AGILE: A phase 3, multicenter, double-blind, randomized, placebo-controlled study of ivosidenib in combination with azacitidine in adult patients with previously untreated acute myeloid leukemia with an *IDH1* mutation

Pau Montesinos Fernandez[1], Christian Recher[2], Vadim Doronin[3], Rodrigo T Calado[4], Jun Ho Jang[5], Yasushi Miyazaki[6], Jianxiang Wang[7], Diego A Gianolio[8], Scott R Daigle[8], Thomas Winkler[8], Vickie Zhang[8], Peter Paschka[9]

[1]Hospital Universitari i Politècnic La Fe, València, Spain; [2]Institut Universitaire du Cancer de Toulouse Oncopole, CHU de Toulouse and Université de Toulouse III, Toulouse, France; [3]City Clinical Hospital # 40, St. Petersburg, Russian Federation; [4]Ribeirão Preto School of Medicine, University of São Paulo, São Paulo, Brazil; [5]Samsung Medical Centre, Sungkyunkwan University School of Medicine, Seoul, South Korea; [6]Atomic Bomb Disease Institute, Nagasaki University, Nagasaki, Japan; [7]Institute of Hematology & Hospital of Blood Disease – Peking Union Medical College, Beijing, China; [8]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [9]University of Ulm, Ulm, Germany

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

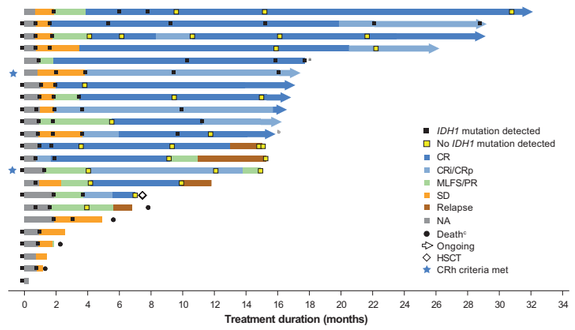
- As of February 19, 2019, 10 patients (43.5%) remained on study treatment. Patients had been treated for a median of 15 cycles (range, 1–30), and adverse events were consistent with the single-agent experience for both agents. Four cases of IDH differentiation syndrome were reported; of these, three 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 m*IDH1* 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
CRi/CRp = CR with incomplete hematologic or platelet recovery; MLFS = morphologic leukemia-free state; NE = not estimable

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; HSCT = hematopoietic stem cell transplant; 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

- See **Poster 2706** (Daigle et al.) in **Session 617** for additional molecular data.

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 Europe participating in the study.
- Further information is available at https://clinicaltrials.gov/ct2/show/NCT03173248.
- Contact medinfo@agios.com.

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Figure 2. AGILE study design

AGILE

Key inclusion criteria
- Patients with previously untreated AML (according to WHO criteria) who are not candidates for or not willing to receive intensive chemotherapy
- ≥18 years of age
- Documented m*IDH1* by central or local laboratory testing
- ECOG performance status score 0–2
- Patients with antecedent hematological disorder (e.g. MDS, MPN) if not pretreated with an mIDH1 inhibitor or HMA

Key exclusion criteria
- Patients who are candidates for and willing to receive intensive chemotherapy
- 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 the last dose

Eligible patients with untreated m*IDH1* AML

1:1 double-blind randomization (N=392) — 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

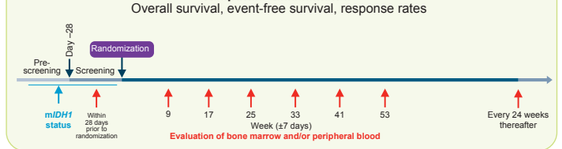
Matched placebo orally Days 1–28 + **Azacitidine** 75 mg/m^2 SC or IV Days 1–7 or Days 1–5 and 8–9

Assessments

Primary
- Overall survival[a]

Secondary
- Event-free survival
- Rate of CR
- Rate of CR+CRh[b]
- ORR[c]
- Time to response and duration of response
- Safety
- Transfusion requirements
- Rates of infection and hospitalization
- Quality of life (EORTC QLQ-C30 and EQ-5D-5L)

Response assessments
Overall survival, event-free survival, response rates



Statistics
The study has 80% power to detect a hazard ratio of 0.71 for overall survival (ivosidenib + azacitidine vs placebo + azacitidine), with a one-sided alpha of 0.025

[a]An amendment to revise the primary endpoint to event-free survival is in progress
[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
ANC = absolute neutrophil count; 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; MDS = myelodysplastic syndrome; MPN = myeloproliferative neoplasms; WHO = World Health Organization