AGILE: 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

- Mutations in *IDH1* occur in ~6–10% of AML cases[1–4]
- Ivosidenib (AG-120) is a first-in-class, oral, potent, targeted, small-molecule inhibitor of the m*IDH1* 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
- Azacitidine is an analog of the naturally occurring pyrimidine cytidine that is approved by the FDA and European Commission for the treatment of adult subjects who are not eligible for HSCT and have intermediate- and high-risk MDS, CML, and AML

AML = acute myeloid leukemia; CML = chronic myelomonocytic leukemia; FDA = Food and Drug Administration; HSCT = hematopoietic stem-cell transplantation; *IDH1* = isocitrate dehydrogenase 1; MDS = myelodysplastic syndromes; m*IDH1* = mutant *IDH1*.

1. Mardis ER et al. *N Engl J Med* 2009;361:1058–66. 2. Ward PS et al. *Cancer Cell* 2010;17:225–34. 3. Patel KP et al. *Am J Clin Pathol* 2011;135:35–45. 4. DiNardo CD et al. *Am J Hematol* 2015;90:732–6.

Background: Phase 1b study

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 out 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 QD + azacitidine 75 mg/m^2/day SC on Days 1–7 in a 28-day schedule

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)
- AEs were consistent with the single-agent experience for both agents
  - Four cases of IDH differentiation syndrome were reported; 3 were deemed to be serious AEs, all 4 cases resolved

AE = adverse event; AML = acute myeloid leukemia; CR = complete remission; CRh = CR with partial hematologic recovery; m*IDH1* = mutant isocitrate dehydrogenase 1; QD = once daily; SC = subcutaneous.
DiNardo CD et al. *J Clin Oncol*. 2020. DOI: 10.1200/JCO.20.01632.

Background: Phase 1b study

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

- Objective responses were observed in 18 of 23 (78.3%) patients, with 14 (60.9%) achieving a CR and 2 (8.7%) achieving CRh
- 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[d]

[a]Sponsor derived. [b]Modified International Working Group criteria. [c]Determined using Kaplan–Meier method. [d]m*IDH1* clearance assessed by BEAMing digital PCR (detection limit 0.02–0.04%).
CI = confidence interval; CR = complete remission; CRh = CR with partial hematologic recovery; CRi/CRp = CR with incomplete hematologic or platelet recovery; m*IDH1* = mutant isocitrate dehydrogenase 1; MLFS = morphologic leukemia-free state; NE = not estimable; ORR = overall response rate.
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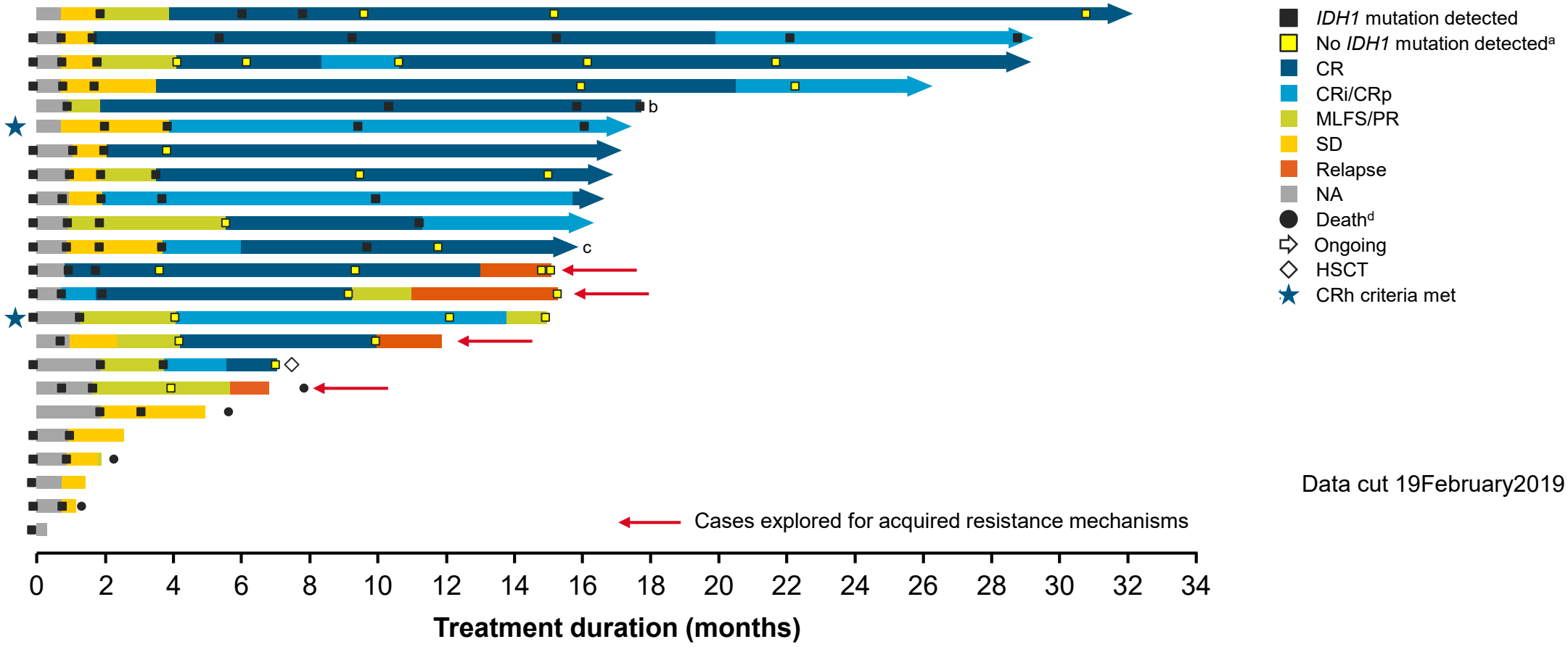
Background: Phase 1b study



Data cut 19February2019

[a]m*IDH1* clearance, assessed in bone marrow mononuclear cells by BEAMing digital PCR (detection limit 0.02–0.04%), was observed in 69% (11/16) of CR/CRh patients; [b]Patient continued on commercially available ivosidenib; [c]Patient had m*IDH1* clearance in PBMCs only (BMMCs not available); all other patients had m*IDH1* clearance in both BMMCs and PBMCs; [d]Only deaths occurring within 60 days of last dose were included.
BMMCs = bone marrow mononuclear cells; CR = complete remission; CRh = CR with partial hematologic recovery; CRi/CRp = CR with incomplete hematologic or platelet recovery; HSCT = hematopoietic stem cell transplant; IDH = isocitrate dehydrogenase 1; MLFS = morphologic leukemia-free state; NA = not assessed; PBMCs = peripheral blood mononuclear cells; PCR = polymerase chain reaction; PR = partial remission; SD = stable disease.

Objective and study design

Objective

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

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
- 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

AML = acute myeloid leukemia; m*IDH1* = mutant isocitrate dehydrogenase 1.

AGILE study design

Key inclusion criteria

- At least 1 of the following criteria defining ineligibility for intensive IC:
  a. ≥ 75 years old
  b. ECOG PS = 2
  c. Severe cardiac disorder (eg, congestive heart failure requiring treatment, LVEF ≤ 50%)
  d. Severe pulmonary disorder (eg, diffusing capacity of the lungs for carbon monoxide ≤ 65%)
  e. Creatinine clearance < 45 mL/minute
  f. Bilirubin > 1.5 times upper limit of normal (× ULN)
  g. Any other comorbidity that the Investigator judges to be incompatible with intensive IC
- Have previously untreated AML, defined according to WHO criteria, with ≥ 20% leukemic blasts in the bone marrow
- Have an *IDH1* mutation resulting in an R132C, R132G, R132H, R132L, or R132S substitution, determined in the bone marrow aspirate, or peripheral blood

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

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

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

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

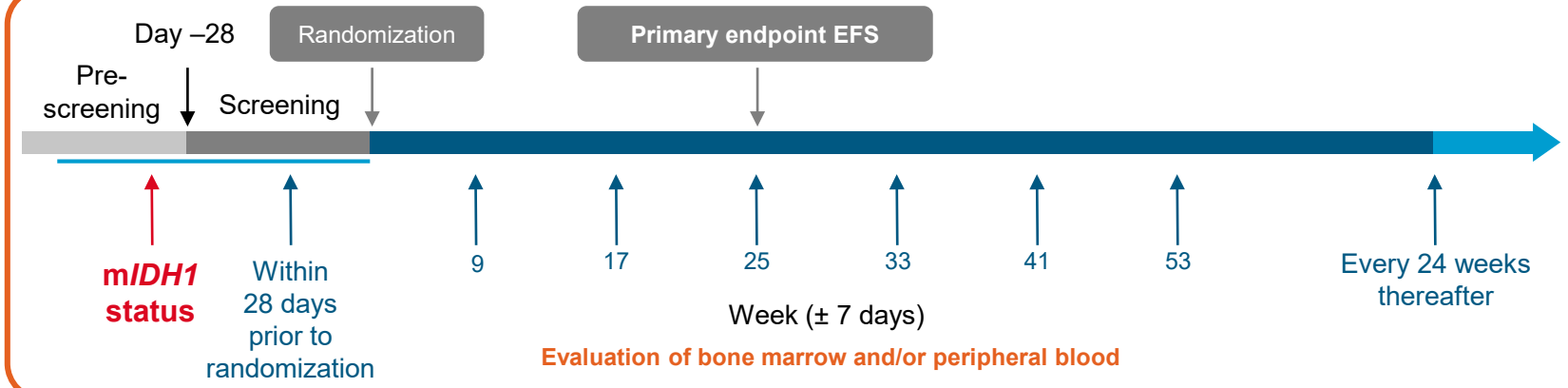
AML = acute myeloid leukemia; ECOG PS = Eastern Cooperative Oncology Group Performance Score; IC = induction chemotherapy; IV = intravenously; LVEF = left ventricular ejection fraction; MDS = myelodysplastic syndrome; m*IDH1* = mutant isocitrate dehydrogenase 1; QD = once daily; SC = subcutaneous; ULN = upper limit of normal; WHO = World Health Organization.

AGILE study design (cont'd)

Primary endpoint
- EFS

Secondary endpoints
- Overall survival
- Rate of CR
- Rate of CR+CRh[a]
- ORR[b]

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)



EFS Definition

Time from randomization until treatment failure, relapse from remission, or death from any cause, whichever occurs first. Treatment failure is defined as failure to achieve CR by Week 24

[a]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. [b]Includes CR, CRi/CRp, partial response, and MLFS. The study has 80% power for EFS (ivosidenib + azacitidine arm vs placebo + azacitidine arm), with a one-sided alpha of 0.025. ANC = absolute neutrophil count; CR = complete remission; CRh = CR with partial hematologic recovery; EFS = event-free survival; EORTC QLC-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; m*IDH1* = mutant isocitrate dehydrogenase 1; MLFS = morphologic leukemia-free state; ORR = overall response rate.

Summary

- In the phase 1b ivosidenib + azacitidine combination study ORR was 78.3%, which included investigator-reported responses of CR (60.9%), CRi/CRp (8.7%), and MLFS (8.7%)[1]
  - After median follow-up of 16 months, median duration of response in responders had not been reached
- The safety profile was consistent with those of ivosidenib or azacitidine alone
- Deep and durable remissions in m*IDH1* newly diagnosed AML patients treated with ivosidenib and azacitidine were observed in a phase 1b study
- These results warrant a timely and accurate confirmation of the clinical benefit in this difficult to treat patient population with the phase 3 AGILE study
  - Enrollment is open and ongoing globally
- Please also see **Poster #1943, Daigle et al.** and **Poster #2900, Choe et al.** for additional ivosidenib studies

AML = acute myeloid leukemia; CR = complete remission; CRi/CRp = CR with incomplete hematologic or platelet recovery; MLFS = morphologic leukemia-free state; m*IDH1* = mutant isocitrate dehydrogenase 1; ORR = overall response rate.

1. DiNardo CD et al. *J Clin Oncol*. 2020. DOI: 10.1200/JCO.20.01632.

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