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Ivosidenib in Chinese patients with relapsed/refractory acute myeloid leukemia (R/R AML) with an IDH1 mutation: results from a bridging registrational study

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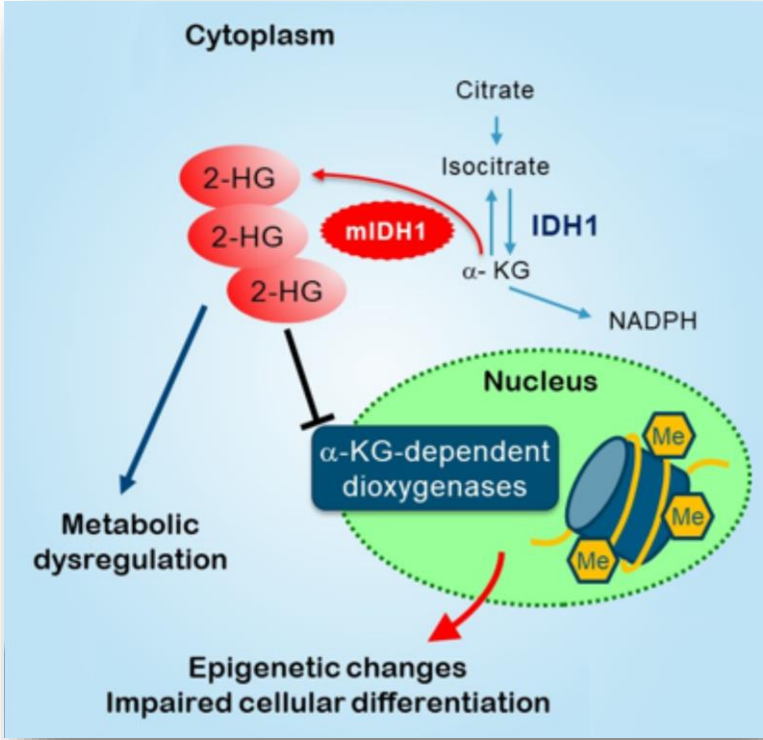
Declaration of Interests

No conflicts of interest to declare

Background

- IDH1 mutations occur in 6-10% of patients with AML and are associated with poor prognosis[1,2]
- Ivosidenib is a first-in-class, oral, small-molecule inhibitor of mIDH1
- Ivosidenib was approved by the US FDA for mIDH1 R/R AML and newly diagnosed AML
- However, currently no IDH1 inhibitor is available for mIDH1 AML in China
- CS3010-101 is a bridging, registrational study of ivosidenib conducted in China



1. Patel KP, Ravandi F, Ma D, et al. Acute myeloid leukemia with IDH1 or IDH2 mutation: frequency and clinicopathologic features. Am J Clin Pathol. 2011;135(1):35-45
2. Xu Q, Li Y, Lv N, et al. Correlation between isocitrate dehydrogenase gene aberrations and prognosis of patients with acute myeloid leukemia: a systematic review and meta-analysis. Clin Cancer Res. 2017;23(15): 4511-4522.

IDH1, isocitrate dehydrogenase 1; mIDH1, mutant IDH1; R/R AML, relapsed/refractory acute myeloid leukemia.

Study Design

CS3010-101 – Ivosidenib R/R AML China Bridging Study

Key Eligibility Criteria

Inclusion Criteria

- ≥ 18 years of age
- Diagnosed with R/R AML as specified in protocol
- Confirmed IDH1 R132 mutation
- ECOG 0-2
- Adequate organ function per protocol

Exclusion Criteria

- Prior treatment with IDH1 inhibitors
- Active severe infection
- Curative anticancer therapy is available
- QTcF ≥ 450 msec
- Medical history of progressive multifocal leukoencephalopathy

- **Ivosidenib 500 mg QD in continuous 28-day cycles**

  N=30

- **Clinical efficacy assessment: every 28 days for the first 12 months, and every 56 days thereafter**

HSCT → **If relapse, retreatment with ivosidenib**

PD/Relapse → **Follow up**

PD/Relapse → **Follow up**

Primary endpoint

- **PK**

Secondary endpoints

- **Efficacy** (**CR+CRh rate**, CR rate, ORR, Duration of CR+CRh, DOCR, DOR, Time to CR+CRh, TTR, EFS and OS)
- **Safety**
- **PK/PD relationship**
- **CDx development**

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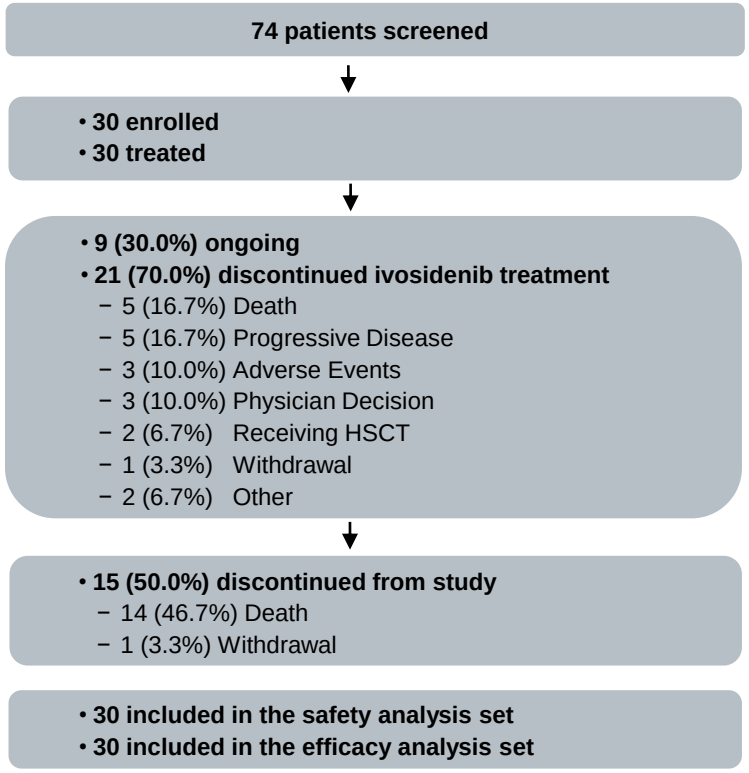
CR, complete response; CRh, CR with partial hematologic recovery; DOCR, duration of CR; DOR, duration of response; EFS, event free survival; HSCT, hematopoietic stem cell transplantation; ORR, overall response rate; OS, overall survival; PD, progressive disease; PK, pharmacokinetics; QD, once daily; QTcF, heart rate corrected QT interval using Fridericia's equation; TTR, time to response.

Demographics and Baseline Disease Characteristics



Median treatment duration (range): 4.2 (0.6, 18.0) months

Demographics and Baseline Disease Characteristics	Ivosidenib 500 mg QD (N=30)
Median Age, years (min, max)	63.0 (28, 77)
Age Group, n (%)	
<65	18 (60.0)
≥65	12 (40.0)
Sex, n (%)	
Male	11 (36.7)
Female	19 (63.3)
Baseline ECOG Performance Status, n (%)	
0	5 (16.7)
1	19 (63.3)
2	6 (20.0)
Nature of AML, n (%)	
De Novo	26 (86.7)
Secondary	4 (13.3)
IDH1 Mutation, n (%)	
R132C	14 (46.7)
R132H	12 (40.0)
R132G	3 (10.0)
R132L	1 (3.3)
R132S	0
Prior Anti-leukemia Regimen Number*, n (%)	
1	8 (26.7)
2	16 (53.3)
≥3	6 (20.0)
Prior HSCT, n (%)	1 (3.3)

*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; Non-cytotoxic investigational therapies.

Data cutoff date: May 20, 2021

AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; HSCT, hematopoietic stem cell transplantation.

PK Characteristics

Summary of PK parameters of Chinese Patients after Single and Repeated QD Oral Administrations of 500 mg Ivosidenib

	Dose	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng*h/mL)	T_{last} (h)	AUC_{0-24} (ng*h/mL)	CL/F (L/h)	Rac C_{max}	Rac AUC
Ivosidenib	500 mg (single dose) Day -3 (N=10)	4,730 (36)	3.98 (1.87, 10.02)	137,000 (53)	71.62 (69.40, 73.02)	62,100 (42)	NC	-	-
	500 mg QD (repeated dose) C2D1 (N=9)	5,290 (25)	2.00 (1.00, 4.08)	80,100 (44)	23.50 (22.67, 24.80)	80,100 (44)	6.25 (44)	1.11 (40)	1.27 (38)

T_{max} and T_{last} were presented as medians (minimum, maximum); other parameters were presented as geometric means (geometric coefficient of variation); λ_z could not be accurately calculated for all patients ($AUC_{\%Extrap}$ greater than 20%), therefore AUC_{0-inf}, V_z/F or $t_{1/2}$ could not be accurately calculated. 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.

- For single and repeated administration, the median T_{max} was 3.98 h and 2.00 h, respectively
- After repeated QD doses, the geometric mean CL/F was 6.25 L/h
- No significant accumulation was observed with Rac AUC 1.27
- The inter-individual variability of exposure (C_{max} and AUC) was moderate in Chinese patients (CV%: 25% to 53%)

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Data cutoff date: January 18, 2021

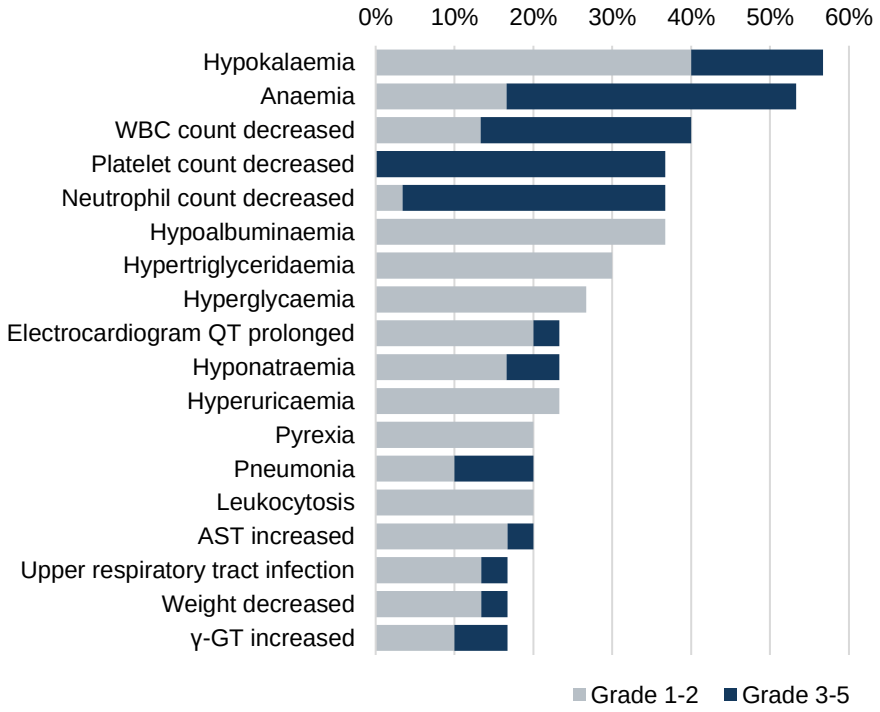
AUC_{0-24}, area under the plasma concentration-time curve from time zero to time 24 hours; AUC_{0-t}, area under the plasma concentration-time curve from time zero to time of the last quantifiable concentration; CL/F, apparent clearance; C_{max}, maximum observed plasma concentration; CV, coefficient of variation percentage; NC, not calculated; QD, once daily; R_{ac}, accumulation ratio; T_{last}, time to the last quantifiable concentration; T_{max}, time to maximum plasma concentration.

Summary of AEs and TEAEs in ≥ 15% Patients

Summary of AEs

	Ivosidenib 500 mg QD (N=30)
Any TEAE	**30 (100.0%)**
Treatment-related TEAE	24 (80.0%)
Grade 3-5 TEAE	26 (86.7%)
Treatment-related Grade 3-5 TEAE	14 (46.7%)
SAE	19 (63.3%)
Treatment-related SAE	10 (33.3%)
TEAE Leading to Dose Reduction	2 (6.7%)
TEAE Leading to Dose Interruption	4 (13.3%)
TEAE Leading to Study Drug Permanently Discontinued	3 (10.0%)
TEAE Leading to Death	3 (10.0%)

TEAEs Occurred in ≥ 15% Patients

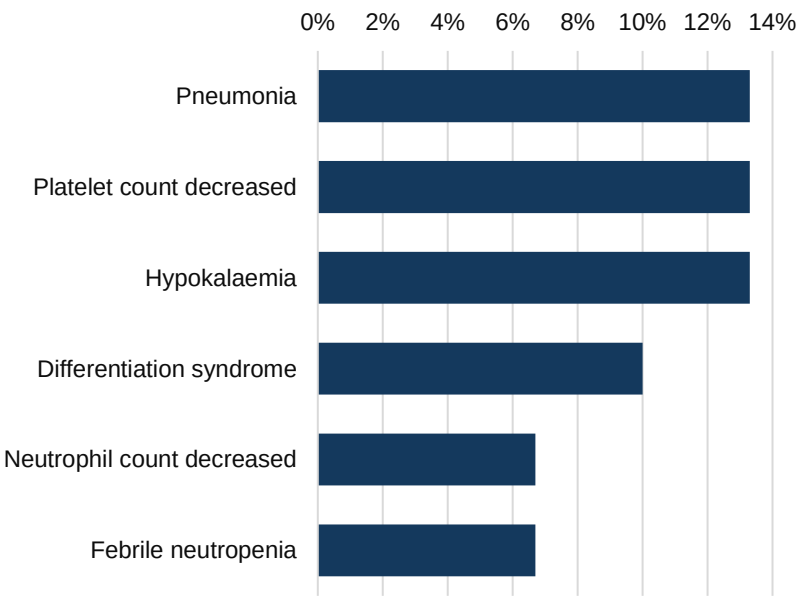


Data cutoff date: May 20, 2021

AE, adverse event; TEAE, treatment-emergent adverse event; SAE, serious adverse event.

SAEs in ≥ 5% Patients and AEs of Special Interest

SAEs in ≥ 5% Patients



AEs of Special Interest

IDH differentiation syndrome (IDH-DS)

- A total of 3 (10.0%) patients developed IDH-DS, including grade 3 IDH-DS in 2 (6.7%) and grade 2 in 1 (3.3%)
- No instances of IDH-DS led to dose reduction, dose interruption, permanent treatment discontinuation, or death
- Resolved in 2 patients, ongoing in 1 patient at data cut

Electrocardiogram QT prolonged

- Grade 3 QT prolongation reported in 1 (3.3%) patient
  - Study drug was interrupted for 3 days
  - Patient resumed treatment at 250 mg for 14 days before re-escalating to 500 mg
  - Resolved in 4 days

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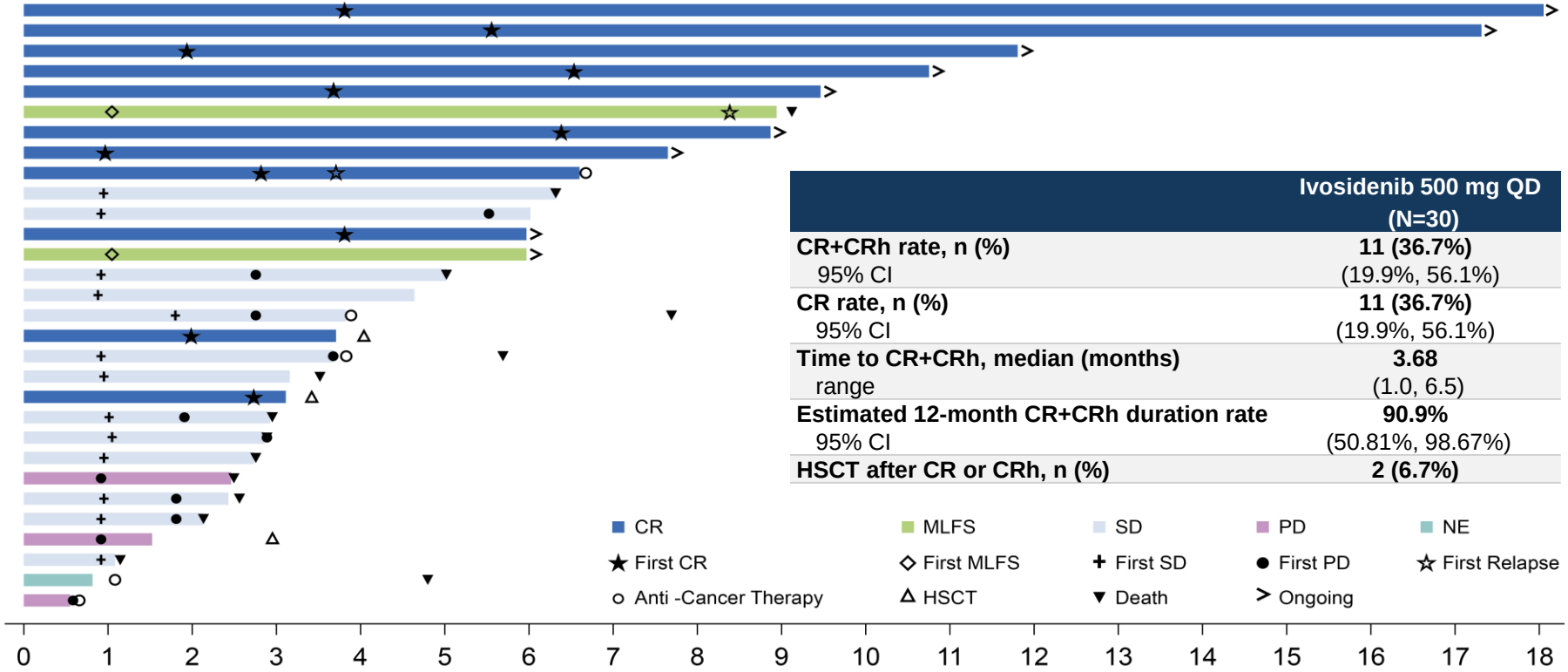
SAE, serious adverse event.

Duration of Treatment and Best Overall Response



	Ivosidenib 500 mg QD (N=30)
CR+CRh rate, n (%)	**11 (36.7%)**
95% CI	(19.9%, 56.1%)
CR rate, n (%)	**11 (36.7%)**
95% CI	(19.9%, 56.1%)
Time to CR+CRh, median (months)	**3.68**
range	(1.0, 6.5)
Estimated 12-month CR+CRh duration rate	**90.9%**
95% CI	(50.81%, 98.67%)
HSCT after CR or CRh, n (%)	**2 (6.7%)**

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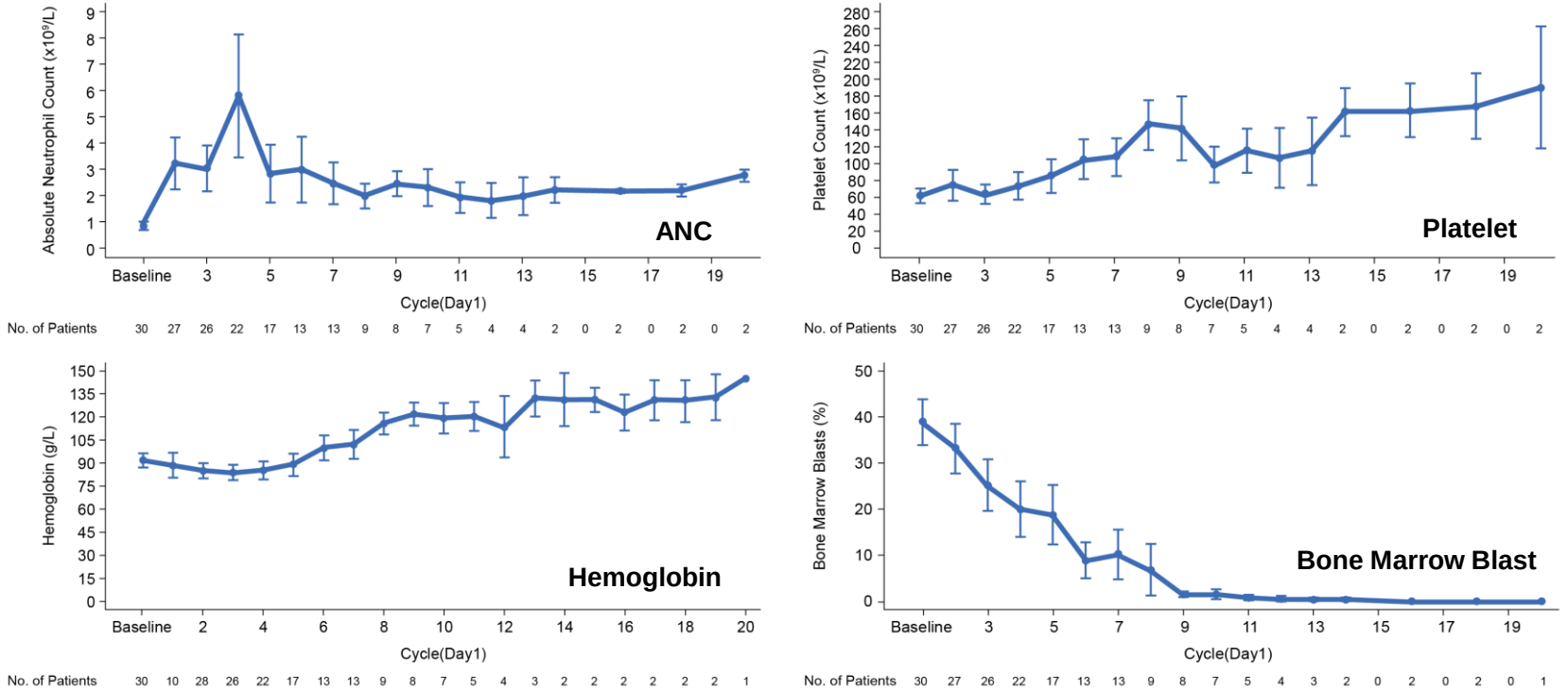
CR, complete response; CRh, CR with partial hematologic recovery; HSCT, hematopoietic stem cell transplantation; MLFS, morphologic leukemia-free state; NE, not evaluable; PD, progressive disease; SD, stable disease.

Improvement of Hematologic Variables



Acquisition (9/18 [50.0%] dependent→ independent) and **maintenance (8/12 [66.7%] independent → independent)** of transfusion independence were observed across response categories.

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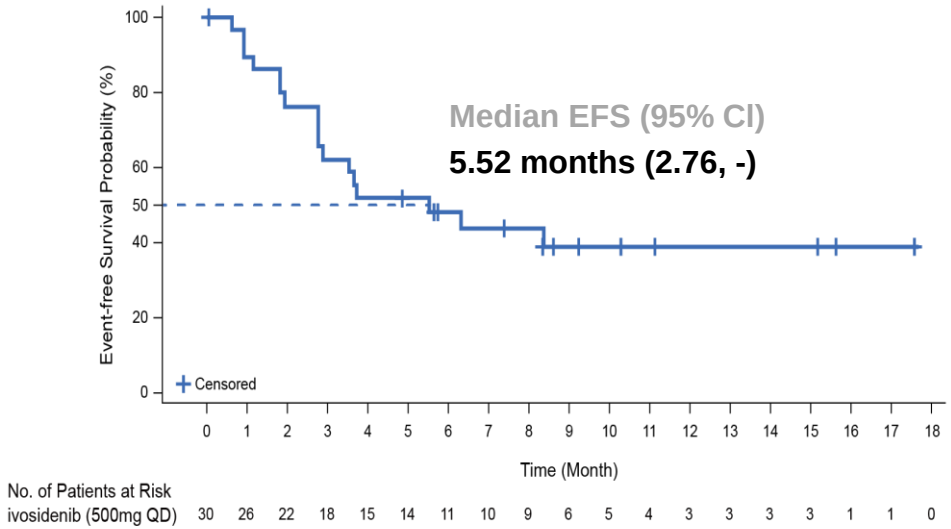
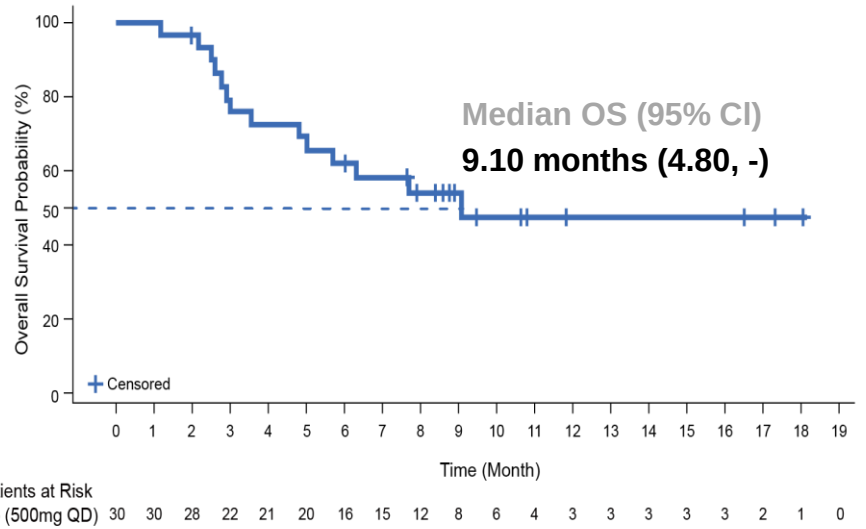
ANC, absolute neutrophil count. Post-baseline transfusion independence defined as no transfusion for at least one 56-day period.

Event-free Survival and Overall survival

EFS



OS



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EFS, event free survival; OS, overall survival.

Conclusion

- **PK, safety and efficacy data observed in this bridging study are comparable to those observed in the pivotal study AG120-C-001 conducted in the US and France**
  - Ivosidenib demonstrated rapid oral absorption (median T_{max} 2 hours) and slow elimination (GeoMean CL/F was 6.25 L/h) after repeated dose at 500 mg QD. No obvious accumulation was observed
  - Ivosidenib appears to be well tolerated, without findings of unexpected safety signal, AEs of special interest are manageable following the protocol guidance or through routine clinical management
  - Ivosidenib is the first IDH1 inhibitor that has demonstrated robust efficacy and durable remission in Chinese patients with mIDH1 R/R AML
    - CR+CRh rate is 36.7%; estimated 12-month CR+CRh duration rate is 90.9%
    - 2 (6.7%) received HSCT after achieving responses of CR or CRh
- **Ivosidenib potentially fulfills an unmet medical need for mIDH1 R/R AML patients in China**

CL/F: apparent clearance; CR, complete response; CRh, CR with partial hematologic recovery; HSCT, hematopoietic stem cell transplantation; PK, pharmacokinetics; QD, once daily; T_{max}, time to maximum plasma concentration.

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