656 Safety, Efficacy, and Patient-Reported Outcomes of Venetoclax in Combination with Azacitidine for the Treatment of Patients with Higher-Risk Myelodysplastic Syndrome: A Phase 1b Study

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Background

Hypomethylating agents (HMA) form the current standard treatment for patients with higher-risk myelodysplastic syndrome (HR-MDS) who are not eligible for allogeneic hematopoietic stem cell transplantation (HSCT). However, overall response rates (ORRs) remain low in patients receiving azacitidine (Aza), and median overall survival (OS) is reported as ~15 months (Sekeres et al. *J Clin Oncol*. 2017). In addition, there are few data on patient-reported outcomes (PROs) published in this population while on treatment. Venetoclax (Ven) is a selective, potent, orally bioavailable BCL-2 inhibitor, which has demonstrated synergy with HMA in preclinical studies of HR-MDS.

From an ongoing, open-label, dose-escalation, Phase 1b study (NCT02942290) evaluating Ven+Aza for the treatment of treatment-naïve HR-MDS, we report the updated safety and efficacy in all treated patients and the exploratory analysis of key PROs in patients who received the recommended Phase 2 dose (RP2D).

Methods

Patients aged ≥18 years with treatment-naïve HR-MDS, International Prognostic Scoring System intermediate-2 or high, bone marrow blasts <20% at baseline, and an Eastern Cooperative Oncology Group (ECOG) score ≤2 were enrolled; patients with chronic myelomonocytic leukemia or therapy-related MDS and candidates for intensive chemotherapy or HSCT were excluded. Ven was initially given at a dose of 400 mg or 800 mg for 28 days in a 28-day cycle. Due to intolerance among patients with MDS, this was later amended to an escalating dose (100, 200, and 400 mg) for 14 days in a 28-day cycle. Aza was administered at 75 mg/m^2 subcutaneously or intravenously on Days 1-7 of each 28-day cycle. The primary objectives of the study were to assess the Ven+Aza safety profile and to establish the RP2D. Key secondary objectives included assessment of ORR and OS. Safety and efficacy assessments were carried out on all patients who received ≥1 dose of study drug, and efficacy endpoints were evaluated according to the 2006 International Working Group response criteria, with OS analyzed using Kaplan-Meier methodology. PROs were exploratory and included the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30) scale.

Results

At data cutoff, December 31, 2019, 57 patients had received Ven+Aza, with a median follow-up of 13.0 months (95% confidence interval [CI] 11.3, 15.6 months). The majority of patients were male (75%); median age was 71 years (range 26-85 years); and 89% had ECOG score 0-1. All patients experienced ≥1 adverse event (AE), the most common being constipation (54%), neutropenia (51%), and nausea (51%). Grade ≥3 AEs were experienced by 97% of patients, with neutropenia (51%), febrile neutropenia (46%), and thrombocytopenia (30%) the most common. Febrile neutropenia was the most common serious AE (42%). The 30-day mortality rate was 2%. The ORR was 77%, including complete remission (CR) and marrow CR (mCR) achieved by 42% and 35% of patients (of whom 40% achieved mCR + hematological improvement), respectively; none achieved partial remission. Median OS was not reached (95% CI 16.2 months, not estimable; Figure 1). Median duration of response was 14.8 months (95% CI 12.9 months, not estimable). Median progression-free survival was 17.5 months (14.5, not estimable). Of the patients who received the RP2D of Ven 400 mg for 14 days/28-day cycle in combination with Aza, physical functioning, as measured by the EORTC QLQ-C30, was maintained through 48 weeks of treatment. In addition, clinically meaningful improvement in fatigue and dyspnea, as measured by the EORTC QLQ-C30, was achieved by the beginning of Cycle 5 and was maintained through Week 48 (Cycle 13; Figure 2).

Conclusion

The combination of Ven+Aza demonstrates promising efficacy, including response durability, and an acceptable safety profile for patients with HR-MDS. Maintenance in physical functioning and clinically meaningful improvement in dyspnea and fatigue were observed throughout the first 48 weeks, although these data are not yet mature and low patient numbers beyond Cycle 7 limit conclusions. Additional follow-up data and correlation with disease risk features including mutations will be presented at the meeting.

Figure 1. Kaplan–Meier Curve for Overall Survival of All Patients

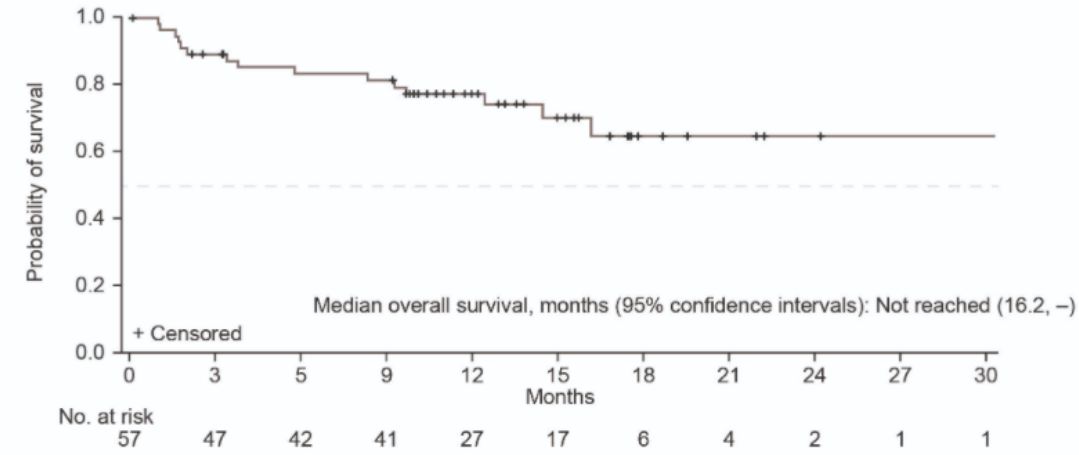
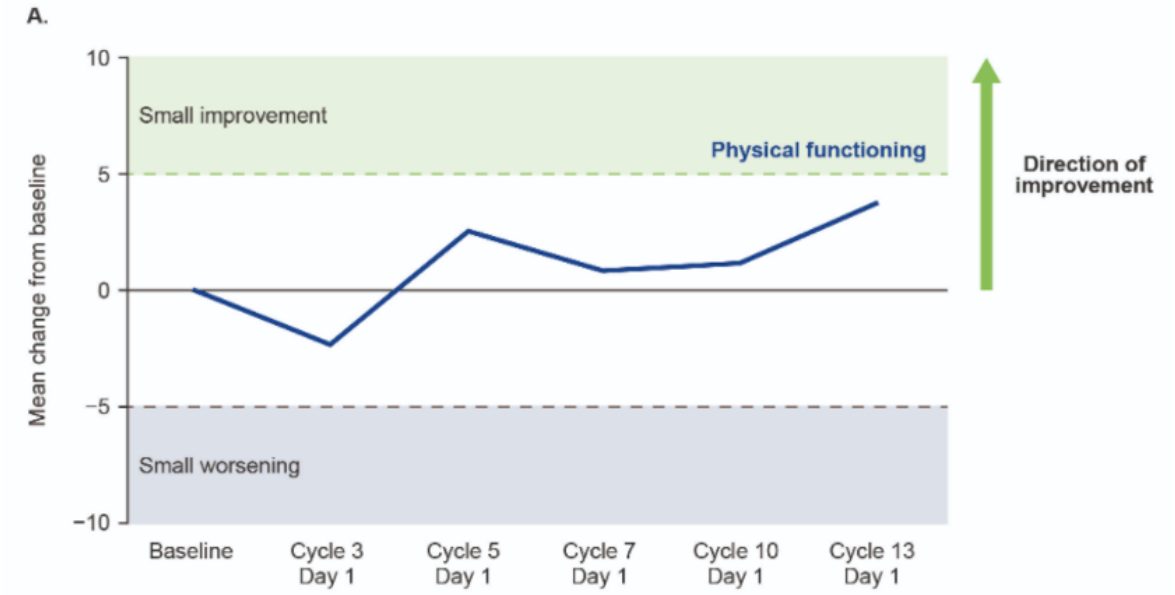
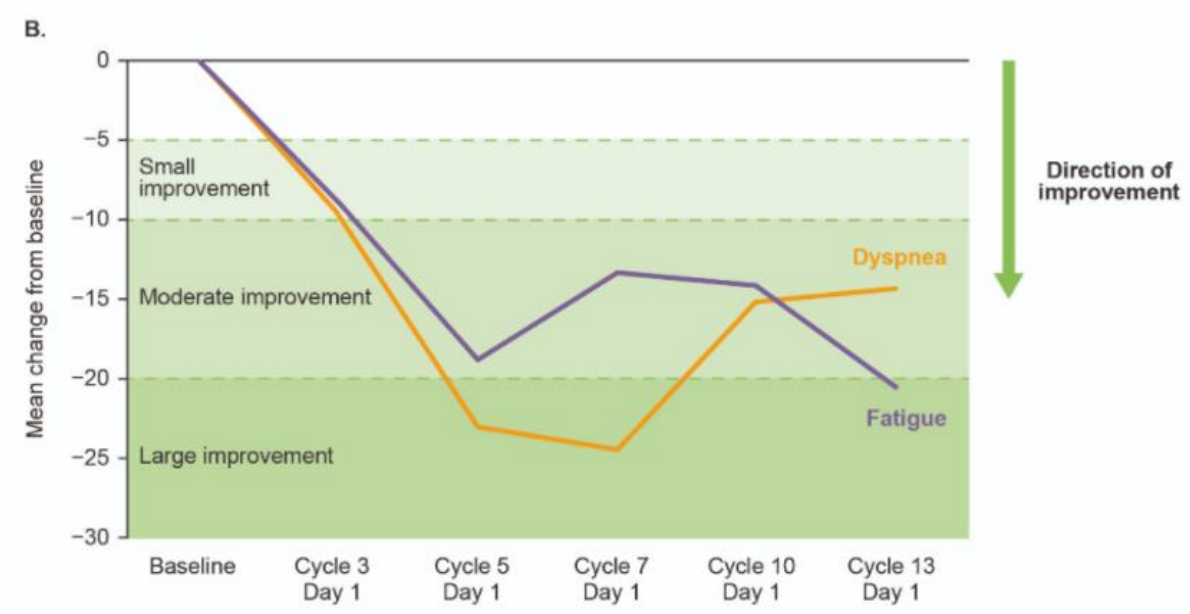


Figure 2. Mean Changes from Baseline in A. Physical Functioning and B. Fatigue and Dyspnea for Patients Who Received Venetoclax 400 mg, as Measured by the EORTC QLQ-C30





Improvement is indicated by a positive change for physical functioning (A) and by a negative change for dyspnea and fatigue (B).
Number of patients: baseline n=49; Cycle 3 Day 1 n=28; Cycle 5 Day 1 n=13; Cycle 7 Day 1 n=15; Cycle 10 Day 1 n=11; Cycle 13 Day 1 n=7.
Change thresholds were defined as described by Osoba et al. *J Clin Oncol*. 1998.
EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core.