Original Study

Real-world Effectiveness of Azacitidine in Treatment-Naive Patients With Higher-risk Myelodysplastic Syndromes

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Abstract

This real-world, retrospective study evaluated effectiveness of azacitidine in 382 treatment-naive patients with HR-MDS from a US electronic health record–derived database, in which limited complete remissions and short overall survival were observed. This study highlights an important unmet need for new therapies and combinations that improve complete remission and survival rates in patients with HR-MDS.

Introduction: Azacitidine (AZA) is an approved frontline therapy for higher-risk myelodysplastic syndromes (HR-MDS); however, poor survival denotes unmet needs to increase depth/duration of response (DOR). **Methods:** This retrospective study with patient chart review evaluated AZA effectiveness in 382 treatment-naive patients with HR-MDS from a US electronic health record (EHR)–derived database. Responses were assessed using International Working Group (IWG) 2006 criteria; real-world equivalents were derived from EHRs. Primary endpoint was IWG 2006-based complete remission rate (CRR). Secondary endpoints were EHR-based CRR, IWG 2006- and EHR-based objective response rates (ORRs), duration of CR, DOR, progression-free survival, time-to-next-treatment, and overall survival (OS). **Results:** Using IWG 2006 criteria, the CRR was 7.9% (n = 30); median duration of CR was 12.0 months (95% CI, 7.7-15.6). In poor cytogenetic risk (n = 101) and *TP53* mutation (n = 46) subgroups, CRRs were 7.9% (n = 8) and 8.7% (n = 4), respectively. ORR was 62.8% (n = 240), including a hematologic improvement rate (HIR) of 46.9% (n = 179). Using EHR-based data, CRR was 3.7% (n = 14); median duration of CR was 13.5 months (95% CI, 4.5-21.5). ORR was 67.8% (n = 259), including an HIR of 29.3% (n = 112). Median follow-up was 12.9 months; median OS was 17.9 months (95% CI, 15.5-21.7). **Conclusions:** Consistent with other studies, CRRs and median OS with AZA in treatment-naive patients with HR-MDS were low in this large, real-world cohort. Novel agents/combinations are urgently needed to improve these outcomes in HR-MDS.

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Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematologic malignancies characterized by clonal hematopoiesis and ineffective blood cell production, resulting in peripheral blood cytopenias.[1,2] Higher-risk MDS (HR-MDS), defined as intermediate-, high-, or very high-risk MDS by the revised International Prognostic Scoring System (IPSS-R), is associated with overall poor prognosis characterized by lower overall survival (OS) and an increased risk for transformation to acute myeloid leukemia (AML).[3] Additionally, molecular subgroups, such as poor cytogenetic risk or *TP53* mutation, are associated with poorer overall outcomes.[3-5]

The hypomethylating agent (HMA) 5-azacitidine (AZA) is a frontline standard-of-care treatment for patients with HR-MDS in most of the world.[6-9] Results from randomized phase III trials

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demonstrate improved hematologic responses (complete remission [CR] rate for AZA, 7%-17%), delayed progression to AML (median time to transformation to AML/death for AZA, 17.8-21 months), and improved survival (median OS for AZA, 20-24.5 months) of patients receiving AZA compared with patients receiving best supportive care or conventional chemotherapy.[6,7] However, despite these improvements, responses are often transient (median duration of hematologic response in phase III trials, 13.6-15 months),[6,7] and many patients experience relapse or resistance to AZA.[8,10]

Recent real-world experience has also highlighted the limitations of single-agent AZA for HR-MDS with variable and often shorter survival benefit than that previously observed in the AZA-001 trial.[6,11,12] The real-world outcomes from AZA have been lower than expected with a registry of the Spanish cooperative group on MDS reporting a median OS of 13.4 months from 251 patients with HR-MDS receiving AZA in frontline.[13] A recent systematic review of randomized clinical trials and prospective and retrospective observational studies of patients with HR-MDS treated with AZA reported a pooled CR rate of 16% (95% CI, 13%-19%), a pooled marrow CR (mCR) rate of 19% (95% CI, 13%-25%), and a pooled median OS estimate of 16.4 months (95% CI, 12.0-17.3 months) based on data from randomized clinical trials and observational studies.[12] Furthermore, this systematic review indicated no substantial difference between the outcomes of the included clinical trials and observational studies.[12] To our knowledge, large- scale real-world studies of AZA in the United States (US) in frontline HR-MDS have been limited. Here, we report the findings from an analysis of retrospective, real-world data on the effectiveness of AZA monotherapy in treatment-naive adult patients with HR-MDS in the US using both International Working Group (IWG) 2006 criteria and electronic health record (EHR)–based responses.

Methods

Study Design

This was an observational cohort study that used a retrospective chart review to examine outcomes in treatment-naive adult patients with HR-MDS treated with AZA according to routine clinical practice in the US. All enrolled patients received ≥1 dose of frontline AZA between January 1, 2014, and January 1, 2020. To allow for a minimum of 1 year of follow-up after the initiation of AZA, the last patient initiation was on or before January 1, 2020. This study used the iKnowMed (iKM) EHR database of the US Oncology Network provided by Ontada LLC. A chart review was conducted to extract ancillary data from the EHR database for all patients. Data from the EHR database were also supplemented with vitality status data from the Social Security Limited Access Death Master File.[14] Data abstraction from patients' records occurred between January 2021 and March 2021. Data were abstracted into an electronic case report form (eCRF) by structured data query and chart review of unstructured data. Data extracted from the EHR through an eCRF were collected into an electronic data capture (EDC) system. Data from the structured query and chart abstraction were compiled with EDC data for analysis.

Patient demographics and baseline characteristics, including IPSS-R risk category, clinical characteristics, all supportive treatment before initiating AZA, concomitant medications, progression data, next line of therapy for the treatment of MDS, and survival status, were collected from the date of AZA initiation until January 1, 2021, or death, whichever was earlier.

Patient Population

Eligible patients were aged ≥ 18 years with a histological diagnosis of MDS documented in the EHR and an IPSS-R MDS risk category of intermediate, high, or very high risk. Patients must have received ≥1 dose of AZA in accordance with the US prescribing information during the study period, with the following regimens permitted: AZA 75 mg/m^2 on days 1-7 of a monthly cycle; AZA 75 mg/m^2 on days 1-5, 8, and 9 of a monthly cycle (5 days on, 2 days off, and 2 days on); or AZA 75 mg/m^2 on days 1-5 of a monthly cycle. Additional inclusion criteria were a record of ≥ 1 posttreatment encounter in the EHR, white blood cell count of ≤ 20×10^3/μL at the time of AZA initiation (use of hydroxyurea to reduce white blood cell count prior to AZA initiation, as documented in the EHR, was permitted). In order to enable the results of this real-world study to be compared against those from clinical trials, some additional inclusion criteria were implemented so that patients had to have adequate liver/renal function (similar to the requirements in clinical trials). Therefore, patients had to have aspartate aminotransferase or alanine aminotransferase ≤ 5 × the upper limit of normal (ULN), bilirubin ≤ 1.5 × ULN (≤ 3.0 × ULN in the presence of a known or suspected history of Gilbert syndrome or genetic equivalent), serum creatine ≤ 1.5 × ULN, or estimated glomerular filtration rate ≥ 40 mL/min/1.73 m^2.

Patients were excluded from the study if they had received any prior antileukemic therapy, including chemotherapy, targeted therapies, immunotherapy, or radiotherapy (prior and concurrent hydroxyurea, oral etoposide, erythroid and/or myeloid growth factors, or any symptomatic treatment were permitted, as was prior anticancer therapy for prior malignancies), or a stem cell transplant (SCT) within 6 months of AZA initiation. Prior treatment with lenalidomide or similar agents was permitted if treatment was used for symptomatic support. Additional exclusion criteria included transformation of MDS into AML prior to initiation of AZA, active secondary malignancies (except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancies for which patients were not receiving active anticancer therapy), acute promyelocytic leukemia, known inherited or acquired bleeding disorders, EHR documentation of clinical suspicion or radiological evidence of active central nervous system involvement by leukemia, participation in a clinical trial during the study period, and off-label use of AZA regimens.

Outcomes

The primary endpoint was CR rate based on IWG 2006. CR rate is a widely accepted surrogate for survival in oncology.[15,16] The secondary endpoints were EHR-based CR rate, IWG 2006-based and EHR-based objective response rates (ORRs), duration of CR, duration of response (DOR), progression-free survival (PFS), time to next treatment (TTNT), and OS. A key exploratory objective was the CR + partial remission (PR) rate (IWG 2006 and EHR based).

Table 1 Demographic and Other Baseline Characteristics

	All Patients (N = 382)
Age, median (range), y	74 (37-85)
≥ 65 y, n (%)	329 (86.1)
Male, n (%)	243 (63.6)
ECOG PS, n (%)	
0	50 (13.1)
1	191 (50.0)
2	59 (15.4)
> 2	2 (0.5)
Missing	80 (20.9)
IPSS-R risk category, n (%)	
Intermediate	164 (42.9)
High	150 (39.3)
Very high	68 (17.8)
Cytogenetic risk category, n (%)	
Favorable	147 (38.5)
Intermediate	57 (14.9)
Poor	101 (26.4)
Unknown	77 (20.2)
TP53 mutation, n (%)	46 (12.0)
Secondary MDS, n (%)[a]	19 (5.0)
Hb, median (range), g/dL	8.8 (5.1-15.7)
WBC count, median (range), 10^9/L	2.9 (0.6-19.9)
ANC, median (range), 10^9/L	1.2 (0-13.7)
Platelets, median (range), 10^9/L	73 (4-1377)
RBC count, median (range), 10^{12}/L	2.7 (1.7-4.9)
BM blasts, n (%)	
> 5%	139 (36.4)
≤ 5%	80 (20.9)
Missing	163 (42.7)
Time from diagnosis to baseline, median (range), mo	1.0 (0.1-229.0)

Abbreviations: ANC = absolute neutrophil count; BM = bone marrow; ECOG PS = Eastern Cooperative Oncology Group performance status; Hb = hemoglobin; IPSS-R = Revised International Prognostic Scoring System; mo = month(s); RBC = red blood cell; WBC = white blood cell.
[a] Includes therapy-related MDS.

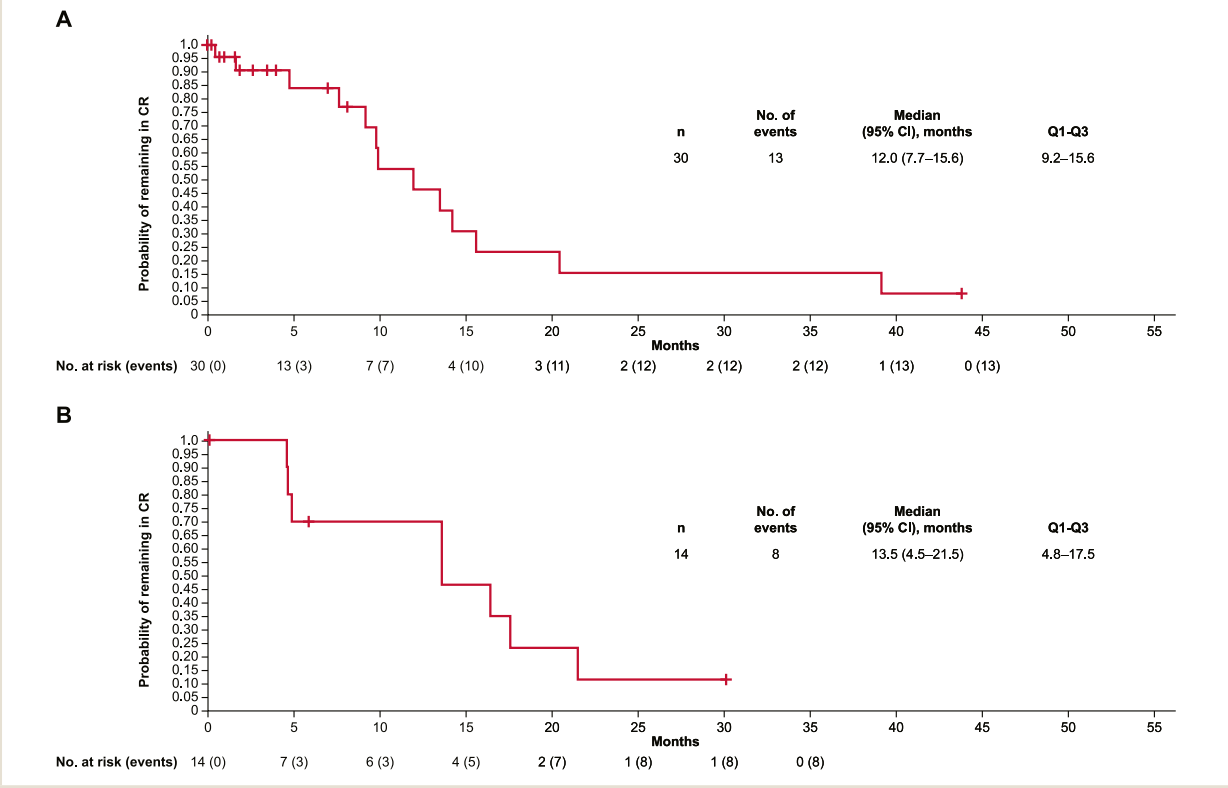
Response Assessments

The effectiveness of frontline AZA in this HR-MDS population was assessed using IWG 2006 criteria. IWG 2006-based response categories were defined as having EHR documentation of the endpoint as well as meeting IWG 2006 criteria. Real-world equivalents of these endpoints were also derived and were defined as having EHR documentation of the endpoint, regardless of IWG 2006 criteria. CR and PR were confirmed as defined per IWG 2006 MDS response criteria[17] and are denoted as "IWG 2006". CR and PR with or without IWG 2006 MDS response criteria confirmation[17] are denoted as "EHR based".

All responses meeting the CR and PR criteria were adjudicated by an independent assessor (hematology/oncology clinician) who specialized in the treatment of MDS. Derived responses were individually scrutinized and approved by the assessor. IWG 2006-based response categories, including CR, mCR, PR, and hematologic improvement (HI), were derived from EHR documentation, along with corresponding peripheral blood results and bone marrow biopsies within a 4-week period before or after the response documentation date. An independent assessor adjudicated cases that had the required peripheral blood and BM indices and met the threshold for CR and PR defined in the IWG 2006 MDS response criteria but lacked EHR documentation. The definition for mCR was based on BM blast count (≤ 5% myeloblasts and a decrease of ≥ 50% compared with pretreatment count) and did not require EHR documentation. The definition of HI was solely based on peripheral blood results per IWG 2006 without requirement for EHR documentation. The ORR (IWG 2006 and EHR based) was defined as the proportion of patients who achieved a CR, PR, mCR, or HI during the treatment period with AZA or prior to initiation of the next MDS treatment.

Duration of CR and DOR were defined as the interval from documentation of a CR or objective response (per IWG 2006 criteria), respectively, to the first documentation of relapse, disease progression, or death from any cause, whichever was earliest. Patients who were not observed to have any of these events were

Figure 1 (A) Duration of CR based on IWG 2006 criteria.[a] (B) Duration of CR based on EHR only.[b] Abbreviations: CR = complete remission; DCR = duration of CR; EHR = electronic health record; IWG = International Working Group; Q = quartile. [a]Median follow-up (range), 3.8 months (0-43.9 months). [b]Median follow-up (range), 5.3 months (0-30.2 months).



censored at their last assessment day if the patient had not initiated a next MDS treatment, or were censored at the start day of the next MDS treatment if the patient had initiated a next MDS treatment. PFS was defined as the interval from the date of AZA initiation to the first documentation of relapse, disease progression, or death from any cause, whichever was earliest. OS was defined as the interval from the date of AZA initiation to death from any cause. TTNT was defined as the interval from the date of AZA initiation to the date of initiation of the next antileukemic treatment of MDS (excluding palliative care or palliative radiation) including SCT, or death from any cause, whichever was earlier. For OS and TTNT, patients without any observed events for each outcome were censored at the last contact day if it was earlier than end of study. For PFS, patients without any observed events were censored at their contact day if they had not initiated next MDS treatment (excluding SCT), or were censored at the start day of the next MDS treatment (excluding SCT) if they had initiated next MDS treatment.

Statistical Analyses

Demographic and baseline measurements were summarized via standard descriptive methods. CR rate (IWG 2006 and EHR based), ORR (IWG 2006 and EHR based), and CR + PR rate (IWG 2006 and EHR based) were analyzed via point estimates and corresponding 95% CIs based on the Clopper-Pearson exact method. PFS, duration of CR, DOR, TTNT, and OS curves and medians were analyzed using the Kaplan-Meier method.

Ethics

This study was performed in accordance with the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices. Informed consent was not obtained for this study. All data were anonymized and collected in real-world data vendor databases and/or an eCRF with a unique patient identifier for each patient; patient anonymity was strictly maintained.

Results

Patients and Treatment

This study initially identified 888 adult HR-MDS patients who received AZA therapy during the study period, of which, 382 were eligible for the final analysis (Supplemental Figure 1).

Baseline demographic and clinical characteristics are presented in Table 1. Overall, the median age of patients was 74 years (range, 37-85 years), and the majority of patients were male (63.6%) and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (63.1%). IPSS-R intermediate-, high-, and very-high-risk categories were reported in 164 (42.9%), 150 (39.3%), and 68 patients (17.8%), respectively. Cytogenetic risk was poor

Table 2 Response Summary

	All Patients (N = 382)		Poor Cytogenetic Risk (n = 101)	*TP53* Mutation (n = 46)
	IWG 2006	EHR based	IWG 2006	
CR, n (%)	30 (7.9)	14 (3.7)	8 (7.9)	4 (8.7)
95% CI	5.4-11.0	2.0-6.1	3.5-15.0	2.4-20.8
mCR, n (%)	31 (8.1)	13 (3.4)	10 (9.9)	4 (8.7)
PR, n (%)	0	120 (31.4)	0	0
HI, n (%)	179 (46.9)	112 (29.3)	43 (42.6)	21 (45.7)
Erythroid	115 (30.1)	71 (18.6)	26 (25.7)	13 (28.3)
Platelet	91 (23.8)	56 (14.7)	22 (21.8)	14 (30.4)
Neutrophil	59 (15.4)	39 (10.2)	19 (18.8)	10 (21.7)
ORR, n (%)	240 (62.8)	259 (67.8)	61 (60.4)	29 (63.0)
95% CI	57.8-67.7	62.9-72.5	50.2-70.0	47.5-76.8
Duration of CR, median, mo	12.0	13.5	15.6	NA
95% CI	7.7-15.6	4.5-21.5	1.7-39.2	1.7-NA
Duration of OR, median, mo	9.5	9.3	7.7	9.3
95% CI	7.7-10.6	7.4-10.6	5.5-10.4	4.8-10.9
Time to CR, median, mo	4.8	6.0	3.9	3.3
Range	0.9-22.2	3.3-37.4	2.0-14.6	2.0-4.9
Kaplan-Meier estimate of CR rate (95% CI)				
6-month remission	84.1 (57.7-94.7)	70 (32.9-89.2)	83.3 (27.3-97.5)	50 (0.6-91.0)
12-month remission	46.3 (19.9-69.2)	70 (32.9-89.2)	55.6 (7.3-87.6)	NA

Abbreviations: CR = complete remission; EHR = electronic health record; HI = hematologic improvement; IWG = International Working Group; mCR = marrow CR; mo = month(s); NA = not assessable; OR = objective response; ORR = objective response rate; PR = partial remission.

in 101 patients (26.4%) and 46 patients (12.0%) had a *TP53* mutation.

The median time from diagnosis to AZA initiation was 1.0 month (range, 0.1-229.0 months). Overall median follow-up was 12.9 months (range, 0.3-76.4 months) and 364 patients discontinued AZA treatment (95.3%). Most commonly patients discontinued AZA treatment due to disease progression (35.3%); other common (≥ 10%) reasons included adverse events (14.4%) and death (10.7%) (Supplemental Table 1).

Response

Based on IWG 2006 criteria, the CR rate was 7.9% (95% CI, 5.4%-11.0%) and the ORR was 62.8% (n = 240) among all patients. mCR and HI were reported in 31 patients (8.1%) and 179 patients (46.9%), respectively (no patients with mCR were counted as having HI); no PRs were reported (Table 2). In the subgroup of patients with poor cytogenetic risk, the ORR was 60.4%, with 8 patients (7.9%) achieving CR. In the subgroup of patients with *TP53* mutation, the ORR was 63.0%, with 4 patients (8.7%) achieving CR (Table 2).

In the 30 patients who achieved CR per IWG 2006 criteria, the median duration of CR was 12.0 months (95% CI, 7.7-15.6 months), with a median follow-up of 3.8 months (range, 0-43.9 months); median time to CR was 4.8 months (range, 0.9-22.2 months) (Table 2 and Figure 1). The Kaplan-Meier estimate of the CR rate was 84.1% (95% CI, 57.7%-94.7%) at the 6-month remission point and 46.3% (95% CI, 19.9%-69.2%) at the 12-month remission point. The median duration of objective response was 9.5 months (95% CI, 7.7-10.6 months), with a median follow-up of 6.1 months (range, 0-51.9 months); median time to objective response was 2.0 months (range, 0.1-16.8 months) (Table 2 and Figure 2).

Among all patients, estimates for response categories differed between those confirmed with IWG 2006 criteria and those for which only EHR-based data were available; however, ORRs were similar (Table 2). With EHR-based data, the CR rate was 3.7% (95% CI, 2.0%-6.1%), and the ORR was 67.8% (n = 259). Median duration of CR was 13.5 months (95% CI, 4.5-21.5 months), with a median follow-up of 5.3 months (range, 0-30.2 months) (Table 2 and Figure 1); median duration of objective response was 9.3 months (95% CI, 7.4-10.6 months), with a median follow-up of 6.1 months (range, 0-51.9 months); and median time to objective response was 2.0 months (range, 0.1-18.9 months) (Table 2 and Figure 2). Median TTNT was 11.5 months (95% CI, 9.5-12.6 months), with a median follow-up of 9.0 months (range, 0.3-76.4 months). Of the 267 patients (69.9%) with events, 109 patients (28.5%) initiated next antileukemic treatment of MDS (including SCT).

Survival

Among all patients, the median PFS was 9.1 months (95% CI, 8.0-10.8 months), with a median follow-up of 6.2 months (range, 0-53.7 months) (Figure 3). Median OS in these patients was 17.9 months (95% CI, 15.5-21.7 months), with a median follow-up of 12.9 months (range, 0.3-76.4 months) (Table 3 and Figure 4). The 1-, 2-, and 3-year OS rates were 67.3% (95% CI, 62.0%-72.0%), 40.9% (95% CI, 35.1%-46.6%), and 30.6% (95% CI, 24.6%-36.7%), respectively (Table 3). In the subgroups of patients

Table 3 Overall Survival

	All Patients (N = 382)	Poor Cytogenetic Risk (n = 101)	*TP53* Mutation (n = 46)
Median follow-up duration for OS, mo	12.9	10.3	13.7
Range	0.3-76.4	0.5-76.4	0.5-46.5
Kaplan-Meier estimate of median OS, mo	17.9	12.8	15.6
95% CI	15.5-21.7	10.3-15.5	13.0-26.9
Kaplan-Meier estimate of OS rate, % (95% CI)			
1 year	67.3 (62.0-72.0)	54.4 (43.4-64.2)	68.0 (51.3-80.1)
2 year	40.9 (35.1-46.6)	24.3 (15.1-34.7)	34.5 (18.9-50.6)
3 year	30.6 (24.6-36.7)	15.2 (7.2-26.1)	29.5 (14.4-46.4)

Abbreviations: mo = month(s); OS = overall survival.

with poor cytogenetic risk or *TP53* mutation, median OS was 12.8 months (95% CI, 10.3-15.5 months) or 15.6 months (95% CI, 13.0-26.9 months) (Table 3).

Discussion

We retrospectively analyzed response and survival data from one of the largest real-world cohorts of patients with HR-MDS (382 patients). In this study of AZA in treatment-naive patients, objective response categories were documented in the EHR and assessed with standardized IWG 2006 criteria.[17] EHR-based equivalents were also reported. All response categories (CR, mCR, PR, and HI) differed between IWG 2006-based and EHR-based except ORRs, which were similar among all patients (62.8% vs. 67.8%). Of note, in this analysis, mCR and HI did not require EHR documentation and were based on BM blast count and IWG 2006 criteria, respectively. Additionally, PR was higher using EHR-based criteria, compared to that of IWG 2006 criteria. Despite the difference in the number of patients achieving PR, the DOR was similar between IWG 2006-based and EHR-based criteria.

In this study, CR rates were low in all patients regardless of the criteria used (IWG 2006, 7.9%; EHR based, 3.7%), and median OS was limited and very similar to a recent prospective clinical trial of patients treated with AZA monotherapy (17.9 vs. 17.5 months).[18] The presence of poor cytogenetic risk or *TP53* mutation appeared to decrease OS (median OS of 12.8 and 15.6 months, respectively). The observed differences in CRs occurred because EHR-based responses were documented with or without corresponding BM or blood parameters, whereas IWG 2006-based responses were assessed against the response criteria for these parameters. Additionally, although patients with poor cytogenetic risk or *TP53* mutations are known to have overall poorer prognoses than patients without these risk factors,[3-5] CR rates in the poor cytogenetic risk or *TP53* mutation subgroups did not differ from those in the overall population in our study. This unexpected finding is likely due to the small sample sizes in these subgroups.

Regardless of confirmation of responses with IWG 2006 criteria, real-world outcomes in patients treated with AZA monotherapy were poorer in this study than those achieved in the initial phase III clinical trials,[6,7] underscoring the limited clinical benefit of HMA therapy in routine clinical practice. The CR rate was 17%, and median OS was 24.5 months with AZA in the landmark randomized phase III clinical trial.[6] In addition, other real-world studies in HR-MDS have reported variations in clinical outcomes in routine practice, thought to be due to differences in receipt and continuation of HMA therapy.[19] Baseline patient and disease characteristics are often dissimilar between clinical trial and real-world populations, and this may play a role in the discrepant outcomes for AZA observed in these two settings. For example, our real-world study had a numerically larger proportion of patients aged ≥ 65 years compared with the landmark randomized phase III clinical trial (86.1% vs. 68.2%).[6] Furthermore, our study had a numerically higher proportion of patients with ECOG performance status scores of ≥ 2 than in the above-mentioned phase III clinical trial (15.9% vs. 7%).

The retrospective and observational nature of this study is associated with several inherent limitations. The broad geographic distribution of healthcare providers who have contributed data to the EHR database helped to reduce selection bias. However, stringent patient selection criteria (eg, IPSS-R HR-MDS criteria, and liver and kidney function requirements) might have resulted in exclusion of eligible patients and restricted generalizability. The use of standard measurement instruments, including use of the eCRF and appropriate partner personnel training, helped reduce the risk of information bias. As the standard of care for first-line treatment of MDS did not change over the study index period, the risk of cohort effects was minimal. Some variables of interest may have been missing and may not have been uniformly captured across patient records (eg, laboratory values were missing for many, and units needed standardization across patients); also, since these records are associated with dedicated provider networks, services and procedures provided outside of the network were not captured in these analyses. However, the extent or direction of any biases resulting from these limitations could not be ascertained. Although this study included one of the largest cohorts of MDS patients, the median follow-up time was 12.9 months. Lack of longer follow-up could have impacted median OS and 2- and 3-year survival rates. The reliability of the response endpoints in this study depends on the quality and completeness of the data, some of which may not be easily captured in the real world. For example, BM biopsy results were unavailable for 42.7% of patients in this study, which reflects the fact that BM biopsies are not routinely performed in standard clinical practice, other than at diagnosis and suspected disease

Figure 2 (A) Duration of OR based on IWG 2006 criteria.[a] (B) Duration of OR based on EHR only.[a] Abbreviations: EHR = electronic health record; IWG = International Working Group; OR = objective response. [a]Median follow-up (range), 6.1 months (0-51.9 months).

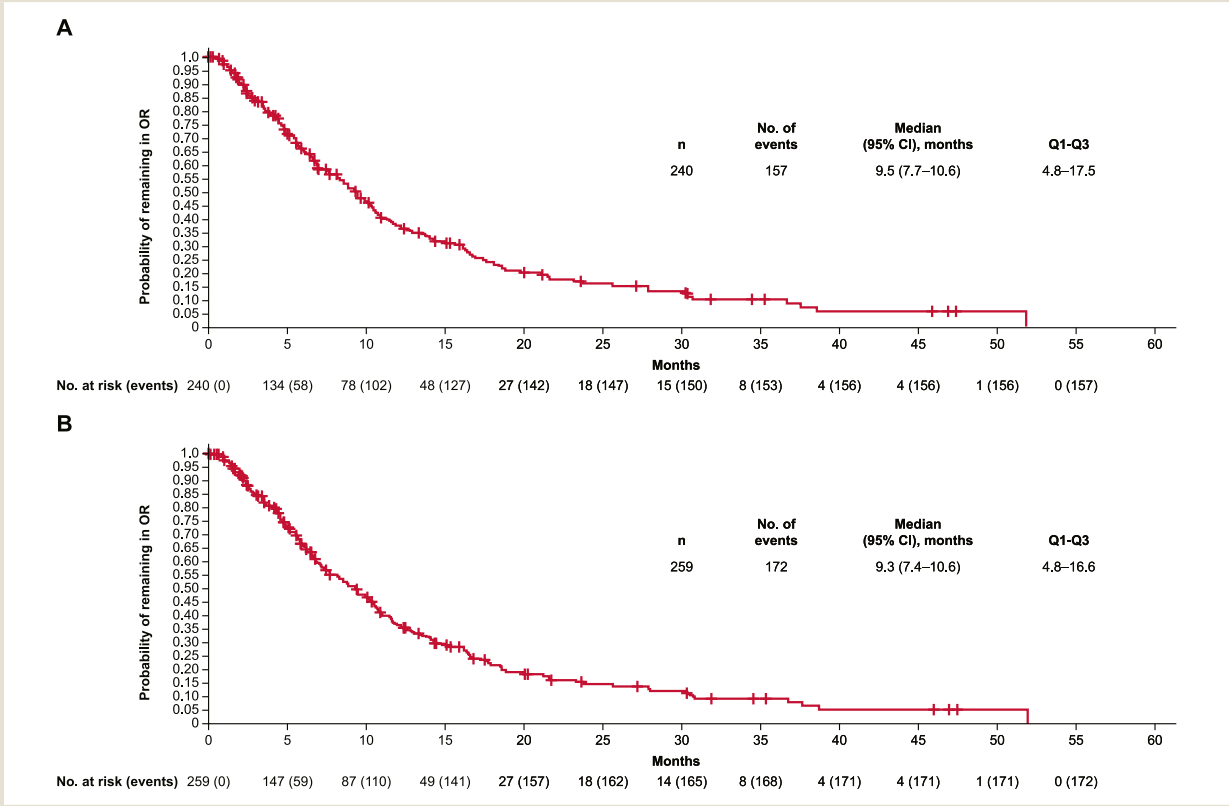
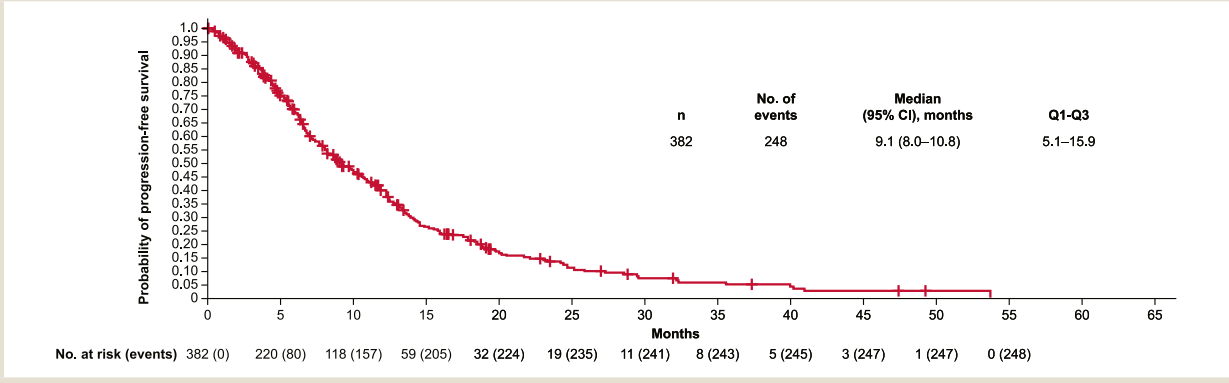
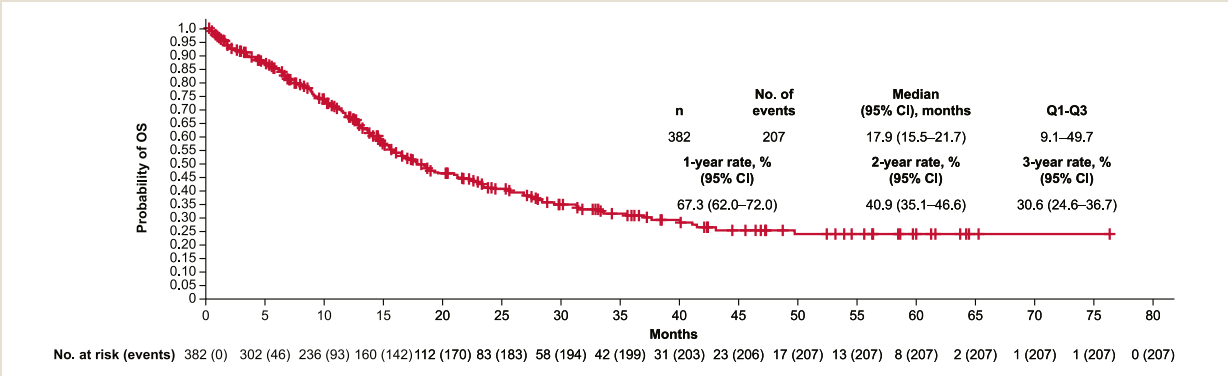


Figure 3 Probability of progression-free survival among all patients. Median follow-up (range), 6.2 months (0-53.7 months). Abbreviations: Q = quartile.



progression. This and the likely low frequency of BM biopsies in the remainder of patients could have led to underestimation of the CR and PR rates compared with corresponding rates reported in clinical trials (where periodic BM assessments are routinely performed). Additionally, IPSS-R scores were not available in the EHR and consequently all patients with IPSS-R intermediate risk category were included as HR-MDS; this analysis therefore included some patients with IPSS-R scores of < 3.5. It has been empirically determined that IPSS-R scores of ≥ 3.5 dichotomize patient risk into HR-MDS versus lower-risk MDS.[20] The results may include data

Figure 4 Probability of overall survival among all patients. Median follow-up (range), 12.9 months (0.3-76.4 months). Abbreviations: OS = overall survival; Q = quartile.



from patients with less severe symptoms and better prognosis and the response and survival results observed here may be bias toward better outcomes than had IPSS-R scores been available. The use of standard measurement instruments, including eCRF and independent adjudication by assessors specializing in the treatment of MDS, was incorporated to mitigate these limitations. Inclusion of chart review in this study was also expected to improve on the reliability of response endpoints over the use of EHR-only data.

Overall, our study highlights an important unmet need for new therapies and combinations that improve CR and survival rates in patients with HR-MDS. Based on encouraging phase I/II data, several novel agents with unique mechanisms of action are being investigated in combination with AZA in phase III studies. These include the anti-CD47 monoclonal antibody magrolimab (NCT04313881), the anti-TIM-3 monoclonal antibody sabatolimab (NCT04266301), the Bcl-2 inhibitor venetoclax (NCT04401748), and the RARα agonist tamibarotene (NCT04797780). Other new therapies for HR-MDS are also being evaluated in earlier-stage trials.[21]

Conclusion

In conclusion, these findings of one of the largest real-world HR-MDS cohorts corroborate the results of a growing body of evidence indicating poor survival in HR-MDS patients treated with AZA. More effective therapeutic approaches are needed to improve outcomes for patients with HR-MDS.

Clinical Practice Points

- Azacitidine (AZA) is a standard-of-care frontline treatment for patients with higher-risk myelodysplastic syndromes (HR-MDS); however, responses are often transient, many patients experience relapse or resistance to AZA, and survival benefits are often variable and shorter than those previously observed in clinical trials. To date, large-scale real-world studies of AZA in the US in frontline HR-MDS have been limited.
- This retrospective study evaluated AZA effectiveness in 382 treatment-naive patients with HR-MDS from a US electronic health record (EHR)-derived database. Using International Working Group (IWG) 2006 criteria, the complete remission rate (CRR) was 7.9% (n = 30); median duration of CR was 12.0 months (95% CI, 7.7-15.6). In poor cytogenetic risk (n = 101) and *TP53* mutations (n = 46) subgroups, CR rates were 7.9% (n = 8) and 8.7% (n = 4), respectively. The objective response rate (ORR) was 62.8% (n = 240), including a hematologic improvement (HI) rate of 46.9% (n = 179). Using EHR-based data, CR rate was 3.7% (n = 14); median duration of CR was 13.5 months (95% CI, 4.5-21.5). ORR was 67.8% (n = 259), including an HI rate of 29.3% (n = 112). Median follow-up was 12.9 months; median overall survival was 17.9 months (95% CI, 15.5-21.7).
- This study highlights an important unmet need for new therapies and combinations that improve CR and survival rates in patients with HR-MDS.

Data Sharing Statement

Data supporting the findings of this study were provided by Ontada LLC. Approval of requests for data access is at the discretion of Gilead Sciences, Inc. and Ontada LLC and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data and is subject to a license agreement with Ontada LLC. Interested researchers should contact datarequest@gilead.com to determine licensing terms.

Disclosure

N.R., S.M., S.I., M.C., and R.K. are current equity holders at Gilead Sciences Inc. and were employed by Gilead Sciences Inc. at the time of this study. A.H.W. receives institutional research funding from Abbvie, Amgen, Astex, Astra Zeneca, BMS, Novartis, Servier, and Syndax; is an employee of the Walter and Eliza Hall Institute, and is eligible for a fraction of the royalty stream related to venetoclax; serves on speaker's bureaus for Abbvie, Astellas, BMS, and Novartis; and served on advisory boards for Abbvie, Agios, Amgen, Astellas, BMS, Gilead Sciences Inc., Janssen, Macrogenics, Novartis, Pfizer, Roche, and Servier. D.A.S. received consulting fees from AbbVie, Affimed, Gilead Sciences Inc., Incyte, Intellisphere, Molecular Partners, PGEN Therapeutics, Takeda, and Zentalis;

served on advisory boards for AvenCell, Bluebird Bio, BMS, Intellia, Jasper Therapeutics, Kite, Magenta Therapeutics, Nkarta, Novartis, Shattuck Labs, Servier, Syndax, and Syros; and has financial or nonfinancial interests in Aprea, Jazz, and Moffit. M.G. served on advisory boards for GSK, Janssen, Karyopharm, Sanofi, and TG Therapeutics. N.G.D. receives institutional research funding from AbbVie, Amgen, Astellas, Bristol-Meyers Squibb, Daiichi-Sankyo, FATE Therapeutics, Genentech, Gilead Sciences Inc., Glycomimetics, Hanmi, ImmunoGen, Novimmune, Pfizer, Servier, Trillium, and Trovagene; and received consulting fees from AbbVie, Agios, Amgen, Arog, Astellas, Bristol-Meyers Squibb, Celgene, Daichii-Sankyo, Genentech, Gilead Sciences Inc., ImmunoGen, Jazz, Novartis, Pfizer, Servier, Shattuck Labs, Syndax, and Trillium. Y.W. has received support for the current study from Gilead Sciences Inc.; and is a current equity holder in McKesson. P.V. has received support for the current study from Gilead Sciences Inc. and Scimentum.

CRediT authorship contribution statement

Nishanthan Rajakumaraswamy: Conceptualization, Data curation, Formal analysis, Investigation, Writing – review & editing, Methodology, Project administration, Supervision. **Mitul Gandhi:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Andrew H. Wei:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **David A. Sallman:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Naval G. Daver:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Shuyuan Mo:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Shahed Iqbal:** Methodology, Conceptualization, Data curation, Formal analysis, Investigation, Writing – review & editing. **Roshan Karalliyadda:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Manli Chen:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Yunfei Wang:** Formal analysis, Writing – review & editing. **Paresh Vyas:** Conceptualization, Formal analysis, Methodology, Writing – review & editing.

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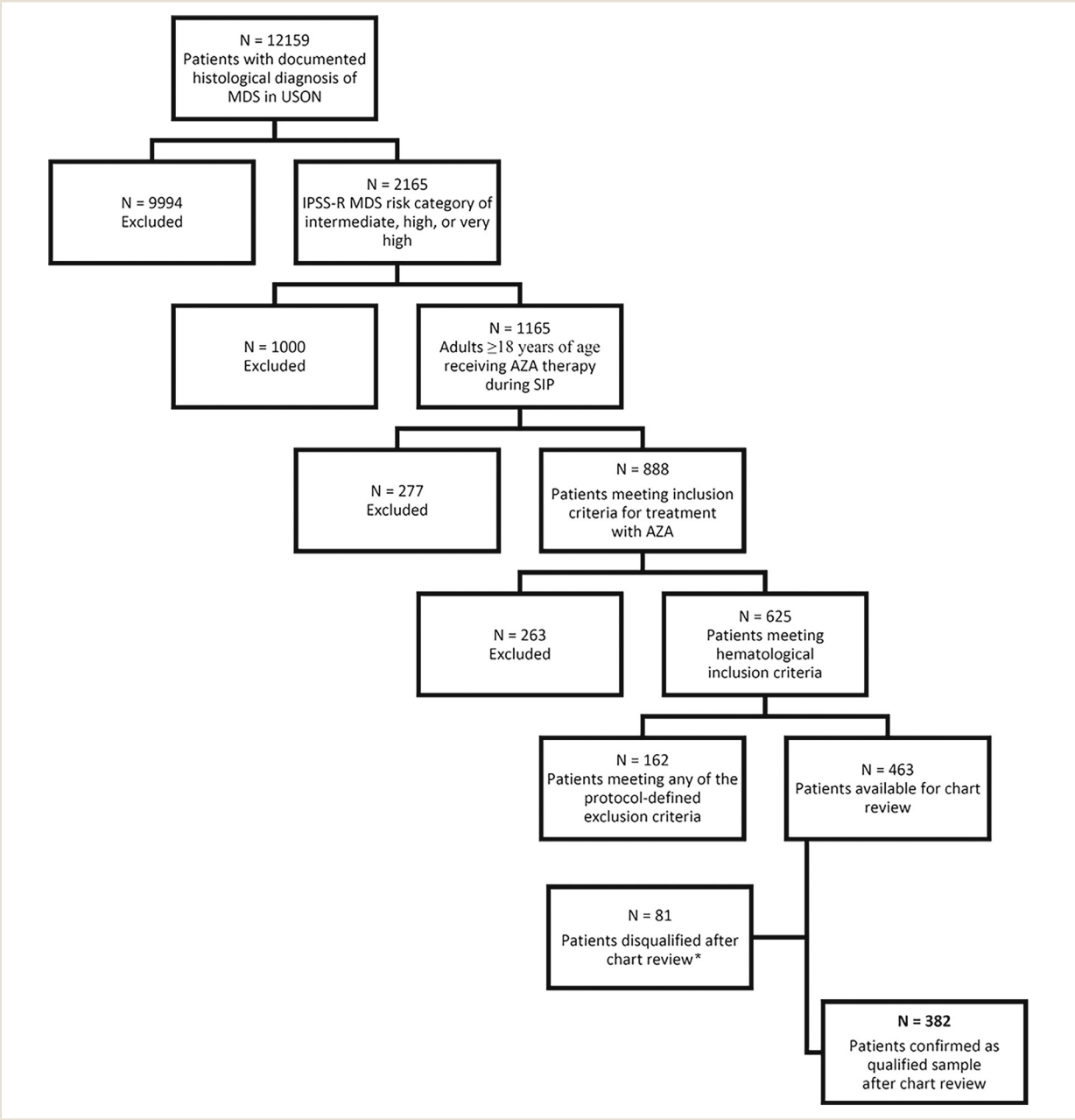
Supplementary materials

Supplemental Figure 1 Study attrition flowchart showing the patient selection and attrition process leading to the final set of patients analyzed.
*Certain eligibility criteria were either confirmed or only applied during chart review. Three exclusion criteria were only assessed during chart review: known inherited or acquired bleeding disorders; EHR documentation of clinical suspicion/radiological evidence of active central nervous system involvement by leukemia; and initiation of AZA treatment outside the approved label.
AZA = azacitidine; IPSS-R = Revised International Prognostic Scoring System; MDS = myelodysplastic syndrome; N = number of patients; USON = The United States Oncology Network.



Supplemental Table 1 End-of-Treatment Disposition

	All Patients (N = 382)
Continued AZA, n (%)	18 (4.7)
Discontinued AZA, n (%)	364 (95.3)
Reasons for AZA discontinuation, n (%)	
Progression	135 (35.3)
Adverse event	55 (14.4)
Completed planned treatment	41 (10.7)
Death	41 (10.7)
Hospice	36 (9.4)
Physician decision[a]	32 (8.4)
Lost to follow-up	26 (6.8)
Decline in performance status	25 (6.5)
Patient preference[a]	22 (5.8)
Other	20 (5.2)
Not reported	2 (0.5)

Abbreviations: AZA = azacitidine.
[a] If other categories did not apply.