Ivosidenib (AG-120) in patients with *IDH1*-mutant relapsed/refractory myelodysplastic syndrome: Updated enrollment of a phase 1 dose escalation and expansion study

James M Foran[1], Courtney D DiNardo[2], Justin M Watts[3], Eytan M Stein[4], Stéphane de Botton[5], Amir T Fathi[6], Gabrielle T Prince[7], Anthony S Stein[8], Richard M Stone[9], Prapti A Patel[10], Martin S Tallman[4], Hongfang Wang[11], Vickie Zhang[11], Bin Fan[11], Katharine E Yen[11], Abdulafeez Oluyadi[11], Sumita Rai[11], Hua Liu[11], Bin Wu[11], Thomas Winkler[11], Hagop M Kantarjian[2]

[1]Mayo Clinic, Jacksonville, FL, USA; [2]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Sylvester Comprehensive Cancer Center, Miami, FL, USA; [4]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [5]Institut Gustave Roussy, Villejuif, France; [6]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [7]Johns Hopkins University, Baltimore, MD, USA; [8]City of Hope Medical Center, Duarte, CA, USA; [9]Dana-Farber Cancer Institute, Boston, MA, USA; [10]University of Texas Southwestern Medical Center, Dallas, TX, USA; [11]Agios Pharmaceuticals, Inc., Cambridge, MA, USA

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 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 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 ivosidenib (NCT02074839) enrolled adults with m*IDH1* advanced hematologic malignancies, including R/R MDS. The study is ongoing (**Figure 1**).[8]

Figure 1. Study design

Single-arm, open-label, phase 1, multicenter trial (ClinicalTrials.gov NCT02074839)[8]

Dose escalation (n=78)

Patients with m*IDH1*+ advanced hematologic malignancies
Oral ivosidenib daily in continuous 28-day cycles
Doses included
100 mg BID,
300, 500, 800, 1200 mg QD

Dose expansion (n=180)
Enrollment complete: 500 mg QD in continuous 28-day cycles

1. R/R AML in 2nd+ relapse, relapse after SCT, refractory to induction or reinduction, or relapse within 1 year, **n=126**
2. Untreated AML not eligible for standard of care, **n=25**
3. Other non-AML m*IDH1* R/R advanced hematologic malignancies, **n=11**
4. Other R/R AML not eligible for Arm 1, **n=18**

BID = twice daily; QD = once daily; SCT = stem cell transplant

- In the initial phase of the study, 12 patients with R/R MDS received 500 mg ivosidenib QD orally[a]:
  - Nine patients in expansion Arm 3 and three patients in dose escalation whose starting dose was 500 mg QD
  - Enrollment was completed on May 8, 2017.
- As of the data cutoff (November 2, 2018), three patients remained on treatment:
  - Six patients discontinued treatment owing to progressive disease (PD).
  - One patient discontinued treatment for SCT.
  - Two patients remain in survival follow-up; one remains in posttransplant 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

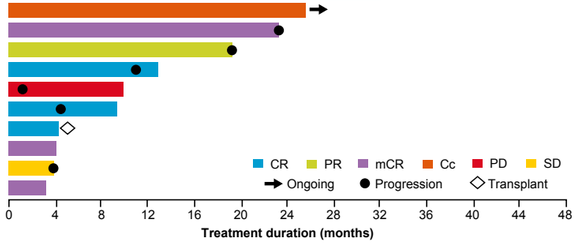
- Responses reported by investigators were assessed according to International Working Group (IWG) 2006 criteria for MDS (**Table 1** and **Figure 2**):
  - Five patients achieved complete remission (CR) (41.7%; 95% CI 15.2%, 72.3%).
    - 60% remained relapse free at 12 months.
  - Median duration of 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; NE = not estimable; SD = stable disease

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

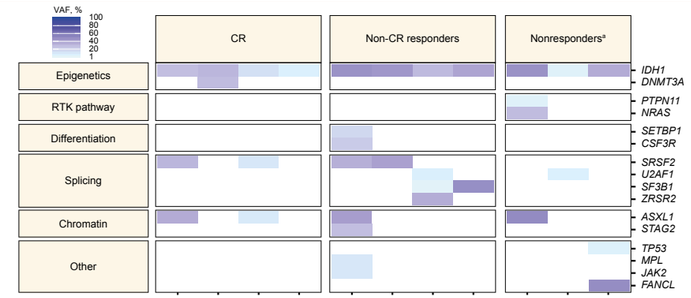
[a]Postbaseline transfusion independence defined as no transfusion for at least one 56-day period

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^{-3}) by digital PCR for at least one on-study time point
[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 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
[a]Includes Cc response

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

Key inclusion criteria
- ≥18 years of age
- R/R disease after treatment with standard-of-care agents for MDS
- Documented m*IDH1*-R132 by central laboratory testing during screening
- Bone marrow blasts >5% and/or transfusion dependence
- Platelet count of ≥20,000/μL
- Adequate hepatic function (total bilirubin ≤1.5 × ULN, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase ≤3.0 × ULN) and renal function (serum creatinine ≤2.0 × ULN or creatinine clearance >40 mL/min)
- ECOG PS score of 0–2

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

Screening → Ivosidenib 500 mg QD orally Days 1 to 28 of 28-day cycles N≈23 → Treatment with ivosidenib until disease progression, development of unacceptable toxicity, HSCT, or other prespecified end-of-treatment criteria → 28-day safety follow-up → Survival follow-up

Primary objectives
- Safety
- Tolerability
- Clinical activity

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

Exploratory objective
- Pharmacodynamic effects of ivosidenib

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 ivosidenib and blood and bone marrow sampling for determination of 2-HG levels

[a]Hydroxyurea is allowed prior to enrollment and after the start of ivosidenib for the control of peripheral leukemic blasts in patients with leukocytosis (e.g. white blood cell counts >30,000/μL)
[b]The ECHO/MUGA scan only occurs at screening, Cycle 3 Day 1, and end of treatment
ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HSCT = hematopoietic stem cell transplant; MUGA = multigated acquisition scan; SAE = serious AE; ULN = upper limit of normal

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 ivosidenib 500 mg.
  - Secondary: to characterize the pharmacokinetics of ivosidenib and to evaluate the pharmacokinetic/pharmacodynamic relationship of ivosidenib and 2-HG.
  - Exploratory: to assess the pharmacodynamic effects of ivosidenib.

SUMMARY AND CURRENT STATUS

Summary

- The favorable efficacy and safety of ivosidenib 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 ivosidenib 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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