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Ivosidenib+azacitidine vs placebo+azacitidine in patients with newly diagnosed acute myeloid leukemia: Updated long-term efficacy and safety results from the AGILE study

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INTRODUCTION

- Acute myeloid leukemia (AML) is a disease with a dynamic mutational landscape. Somatic mutations in the gene encoding isocitrate dehydrogenase 1 (*IDH1*) occur in 6–10% of patients,[1-4] and can drive oncogenesis.[5-7]
- Ivosidenib (IVO) is a potent oral targeted inhibitor of mutant IDH1 (mIDH1).
- AGILE (NCT03173248) is a global, double-blind, randomized, placebo-controlled phase 3 study of IVO plus azacitidine (AZA) vs placebo (PBO) plus AZA in patients with newly diagnosed *IDH1*-mutated AML and ineligible for intensive induction chemotherapy.[8]
- Data as of March 2021 showed that IVO+AZA significantly improved key efficacy end points vs PBO+AZA, including median overall survival ([mOS] 24.0 vs 7.9 months; hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.27–0.73; 2-sided *P* value=0.001).[8]
- In addition, event-free survival (EFS), complete remission (CR), and CR or CR with partial hematologic recovery (CR+CRh) were significantly improved with IVO+AZA compared with PBO+AZA.
- Blood counts recovered more rapidly and rates of conversion and/or maintenance of transfusion independence were higher with IVO+AZA compared with PBO+AZA.[9]

OBJECTIVES

- To evaluate long-term follow-up data (as of June 2022) from AGILE on overall survival (OS), transfusion independence, blood count recovery, and safety in patients with newly diagnosed *IDH1*-mutated AML receiving IVO+AZA.

METHODS

- Patients were randomized 1:1 to receive IVO 500 mg once daily plus AZA 75 mg/m^2 subcutaneously or intravenously for 7 days in 28-day cycles, or PBO+AZA.[8]
- OS was estimated in all randomized patients using the Kaplan-Meier method, with point estimates and 95% CI.
  - As of July 2021, serial bone marrow assessments were not mandated per the study protocol, therefore, updated results for the primary end point (EFS) are not available.
- Peripheral blood samples were obtained at screening, and during weeks 9, 17, 25, 33, 41, 53, and every 24 weeks thereafter, and at end of treatment. Samples were analyzed at each local site according to International Council for Standardization of Hematology guidelines.
  - Changes in blood counts were analyzed in all patients who received ≥1 dose of study treatment.
- Red blood cell (RBC) and platelet transfusion history were assessed at screening and follow-up.
- Transfusion independence analysis (baseline [BL] vs post-BL) was performed based on all randomized patients
  - Transfusion independence is defined as a period of ≥56 days with no transfusion after the start of study treatment and on or before the end of study treatment + 28 days, or disease progression, or confirmed relapse, or death or data cutoff date, whichever is earlier.
  - Odds ratios (ORs) were calculated using the Cochran-Mantel-Haenszel estimate, with PBO+AZA as the denominator.

RESULTS

Study participants

- Overall, 148 patients were included in this analysis using the June 2022 data cutoff (73 IVO+AZA; 75 PBO+AZA). BL characteristics including demographics, cytogenetic risk, and m*IDH1* variant allele frequency were well balanced between treatment arms, consistent with that previously reported for 146 patients included at the March 2021 data cutoff.[8]
- Median treatment duration was 10.8 months and 3.2 months for the IVO+AZA and PBO+AZA treatment arms, respectively.
- Five (6.7%) patients who were initially randomized to PBO+AZA crossed over to IVO+AZA after March 2021 (**Table 1**). No adjustment was made for crossover in the updated OS analysis presented.
- By June 2022, most patients had discontinued IVO or PBO (**Table 1**) most frequently due to adverse events (AEs; 29.1%), progression/relapse (21.6%), or patient withdrawal (10.8%).

Table 1: Patient disposition at June 2022 analysis

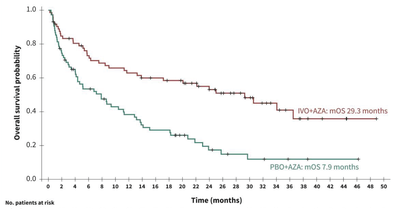
Patients, n (%)	IVO+AZA n=73	PBO+AZA n=75
Randomized but not treated	1 (1.4)	1 (1.3)
On-treatment with IVO/PBO	21 (28.8)	0
Discontinued IVO/PBO	51 (69.9)	74 (98.7)
On-treatment with AZA	19 (26.0)	3 (4.0)
Discontinued AZA	53 (72.6)	71 (94.7)
Crossed over to IVO+AZA	–	5 (6.7)
Discontinued IVO	–	2 (2.7)
Ongoing with IVO	–	3 (4.0)

Overall survival

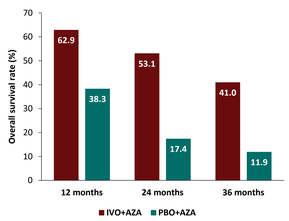
- At a median follow-up of 28.6 months, mOS was 29.3 months (95% CI: 13.2, not reached) for IVO+AZA vs 7.9 months (95% CI, 4.1–11.3) for PBO+AZA (HR [95% CI], 0.42 [0.27–0.65]; one-sided *P*<0.0001; **Figure 1A**).
- There were 37 (50.7%) and 58 (77.3%) deaths with IVO+AZA and PBO+AZA, respectively.
- OS rates at 12, 24, and 36 months were higher following treatment with IVO+AZA vs PBO+AZA (**Figure 1B**).

Figure 1: Long-term OS for IVO+AZA vs PBO+AZA

A. Kaplan-Meier plot of OS



B. OS rates at 12, 24, and 36 months



Changes in blood counts in the IVO+AZA arm

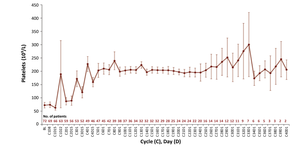
- Hemoglobin levels steadily increased from BL (88.8 g/L) to cycle 8, and then stabilized (**Figure 2A**).
- Mean platelet count recovered from BL values (72.7 × 10^9/L) as early as week 8 (171.9 × 10^9/L) and remained stable (**Figure 2B**).
- Mean neutrophil counts rapidly increased from BL (0.98 × 10^9/L) to week 3 (4.0 × 10^9/L) and week 4 (4.36 × 10^9/L), and then stabilized to within the normal range (**Figure 2C**). See Poster AML-446 for further analysis.

Figure 2: Recovery of blood counts in IVO+AZA treated patients[a]

A. Mean absolute hemoglobin over time



B. Mean absolute platelets over time



C. Mean absolute neutrophils over time



Error bars indicate mean ± standard error

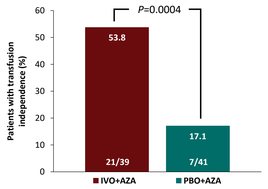
[a]Blood counts are reported for IVO+AZA only, as 5 patients that started on PBO+AZA subsequently crossed over to IVO+AZA

Conversion to transfusion independence

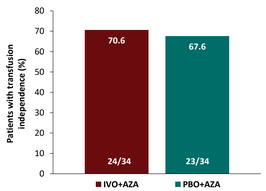
- Among patients who were RBC and/or platelet transfusion dependent at BL (~54.0% in both groups), 53.8% (95% CI, 37.2–69.9) in the IVO+AZA group achieved RBC and platelet transfusion independence compared with 17.1% (95% CI, 7.2–32.1) in the PBO+AZA arm (OR [95% CI], 6.2 [2.0–19.1]; one-sided *P*=0.0004; **Figure 3A**).
- Maintenance of RBC and platelet transfusion independence (BL vs post-BL) was similar for IVO+AZA- and PBO+AZA-treated patients (**Figure 3B**).

Figure 3: Conversion to, or maintenance of, transfusion independence

A. RBC and platelet transfusion independence in patients with RBC and/or platelet transfusion dependence at BL



B. Maintenance of RBC and platelet transfusion independence (BL vs post-BL)



Safety

- Overall, 66/72 (91.7%) patients in the IVO+AZA arm and 71/74 (95.9%) patients in the PBO+AZA arm had a grade ≥3 treatment-emergent AE (TEAE).
- TEAEs led to dose reduction of IVO only or PBO only in 18.1% and 8.1% of patients, and to discontinuation of IVO+AZA or PBO+AZA in 26.4% and 25.7% of patients.
- No treatment-related TEAEs lead to death in either treatment arm.
- Of hematologic TEAEs, there were fewer any grade or grade ≥3 neutropenic fever events with IVO+AZA than with PBO+AZA (**Table 2**).
- Of non-hematologic TEAEs, any grade or grade ≥3 pneumonia and infection events (based on broad Standardized MedDRA Queries opportunistic infections) were lower in IVO+AZA vs PBO+AZA treatment arms (**Table 3**).

Table 2: Hematologic AEs[a]

	IVO+AZA n=72		PBO+AZA n=74	
Event, n (%)	**All grades[b]**	**Grade ≥3[b]**	**All grades[b]**	**Grade ≥3[b]**
Anemia	24 (33.3)	19 (26.4)	23 (31.1)	20 (27.0)
Neutropenia	22 (30.6)	22 (30.6)	16 (21.6)	16 (21.6)
Thrombocytopenia	21 (29.2)	18 (25.0)	14 (18.9)	14 (18.9)
Febrile neutropenia	**20 (27.8)**	**20 (27.8)**	**25 (33.8)**	**25 (33.8)**
Platelet count decreased	10 (13.9)	8 (11.1)	6 (8.1)	6 (8.1)
Neutrophil count decreased	9 (12.5)	9 (12.5)	5 (6.8)	5 (6.8)
Leukocytosis	8 (11.1)	0	2 (2.7)	1 (1.4)

MedDRA version 25.0 preferred terms
[a]The safety population included all patients who received ≥1 dose of study treatment. [b]AEs reported in ≥10% of patients in the IVO+AZA arm, corresponding grade ≥3 frequencies, and corresponding all-grade and grade ≥3 frequencies in the PBO+AZA arm

Table 3: Non-hematologic AEs[a]

	IVO+AZA n=72		PBO+AZA n=74	
Event, n (%)	**All grades[b]**	**Grade ≥3[b]**	**All grades[b]**	**Grade ≥3[b]**
Nausea	32 (44.4)	2 (2.8)	29 (39.2)	3 (4.1)
Vomiting	30 (41.7)	0	20 (27.0)	1 (1.4)
Pyrexia	27 (37.5)	2 (2.8)	32 (43.2)	2 (2.7)
Diarrhea	26 (36.1)	1 (1.4)	29 (39.2)	6 (8.1)
Constipation	23 (31.9)	0	39 (52.7)	1 (1.4)
Pneumonia	**17 (23.6)**	**16 (22.2)**	**24 (32.4)**	**22 (29.7)**
Electrocardiogram QT prolonged	16 (22.2)	8 (11.1)	5 (6.8)	2 (2.7)
Decreased appetite	13 (18.1)	1 (1.4)	21 (28.4)	6 (8.1)
Insomnia	13 (18.1)	1 (1.4)	9 (12.2)	0
Asthenia	12 (16.7)	0	25 (33.8)	6 (8.1)
Arthralgia	11 (15.3)	0	4 (5.4)	0
Dyspnea	11 (15.3)	1 (1.4)	10 (13.5)	3 (4.1)
Hypokalemia	11 (15.3)	2 (2.8)	21 (28.4)	7 (9.5)
Pain in extremity	11 (15.3)	1 (1.4)	4 (5.4)	2 (2.7)
Differentiation syndrome	10 (13.9)	3 (4.2)	6 (8.1)	3 (4.1)
Hematoma	10 (13.9)	0	1 (1.4)	0
Headache	10 (13.9)	0	2 (2.7)	0
Back pain	9 (12.5)	1 (1.4)	3 (4.1)	0
Dizziness	9 (12.5)	1 (1.4)	4 (5.4)	0
Fatigue	9 (12.5)	2 (2.8)	10 (13.5)	2 (2.7)
Edema peripheral	9 (12.5)	0	17 (23.0)	1 (1.4)
Pruritus	9 (12.5)	0	4 (5.4)	0
Bleeding	31 (43.1)	5 (6.9)	23 (31.1)	6 (8.1)
Infections	**25 (34.7)**	**16 (22.2)**	**38 (51.4)**	**23 (31.1)**

MedDRA version 25.0 preferred terms
[a]The safety population included all patients who received ≥1 dose of study treatment. [b]AEs reported in ≥10% of patients in the IVO+AZA arm, corresponding grade ≥3 frequencies, and corresponding all-grade and grade ≥3 frequencies in the PBO+AZA arm

CONCLUSIONS

- **Long-term follow-up data support the superior efficacy of IVO+AZA vs PBO+AZA in patients with newly diagnosed *IDH1*-mutated AML; mOS following treatment with IVO+AZA is >5 months longer and risk reduction in deaths is greater compared with the initial analysis.**
- **The long-term hematologic recovery and reduction in transfusion burden further support the clinical benefit of IVO+AZA vs PBO+AZA.**
- **The safety profile of IVO+AZA was maintained with long-term treatment.**
- **Long-term follow-up indicates that treatment with IVO+AZA results in durable responses.**

Acronyms: AE, adverse event; AML, acute myeloid leukemia; AZA, azacitidine; BL, baseline; CI, confidence interval; CR, complete remission; CRh, CR with partial hematologic recovery; EFS, event-free survival; HR, hazard ratio; IDH1, isocitrate dehydrogenase 1; IVO, ivosidenib; mIDH1, mutant IDH1; mOS, median overall survival; OR, odds ratio; OS, overall survival; PBO, placebo; RBC, red blood cell; TEAE, treatment-emergent AE

References: **1.** Mardis ER et al. *N Engl J Med.* 2009;361:1058–1066. **2.** Ward PS et al. *Cancer Cell.* 2010;17:225–234. **3.** Patel KP et al. *Am J Clin Pathol.* 2011;135:35–45. **4.** DiNardo CD et al. *Am J Hematol.* 2015;90:732–736. **5.** Lu C et al. *Nature.* 2012;483:474–478. **6.** Saha SK et al. *Nature.* 2014;513:110–114. **7.** Xu W et al. *Cancer Cell.* 2011;19:17–30. **8.** Montesinos P et al. *N Engl J Med.* 2022;386:1519-1531. **9.** Dohner H et al. *J Clin Oncol.* 2022;40:7042–7042.

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