PS1337

Ivosidenib (AG-120) induces durable remissions and transfusion independence in patients with IDH1-mutant relapsed/refractory myelodysplastic syndrome in 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], Sung Choe[11], Hongfang Wang[11], Vickie Zhang[11], David Dai[11], Bin Fan[11], Katharine E Yen[11], Stephanie M Kapsalis[11], Denice Hickman[11], Samuel V Agresta[11], Hua Liu[11], Bin Wu[11], Eyal C Attar[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]UT 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 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 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.

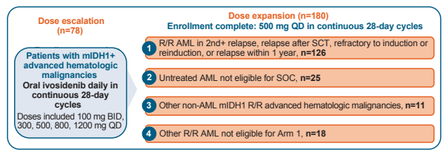
OBJECTIVE

- 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

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



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 November 2, 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 (PD).
    - One patient discontinued treatment for stem cell transplant.
  - Two patients remain in survival follow-up; one remains in post-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, 3.3–42.5).
- 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 ≥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,[a] n (%)	
Intensive chemotherapy	3 (25.0)
Hypomethylating agent	9 (75.0)
Investigational therapy	3 (25.0)
Stem cell transplant	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)
IDH1 mutation type,[b] n (%)	
R123C	5 (55.6)
R132H	3 (33.3)
R132G	1 (11.1)
IDH1 VAF,[b] 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]Patients may be counted in more than one category
[b]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

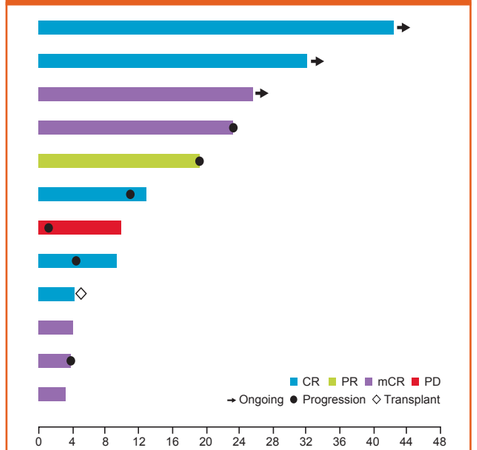
	R/R MDS 500 mg (n=12)	
	Any grade, n (%)	Grade ≥3, n (%)
Back pain	4 (33.3)	2 (16.7)
Diarrhea	4 (33.3)	0
Fatigue	4 (33.3)	1 (8.3)
Rash	4 (33.3)	0
Anemia	3 (25.0)	2 (16.7)
Arthralgia	3 (25.0)	1 (8.3)
Decreased appetite	3 (25.0)	0
Dyspnea	3 (25.0)	0
Hypokalemia	3 (25.0)	0
Pruritus	3 (25.0)	0
Hypotension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

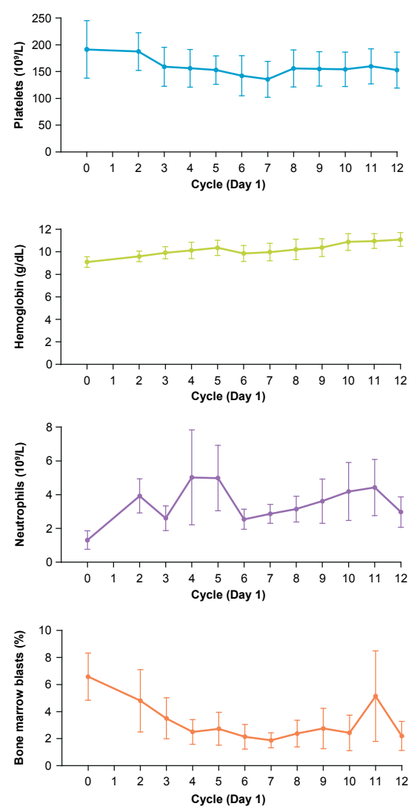
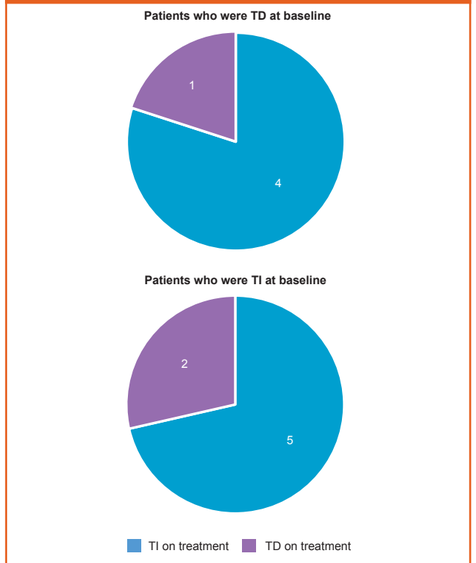
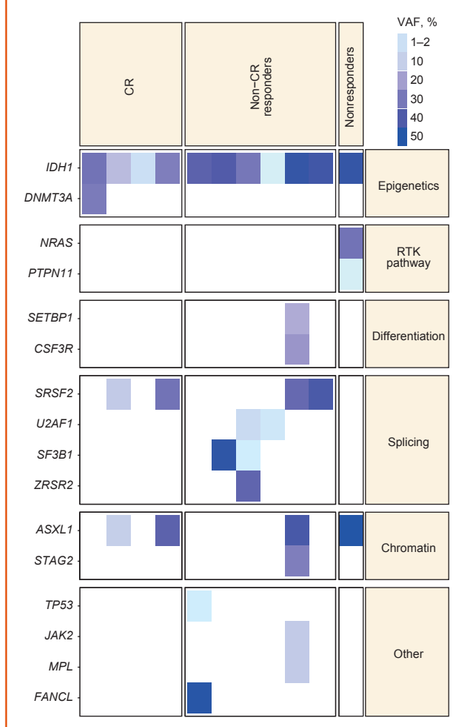


Figure 4. Transfusion status at baseline and post baseline: R/R MDS 500 mg (n=12)



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)	1.9 (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
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.

Acknowledgments

We would like to thank the patients who took part in this study, the principal investigators, their staff, and their institutions.

Disclosures

This study was funded by Agios Pharmaceuticals, Inc.

JMF: Agios – research funding. CDD: Agios, Celgene – consultant or advisor; AbbVie, Agios, Bayer, Celgene, Karyopharm, Medimmune – honoraria; Agios, AbbVie, Celgene, Daiichi Sankyo – research funding. JMW: Celgene, Jazz Pharmaceuticals, Pfizer – consultant or advisor role; Jazz Pharmaceuticals – speaker bureau; Takeda – research funding. EMS: AbbVie, Agios, Astellas, Bayer, BioLineRx, Celgene, Daiichi Sankyo, Novartis, Pfizer, PTC Therapeutics, Syros Pharmaceuticals – consultant or advisor; Agios, Amgen, Bayer, Celgene, Syros Pharmaceuticals – research funding; AbbVie, Astellas, Celgene, Daiichi Sankyo, Novartis, Syros Pharmaceuticals – travel expenses; Auron Therapeutics – stock/ownership interest. SdB: AbbVie, Agios, Bayer, Carthagenetics, Celgene, Forma Therapeutics, Novartis, Pfizer, Pierre Fabre, Seattle Genetics, Servier – honoraria; Agios, Bayer, Carthagenetics, Celgene, Forma Therapeutics, Novartis, Pfizer, Pierre Fabre, Seattle Genetics, Servier – research funding; AbbVie, Agios – speaker bureau; Agios, Carthagenetics, Celgene, Forma Therapeutics, Novartis, Pfizer, Pierre Fabre, Seattle Genetics, Servier – travel expenses. ATF: Agios – honoraria and travel expenses; Seattle Genetics – honoraria and research funding; Celgene, Exelixis, Takeda – research funding; Baxalta, Merck, Tolero Pharmaceuticals – honoraria. GTP: no conflict of interest to disclose. ASS: Amgen, Celgene – speaker bureau. RMS: AbbVie, Actinium Pharmaceuticals, Agios, Amgen, Argenx, Arog, Astellas, AstraZeneca, Celgene, Cornerstone, Jazz Pharmaceuticals, Macrogenics, Novartis, Otsuka, Pfizer, Roche/Genentech, Stemline Therapeutics, Takeda – consultant or advisor; DAVA Pharmaceuticals, Medscape, Prime Oncology, Research to Practice – honoraria; AbbVie/Genentech, Agios, Novartis – research funding. PAP: Celgene – consultant/advisor and speaker bureau; DAVA Oncology, France Foundation – honoraria. MST: AbbVie, Arog, BioLineRx, Biosight, Cellerant, Daiichi-Sankyo, Delta-Fly Pharma, KAHR, NOHLA Therapeutics, Orsenix, Rigel – consultant/advisor; AbbVie, ADC Therapeutics, Arog, Biosight, Cellerant, Orsenix – research funding; UpToDate – patents/royalties/other IP. SC, BW: Agios – employment, stockholder, patents/royalties/other IP. HW, VZ, BF, SMK, DH, and HL: Agios – employment and stockholder. DD, SVA: Agios – employment and stockholder at time of study. KEY: Agios – employment and stockholder at time of study, consultant/advisor, research funding, patents/royalties/other IP, travel expenses; Auron Therapeutics – employment, stockholder, travel expenses; UCLA – patents/royalties/other IP. ECA: Agios – employment and stockholder at time of study; Advance Medical – consultant/advisor. HMK: AbbVie, Immunogen, Orsenix – honoraria; Amgen, ARIAD, Bristol-Myers Squibb, Pfizer – honoraria and research funding; Astex, Novartis – research funding.

Editorial assistance was provided by Helen Varley, PhD, CMPP, Excel Medical Affairs, Horsham, UK, and supported by Agios.

References

1. DiNardo CD et al. *Leukemia* 2016;30:980-4.
2. Medeiros BC et al. *Leukemia* 2017;31:272-81.
3. Dang L et al. *Nature* 2009;462:739-44.
4. Lu C et al. *Nature* 2012;483:474-8.
5. Saha SK et al. *Nature* 2014;513:110-4.
6. Xu W et al. *Cancer Cell* 2011;19:17-30.
7. Popovici-Muller J et al. *ACS Med Chem Lett* 2018;9:300-5.
8. DiNardo CD et al. *N Engl J Med* 2018;378:2386-98.

Scan code to receive PDF file of the poster or visit http://bit.ly/2Jtzb6L

Presented at the 24th Congress of the European Hematology Association (EHA), June 13–16, 2019, Amsterdam, the Netherlands