

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 Foran¹, Courtney D DiNardo², Justin M Watts³, Eytan M Stein⁴, Stéphane de Botton⁵, Amir T Fathi⁶, Gabrielle T Prince⁷, Anthony S Stein⁸, Richard M Stone⁹, Prapti A Patel¹⁰, Martin S Tallman⁴, Hongfang Wang¹¹, Vickie Zhang¹¹, Bin Fan¹¹, Katharine E Yen¹¹, Abdulafeez Oluyadi¹¹, Sumita Rai¹¹, Hua Liu¹¹, Bin Wu¹¹, Thomas Winkler¹¹, Hagop M Kantarjian²

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

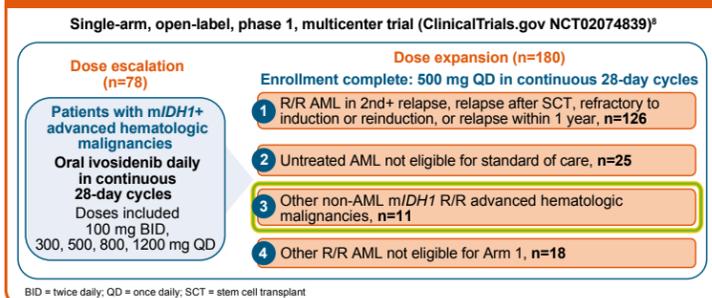
BACKGROUND

- 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* (m*IDH1*) 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 m*IDH1* 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



- 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] |

^aOne 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)

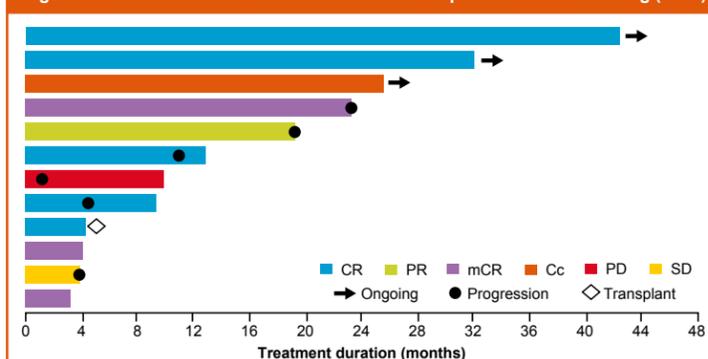


Table 2. Transfusion status at baseline and post baseline in patients with R/R MDS receiving 500 mg dose (n=12)

| Baseline | Post baseline ^a | |
|-------------------------------|-----------------------------|-------------------------------|
| | Transfusion dependent (n=3) | Transfusion independent (n=9) |
| Transfusion dependent (n=5) | 1 | 4 |
| Transfusion independent (n=7) | 2 | 5 |

^aPostbaseline 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 | <i>IDH1</i> mutation clearance, ^a n |
| CR | 5 | 1 |
| Other | | |
| Non-CR responder | 4 | 0 |
| Nonresponder ^b | 3 | 1 |

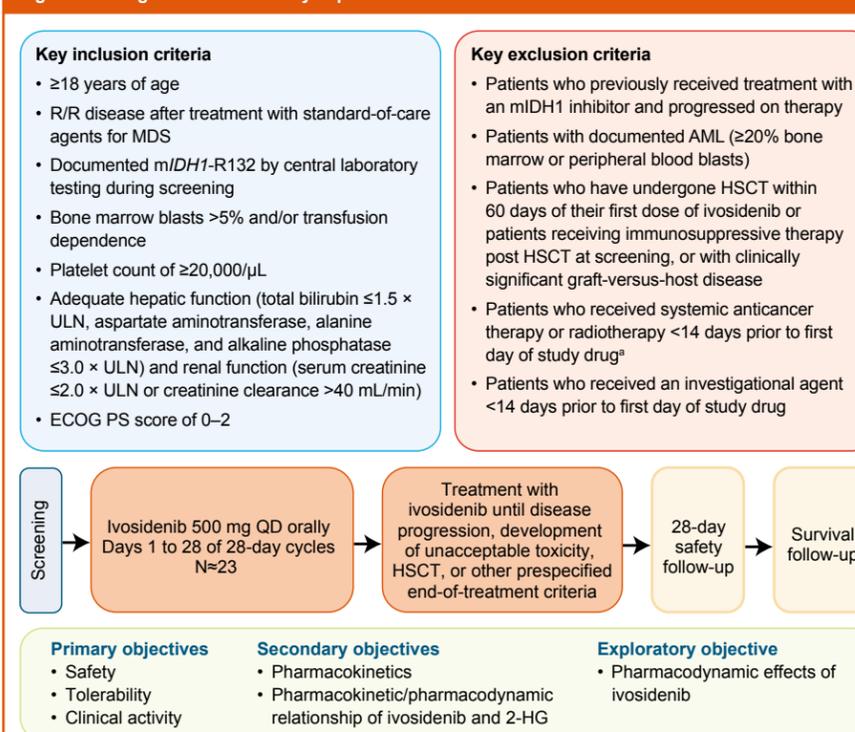
^aDefined as a reduction in m*IDH1* variant allele frequency (VAF) in bone marrow mononuclear cells to below the limit of detection of 0.02–0.04% (2–4 × 10⁻⁵) by digital PCR for at least one on-study time point
^bIncludes Cc response

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
^aIncludes Cc response

Figure 4. 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 ivosidenib and blood and bone marrow sampling for determination of 2-HG levels

^aHydroxyurea 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)
^bThe 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 AEs; 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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