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

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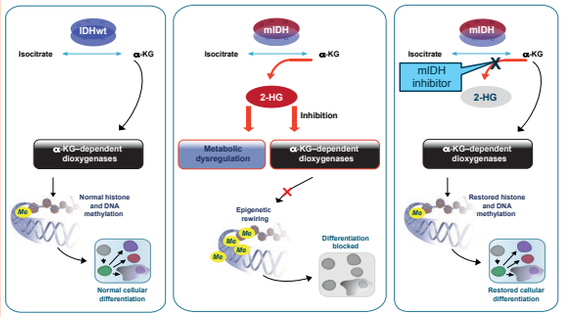
BACKGROUND

- Acute myeloid leukemia (AML) has a poor prognosis, and is associated with a high risk of relapse and limited overall survival.[1-3]
- Systemic treatment for adults with AML takes two general approaches:
  - Intensive induction and consolidation chemotherapy for patients who can tolerate the rigors of therapy.
  - Single-agent treatment with hypomethylating agents or cytarabine for older individuals with comorbid conditions, poor performance status, or AML-related adverse prognostic risk factors.
- 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 α-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 (**Figure 1**).[9-11]
- Inhibitors of mIDH enzymes that block 2-HG production and restore cellular differentiation and maturation are in development (**Figure 1**).

Figure 1. IDH mutations in malignancy



wt = wild-type

Ivosidenib

- 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.
- In a phase 1 study of patients with mIDH1 advanced hematologic tumors, including AML (NCT02074839), ivosidenib showed robust clinical activity and a manageable safety profile as a single agent.
  - The overall response rate was 42% and the complete remission (CR) rate was 24% in patients with mIDH1 relapsed and/or refractory AML (see ASCO 2018 abstract 7000, Pollyea D et al.).

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.[12]
- In a preclinical study using an mIDH1 cell model, concurrent treatment with ivosidenib and azacitidine resulted in enhanced differentiation and apoptosis.[13]

References

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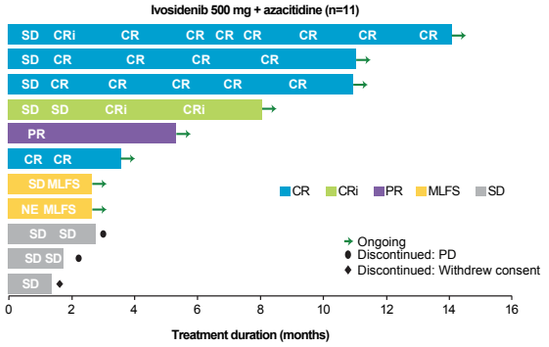
- A phase 1 study of ivosidenib in combination with azacitidine in patients with untreated mIDH1 AML is ongoing (NCT02677922).
  - As of September 1, 2017, 11 patients had been treated with ivosidenib 500 mg once daily (QD) + azacitidine 75 mg/m²/day subcutaneously (SC) for 7 days in a 28-day schedule.[14]
  - Patients had been treated for a median of 3 cycles (range, 1–13), and adverse events were consistent with the single-agent experience for both agents. One case of IDH differentiation syndrome was reported.
  - Objective responses were observed in 8 of 11 patients, with 4 achieving a CR (**Figure 2**).
  - See ASCO 2018 poster 7042 for updated clinical data (June 4, 8:00–11:30 am).

Figure 2. Interim results from the phase 1 trial: treatment duration, response, and disposition



One additional patient was enrolled but did not have response data available at data cutoff of Sep 1, 2017
CR = complete remission; CRi = complete remission with incomplete neutrophil recovery; MLFS = morphologic leukemia-free state; NE = not evaluable; PD = progressive disease; PR = partial remission; SD = stable disease

OBJECTIVE

- To evaluate the efficacy and safety of ivosidenib + azacitidine versus placebo + azacitidine in adults with previously untreated mIDH1 AML who are candidates for nonintensive treatment.

TRIAL DESIGN

- AGILE is a global, phase 3, multicenter, randomized, double-blind, placebo-controlled trial in adult patients with previously untreated mIDH1 AML who are candidates for nonintensive treatment.
  - ClinicalTrials.gov NCT03173248.
- Study design is shown in **Figure 3**.
- Central or local confirmation of mIDH1 status is required for study entry.
- An independent data monitoring committee will monitor the data throughout the study.

SUMMARY AND CURRENT STATUS

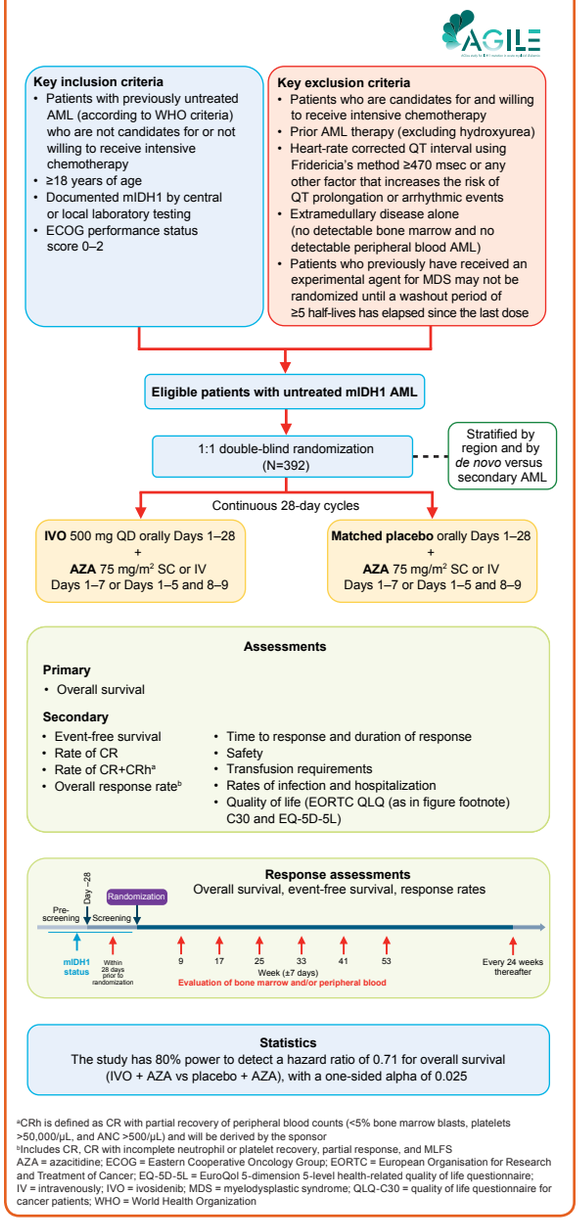
Summary

- The favorable safety profile and encouraging clinical activity of the ivosidenib + azacitidine combination in the treatment of mIDH1 AML support the development of this combination in the AGILE study described here.
- AGILE is a global, double-blind, randomized, placebo-controlled trial in patients with previously untreated mIDH1 AML who are candidates for nonintensive treatment.
- Further information is available at https://clinicaltrials.gov/ct2/show/NCT03173248.

Study status

- AGILE is currently enrolling patients at participating sites globally.

Figure 3. AGILE study design



[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, CR with incomplete neutrophil or platelet recovery, partial response, and MLFS
AZA = azacitidine; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = EuroQol 5-dimension 5-level health-related quality of life questionnaire; IV = intravenously; IVO = ivosidenib; MDS = myelodysplastic syndrome; QLQ-C30 = quality of life questionnaire for cancer patients; WHO = World Health Organization

Acknowledgments

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Disclosures

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