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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Olutasidenib Alone or in Combination with Azacitidine Induces Durable Complete Remissions in Patients with *mIDH1* 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 relapsed/refractory (R/R) acute myeloid leukemia (AML) based on the pivotal cohort (n=153) of a registrational Phase 1/2 trial (NCT02719574), which demonstrated a rate of complete remission (CR) or CR with partial hematologic recovery (CRh) of 35%, with a duration of response of 25.9 months. The Phase 1/2 study also enrolled patients with mIDH1 myelodysplastic syndromes/neoplasms (MDS), and here we report results from this subset of 22 patients.

Methods

The Phase 1/2 open-label study enrolled 332 adult patients with mIDH1 AML or intermediate-, high-, or very high-risk MDS- from 57 centers in 9 countries. Inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and adequate liver and renal function. Patients were R/R to prior therapy or, if treatment-naïve (TN), had to be eligible for azacitidine therapy (to be enrolled in a combination therapy cohort). Olutasidenib was administered at 150 mg BID (n=3) or 100-150 QD (n=3) as monotherapy or in combination with azacitidine (n=16), given at 75 mg/mm ^{2} daily for 7 consecutive days, in 28-day cycles. The primary efficacy endpoint for MDS was the CR rate, based on response criteria of the International Working Group in MDS. Secondary efficacy endpoints included overall response (CR/PR/marrow CR), time to response, duration of response and safety.

Results

Twenty-two patients with MDS were enrolled, including 6 who received monotherapy (4 R/R and 2 TN) and 16 who received combination therapy (11 R/R and 5 TN). Baseline demographics and disease characteristics are shown in **Table 1**. The age ranged from 59-87 years, and 59% of the study population were male. Seven patients were treatment-naïve and 15 were R/R with 1-4 prior treatment regimens.

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**). 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%. All patients with MDS experienced at least 1 treatment-emergent adverse event (TEAE). The most frequent TEAEs in the study were nausea, constipation, vomiting, thrombocytopenia, neutropenia, diarrhea, and fatigue. Grade 3 TEAEs occurred in 19/22 (86%) patients, and Grade 4 TEAEs in 9/22 (41%). The most frequent Grade 3/4 TEAEs reported were cytopenias. Grade 3 transaminitis occurred in 4 patients. Grade 3 differentiation syndrome was reported in 1 patient, who discontinued treatment after 23 days due to pneumonia, which lead 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). The overall

safety profile in patients with MDS was consistent with what has been reported in patients with AML in this study (Watts, et al., Lancet Hematol, 2022; de Botton et al., Blood Adv, 2023).

Conclusions

Olutasidenib, both as monotherapy and in combination with azacitidine, induced durable remissions in patients with intermediate-, high-, or very high-risk MDS. Patients had varying treatment backgrounds, including treatment-naïve and up to four prior regimens. This treatment had a tolerable and manageable safety profile. These encouraging results, which warrant further investigation with a larger number of patients, show that olutasidenib has clinically meaningful activity in patients with *mIDH1* MDS.

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Table 1: Patient Baseline 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, n (%)			
Treatment-naïve	2 (33)	5 (31)	7 (32)
Relapsed / Refractory	4 (67)	11 (69)	15 (68)
Prior number of regimens, median (range)	1 (1, 4)	2 (1,4)	1 (1, 4)
Olutasidenib treatment received			
Monotherapy, 100-150 QD	3 (50)	0	3 (14)
Monotherapy, 150 BID	3 (50)	0	3 (14)
Combination	0	16 (100)	16 (73)
Hematologic laboratory parameters, median (range)			
Percentage of bone marrow blasts	6.5 (0, 16)	7.5 (0, 16)	7.5 (0, 16)
White blood cells $x10^9/L$	2 (0.8, 7.5)	1.6 (0, 3.1)	2.0 (0, 7.5)
Absolute neutrophil count $x10^9/L$	0.87 (0, 4.9)	0.56 (0.1, 3.5)	0.57 (0, 4.9)
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)

Table 2: Response to Olutasidenib Monotherapy and Combination Therapy

Parameter	Monotherapy[c] (N=6)	Combination Therapy (N=16)	Pooled (N=22)
Best response, n (%)			
ORR[a]	2 (33)	11 (69)	13 (59)
CR	1 (17)	5 (31)	6 (27)
Marrow CR	1 (17)	6 (38)	7 (32)
Partial remission (PR)	0	0	0
Stable disease (SD)	1 (17)	3 (19)	4 (18)
Clinical Benefit (CB)	1 (17)	0	1 (5)
Disease Progression (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] ORR, overall response (CR, marrow CR, and PR); NR, not reached
[b] 3 patients were not evaluated due to short duration of treatment (1-2.5 months).
[c] 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.

Figure 1

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