54] in the 1-2 and ≥3 prior regimens groups, respectively)
- TEAEs ≥grade 3 occurred in 89% (83/93) and 91% (49/54) in the 1-2 and ≥3 prior regimens groups, respectively
- No new safety signals were identified

Table 3. Grade ≥3 TEAEs Reported in ≥10% of Patients by Number of Prior Regimens

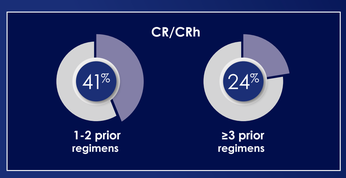
	1-2 Prior Regimens n=93	≥3 Prior Regimens n=54
Patients with any TEAE grade ≥3, n (%)	83 (89)	49 (91)
Red blood cell count decreased	22 (24)	7 (13)
Platelet count decreased	18 (19)	10 (19)
Febrile neutropenia	16 (17)	16 (30)
Neutrophil count decreased	14 (15)	6 (11)
Pneumonia	9 (10)	7 (13)
Differentiation syndrome	11 (12)	2 (4)
White blood cell count decreased	7 (8)	7 (13)

TEAE, treatment-emergent adverse event.

Figure 2. Median Overall Survival (OS) With Olutasidenib by Number of Prior Regimens



Conclusions



- Higher response rates in the 1-2 prior regimens group supports the rationale for earlier use of olutasidenib in the R/R treatment paradigm
- While 55% of patients with *mIDH1* R/R AML achieved responses within 1 to 2 months of treatment, 45% of patients required more than 2 months, and 12% required more than 4 months

CR/CRh after at least 2 months of treatment

1-2 prior regimens	≥3 prior regimens
47% (11% required 4+ months)	38% (15% required 4+ months)



The most common TEAEs were nausea, decreased red blood cell count, and fatigue

These safety findings were consistent with the known safety profile of olutasidenib[3]

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ACKNOWLEDGMENTS

We thank all the patients and families for their participation and the physicians and staff members who supported the study. For more information, contact Aaron Sheppard at asheppard@rigel.com. Medical writing and editorial assistance were provided by Cynthia D. Gioiello, PharmD, and Scott Bergfeld, PhD, of the Spark Division of Woven Health Collective, LLC, and were funded by Rigel Pharmaceuticals, Inc.

Presented at the Society of Hematologic Oncology 2025 Annual Meeting, September 3-6, 2025, Houston, Texas, USA