Venetoclax and Azacitidine in the Treatment of Patients with Relapsed/Refractory Myelodysplastic Syndrome

Authors:
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Introduction:
Patients (pts) with relapsed/refractory (R/R) higher-risk myelodysplastic syndromes (MDS) have a dismal median overall survival (OS) of 4.3 - 5.6 months (mos) and a 1-year survival probability of 28% after failure of the 2 approved hypomethylating agents (HMAs) azacitidine (Aza), and decitabine (Dec). There is no existing standard of care for pts after failure of HMA therapy; hence, there is a critical need for effective therapeutic strategies. Venetoclax (Ven) is a selective, potent, oral BCL-2 inhibitor that in combination with Aza improved clinical outcomes as frontline therapy in pts with higher-risk MDS in an early phase clinical trial. We present an updated analysis of the safety and efficacy of Ven+Aza for the treatment of pts with R/R MDS.

Methods:
This ongoing, phase 1b, open-label, multicenter study (NCT02966782) evaluated the safety and efficacy of either Ven monotherapy or Ven+Aza combination. Pts enrolled and treated with Ven+Aza were ≥18 yrs with R/R MDS and Eastern Cooperative Oncology Group performance status ≤2. Pts were considered R/R if they received a prior therapy with no response or had a response but subsequently relapsed after receiving at least 4 cycles of Aza or Dec within the last 5 yrs. Pts were excluded if they had myelodysplastic/myeloproliferative overlap neoplasms, had prior therapy with a BH3 mimetic, or underwent allogeneic hematopoietic stem cell or solid organ transplantation. For the Ven+Aza combination, pts were treated with escalating oral doses of Ven: 100, 200, or 400 mg daily for 14 days (d) every 28-d cycle. Aza was administered at 75 mg/m 2/d on 1–7 d every cycle. Responses were assessed per modified International Working Group 2006 criteria.

Results:
Due to limited efficacy with Ven monotherapy, this analysis focuses on outcomes in pts treated with Ven+Aza combination only. As of April 30, 2021, 44 pts were treated with Ven+Aza (male 86%, median age 74 yrs [range 44-91]). Prior to enrollment, pts received a median of 1 HMA regimen and 65% of pts received >6 cycles of HMAs.

The median follow-up was 21.2 mos, range 0.4 – 37.5. Pts received a median of 4 cycles (range 1 – 32) of Ven treatment. Forty-two pts (96%) reported ≥3 grade treatment-emergent adverse events (AEs). The most common ≥3 grade hematological AEs were febrile neutropenia (34%), thrombocytopenia (32%), neutropenia (27%), and anemia (18%). Pneumonia (23%) was the most common ≥3 grade infection. Serious AEs were reported in 61%. There were 29 (66%) deaths, of which 1 (2%) occurred ≤30 d after the first Ven dose, and 3 (7%) occurred within ≤60 d of first dose. Nine (21%) deaths occurred due to disease progression, and 4 (9%) were due to AEs (gastrointestinal hemorrhage [n=1], and infections [n=3]). Twenty-one (48%) pts required Ven dose interruptions due to an AE, most frequently due to febrile neutropenia (n=7; 15%) and neutropenia (n=4; 9%). Five (11%) pts required

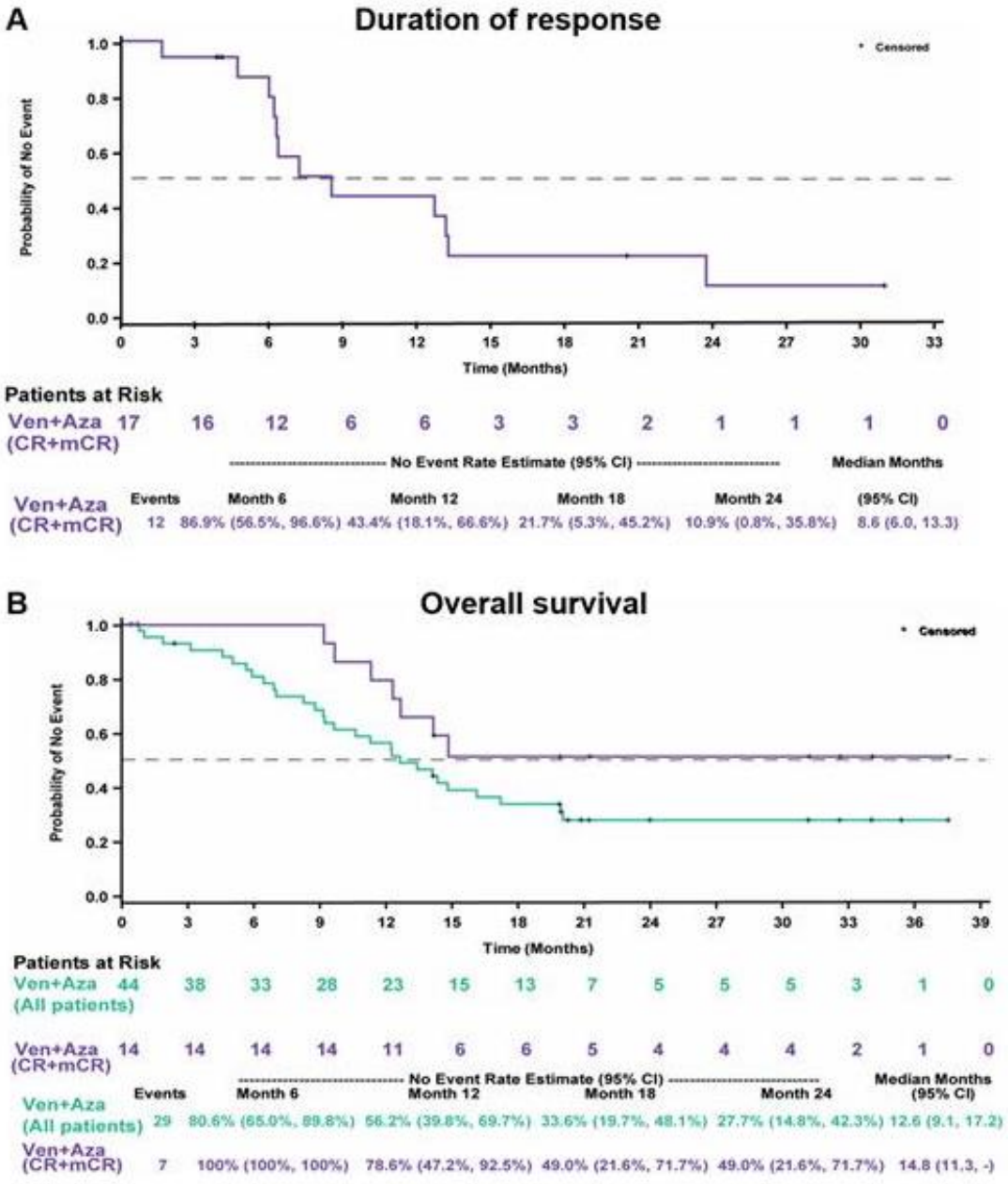
dose duration reductions, and 9 (21%) pts required Ven discontinuation. Fifteen (34%) pts were alive at the time of data cutoff.

The objective response rate (mORR, defined as complete remission [CR] + marrow CR [mCR] + partial remission [PR]) rate was 38.6%, observed in 17 pts (CR 3, mCR 14, PR 0). Median time to first response of CR or mCR was 1.2 mos (range 0.7 – 6.3), and the duration of response for mORR was 8.6 mos (95% CI 6.0 – 13.3) (Fig A). Overall median progression-free survival was 8.6 mos (95% CI 5.4 – 14.3) and median OS was 12.6 mos (95% CI 9.1 – 17.2); mOS for pts with mORR was 14.8 mos (95% CI 11.3 – not estimable) (Fig B). Six pts with mCR also achieved hematological improvement. Post-baseline RBC and platelet transfusion independence (TI) was achieved by 16 (36%) pts overall with a median first duration of 4.0 mos (range 1.9 – 8.3). Nine pts (20.5%) moved to post-study transplant. Nine pts (20.5%) progressed to acute myeloid leukemia (AML). The median time to AML progression was 4.97 mos (range 0.03 – 19.84), and the median time to subsequent therapy was 5.7 mos (95% CI 4.8 – 8.8).

Conclusion:

With longer follow-up, the tolerability and efficacy of the Ven+Aza combination in pts with R/R MDS were consistent with what was previously reported. In a very difficult-to-treat pt population, an ORR of 39%, RBC and platelet TI rate of 36%, and a median OS of 12.6 mos all suggest that Ven+Aza treatment leads to meaningful clinical benefits. Additional analyses, including associations of genetic mutations with clinical outcomes and patient-reported outcomes, will be presented.

Figure 1


A
Duration of response
Censored
Probability of No Event
1.0
0.8
0.6
0.4
0.2
0.0
0 3 6 9 12 15 18 21 24 27 30 33
Time (Months)
Patients at Risk
Ven+Aza (CR+mCR) 17 16 12 6 6 3 3 2 1 1 1 0
No Event Rate Estimate (95% CI)
Median Months
Ven+Aza (CR+mCR) Events Month 6 Month 12 Month 18 Month 24 (95% CI)
12 86.9% (56.5%, 96.6%) 43.4% (18.1%, 66.6%) 21.7% (5.3%, 45.2%) 10.9% (0.8%, 35.8%) 8.6 (6.0, 13.3)
B
Overall survival
Censored
Probability of No Event
1.0
0.8
0.6
0.4
0.2
0.0
0 3 6 9 12 15 18 21 24 27 30 33 36 39
Time (Months)
Patients at Risk
Ven+Aza (All patients) 44 38 33 28 23 15 13 7 5 5 5 3 1 0
Ven+Aza (CR+mCR) 14 14 14 14 11 6 6 5 4 4 4 2 1 0
No Event Rate Estimate (95% CI)
Median Months (95% CI)
Ven+Aza Events Month 6 Month 12 Month 18 Month 24
Ven+Aza (All patients) 29 80.6% (65.0%, 89.8%) 56.2% (39.8%, 69.7%) 33.6% (19.7%, 48.1%) 27.7% (14.8%, 42.3%) 12.6 (9.1, 17.2)
Ven+Aza (CR+mCR) 7 100% (100%, 100%) 78.6% (47.2%, 92.5%) 49.0% (21.6%, 71.7%) 49.0% (21.6%, 71.7%) 14.8 (11.3, -)