Mutant IDH1 inhibitor ivosidenib (AG-120) in combination with azacitidine for newly diagnosed acute myeloid leukemia (ND AML)

Courtney D DiNardo[1], Anthony S Stein[2], Eytan M Stein[3], Amir T Fathi[4], Olga Frankfurt[5], Andre C Schuh[6], Giovanni Martinelli[7], Prapti Patel[8], Emmanuel Raffoux[9], Peter Tan[10], Amer Zeidan[11], Stéphane de Botton[12], Hagop M Kantarjian[1], Richard M Stone[13], Du Lam[14], Jing Gong[14], Vickie Zhang[15], Thomas Winkler[15], Bin Wu[15], Paresh Vyas[16]

[1]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]City of Hope Medical Center, Duarte, CA, USA; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [5]Northwestern University, Chicago, IL, USA; [6]Princess Margaret Cancer Centre, Toronto, ON, Canada; [7]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; [8]University of Texas Southwestern Medical Center, Dallas, TX, USA; [9]Hôpital Saint-Louis, Paris, France; [10]Royal Perth Hospital, Perth, Australia; [11]Yale Cancer Center, New Haven, CT, USA; [12]Institut Gustave Roussy, Villejuif, France; [13]Dana-Farber Cancer Institute, Boston, MA, USA; [14]Celgene Corp., Summit, NJ, USA; [15]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [16]University of Oxford, Oxford, UK

Contact: Thomas.Winkler@agios.com

BACKGROUND

- Somatic mutations in the isocitrate dehydrogenase (*IDH*) 1 and 2 genes occur in ~20% of patients with acute myeloid leukemia (AML).[1]
- The mutant IDH1/2 (mIDH1/2) enzyme catalyzes the reduction of alpha-ketoglutarate to the oncometabolite D-2-hydroxyglutarate (2-HG),[2,3] and the resulting 2-HG accumulation leads to epigenetic dysregulation and impaired cellular differentiation.[4-6]
- Ivosidenib (formerly AG-120) and enasidenib (formerly AG-221) are oral inhibitors of the mIDH1 and mIDH2 proteins, respectively.
- An ongoing phase 1b/2 study is assessing the combination of ivosidenib or enasidenib with the hypomethylating agent azacitidine in patients with mIDH1/2 newly diagnosed (ND) AML.

Ivosidenib

- Ivosidenib is a first-in-class, oral, targeted inhibitor of the mIDH1 enzyme that 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 ND 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 AML. It is currently under review for approval in Europe.
- In 33 patients with mIDH1 ND AML (see Poster 7028, Roboz et al), ivosidenib monotherapy resulted in:[7]
  - An overall response rate (ORR) of 54.5% (95% CI 36.4, 71.9)
  - A rate of complete remission (CR) or CR with partial hematologic recovery (CRh) of 42.4%
  - CR and CR with incomplete hematologic or platelet recovery (CRi/CRp) rates of 30.3% and 18.2%, respectively
  - A CR or CRh duration with a 95% CI lower bound of 4.6 months (median duration not estimable).

Azacitidine

- Azacitidine reduces DNA methylation by inhibiting DNA methyltransferases.
- In older patients with ND AML, azacitidine monotherapy was associated with:[8]
  - Longer median overall survival (OS) than conventional care (10.4 vs 6.5 months; p=0.101)
  - A CR rate of 19.5%.

Rationale for combination

- *In vitro* studies of mIDH1-R132H erythroleukemia cell lines treated with ivosidenib and azacitidine showed enhanced cell differentiation and potentiation of apoptosis compared with either agent alone.[9]

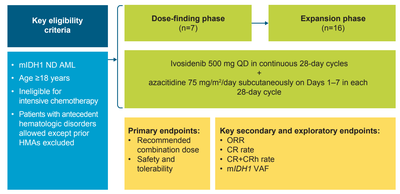
OBJECTIVES

- The aim of this poster is to report preliminary results for all patients with mIDH1 ND AML treated with oral ivosidenib 500 mg once daily (QD) + azacitidine in the phase 1b portion of the ongoing study of mIDH1/2 inhibitors + azacitidine in patients with ND AML who are ineligible for intensive chemotherapy.
  - Primary objective: to assess the safety and tolerability of the ivosidenib + azacitidine combination.
  - Secondary objective: to investigate preliminary efficacy of this combination.
  - Exploratory objectives include the evaluation of changes in m*IDH1* variant allele frequency (VAF) during treatment.

METHODS

- Here we report preliminary data from the ivosidenib + azacitidine phase 1b dose-finding and expansion portions of the ongoing phase 1b/2, open-label, randomized, multicenter trial assessing the combination of ivosidenib or enasidenib with azacitidine in patients with mIDH1/2 ND AML who are ineligible for intensive chemotherapy (ClinicalTrials.gov NCT02677922; enrollment complete).
  - Study design, eligibility criteria, and endpoints are shown in **Figure 1**.

Figure 1. Study design for phase 1b dose-finding and expansion ivosidenib + azacitidine arm (N=23; enrollment complete)



The dose-finding phase had a standard 3 + 3 design; enasidenib arm not shown
HMA = hypomethylating agent

- The ORR comprises CR, CRi/CRp, morphologic leukemia-free state (MLFS), and partial remission (PR), per investigator-reported responses according to the modified International Working Group 2003 criteria for AML.[10]
- CRh was derived by the sponsor, and defined as CR except absolute neutrophil count >0.5 × 10^9/L (500/μL) *and* platelet count >50 × 10^9/L (50,000/μL).
- m*IDH1* VAF in bone marrow mononuclear cells (BMMCs) and peripheral blood mononuclear cells (PBMCs) was quantified by digital PCR (Sysmex OncoBEAM™).
  - *IDH1* mutation clearance was defined as a reduction in m*IDH1* VAF to below the limit of detection of 0.02–0.04% (2–4 × 10^{-4}) for at least one on-study time point.
- The data cutoff date for this analysis was February 19, 2019.

RESULTS

Disposition and demographics

- 23 patients were treated with ivosidenib + azacitidine (**Tables 1–2**).
- As of February 19, 2019, 10 patients (43.5%) remained on study treatment.
- The median number of treatment cycles was 15 (range 1–30).

Table 1. Disposition

	All patients N=23
Treatment ongoing, n	10
Discontinued treatment, n	13
Progressive disease	2
Withdrawal by patient	2
Physician decision	2
Other	2
AE	1
Lack of efficacy	1
Transition to commercially available treatment	1
Disease relapse	1
Allogeneic stem cell transplant	1

AE = adverse event

Table 2. Baseline demographic and disease characteristics

	All patients N=23
Age, median (range), years	76 (61–88)
Age ≥75 years, n (%)	12 (52)
Male/female, n	11/12
m*IDH1* VAF in BMMCs, median (range), %[a,b]	35 (16–76)
ECOG PS, n (%)	
0	5 (22)
1	14 (61)
2	4 (17)
Disease history, n (%)	
De novo AML	15 (65)
Secondary AML	8 (35)
Cytogenetic risk status, n (%)	
Intermediate	15 (65)
Poor	5 (22)
Failure/missing	3 (13)
Hematologic parameters, median (range)	
Hemoglobin, g/dL	9.0 (6.5–14.1)
Platelets, 10^9/L	42 (11–200)
White blood cells, 10^9/L	1.8 (0.6–24.9)

[a]17 of 23 patients had baseline BMMC samples available for analysis
[b]VAF quantified by digital PCR (Sysmex OncoBEAM™)
ECOG PS = Eastern Cooperative Oncology Group performance status

Safety

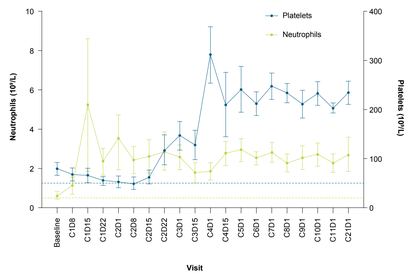
- All-grade AEs occurring in ≥30% of patients were thrombocytopenia (65%), nausea (61%), diarrhea (57%), anemia (52%), constipation (52%), febrile neutropenia (44%), pyrexia (44%), vomiting (35%), fatigue (35%), hypokalemia (35%), dizziness (35%), neutropenia (35%), insomnia (35%), and back pain (30%).
- Serious AEs observed in ≥2 patients included febrile neutropenia (n=9), IDH differentiation syndrome (DS) (n=3), sepsis (n=3), pyrexia (n=3), lung infection (n=2), pneumonia (n=2), and syncope (n=2).
- Grade 3/4 AEs occurring in ≥2 patients are shown in **Table 3**.
- Mean neutrophil and platelet counts were maintained near or above CRh thresholds while on study treatment with ivosidenib + azacitidine (**Figure 2**).
- There were six deaths (three on-treatment deaths: sepsis, enterococcal infection, and enterobacter bacteremia; three deaths in follow-up: disease complication, disease progression, and unknown cause); none were considered related to treatment.
- The 30-day and 60-day mortality rates were 0% and 4%, respectively.

Table 3. Grade 3/4 AEs occurring in ≥2 patients

	All patients N=23
Any grade 3/4 AE regardless of cause, n (%)	22 (96)
Thrombocytopenia	14 (61)
Anemia	10 (44)
Febrile neutropenia	10 (44)
Neutropenia	7 (30)
ECG QT prolonged	3 (13)
Sepsis	5 (22)
IDH DS	2 (9)
Lung infection	2 (9)
Pneumonia	2 (9)
Neutrophil count decreased	2 (9)
Hyponatremia	2 (9)
Atrioventricular block complete	2 (9)
Syncope	2 (9)

ECG = electrocardiogram

Figure 2. Neutrophils and platelets over time (mean ± SEM)



Dashed lines represent neutrophil and platelet thresholds for CRh
C = Cycle; D = Day; SEM = standard error of the mean

IDH DS

- There were four cases of DS, of which three were serious AEs.
  - DS resolved in all four patients.
  - Three patients required treatment and the study drug was held in one patient only.
- There were no discontinuations or deaths due to DS.
- Three of the four patients with DS were managed with steroids (one had co-occurring leukocytosis and also received hydroxyurea).
- Best responses in patients with DS were CR (n=2) and stable disease (SD; n=1); one patient withdrew consent before disease response assessment.

Efficacy

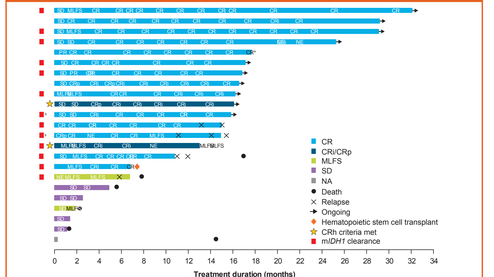
- The ORR was 78.3% (n=18), which included investigator-reported responses of CR (60.9%; n=14), CRi/CRp (8.7%; n=2), and MLFS (8.7%; n=2) (**Table 4** and **Figure 3**).
- Median time to response was 1.8 months (range 0.7–3.8), and median time to CR was 3.7 months (range 0.8–15.7).
- Median durations of response and CR were not estimable (NE) (95% CI 10.3, NE and 9.3, NE, respectively).

Table 4. Response rates

Response parameter	All patients N=23
CR, n (%) [95% CI]	14 (60.9) [38.5, 80.3]
Time to CR, median (range), months	3.7 (0.8–15.7)
Duration of CR, median [95% CI], months	NE [9.3, NE]
CR+CRh,[a] n (%) [95% CI]	16 (69.6) [47.1, 86.8]
Time to CR+CRh, median (range), months	2.8 (0.8–11.5)
Duration of CR+CRh, median [95% CI], months	NE [12.2, NE]
CRh, n (%)	2 (8.7)
ORR, n (%) [95% CI]	18 (78.3) [56.3, 92.5]
Time to response, median (range), months	1.8 (0.7–3.8)
Duration of response, median [95% CI], months	NE [10.3, NE]
Best response[b]	
CR, n (%) [95% CI]	14 (60.9) [38.5, 80.3]
CRi/CRp, n (%)	2 (8.7)
MLFS, n (%)	2 (8.7)
OS, 12-month rate, % [95% CI][c]	82.0 [58.8, 92.8]
Duration of follow-up, median (range), months	16.1 (1.3–31.7)

[a]Sponsor derived
[b]Modified International Working Group criteria
[c]Determined using Kaplan-Meier method

Figure 3. Treatment duration and best overall response



[a]Patient continued on commercially available ivosidenib
[b]Patient had m*IDH1* clearance in PBMCs only (BMMCs not available); all other patients had m*IDH1* clearance in both BMMCs and PBMCs
NA = not assessed; NE = not evaluable

Exploratory findings

- Longitudinal m*IDH1* VAF was available from both BMMCs and PBMCs for 21 patients, including all 14 with CR (**Table 5**).
  - Two nonresponding patients had VAF data available from PBMCs only.
- Good concordance was observed between VAF data collected from BMMCs and PBMCs.

Table 5. *IDH1* mutation clearance[a] by best overall response

	BMMCs N=21	PBMCs N=23
	n/N (%)	
CR/CRh	10/16 (63)	12/16 (75)
CR	9/14 (64)	11/14 (79)
CRh	1/2 (50)	1/2 (50)
Non-CR/CRh responders	1/2 (50)	1/2 (50)
Nonresponders	0/3 (0)	0/5 (0)

[a]Reduction in m*IDH1* VAF to below the limit of detection of 0.02–0.04% (2–4 × 10^{-4}) for at least one on-study timepoint

DISCUSSION

- **The ivosidenib + azacitidine combination was well tolerated in patients with mIDH1 ND AML who are ineligible for intensive chemotherapy.**
  - The safety profile was consistent with those of ivosidenib and azacitidine alone in this patient population.[7,8]
  - Cytopenias were in line with those seen for azacitidine alone,[8] and favorable compared with other emerging hypomethylating agent combinations.
- **At the time of data cutoff, efficacy data were promising for ivosidenib + azacitidine.**
  - ORR was 78%, with 61% of patients achieving a CR.
  - Median duration of CR was not reached at data cutoff (95% CI 9.3, NE).
  - The 12-month survival rate was 82%.
- **The majority of patients with CR also had *IDH1* mutation clearance, as assessed by digital PCR, suggesting direct impact on the biology of mIDH1 AML.**
- **Based on these phase 1b results, the ivosidenib + azacitidine combination is currently being investigated in the phase 3 AGILE study in patients with ND AML who are ineligible for intensive therapy (ClinicalTrials.gov NCT03173248), and the study is actively enrolling.**

Acknowledgments

We thank the patients, families, co-investigators, and all study personnel who participated in this trial.

Disclosures

This study was funded by Agios Pharmaceuticals, Inc. and Celgene Corp.

CDD, ASS, EMS, ATF, OF, ACS, GM, PP, ER, PT, AZ, SdB, HMK, RMS, and PV: disclosures are available through the ASCO meeting library. DL: Celgene – employment and stockholder. JG: Celgene – employment. VZ and TW: Agios – employment and stockholder. BW: Agios – employment, stockholder, and patents.

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

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