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Ivosidenib in Chinese patients with relapsed or refractory isocitrate dehydrogenase 1 mutated acute myeloid leukemia: a registry study

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Abstract

Ivosidenib, an isocitrate dehydrogenase 1 (*IDH1*) inhibitor, has demonstrated clinical benefits in a pivotal study (AG120-C-001) in patients with *IDH1*-mutated (m*IDH1*) acute myeloid leukemia (AML). A registry study (CS3010-101: NCT04176393) was conducted to assess the pharmacokinetic (PK) characteristics, safety, and efficacy of ivosidenib in Chinese patients with relapsed or refractory (R/R) m*IDH1* AML. Patients received ivosidenib 500 mg once daily for 28-day cycles until disease progression. Ten subjects underwent intensive PK/progressive disease (PD) assessments. All subjects had the clinical response assessed at screening, every 28 days through month 12, and then every 56 days. Between November 12, 2019, and April 2, 2021, 30 patients were enrolled; 26 (86.7%) had de novo AML and 18 (60.0%) were transfusion-dependent at baseline. Following single and repeated doses of ivosidenib, median time to maximum plasma concentration (T_{max}) was 4.0 and 2.0 hours, respectively. The inter-individual variability of pharmacokinetic exposure was moderate to high (coefficient of variation [CV], 25%–53%). No obvious accumulation was observed after repeated doses at cycle 2 day 1. Regarding the clinical response, the CR + CRh rate was 36.7% (95% confidence interval [CI]: 19.9%–56.1%), the median duration of CR + CRh was 19.7 months (95% CI: 2.9 months–not reached [NR]), and median duration of response (DoR) was 14.3 months (95% CI: 6.4 months–NR). Consistent clinical benefits and safety of ivosidenib were consistently observed at the final data cutoff with median follow-up time 26.0 months, as compared with primary data cutoff, and the data from Chinese R/R m*IDH1* AML patients were also consistent with results from pivotal study.

Key Words: China; *IDH1* mutation; Ivosidenib; Relapsed or refractory acute myeloid leukemia

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M.S. and Q.Y. contributed equally to this work.

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IMPLICATIONS FOR PRACTICE

This phase I trial assessed the pharmacokinetic characteristics, safety, and efficacy of ivosidenib in Chinese patients with relapsed or refractory (R/R) mutated isocitrate dehydrogenase 1 (m*IDH1*) acute myeloid leukemia (AML). A consistent benefit trend was observed with the final data cutoff compared with the primary data cutoff. The data presented indicate the potential of ivosidenib in the difficult-to-treat population of patients with R/R AML in China, for whom there are limited therapeutic options. Given its manageable safety profile, targeting m*IDH1* with ivosidenib could provide a single-agent therapy with sustained efficacy, particularly in older adult or frail patients.

1. INTRODUCTION

Acute myeloid leukemia (AML) is the most common type of acute leukemia affecting adults, accounting for approximately 80% of all cases. In China, there are approximately 75,300 new cases of leukemia annually, approximately 59% of which are AML.[1,2] AML is a heterogeneous hematological malignancy characterized by rapid disease progression and poor prognosis, with up to 57% of patients developing relapsed or refractory (R/R) disease or dying within 12 months of diagnosis.[3,4] R/R AML is associated with poor survival, with a median overall survival (OS) of approximately 5 months.[4,5]

Until recently, the standard of care for patients with AML who were medically fit was traditional intensive induction chemotherapy or less intensive chemotherapy for unfit patients, followed by, if applicable, allogeneic hematopoietic stem cell transplantation (HSCT) or consolidation chemotherapy.[4,6,7] More than 50% of the patients who initially achieve complete remission (CR) after intensive chemotherapy may experience relapse. Long-term survival is only achievable among younger patients with good prognostic indicators, as intensive chemotherapy is only appropriate for patients with a lower comorbidity burden and better performance status.[8–13] The most recent treatment options for patients with R/R AML include intensive salvage reinduction therapy for fit patients, less intensive regimens for older/unfit patients (such as venetoclax-based regimens and targeted therapy for patients with targetable mutations), and the best supportive care (hydroxyurea, transfusions). Unfortunately, the guideline-recommended treatments for R/R AML remain limited.[3,4,6,7,14] Despite the recent availability of novel therapies,[13] AML remains a serious disease with poor prognosis. Therefore, there remains an unmet need for more effective and less toxic novel treatments to improve the outcomes of patients with AML, especially R/R AML, in China.

Mutations in the gene encoding isocitrate dehydrogenase 1 (*IDH1*) occur in 2% to 14% of patients with AML globally[8,15,16] and in 2% to 10% of patients with AML in China.[17,18] One of the most common in AML is mutation of the arginine residue at codon 132 at the active site of the enzyme.[19] *IDH1* catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate in the tricarboxylic acid cycle, which plays a crucial role in cellular energy metabolism. Mutated *IDH1* (m*IDH1*) is a neomorphic enzyme that catalyzes the reduction of α-ketoglutarate to the oncometabolite D-2-hydroxyglutarate (2-HG), which is a competitive inhibitor of α-ketoglutarate–dependent enzymes. This reaction ultimately results in epigenetic alterations, impaired hematopoietic differentiation, and potential leukemogenic effects.[15,19–21] Clinically, AML with m*IDH1* is often associated with poor prognosis.[15,16] In the largest and most recently published meta-analysis, which included 12,747 AML cases reported in 33 studies across Europe, Asia, Australia, and the United States, the expression of m*IDH1* conferred worse OS (P = .0047) and event-free survival (EFS; P = .0110), including in patients with normal cytogenetics (OS, P = .0388; EFS, P = .0002).[16] In addition, treatment outcomes were poor in patients with m*IDH1* AML.

Ivosidenib (formerly AG-120) is a first-in-class oral small molecule inhibitor of mutant *IDH1*. Ivosidenib monotherapy was approved by the United States Food and Drug Administration in 2019 for the treatment of adult patients with a susceptible *IDH1* mutation with R/R AML[22] based on the findings of the pivotal phase 1 study AG120-C-001 (NCT02074839).[15,23–25]

CS3010-101 (NCT04176393) is a registration bridging study conducted to evaluate the pharmacokinetic and pharmacodynamic characteristics, safety, and clinical efficacy of ivosidenib in the treatment of patients with R/R m*IDH1* AML in China.[26] The primary data cutoff date of this study was May 20, 2021, and a long-term follow-up was conducted for the patients enrolled in this study, with the final data cutoff date of November 20, 2022. The results for both cutoff dates are presented in this article.

2. MATERIALS AND METHODS

2.1. Patients

Patients aged ≥18 years with R/R AML and a confirmed *IDH1* mutation for whom there was no potentially curative therapy were enrolled at 12 sites in China. The m*IDH1* status (ie, R132C, R132H, R132G, R132S, or R132L substitutions) was confirmed at screening in all patients. Bone marrow aspirate samples were analyzed centrally using polymerase chain reaction. The study eligibility criteria are provided in the Supplementary File, http://links.lww.com/BS/A100.

This study was conducted in accordance with the ethical principles founded in the Declaration of Helsinki. Approval for this study was obtained from Independent Ethics Committees at all 18 sites, and the ethical approval number for leading site was XY2019009-EC-1. Written informed consent to participate in this trial was provided by all patients before screening and enrollment.

2.2. Study design

Eligible patients received oral ivosidenib 500 mg once daily in continuous 28-day cycles. Ten patients were scheduled to receive an additional single dose of ivosidenib 500 mg to allow intensive pharmacokinetic and pharmacodynamic assessments of plasma ivosidenib and 2-HG concentrations over the subsequent 72 hours. Repeated dosing with ivosidenib was continued until disease progression, unacceptable toxicity, HSCT, death, withdrawal of consent, or study termination, whichever occurred first.

After treatment discontinuation, the patients underwent end-of-treatment assessments and safety and survival follow-ups. Patients who achieved an adequate response to ivosidenib and subsequently underwent HSCT were followed-up for disease evaluation and notification of any antineoplastic therapy received until disease relapse or death.

2.3. Study objectives

The primary objective of this study was to characterize the pharmacokinetic profile of ivosidenib in Chinese patients with R/R m*IDH1* AML. The pharmacokinetic parameters of ivosidenib included the observed maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal half-life ($t_{½}$), and area under the plasma concentration vs time curve (AUC), etc. The secondary objectives were to assess the safety and clinical efficacy of ivosidenib, and to explore the pharmacokinetic/pharmacodynamic relationship between ivosidenib and 2-HG in Chinese patients with R/R m*IDH1* AML

where applicable. The primary efficacy endpoint was CR+ complete remission with partial hematological recovery (CRh) rate. The secondary efficacy endpoints included the CR rate (CRR), objective response rate (ORR), duration of CR + CRh, duration of CR, duration of response (DOR), time to CR + CRh, time to response (TTR), EFS, and OS. The definitions of all endpoints are provided in Table S1, http://links.lww.com/BS/A100.

2.4. Assessments

Blood samples for pharmacokinetic and pharmacodynamic analyses were collected from all patients (schedules are provided in Figure S1, http://links.lww.com/BS/A101). Safety was assessed from enrollment to 28 days after the last dose of ivosidenib. Adverse events of special interest (AESIs) were defined as grade ≥3 prolongation of the QT interval on electrocardiograms (ECGs), grade ≥3 leukocytosis, and grade ≥2 IDH differentiation syndrome. Disease response was determined based on investigator assessment according to the 2003 modified International Working Group response criteria for AML (Table S2, http://links.lww.com/BS/A100).[27] CRh was determined by the sponsor (Table S1, http://links.lww.com/BS/A100).

2.5. Statistical analyses

The methodology for calculating the sample size is described in the Supporting Information and Table S3, http://links.lww.com/BS/A100. The pharmacokinetic parameters for single and repeated doses of ivosidenib were calculated from the plasma concentration–time data using a standard non-compartmental method. The safety data were summarized descriptively. The efficacy endpoints of the CR + CRh rate, CRR, and ORR were summarized descriptively, together with the 2-sided, exact binomial, 95% confidence interval (CI; Clopper-Pearson method[28]). The time to CR + CRh and TTR were summarized descriptively. Time-to-event endpoints were estimated using the Kaplan–Meier method. Red blood cell and platelet transfusion independence were evaluated by comparing the requirements for red blood cell and platelet transfusions pre- and post-baseline. Additional supportive analyses were conducted to examine transfusion independence according to the best overall response category adjusted for person-time. Any-grade and grade ≥3 infections and infestations, hemorrhage events, and febrile neutropenia were summarized by best overall response category adjusted by person-time. Where applicable, we explored the pharmacokinetic and pharmacodynamic relationship between ivosidenib and 2-HG.

3. RESULTS

3.1. Patient disposition

Between November 12, 2019, and April 2, 2021, 74 patients were screened, and 30 were enrolled and treated. The efficacy and safety analysis set (defined as all patients who received at least 1 dose of ivosidenib) included 30 patients. The pharmacokinetic analysis set (defined as all patients with at least 1 valid pharmacokinetic parameter) for single-dose intensive pharmacokinetic analyses comprised 10 patients; among whom, blood samples for one patient were collected only until the predose on C1D15 because the patient withdrew from treatment (ie, intensive sampling was not performed in the repeated-dosing phase). Therefore, the pharmacokinetic analysis set for the repeated-dose phase comprised nine patients. The pharmacodynamic analysis set (defined as all patients with at least 1 measurable 2-HG concentration after dosing) included 30 enrolled patients who received repeated ivosidenib doses (patient numbers varied at each measurement time point according to the availability of 2-HG data).

At the final data cutoff (November 20, 2022), 4 (13.3%) patients remained on treatment and 26 (86.7%) patients discontinued ivosidenib treatment, mostly due to disease progression (n = 9, 30.0%) or death (n = 5, 16.7%) (Figure S2, http://links.lww.com/BS/A102). Twenty-three patients (76.7%) discontinued the study. The main reasons for discontinuation were death (n = 21, 70.0%), lost to follow-up (n = 1, 3.3%), and withdrawal (n = 1, 3.3%) (Table S4, http://links.lww.com/BS/A100).

3.2. Patient demographics and baseline characteristics

The enrolled patients had a median age of 63.0 years; 40% were older adults (≥65 years), 63.3% were female, and 83.3% had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1 or 2 (Table 1). Most patients had de novo AML (n = 26, 86.7%), and the remaining patients (n = 4, 13.3%) had secondary AML, including 3 with a history of myelodysplastic syndrome and 1 with treatment-related AML.

Table 1

Summary of patient baseline demographics and disease characteristics.

Demographic and baseline disease characteristics	Ivosidenib 500 mg QD (N = 30)
Age, median (range)	63 (28–77)
Age group, n (%)	
<65 y	18 (60.0)
≥65 y	12 (40.0)
Sex, n (%)	
Male	11 (36.7)
Female	19 (63.3)
ECOG PS, n (%)	
0	5 (16.7)
1	19 (63.3)
2	6 (20.0)
R/R AML type, n (%)	
Relapse after transplantation	1 (3.3)
Second or later relapse	7 (23.3)
Relapsed patients who failed SOC/unable to receive SOC*	11 (36.7)
Refractory to initial induction or reinduction therapy	11 (36.7)
Nature of AML, n (%)	
De novo	26 (86.7)
Secondary	4 (13.3)
Treatment-related AML	1 (3.3)
History of MDS	3 (10.0)
IDH1 mutation, n (%)	
R132C	14 (46.7)
R132H	12 (40.0)
R132G	3 (10.0)
R132L	1 (3.3)
R132S	0
Investigator assessment of cytogenetic risk, n (%)	
Favorable	4 (13.3)
Intermediate	9 (30.0)
Poor	2 (6.7)
Unknown	7 (23.3)
Missing	8 (26.7)
Prior anti-leukemia regimens,† n (%)	
1	8 (26.7)
2	16 (53.3)
≥3	6 (20.0)
Baseline transfusion status,‡ n (%)	
Dependent	18 (60.0)
Independent	12 (40.0)
Prior allo-HSCT, n (%)	1 (3.3)

Allo-HSCT = allogeneic hematopoietic stem cell transplant, AML = acute myeloid leukemia, ECOG PS = Eastern Cooperative Oncology Group performance status, HSCT = hematopoietic stem cell transplantation, *IDH1* = isocitrate dehydrogenase 1, MDS = myelodysplastic syndromes, QD = once daily, R/R = relapsed/refractory, SOC = standard of care.

*Due to age, comorbid condition, ECOG PS, and/adverse risk factors.

†Prior regimens include cytotoxic agents administered to induce a remission, consolidation chemotherapy administered to subjects in remission should be counted as the part of the induction regimen, noncytotoxic investigational therapies.

‡Baseline transfusion dependence was defined as having had ≥1 transfusion during the 56 d prior to the first dose of ivosidenib.

Table 2

Summary of pharmacokinetic characteristics of ivosidenib in patients with R/R m*IDH1* AML in China*.

Ivosidenib dose	C_{max} (ng/mL) GM (CV, %)	T_{max} (h) median (range)	AUC_{0-t} (ng·h/mL) GM (CV, %)	T_{last} (h) median (range)	AUC_{0-24} (ng·h/mL) GM (CV, %)	CL/F (L/h) GM (CV, %)	$R_{ac}C_{max}$ GM (CV, %)	$R_{ac}AUC$ GM (CV, %)
500 mg (single dose) Day −3 (n = 10)	4730 (36)	4.0 (1.9–10.0)	137,000 (53)	71.6 (69.4–73.0)	62,100 (42)	NC	NA	NA
500 mg QD (repeated dose) C2D1 (n = 9)	5290 (25)	2.0 (1.0–4.1)	81,100 (44)	23.5 (22.7–24.8)	81,100 (44)	6.3 (44)	1.1 (40)	1.3 (38)

AML = acute myeloid leukemia, AUC = area under the plasma concentration vs time curve, $AUC_{\%extrap}$ = area under the plasma concentration–time curve extrapolated from time *t* to infinity as a percentage of total AUC, AUC_{0-24} = AUC from time 0–24 h, AUC_{0-inf} = AUC from time 0 to infinity, AUC_{0-t} = AUC from time 0 to the last quantifiable concentration time, C2D1 = cycle 2, day 1, CL/F = apparent total clearance, C_{max} = maximum plasma concentration, CV = coefficient of variation, GM = geometric mean, m*IDH1* = mutation of the gene encoding isocitrate dehydrogenase 1, NA = not applicable, NC = not calculated, QD = once daily, $R_{ac}AUC$ = accumulation ratio calculated from AUC at steady state and AUC after a single dose, $R_{ac}C_{max}$ = accumulation ratio calculated from steady-state C_{max} and single dose C_{max}, R/R = relapsed/refractory, $t_{½}$ = elimination half-life, T_{last} = time of last quantifiable concentration, T_{max} = time to maximum plasma concentration, V_z/F = apparent volume of distribution during the terminal phase after nonintravenous administration.

*λ_z could not be accurately calculated for all patients ($AUC_{\%extrap}$ >20), therefore AUC_{0-inf}, CL/F (single dose), V_z/F, and *t*½ could not be accurately calculated. After repeated doses, most subjects with the T_{last} <24 h, so AUC_{0-24} could not be accurately calculated. Since the T_{last} of each subject was close to 24 h after repeated doses, AUC_{0-24} in repeated doses was replaced with AUC_{0-t}, and AUC_{0-t} was used for the calculation of CL/F and RacAUC.

Table 3

Summary of efficacy data at primary and final data cutoff date (efficacy analysis set, N = 30).

Efficacy outcome	Ivosidenib 500 mg QD N = 30 (primary data cutoff May 20, 2021)	Ivosidenib 500 mg QD N = 30 (final data cutoff November 20, 2022)
CR + CRh*		
Patients, n	11	11
% (95% CI)	36.7 (19.9–56.1)	36.7 (19.9–56.1)
Median time to CR or CRh (range), mo	3.7 (1.0–6.5)	3.7 (1.0–6.5)
Median duration of CR + CRh* (95% CI), mo	NR (NR–NR)	19.7 (2.9–NR)
CR		
Patients, n	11	11
% (95% CI)	36.7 (19.9–56.1)	36.7 (19.9–56.1)
Median time to CR (range), mo	3.7 (1.0–6.5)	3.7 (1.0–6.5)
Median duration of CR (95% CI), mo	NR (NR–NR)	19.7 (2.9–NR)
ORR†‡		
Patients, n	13	13
% (95% CI)	43.3 (25.5–62.6)	43.3 (25.5–62.6)
Median time to first response (range), mo	1.5 (0.9–3.8)	1.5 (0.9–3.8)
Median duration of response (95% CI), mo	NR (7.4 mo–NR)	14.3 (6.4–NR)
Best overall response, n (%)		
CR	11 (36.7)	11 (36.7)
MLFS	2 (6.7)	2 (6.7)
SD	13 (43.3)	13 (43.3)
PD	3 (10.0)	3 (10.0)
NE	1 (3.3)	1 (3.3)
EFS		
Patients, n	17	23
Median event-free survival (95% CI), mo	5.5 (2.8–NR)	5.5 (2.8–11.2)
OS		
Patients, n	14	21
Median overall survival (95% CI), mo	9.1 (4.8–NR)	9.1 (4.8–18.2)

CI = confidence interval, CR = complete response, CRh = complete response with partial hematologic recovery, CRi = complete response with incomplete recovery, CRp = complete response with incomplete platelet recovery, MLFS = morphologic leukemia-free state, NE = not evaluable, NR = not reached, ORR = objective response rate, PD = progressive disease, PR = partial response, QD = once daily, SD = stable disease.

*Met all criteria except absolute neutrophil count (>0.5 × 10^9/L [500/μL]) and platelet count (>50 × 10^9/L [50,000/μL]).

†Includes best response of CR, CRi, CRp, PR, and MLFS.

‡There were no cases of CRh, CRi, or CRp.

The most common m*IDH1* type was R132C (n = 14, 46.7%), followed by R132H (n = 12, 40.0%). At baseline, 9 (30.0%) patients had intermediate cytogenetic risk and 2 (6.7%) had poor cytogenetic risk, as assessed by the investigators. Eighteen (60.0%) patients were transfusion-dependent at baseline and 12 (40.0%) were transfusion-independent. Most patients had previously been exposed to multiple anti-leukemia therapies, with 16 (53.3%) having received 2 prior regimens and 6 (20.0%) receiving at least 3 prior regimens.

3.3. Pharmacokinetic analysis

The median T_{max} for single and repeated administrations of ivosidenib was 4.0 hours (range 1.9–10.0 hours) and 2.0 hours (range 1.0–4.1 hours), respectively (Table 2). After a single dose, the C_{max} was 4730 ng/mL and AUC_{0-t} were 137,000 ng·h/mL, respectively. At steady state (C2D1), C_{max} and AUC_{0-t} were 5290 ng/mL and 80,100 ng·h/mL, respectively. The inter-individual variability of the exposure parameters (C_{max} and

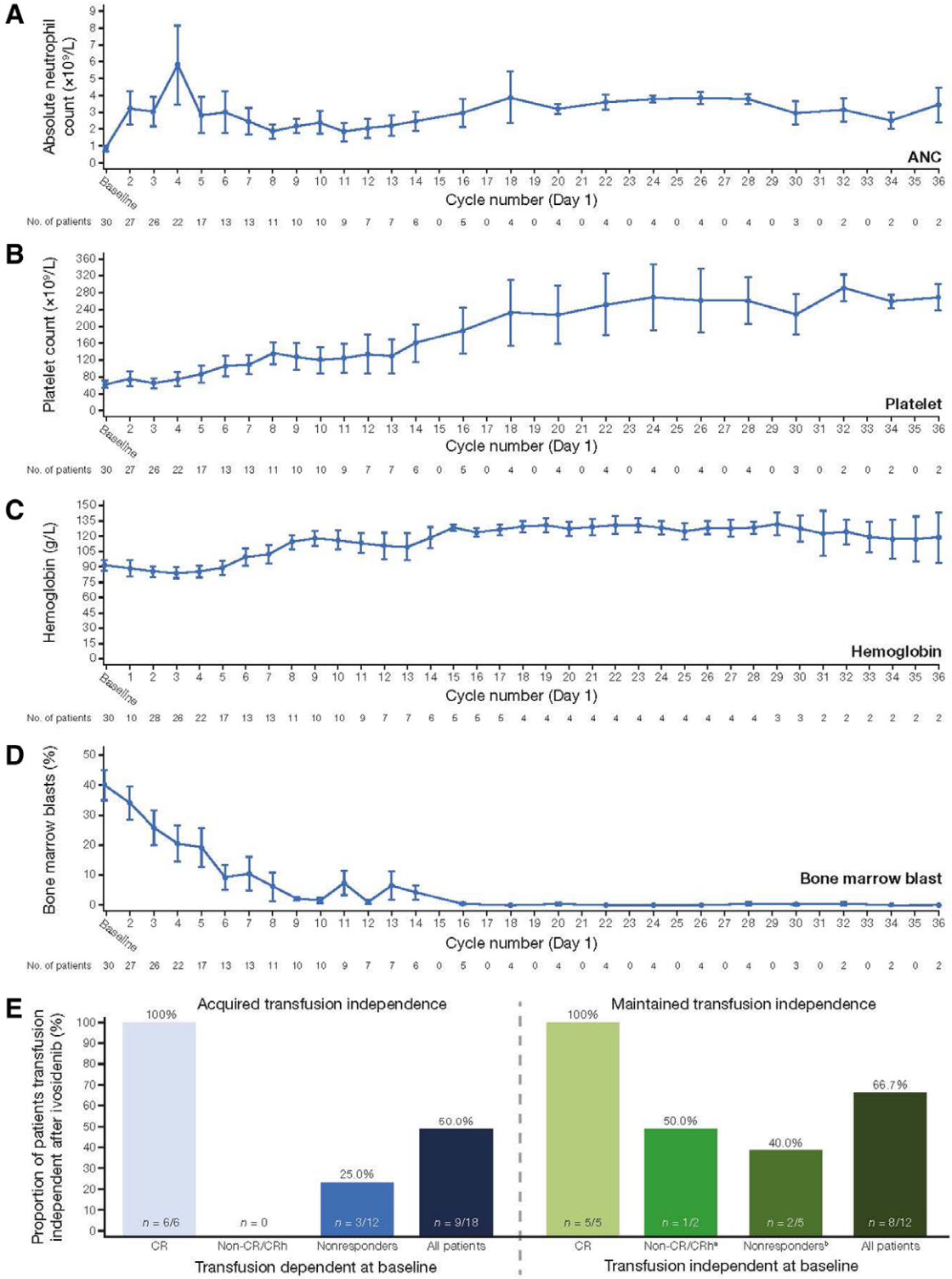

Figure 1. Improvement in hematological variables: absolute neutrophil count (A), platelet count (B), hemoglobin (C), and levels of bone marrow blasts (D). Data are presented as the mean ± SEM. (E) Proportion of patients who acquired or maintained transfusion independence (any type, ≥56 consecutive days) after treatment with ivosidenib for all patients and by disease response. ANC = absolute neutrophil count, CR = complete remission, CRh = complete remission with partial hematological response, MLFS = morphologic leukemia-free state, SEM = standard error of the mean. [a]Both patients in this group achieved MLFS. [b]One patient was not evaluated.

AUC_{0-t}) was moderate to high (coefficient of variation [CV], 25%–53%). No obvious accumulation was observed, with an R_{ac}AUC of 1.3 (geometric CV [GCV] 38%) and $R_{ac}C_{max}$ of 1.1 (GCV 40%). The pharmacokinetic parameters $t_{½}$, CL/F, V_z/F, and AUC_{0-inf} could not be accurately calculated in this study because of values >20% for AUC_{0-inf} extrapolation as a percentage of the total AUC.

3.4. Efficacy analyses

At the primary data cutoff (May 20, 2021), 11 (36.7%) patients achieved the best response of CR. Two (6.7%) patients achieved a morphologic leukemia-free state (MLFS), but none met the CRh criteria. The CR + CRh rate was 36.7% (11/30, 95% CI: 19.9%–56.1%) and the median time to CR + CRh was 3.7 months (range 1.0–6.5 months) (Table 3). Ten of the 11

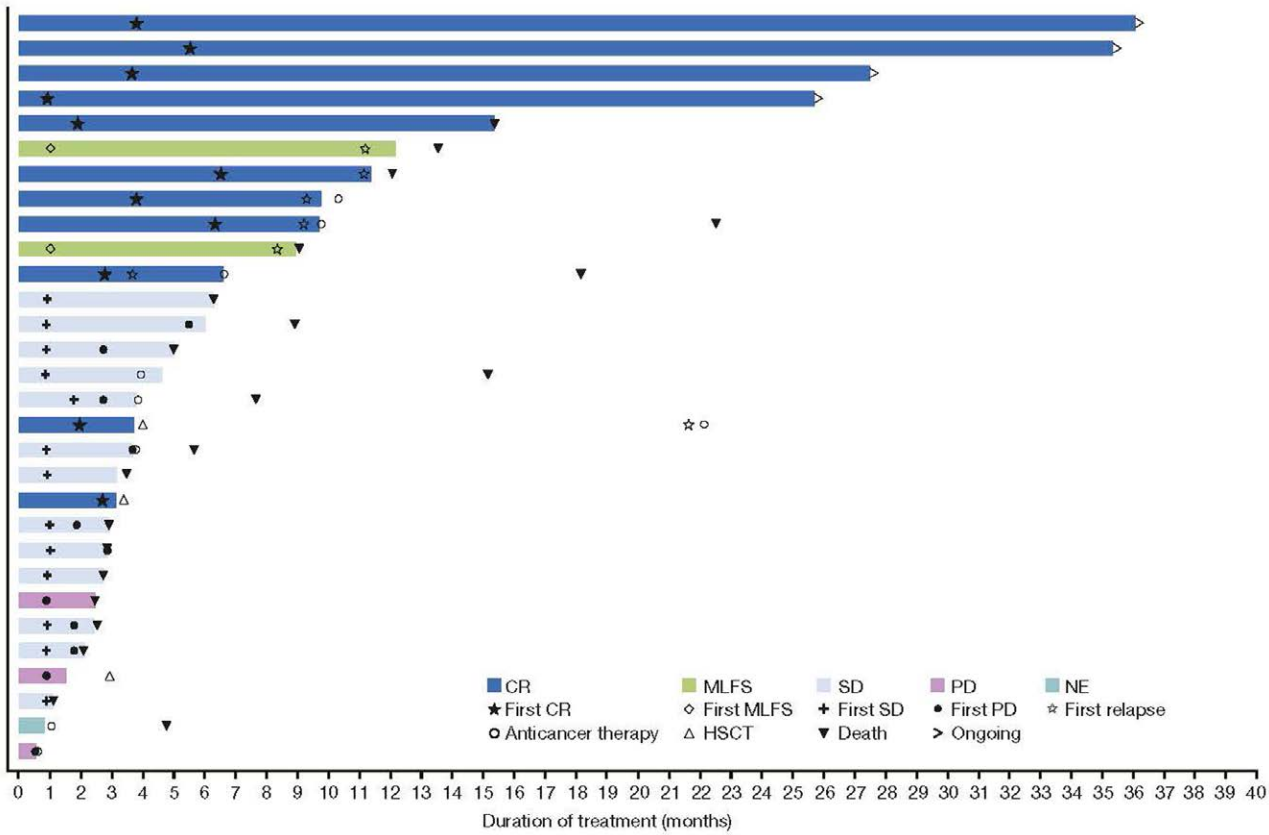

Figure 2. Duration of response, the best overall response, and patient treatment and trial status at the data cutoff date (November 20, 2022). CR = complete response, HSCT = hematopoietic stem cell transplantation, MLFS = morphologic leukemia-free state, NE = not evaluable, PD = progressive disease, SD = stable disease.

patients who achieved CR continued to respond to ivosidenib treatment at the data cutoff, and the median duration of CR + CRh was not reached (NR; 95% CI: NR–NR). The estimated 6-month CR + CRh rate was 90.9% (95% CI: 50.8%–98.7%). Two patients (6.7%) underwent HSCT after achieving a CR. The ORR was 43.3% (13/30, 95% CI: 25.5%–62.6%). Median TTR was 1.5 months (range 0.9–3.8 months) and median DOR was NR (95% CI: 7.4 months–NR).

The median EFS was 5.5 months (95% CI: 2.8 months–NR) and the estimated 12-month EFS rate was 38.8% (95% CI: 20.7%–56.7%). Median OS was 9.1 months (95% CI: 4.8 months–NR) after a median follow-up duration of 8.9 months (95% CI: 7.9–11.8 months). The 12-month OS rate was 47.3% (95% CI: 26.4%–65.7%).

Improvements over time were observed in the plasma absolute neutrophil count, platelet count, and hemoglobin levels, and a reduction in the percentage of bone marrow blasts was observed (**Fig. 1A–D**). Exposure-adjusted rates of grade ≥3 infection and infestations were comparable among patients with a best response of CR and those with the non-CR/CRh responders and numerically lower than non-responders. The exposure-adjusted rate of febrile neutropenia was low, irrespective of the best overall response, with 2 isolated events observed (Table S5, http://links.lww.com/BS/A100).

There was an overall shift in baseline transfusion status (any type of transfusion, ≥56 consecutive days post-baseline) from dependence to independence during ivosidenib treatment in 9/18 (50.0%) patients. Eight of the remaining 12 patients (66.7%) maintained a baseline transfusion-independent status (**Fig. 1E**). All CR responders either acquired (n = 6, 100%) or maintained (n = 5, 100%) transfusion independence for ≥56 consecutive days. In addition, 3/12 (25.0%) non-responders who were transfusion-dependent at baseline acquired transfusion independence, and 2/5 (40.0%) who were transfusion-independent at baseline maintained their status after receiving ivosidenib treatment (**Fig. 1E**).

At final data cutoff (November 20, 2022), the median follow-up time was 26.0 months (95% CI: 23.7–35.4 months). Five of the 11 patients who achieved CR continued to respond to ivosidenib, and the median duration of CR + CRh was 19.7 months (95% CI: 2.9 months–NR), same as the median duration of CR (Table 3, **Fig. 2**). The estimated 6-month CR + CRh rate was 63.6% (95% CI: 29.7%–84.5%), the 24 and 30 months CR + CRh rates were 45.5% (95% CI: 16.7%–70.7%). Of the 3 (10.0%) patients who received HSCT, 1 patient achieved CR, 1 achieved CRh (CRp), and 1 patient had progressive disease (PD) at the end of treatment (EOT) visit and was not evaluable when receiving HSCT. The median DoR was 14.3 months (95% CI: 6.4 months–NR).

The median EFS was 5.5 months (95% CI: 2.8–11.2 months) and the estimated 12-month EFS rate was 25.9% (95% CI: 11.6%–42.8%), the 24- and 30-month EFS rate were both 18.5% (95% CI: 6.8%–34.6%) (**Fig. 3A**). Median OS was 9.1 months (95% CI: 4.8–18.2 months) and the 12-month OS rate was 48.3% (95% CI: 29.5%–64.8%), the 24- and 36-month OS rate were both 27.6% (95% CI: 13.1%–44.3%) (**Fig. 3B**).

3.5. Safety

By the final data cutoff (November 20, 2022), the overall median treatment duration was 4.2 months (range 0.6–36.1 months) and the median number of treatment cycles was 5 (range 1–36). Almost half of the patients (n = 14, 46.7%) received at least 6 cycles of treatment. All 30 patients

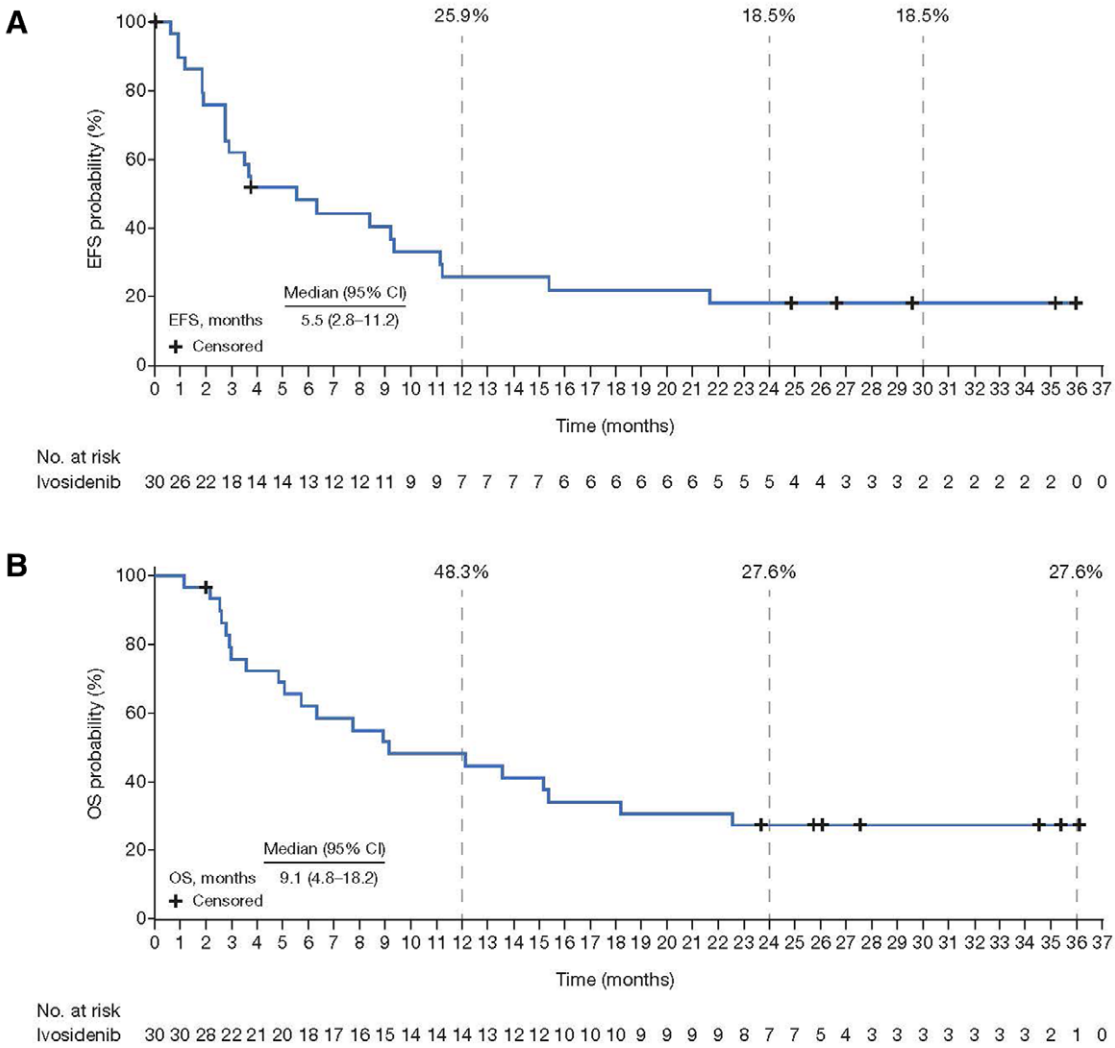

Figure 3. Kaplan–Meier estimates of (A) EFS and (B) OS at data cutoff Nov 20, 2022. CI = confidence interval, EFS = event-free survival, NR = not reached, OS = overall survival.

experienced at least 1 treatment-emergent adverse event (TEAE), with the most common being hypokalemia (n = 18, 60.0%), anemia (n = 16, 53.3%), and white blood cell count (WBC) decreased (n = 13, 43.3%) (Table 4). Grade ≥3 TEAEs occurred in 90.0% of patients. TEAEs were considered by the investigator to be related to ivosidenib (treatment-related adverse events [TRAEs]) occurred in 24 (80.0%) patients and were predominantly hematological events (Figure S3, http://links.lww.com/BS/A103). The most common TRAEs were anemia, neutrophil count decreased, and WBC decreased (n = 8; 26.7% each). Grade ≥3 TRAEs occurred in 15 (50.0%) patients; the most frequently reported TEAEs were neutrophil count decreased (n = 7, 23.3%), anemia, and WBC decreased (n = 6, 20.0% for each) (Figure S3, http://links.lww.com/BS/A103). TEAEs leading to death were reported in 5 (16.7%) patients (multiple organ dysfunction syndrome, brain herniation with subdural hemorrhage, myocardial infarction, cerebral hemorrhage, and death [1 patient each]; the etiology of death remained unknown). The investigator considered death to be due to multiple organ dysfunction syndrome related to ivosidenib. Serious adverse events (SAEs) were reported in 20 patients (66.7%), with the most common being hypokalemia, platelet count decreased, and pneumonia (n = 4, 13.3% each). SAEs were related to ivosidenib in 10 (33.3%) patients; those occurring in more than 1one patient were pneumonia, platelet count decreased, and IDH differentiation syndrome (all occurring in 3 patients [10.0%]). A full list of the SAEs is provided in Table S6, http://links.lww.com/BS/A100.

TEAEs leading to dose reductions were reported in 3 (10.0%) patients during the study, due to γ-glutamyltransferase increase (n = 1, 3.3%) and ECG QT prolonged (n = 2, 6.7% for each), all of which were related to ivosidenib treatment. Dose interruption due to TEAEs occurred in 5 (16.7%) patients, primarily because of abnormal laboratory investigation parameters: ECG QT prolonged in 2 patients (6.7%), blood bilirubin increased, neutrophil count decreased, WBC decreased, febrile neutropenia, vomiting, and pneumonia (all occurring in 1 patient [3.3%] each). Of these, only vomiting was considered not related to ivosidenib treatment. TEAEs leading to permanent discontinuation of ivosidenib occurred in 3 (10.0%) patients: grade 4 cardiac failure with sepsis (n = 1, 3.3%); grade 5 multiple organ dysfunction syndrome (n = 1, 3.3%), which was considered to be related to ivosidenib treatment by the investigator; and grade 5 brain herniation with subdural hemorrhage (n = 1, 3.3%).

AESIs were reported by 5 (16.7%) patients, including IDH differentiation syndrome (n = 3, 10.0%) and ECG QT prolonged (n = 2, 6.7%), and all were considered treatment-related. IDH differentiation syndrome was grade 3 in 2 (6.7%) patients and grade 2 in 1 (3.3%) patient; none led to dose reduction, dose interruption, permanent treatment discontinuation,

Table 4

Summary of TEAEs and TEAEs occurring in ≥15% of patients (any grade, by preferred term; safety analysis set, N = 30).

TEAE summary	Any grade n (%) patients	Grade 1–2 n (%) patients	Grade ≥3 n (%) patients
Any TEAE	30 (100.0)	3 (10.0)	27 (90.0)
Treatment (ivosidenib)-related TEAE	24 (80.0)	9 (30.0)	15 (50.0)
SAE	20 (66.7)	0	20 (66.7)
Treatment (ivosidenib)-related SAE	10 (33.3)	0	10 (33.3)
TEAE leading to dose reduction	3 (10.0)	2 (6.7)	1 (3.3)
TEAE leading to dose interruption	5 (16.7)	1 (3.3)	4 (13.3)
TEAE leading to permanent ivosidenib discontinuation	3 (10.0)	0	3 (10.0)
TEAE leading to death	5 (16.7)	0	5 (16.7)
Treatment (ivosidenib)-related TEAE leading to death	1 (3.3)	0	1 (3.3)
TEAEs in ≥15% of patients, by preferred term			
Hypokalemia	18 (60.0)	13 (43.3)	5 (16.7)
Anemia	16 (53.3)	5 (16.7)	11 (36.7)
WBC count decreased	13 (43.3)	5 (16.7)	8 (26.7)
Neutrophil count decreased	12 (40.0)	2 (6.7)	10 (33.3)
Hypoalbuminemia	11 (36.7)	11 (36.7)	0
Platelet count decreased	11 (36.7)		11 (36.7)
Hypertriglyceridemia	9 (30.0)	9 (30.0)	0
Hyperglycemia	8 (26.7)	8 (26.7)	0
Hyperuricemia	8 (26.7)	8 (26.7)	0
ECG QT prolonged	7 (23.3)	5 (16.7)	2 (6.7)
Hyponatremia	7 (23.3)	5 (16.7)	2 (6.7)
Pneumonia	7 (23.3)	3 (10.0)	4 (13.3)
Upper respiratory tract infection	7 (23.3)	6 (20.0)	1 (3.3)
AST increased	6 (20.0)	5 (16.7)	1 (3.3)
Leukocytosis	6 (20.0)	6 (20.0)	0
Pyrexia	6 (20.0)	6 (20.0)	0
ALT increased	5 (16.7)	5 (16.7)	0
γ-Glutamyl transferase increased	5 (16.7)	3 (10.0)	2 (6.7)
Weight decreased	5 (16.7)	4 (13.3)	1 (3.3)
Blood lactate dehydrogenase increased	5 (16.7)	0	0
Urinary tract infection	5 (16.7)	4 (13.3)	1 (3.3)
Constipation	5 (16.7)	5 (16.7)	0

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ECG = electrocardiogram, SAE = serious adverse event, TEAE = treatment-emergent adverse event, WBC = white blood cell.

or death. All 3 patients received treatment for the condition, which resulted in resolution in 2 patients. One patient had not yet recovered from IDH differentiation syndrome before death because of disease progression by the data cutoff date. ECG QT prolonged was grade 3 in 2 patients; 1 patient received treatment for this condition and had dose interruption for 3 days; the condition resolved within 4 days; another patient did not receive treatment and had dose interruption for 29 days; the dose continued after AE resolved; and the condition resolved within 30 days. There were no cases of grade ≥3 leukocytosis.

3.6. Pharmacodynamic analysis

Mean ± standard deviation plasma 2-HG concentration decreased from 5.9 ± 6.1 μM (range 0.5–30.0 μM, CV 104.3%) at screening to 0.4 ± 0.2 μM (range 0.1–1.1 μM, CV 58.3%) at predosing on C4D1 (Table S7, http://links.lww.com/BS/A100). The mean ± standard deviation predose concentration of 2-HG declined to 0.5 ± 0.7 μM after continuous dosing for 1 cycle (28 days), plateauing thereafter to levels close to the concentrations observed in healthy subjects (0.38 ± 0.11 μM).[29] The relationship between the plasma concentrations of ivosidenib and 2-HG was not performed due to the limited data.

4. DISCUSSION

Overall, the findings of this study in China are comparable with those observed in the pivotal AG120-C-001 study.[24,30] Ivosidenib pharmacokinetic exposure in the Chinese population was comparable with that in a pivotal study population.[30]

The efficacy findings of the present study are also consistent with those of the AG120-C-001 study. Notably, a post-hoc analysis of the present study population revealed that 5 of the 11 patients who achieved CR could be classified at baseline as belonging to the adverse risk category according to the European LeukemiaNet (ELN) risk stratification guidelines.[31] One additional patient with an ELN adverse risk classification achieved the best overall response to MLFS.

Overall, ivosidenib treatment provided durable remission in Chinese patients with R/R m*IDH1* AML (median duration of CR + CRh and overall response had not yet reached), as well as general hematologic improvements with a reduction in bone marrow blasts. More than half of the patients developed or maintained transfusion independence during ivosidenib treatment, including non-CR/CRh responders and non-responders. The need for therapies to mitigate the transfusion burden in hematological diseases has long been recognized to improve patient quality of life and outcomes.[32]

A comparison of the safety profile of ivosidenib in Chinese patients with that of patients in the pivotal AG120-C-001 study revealed no new safety signals.[24] TEAEs associated with abnormal hematological and biochemical test parameters were reported to have a higher incidence in the present study than in the pivotal study. However, the shifts from baseline in hematologic and biochemistry laboratory test results during ivosidenib treatment in this study in China were not markedly different from those in the pivotal study. The numerical differences were due to differences in judgement in clinical practice, such that abnormal hematological and laboratory investigation parameters may have been reported conservatively by Chinese investigators.

The data presented here indicate the potential of ivosidenib in the difficult-to-treat population of patients with R/R AML in China for whom there are limited therapeutic options. Given its manageable safety profile, targeting m*IDH1* with ivosidenib could provide a single-agent therapy with sustained efficacy, particularly in older adult or frail patients.

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AUTHOR CONTRIBUTIONS

J.W., J.J., Y.Z., Z.S., S.W., and J.Y. provided substantial contributions to the conception and design of the study. M.S., Q.Y., Y.L., C.C., J.Z., J.L., C.J., H.Q., J.L., Y.G., S.L., J.J., and J.W. enrolled and treated patients. Z.S. performed the statistical analyses. Z.Y. performed the pharmacokinetic and pharmacodynamic analyses. M.S., Q.Y., J.J., J.W., Y.Z., R.C., Z.S., and J.Y. analyzed and interpreted the data. M.S., Q.Y., J.J., J.W., Y.Z., R.C., Z.S., Q.S., and J.Y. drafted the manuscript and provided critical revision of the manuscript for important intellectual content. M.S., Q.Y., J.J., J.W., Y.Z., R.C., and Z.S. verified the data. All authors have reviewed the data, contributed to the development of the manuscript, and approved the final version for publication.

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