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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Combination of Venetoclax and Azacitidine in Patients with Treatment-Naive, High-Risk Myelodysplastic Syndromes with Responses Leading to Stem Cell Transplantation

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Introduction: The standard of care for patients with high-risk myelodysplastic syndrome (HR-MDS) who are eligible for intensive therapy includes allogeneic stem cell transplantation (SCT), which is potentially curative. Venetoclax (Ven) is a potent, selective, orally bioavailable BCL-2 inhibitor, which has a synergistic effect when combined with hypomethylating agents in preclinical and clinical investigations of myeloid malignancies. Previous results showed that the combination of Ven and azacitidine (Aza) is associated with an acceptable safety profile and leads to rapid and durable responses in patients with treatment-naive HR-MDS. Here, we report the clinical outcomes of patients with HR-MDS who proceeded to SCT following combination Ven+Aza treatment on the M15-531 clinical trial.

Methods: M15-531 is a global, open-label, phase 1b clinical trial (NCT02942290) to identify the recommended phase 2 dose and to study the safety and efficacy of Ven+Aza. Eligible patients were aged ≥18 years with the following criteria: *de novo* treatment-naïve HR-MDS; International Prognostic Scoring System (IPSS) risk categories of Int-2 or High, or Revised IPSS (IPSS-R) categories of Intermediate, High, or Very High; <20% blasts in bone marrow aspirate/biopsy; and an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤2. Aza was administered at 75 mg/m ^{2} subcutaneously or intravenously on Days 1-7 or on Days 1-5, 8, and 9 of each 28-day cycle. Ven was first evaluated at 100 once daily for 14 days of a 28-day cycle, then escalated to 200 and 400 mg in separate cohorts. Clinical outcomes with Ven+Aza treatment for patients who discontinued study treatment to undergo SCT and who did not experience disease progression are reported.

Results: At the data cutoff of May 31, 2023, 124 patients were treated with all doses of Ven-based therapy, and 51 (41.1%) proceeded to allogeneic SCT. Key demographics and baseline characteristics for those who received SCT are shown in the **Table**. Median age was 64 years (range, 26-78), 58% had an ECOG PS of 0, and 25% had poor or very poor cytogenetic risk by IPSS-R. The median number of cycles of Ven+Aza was 3 (range, 1-22). Median time on study drug was 124 days (range, 28-763), and the median time from first dose of study treatment to SCT was 5.6 months (range, 1.4-29.7). Before SCT, 21 of 51 (41.2%) patients achieved complete remission (CR). Marrow CR (mCR) was achieved by 23 of 51 (45.1%) patients, and the composite response rate (mCR with Hematologic Improvement) was 30.4% (7 of 23; 95% CI, 13.2-52.9). The median time to best overall response (time from first dose of study drug to best response of CR, mCR, partial response, or stable disease) for Ven+Aza was 2.0 months (range, 1.0-10.4). The median overall survival was not reached for patients who achieved CR or mCR

and proceeded to transplant. Among patients who underwent transplant, 64.7% (33/51) remained alive at the data cut-off date

Conclusion: Early responses after Ven+Aza in patients with HR-MDS enabled them to receive allogeneic SCT. After escalating doses of the combination of Ven+Aza, 41% of patients went on to SCT. These results suggest that Ven-based regimens before SCT may provide a path to curative therapy.

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OffLabel Disclosure: Venetoclax Plus Azacitidine for treatment-naive high-risk MDS

Table. Demographics and Baseline Characteristics for Patients Who Received SCT

Characteristic	N=51
Treatment regimen, n (%)	
Ven 100 mg for 14 days + Aza	4 (8)
Ven 200 mg for 14 days + Aza	1 (2)
Ven 400 mg for 14 day + Aza	46 (90)
Median age, years (range)	64 (26–78)
<65 years, n (%)	31 (61)
≥65 years, n (%)	20 (39)
≥75 years, n (%)	1 (2)
ECOG PS, n (%)[a]	
0	29 (58)
1	21 (42)
IPSS-R cytogenetic risk, n (%)	
Very good	0 (0)
Good	21 (41)
Intermediate	17 (33)
Poor	3 (6)
Very poor	10 (20)
Baseline mutations, n/N (%)	
ASXL1	16/38 (42)
RUNX1	11/38 (29)
TP53	7/38 (18)
SRSF2	9/38 (24)
Best response before transplantation, n (%)	
CR	21 (41)
mCR	23 (45)
mCR with HI, n/n (%)	7/23 (30)
PR	0
SD	7 (14)

[a]ECOG PS missing for 1 patient.

Aza, azacitidine; CR, complete remission; ECOG PS, Eastern Cooperative Oncology Group performance status; HI, Hematological Improvement; SCT, stem cell transplantation; mCR, marrow complete remission; PR, partial response; SD, stable disease; Ven, venetoclax.

Figure 1

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