Safety and clinical activity of 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], Hartmut Döhner[7], Giovanni Martinelli[8], Prapti Patel[9], Emmanuel Raffoux[10], Peter Tan[11], Amer Zeidan[12], Stéphane de Botton[13], Hagop M Kantarjian[1], Richard M Stone[14], Du Lam[15], Xiwei Wang[15], Jing Gong[15], Stephanie M Kapsalis[16], Denice Hickman[16], Vickie Zhang[16], Thomas Winkler[16], Bin Wu[16], Paresh Vyas[17]

[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]Ulm University Hospital, Ulm, Germany; [8]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; [9]University of Texas Southwestern Medical Center, Dallas, TX, USA; [10]Hôpital Saint-Louis, Paris, France; [11]Royal Perth Hospital, Perth, Australia; [12]Yale Cancer Center, New Haven, CT, USA; [13]Institut Gustave Roussy, Villejuif, France; [14]Dana-Farber Cancer Institute, Boston, MA, USA; [15]Celgene Corp., Summit, NJ, USA; [16]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [17]University of Oxford, Oxford, UK

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 (TIBSOVO®; formerly AG-120) and enasidenib (IDHIFA®; 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 (Vidaza®) in patients with mIDH1/2 newly diagnosed AML (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 adult patients with relapsed or refractory (R/R) AML with a susceptible *IDH1* mutation as detected by an FDA-approved test, and is currently under review for approval in Europe.
- In patients with mIDH1 R/R AML, ivosidenib monotherapy resulted in:[7]
  - An overall response rate (ORR) of 41.6% (95% CI 32.9, 50.8)
  - A rate of complete remission (CR) or CR with partial hematologic recovery (CRh) of 30.4%
  - CR and CR with incomplete hematologic or platelet recovery (CRi/CRp) rates of 21.6% and 12.8%, respectively
  - A median duration of CR or CRh of 8.2 months.

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]

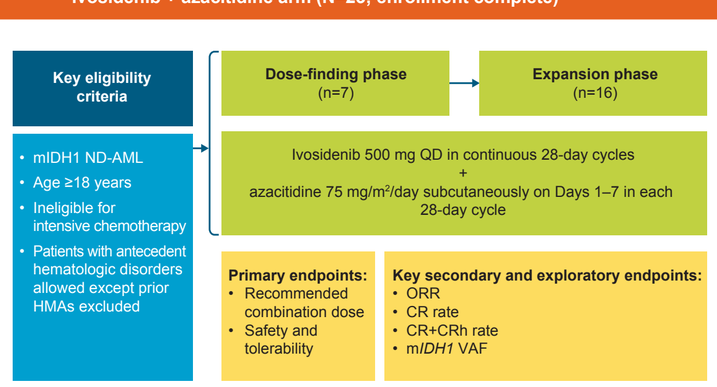
OBJECTIVES

- 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

- This is a phase 1b/2 open-label, randomized, multicenter trial to assess the combination of ivosidenib or enasidenib with azacitidine in patients with mIDH1/2 ND-AML who are ineligible for intensive chemotherapy (NCT02677922).
- Here we report preliminary data from the ivosidenib + azacitidine phase 1b dose-finding and expansion portions of this ongoing study (enrollment complete).
  - Study design, eligibility criteria, and endpoints are shown in **Figure 1**.
- 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 1 August 2018.

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

RESULTS

Disposition and demographics

- 23 patients were treated with ivosidenib + azacitidine (**Tables 1–2**).
- As of 1 August 2018, 14 patients (61%) remained on study treatment.
- The median number of treatment cycles was 8 (range 1–22).

Table 1. Disposition

	All patients N=23
Treatment ongoing, n	14
Discontinued treatment, n	9
Progressive disease	3
Disease relapse	1
Lack of efficacy	1
Withdrawal by patient	2
Death	1
Allogeneic stem cell transplant	1

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	17 (74)
Secondary AML	6 (26)
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 adverse events (AEs) occurring in ≥30% of patients were nausea (61%), diarrhea (57%), anemia (52%), thrombocytopenia (52%), constipation (48%), febrile neutropenia (44%), vomiting (39%), pyrexia (39%), fatigue (35%), hypokalemia (35%), dizziness (35%), and insomnia (30%).
- Serious AEs observed in ≥2 patients included febrile neutropenia (n=8), 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 four deaths (three on-treatment deaths: sepsis, enterococcal infection, and enterobacter bacteremia; one death in follow-up: disease complication); none were considered related to treatment.
- The 30-day and 60-day mortality rates were 0% and 4%, respectively.

IDH DS

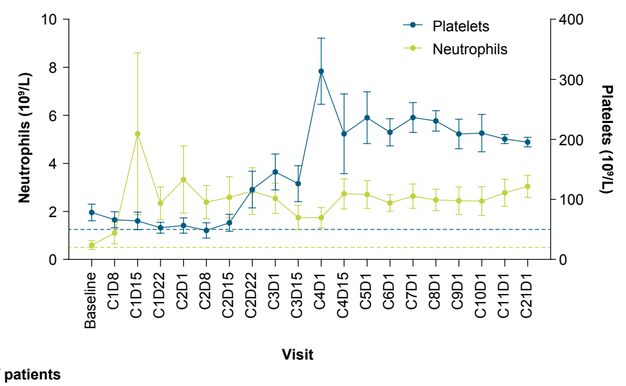
- There were four cases of DS, of which three were serious AEs.
  - DS resolved in all four patients.
  - Three patients required treatment and the study drug was held in one patient only.
- There were no discontinuations or deaths due to DS.
- Three of the four patients with DS were managed with steroids (one had cooccurring 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.

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	11 (48)
Anemia	10 (44)
Febrile neutropenia	10 (44)
Neutropenia	6 (26)
ECG QT prolonged	3 (13)
Sepsis	5 (22)
IDH DS	2 (9)
Lung infection	2 (9)
Pneumonia	2 (9)
Neutrophil count decreased	2 (9)
Platelet 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)



Number of patients

Neutrophils	22	21	22	20	19	19	17	17	18	17	16	15	14	16	16	18	12	11	6	5
Platelets	21	22	22	22	20	17	18	18	18	17	16	14	14	16	17	17	13	11	6	5

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

Efficacy

- The ORR was 78.3% (n=18), which included investigator-reported responses of CR (56.5%; n=13), CRi/CRp (13.0%; n=3), 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 3.5 months (range 0.8–6.0).
- Median durations of response and CR were not estimable (NE) (95% CI 9.5, NE and 7.7, NE, respectively).

Exploratory findings

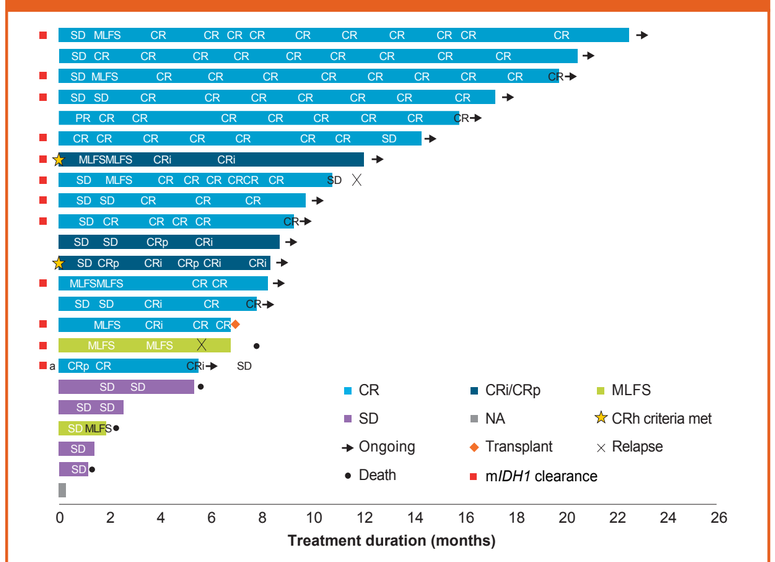
- Longitudinal m*IDH1* VAF was available from both BMMCs and PBMCs for 21 patients, including all 13 with CR (**Table 5**).
  - Two nonresponding patients had VAF data available from PBMCs only.
- Good concordance was observed between VAF data collected from BMMCs and PBMCs.

Table 4. Response rates

Response parameter	All patients N=23
CR, n (%) [95% CI]	13 (56.5) [34.5, 76.8]
Time to CR, median (range), months	3.5 (0.8–6.0)
Duration of CR, median [95% CI], months	NE [7.7, NE]
CR+CRh,[a] n (%) [95% CI]	15 (65.2) [42.7, 83.6]
Time to CR+CRh, median (range), months	2.2 (0.8–6.0)
Duration of CR+CRh, median [95% CI], months	NE [7.7, 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 [9.5, NE]
Best response[b]	
CR, n (%) [95% CI]	13 (56.5) [34.5, 76.8]
CRi/CRp, n (%)	3 (13)
MLFS, n (%)	2 (8.7)
OS, 12-month rate, % [95% CI][c]	82 [59, 93]
Duration of follow-up, median (range), months	9.5 (1.3–24.0)

[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 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

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

	BMMCs (N=21)	PBMCs (N=23)
	n/N (%)	
CR/CRh	10/15 (67)	11/15 (73)
CR	9/13 (69)	10/13 (77)
CRh	1/2 (50)	1/2 (50)
Non-CR/CRh responders	1/3 (33)	1/3 (33)
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 57% of patients achieving a CR.
  - Median duration of CR was not reached at data cut off (95% CI 7.7, 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 (NCT03173248), and the study is actively enrolling.**

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Disclosures

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