Predictors of Long-Term Response to Olutasidenib in Mutant *IDH1* Acute Myeloid Leukemia (AML)

Poster # AML - 562

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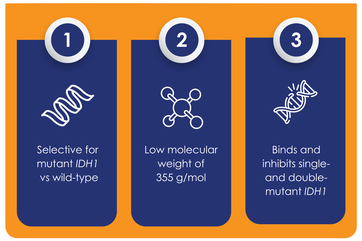
Introduction

- Mutations in isocitrate dehydrogenase 1 (m*IDH1*) occur in 7%-14% of patients with AML[1]
- Olutasidenib is a potent, oral small-molecule m*IDH1* inhibitor that selectively inhibits *IDH1* variants but preserves wild-type *IDH1* function[2]



- The registrational phase 2 trial (NCT02719574) of olutasidenib enrolled 147 patients with relapsed/refractory (R/R) AML with confirmed m*IDH1* and reported an overall response rate of 48% (71/147)[3]
  - The complete remission/complete remission with partial hematologic recovery (CR/CRh) rate was 35%, with a median duration of CR/CRh of 25.3 months (range, 1.8-54.6 months)
  - CR/CRh rates and duration of response (DOR) were higher among those with an R132C mutation (42% [36/85]; 25.3 months) than an R132H mutation (17% [6/35]; 13.5 months)
  - Among the 51 patients with a CR/CRh, median overall survival (OS) was not reached
- Of the 147 patients with confirmed m*IDH1*, 16 (10.9%) proceeded to allogeneic hematopoietic stem cell transplant (HSCT)
- Among patients who did not proceed to HSCT, durable CR/CRh as long as 54.6 months was observed as of the final data cutoff[3]

Objective

To examine patient, disease, and molecular characteristics of patients with a long-term (>12 month) CR/CRh response to olutasidenib who did not proceed to transplant

Methods

- Adults with R/R m*IDH1* AML treated with olutasidenib 150 mg twice daily were assessed for a response
  - Patients with CR/CRh >12 months were included in the primary analysis
- OS, DOR, event-free survival (EFS), and treatment-emergent adverse events (TEAEs) while on treatment were assessed
- Univariate and stepwise multivariate logistic regression analyses were used to examine baseline factors that predicted DOR >12 vs ≤12 months among all patients who achieved a response
  - Patients were excluded from analyses when there was no reported baseline data
- In the multivariate analysis, non-significant covariates were removed in a stepwise manner until only significant predictors of response remained

Results

- Of 147 evaluable patients, 51 (35%) achieved a CR/CRh; this response was maintained for >12 months in 32 (63%) of these patients, including 6 who proceeded to HSCT
- 26/51 (51%) patients had a DOR >12 months without subsequent HSCT, 19 of whom had a DOR >24 months (**Table 1**, **Figure 1**)
  - Median (95% CI) time to response was 1.9 (1.0, 1.9) months

Results

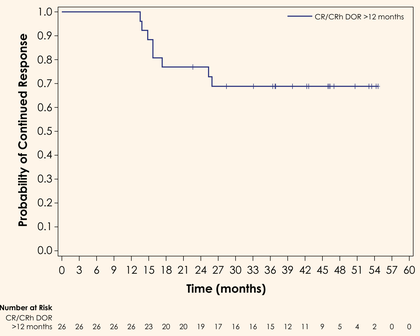
- The 23/26 patients who had relapsed disease received a median of 2 (range, 1-6) prior lines of therapy
  - All 3/26 patients who had refractory disease received 1 prior line of therapy
- Median OS and EFS were not reached
  - Estimated 48-month OS was 74% (95% CI: 51%, 88%)
  - Estimated 48-month EFS was 69% (95% CI: 47%, 83%)
- 6 (23%) patients relapsed (including 2 after 24 months)
  - No relapses occurred after >30 months of follow-up
- 10 (38%) patients remained on treatment at data lock, and 7 (27%) continued on olutasidenib through post-trial access (**Figure 2**)

Table 1. Baseline Characteristics of Patients With a CR/CRh Who Did Not Proceed to HSCT

	Patients With CR/CRh <12 months n=12	Patients With CR/CRh >12 months n=26[a]	Patients With CR/CRh >24 months n=19
Age, y, median (range)	72.5 (50, 80)	72 (52, 81)	72 (61, 81)
Female sex, n (%)	5 (42)	18 (69)	13 (68)
ECOG PS, n (%)			
0	5 (42)	7 (27)	6 (32)
1	3 (25)	18 (69)	13 (68)
2	4 (33)	1 (4)	0
Relapsed/refractory status, n (%)			
Relapsed	6 (50)	23 (88)	16 (84)
Refractory	6 (50)	3 (12)	3 (16)
***IDH1* mutation, n (%)**			
R132C	8 (67)	19 (73)	15 (79)
R132H	2 (17)	2 (8)	0
R132L/G/S	2 (17)	5 (19)	4 (21)
Co-mutations, median (range)	1.5 (1, 3)	2 (0, 5)	1.5 (0, 5)
Number of prior therapies, median (range)	2 (1, 5)	2 (1, 6)	2 (1, 4)
Platelet TI, n (%)	9 (75)	23 (88)	17(89)
Red blood cell TI, n (%)	8 (67)	19 (73)	15 (79)

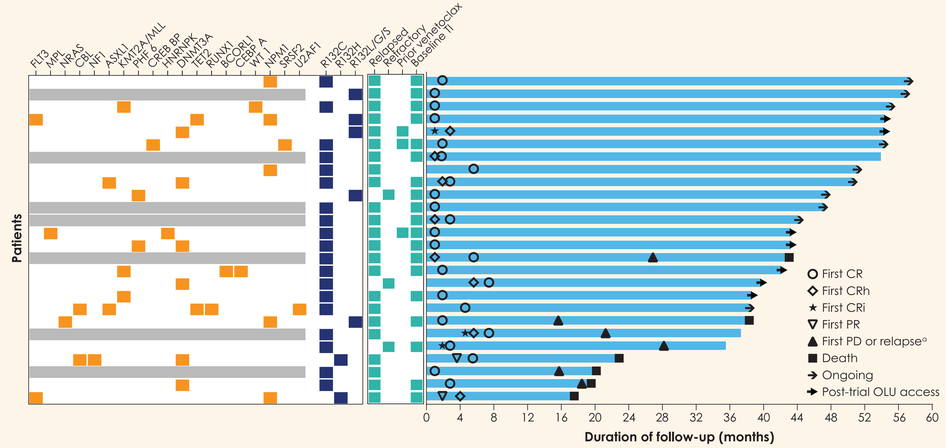
[a]Includes 19 patients who had a CR/CRh >24 months.
CR, complete remission; CRh, complete remission with partial hematologic recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplant; IDH1, isocitrate dehydrogenase 1; TI, transfusion-independent.

Figure 1. Duration of CR/CRh in Patients With CR/CRh >12 Months



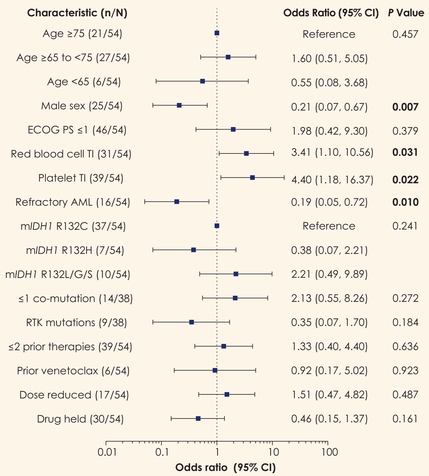
CR, complete remission; CRh, complete remission with partial hematologic recovery; DOR, duration of response.

Figure 2. Mutational Profile, Disease Characteristics, and Duration of Follow-Up Among Patients With CR/CRh >12 Months



Gray bars indicate that no co-mutation data were available.
[a]Includes 5 relapses and 1 PD.
CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; OLU, olutasidenib; PD, progressive disease; PR, partial remission; TI, transfusion-independent.

Figure 3. Univariate Logistic Regression Analysis of Predictors of >12 Month vs ≤12 Month Response to Olutasidenib



Bold *P* values indicate statistical significance.
AML, acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; mIDH1, mutant isocitrate dehydrogenase 1; RTK, receptor tyrosine kinase pathway; TI, transfusion-independent.

- Multivariate analysis identified only female sex (odds ratio for male vs female sex: 0.21; *P*=0.013) and relapsed AML (odds ratio for refractory AML vs relapsed AML: 0.19; *P*=0.022) as significant predictors of CR/CRh >12 months

Table 2. Treatment-Emergent Adverse Events (≥5 Patients in Any Group) Among Patients With a CR/CRh Who Did Not Proceed to HSCT

Preferred Term, n (%)	Patients With CR/CRh <12 months n=12	Patients With CR/CRh >12 months n=26	Patients With CR/CRh >24 months n=19
Nausea	4 (33)	9 (35)	7 (37)
ALT increased	1 (8)	8 (31)	7 (37)
Asthenia	1 (8)	8 (31)	6 (32)
Constipation	3 (25)	8 (31)	6 (32)
Cough	1 (8)	8 (31)	5 (26)
AST increased	1 (8)	7 (27)	6 (32)
GGT increased	0	7 (27)	6 (32)
Back pain	0	6 (23)	4 (21)
URTI	0	6 (23)	4 (21)
Amylase increased	0	5 (19)	4 (21)
Blood creatinine increased	0	5 (19)	4 (21)
Fatigue	2 (17)	5 (19)	4 (21)
Lipase increased	0	5 (19)	4 (21)
Pruritis	0	5 (19)	4 (21)
RBC count decreased	3 (25)	5 (19)	3 (16)
UTI	1 (8)	5 (19)	3 (16)

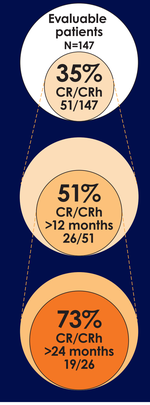
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CR, complete remission; CRh, complete remission with partial hematologic recovery; GGT, gamma-glutamyltransferase; RBC, red blood cell; URTI, upper respiratory tract infection; UTI, urinary tract infection.

- Grade ≥3 TEAEs that occurred in >3 patients with a CR/CRh >12 months were alanine aminotransferase increased, gamma glutamyltransferase increased (19% each), and RBC count decreased (15%)
- 9 (35%) patients experienced grade ≥3 all-cause TEAEs that occurred after 12 months or more of treatment
  - Each of these TEAEs occurred in 1 patient, except for coronavirus infection, which occurred in 2 patients
  - One patient had a grade ≥3 TEAE of differentiation syndrome after 12 months

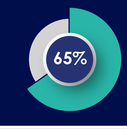
Conclusions

- Among patients with R/R m*IDH1* AML who achieved a CR/CRh with olutasidenib monotherapy, 51% maintained a response >12 months, and 37% maintained a response >24 months (excluding patients who proceeded to HSCT)
- No new safety signals were observed in this long-term responder patient population compared with the overall study population[3]
- Multivariate analysis identified relapsed (vs refractory) AML and female sex, but not baseline TI or molecular factors, as significant predictors of maintaining a CR/CRh for more than 12 months with olutasidenib treatment

Patients With Long-Term Response to Olutasidenib



Among Patients With CR/CRh >12 Months Without Proceeding to HSCT



17/26 patients continued olutasidenib treatment

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