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).[6]
  - 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, *mIDH1* 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).[6]
- 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)[8]	<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 *mIDH1* 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 *mIDH1* (**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

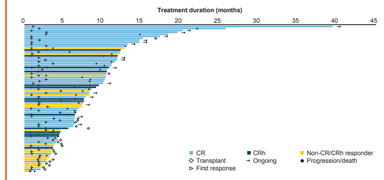
[a]Grade 3: white blood cells >100,000/mm³; Grade 4: clinical manifestations of leukostasis, urgent intervention indicated
CRi = CR with incomplete hematologic recovery; CRp = CR with incomplete platelet recovery; DS = differentiation syndrome; MLFS = morphologic leukemia-free state; SD = stable disease

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 *mIDH1* 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 *mIDH1* 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

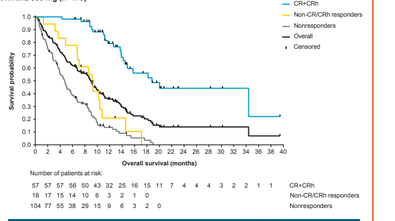
Figure 1. Duration of treatment and best overall response in responders



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

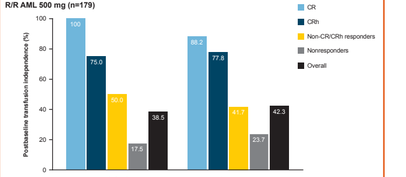
Figure 2. Overall survival by best response



	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 CRi, CRp, 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



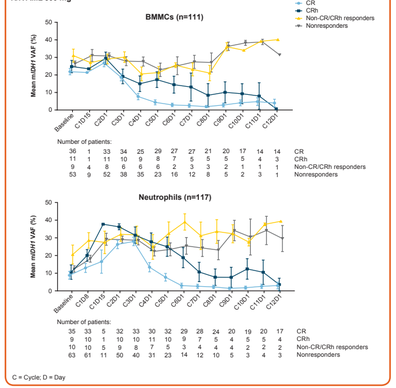
Posttreatment transfusion independence defined as no transfusion for at least one 56-day period
Non-CR/CRh responders includes those with CRi, CRp, or MLFS who do not have CRh

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)

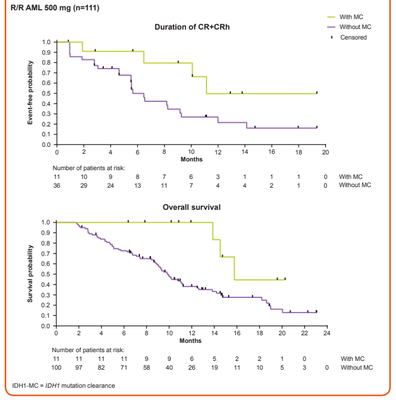
Incidence rate reported as 100 patients/month (95% CI), calculated as total number of specific AEs per total person-exposure time in months × 100 for all patients with the same best overall response
[a]Preferred term, including febrile bone marrow aplasia preferred term. [b]Based on MedDRA V20.0 System 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 mIDH1 VAF to below the limit of detection of 0.02–0.04% (2–4×10⁻⁴) 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]

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