Efficacy, safety and pharmacokinetics of subcutaneous azacitidine in Chinese patients with higher risk myelodysplastic syndromes: Results from a multicenter, single-arm, open-label phase 2 study

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Abstract

Background: Azacitidine safety and efficacy were established in studies of mainly Caucasian patients. Differences in drug metabolism enzymes between Caucasian and East Asian populations prevent extrapolation of drug effects between these groups. This phase 2 study evaluated azacitidine safety, efficacy and pharmacokinetics in patients with higher-risk myelodysplastic syndromes (HR-MDS) in mainland China.

Methods: Patients aged ≥18 years with HR-MDS were to receive subcutaneous azacitidine 75 mg/m²/day for 7 days per 28-day cycle, for ≥6 cycles. Pharmacokinetic blood samples were collected in cycle 1 predose on days 5–7, and postdose on day 7. Pharmacokinetic outcomes are descriptively compared with those of a historical North American cohort.

Results: Of 72 participants, 46 (64%) completed ≥6 cycles. Response rate was 96%, driven primarily by stable disease (94%); one patient achieved complete remission. Hematologic improvement was attained by 53% of patients. Azacitidine mean plasma concentration versus time profiles were similar in shape for Chinese (n = 12) and North American (n = 45) patients. Maximum plasma concentration (Cmax) was higher in Chinese patients; however, mean azacitidine exposure (1190 ng⋅h/mL) was similar to the North American cohort (1021 ng⋅h/mL). Most common grade 3–4 treatment-emergent adverse events (TEAEs) were thrombocytopenia (69%) and neutropenia (67%).

Conclusions: Azacitidine was safe and effective in Chinese patients with HR-MDS. Clinical outcomes were comparable to those for primarily Caucasian patients in the phase 3 AZA-001 study. Cmax differences between Chinese and North American patients were not associated with differences in TEAE frequency or severity. No initial azacitidine dose adjustment is required for Chinese patients with HR-MDS.

Keywords: azacitidine, Chinese, higher risk, myelodysplastic, pharmacokinetics, syndromes
1 | INTRODUCTION

Myelodysplastic syndromes (MDS) comprise a heterogeneous group of hematopoietic disorders characterized by bone marrow (BM) dysplasia, impaired cellular differentiation with resulting peripheral cytopenias and increased risk of transformation to acute myeloid leukemia (AML). MDS is more common in Western than Eastern countries; estimated prevalence is ≥12/100 000 persons in the United Kingdom and 1/100 000 persons in Japan.1 Differences in MDS incidence among countries may reflect ethnic and environmental differences and/or use of variable diagnostic criteria.

Azacitidine (Vidaza®; Celgene Corporation, Summit, NJ, USA) is a cytidine analog epigenetic modifier and hypomethylating agent approved for treatment of MDS in many countries. Among key pathogenic mechanisms implicated in MDS are histone modifications and DNA hypermethylation, leading to silencing of genes integral to normal cell-cycle regulation, cellular differentiation and apoptosis.2–5 Azacitidine is incorporated into DNA during active cell cycling,6–9 where it inhibits DNA methyltransferase activity, leading to reduced DNA methylation, and potentially, to reexpression of genes involved in healthy hematopoiesis.10,11

Most clinical trial experience with azacitidine is from studies conducted in Western countries with primarily Caucasian patients.12,13 The phase 3, international, randomized AZA-001 study, which showed azacitidine to be the first treatment to prolong overall survival (OS) in patients with higher-risk MDS (HR-MDS) compared with conventional care regimens (CCR), enrolled most patients from sites in the United States and European Union.13

The estimated prevalence of MDS in China is 1.5/100 000 persons.1 Compared with Western patients, Chinese patients tend to be younger; reported median ages at diagnosis in different Chinese MDS patient cohorts range from 49 to 62 years,14–16 compared with median ages ≥70 years17 for Western patients. Differences in population ages can influence drug metabolism and toxicity.18 Additionally, genetic polymorphisms in metabolic pathways and drug-metabolizing enzymes may vary between Eastern and Western populations.19 The primary metabolic pathway for azacitidine involves cytidine deaminase (CDA). The CDA gene can harbor single nucleotide polymorphisms (SNPs) that may directly affect the potential toxicity of azacitidine.20,21 Further, proportions of patients with specific MDS subtypes are different between Chinese and Western patient populations, as is prevalence of certain cytogenetic abnormalities, which both have implications for drug efficacy.1,14 The prevalence of WHO-defined refractory cytopenia with multilineage dysplasia (RCMD) in Chinese patients is as high as 60–70%, whereas ~30% of Western patients have RCMD.15,22 Similarly, Chinese patients are less likely to have -5/5q- or -7/7q- cytogenetic abnormalities than Western patients, but more likely to have trisomy 8 (+8).14,15,22,24

Reported here are results of a phase 2 study conducted in mainland China assessing the efficacy, safety and steady-state pharmacokinetics (PK) of subcutaneous (SC) azacitidine in patients with HR-MDS. Clinical results in Chinese patients are descriptively compared with results of the phase 3 AZA-001 trial, and PK results are descriptively compared with those in a North American cohort of patients with hematologic malignancies.

2 | METHODS

This multicenter, single-arm, open-label, phase 2 study (NCT01599325) was conducted at 11 investigational sites in China. The study was approved by each site’s institutional review board or independent ethics committee and was conducted in accordance with ethical principles outlined in the Declaration of Helsinki. Each patient or his/her authorized representative provided written or witnessed oral consent before enrollment. Authors had access to all study data. Analyses were performed by Celgene Corporation. The conduct of this study was generally consistent with that of the pivotal AZA-001 study, with some exceptions: the current study lacked comparator treatments and randomization, and study duration was shorter (12 months vs 24 months for AZA-001).13

2.1 | Patients

Eligible patients were aged ≥18 years and had refractory anemia with excess blasts (RAEB) or RAEB in transformation (RAEB-t) per French–American–British (FAB) classification.25 International Prognostic Scoring System (IPSS26)-defined Intermediate-2 or High risk MDS or chronic myelomonocytic leukemia (CMML; 10–29% BM blasts), and Eastern Cooperative Group performance status (ECOG PS) score ≤2. Patient eligibility was confirmed by central pathology review of BM aspirates, BM biopsies and/or peripheral blood smears collected at screening. IPSS score was calculated using centrally reviewed BM blast percentages, central laboratory-assessed number of cytopenias and local assessment of karyotype.

Exclusion criteria included previous treatment with azacitidine or decitabine, eligibility for BM or stem cell transplant, or prior transplantation or cytotoxic therapy for MDS. Patients could not have received erythropoietin or myeloid growth factors (granulocyte colony-stimulating factor [G-CSF] or granulocyte-macrophage colony-stimulating factor [GM-CSF]) within 21 days, or other investigational drugs within 30 days, before beginning treatment.

2.2 | Study design

Patients underwent screening within 28 days before the first azacitidine dose. All patients were to receive azacitidine 75 mg/m²/day SC for 7 days per 28-day treatment cycle for ≥6 cycles. Antiemetic therapy was to be administered ~30 min before azacitidine administration. Best supportive care (BSC), including antibiotics, G-CSF, GM-CSF and transfusions, was given as needed.

Site visits occurred weekly during the first two cycles, then every-other-week from cycle 3 onward. Assessments at each site visit included hematologic measures (hemoglobin [Hgb], absolute neutrophil counts [ANC], white blood cell [WBC] counts and red blood cell [RBC] counts), safety monitoring and evaluation of hematologic...
response. BM aspirates were collected at baseline and at cycle 6 day 15 and/or study discontinuation. Patients who achieved complete remission (CR), partial remission (PR), or hematologic improvement (HI) on cycle 6 day 15 continued to receive azacitidine on-study until relapse, disease progression, unacceptable toxicity or withdrawal of consent. For those who continued beyond cycle 6, BM aspirates were collected every 16 weeks thereafter. Those who did not achieve a response or HI by cycle 6 day 15 were discontinued.

Patients were followed from time of informed consent until 28 days following the last dose of azacitidine for collection of adverse events (AEs), concomitant medications and transfusion status. All patients who received ≥1 azacitidine dose were followed for survival and progression to AML unless the patient withdrew consent, died or was lost to follow-up, or the study was terminated.

The study concluded when all patients had been followed for 12 months from enrollment or had died, whichever came first. Upon study closure, remaining patients were given the opportunity to enter a study extension and continue to receive azacitidine.

2.3 | Efficacy

The primary end point was overall response rate (ORR), which included CR + PR + stable disease (SD; failure to achieve CR or PR, but with no evidence of disease progression for at least 2 months) according to IWG 2000 MDS criteria. ORR was reported by the investigators and also evaluated programmatically by the study sponsor, based on centrally reviewed BM and central laboratory reports. Response was assessed for each patient at cycle 6 day 15, or at the time of study discontinuation, whichever came first. HI was evaluated by the sponsor. The prospective choice to use IWG 2000 criteria for the primary end point was to emulate response assessments in the AZA-001 study, to facilitate descriptive comparisons of clinical outcomes between Chinese and Western patients with HR-MDS. Supportive assessments were performed by the sponsor using 2006 IWG response criteria for MDS.

OS was a secondary end point, defined as time from first azacitidine dose to death. Patients who were lost to follow-up or withdrew consent were censored at time of last contact. Other secondary end points included rates of infections requiring intravenous (IV) antibiotics, platelet and RBC transfusion independence (TI) in patients who were transfusion-dependent at baseline, number of platelet and RBC transfusions required on-study and changes in peripheral blood counts from baseline. Baseline transfusion-dependence was defined as having received ≥1 transfused unit of RBCs or platelets within 56 days before the first azacitidine dose. TI was defined as receiving no transfusions during any consecutive 56-day period while receiving azacitidine.

2.4 | Safety

The safety population included patients who received ≥1 azacitidine dose and had ≥1 postbaseline safety assessment. Safety assessments and treatment-emergent AE (TEAE) reporting were performed at scheduled site visits from date of informed consent through 28 days following the last azacitidine dose, inclusive. Any AE that occurred after this time frame assessed by the investigator as related to study drug was also considered a TEAE. TEAEs were coded according to MedDRA v15.1 and graded for severity using NCI-CTCAE v4.0.

2.5 | Statistical analyses

As this was a single-arm study, no formal sample size or power calculations were performed. Based on the HI rate in the pivotal AZA-001 study (49%13), a sample size of 70 patients was selected for the current trial as sufficient to compare efficacy between the two studies. This sample size would provide a two-sided 90% confidence interval for the estimated proportion of HI responders, assuming an HI response rate of 49% and a margin of error of ±10%. Efficacy analyses were performed for the intention-to-treat (ITT) population.

2.6 | Pharmacokinetics

Azacitidine PK parameters were assessed during cycle 1 in a subgroup of patients. Blood samples were collected predose on cycle 1, days 5, 6 and 7; and postdose on day 7 at 0.25, 0.5, 1, 2, 3, 4, 6 and 8 hours (h). Azacitidine plasma concentrations were determined using a validated proprietary high-performance liquid chromatography/tandem mass spectrometric method. PK parameters were calculated from plasma concentration-time profiles using noncompartmental methods. The parameters assessed were: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve from time 0 to infinity (AUCinf), terminal phase rate constant (λz), terminal half-life (t1/2), apparent total clearance (CL/F) and apparent volume of distribution (Vp/F). PK parameters are summarized descriptively as mean ±SD and median (range), except for Tmax (median and range only) and percent coefficient of variation (% CV). PK assessments of plasma concentrations were performed by Covance Bioanalytical Services (Indianapolis, IN, USA). Because no PK samples were collected in the phase 3 AZA-001 study, azacitidine PK parameters on cycle 1 day 7 in these Chinese patients are descriptively compared with those from a North American cohort of primarily Caucasian patients with MDS, CMML or AML who received a single cycle of SC azacitidine in a phase 1 study (CL005). Azacitidine dose and dosing schedule were identical in the two studies. In CL005, blood samples were also collected predose on cycle 1 day 7, and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6 and 8 h postdose.

3 | RESULTS

In all, 72 patients in mainland China comprised the ITT population (Figure S1). The first patient enrolled in August 2012, and the last patient completed the study in January 2015. Patient characteristics were fairly comparable to those of Western patients in AZA-001 (Table 1). All patients had IPSS-defined HR-MDS (Intermediate-2, 65%;
**TABLE 1** Baseline demographics and disease characteristics of Chinese patients and azacitidine-treated patients in AZA-001

|                         | Chinese HR-MDS Patients (N = 72) | AZA-001 Cohort\(^{13}\) (N = 179) |
|-------------------------|----------------------------------|----------------------------------|
| Age (Years), median (min, max) | 58 (19, 73)                     | 69 (42, 83)                     |
| Gender, n (%)           |                                  |                                 |
| Male                    | 38 (53)                          | 132 (74)                        |
| Female                  | 34 (47)                          | 47 (26)                         |
| FAB classification\(^{a}\), n (%) |                                |                                 |
| MDS RAEB                | 56 (78)                          | 104 (58)                        |
| MDS RAEB-t              | 14 (19)                          | 61 (34)                         |
| CMML                    | 2 (3)                            | 6 (3)                           |
| AML                     | 0                                | 1 (1)                           |
| WHO classification\(^{a}\), n (%) |                                |                                 |
| MDS RAEB-1              | 11 (15)                          | 14 (8)                          |
| MDS RAEB-2              | 45 (63)                          | 98 (55)                         |
| AML                     | 13 (18)                          | 55 (31)                         |
| CMML                    | 1 (1)                            | 11 (6)                          |
| MDS/MPD                 | 2 (3)                            | 0                               |
| Indeterminate           | 0                                | 1 (1)                           |
| IPSS risk classification, n (%) |                                |                                 |
| Intermediate-1          | 0                                | 5 (3)                           |
| Intermediate-2          | 47 (65)                          | 76 (43)                         |
| High                    | 25 (35)                          | 82 (46)                         |
| Karyotype risk, n (%)   |                                  |                                 |
| Good                    | 36 (50)                          | 83 (46)                         |
| Intermediate            | 17 (24)                          | 37 (21)                         |
| Poor                    | 18 (25)                          | 50 (28)                         |
| Missing                 | 1 (1)                            | 9 (5)                           |
| ECOG performance status, n (%) |                                |                                 |
| 0                       | 12 (17)                          | 78 (44)                         |
| 1                       | 47 (65)                          | 86 (48)                         |
| 2                       | 13 (18)                          | 13 (7)                          |
| Missing                 | 0                                | 2 (1)                           |
| Hematology, median (min, max) |                                |                                 |
| ANC (10^9/L)            | 0.8 (0, 18)                      | 0.9 (0, 38)                     |
| Platelets (10^9/L)      | 49 (8, 223)                      | 61 (7, 546)                     |
| WBC (10^9/L)            | 2.5 (0.3, 44)                    | 2.6 (0.6, 50)                   |
| Hemoglobin (g/L)        | 74 (41, 124)                     | 96 (65, 142)                    |

\(^{a}\)Central assessment.

AML, acute myeloid leukemia; ANC, absolute neutrophil count; CMML, chronic myelomonocytic leukemia; ECOG, Eastern Cooperative Oncology Group; FAB, French–American–British; HR-MDS, higher risk MDS; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; MPD, myeloproliferative disorders; RAEB, refractory anemia with excess blasts; RAEB-t, RAEB in transition; WBC, white blood cell count; WHO, World Health Organization

High, 35%). Per FAB classification the majority of patients (78%) had RAEB, 19% of patients had RAEB-t and two patients had CMML. Per WHO criteria, most patients (63%) had RAEB-2 MDS. Sixteen patients (22%) had received prior MDS therapy, including six patients who had received prior thalidomide treatment.

The median number of treatment cycles was eight (range 1–27) and median cycle length was 38 days (12–65). In total, 46 patients (64%) remained on-study for at least six treatment cycles and 39 patients received >6 cycles during the study. The majority of patients (61%) received azacitidine 75 mg/m²/day with no dose modifications. After study closure, 15 patients chose to continue to receive azacitidine in the extension phase. The remaining 57 patients discontinued, most commonly due to withdrawal of consent (n = 20; Figure S1).
### TABLE 2  Response with SC azacitidine in Chinese patients and in patients from AZA-001

|                      | Chinese HR-MDS Patients\(^a\) \((N = 72)\) | AZA-001 Cohort\(^b\) \((N = 179)\) |
|----------------------|---------------------------------------------|-----------------------------------|
| Overall response rate (CR + PR + SD) | 69/72 (96)                                  | 126/179 (70)                      |
| Complete remission   | 1/72 (1)                                    | 30/179 (17)                       |
| Partial remission    | 0/72 (0)                                    | 21/179 (12)                       |
| Stable disease       | 68/72 (94)                                  | 75/179 (42)                       |
| Hematologic improvement| 38/72 (53)                                | 87/177 (49)                      |
| HI-Erythroid         | 24/67 (36)                                  | 62/157 (40)                      |
| HI-Platelet          | 22/58 (38)                                  | 46/141 (33)                      |
| HI-Neutrophil        | 12/55 (22)                                  | 25/131 (19)                      |
| Transfusion independence |                                         |                                   |
| RBC TI               | 21/44 (48)                                  | 50/111 (45)                      |
| Platelet TI          | 16/25 (64)                                  | NR                               |
| Disease progression  | 12/72 (17)                                  | NR                               |

Note. IWG 2000 criteria for MDS.

\(^a\)Programatically adjudicated by sponsor; SD was defined as no attainment of CR or PR, or evidence of disease progression sustained for 2 months.

\(^b\)n patients who had a response/N patients eligible for that response.

CR, complete remission; HI, hematologic improvement; PR, partial remission; SD, stable disease; RBC, red blood cell; TI, transfusion independence.

### 3.1 Efficacy

The sponsor-determined ORR (CR + PR + SD) per IWG 2000 criteria was 96% (69/72; Table 2). More than one-half of all patients (53%) achieved HI in one or more cell lineages. When limited to outcomes showing improvement in hematological indices (i.e. CR + PR + HI), response rate was 53%. In supporting analyses using IWG 2006 criteria, ORR was identical to that using IWG 2000 criteria (96%; 69/72), but a notably higher number of patients achieved a CR (n = 7, compared with 1 CR per IWG 2000 criteria; Table S1). No patient achieved a PR and 62 patients (86%) maintained SD on-study per IWG 2006 criteria. Thirty-one patients (43%) achieved HI; this rate is consistent with the HI rate for azacitidine-treated mainly Caucasian patients in the AZA-001 trial (49%; Table 2). Investigator-reported ORR was 71%; the difference between sponsor- and investigator-assessed ORR reflects differences in SD rates, which were 94% and 58%, respectively. Investigators assessed higher rates of CR (7% vs 1% per sponsor assessment) and PR (6% vs 0), and lower rates of disease progression (7% vs 17%).

Median OS was 22.0 months (95% CI 15.1–NR; Figure 1). Rates of 1-year and 2-year survival were 71% and 49%, respectively. Overall, 34 patients (47%) died and 38 patients were censored at study closure (n = 28), had withdrawn consent for further survival follow-up (n = 8) or were lost to follow-up (n = 2). Survival estimates for patients were similar regardless of patients' IPSS risk status: median OS was 22.0 months (95% CI 15.6–NR) for patients with Intermediate-2 risk MDS (n = 47) and 24.0 months (6.9–NR) for patients with High risk MDS (n = 25). Likewise, survival was not apparently affected by azacitidine dose modifications: median OS for patients who had ≥1 dose modification was 22.0 months (95% CI 13.8–NR), and was 24.0 months (12.9–NR) for patients with no dose modifications.

Almost one-half of all patients who were RBC transfusion-dependent at baseline achieved RBC TI, and approximately one-third of platelet transfusion-dependent patients achieved platelet TI (Table 2). Of patients who were RBC transfusion-independent at baseline, 19 of 28 (68%) retained TI on-study, and 35 of 47 patients (75%) who were
platelet transfusion-independent at baseline retained TI. The mean (±SD) number of RBC transfusions at baseline was 1.1 (±1.8) and overall mean change from baseline was an increase of 0.5 (±2.1) transfusions. The mean number of platelet transfusions at baseline was 0.8 (±2.4) and overall mean change from baseline was an increase of 0.8 (±3.3) transfusions.

Generally, peripheral blood Hgb and platelet measures remained stable or improved on-study (Figure S2). Increases in Hgb were observed at almost all time points: mean (±SD) baseline Hgb was 78 (±62) g/L and overall postbaseline average was 82 (±20) g/L, representing an increase of 2.2 g/L. Platelet counts were generally low at baseline (mean 62 [±47] × 10^9/L) but remained stable on-study from baseline until cycle 21. A single patient remained on-study in cycles 22–27, during which time platelet count dropped to grade 3 thrombocytopenia (39.5 × 10^9/L; Figure S2). Despite stable to moderately increasing mean platelet counts for all patients during the study, mean overall change from baseline platelet count was -2.0 ± 48 × 10^9/L. Mean ANC and WBC changed little over the course of the study. Mean baseline ANC was 1.7 × 10^9/L (±2.7) with mean change from baseline of -0.4 × 10^9/L (±2.2), and mean baseline WBC was 4.4 × 10^9/L (±6) with mean change of -0.8 × 10^9/L (±6.9).

The incidence of infections requiring IV anti-infective therapy remained low throughout the study, with no meaningful increase during azacitidine treatment. At baseline, mean number of infections requiring IV anti-infective therapies was 0 (±0.2) and overall change from baseline on-study was 0.5 (±1.5) events.

### 3.2 Safety

All patients experienced at least 1 TEAE while on-study, and 70 patients (97%) experienced a grade 3–4 TEAE. Azacitidine dose adjustments due to TEAEs included dose delays (68% of patients), dose reductions (26%) and drug discontinuations (19%). The most frequently reported TEAEs (any grade) were hematological: thrombocytopenia (72%), leukopenia (67%), neutropenia (67%) and anemia (53%); these were also the most frequent grade 3–4 TEAEs (Table 3). Non-hematologic TEAEs occurring in >20% of patients were upper respiratory tract infection (38%), constipation (31%), pyrexia (31%), pneumonia (29%), nausea (26%), gingivitis (22%) and diarrhea (21%) and vomiting (21%). Overall TEAE incidence was highest during the first 2 azacitidine cycles and decreased as treatment continued (Table S2). TEAEs led to study discontinuation for 14 patients (19%); those that occurred in >1 patient were cardiac failure and pneumonia (n = 2 each).

Serious TEAEs considered to be related to study drug were reported for 28 patients (39%). Those occurring in two or more patients were: pneumonia (n = 9); febrile neutropenia (n = 5); upper respiratory tract infection, agranulocytosis, thrombocytopenia and mouth hemorrhage (n = 3 each); and BM failure and cardiac failure (n = 2 each). TEAEs leading to death over the entire treatment and follow-up periods (n = 11, 15.3%) included pneumonia and cardiac failure (n = 2 each), and gastrointestinal hemorrhage, cerebral hemorrhage, MDS, BM failure, fungal sepsis, hemorrhagic shock and bronchopneumonia (n = 1 each).

Only four deaths occurred during the safety evaluation period; that is, between the time of first azacitidine dose and 28 days after the last dose. These deaths were due to disease progression, cerebral hemorrhage, hemorrhagic shock and acute cardiac failure. Of them, cerebral hemorrhage occurred within 30 days of study drug initiation, and cardiac failure was the only event suspected to be related to study drug.

### 3.3 Pharmacokinetics

The PK population comprised 12 patients (17%) with evaluable PK samples from cycle 1 day 7. Patients in the Chinese PK cohort tended to be younger than patients in the CL005 North American PK comparator cohort (N = 45; Table S3). Thirty patients (67%) from the CL005 North American cohort had MDS (including 13 patients [43%] with HR-MDS), 11 (24%) had AML and 4 (9%) had CMML.

Predose azacitidine plasma concentrations on cycle 1, days 5, 6 and 7 were below the limit of detection for both cohorts, indicating no azacitidine accumulation following multiple-dose administration. Azacitidine mean plasma concentrations versus time profiles were

#### Table 3

| Event                        | Chinese HR-MDS Patients^a  | AZA-001 Cohort^b,12 |
|------------------------------|----------------------------|---------------------|
| (N = 72)                     |                            | (N = 175^a)         |
| Patients with ≥1 grade 3–4 TEAE | 70 (97)                   | NR                  |
| Thrombocytopenia             | 50 (69)                    | 102 (85)            |
| Neutropenia                  | 48 (67)                    | 107 (91)            |
| Leukopenia                   | 44 (61)                    | NR                  |
| Anemia                       | 35 (49)                    | 24 (57)             |
| Pneumonia                    | 14 (19)                    | NR                  |
| Upper respiratory tract infection | 11 (15)                 | NR                  |

Note. TEAEs coded by MedDRA version 15.1.

^a Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

^b CTCAE v2.0.

^c Four patients did not receive study drug and were excluded from safety reporting. Multiple reports of the same preferred term for a patient were counted only once.

HR-MDS, higher risk myelodysplastic syndromes; NR, not reported; TEAE, treatment-emergent adverse event.
Chinese patients with HR-MDS treated with azacitidine had an ORR of 96%, driven in large part by the high proportion of patients who maintained SD during treatment. Azacitidine has been shown to prolong OS in Western patients with HR-MDS who maintained SD as a best response to treatment. Median OS for these Chinese patients, 22.0 months, is promising. Untreated Western patients with IPSS Intermediate-2 or high-risk MDS have an anticipated median OS of only 14 or 5 months, respectively. While no direct comparison can be made, median OS in the current study was greater than that for patients treated with CCR (intensive chemotherapy, low-dose cytarabine or BSC only) in the AZA-001 trial (15.0 months).

As the current trial was conducted only within China and included far fewer patients than the AZA-001 trial, comparisons should be interpreted with caution. Consistent with other reports, these Chinese patients tended to be younger than patients in AZA-001 (median age 58 vs 69 years, respectively), and a higher proportion were male (74% vs 53%). However, in AZA-001, patients received a similar median number of treatment cycles (9 [range 1–39]) and approximately the same proportion of patients in AZA-001 completed ≥6 azacitidine treatment cycles (68%). Median OS of these Chinese patients was comparable to that of azacitidine-treated patients in AZA-001 (24.5 months) as were 1-year and 2-year survival rates (71% and 49%, respectively, compared with 68% and 51% in AZA-001). The HI rate with azacitidine treatment in the current study was also similar to that in AZA-001 (53% and 49%) as were the proportions of patients attaining RBC TI (48% and 45%; Table 3).

Peripheral blood counts generally remained stable during azacitidine treatment and there was no meaningful increase in infections requiring IV antibiotic treatment.

The safety profile of SC azacitidine in these Chinese patients was also largely comparable to that reported for Western patients in AZA-001. In both studies, most patients experienced at least 1 grade 3–4 TEAE, which were most often hematological, and TEAE incidences were highest during initial cycles and decreased with continued azacitidine treatment. While \( C_{max} \) in Chinese patients was approximately twice as high as that observed in mainly Caucasian patients from North America, no unexpected TEAEs occurred and grade 3–4 cytopenias were reported less frequently in the Chinese cohort. Besides \( C_{max} \), no major differences in azacitidine PK parameters were observed between Chinese and North American cohorts. These data suggest no initial azacitidine dose adjustment is necessary to treat HR-MDS patients in China.

Azacitidine has been evaluated in other Asian subpopulations of patients with MDS, including a prospective phase 1/2 study in Japan and two retrospective studies in South Korea. In these studies, hematologic responses, HI rates and azacitidine tolerability were also similar to what has been reported for Western patients. Polymorphisms in PK- and pharmacodynamic (PD)-related alleles can vary even among ethnic Chinese, Korean, and Japanese patients; therefore, it was important to evaluate azacitidine in this ethnic Chinese population.

Azacitidine was the first MDS treatment shown to alter the natural history of MDS. These data support the clinical benefit of azacitidine in Chinese patients with HR-MDS.

4 | DISCUSSION

Chinese patients with HR-MDS treated with azacitidine had an ORR of 96%, driven in large part by the high proportion of patients who maintained SD during treatment. Azacitidine has been shown to prolong OS in Western patients with HR-MDS who maintained SD as a best response to treatment. Median OS for these Chinese patients, 22.0 months, is promising. Untreated Western patients with IPSS Intermediate-2 or high-risk MDS have an anticipated median OS of only 14 or 5 months, respectively. While no direct comparison can be made, median OS in the current study was greater than that for patients treated with CCR (intensive chemotherapy, low-dose cytarabine or BSC only) in the AZA-001 trial (15.0 months).

As the current trial was conducted only within China and included far fewer patients than the AZA-001 trial, comparisons should be interpreted with caution. Consistent with other reports, these Chinese patients tended to be younger than patients in AZA-001 (median age 58 vs 69 years, respectively), and a higher proportion were male (74% vs 53%). However, in AZA-001, patients received a similar median number of treatment cycles (9 [range 1–39]) and approximately the same proportion of patients in AZA-001 completed ≥6 azacitidine treatment cycles (68%). Median OS of these Chinese patients was comparable to that of azacitidine-treated patients in AZA-001 (24.5 months) as were 1-year and 2-year survival rates (71% and 49%, respectively, compared with 68% and 51% in AZA-001). The HI rate with azacitidine treatment in the current study was also similar to that in AZA-001 (53% and 49%) as were the proportions of patients attaining RBC TI (48% and 45%; Table 3).

Peripheral blood counts generally remained stable during azacitidine treatment and there was no meaningful increase in infections requiring IV antibiotic treatment.

The safety profile of SC azacitidine in these Chinese patients was also largely comparable to that reported for Western patients in AZA-001. In both studies, most patients experienced at least 1 grade 3–4 TEAE, which were most often hematological, and TEAE incidences were highest during initial cycles and decreased with continued azacitidine treatment. While \( C_{max} \) in Chinese patients was approximately twice as high as that observed in mainly Caucasian patients from North America, no unexpected TEAEs occurred and grade 3–4 cytopenias were reported less frequently in the Chinese cohort. Besides \( C_{max} \), no major differences in azacitidine PK parameters were observed between Chinese and North American cohorts. These data suggest no initial azacitidine dose adjustment is necessary to treat HR-MDS patients in China.

Azacitidine has been evaluated in other Asian subpopulations of patients with MDS, including a prospective phase 1/2 study in Japan and two retrospective studies in South Korea. In these studies, hematologic responses, HI rates and azacitidine tolerability were also similar to what has been reported for Western patients. Polymorphisms in PK- and pharmacodynamic (PD)-related alleles can vary even among ethnic Chinese, Korean, and Japanese patients; therefore, it was important to evaluate azacitidine in this ethnic Chinese population.

Azacitidine was the first MDS treatment shown to alter the natural history of MDS. These data support the clinical benefit of azacitidine in Chinese patients with HR-MDS.

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CONFLICT OF INTEREST
All authors declare that they have no conflict of interest.

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SUPPORTING INFORMATION

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