Abstract 7042

Mutant-IDH Inhibitors, Ivosidenib or Enasidenib, in Combination with Azacitidine (AZA) in Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) Ineligible for Chemotherapy

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BACKGROUND

Mutant-IDH inhibitors

- Ivosidenib (AG-120) and enasidenib (IDHIFA®; AG-221) are oral, small-molecule inhibitors of mutant IDH1 and IDH2 proteins, respectively, that have shown clinical activity in patients with relapsed/refractory (R/R) AML, with overall response rates (ORRs) of ~40% and complete remission (CR) rates of ~20%[1,2]
- As monotherapy in older patients with newly diagnosed mutant-*IDH* AML, ORR with ivosidenib (N=34) was 55.9% (95% CI 37.9%, 72.8%),[3] and with enasidenib (N=39) was 37.8% (95% CI 17.0%, 47.6%)[4]

Azacitidine (AZA)

- AZA reduces DNA methylation by inhibiting DNA methyltransferases
- In a phase 3 study in older patients with newly diagnosed AML, AZA monotherapy nominally prolonged overall survival *vs.* conventional care regimens (median OS 10.4 *vs.* 6.5 months; P=0.101); CR rate with AZA was 19.5%[5]

Mutant-IDH inhibitors + AZA

- Combining ivosidenib or enasidenib with AZA *in vitro* enhanced single-agent effects on releasing differentiation block in mutant-*IDH* leukemia models.[6,7] These combinations showed greater-than-additive increases in hemoglobinization and expression of erythroid differentiation markers, reduced leukemic stem/progenitor cell populations, and potentiated apoptosis[6,7]
- Here we report interim results from the phase 1b portion of an ongoing, open-label, phase 1b/2 study (NCT02677922) of combination therapy with mutant-IDH inhibitors plus AZA in patients with newly diagnosed AML who are not candidates for intensive chemotherapy

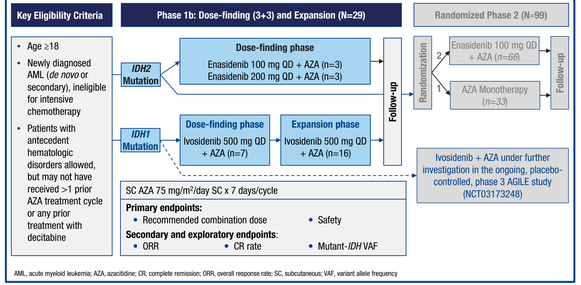
OBJECTIVES

- *Primary:* Assess the safety and tolerability of ivosidenib + AZA or enasidenib + AZA in patients with an *IDH1* or *IDH2* mutation, respectively
- *Secondary:* Investigate the preliminary efficacy of these combination regimens
- *Exploratory:* Evaluate changes in mutant *IDH1* and *IDH2* variant allele frequencies (VAF) during treatment

METHODS

- Phase 1b eligibility criteria, study design and endpoints are detailed in **Figure 1**
- Ivosidenib or enasidenib taken orally once-daily in continuous 28-day treatment cycles
- AZA dosing: 75 mg/m^2/day SC x 7 days/cycle
- Overall response rate (ORR) comprises CR, CR with incomplete hematologic or platelet recovery (CRi/CRp), morphologic leukemia-free state (MLFS), and partial remission (PR), per modified International Working Group 2003 criteria for AML[8]
- *IDH* VAF was quantified by digital PCR (Sysmex OncoBEAM™) using bone marrow mononuclear cells (BMMC). *IDH* mutational clearance was defined as a reduction of mutant-*IDH1* or mutant-*IDH2* VAF to below the limit of detection of 0.02–0.04% (2–4 × 10^{-4}) at any time on-study
- The phase 1b study portion included an expansion of the ivosidenib 500 mg QD + AZA combination regimen. The activity of enasidenib + AZA will be assessed in a larger patient cohort in the randomized phase 2 portion of this study

Figure 1. Key Eligibility Criteria, Study Design, and Endpoints



AML, acute myeloid leukemia; AZA, azacitidine; CR, complete remission; ORR, overall response rate; SC, subcutaneous; VAF, variant allele frequency

Trial Registry: ClinicalTrials.gov NCT02677922

RESULTS

Patients

- In all, 29 patients were enrolled: ivosidenib + AZA, n=23; enasidenib + AZA, n=6 (**Table 1**)
- At data cutoff (March 15, 2018), 19 patients remained on study (ivosidenib + AZA, n=17; enasidenib + AZA, n=2)
  - Treatment exposure in each arm is reported in **Table 2**
  - Reasons for treatment discontinuation:
    - *Ivosidenib + AZA:* patient decision, death (n=2 each); disease progression, treatment failure (n=1 each)
    - *Enasidenib + AZA:* disease progression (n=2); patient decision, allogeneic stem cell transplant (n=1 each)

Safety

- No unexpected treatment-emergent adverse events (TEAEs) emerged with these combination regimens. The most common TEAEs (any grade/cause) were gastrointestinal events and enasidenib-related bilirubin increases (**Table 3** and **Table 4**)
- *Ivosidenib + AZA:*
  - The most common grade 3-4 TEAEs (any cause) were hematological events (**Table 3**)
  - Twenty-two patients (96%) experienced a treatment-related TEAE. The most common were nausea (n=12), vomiting (n=7), QT interval prolongation (n=6), and fatigue (n=5)
  - Serious TEAEs reported in >2 patients were febrile neutropenia (n=8) and IDH differentiation syndrome (IDH-DS; n=3)
- *Enasidenib + AZA:*
  - There was no meaningful difference in type or frequency of TEAEs between the enasidenib 100 mg and 200 mg daily dosing regimens
  - Hyperbilirubinemia (any grade) was reported in 5 patients. The most common grade 3-4 TEAEs were hematological events (**Table 4**)
  - Treatment-related TEAEs were reported for all 6 patients. Those occurring in >1 patient were nausea (n=4); and vomiting, hyperbilirubinemia, neutropenia, diarrhea and fatigue (n=2 each)
  - Serious TEAEs in >1 patient were hyperbilirubinemia, pneumonia, and pyrexia (n=2 each)

Response

- *Ivosidenib + AZA:*
  - In all, 18/23 patients (78%) achieved a response, 10 of whom attained CR (**Table 5**)
    - Among patients with poor-risk cytogenetics at baseline, 4/5 achieved a response on-study
  - Median time to first response was 1.8 months (range 0.7–3.8) and to best response was 3.6 months (0.8–6.7) (**Figure 2**)
  - Median duration of response was not reached (NR)
- *Enasidenib + AZA:*
  - Four of 6 patients responded, including 3 who attained CR (**Table 5**)
  - One patient maintained stable disease and 1 experienced only disease progression on study (**Figure 2**)

IDH Mutation Clearance

- Among patients with available longitudinal VAF profiling, *IDH* mutation clearance was observed in 7 of 21 patients in the ivosidenib + AZA arm and in 3 of 6 patients in the enasidenib + AZA arm (**Figure 3**)

Table 1. Baseline Demographic and Disease Characteristics

	Ivosidenib + AZA (N=23)	Enasidenib 100 mg + AZA (n=3)	Enasidenib 200 mg + AZA (n=3)	Enasidenib + AZA Total (N=6)
Age (years), median (range)	**76 (61–88)**	76 (69–79)	65 (64–67)	**68 (64–79)**
Age ≥65, n (%)	**20 (87)**	3 (100)	2 (67)	**5 (83)**
Gender, n Male/Female	**11/12**	1/2	1/2	**2/4**
***IDH2* mutation site**, n (%)				
R140	**NA**	2 (67)	2 (67)	**4 (67)**
R172	**NA**	1 (33)	1 (33)	**2 (33)**
ECOG PS, n (%)				
0	**5 (22)**	0	1 (33)	**1 (17)**
1	**14 (61)**	3 (100)	2 (67)	**5 (83)**
2	**4 (17)**	0	0	**0**
Co-mutations, n (%)	**n=13**	n=2	n=3	**n=5**
FLT3 (–ITD or –TKD)	**0**	1 (50)	2 (67)	**3 (60)**
RUNX1	**3 (23)**	0	0	**0**
NPM1	**1 (8)**	0	1 (33)	**1 (20)**
TP53	**2 (15)**	0	0	**0**
Cytogenetic risk, n (%)	**n=20**			
Intermediate	**15 (75)**	3 (100)	3 (100)	**6 (100)**
Poor	**5 (25)**	0	0	**0**
Hemoglobin (g/dL), median (range)	**9.0 (6.5–14.1)**	9.8 (9.8–9.8)	9.7 (9.3–10.8)	**9.8 (9.3–10.8)**
Platelets (10^9/L), median (range)	**42.0 (11–200)**	141.5 (87–196)	42.0 (19–100)	**87.0 (19–196)**
WBC (10^9/L), median (range)	**1.8 (0.6–24.9)**	10.2 (0.8–19.6)	6.7 (1.3–19.2)	**6.7 (0.8–19.6)**

AZA, azacitidine; ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not applicable; WBC, white blood cells

Table 2. Treatment Exposure

	Ivosidenib + AZA (N=23)	Enasidenib + AZA (N=6)
Number of cycles, median (range)	5.0 (1–19)	11.0 (1–18)
Received ≥6 cycles, n	9	4
Received >12 cycles, n	4	3
Number of cycles in dose-finding phase, median (range)	13.0 (1–19)	-
Number of cycles in expansion phase, median, (range)	4.0 (1–11)	-

Table 4. Enasidenib + AZA: Treatment-emergent Adverse Events (Any Cause) in >20% of Patients

	Enasidenib + AZA (N=6)	
	Any Grade	Grade 3-4
	n (%)	
Any TEAE	**6 (100)**	**6 (100)**
Hyperbilirubinemia	5 (83)	2 (33)
Abdominal pain	4 (67)	0
Nausea	4 (67)	0
Vomiting	4 (67)	0
Pyrexia	4 (67)	0
Anemia	3 (50)	3 (50)
Thrombocytopenia	3 (50)	3 (50)
Constipation	3 (50)	1 (17)
Dysgeusia	3 (50)	0
Diarrhea	3 (50)	0
Hypotension	3 (50)	0
Neutropenia	2 (33)	2 (33)
Lung infection	2 (33)	2 (33)
Pneumonia	2 (33)	2 (33)
Hypoxia	2 (33)	1 (17)
Fatigue	2 (33)	0
Gait disturbance	2 (33)	0
Rhinorrhea	2 (33)	0
Fall	2 (33)	0
Peripheral edema	2 (33)	0
Delirium	2 (33)	0
Decreased appetite	2 (33)	0
Cough	2 (33)	0

Table 3. Ivosidenib + AZA: Treatment-emergent Adverse Events (Any Cause) in >20% of Patients

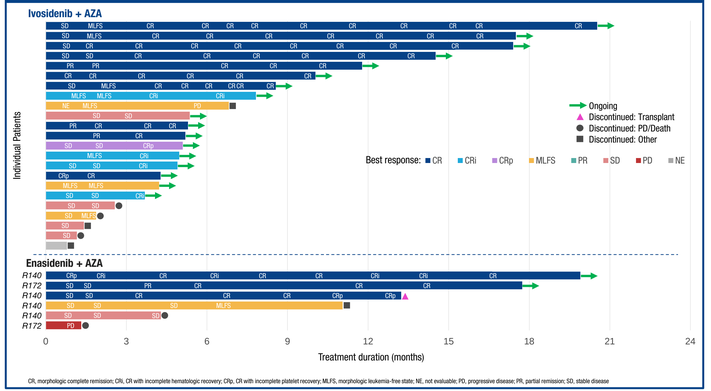
	Ivosidenib + AZA (N=23)	
	Any Grade	Grade 3-4
	n (%)	
Any TEAE	**23 (100)**	**22 (96)**
Nausea	14 (61)	1 (4)
Anemia	12 (52)	10 (44)
Thrombocytopenia	11 (48)	10 (44)
Febrile neutropenia	9 (39)	9 (39)
Constipation	9 (39)	1 (4)
Diarrhea	9 (39)	1 (4)
Vomiting	8 (35)	1 (4)
Dizziness	8 (35)	1 (4)
Pyrexia	7 (30)	1 (4)
Fatigue	7 (30)	0
Insomnia	7 (30)	0
Hypokalemia	7 (30)	0
QT interval prolongation	6 (26)	3 (13)
Back pain	5 (22)	0
Headache	5 (22)	0
Cough	5 (22)	0

Table 5. Hematologic Responses

	Ivosidenib + AZA (N=23)	Enasidenib + AZA (N=6)
Overall response, n (%) (ORR 95% CI)	**18 (78)** (56%, 93%)	**4 (67)** (22%, 96%)
CR, n (%) (CR rate 95% CI)	10 (44) (23%, 66%)	3 (50) (12%, 88%)
CRi/CRp, n (%)	5 (22)	0
PR, n (%)	0	0
MLFS, n (%)	3 (13)	1 (17)
Stable disease, n (%)	4 (17)	1 (17)
Disease progression, n (%)	0	1 (17)
Not evaluable, n (%)	1* (4)	0

*Patient withdrew consent for further treatment on cycle 1 day 5 and did not undergo a response evaluation on-study
CR, complete remission; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; ORR, overall response rate; PR, partial remission

Figure 2. Treatment Durations, Hematologic Responses, and Study Disposition

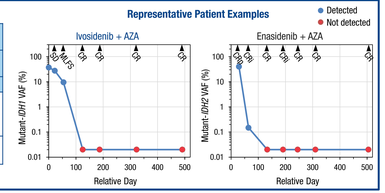


CR, morphologic complete remission; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; NE, not evaluable; PD, progressive disease; PR, partial remission; SD, stable disease

Figure 3. *IDH* Mutation Clearance

	Ivosidenib + AZA (N=21)	Enasidenib + AZA (N=6)
	IDH1 mutation clearance	*IDH2* mutation clearance
Best response	**n/N (%)**	
CR	5/10 (50)	2/3 (66)
Non-CR responders	2/8 (25)	1/1 (100)
Non-responders	0/3	0/2

Includes patients with mutant-*IDH* assessment at one or more post-baseline time point.
Mutation clearance defined as a reduction of mutant-*IDH1* or mutant-*IDH2* VAF in bone marrow mononuclear cells to below the limit of detection (0.02%–0.04%)



DISCUSSION

- Ivosidenib or enasidenib + AZA combinations were well tolerated in patients with newly diagnosed AML
  - At data cutoff, 17 of 23 patients in the ivosidenib + AZA arm and 2 of 6 patients in the enasidenib + AZA arms remained on-study
- TEAE frequencies did not appear higher in the combination treatment arms compared with what has been reported for mutant-IDH inhibitors or AZA alone[5]
- No unexpected safety signals emerged with combination therapy
- Preliminary efficacy of these combination regimens is promising: the CR rate for patients treated with AZA or a mutant-IDH inhibitor as monotherapy is ~20%[1,5]; in this study, almost one-half of patients (45%) treated with AZA + ivosidenib or enasidenib achieved a CR
  - CR/CRi/CRp rates were 65% with ivosidenib + AZA and 50% with enasidenib + AZA, compared with 28% with AZA monotherapy[5]
- *IDH* mutation clearance was observed in more than one-half of patients (7/13) who attained morphologic CR
- Based on these phase 1b results, AZA combinations with ivosidenib 500 mg and enasidenib 100 mg are moving forward for further study
- Ongoing studies of mutant-IDH inhibitors + AZA:
  - Randomized phase 2 portion of the current study of enasidenib + AZA *vs.* AZA monotherapy
  - Phase 3, placebo-controlled AGILE study of ivosidenib + AZA (NCT03173248) in newly diagnosed AML patients ineligible for intensive therapy

REFERENCES

1. Stein et al. *Blood* 2017;130(6):722-31
2. DiNardo et al. *Blood* 2017;130:Abstract 725
3. DiNardo et al. *N Engl J Med* 2018:In Press
4. Pollyea et al. *Blood* 2017;130(Suppl. 1):Abstract 638
5. Dombret et al. *Blood* 2015;126(3):291-9
6. Yen et al. *Cancer Res* 2018;8(Suppl. 1):Abstract 4956
7. Chopra et al. *Cancer Res* 2016;76(14 Suppl.):Abstract 2280
8. Cheson et al. *J Clin Oncol* 2003;21:4642-9

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DISCLOSURES

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