AML-221

Ivosidenib (AG-120) in mutant IDH1 relapsed/refractory acute myeloid leukemia: Results of a phase 1 study

Courtney D DiNardo[1], Eytan M Stein[2], Stéphane de Botton[3], Gail J Roboz[4], Jessica K Altman[5], Alice S Mims[6], Ronan Swords[7], Robert H Collins[8], Gabriel N Mannis[9], Daniel A Pollyea[10], Will Donnellan[11], Amir T Fathi[12], Arnaud Pigneux[13], Harry P Erba[14], Gabrielle T Prince[15], Anthony Stein[16], Geoffrey L Uy[17], James M Foran[18], Elie Traer[19], Robert K Stuart[20], Martha L Arellano[21], Mikkael A Sekeres[22], Christophe Willekens[3], Sung Choe[23], Hongfang Wang[23], Vickie Zhang[23], Katharine E Yen[23], Stephanie M Kapsalis[23], Denice Hickman[23], Hua Yang[23], David Dai[23], Bin Fan[23], Meredith Goldwasser[23], Hua Liu[23], Sam Agresta[23], Bin Wu[23], Eyal C Attar[23], Martin S Tallman[2], Richard M Stone[24], Hagop M Kantarjian[1]

[1]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Institut Gustave Roussy, Villejuif, France; [4]Weill Cornell Medical College, New York, NY, USA; [5]Northwestern University, Chicago, IL, USA; [6]Ohio State University Wexner Medical Center, Columbus, OH, USA; [7]Sylvester Comprehensive Cancer Center, Miami, FL, USA; [8]UT Southwestern Medical Center, Dallas, TX, USA; [9]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [10]University of Colorado School of Medicine, Aurora, CO, USA; [11]Sarah Cannon Research Institute, Nashville, TN, USA; [12]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [13]CHU Bordeaux, Bordeaux, France; [14]University of Alabama at Birmingham, Birmingham, AL, USA; [15]Johns Hopkins University, Baltimore, MD, USA; [16]City of Hope Medical Center, Duarte, CA, USA; [17]Washington University School of Medicine, St Louis, MO, USA; [18]Mayo Clinic, Jacksonville, FL, USA; [19]OHSU Knight Cancer Institute, Portland, OR, USA; [20]Hollings Cancer Center, Medical University of South Carolina, Charleston, SC, USA; [21]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [22]Cleveland Clinic, Cleveland, OH, USA; [23]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [24]Dana-Farber Cancer Institute, Boston, MA, USA

BACKGROUND

- Somatic mutations in the isocitrate dehydrogenase 1 (*IDH1*) gene occur in ~6–10% of patients with acute myeloid leukemia (AML).
- The mutant IDH1 (mIDH1) enzyme catalyzes the reduction of α-ketoglutarate to the oncometabolite D-2-hydroxyglutarate (2-HG),[1] and the resulting 2-HG accumulation leads to epigenetic dysregulation and impaired cellular differentiation.[2-4]
- Ivosidenib (AG-120) is a first-in-class, oral, potent, targeted, small-molecule inhibitor of the mIDH1 enzyme.[5]
- Ivosidenib is under evaluation in an ongoing phase 1 dose escalation and expansion study of mIDH1 advanced hematologic malignancies, including relapsed/refractory acute myeloid leukemia (R/R AML).[5]
  - On the basis of data from this study, ivosidenib received US FDA approval on July 20, 2018 for the treatment of adult patients with R/R AML with a susceptible *IDH1* mutation, as detected by an FDA-approved test.
- The prognosis for patients with R/R AML is poor, with a median overall survival of ≤6 months,[7] and there is no standard-of-care treatment.

OBJECTIVE

- To report updated efficacy, safety, m*IDH1* variant allele frequency (VAF), and baseline co-mutation data from all patients with R/R AML receiving ivosidenib 500 mg once daily (QD) in the phase 1 study.

METHODS

- The ivosidenib phase 1, open-label, multicenter, dose escalation and expansion study includes the evaluation of safety, tolerability, maximum tolerated dose, pharmacokinetics and pharmacodynamics (including 2-HG levels), and clinical activity in patients with mIDH1 advanced hematologic malignancies (NCT02074839).[8]
- Single-agent ivosidenib is administered orally QD or twice daily (BID) in continuous 28-day cycles.
  - Doses in the escalation phase were 100 mg BID and 300, 500, 800, and 1200 mg QD.
  - 500 mg QD was selected for the expansion phase.
- The primary efficacy endpoint for R/R AML was the rate of complete remission plus complete remission with partial hematologic recovery (CR+CRh; **Table 1**).
  - International working group (IWG) responses were reported by the investigator; CRh was derived by the sponsor.

Table 1. Definitions of CR and CRh

Response	Bone marrow blasts (%)	ANC/μL	Platelets/μL
CR (per modified IWG 2003 criteria)[a]	<5	>1000	>100,000
CRh	<5	>500	>50,000

ANC, absolute neutrophil count

- Here we report data for all patients with R/R AML whose ivosidenib starting dose was 500 mg QD.
- The data cutoff date for this analysis was November 10, 2017.

RESULTS

- The baseline characteristics of 179 R/R AML patients who received ivosidenib 500 mg QD are shown in **Table 2**.
  - 17 (9.5%) remained on treatment at data cutoff.
  - 17 (9.5%) discontinued treatment to proceed to stem cell transplant.
- Median treatment duration was 3.9 months (range, 0.1–39.5).
- The majority of adverse events (AEs) were grade 1–2 (**Table 3**) and unrelated to treatment.
- AEs of interest (**Table 4**) were managed using standard-of-care treatments and ivosidenib dose modifications, as required.
- Ivosidenib induced durable responses (**Table 5**, **Figures 1** and **2**) and provided additional clinical benefits (**Figure 3**, **Table 6**).
  - Transfusion independence was observed across all response categories in patients who were dependent at baseline.
- Ivosidenib induced *IDH1* mutation clearance (IDH1-MC) in bone marrow mononuclear cells (BMMCs) from patients with a best overall response of CR or CRh (**Table 7**), and reduced m*IDH1* VAF in BMMCs and neutrophils from patients with a best overall response of CR or CRh (**Figure 4**).
  - 26% of patients with a best response of CR/CRh for whom molecular data were available had IDH1-MC in both BMMCs and neutrophils.
- Patients with IDH1-MC had improved durations of CR+CRh and overall survival versus patients with detectable m*IDH1* (**Figure 5**).

Table 2. Baseline characteristics

Characteristic	R/R AML 500 mg (n=179)
Women/men, n	89/90
Age, median (range), years	67.0 (18–87)
Age category, n (%)	
<60 years	47 (26.3)
60 to <75 years	92 (51.4)
≥75 years	40 (22.3)
ECOG Performance Status at baseline, n (%)	
0	36 (20.1)
1	99 (55.3)
2	42 (23.5)
3	2 (1.1)
De novo AML, n (%)	120 (67.0)
Secondary AML, n (%)	59 (33.0)
No. of prior therapies, median (range)	2.0 (1–6)
Prior AML therapy outcomes[a], n (%)	
Relapsed after transplant	43 (24.0)
In 2nd or later relapse	26 (14.5)
Refractory to initial induction/reinduction therapy	106 (59.2)
Relapsed within 1 year of initial therapy	17 (9.5)
In 1st relapse	15 (8.4)
Other	5 (2.8)
Cytogenetic risk status by investigator, n (%)	
Intermediate	105 (58.7)
Poor	50 (27.9)
Unknown/missing	24 (13.4)
Most common baseline co-mutations[b], %	
DNMT3A	34
mRNA splicing gene[c]	31
NPM1	25
RAS pathway[d]	24
ASXL1	19
RUNX1	18
P53	14

[a]Not mutually exclusive, patients may be in >1 category. [b]Assessed in 178 patients; mutations were identified using next-generation sequencing (FoundationOne™ Heme Panel in the escalation phase and Rapid Heme Panel in expansion). [c]Includes *SF3B1*, *SRSF2*, *U2AF1*, *U2AF2*, and *ZRSR2*. [d]Includes *MAP2K4*, *NRAS*, *PTPN11*, *KRAS*, *NF1*, *BRAF*, and *KIT*
ECOG = Eastern Cooperative Oncology Group

Table 3. Most common AEs (≥20%) by preferred term, regardless of causality

R/R AML 500 mg (n=179)	Any grade, n (%)	Grade ≥3, n (%)
Any AE	179 (100)	148 (82.7)
Diarrhea	60 (33.5)	4 (2.2)
Leukocytosis	56 (31.3)	14 (7.8)
Nausea	56 (31.3)	1 (0.6)
Febrile neutropenia	52 (29.1)	52 (29.1)
Fatigue	51 (28.5)	3 (1.7)
ECG QT prolonged	46 (25.7)	18 (10.1)
Dyspnea	44 (24.6)	7 (3.9)
Edema peripheral	43 (24.0)	0 (0.0)
Pyrexia	41 (22.9)	2 (1.1)
Anemia	40 (22.3)	36 (20.1)
Cough	38 (21.2)	1 (0.6)

ECG = electrocardiogram

Table 4. Investigator-reported AEs of interest by preferred term

AEs of interest	R/R AML 500 mg (n=179)	
	n (%)	Details
Grade ≥3 leukocytosis[a]	14 (8)	• Managed with hydroxyurea • None were fatal
Grade ≥3 ECG QT prolongation	18 (10)	• Study drug was reduced in 2 patients and held in 13 patients (all grades) • None were fatal • QT-prolonging medications such as antifungals and fluoroquinolone anti-infectives were allowed on study with monitoring
IDH-DS (all grades)	19 (10.6)	• Resolved in 17 patients, ongoing in 2 patients at data cutoff • Grade ≥3 IDH-DS in 9 patients (5.0%) • 7/19 patients with IDH-DS had co-occurring leukocytosis • Study drug held in 6 patients (3.4%) • No instances of IDH-DS led to dose reduction, permanent treatment discontinuation, or death • Managed with corticosteroids and diuretics, and hydroxyurea if accompanied by leukocytosis • Best response for the 19 patients with IDH-DS: 5 CR, 3 CRi/CRp, 2 MLFS, 8 SD, and 1 not evaluable

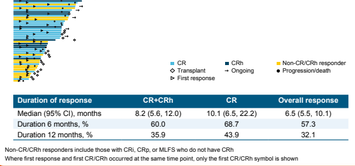
[a]Grade 3: white blood cells >100,000/mm³; Grade 4: clinical manifestations of leukostasis, urgent intervention indicated
CRi = CR with incomplete hematologic recovery; CRp = CR with incomplete platelet recovery; DS = differentiation syndrome; MLFS = morphologic leukemia-free state; SD = stable disease

Table 5. Response rates

	R/R AML 500 mg (n=179)
CR+CRh rate, n (%) [95% CI]	57 (31.8) [25.1, 39.2]
Time to CR/CRh, median (range), months	2.0 (0.9–5.6)
Duration of CR/CRh, median [95% CI], months	8.2 [5.6, 12.0]
CR rate, n (%) [95% CI]	43 (24.0) [18.0, 31.0]
Time to CR, median (range), months	2.8 (0.9–8.3)
Duration of CR, median [95% CI], months	10.1 [6.5, 22.2]
CRh rate, n (%)	14 (7.8)
Duration of CRh, median [95% CI], months	3.6 [1.0, 5.5]
Overall response rate, n (%) [95% CI]	75 (41.9) [34.6, 49.5]
Time to first response, median (range), months	1.9 (0.8–4.7)
Duration of response, median [95% CI], months	6.5 [5.5, 10.1]
Best response, n (%)	
CR	43 (24.0)
CRi or CRp	21 (11.7)
MLFS	11 (6.1)
SD	68 (38.0)
PD	15 (8.4)
NA	21 (11.7)

CRh includes 9 patients with investigator-assessed responses of CRi/CRp and 5 with MLFS
Overall response rate includes CR, CRi/CRp, MLFS, and PR
At the time of the database lock, among the 179 patients with R/R AML, 5 from dose escalation and 1 from dose expansion were not positive for m*IDH1* by the companion diagnostic test and none of these 6 patients achieved a CR or CRh. The patient from dose expansion was found to be positive for m*IDH1* by the companion diagnostic test after database lock
CR+CRh rate was consistent across baseline age groups, including patients who were >65 years of age
NA = not assessed; PD = progressive disease

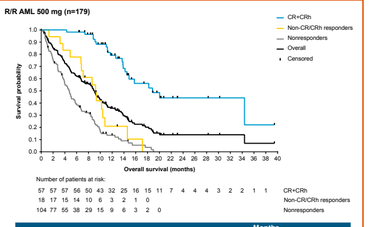
Figure 1. Duration of treatment and best overall response in responders



Duration of response	CR+CRh	CR	Overall response
Median (95% CI), months	8.2 (5.6, 12.0)	10.1 (6.5, 22.2)	6.5 (5.5, 10.1)
Duration 6 months, %	60.0	68.7	57.3
Duration 12 months, %	35.9	43.9	32.1

Non-CR/CRh responders include those with CRi, CRp, or MLFS who do not have CRh
Where first response and first CR/CRh occurred at the same time point, only the first CR/CRh symbol is shown

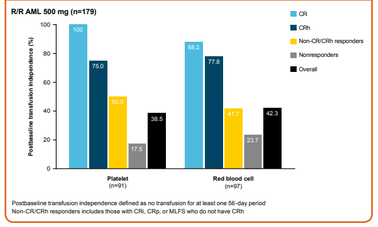
Figure 2. Overall survival by best response



	Months
Overall survival, median (95% CI)	
CR+CRh	18.8 (14.2, NE)
Non-CR/CRh responders	9.2 (6.7, 10.8)
Nonresponders	4.7 (3.7, 5.7)
All	9.0 (7.1, 10.0)
Overall follow-up, median (range)	15.3 (0.2–39.5)

Non-CR/CRh responders includes those with CR, CRh, or MLFS who do not have CRh; nonresponders includes all others, including those with best responses of SD, PD, or not evaluable
NE = not estimable

Figure 3. Transfusion independence in patients who were dependent at baseline



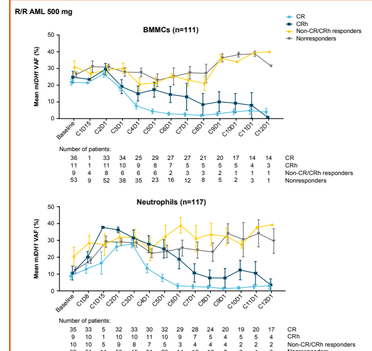
Postbaseline transfusion independence defined as no transfusion for at least one 56-day period
Non-CR/CRh responders includes those with CRi, CRp, or MLFS who do not have CRh

Table 6. Exposure-adjusted incidence of febrile neutropenia and grade ≥3 infections

	R/R AML 500 mg				
	Best response				Overall (n=179)
	CR (n=43)	CRh (n=14)	Non-CR/CRh responders (n=18)	Nonresponders (n=104)	
All grade febrile neutropenia[a]	2.0 (1.0, 3.8)	3.7 (1.4, 9.8)	6.1 (2.7, 13.5)	12.1 (8.8, 16.5)	5.9 (4.5, 7.6)
Grade ≥3 infections[b]	2.6 (1.5, 4.6)	6.4 (3.1, 13.5)	13.1 (7.6, 22.6)	21.3 (16.8, 27.0)	10.2 (8.4, 12.4)

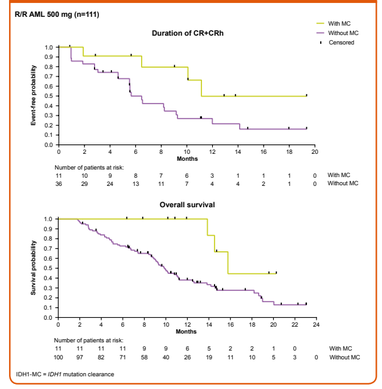
Incidence rate reported as 100 patients/month (95% CI), calculated as total number of specific AEs per total person exposure time in months × 100 for all patients with the same best overall response
[a]Preferred term, including febrile bone marrow aplasia preferred term. [b]Based on MedDRA V20.0 System Organ Class of infections and infestations

Figure 4. Longitudinal mean m*IDH1* VAF by best overall response



C = Cycle; D = Day

Figure 5. Duration of response and overall survival in patients with IDH1-MC



IDH1-MC = *IDH1* mutation clearance

Table 7. *IDH1* mutation clearance in BMMCs

Response	R/R AML 500 mg (n=111)		
	n	*IDH1* mutation clearance,[a] n (%)	Detectable *IDH1* mutation, n (%)
CR+CRh	47	11 (23)	36 (77)
CR	36	10 (28)	26 (72)
CRh	11	1 (9)	10 (91)
Others	64	0	64 (100)
Non-CR+CRh responders	9	0	9 (100)
Nonresponders	55	0	55 (100)
p-value[b]		<0.001	

[a]Defined as a reduction in m*IDH1* VAF to below the limit of detection of 0.02–0.04% ($2–4\times10^{-2}$) by digital PCR for at least one on-study time point. [b]p-value based on Fisher's exact test comparing *IDH1* mutation clearance in patients who had a best overall response of CR+CRh with patients who had other responses (non-CR+CRh responders and nonresponders)

CONCLUSIONS

- In this high-risk, molecularly defined mIDH1 R/R AML patient population, ivosidenib induced durable responses:
  - CR+CRh rate 32%, median duration 8.2 months, median overall survival 18.8 months
  - Overall response rate 42%, median duration 6.5 months.
- Additional benefits:
  - Transfusion independence across response categories
  - Decreased frequency of febrile neutropenia and infections in responders.
- Ivosidenib induced IDH1-MC in BMMCs in 23% of patients with a best overall response of CR or CRh.
- Ivosidenib was well tolerated.
  - AEs of interest were managed with standard-of-care treatments and ivosidenib dose modifications, as required.
- Ongoing AML studies:
  - Phase 1 ivosidenib or enasidenib + azacitidine (AZA)[9]
  - AGILE: global, phase 3, first-line ivosidenib + AZA versus placebo + AZA[10]
  - Phase 1 ivosidenib or enasidenib in combination with standard AML induction and consolidation therapy.[11]

References

1. Dang L et al. *Nature* 2009;462:739-44.
2. Lu C et al. *Nature* 2012;483:474-8.
3. Saha SK et al. *Nature* 2014;513:110-4.
4. Xu W et al. *Cancer Cell* 2011;19:17-30.
5. Popovici-Muller J et al. *ACS Med Chem Lett* 2018;9:300-5.
6. DiNardo CD et al. *N Engl J Med* 2018;378:2386-98.
7. Roboz GJ et al. *J Clin Oncol* 2014;32:1919-26.
8. Cheson B et al. *J Clin Oncol* 2013;21:4642-9.
9. DiNardo CD et al. *2018 ASCO Annual Meeting*: Oral presentation S1562.
10. Stein EM et al. *2018 ASCO Annual Meeting*: Poster TPS7074.
11. Stein EM et al. *2017 ASH Annual Meeting*: Oral presentation 726.

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.

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

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

Presented at the Society of Hematologic Oncology (SOHO) 6th Annual Meeting, September 12–15, 2018, Houston, TX, USA