

Venetoclax Plus Hypomethylating Agents for Treatment-Naïve Myelodysplastic Syndromes with Increased Blasts: A Prospective Multicenter Cohort Study

Na Zhao^{1,2,*}, Lijun Zhu^{1,*}, Xing Hu^{1,*}, Juan Tong¹, Hongfeng Ge³, Li Ye⁴, Xijun Zhu⁵, Can Gai⁶, Yuhu Feng⁷, Lei Zhang¹, Li Wang¹, Guangyu Sun¹, Lei Xue¹, Xiaoyu Zhu¹, Changcheng Zheng^{1,8}

¹Department of Hematology, the First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, 230000, People's Republic of China; ²State Key Laboratory of Immune Response and Immunotherapy, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, 230000, People's Republic of China; ³Department of Hematology, Bozhou People's Hospital, Bozhou, Anhui, 233500, People's Republic of China; ⁴Department of Hematology, Lu'an People's Hospital, Lu'an, Anhui, 237000, People's Republic of China; ⁵Department of Hematology, Xuancheng People's Hospital, Xuancheng, Anhui, 242000, People's Republic of China; ⁶Department of Hematology, Huaibei People's Hospital, Huaibei, Anhui, 235000, People's Republic of China; ⁷Department of Hematology, Fuyang People's Hospital, Fuyang, Anhui, 236000, People's Republic of China; ⁸Department of Hematology, Centre for Leading Medicine and Advanced Technologies of IHM, the First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, 230000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Changcheng Zheng, Department of Hematology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, 230001, People's Republic of China, Email zhengchc1123@ustc.edu.cn

Purpose: Evidence supporting venetoclax combined with hypomethylating agents (HMAs) in treatment-naïve myelodysplastic syndromes with increased blasts (MDS-IB), a biologically aggressive subset with high risk of leukemic transformation, remains lacking. We conducted a prospective, multicenter cohort study to evaluate the efficacy and safety of venetoclax plus HMAs in newly diagnosed MDS-IB.

Patients and Methods: In this prospective, multicenter, single-arm trial conducted at six hospitals in China (August 2022–September 2024), 43 newly diagnosed adults with MDS-IB received venetoclax (ramp-up to 400 mg on days 1–14) plus azacitidine or decitabine in 28-day cycles. Dose adjustments were made for cytopenias, infections, or drug interactions. Primary endpoints were overall response rate (ORR), duration of response (DoR), and safety. Secondary endpoints included overall survival (OS) and transformation to acute myeloid leukemia. The study was registered in the Chinese Clinical Trial Registry (registration number: [ChiCTR2200055204]).

Results: The ORR was 74.4% (95% CI, 58.8–86.5%), comprising 34.4% complete remission (CR), 59.4% marrow CR (mCR), and 6.3% partial response (PR). Among the thirty-two patients who got ORR, the median DoR was 8.1 months (range, 0.9–29.0). The 6-, 12-, and 24-month DoR rates were 68.8% (95% CI, 49.7–81.8%), 53.2% (95% CI, 33.7–69.4%), and 47.7% (95% CI, 27.8–65.1%), respectively. Median OS was 12.8 months, with 12- and 24-month OS rates of 62.4% (95% CI, 46.1–75.1%) and 49.3% (95% CI, 32.2–64.3%), respectively. Grade 3/4 neutropenia/febrile neutropenia occurred in 60% (26/43), and pneumonia in 16% (7/43). The median interval between cycles was 59 days (range 33–113), mainly due to hematologic toxicity.

Conclusion: Venetoclax plus HMAs demonstrated promising clinical activity with manageable toxicity in newly diagnosed MDS-IB, supporting further prospective evaluation of this combination in treatment-naïve patients with increased-blast MDS.

Trial Registration: Chinese Clinical Trial Registry, ChiCTR2200055204, <https://www.chictr.org.cn/index.html>.

Keywords: venetoclax, hypomethylating agents, myelodysplastic syndromes

Introduction

Myelodysplastic syndromes with increased blasts (MDS-IB) are a group of clonal disorders originating from hematopoietic stem cells, characterized by ineffective hematopoiesis, cytopenia, and a high risk of transformation to acute myeloid leukemia (AML).^{1,2} Among these, MDS-IB, where the proportion of blasts in the bone marrow ranges from 5% to 19% (MDS-IB-1, 5–9%; MDS-IB-2, 10–19%), is associated with a more aggressive clinical course and a higher risk of leukemic progression than lower-blast MDS subtypes.² These patients often present with complex cytogenetic abnormalities, high-frequency gene mutations and generally have a poor clinical prognosis. According to the Revised International Prognostic Scoring System (IPSS-R), patients with lower-risk MDS have a median survival of approximately 3 to 10 years, whereas those with higher-risk (HR) disease have a median survival of less than 3 years and a substantially increased risk of leukemic transformation, posing a major challenge in current clinical management.² Currently, for patients with HR MDS according to IPSS-R, hypomethylating agents (HMAs) remain the standard of care. However, the clinical benefit of HMAs remains limited. In randomized studies, azacitidine improved median overall survival to 24.5 months compared with 15.0 months with conventional care, whereas decitabine was associated with a complete response (CR) rate of 9% and an overall response rate (ORR) of 17% without a clear survival advantage.^{2,3} Once HMAs therapy fails, prognosis becomes even poorer, with median survival typically less than 6 months.²

Venetoclax, a selective BCL-2 inhibitor, induces apoptosis in leukemia cells dependent on BCL-2 for survival and demonstrates potent antileukemic activity.⁴ In combination with azacitidine or decitabine, venetoclax has demonstrated high clinical activity in elderly or unfit patients with newly diagnosed AML, achieving CR/CRi rates of 71% and 74%, respectively, with median overall survival of 16.4 and 16.2 months in long-term follow-up from a Phase 1b study.⁵

Preliminary studies have explored the efficacy and safety of venetoclax combined with HMAs in HR or relapsed/refractory MDS, and encouraging response rates have been demonstrated, ranging from approximately 59% to 87%.^{6–8} However, these studies were either early-phase clinical trial with relatively small sample sizes or retrospective analyze with clinically heterogeneous cohorts, and they often included patients with prior treatment exposure or HMAs failure. Moreover prospective data specifically focused on treatment-naïve MDS-IB therefore remain limited. To address this gap, we conducted a prospective multicenter cohort study to evaluate the efficacy and safety of venetoclax combined with HMAs in newly diagnosed MDS-IB, with particular focus on response, survival, and toxicity.

Materials and Methods

Patient Eligibility

This was a prospective, single-arm clinical study conducted at six tertiary referral hospitals in China between August 1, 2022, to September 30, 2024, with follow-up concluded on May 30, 2025. Forty-three consecutive patients with newly diagnosed MDS-IB defined according to the fifth edition of the WHO MDS classification criteria as having 5–19% blasts in the bone marrow or 2–19% in peripheral blood, along with dysplasia in one or more myeloid lineages, were enrolled (Figure 1). MDS-IB-1 was classified by 5–9% bone marrow blasts or 2–4% peripheral blood blasts without Auer rods, while MDS-IB-2 was defined by 10–19% bone marrow blasts, 5–19% peripheral blood blasts, or the presence of Auer rods.⁶ Eligible patients were aged ≥ 18 years and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3 if younger than 75 years, or 0–2 if aged 75 years or older. All participants had adequate hepatic, renal, and cardiac function and provided written informed consent. Key exclusion criteria included MDS/myeloproliferative neoplasms (MPN) overlap syndromes, prior allogeneic or solid organ transplantation, active severe cardiovascular disease, HIV positivity, pregnancy or lactation, poor compliance.

This study was approved by the Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China (approval number: 2022-KY-161) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment. The study was registered in the Chinese Clinical Trial Registry (registration number: [ChiCTR2200055204]).

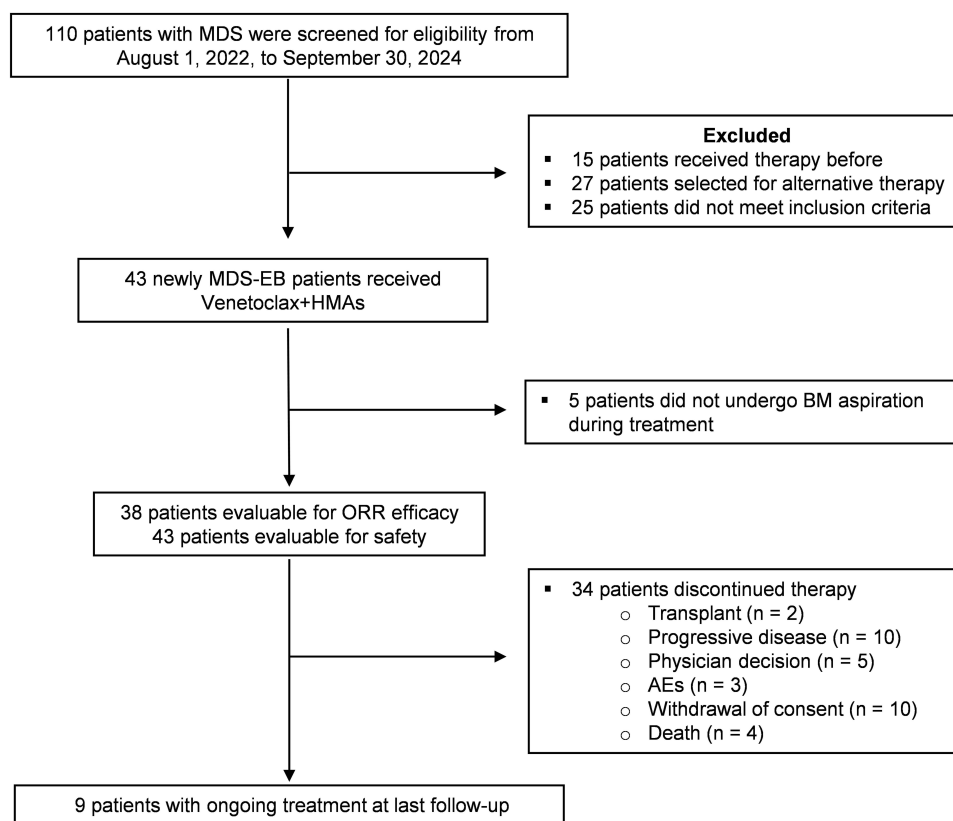


Figure 1 CONSORT diagram for the study population.

Abbreviations: MDS, myelodysplastic syndromes; MDS-IB, myelodysplastic syndromes with excess blasts; AML, acute myeloid leukemia; BM, bone marrow; ORR, overall response rate; AEs, adverse events.

Treatment Protocol

Each treatment cycle lasted 28 days. Patients received venetoclax orally after meals, starting at 100 mg on Day 1, 200mg on Day 2, 400 mg per day on days 3–14 of each 28-day cycle. The HMAs was either decitabine (20 mg/m²/day for 5 consecutive days, administered intravenously) or azacitidine (75 mg/m²/day for 7 consecutive days, subcutaneously).

If treatment postponement was required because of unresolved cytopenias, active infection, or insufficient hematologic recovery, the subsequent cycle could be delayed, and HMA administration was generally delayed together with venetoclax to allow hematologic recovery. Expected nadir cytopenias without clear clinical significance did not routinely require intracycle interruption, whereas severe hematologic toxicity, including profound neutropenia, severe thrombocytopenia, or grade 4 febrile neutropenia, could prompt venetoclax interruption and delay of the subsequent cycle ([eTable 1](#)).

Venetoclax is primarily metabolized by CYP3A and is also a substrate of P-glycoprotein (P-gp). When administered concomitantly with moderate CYP3A or P-gp inhibitors, the venetoclax dose was generally reduced by 50%. When used with strong CYP3A inhibitors, the dose was reduced to 50 mg daily (See [Table 2](#) in the [Supplementary Trial Protocol](#)).

Hematologic parameters were closely monitored throughout treatment. Bone marrow assessment was performed when clinically indicated to help distinguish treatment-related myelosuppression from persistent disease. Supportive care, including anti-infective treatment, G-CSF use after blast clearance, and concomitant drug-related venetoclax dose adjustment, was provided according to protocol-guided principles and institutional practice. Cycles were repeated every 28 days in the absence of unacceptable toxicity or disease progression.

Sample Size Calculation

This clinical trial enrolled patients aged 18 years and older with MDS-IB. Currently, intensive chemotherapy is generally considered for patients who are fit for intensive treatment, whereas HMAs and/or lower-intensity therapy are more

commonly used in patients considered unsuitable for intensive chemotherapy because of age, frailty, comorbidity burden, or poor treatment tolerance. The target enrollment of 43 patients was prespecified using a one-sample binomial design with a two-sided significance level (α) of 0.05 and a power of 80% (Type II error rate $\beta = 0.2$). Because published response rates in MDS-IB vary across clinically relevant patient populations and treatment settings, including differences in age, fitness, and conventional therapy, sample size estimation during protocol development considered several historical response benchmarks derived from prior studies. The largest estimated sample size across these scenarios was forty-three patients, and this value was selected to ensure adequate statistical power while accounting for clinical heterogeneity in the study population.

Outcomes

The primary outcomes were ORR, defined as the proportion of patients achieving CR, marrow CR (mCR), or partial response (PR), duration of response (DoR) assessed by investigators using the modified IWG 2006 criteria,⁹ and safety profile, including adverse events (AEs), which were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.¹⁰

Secondary outcomes included overall survival (OS), defined as the time from enrollment to death from any cause, and time to transformation to AML, calculated from the first dose to the date of confirmed AML diagnosis. Additional exploratory endpoints included hematologic improvement and time to next treatment.

DoR was defined as the time from the first documentation of response (CR, mCR, or PR) to the earliest occurrence of disease progression, clinical relapse during follow-up, initiation of a new antileukemic therapy, or death. For patients who had not died, OS was censored at the last follow-up.

Statistical Analysis

Patients who died before completion of cycle 1 were not included in the original response-evaluable population. Baseline characteristics were summarized using descriptive statistics. Continuous variables were reported as median, minimum, and maximum. Categorical variables were presented as frequencies and percentages. ORR and its 95% confidence intervals (CIs) were calculated using the Clopper-Pearson exact method. Time-to-event outcomes (DoR, OS, and time to AML transformation) were analyzed by the Kaplan-Meier method and reported as medians with corresponding 95% CIs.

Results

Patient Characteristics

A total of 43 treatment-naïve patients with MDS-IB were enrolled in this cohort. Baseline characteristics are summarized in Table 1 and eTable 2. The median age was 65 years (range, 38–82), and 37% of patients (16/43) were aged ≥ 70 years. Male patients comprised 67% (29/43) of the cohort. The subtypes included 20 patients with MDS-IB-1 (47%) and 23

Table 1 Baseline Characteristics of the MDS Cohort

Characteristic	Total (n = 43)	IB-1 (n = 20)	IB-2 (n = 23)
Age, y, median (range)^a	65 (38–82)	63 (38–82)	67 (39–80)
<70, n (%)	27 (63)	13 (65)	14 (61)
≥ 70 , n (%)	16 (37)	7 (35)	9 (39)
Sex			
Male	29 (67)	14 (70)	15 (65)
Female	14 (33)	6 (30)	8 (35)
ECOG PS, n (%)^a			
0	2 (5)	1 (5)	1 (4)
1	20 (47)	11 (55)	9 (39)
2	21 (49)	8 (40)	13 (57)

(Continued)

Table 1 (Continued).

Characteristic	Total (n = 43)	IB-1 (n = 20)	IB-2 (n = 23)
IPSS-R risk categories, n (%)^a			
Very low	0	0	0
Low	2 (5)	0	2 (9)
Intermediate	7 (16)	7 (35)	0
High	14 (33)	6 (30)	8 (35)
Very high	20 (47)	7 (35)	13 (57)
IPSS risk categories, n (%)			
Low	2(5)	2 (10)	0
Intermediate	28 (65)	17 (85)	11 (48)
High	13 (30)	1 (5)	12 (52)
WPSS risk categories, n (%)^a			
Very low	0	0	0
Low	2 (5)	1 (5)	1 (4)
Intermediate	4 (9)	4 (20)	0
High	17 (40)	9 (45)	8 (35)
Very high	20 (47)	6 (30)	14 (61)
IPSS-M risk categories, n (%)^a			
Moderate low	1 (2)	1 (5)	0
Moderate high	2 (5)	2(10)	0
Very high	12 (28)	3 (15)	9 (39)
NA	28 (65)	14 (70)	14 (61)

Notes: ^aPercentages may not total 100% due to rounding.

Abbreviations: ECOG PS, eastern cooperative oncology group performance status; IPSS, international prognostic scoring system; IPSS-R, revised international prognostic scoring system; WPSS, world health organization based prognostic scoring system; IPSS-M, molecular international prognostic scoring system; NA, not available.

with MDS-IB-2 (53%). ECOG performance status (PS) were mainly 1–2 (n = 41, 95%). Risk classification by IPSS-R revealed 79% (34/43) of patients were high or very high risk, with 65% (13/20) in MDS-IB-1 and 91% (21/23) in IB-2. WPSS risk shows both subtypes are mainly high and very high, with 75% (15/20) in IB-1 and 96% (22/23) in IB-2. Genetic testing showed a heterogeneous profile with frequent mutations, including TP53 (n = 5).

Efficacy

The median number of treatment cycles was 5 (range, 1–16). At the data cutoff of May 30, 2025, 9 patients (21%) remained on study treatment, including 4 in the IB-1 group and 5 in the IB-2 group, while 34 patients (79%) had discontinued (Figure 2). The primary reasons for discontinuation were disease progression (n = 10), withdrawal of consent (n = 10), physician decision (n = 5), adverse events (n = 3), death (n = 4), and transplantation (n = 2) (Table 2 and Table 3).

Among 43 patients enrolled, thirty-eight patients were evaluable for response and five patients were not been evaluated due to early death before completing cycle 1 (n = 4) or withdrawal after one treatment cycle (n = 1). The four early dead patients, with age between 56 to 72 years old, had cytogenetic data available, including 3 with IPSS-R very high-risk disease and 1 with IPSS-R high-risk disease. Among those 4 patients, only 1 patient underwent NGS (Next-generation sequencing) testing and was classified as IPSS-M very high risk. Thirty-two patients got overall remission including CR, mCR and PR. The ORR was 74.4% (32 of 43; 95% CI, 58.8–86.5%), including 80.0% (16 of 20; 95% CI, 56.3–94.3%) in the IB-1 group and 69.6% (16 of 23; 95% CI, 47.1–86.8%) in the IB-2 group. Among the 32 responders, CR was achieved in 11 patients (34.4%; 95% CI, 19.1–52.2%), mCR in 19 (59.4%; 95% CI, 42.4–75.2%), and PR in 2 (6.3%; 95% CI, 0.8–20.8%). One patient experienced only hematologic improvement without morphologic response. The median number of cycles to first response was 2 (range, 1–4) (Table 2).

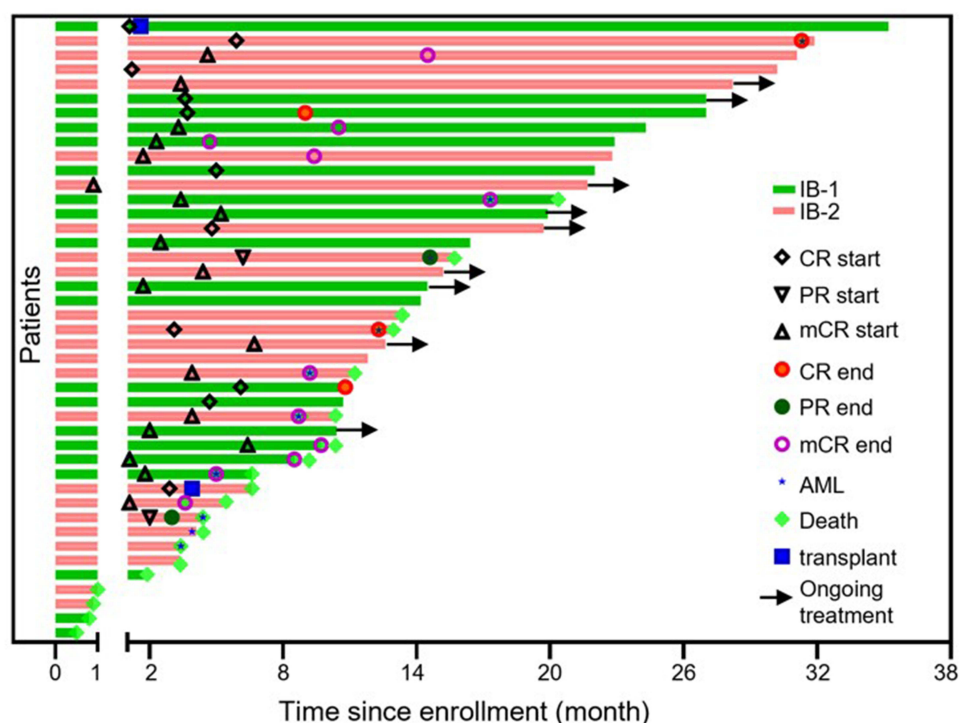


Figure 2 Swimmer plot showing individual patient timelines from treatment initiation, indicating response onset, duration, and relevant clinical events. Each bar represents an individual participant.

Among the 32 patients who got overall remission, the median DoR was 8.1 months (range, 0.9–29.0) (Table 2). The estimated 6-month DoR rate was 68.8% (95% CI, 49.7–81.8%), with 12-month and 24-month DoR rates of 53.2% (95% CI, 33.7–69.4%) and 47.7% (95% CI, 27.8–65.1%), respectively (Figure 3A). No significant difference in DoR was observed between subtypes (eFigures 1–3).

AML transformation occurred in 10 patients (23%) during follow-up. The median time to transformation was 9.0 months (range, 3.4–31.3). The median OS was 12.8 months (0.5–35.2). The estimated 12-month OS rate was 62.4% (95% CI, 46.1–75.1%), with 24-month OS rate of 49.3% (95% CI, 32.2–64.3%) (Figure 3B). No significant difference in OS was observed between subtypes (eFigures 4–6).

Safety

The median duration between treatment cycles was 59 days (range, 33–113), substantially exceeding the standard 28-day interval in the majority of patients (Table 2). Treatment delays were most frequently attributable to grade ≥ 3 neutropenia or infection-related complications. Grade 3/4 neutropenia were recorded in 26 patients (60%), febrile neutropenia (26 patients, 60%), pneumonia ($n = 7$, 16%), and sepsis ($n = 6$, 14%). Grade 3/4 thrombocytopenia occurred in 42% patients ($n = 18$). Gastrointestinal side effects such as nausea and diarrhea were reported in 21% patients ($n = 9$) (Table 4). And 3 patients discontinued treatment due to treatment-related AEs (Table 3).

Discussion

This study represents a prospective evaluation of the efficacy and safety of venetoclax combined with HMAs in treatment-naïve patients with MDS-IB. The results show that in this HR population with limited treatment options, the combination regimen induced a high CR+mCR+PR rate (74.4%) and CR rate (34.4%), with a median OS of 12.8 months. However, treatment was accompanied by considerable hematologic toxicity, primarily grade 3/4 neutropenia and infections. Overall, these findings suggest that venetoclax plus HMAs has clinically relevant activity in newly diagnosed MDS-IB, although interpretation should remain cautious given the single-arm design.

Table 2 Efficacy Among Patients Treated with Venetoclax and HMAs

Characteristic	Total (n = 43)	IB-1 (n = 20)	IB-2 (n = 23)
Response raters, n (%; 95% CI)			
ORR	32, 74.4% (95% CI: 58.8–86.5%)	16, 80.0% (95% CI: 56.3–94.3%)	16, 69.6% (95% CI: 47.1–86.8%)
CR	11, 34.4% (95% CI: 19.1–52.2%)	6, 37.5% (95% CI: 11.9–54.3%)	5, 21.7% (95% CI: 7.5–43.7%)
mCR	19, 59.4% (95% CI: 42.4–75.2%)	10, 62.5% (95% CI: 27.2–72.8%)	9, 39.1% (95% CI: 19.7%–61.5%)
PR	2, 6.3% (95% CI: 0.8–20.8%)	0, 0% (95% CI: 0.0–16.8%)	2, 8.7% (95% CI: 1.1–28.0%)
ORR			
Cycles number to ORR, median (range)	2 (1–4)	2 (1–4)	2 (1–4)
Duration ORR, month, median (range)	8.1 (0.9–29.0)	7.3 (0.9–23.5)	8.8 (1.0–29.0)
AML transformation			
AML transformation, n (%)	10 (23)	2 (10)	8 (35)
Time to AML transformation, month, median (range)	9.0 (3.4–31.3)	11.2 (5.0–19.6)	8.7 (3.4–31.3)
Treatment delivery			
Number of cycles, median (range)	5 (1–16)	6 (1–14)	5 (1–16)
Patients receiving >1 cycle, n (%)	37 (86)	17 (85)	20 (87)
Time to Initiation of the next cycle, day, median (range)	59 (33–113)	56 (33–111)	65 (38–113)
Survival and follow-up			
Survivals, n (%)	23 (54)	13 (65)	10 (43)
Duration of follow-up for survivals, month, median (range)	21.7 (10.4–35.2)	22.0 (10.4–35.2)	22.3 (11.8–31.9)

Abbreviations: HMAs, hypomethylating agents; ORR, overall response rate; CR, complete response; mCR, marrow complete remission; PR, partial response; MDS, myelodysplastic syndromes; AML, Acute myeloid leukemia.

Table 3 Patient Disposition

Patient Disposition	Total (n = 43)	IB-1 (n = 20)	IB-2 (n = 23)
Ongoing treatment, n (%)	9 (21)	4 (20)	5 (22)
Discontinued treatment, n (%)	34 (79)	16 (80)	18 (78)
Transplant	2 (5)	1 (5)	1 (4)
Progressive to AML	10 (23)	2 (10)	8 (35)
Physician decision	5 (12)	5 (25)	0
AEs	3 (7)	2 (10)	1 (4)
Withdrawal of consent	10 (23)	4 (20)	6 (26)
Death	4 (9)	2 (10)	2 (9)

Abbreviation: AEs, adverse events.

The response rate observed in our study is higher than the historically reported response of single-agent HMAs in HR MDS. Silverman LR et al reported the 6% CR and 17% PR in single AZA group for HR MDS patients.¹¹ In another randomised, open-label, Phase III study, Fenaux P et al reported the proportion of patients with complete and partial remission was 51% in the azacitidine group.¹² More importantly, when interpreted in the context of previously published venetoclax-HMAs studies in MDS, our findings appear broadly comparable to those reported in frontline prospective studies as well as in retrospective or real-world cohorts.^{6–8,13,14} These cross-study comparisons should, however, be interpreted cautiously because of differences in study design, prior treatment exposure, baseline disease risk, disease composition, and response definitions. In particular, some earlier studies incorporated hematologic improvement into the ORR.

Among prospective studies, Bazinet et al reported phase 1 results in HR MDS/CMML treated with azacitidine plus venetoclax, with an ORR of 87% in a small mixed cohort. This trial included both treatment-naïve and previously treated patients and was primarily designed to assess safety and dosing.⁶ In relapsed/refractory MDS after prior HMAs failure, Zeidan et al reported an ORR of 39% and a median OS of 12.6 months for venetoclax plus azacitidine.¹³ By contrast, Garcia et al reported efficacy data in 107 treatment-naïve HR MDS patients treated with venetoclax plus azacitidine, with a CR rate of 29.9%, marrow CR of 50.5%, and median OS of 26.0 months.¹⁴ Compared with the study by Garcia et al, our CR rate was similar, whereas ORR and OS were somewhat lower. These differences may reflect the exclusive inclusion of MDS-IB in our cohort, the poorer-risk biology of this subtype. Thus, our study provides more disease-specific prospective evidence in treatment-naïve MDS-IB, a subgroup characterized by higher blast burden and increased risk of leukemic progression.

Retrospective and real-world studies have also suggested activity of venetoclax-HMA regimens in MDS, although these cohorts generally included more heterogeneous populations than the present study. For example, Liu et al reported an overall CR rate of 61% in relapsed/refractory MDS,¹⁵ and Ball et al reported an ORR of 59% in treatment-naïve and relapsed/refractory MDS patients treated with venetoclax and HMAs.⁸ In the latter study, 63% of responders subsequently proceeded to allogeneic stem cell transplantation (allo-SCT), and post-transplant survival appeared prolonged.⁸ These findings suggest that venetoclax-HMAs may have potential as a disease-control platform before transplantation. A similar results was observed in a retrospective GESMD study of HR MDS/CMML, in which HMAs plus venetoclax used as bridge therapy was associated with an ORR of 90%, a composite complete response rate of 77%, and an allo-SCT rate of 83%.¹⁶ In addition, the favorable frontline activity reported by Garcia et al in treatment-naïve HR MDS is consistent with the possibility that this regimen may facilitate disease control before subsequent therapeutic consolidation.¹⁴ However, because these data derive from studies with different populations, treatment settings, and endpoints, the role of venetoclax-HMAs as a formal bridge-to-transplant strategy remains to be better defined.

Notably, the ORR still reached 69.6% in the MDS-IB-2 subgroup, suggesting that this regimen may retain activity even in patients with higher marrow blast burden. This observation is biologically plausible. Mechanistically, the activity of venetoclax plus HMAs may be related to enhanced mitochondrial apoptosis in BCL-2-dependent myeloid cells, together with HMAs-mediated apoptosis priming and metabolic remodeling. Preclinical studies have suggested that venetoclax-based regimens may suppress oxidative phosphorylation in primitive myeloid cells, whereas resistance may develop through metabolic adaptation, including increased fatty acid oxidation, or through reduced dependence on BCL-2.^{17,18} In

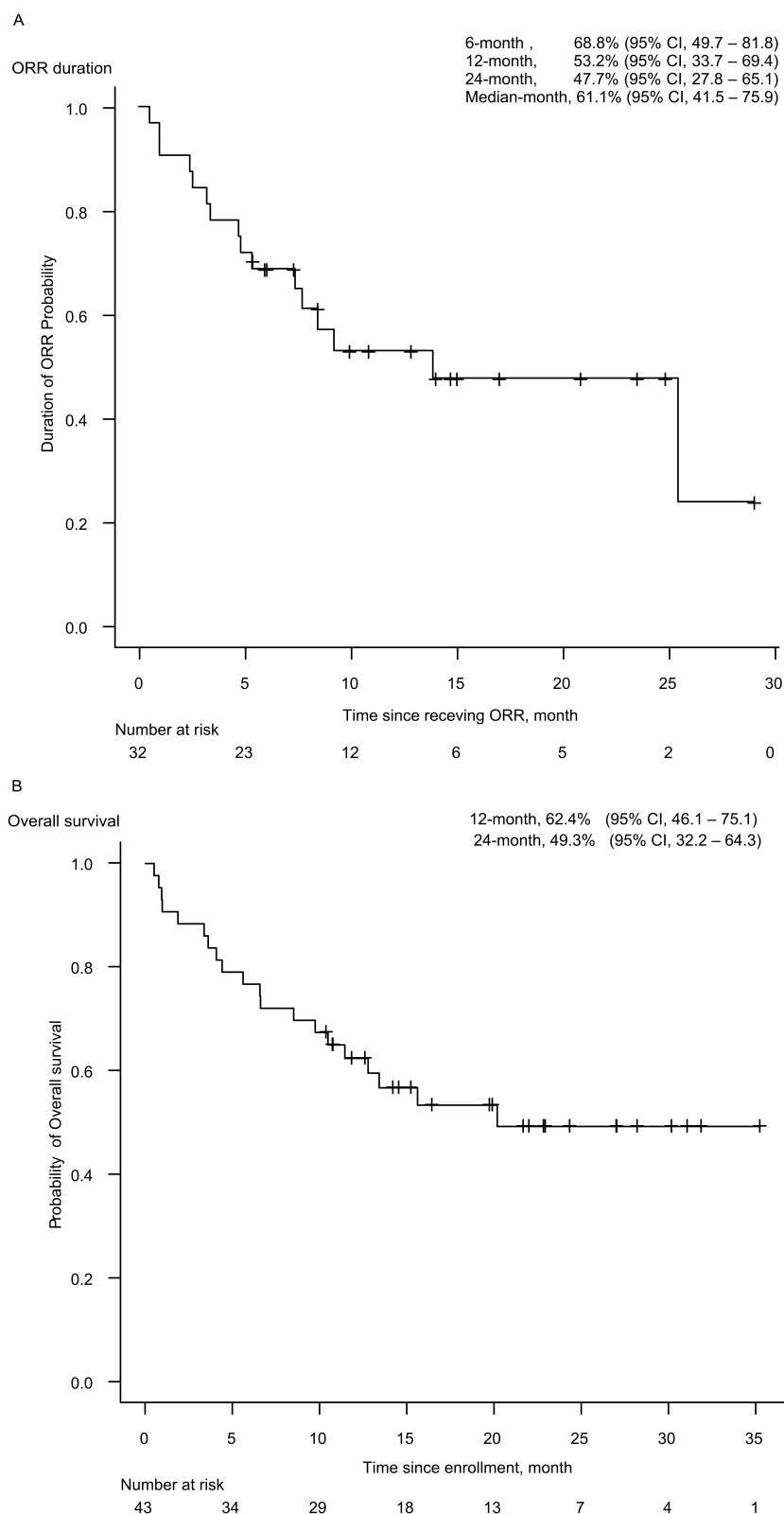


Figure 3 Duration of overall response (**A**) and OS (**B**). Duration of overall response is defined as the number of months from the date of CR+mCR+PR to the earliest documentation of progressive disease, clinical disease progression during posttreatment follow-up, discontinued treatment or death of any cause, whichever occurred earlier. OS was defined as the number of months from the date of the first dose of study drug to the date of death of any cause or the date of last follow-up for survivors. **Abbreviations:** CR, complete response; mCR, marrow complete remission; PR, partial response; OS, overall survival.

Table 4 Adverse Events of Patients

Adverse Event Category (n, %)	Total (n = 43)	IB-1 (n = 20)	IB-2 (n = 23)
Grade 3/4 Neutropenia	26 (60)	11 (55)	15 (65)
Febrile neutropenia	26 (60)	11 (55)	15 (65)
Pneumonia	7 (16)	2 (10)	5 (22)
Sepsis	6 (14)	3 (15)	3 (13)
Grade 3/4 Thrombocytopenia	18 (42)	7 (35)	11 (48)
Grade 3/4 Anemia	10 (23)	4 (20)	6 (26)
Nausea	7 (16)	3 (15)	4 (17)
Diarrhea	2 (5)	1 (5)	1 (4)

parallel, epigenetic lesions may also influence treatment sensitivity. For example, ASXL1-mutant myeloid cells have been reported to exhibit increased BCL2 expression and greater sensitivity to venetoclax and azacitidine.¹⁹ More broadly, ROS-associated mitochondrial apoptotic signaling has also been described in other hematologic models, although the direct relevance of these observations to venetoclax-HMAs therapy in MDS remains to be established.^{20,21}

The median OS in our study was 12.8 months, with 12- and 24-month OS rates of 62.4% and 49.3%, respectively. Given that 79% of patients were classified as IPSS-R high or very high risk and the median age was 65 years, these data suggest a potentially favorable efficacy signal relative to historical lower-intensity approaches, although the magnitude of survival benefit requires confirmation in randomized trials.

The toxicity profile of this study is consistent with the known safety characteristics of venetoclax combination regimens in AML and MDS, with myelosuppression and its associated complications being the core management challenges.^{13,14,22,23} Grade 3/4 neutropenia and febrile neutropenia, observed in up to 60% of patients, led to substantial treatment delays in practice. This is evidenced by a median inter-cycle interval of 59 days, which notably exceeded the standard 28-day schedule. Similar treatment-delivery challenges have also been reported in prior studies. Garcia et al noted that treatment interruption was common and dose reduction was frequently required¹⁴ These findings suggest that optimization of venetoclax exposure may be important for improving treatment deliverability. Shortened venetoclax schedules, such as 7-day regimens, have shown comparable efficacy with improved tolerability in AML,²⁴ and may warrant further evaluation in MDS-IB, although direct evidence in this setting remains limited.

Overall, for clinicians, the main takeaway is that venetoclax plus HMAs may provide meaningful disease control in selected patients with newly diagnosed MDS-IB, but at the cost of substantial myelosuppression, infectious risk, and frequent treatment delay.

A key strength of our study is its prospective design and its focus on a homogeneous cohort consisting exclusively of treatment-naïve MDS-IB patients. Previous relevant studies often included heterogeneous populations comprising MDS/MPN overlap syndromes, prior treatment exposure, or AML, making it difficult to extrapolate their findings directly to the MDS-IB population. In exploratory subgroup analyses, no statistically significant differences in overall response rate, duration of response, or overall survival between the MDS-IB-1 and MDS-IB-2.

Several limitations should be acknowledged. First, a relatively small sample size of 43 patients without a comparator arm limits statistical power and the robustness of subgroup analyses. Second, the follow-up remains relatively limited for full assessment of long-term survival, late relapse, and uncommon late toxicities. Third, although a standard protocol was followed, variability in cycle extension and dose modification across patients may influence the standardized assessment of efficacy and toxicity. Additionally, given the observed transformation rate to acute myeloid leukemia of 23% at a median of 9.0 months in this cohort, strategies to prevent or delay leukemic evolution constitute another critical objective for future investigation. At present, although several emerging options for HR MDS are under active investigation, no clearly superior low-toxicity alternative has yet displaced HMAs-based therapeutic strategies. Future studies should include randomized comparative trials and biomarker-driven investigations to better define patient selection, optimize treatment scheduling, and determine whether venetoclax plus HMAs can meaningfully delay leukemic evolution and improve long-term outcomes in MDS-IB.

In conclusion, this prospective multicenter cohort suggests that venetoclax combined with HMAs has promising activity in treatment-naïve MDS-IB. Although hematologic toxicity and frequent cycle delays require careful supportive care and individualized treatment modification, this regimen may represent a therapeutic option for selected patients, particularly those who are not candidates for intensive chemotherapy or transplantation. Further randomized and biologically informed studies are needed to confirm its efficacy and define its optimal clinical role.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China (approval number: 2022-KY-161) and was registered in the Chinese Clinical Trial Registry (registration number: [ChiCTR2200055204]).

Consent for Publication

All authors contributed to the review of the manuscript and agree to publish.

Author Contributions

C.Z. and N.Z. designed the study. N.Z. and L.J.Z. drafted the manuscript. N.Z., L.J.Z., and X.H. performed the statistical analysis. N.Z., L.J.Z., X.H., C.Z., H.G., L.Y., Y.F., C.G., and X.J.Z. acquired and/or interpreted the data. N.Z., L.J.Z., X.H., J.T., H.G., L.Y., Y.F., C.G., X.J.Z., L.Z., L.W., G.S., L.X., X.Y.Z. and C.Z. contributed to study conduct, project administration, and supervision. All authors contributed significantly to the work reported; participated in revising or critically reviewing the article; reviewed and approved all versions of the manuscript before submission, during revision, and the final version accepted for publication; agreed on the journal to which the article was submitted; and agree to be accountable for all aspects of the work. N.Z., L.J.Z., and X.H. contributed equally to this work.

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Disclosure

The authors declare no competing interest.

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