Abstract PB1862

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: Somatic mutations in isocitrate dehydrogenase 1 (IDH1) are reported in 6–10% of patients (pts) with acute myeloid leukemia (AML). Ivosidenib (IVO) is an oral, potent inhibitor of mutant IDH1 (mIDH1) and is FDA–approved for the treatment of m*IDH1* newly diagnosed (ND) AML in adults ≥75 y of age or who have comorbidities precluding the use of intensive chemotherapy (IC), and for the treatment of m*IDH1* relapsed/refractory AML. In an ongoing phase 1b study (NCT02677922), 23 ND pts with m*IDH1* AML were treated with IVO 500 mg once daily (QD) in combination with subcutaneous azacitidine (AZA) 75 mg/m^2 for 7 days (in a 28-day schedule). Pts had a median age of 76 y (range 61–88), 12 pts (52%) were ≥75 y of age, and 12 of 23 were female. Secondary AML was present in 8 (34.8%) pts. As of 19Feb2019, 10 pts (43.5%) remained on study treatment. Pts have been treated for a median of 15 cycles (range 1–30), and the spectrum of adverse events has been consistent with monotherapy experiences with IVO or AZA. Investigators reported 4 cases of IDH differentiation syndrome. Of those, 3 were deemed to be serious adverse events, but all 4 cases resolved. The overall response rate (ORR) was 78.3% (18 of 23 pts), including 60.9% (14 of 23 pts) who achieved a complete remission (CR). Median time to response was 1.8 mo (range 0.7–3.8) and to CR was 3.7 mo (range 0.8–15.7); median response duration has not been reached. Overall survival probability, 12-mo rate, was 82.0%. m*IDH1* clearance (<0.02–0.04%) in bone marrow mononuclear cells was observed in 71% (10 of 14) pts with CR.

Aims: To report updates to key inclusion criteria and study design of the ongoing AGILE phase 3 trial of IVO+AZA in adults with m*IDH1* ND AML who are not candidates for intensive treatment.

Methods: AGILE is a global, double-blind, randomized, placebo-controlled, phase 3 trial with a total of 166 participating study centers in North America, South America, Asia, and Europe. Pts are randomized 1:1 to receive either IVO 500 mg QD + AZA 75 mg/m^2 subcutaneously or intravenously for 7 days in 28-day cycles, or matched placebo + AZA. Randomization is stratified by region and by *de novo* vs secondary AML. Key eligibility criteria include pts with previously untreated m*IDH1* AML (according to World Health Organization criteria) who are not candidates to receive IC, and who have not received prior treatment with a hypomethylating agent or mIDH1 inhibitor. The recent amendment further specifies criteria for IC-ineligibility as ≥75 y of age or reduced performance (Eastern Cooperative Oncology Group performance status = 2) or significant organ dysfunction (ie, severe cardiac or pulmonary disorder, impaired renal or liver function). The primary endpoint has been changed to event-free survival, defined as the 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. Key secondary efficacy endpoints are amended to overall survival, CR rate, CR+CR with partial hematologic recovery rate, and ORR. AGILE is currently open for enrollment globally.

Results: Not yet available.

Summary/Conclusion: The favorable safety profile and encouraging clinical activity observed in the phase 1b IVO+AZA combination study for the treatment of IC-ineligible m*IDH1* AML warrant a timely and accurate confirmation of the clinical benefit in this difficult to treat population with the phase 3 AGILE study (NCT03173248). Inclusion criteria and endpoints were modified to better define eligible pts and asses clinical benefit of the IVO+AZA combination.