Ivosidenib (AG-120) induced durable remissions and transfusion independence in patients with IDH1-mutant relapsed or refractory myelodysplastic syndrome: results from a phase 1 dose escalation and expansion study

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BACKGROUND

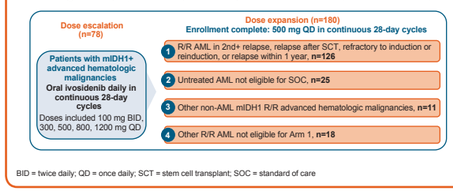
- Somatic mutations in the isocitrate dehydrogenase 1 (*IDH1*) gene occur in ~3% of patients with myelodysplastic syndrome (MDS) and have been linked with increased transformation to acute myeloid leukemia (AML).[1,2]
- The mutant IDH1 (mIDH1) enzyme catalyzes the reduction of alpha-ketoglutarate to the oncometabolite D-2-hydroxyglutarate (2-HG),[3] and the resulting 2-HG accumulation leads to epigenetic dysregulation and impaired cellular differentiation.[4-6]
- Ivosidenib (AG-120) is a first-in-class, oral, potent, targeted, small-molecule inhibitor of the mIDH1 enzyme.[7]
  - Ivosidenib suppresses the production of 2-HG, leading to clinical responses via differentiation of malignant cells.
- Ivosidenib received US FDA approval on July 20, 2018 for the treatment of adult patients with relapsed or refractory (R/R) AML with a susceptible IDH1 mutation as detected by an FDA-approved test.

OBJECTIVE

- To report safety and efficacy data from patients with R/R MDS enrolled in the first-in-human phase 1 study of ivosidenib in patients with mIDH1 advanced hematologic malignancies.

METHODS

Figure 1. Study design



BID = twice daily; QD = once daily; SCT = stem cell transplant; SOC = standard of care

- Patients with R/R MDS were eligible for study treatment.
- The objective response rate (ORR) for MDS was defined as complete remission (CR) + partial remission (PR) + marrow CR (mCR), per the International Working Group (IWG) 2006 MDS response criteria.
- Baseline co-occurring mutations were assessed using a targeted next-generation sequencing panel that detects common variants in hematologic malignancies.
- m*IDH1* variant allele frequency (VAF) in bone marrow mononuclear cells was detected using BEAMing Digital PCR (Sysmex Inostics; lower limit of detection for m*IDH1*, 0.02–0.04%).
- The data cutoff date for this analysis was May 11, 2018.

RESULTS

- Safety and efficacy data are presented for the patients with R/R MDS in expansion Arm 3 (n=9) and in dose escalation whose starting dose was 500 mg QD (n=3).
  - Three patients remained on treatment at data cutoff.
    - Six patients discontinued treatment due to progressive disease.
    - One patient discontinued treatment for stem cell transplant.
  - Four patients remain in survival follow-up; one remains in transplant follow-up.
- The baseline characteristics of the 12 patients with R/R MDS are shown in **Table 1**.
  - Median treatment duration was 11.4 months (range, 3.3–36.9).
- The majority of adverse events (AEs) were grade 1–2 (**Table 2**).
  - No AEs led to permanent discontinuation of treatment.
- AEs of interest were managed using standard-of-care treatments and ivosidenib dose modification as required (**Table 3**).
- Ivosidenib induced durable responses (**Table 4**, **Figure 2**).
- There was an improvement in mean neutrophil and hemoglobin values, and platelets were stable considering the wide range at baseline (**Figure 3**).
- Among five patients who were transfusion dependent at baseline, four became transfusion independent for at least 56 days on treatment (**Figure 4**).
- The most frequent co-occurring mutations and mutational burden by clinical response are shown in **Figure 5**.
- Mutation clearance was observed in two patients (**Table 5**).

Table 1. Baseline characteristics

Characteristic	R/R MDS 500 mg (n=12)
Women / men, n	3 / 9
Age, years, median (range)	72.5 (52–78)
Age category, years, n (%)	
<60	1 (8.3)
60 to <75	6 (50.0)
≥75	5 (41.7)
ECOG PS at baseline, n (%)	
0	4 (33.3)
1	6 (50.0)
2	2 (16.7)
Prior therapies, n (%)	
Hypomethylating agent	9 (75.0)
Two hypomethylating agents	1 (8.3)
Intensive chemotherapy	1 (8.3)
Intensive chemotherapy	2 (16.7)
Stem cell transplant	1 (8.3)
Investigational therapy	1 (8.3)
Number of prior therapies, median (range)	1 (1–3)
1 prior therapy, n (%)	7 (58.3)
2 prior therapies, n (%)	4 (33.3)
≥3 prior therapies, n (%)	1 (8.3)
Cytogenetic risk status by investigator, n (%)	
Favorable	1 (8.3)
Intermediate	4 (33.3)
Diploid	4 (33.3)
Poor	5 (41.7)
Unknown/missing	2 (16.7)
IDH mutation type[a]	
R123C	5 (55.6)
R132H	3 (33.3)
R132G	1 (11.1)
IDH1 VAF[a], median (min, max)	30.9 (2.8, 47.3)
Baseline hematologic parameters, median (min, max)	
Neutrophils, 10^9/L	0.53 (0.08, 5.66)
Hemoglobin, g/dL	8.6 (6.7, 11.4)
Platelets, 10^9/L	149.5 (18.0, 660.0)
Bone marrow blasts, %	5.5 (0.0, 19.0)
Baseline transfusion dependent, n (%)	
Red blood cells	5 (41.7)
Platelets	1 (8.3)
Any	5 (41.7)

[a]Dose expansion phase (n=9).
ECOG PS = Eastern Cooperative Oncology Group Performance Status

Table 2. Most common AEs (occurring in ≥20% of patients with R/R MDS) regardless of causality

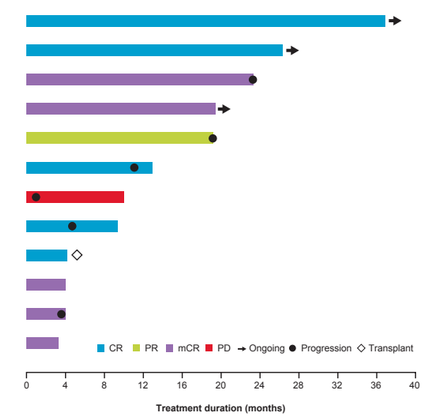
	R/R MDS 500 mg (n=12)	
	Any grade, n (%)	Grade ≥3, n (%)
Back pain	4 (33.3)	2 (16.7)
Fatigue	4 (33.3)	1 (8.3)
Anemia	3 (25.0)	2 (16.7)
Decreased appetite	3 (25.0)	0
Diarrhea	3 (25.0)	0
Dyspnea	3 (25.0)	0
Hypokalemia	3 (25.0)	0
Pruritus	3 (25.0)	0
Rash	3 (25.0)	0

Table 3. Investigator-reported AEs of interest

AEs of interest	R/R MDS 500 mg (n=12)	
	n	Details
IDH differentiation syndrome (all grades)	1	• Grade 2 event • Resolved without sequelae • Study drug was held • Managed with corticosteroids • Best response for this patient was mCR
Grade ≥3 leukocytosis[a]	0	• No grade ≥3 events reported
Grade ≥3 ECG QT prolonged	0	• No grade ≥3 events reported • Medications causing QT prolongation, such as antifungals and fluoroquinolone anti-infectives, were allowed on study with monitoring

[a]Grade 3 = white blood cells >100,000/mm^3; grade 4 = clinical manifestations of leukostasis, urgent intervention indicated
ECG = electrocardiogram

Figure 2. Duration of treatment and best overall response: R/R MDS 500 mg (n=12)



Duration of response	CR	Overall response
Median [95% CI], months	NE [2.8, NE]	21.4 [2.3, NE]
6 months	60.0%	71.6%
12 months	60.0%	61.4%

NE = not estimable

Figure 3. Hematologic parameters over time: R/R MDS 500 mg (n=12)

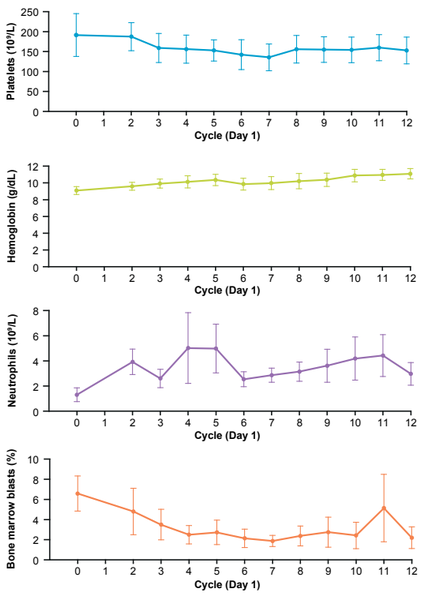
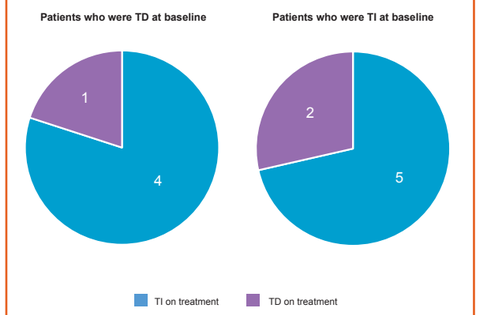
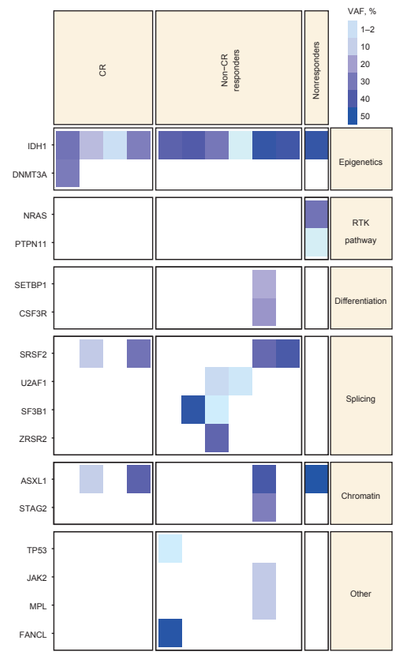


Figure 4. Transfusion status at baseline and post baseline: R/R MDS 500 mg (n=12)



Postbaseline transfusion independence defined as no transfusion for at least one 56-day period
TD = transfusion dependent; TI = transfusion independent

Figure 5. Most frequent co-occurring mutations and mutational burden by clinical response: R/R MDS 500 mg (n=11)



In this heatmap, each column corresponds to a single patient, arranged by best overall response to ivosidenib. Known or likely oncogenic mutations are denoted by boxes and shaded by VAF. No significant associations were detected between baseline co-mutations and clinical efficacy
One patient with CR was excluded because no bone marrow data were available (only peripheral blood)
RTK = receptor tyrosine kinase

Table 4. Responses

	R/R MDS 500 mg (n=12)
ORR, n (%) [95% CI]	11 (91.7) [61.5, 99.8]
Time to first response, months, median (range)	1.6 (1.0–2.8)
Duration of response, months, median [95% CI]	21.4 [2.3, NE]
Best response, n (%)	
CR	5 (41.7)
PR	1 (8.3)
mCR	5 (41.7)
SD	0
PD	1 (8.3)
CR rate, n (%) [95% CI]	5 (41.7) [15.2, 72.3]
Time to CR, months, median (range)	1.9 (1.0–5.6)
Duration of CR, months, median [95% CI]	NE [2.8, NE]

Responses reported by investigators using IWG 2006 MDS response criteria
PD = progressive disease; PR = partial response; SD = stable disease

Table 5. *IDH1* mutation clearance

	R/R MDS 500 mg (n=12)	
	n	*IDH1* mutation clearance,[a] n
CR	5	1
Other		
Non-CR responder	6	1
Nonresponder	1	0

[a]Defined as a reduction in m*IDH1* VAF to below the limit of detection of 0.02–0.04% ($2–4\times10^{-4}$) by digital PCR for at least one on-study time point

CONCLUSIONS

- In this molecularly defined mIDH1 R/R MDS patient population, ivosidenib induced durable responses:
  - CR rate 42%, median duration not estimable
  - ORR 92%, median duration 21.4 months.
- Additional benefits:
  - Conversion from transfusion dependence to independence, and maintenance of independence.
- Mutation clearance was observed in two patients (1 CR and 1 mCR).
- Ivosidenib was well tolerated.
  - Differentiation syndrome occurred in one patient with MDS and was managed with standard-of-care treatments and ivosidenib dose hold.
  - There were no grade ≥3 events of leukocytosis or ECG QT prolongation in the MDS population.
- On the basis of these data, future studies of patients with mIDH1 MDS are in development.

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Disclosures

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