Olutasidenib Alone or in Combination with Azacitidine Induces Durable Complete Remissions in Patients with m*IDH1* Myelodysplastic Syndromes/Neoplasms (MDS)

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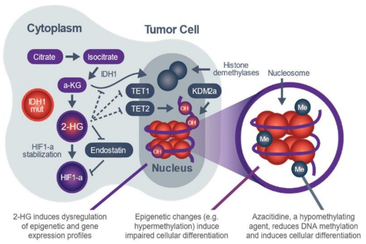
INTRODUCTION

- Olutasidenib is a potent, selective, oral, small-molecule inhibitor of mutant isocitrate dehydrogenase 1 (mIDH1)
- Olutasidenib is approved in the US for the treatment of adults with relapsed/refractory (R/R) acute myeloid leukemia (AML) based on the pivotal cohort of a registrational Phase 1/2 trial (NCT02719574)[1-3]
- The phase 1/2 study included adult patients with AML as well as myelodysplastic syndrome/neoplasms (MDS). We conducted these analyses to better understand the response to olutasidenib in patients with MDS from the Phase 1/2 trial

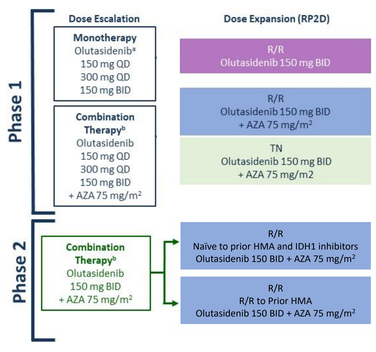
Fig 1. mIDH1 Disease Mechanism[4]



METHODS

- This Phase 1/2, open-label, multi-center study enrolled 22 patients who were R/R or treatment-naïve (when standard therapy was contraindicated)
- Patients with MDS were intermediate-, high- or very high-risk with *IDH1*^{Arg132X} mutation
- Adequate cardiac, renal, hepatic function, plus ECOG performance status 0-2 were required
- Primary endpoints included response by modified International Working Group (IWG) criteria 2003 and CR + CRh rate

Figure 2. Phase 1/2 Study Design



[a]Olutasidenib 100 mg QD was received by a subgroup of patients (n=3).

Olutasidenib was administered orally over continuous 28-day cycles. Azacitidine was IV or SC on days 1-7 of each 28-day cycle.

AZA, azacitidine; BID, twice daily; IDH1, isocitrate dehydrogenase 1; IV, intravenous; RP2D, recommended phase 2 dose; QD, once daily; R/R, relapsed/refractory; SC, subcutaneous; TN, treatment-naive.

RESULTS

Patients

- Twenty-two patients with MDS were enrolled, including 6 who received monotherapy (4 R/R and 2 treatment naive [TN]) and 16 on combination therapy (11 R/R and 5 TN)

Table 1. Demographics and Disease Characteristics

Parameter	Monotherapy (n=6)	Combination Therapy (n=16)	Pooled (N=22)
Median age, years (range)	77 (66, 87)	72 (59, 82)	74 (59, 87)
Sex, n (%)			
Male	4 (67)	9 (56)	13 (59)
Female	2 (33)	7 (44)	9 (41)
Disease state			
TN, n (%)	2 (33)	5 (31)	7 (32)
R/R, n (%)	4 (67)	11 (69)	15 (68)
Prior number of regimens, median (range)	1 (1, 4)	2 (1,4)	1 (1, 4)
Olutasidenib treatment received, n (%)			
Monotherapy, 100-150 QD	3 (50)	0	3 (14)
Monotherapy, 150 BID	3 (50)	0	3 (14)
Combination	0	16 (100)	16 (73)
MDS risk type, n (%)			
Intermediate	0	3 (19)	3 (14)
High	4 (67)	10 (63)	14 (64)
Very High	2 (33)	3 (19)	5 (23)
MDS cytogenetic risk classification, n (%)			
Good	1 (17)	9 (56)	10 (45)
Intermediate	1 (17)	3 (19)	4 (18)
Poor	0	2 (13)	2 (9)
Very poor	2 (33)	0	2 (9)
Unknown	2 (33)	2 (13)	4 (18)
MDS *IDH1* mutation type, n (%)			
R132C	3 (50)	4 (25)	7 (32)
R132H	2 (33)	10 (63)	12 (55)
R132G	1 (17)	1 (6)	2 (9)

IDH1, isocitrate dehydrogenase 1.

Response Rates

- For the pooled Phase 1 and 2 data (n=22), 6 (27%) patients achieved CR and 7 (32%) patients achieved marrow CR with no PRs, generating a 59% overall response rate
- The median time to response was 2.0 months
- The median duration of response was not reached (NR) at 30.1+ months

Table 2. Response Rates, Duration of Response, and Disposition

Parameter	Monotherapy[a] (n=6)	Combination Therapy (n=16)	Pooled (N=22)
Best response, n (%)			
ORR	2 (33)	11 (69)	13 (59)
CR	1 (17)	5 (31)	6 (27)
Marrow CR	1 (17)	6 (38)	7 (32)
PR	0	0	0
SD	1 (17)	3 (19)	4 (18)
CB	1 (17)	0	1 (5)
PD	1 (17)	0	1 (5)
Not Evaluated[b]	1 (17)	2 (13)	3 (14)
Overall Response (CR, marrow CR)			
Time to first response in months, median (range)	4.7 (1.0, 8.3)	2.0 (1.0, 13.0)	2.0 (1.0, 13.0)
Duration of response in months, median (range)	NR (6.7, NR at 29.7+)	NR (0, NR at 30.1+)	NR (0, NR at 30.1+)

[a]3 patients received monotherapy at full dose; 1 had a CR, 1 had a marrow CR, and 1 was not evaluated. The other 3 patients received a lower than approved dose; 1 had SD, 1 had CB, and 1 had PD. [b]3 patients were not evaluated due to short duration of treatment (1-2.5 months). CB, clinical benefit; CR, complete remission; ORR, overall response; NR, not reached; PD, disease progression; PR, partial response; SD, stable disease.

- The overall response rate was 2/6 (33%) for monotherapy and 11/16 (69%) for combination therapy
- Three of 6 patients received monotherapy at a lower dose (100-150 QD) than the approved dose level, and none responded
- Of the 3 patients who received monotherapy at the approved dose level (150mg BID), 2 (66%) responded
- In the 7 TN patients, the overall response rate was 86%. In the 15 R/R patients, the overall response rate was 47%

Transfusion Independence

- Of 22 patients, 13 were dependent on RBC at baseline, and 8 (62%) achieved 56-day transfusion independence (TI).
- 8 patients were platelet dependent at baseline, and 5 (63%) achieved 56-day TI.

Safety

- The overall safety profile in patients with MDS was consistent with what has been reported in patients with AML in this study[2,3]

Table 3. Treatment-Emergent Adverse Events

TEAE	All Grades (n=22) n (%)	Grade 3 or 4 (n=22) n (%)
Any TEAE	22 (100)	21 (95)
Fatigue	14 (64)	3 (14)
Nausea	13 (59)	1 (5)
Constipation	10 (45)	0
Thrombocytopenia	9 (41)	6 (27)
Vomiting	8 (36)	0
Febrile neutropenia	6 (27)	6 (27)
Diarrhea	6 (27)	1 (5)
Differentiation Syndrome	3 (14)	1 (5)
ALT increased	3 (14)	3 (14)
QT prolongation	1 (5)	1 (5)

TEAE, Treatment-emergent adverse event. ALT, alanine aminotransferase increased

- The most frequent TEAEs in the study were fatigue, nausea, constipation, thrombocytopenia, vomiting, neutropenia, and diarrhea
- Grade ≥3 TEAEs occurred in 21/22 (95%) patients, and Grade ≥4 TEAEs in 12/22 (55%)
- The most frequent Grade 3/4 TEAEs reported were cytopenias.
- Grade 3 transaminitis occurred in 1 patient
- Grade 3 differentiation syndrome was reported in 1 patient, who discontinued treatment after 23 days due to pneumonia, which led to respiratory failure and death
- TEAEs resulting in death occurred in 5 patients and included disease progression (3), pneumonia (1, mentioned above) and chest fungal infection (1). These were deemed not related to study treatment

CONCLUSIONS

- Olutasidenib, both as monotherapy and in combination with azacitidine, induced durable remissions in patients with intermediate-, high-, or very high-risk MDS with mIDH1
- Patients had varying treatment backgrounds, including treatment-naive and up to four prior regimens
- Olutasidenib had a tolerable and manageable safety profile
- These encouraging results show that olutasidenib has clinically meaningful activity in patients with m*IDH1* MDS

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