AGILE: A Phase 3, double-blind, randomized, placebo-controlled study of ivosidenib in combination with azacitidine in adults with newly diagnosed acute myeloid leukemia and an *IDH1* mutation

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BACKGROUND

IDH1 mutations and ivosidenib

- Acute myeloid leukemia (AML) has a poor prognosis, and is associated with a high risk of relapse and limited overall survival[1–3]
- Advanced age and comorbidities often preclude curative treatment approaches in elderly patients with AML
- Mutations in isocitrate dehydrogenase 1 (*IDH1*) occur in ~6–10% of AML cases[4–7]
- The mutant IDH1 (mIDH1) enzyme has gain-of-function activity, which catalyzes the reduction of alpha-ketoglutarate (α-KG) to the oncometabolite D-2-hydroxyglutarate (2-HG)[8]
- 2-HG accumulation results in metabolic dysregulation and inhibition of α-KG–dependent enzymes, causing epigenetic dysregulation and a block in cellular differentiation, leading to oncogenesis[9–11]
- Ivosidenib (AG-120) is a first-in-class, oral, potent, targeted, small-molecule inhibitor of the mIDH1 enzyme that is being tested in multiple clinical studies
- Ivosidenib 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 newly diagnosed 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
- In a phase 1 study of patients with m*IDH1* advanced hematologic tumors, including AML (NCT02074839), ivosidenib showed robust clinical activity and a manageable safety profile as a single agent
  - The overall response rate (ORR) was 54.5% and the complete remission (CR) rate was 30.3% in patients with newly diagnosed m*IDH1* AML not eligible for intensive chemotherapy[12]

Preclinical rationale for combining ivosidenib and azacitidine

- The hypomethylating agent azacitidine is a treatment option for patients with AML who are unable to tolerate intensive induction chemotherapy
  - Azacitidine treatment has been found to prolong overall survival versus conventional care regimens in older patients with newly diagnosed AML[13]
- In a preclinical study using an m*IDH1* cell-line model, concurrent treatment with ivosidenib and azacitidine resulted in enhanced cellular differentiation and apoptosis compared with either agent alone[14]

Preliminary evidence for the safety and efficacy of the ivosidenib and azacitidine combination

Study design and methods

- A phase 1b study of ivosidenib in combination with azacitidine in patients with untreated m*IDH1* AML is ongoing (NCT02677922)
- Demographics: median age 76 years (range 61–88), 12 patients (52%) were ≥75 years of age, and 12 of 23 were female. *De novo* and secondary AML were present in 15 (65%) and 8 (35%) patients, respectively. Cytogenetic risk status was intermediate in 65%, poor in 22%, and failed/missing in 13%
- 23 patients were treated with ivosidenib 500 mg once daily (QD) + azacitidine 75 mg/m^2/day subcutaneously (SC) on Days 1–7 in a 28-day schedule[15]

Results

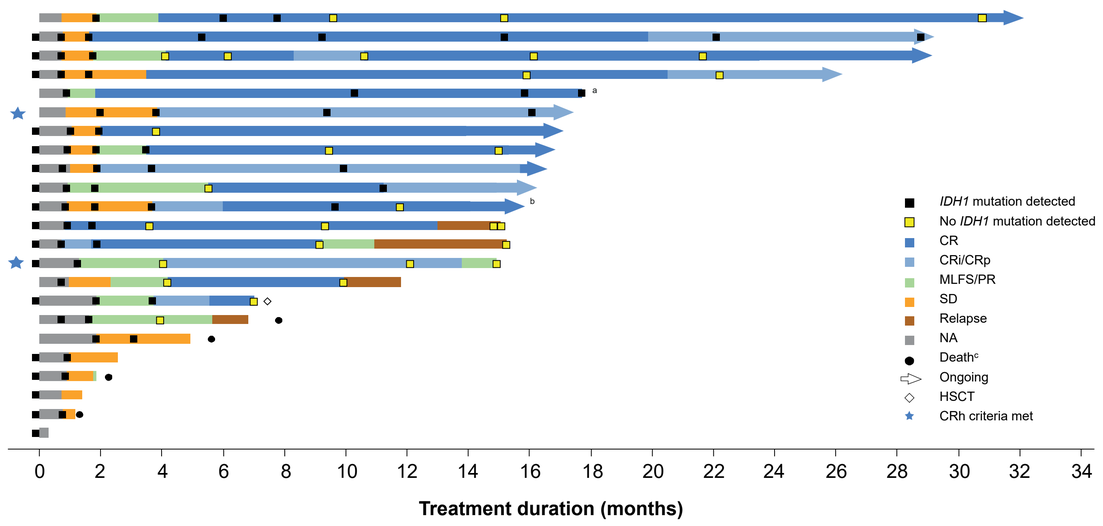
- As of 19February2019, 10 patients (43.5%) remained on study treatment. Patients had been treated for a median of 15 cycles (range, 1–30), and adverse events were consistent with the single-agent experience for both agents. Four cases of IDH differentiation syndrome were reported; of these, three were deemed to be serious adverse events, but all four cases resolved
- Objective responses were observed in 18 of 23 (**78.3%**) patients, with 14 (**60.9%**) achieving a CR and 2 (**8.7%**) achieving CR with partial hematologic recovery (CRh) (**Figure 1** and **Table 1**)
- Preliminary mIDH1 clearance in bone marrow mononuclear cells was observed in **69%** of patients (11 of 16) with CR or CRh, including **71%** (10 of 14) with CR (**Table 2**)

Table 1. Phase 1b study: 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)
Overall survival, 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
CI = confidence interval; CR = complete response; CRh = CR with partial hematologic recovery; CRi/CRp = CR with incomplete hematologic or platelet recovery; MLFS = morphologic leukemia-free state; NE = not estimable; ORR = overall response rate

Figure 1. Phase 1b study: 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; [c]Only deaths occurring within 60 days of last dose were included
BMMCs = bone marrow mononuclear cells; CR = complete response; CRi = CR with incomplete hematologic recovery; CRp = CR with incomplete platelet recovery; HSCT = hematopoietic stem cell transplant; IDH1 = isocitrate dehydrogenase 1; MLFS = morphologic leukemia-free state; NA = not assessed; PBMCs = peripheral blood mononuclear cells; PR = partial remission; SD = stable disease

Table 2. Phase 1b study: *IDH1* mutation clearance[a] by best overall response (BEAMing digital PCR)

	BMMCs[b] (n = 21)	PBMCs (n = 23)
	n/N (%)	
CR/CRh	11/16 (69)	12/16 (75)
CR	10/14 (71)	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)

Using an m*IDH1* variant allele frequency cutoff of 1%, mutation clearance was achieved in 15/16 (94%) patients with CR/CRh (13/14 [93%] with CR and 2/2 [100%] with CRh)
[a]Reduction in m*IDH1* variant allele frequency to below the limit of detection of 0.02–0.04% (2–4 × 10^{-4}) for at least one on-study timepoint; [b]Two nonresponding patients had variant allele frequency data available from PBMCs only. BMMC = bone marrow mononuclear cells; CR = complete remission; CRh = complete remission with partial hematologic recovery; IDH1 = isocitrate dehydrogenase; PCR = polymerase chain reaction.

OBJECTIVE OF PHASE 3 AGILE STUDY

- To evaluate the efficacy and safety of ivosidenib + azacitidine versus placebo + azacitidine in adults with previously untreated m*IDH1* AML who are not candidates for intensive treatment

PHASE 3 AGILE STUDY DESIGN

- AGILE is a global, phase 3, multicenter, randomized, double-blind, placebo-controlled trial in adult patients with previously untreated m*IDH1* AML who are not candidates for intensive therapy
  - ClinicalTrials.gov NCT03173248
- Study design is shown in **Figure 2**
- Central or local confirmation of m*IDH1* status is required for study entry
- An independent data monitoring committee will monitor the data throughout the study

SUMMARY AND CURRENT STATUS

- The favorable safety profile and encouraging clinical activity observed in the phase 1b ivosidenib + azacitidine combination study of the treatment of m*IDH1* AML (CR rate 60.9% and CRh rate 8.7%) support the development of this combination in the phase 3 AGILE study
- The active phase 3 AGILE study is currently recruiting in 20 countries, with a total of 172 study centers in North America, South America, Asia, and participating in the study
- Further information is available at https://clinicaltrials.gov/ct2/show/NCT03173248
- Contact medinfo@agios.com

Figure 2. AGILE study design

Key inclusion criteria
- At least 1 of the following:
  - a. ≥ 75 years old
  - b. ECOG PS = 2
  - c. Severe cardiac disorder (eg, LVEF ≤ 50%)
  - d. Severe pulmonary disorder
  - e. Creatinine clearance <45 mL/minute
  - f. Bilirubin > 1.5 times upper limit of normal
- Patients with antecedent hematologic disorder (eg, MDS, MPN) if not pretreated with an mIDH1 inhibitor or HMA

Key exclusion criteria
- Prior AML therapy (excluding hydroxyurea)
- Heart-rate corrected QT interval using Fridericia's method ≥ 470 msec or any other factor that increases the risk of QT prolongation or arrhythmic events
- Extramedullary disease alone (no detectable bone marrow and no detectable peripheral blood AML)
- Patients who previously have received an experimental agent for MDS may not be randomized until a washout period of ≥ 5 half-lives has elapsed since last dose
- Subjects with a known medical history of progressive multifocal leukoencephalopathy

Eligible patients with untreated m*IDH1* AML

1:1 double-blind randomization (N = 200)

Stratified by region and by *de novo* versus secondary AML

Continuous 28-day cycles

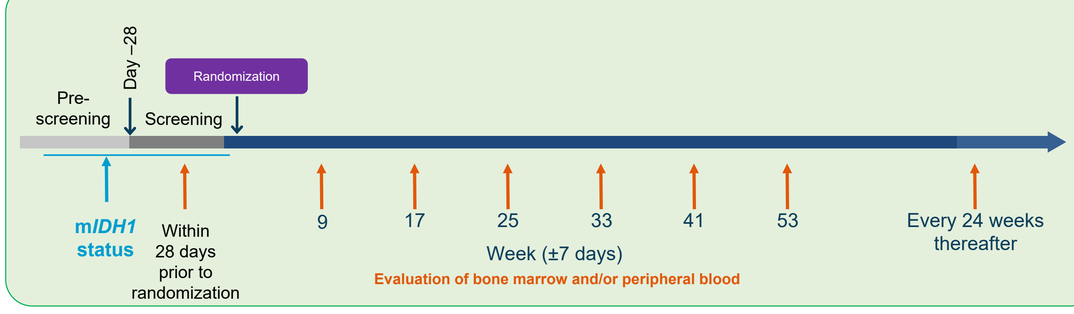
Ivosidenib 500 mg QD orally Days 1–28 + **Azacitidine** 75 mg/m^2 SC or IV Days 1–7 or Days 1–5 and 8–9

Matched placebo orally Days 1–28 + **Azacitidine** 75 mg/m^2 SC or IV Days 1–7 or Days 1–5 and 8–9

Primary Endpoint
- Event-free survival[a]

Secondary Endpoints
- Overall survival
- Rate of CR
- Rate of CR+CRh[b]
- ORR[c]

Other Secondary Endpoints
- Time to response and duration of response
- Safety
- Transfusion requirements
- Rates of infection and hospitalization
- Quality of life (EORTC QLC-C30 and EQ-5D-5L)



Statistics
The study has 80% power for event-free survival (ivosidenib + azacitidine vs placebo + azacitidine arm), with a one-sided alpha of 0.025

[a]The time from randomization until treatment failure, relapse from remission, or death from any cause, whichever comes first; [b]CRh is defined as CR with partial recovery of peripheral blood counts (< 5% bone marrow blasts, platelets > 50,000/μL, and ANC > 500/μL) and will be derived by the sponsor; [c]Includes CR, CRi/CRp, partial response, and MLFS
AML = acute myeloid leukemia; ANC = absolute neutrophil count; CR = complete remission; CRi/CRh = CR with incomplete hematologic or platelet recovery; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer quality of life questionnaire for cancer patients; EQ-5D-5L = EuroQol 5-dimension 5-level health-related quality of life questionnaire; HMA = hypomethylating agent; IV = intravenously; LVEF = left ventricular ejection fraction; MDS = myelodysplastic syndrome; MLFS = morphologic leukemia-free state; MPN = myeloproliferative neoplasms; ORR = overall response rate; PS = performance score; QD = once daily; SC = subcutaneous; WHO = World Health Organization

Acknowledgments

We would like to thank the patients taking part in this study.

Disclosures

This study is funded by Agios Pharmaceuticals, Inc. These data were previously presented at the *61st American Society of Hematology (ASH) Annual Meeting*, December 7–10, 2019, Orlando, FL, USA.
PM: Abbvie, Daiichi Sankyo, Astellas, Agios, Tolero Pharmaceuticals, Glycomimetics and Forma Therapeutics – consultancy; Celgene, Pfizer, Abbvie, Daiichi Sankyo, Astellas, Novartis, Janssen – advisory boards; Celgene, Pfizer, Abbvie, Daiichi Sankyo, Astellas, Novartis, Janssen, Teva – research funding and speakers bureau. **CR:** Celgene, Amgen, Novartis, Daiichi Sankyo – consultant, travel expenses, and research funding; Jazz, Abbvie, Janssen, Astellas, Macrogenics – consultant. **EZ, VD, DM, SVP, RTC**: no conflict of interest. **JJ**: Novartis, Amgen – honoraria. **YM**: Novartis, Kyowa Kirin, Chugai, Otsuka, Astellas, Celgene, Nippon Shinyaku, Sumitomo Dainippon Pharma – honoraria. **JW**: Abbvie – consultancy. **DAG, SRD, TW, VZ**: Agios – employment and stockholder. **PP**: Agios, Astex Pharmaceuticals, Astellas Pharma, Celgene, Jazz Pharmaceuticals, Novartis, Otsuka, Pfizer, Sunesis Pharmaceuticals – consultancy; Astellas Pharma, Agios, Jazz Pharmaceuticals, Novartis, Pfizer, Jazz Pharmaceuticals (Inst) – speakers bureau; AbbVie – travel, accommodations or expenses; Amgen, Janssen Oncology – other; BerGenBio ASA – research funding.
Editorial assistance was provided by Helen Varley, PhD, CMPP, Excel Medical Affairs, Horsham, UK, and supported by Agios.

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