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.6,7
- 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).6
- 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).3,8
- Inhibitors of mIDH enzymes that block 2-HG production and restore cellular differentiation and maturation are in development (Figure 1).

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 adults with previously untreated mIDH1 AML who are candidates for nonintensive treatment.

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.
- AGILE is currently enrolling patients at participating sites globally.

An additional patient enrolled but did not have response data available at data cutoff of Sep 1, 2017.

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

Figure 3. AGILE study design

Figure 1. IDH mutations in malignancy

Ivosidenib
- Ivosidenib (AG-120) is a first-in-class, oral, potent, targeted, α-KG–dependent dioxygenase inhibitor of mIDH enzymes that block 2-HG production and restore α-KG–dependent enzymes, causing epigenetic dysregulation and a block in cellular differentiation, leading to oncogenesis.

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.6,7
- In a preclinical study using an mIDH1 cell model, concurrent treatment of ivosidenib and azacitidine resulted in enhanced differentiation and apoptosis.12

References