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Ivosidenib (IVO) in patients with *IDH1*-mutant relapsed/refractory myelodysplastic syndrome (R/R MDS): Updated enrollment of a phase 1 dose escalation and expansion study

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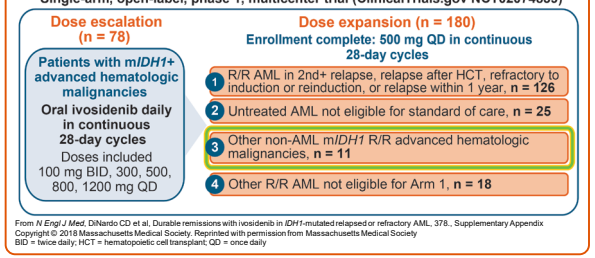
BACKGROUND

- Somatic mutations in the isocitrate dehydrogenase 1 (*IDH1*) gene occur in ~3% of patients with myelodysplastic syndrome (MDS) and have been associated with increased 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] and the resulting 2-HG accumulation leads to epigenetic dysregulation and impaired cellular differentiation[4-6]
- Ivosidenib (IVO; AG-120) is a first-in-class, oral, potent, targeted, small-molecule inhibitor of the mIDH1 enzyme[7]
  - IVO suppresses the production of 2-HG, leading to clinical responses via differentiation of malignant cells
- IVO is approved in the US for the treatment of AML with a susceptible *IDH1* mutation as detected by an FDA-approved test in adults with newly diagnosed AML who are ≥ 75 years of age or who have comorbidities that preclude the use of intensive induction chemotherapy and in adults with relapsed or refractory (R/R) AML

Phase 1 study

- The first-in-human, phase 1 dose escalation and expansion study of IVO (NCT02074839) enrolled adults with m*IDH1* advanced hematologic malignancies, including R/R MDS. The study is ongoing (**Figure 1**)[8]

Figure 1. Study design



From *N Engl J Med*, DiNardo CD et al, Durable remissions with ivosidenib in *IDH1*-mutated relapsed or refractory AML, 378., Supplementary Appendix

BID = twice daily; HCT = hematopoietic cell transplant; QD = once daily

- In the initial phase of the study, 12 patients with R/R MDS received 500 mg IVO QD orally:[9]
  - Nine patients in expansion Arm 3 and three patients in dose escalation whose starting dose was 500 mg QD
  - Enrollment was completed on 8May2017
- As of the data cutoff (2Nov2018), three patients remained on treatment:
  - Six patients discontinued treatment owing to progressive disease (PD)
  - One patient discontinued treatment for HCT
  - Two patients remain in survival follow-up, one of whom remains in post-transplant follow-up
- Patient characteristics:
  - 75.0% were male
  - Median (range) age was 72.5 (52–78) years; 41.7% were ≥ 75 years of age
  - Median (range) number of prior therapies was 1 (1–3)
  - Nine patients (75.0%) had received prior treatment with a hypomethylating agent
  - Transfusion dependent at baseline: 5 (41.7%) red blood cells, 1 (8.3%) platelets, 5 (41.7%) any

Safety

- Adverse events (AEs) of any grade, irrespective of causality, occurring in ≥ 20% of the 12 patients were:
  - Back pain, diarrhea, fatigue, and rash (n = 4 each, 33.3%)
  - Anemia, arthralgia, decreased appetite, dyspnea, hypokalemia, hypotension, pruritus, and urinary tract infection (n = 3 each, 25.0%)
- No AEs led to permanent discontinuation of treatment

Efficacy

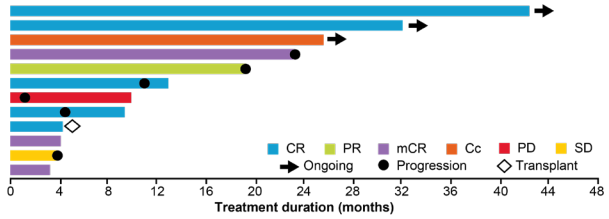
- Responses reported by investigators were assessed according to International Working Group (IWG) 2006 criteria for MDS (**Table 1** and **Figure 2**):
  - Five patients achieved complete remission (CR) (41.7%; 95% CI 15.2%, 72.3%)
    - 60% remained relapse free at 12 months
  - Median duration of CR was not estimable (NE) for these patients (95% CI 2.8 months, NE)
- Nine patients were transfusion independent for ≥ 56 days during study treatment (**Table 2**)
- Most frequent co-occurring mutations at baseline by clinical response are shown in **Figure 3**
- Mutation clearance was observed in one of the five patients who achieved CR (**Table 3**)
- Median (range) treatment duration was 11.4 (3.3–42.5) months

Table 1. Responses reported by investigators using the IWG 2006 MDS response criteria

Response parameter	R/R MDS 500 mg (n = 12)
ORR, n (%) [95% CI]	9 (75.0) [42.8, 94.5]
Time to first response, months, median (range)	1.9 (1.0–2.8)
Duration of response, months, median [95% CI]	21.4 [2.3, NE]
Best response,[a] n (%)	
CR	5 (41.7)
PR	1 (8.3)
mCR	3 (25.0)
SD	1 (8.3)
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]

[a]One patient achieved a Cc response
Cc = complete cytogenetic response; mCR = complete response in marrow; ORR = overall response rate; PR = partial response; SD = stable disease

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%	76.2%
12 months	60.0%	63.5%

Cc = complete cytogenetic response

Table 2. Transfusion status at baseline and post baseline in patients with R/R MDS receiving 500 mg dose (n = 12)

		Post baseline[a]	
		Transfusion dependent (n = 3)	Transfusion independent (n = 9)
Baseline	Transfusion dependent (n = 5)	1	4
	Transfusion independent (n = 7)	2	5

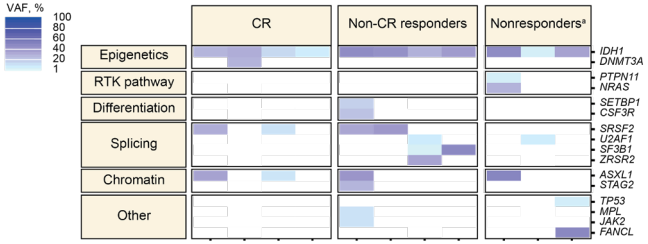
[a]Postbaseline transfusion independence defined as no transfusion for at least one 56-day period

Table 3. *IDH1* mutation clearance

	R/R MDS 500 mg (n = 12)	
	n	*IDH1* mutation clearance,[a] n
CR	5	1
Other		
Non-CR responder	4	0
Nonresponder[b]	3	1

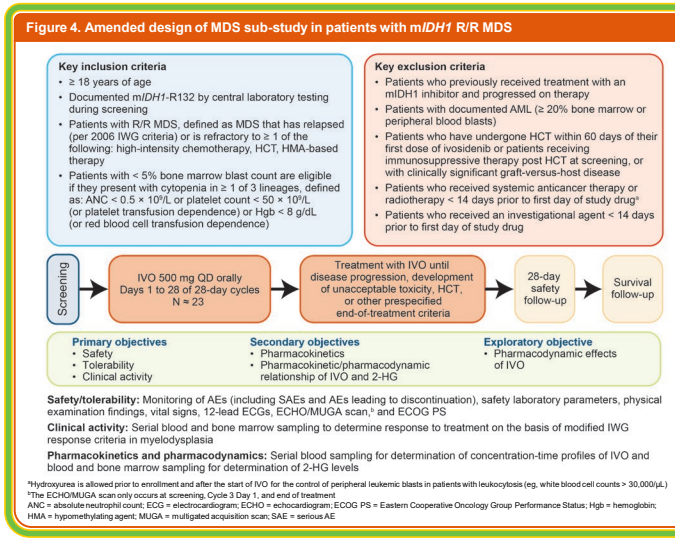
[a]Defined as a reduction in m*IDH1* variant allele frequency (VAF) in bone marrow mononuclear cells to below the limit of detection of 0.02–0.04% (2–4 × 10^{-4}) by digital PCR for at least one on-study timepoint
[b]Includes Cc response

Figure 3. Most frequent co-occurring mutations at baseline 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 IVO. 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)
[a]Includes Cc response
RTK = receptor tyrosine kinase

Figure 4. Amended design of MDS sub-study in patients with m*IDH1* R/R MDS



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 patients 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
ANC = absolute neutrophil count; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; Hgb = hemoglobin; HMA = hypomethylating agent; MUGA = multigated acquisition scan; SAE = serious AE

SUB-STUDY DESIGN

- This is a sub-study of the phase 1 dose escalation and expansion study, enrolling patients with m*IDH1* R/R MDS (**Figure 4**)
- In this population of patients with m*IDH1* R/R MDS, the objectives of this study are:
  - Primary: to assess the safety, tolerability, and clinical activity of IVO 500 mg
  - Secondary: to characterize the pharmacokinetics of IVO and to evaluate the pharmacokinetic/ pharmacodynamic relationship of IVO and 2-HG
  - Exploratory: to assess the pharmacodynamic effects of IVO

SUMMARY AND CURRENT STATUS

Summary

- **The favorable efficacy and safety of IVO in the small population of patients with m*IDH1* R/R MDS in the phase 1 clinical study of patients with m*IDH1* hematological malignancies supports further evaluation in this sub-study**
- **This sub-study will evaluate the efficacy and safety of IVO in ~23 patients with m*IDH1* R/R MDS**
- **Further information is available at https://clinicaltrials.gov/ct2/show/NCT02074839**

Study status

- **Patients are being recruited from 22 sites in the US and France**
- **Contact medinfo@agios.com**

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Disclosures
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