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P490 UPDATED SURVIVAL, BLOOD COUNT RECOVERY AND SAFETY RESULTS FROM THE AGILE STUDY IN PATIENTS WITH ACUTE MYELOID LEUKEMIA TREATED WITH IVOSIDENIB + AZACITIDINE COMPARED TO PLACEBO + AZACITIDINE

Topic: 4. Acute myeloid leukemia - Clinical

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Background:

Acute myeloid leukemia (AML) is a disease with a dynamic mutational landscape; 6–10% of patients have somatic mutations in isocitrate dehydrogenase 1 (*IDH1)*, which can drive oncogenesis. Ivosidenib (IVO) is a potent oral targeted inhibitor of mutant *IDH1*. In the phase 3 AGILE study in patients with newly diagnosed *IDH1*-mutated AML, IVO plus azacitidine (AZA) significantly improved event-free survival (EFS), overall survival (OS), complete remission (CR), and CR or CR with partial hematologic recovery (CR+CRh) rates versus placebo (PBO) plus AZA. As of March 2021, median OS (mOS) was 24 months (IVO+AZA) versus 7.9 months (PBO+AZA; HR: 0.44; one-sided p-value = 0.0005).

Aims:

To evaluate long-term data from AGILE on OS, transfusion independence, blood count recovery and safety in patients with newly diagnosed *IDH1*-mutated AML receiving IVO+AZA.

Methods:

In the global, phase 3, multicenter, double-blind, randomized PBO-controlled AGILE study, patients ineligible for intensive chemotherapy were randomized 1:1 to IVO 500 mg QD + AZA 75 mg/m^2 SC or IV for 7 days in 28-day cycles, or PBO+AZA. Long-term follow-up data (June 2022) for OS, blood count recovery, transfusion independence and safety are described here. As of July 2021, serial bone marrow assessments were not mandated per study protocol, and therefore, updated results for the primary endpoint (EFS) are not available.

Results:

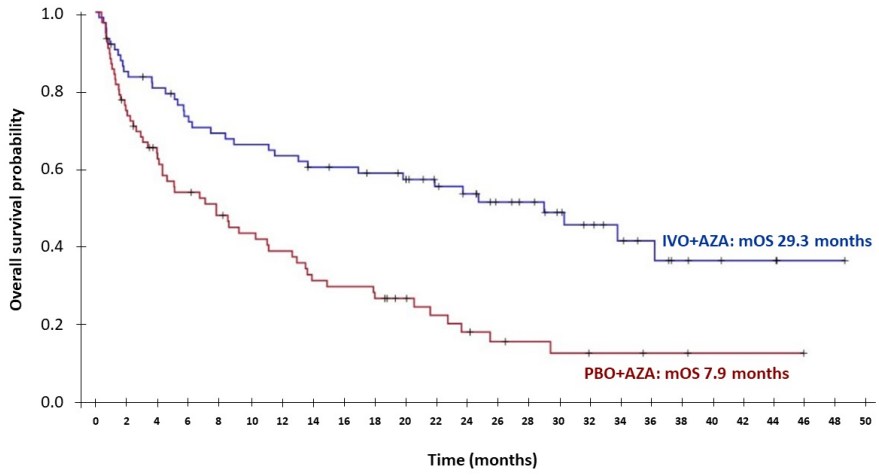
148 patients were randomized: 73 to IVO+AZA; 75 to PBO+AZA. Median treatment duration was 10.8 months (IVO+AZA) versus 3.2 months (PBO+AZA). Five PBO+AZA patients crossed over to IVO+AZA after March 2021, and no adjustment was made for crossover in the updated OS analysis. At a median follow-up of 28.6 months, mOS was 29.3 months (95% CI 13.2, not reached) for IVO+AZA versus 7.9 months (95% CI 4.1, 11.3) for PBO+AZA (HR 0.42 [0.27, 0.65]; one-sided p-value <0.0001; Figure). OS rates were 62.9% and 38.3% at 12 months and 53.1% and 17.4% at 24 months, with IVO+AZA and PBO+AZA, respectively. In the IVO+AZA arm, hemoglobin levels steadily increased from baseline (BL; 88.8 g/L) to cycle 8, and then stabilized; mean platelet count recovered

from BL values (72.7 x 10^9/L) as early as week 8 (171.9 x 10^9/L) and remained stable; and mean neutrophil counts rapidly increased from BL (0.98 x 10^9/L) to week 3 (3.99 x 10^9/L) and week 4 (4.36 x 10^9/L), and then stabilized to within the normal range. Conversion from BL transfusion dependence (red blood cell and/or platelet transfusion dependence) to post-BL transfusion independence was significantly higher with IVO+AZA than PBO+AZA (53.8% versus 17.1%, respectively; one-sided p-value = 0.0004). There were fewer neutropenic fever events (27.8% versus 33.8%) and infections (34.7% versus 51.4%) with IVO+AZA than with PBO+AZA. TEAEs led to discontinuation of IVO+AZA or PBO+AZA in 26.4% and 25.7% of patients, respectively.

Summary/Conclusion:

Updated data on OS (>5 months longer mOS and a greater risk reduction in deaths compared to the initial analysis), transfusion independence, blood count recovery and safety confirms the clinically and statistically robust benefit of treatment with IVO+AZA at long-term follow up.

Figure: Kaplan Meier plot of OS for IVO+AZA versus PBO+AZA.



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