# Ivosidenib in mutant *IDH1* relapsed/refractory myelodysplastic syndrome: Updated substudy results

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## BACKGROUND

- Somatic mutations in the isocitrate dehydrogenase 1 (*IDH1*) gene occur in ~3% of patients (pts) with myelodysplastic syndrome (MDS) and have been associated with an increased rate of transformation to acute myeloid leukemia (AML).[1,2]
- The mutant IDH1 (mIDH1) enzyme catalyzes the reduction of α-ketoglutarate to the oncometabolite D-2-hydroxyglutarate (2-HG).[3]
- 2-HG competitively inhibits demethylating enzymes, leading to a hypermethylation signature that changes gene expression, preventing differentiation of hematopoietic stem cells into mature blood cells and promoting oncogenic transformation.[4–6]
- Ivosidenib (IVO; AG-120) is a first-in-class, oral, potent, targeted, small-molecule inhibitor of the mIDH1 enzyme[7] that suppresses 2-HG production,[8] potentially enabling differentiation of blast cells and, consequently, clinical responses.
- For pts with a susceptible *IDH1* mutation, as detected by a US Food and Drug Administration (FDA)-approved test, IVO is approved in the USA:
  - As monotherapy and as combination therapy with azacitidine in pts with newly diagnosed AML who are ≥75 years of age or who have comorbidities that preclude the use of intensive induction chemotherapy[10,11]
  - As monotherapy in pts with relapsed or refractory (R/R) AML.[12]
- In a substudy of the first-in-human study of IVO in pts with m*IDH1* advanced hematologic malignancies (ClinicalTrials.gov NCT02074839), 12 pts with R/R MDS received IVO 500 mg once daily. Based on encouraging safety and efficacy findings, including an investigator-assessed overall response rate (ORR) of 75%, the FDA granted Breakthrough Therapy designation to IVO in m*IDH1* R/R MDS, and the substudy was amended to enroll additional pts.

## OBJECTIVE

- To report updated results from the ongoing substudy (**Figure 1**).

### Figure 1. Amended design of the MDS substudy in pts with m*IDH1* R/R MDS

**Key inclusion criteria**
- ≥18 years of age
- Documented m*IDH1*-R132 by central laboratory testing during screening
- Pts with R/R MDS, defined as MDS that has relapsed (per 2006 IWG criteria) or is refractory to ≥1 of the following: high-intensity chemotherapy, HCT, or HMA-based therapy
- Pts with <5% bone marrow blast count are eligible if they present with cytopenia in ≥1 of 3 lineages, defined as: ANC <0.5 × 10⁹/L or platelet count <50 × 10⁹/L (or platelet transfusion dependence) or Hgb <8 g/dL (or RBC transfusion dependence)

**Key exclusion criteria**
- Pts who previously received treatment with an mIDH1 inhibitor and progressed on therapy
- Pts with documented AML (≥20% bone marrow or peripheral blood blasts)
- Pts who have undergone HCT within 60 days of their first dose of IVO or pts receiving immunosuppressive therapy post-HCT at screening, or with clinically significant graft vs host disease
- Pts who received systemic anticancer therapy or radiotherapy <14 days prior to first day of study drug[a]
- Pts who received an investigational agent <14 days prior to first day of study drug

Screening → IVO 500 mg QD orally Days 1–28 of 28-day cycles N=23 → Treatment with IVO until disease progression, development of unacceptable toxicity, HCT, or other prespecified end-of-treatment criteria → 28-day safety follow-up → Survival follow-up

**Primary objectives**
- Safety
- Tolerability
- Clinical activity (primary end point: CR+PR)

**Secondary objectives**
- Pharmacokinetics
- Pharmacokinetic/pharmacodynamic relationship of IVO and 2-HG

**Exploratory objective**
- Pharmacodynamic effects of IVO

**Primary efficacy end point**
- Rate of CR+PR

**Key secondary efficacy end points**
- Duration of CR+PR
- Acquisition/maintenance of TI
- Time to TI
- Duration of TI

**Safety/tolerability:** Monitoring of AEs (including SAEs and AEs leading to discontinuation), safety laboratory parameters, physical examination findings, vital signs, 12-lead ECGs, ECHO/MUGA scan,[b] and ECOG PS

**Clinical activity:** Serial blood and bone marrow sampling to determine response to treatment on the basis of modified IWG response criteria in myelodysplasia

**Pharmacokinetics and pharmacodynamics:** Serial blood sampling for determination of concentration-time profiles of IVO, and blood and bone marrow sampling for determination of 2-HG levels

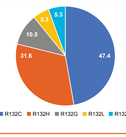
[a]Hydroxyurea is allowed prior to enrollment and after the start of IVO for the control of peripheral leukemic blasts in pts with leukocytosis (eg, white blood cell counts >30,000/μL). [b]The ECHO/MUGA scan only occurs at screening, cycle 3, day 1, and end of treatment

AE, adverse event; ANC, absolute neutrophil count; CR, complete remission; ECG, electrocardiogram; ECHO, echocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; HCT, hematopoietic cell transplant; Hgb, hemoglobin; HMA, hypomethylating agent; IWG, International Working Group; MUGA, multigated acquisition scan; PR, partial remission; QD, once daily; RBC, red blood cell; SAE, serious adverse event; TI, transfusion independence

## RESULTS

- As of 26 September, 2022, 19 pts with m*IDH1* R/R MDS had been enrolled into the substudy and were included in the full analysis set.
  - One pt was excluded from the efficacy analysis due to not meeting an inclusion criterion.
- Pt and disease characteristics are shown in **Table 1**. Of note, 73.7% of pts had a Revised International Prognostic Scoring System score of >3.
- R132C was the most common *IDH1*-R132 variant (**Figure 2**).
- Prior therapies included hypomethylating agents (78.9% of pts), intensive chemotherapy (15.8%), and investigational agents (15.8%).
- At the time of data cut-off, four pts (21.1%) remained on treatment and free from leukemic transformation, and 15 (78.9%) had discontinued treatment, including six (31.6%) for disease progression; 12 pts (63.2%) remained alive.

### Figure 2. *IDH1*-R132 variant, based on central testing (% patients)




## RESULTS

### Table 1. Baseline patient and disease characteristics for the full analysis set (N=19)

| Patient characteristic | | Disease characteristic | |
|---|---|---|---|
| Sex, n (%) | | IPSS-R score at initial diagnosis, n (%) | |
| Male | 15 (78.9) | ≤1.5 (very low) | 0 |
| Female | 4 (21.1) | >1.5–3 (low) | 2 (10.5) |
| Age, median years (min–max) | 73.0 (52–82) | >3–4.5 (intermediate) | 6 (31.6) |
| Race, n (%) | | >4.5–6 (high) | 2 (10.5) |
| White | 15 (78.9) | >6 (very high) | 2 (10.5) |
| Black or African American | 1 (5.3) | Unknown | 7 (36.8) |
| Not reported | 3 (15.8) | | |
| ECOG PS, n (%) | | IPSS-R score at screening, n (%) | |
| 0 | 5 (26.3) | ≤1.5 (very low) | 0 |
| 1 | 11 (57.9) | >1.5–3 (low) | 4 (21.1) |
| 2 | 3 (15.8) | >3–4.5 (intermediate) | 8 (42.1) |
| | | >4.5–6 (high) | 3 (15.8) |
| | | >6 (very high) | 3 (15.8) |
| | | Unknown | 1 (5.3) |

IPSS-R, Revised International Prognostic Scoring System; max, maximum; min, minimum

### Safety

- Median treatment duration was 9.26 (range: 3.3–78.8) months.
- Treatment-related adverse events (TRAEs) occurred in eight (42.1%) pts and included grade 1 corrected QT interval increase (n=1; 5.3% of pts), grade 3 fatigue (n=1), and grade 3 hyponatremia (n=1).
- Two pts permanently discontinued IVO due to a treatment-emergent adverse event (TEAE) (grade 5 sepsis and grade 3 fatigue); neither TEAE was considered related to IVO.
- Three pts (15.8%) experienced serious TRAEs: two (10.5%) pts with grade 2 differentiation syndrome and one (5.3%) pt with grade 2 rash and knuckle skin infection.
- No TRAEs led to permanent discontinuation of IVO.

### Efficacy

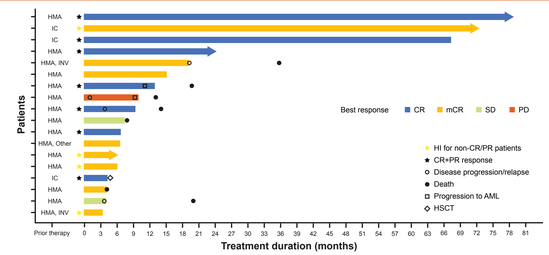
- In the efficacy analysis set (N=18), the CR rate and ORR were 38.9% and 83.3%, respectively; there were no partial remissions (PRs) (**Table 2**).
- Duration of treatment and best overall responses are shown in **Figure 3**.
- Median time to CR was 1.87 (range: 1.0–5.6) months.
- The Kaplan-Meier estimate of median duration of CR+PR was not reached (range: 1.9–80.8* months), and the estimate of median overall survival (OS) was 35.7 (range: 3.7*–88.7*) months, with * denoting censored observations.
- One (5.6%) pt underwent a stem cell transplant; two (11.1%) progressed to AML.
- Eight (44.4%) pts experienced mCR, four (50.0%) of whom had hematologic improvement in at least one lineage (erythroid, platelet, and/or neutrophil).
- 71.4% and 75.0%, respectively, of pts who were RBC or platelet transfusion-dependent at baseline became transfusion independent (TI; no transfusion for ≥56 days).
- 81.8% and 100%, respectively, of pts who were RBC- or platelet-TI at baseline remained TI at data cut-off.

### Table 2. Responses reported by investigators using the IWG 2006 MDS response criteria

| Response parameter | Efficacy analysis set (N=18) |
|---|---|
| CR+PR rate, n (%) [95% CI] | 7 (38.9) [17.3–64.3] |
| Duration of CR+PR,[a] median months [95% CI] | NE [1.9–NE] |
| Time to CR+PR, median months (range) | 1.9 (1.0–5.6) |
| ORR,[b] n (%) [95% CI] | 15 (83.3) [58.6–96.4] |
| Best overall response, n (%) | |
| CR | 7 (38.9) |
| PR | 0 (0.0) |
| mCR | 8 (44.4) |
| SD | 2 (11.1) |
| PD | 1 (5.6) |

[a]Based on a Kaplan-Meier analysis; [b]ORR is defined as CR+PR+mCR rate
CI, confidence interval; mCR, marrow complete remission; NE, not estimable; PD, progressive disease; SD, stable disease

### Figure 3. Treatment duration and best overall response in the efficacy analysis set (N=18)




HI, hematologic improvement; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; INV, investigational agent

### Translational data

- All pts with the R132C variant (n=9) experienced either CR or mCR (**Table 3**).
- Median variant allele frequency (VAF) tended to be higher in pts who achieved mCR than in those who achieved CR (**Figure 4**).
- Non-responders had either very low (two pts with stable disease) or very high (one pt with progressive disease) m*IDH1* VAF at baseline (**Figure 4**).
- Most pts (66.7%) had more than one co-mutation (**Figure 5**).
- Pts with a CR had a median of one co-mutation; non-responders had a median number of three co-mutations (**Table 4** and **Figure 6**).

### Figure 4. Association of baseline m*IDH1* VAF with response in the efficacy analysis set (N=18)

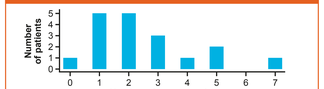



BM, bone marrow; PB, peripheral blood

### Table 3. Distribution of baseline m*IDH1* variant and best overall response

| Best response (% patients) | R132C (N=9) | R132G (N=2) | R132H (N=5) | R132L (N=1) | R132S (N=1) | Total (N=18) |
|---|---|---|---|---|---|---|
| CR (n=7) | 6 (67) | 0 (0) | 0 (0) | 0 (0) | 1 (100) | 7 (39) |
| mCR (n=8) | 3 (33) | 0 (0) | 4 (80) | 1 (100) | 0 (0) | 8 (44) |
| Non-responders (n=3) | 0 (0) | 2 (100) | 1 (20) | 0 (0) | 0 (0) | 3 (17) |
| SD (n=2) | 0 (0) | 2 (100) | 0 (0) | 0 (0) | 0 (0) | 2 (11) |
| PD (n=1) | 0 (0) | 0 (0) | 1 (20) | 0 (0) | 0 (0) | 1 (6) |

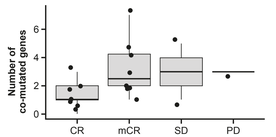
### Figure 5. Distribution of number of co-mutations in the efficacy analysis set (N=18)



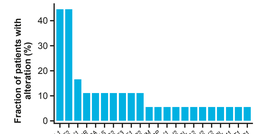

### Table 4. Distribution of number of co-mutations with best response

| Best response (N=18) | Median number of co-mutated genes (range) |
|---|---|
| CR (n=7) | 1.0 (0–3) |
| mCR (n=8) | 2.5 (1–7) |
| Non-response (n=3) | 3.0 (1–5) |

### Figure 6. Distribution of number of co-mutations with best overall response in the efficacy analysis set (N=18)




### Figure 7. Distribution of specific co-mutations in the efficacy analysis set (N=18)




- The most common co-mutations were in *ASXL1* and *SRSF2*, occurring in eight pts each (**Figure 7**).
- All eight pts with *SRSF2* co-mutations and six of eight pts with *ASXL1* co-mutations experienced CR or mCR (**Figure 8**).
- Durations of response were 65.3 and 70.9 months in the two patients with *TP53* co-mutations who experienced a CR and an mCR, respectively; both results were censored and were ongoing at data cut-off.

### Figure 8. Heatmap showing baseline co-mutations, VAF clone size, clinical responses, and OS in the efficacy analysis set (N=18)




In this heatmap, each column corresponds to a single pt, arranged by best overall response to IVO. Known or likely oncogenic mutations are denoted by boxes and shaded by alteration type. Co-mutation analysis was performed using targeted next generation sequencing focused on known or likely oncogenic alterations in a panel of 79 genes associated with hematologic malignancies
[a]VAF for the largest clone shown
IPSS-M, International Prognostic Staging System-Molecular; RTK, receptor tyrosine kinase

## CONCLUSIONS

- **Ivosidenib induced durable remissions, including a substantial proportion of complete remissions, and had an acceptable safety profile in patients with mutant *IDH1* relapsed/refractory myelodysplastic syndrome.**
- **Differentiation syndrome was uncommon and manageable.**
- **A high proportion of patients became or remained transfusion independent, and hematologic improvement was observed in half of patients experiencing marrow complete remission.**
- **Ivosidenib provides an effective treatment option for this molecularly defined patient population.**

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**Acronyms**
AE, adverse event; 2-HG, D-2-hydroxyglutarate; AML, acute myeloid leukemia; ANC, absolute neutrophil count; BM, bone marrow; CR, complete remission; ECHO, echocardiogram; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance; FDA, US Food and Drug Administration; HCT, hematopoietic cell transplant; Hgb, hemoglobin; HI, hematologic improvement; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; INV, investigational agent; IPSS-R, Revised International Prognostic Scoring System; IPSS-M, International Prognostic Staging System-Molecular; IVO, ivosidenib; IWG, International Working Group; ORR, overall response rate; OS, overall survival; PD, progressive disease; PO, progressive disease; PR, partial remission; pt, patient; QD, once daily; RBC, red blood cell; R/R, relapsed or refractory; SD, stable disease; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TI, transfusion independence; TRAE, treatment-related adverse events; VAF, variant allele frequency

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**Disclosures**
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