697 AGILE: A Global, Randomized, Double-Blind, Phase 3 Study of Ivosidenib + Azacitidine Versus Placebo + Azacitidine in Patients with Newly Diagnosed Acute Myeloid Leukemia with an IDH1 Mutation

Authors: Pau Montesinos, Christian Recher, Susana Vives, Ewa Zarzycka, Jianxiang Wang, Giambattista Bertani, Michael Heuser, Rodrigo T. Calado, Andre C. Schuh, Su-Peng Yeh, Scott R. Daigle, Jianan Hui, Vickie Zhang, Shuchi S. Pandya, Diego A. Gianolio, Stephane de Botton, Hartmut Döhner

Abstract

Background:

Somatic mutations in isocitrate dehydrogenase 1 (IDH1) occur in 6–10% of patients with acute myeloid leukemia (AML). Ivosidenib – an oral, potent inhibitor of the mutant IDH1 (mIDH1) enzyme – is FDA-approved for adults with relapsed/refractory mIDH1 AML and adults with newly diagnosed mIDH1 AML who are ≥ 75 years or have comorbidities that preclude use of intensive induction chemotherapy (IC). Data from a phase 1b study of 23 patients with newly diagnosed mIDH1 AML showed a favorable safety profile and encouraging clinical activity of ivosidenib + azacitidine (IVO+AZA; NCT02677922).

Methods:

In this global, double-blind, randomized, placebo-controlled, phase 3 study, patients were randomized 1:1 to IVO 500 mg once daily + AZA 75 mg/m2 subcutaneously or intravenously for 7 days in 28-day cycles, or placebo + AZA (PBO+AZA), and stratified by region and de novo vs secondary AML. Key eligibility: untreated AML (WHO criteria), centrally confirmed mIDH1 status, not eligible for IC, ECOG 0-2. Primary endpoint: event-free survival (EFS; time from randomization until treatment failure, i.e. failure to achieve complete remission [CR] by week 24, relapse from remission, or death from any cause). Key secondary endpoints: CR rate, overall survival (OS), CR + CR with partial hematologic recovery (CRh) rate, and objective response rate (ORR).

Results:

From 19-Mar-2018 to 18-Mar-2021, 146 patients were randomized: 72 to IVO+AZA (median [interquartile range] age, 76.0 [70.5–79.5] years) and 74 to PBO+AZA (median [interquartile range] age, 75.5 [70.0–80.0] years). Fifty-four (75.0%) patients had de novo AML vs 18 (25.0%) with secondary AML in the IVO+AZA arm. Sixteen (22.2%) patients receiving IVO+AZA had poor-risk genetics per ELN guidelines vs 20 (27.0%) patients receiving PBO+AZA. Thirty-nine (26.7%) patients remain on treatment (27/72 patients in the IVO+AZA arm vs 12/74 patients in the PBO+AZA arm). EFS was statistically significant (HR = 0.33 [95% CI 0.16, 0.69]; P = 0.0011)

in favor of the IVO+AZA arm. Median OS with IVO+AZA was 24.0 months vs 7.9 months with PBO+AZA (HR = 0.44 [95% CI 0.27, 0.73]; P = 0.0005). CR rate with IVO+AZA was 47.2% (34/72 patients; 95% CI 35.3%, 59.3%) vs 14.9% (11/74 patients; 95% CI 7.7%, 25.0%) with PBO+AZA (P < 0.0001). Median time to CR was 4.3 months with IVO+AZA vs 3.8 months with PBO+AZA. CR+CRh rate with IVO+AZA was 52.8% (38/72 patients; 95% CI 40.7%, 64.7%) vs 17.6% (13/74 patients; 95% CI 9.7%, 28.2%) with PBO+AZA (P < 0.0001). The CR rate by 24 weeks for IVO+AZA vs PBO+AZA was 37.5% and 10.8%, respectively. ORR with IVO+AZA was 62.5% (45/72 patients; 95% CI 50.3%, 73.6%) vs 18.9% (14/74 patients; 95% CI 10.7%, 29.7%) with PBO+AZA (P < 0.0001). All reported P-values are 1-sided. Common all-grade adverse events (AEs) occurring in > 20% of patients receiving IVO+AZA vs PBO+AZA were nausea (42.3% vs 38.4%), vomiting (40.8% vs 26.0%), diarrhea (35.2% vs 35.6%), pyrexia (33.8% vs 39.7%), anemia (31.0% vs 28.8%), febrile neutropenia (28.2% vs 34.2%), thrombocytopenia (28.2% vs 20.5%), constipation (26.8% vs 52.1%), and pneumonia (23.9% vs 31.5%). Sixty-six (93.0%) patients receiving IVO+AZA vs 69 (94.5%) patients receiving PBO+AZA experienced a grade ≥ 3 AE. Common grade ≥ 3 AEs occurring in > 20% of patients receiving IVO+AZA vs PBO+AZA included febrile neutropenia (28.2% vs 34.2%), anemia (25.4% vs 26.0%), thrombocytopenia (23.9% vs 20.5%), and pneumonia (22.5% vs 28.8%). Frequency of all-grade differentiation syndrome (DS) as assessed by investigators was 14.1% with IVO+AZA vs 8.2% with PBO+AZA, and that of grade ≥ 3 DS was 4.2% with IVO+AZA vs 4.1% with PBO+AZA. Based on the recommendation of the Independent Data Monitoring Committee, further enrollment into the study was prematurely discontinued due to evidence of benefit.

Conclusions:

IVO+AZA significantly improved EFS, OS, and clinical response (CR, CR+CRh, ORR) compared with PBO+AZA in patients with IC-ineligible, newly diagnosed mIDH1 AML. The safety profile of IVO+AZA was favorable and consistent with previous studies. These data demonstrate the clinical benefit of IVO+AZA in this difficult-to-treat AML population.