AGILE: IVOSIDENIB + AZACITIDINE COMPARED TO PLACEBO + AZACITIDINE IN PATIENTS WITH NEWLY-DIAGNOSED ACUTE MYELOID LEUKEMIA

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INTRODUCTION

- Acute myeloid leukemia (AML) is a disease with a dynamic mutational landscape; 6-10% of patients have somatic mutations in isocitrate dehydrogenase 1 (*IDH1*),[1-4] which can drive oncogenesis[5-7]
- Ivosidenib (IVO) is a potent oral targeted inhibitor of mutant *IDH1* (m*IDH1*)
- AGILE (NCT03173248) is a global, double-blind, randomized, placebo (PBO)-controlled Phase 3 study in patients with newly diagnosed *IDH1*-mutated AML who were ineligible for intensive induction chemotherapy[8] (Figure 1)
- In the AGILE study, IVO 500 mg every day (QD) + azacitidine (AZA) 75 mg/m^2 subcutaneous (SC) or intravenous (IV) for 7 days in 28-day cycles was shown to significantly improve median event-free survival (EFS) and median overall survival (OS) compared with PBO+AZA[8]
- Complete remission (CR) + CR with partial hematologic recovery (CRh) rates were also better in the IVO+AZA arm than the PBO+AZA arm (CR/CRh; 52.8% vs 17.6%, respectively)

OBJECTIVES

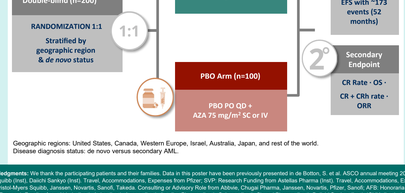
To assess:

- Rate of blood counts recovery and transfusion independence of patients treated with IVO+AZA vs PBO+AZA
- Impact of IVO+AZA on inducing and maintaining *IDH1* mutation clearance (*IDH1*-MC), and the effect of baseline co-mutations on response to IVO+AZA
- Impact of IVO+AZA versus PBO+AZA on health-related quality of life (HRQoL)

METHODS

- Genomic DNA from bone marrow (BM) mononuclear cells (BMMCs) or peripheral blood (PB) mononuclear cells (PBMCs), and/or BM aspirate (BMA) were used for molecular studies
  - *IDH1*-MC analysis was performed by BEAMing digital polymerase chain reaction (PCR; limit of detection 0.02%-0.04% variant allele frequency [VAF], Sysmex Inostics). Patients with undetectable m*IDH1* in at least one on-treatment BMMC sample were considered to have *IDH1*-MC
  - Co-mutation analysis was performed using next-generation sequencing, ACE Extended Cancer Panel (limit of detection 2% VAF, Personalis)
- BM and PB samples were obtained at screening, and during weeks 9, 17, 25, 33, 41, 53, and every 24 weeks thereafter, and at end of treatment and during EFS follow up, and change in blood counts and BM blasts were analyzed
- HRQoL was assessed using European Organization for Research and Treatment of Cancer quality of life (EORTC QLQ-C30) Global health status questionnaire

Figure 1: AGILE study design



Geographic regions: United States, Canada, Western Europe, Israel, Australia, Japan, and rest of the world.
Disease diagnosis status: de novo versus secondary AML.

RESULTS

Baseline characteristics and efficacy

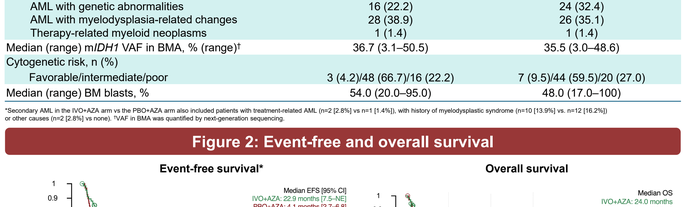
- Baseline characteristics were well balanced between treatment arms (Table 1)
- EFS and OS significantly improved with IVO+AZA compared with PBO+AZA (Figure 2)

Table 1: Baseline characteristics and disease characteristics

Characteristic	IVO+AZA (n=72)	PBO+AZA (n=74)
Median (range) age, years	76.0 (58.0–84.0)	75.5 (45.0–94.0)
Sex, n (%)		
Male/female	42 (58.3)/30 (41.7)	38 (51.4)/36 (48.6)
ECOG PS score, n (%)		
0	14 (19.4)	10 (13.5)
1	32 (44.4)	40 (54.1)
2	26 (36.1)	24 (32.4)
Disease history (per investigator), n (%)		
De novo AML	54 (75.0)	53 (71.6)
Secondary AML*	18 (25.0)	21 (28.4)
WHO classification, n (%)		
AML with genetic abnormalities	16 (22.2)	24 (32.4)
AML with myelodysplasia-related changes	28 (38.9)	26 (35.1)
Therapy-related myeloid neoplasms	1 (1.4)	1 (1.4)
Median (range) m*IDH1* VAF in BMA, % (range)†	36.7 (3.1–50.5)	35.5 (3.0–48.6)
Cytogenetic risk, n (%)		
Favorable/intermediate/poor	3 (4.2)/48 (66.7)/16 (22.2)	7 (9.5)/44 (59.5)/20 (27.0)
Median (range) BM blasts, %	54.0 (20.0–95.0)	48.0 (17.0–100)

*Secondary AML in the IVO+AZA arm vs the PBO+AZA arm also included patients with treatment-related AML (n=2 [2.8%] vs n=1 [1.4%]), with history of myelodysplastic syndrome (n=10 [13.9%] vs. n=12 [16.2%]) or other causes (n=2 [2.8%] vs none). †VAF in BMA was quantified by next-generation sequencing.

Figure 2: Event-free and overall survival



*Exploratory analysis of EFS: the day of the event is the earliest date of treatment failure/relapse/death. Treatment failure was defined as absence of CR, CRi or MLFS by week 24

Blood counts and BM blasts

- In patients receiving IVO+AZA, neutrophil counts increased rapidly from baseline to week 2 and week 5, before stabilizing within the normal range; in the PBO arm, they initially declined before recovering to near-normal levels (Figure 3)
- Other blood count outcomes generally improved more rapidly in the IVO+AZA arm than the PBO+AZA arm and these are summarized in Figure 3
- In patients who were red blood cell and/or platelet transfusion-dependent at baseline, 46.2% in the IVO+AZA group achieved transfusion independence compared with 17.5% in the PBO+AZA arm

Response, mutation clearance and co-mutation analysis

- As of March 2021, analysis of treatment duration, clinical response, and mutation clearance suggested longer OS, a higher rate of CR/CRh response, and improved rates of durable *IDH1*-MC with IVO+AZA versus PBO+AZA (Figure 4)
- In CR/CRh patients with time points available after *IDH1*-MC, suppression of m*IDH1* was durable and *IDH1*-MC was maintained in all subsequent samples in 17/17 (100%) IVO+AZA treated patients and 1/3 (33%) PBO+AZA treated patients
- *DNMT3A*, *SRSF2*, and *RUNX1* were the most frequently co-mutated genes in both treatment arms
- Mutations in several pathways (epigenetics, differentiation, splicing) were associated with improved outcomes with IVO+AZA compared to PBO+AZA. Among these was the RTK pathway, which was previously reported to be associated with primary resistance to IVO monotherapy[9,10]

Figure 3: Recovery of blood counts

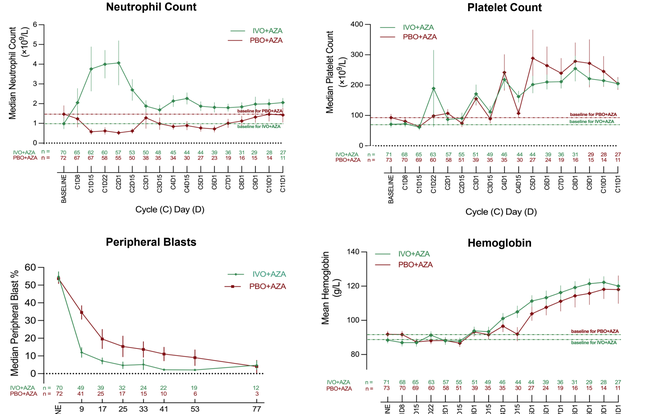
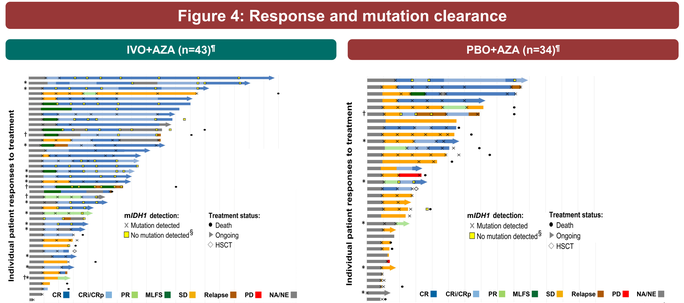


Figure 4: Response and mutation clearance

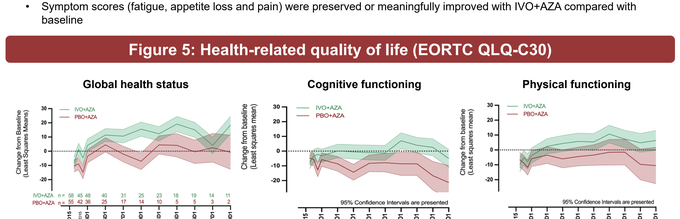


*Treatment duration was adjusted by adding 1.2 months for display purposes. †Patients who did not achieve a CR but achieved a CRh. ‡m*IDH1* VAF below the limit of detection of the Sysmex OncoBEAM test. §N includes patients with *IDH1*-MC testing performed on either PBMC or BMMC. Only BMMC clearance results are displayed

Health-related quality of life

- An initial decline in HRQoL in both arms for approximately 4 months was observed, consistent with median time to CR (Figure 5). Global health status scores were significantly improved for IVO+AZA versus PBO+AZA, and differences between treatment arms were clinically meaningful, at some timepoints
  - Functioning change scores were superior with IVO+AZA versus PBO+AZA at multiple timepoints in all functioning sub-scales (physical, role, emotional, cognitive and social)
  - Symptom scores (fatigue, appetite loss and pain) were preserved or meaningfully improved with IVO+AZA compared with baseline

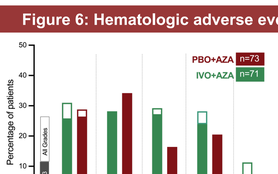
Figure 5: Health-related quality of life (EORTC QLQ-C30)



Adverse events

- There were fewer all grade and grade ≥3 events of febrile neutropenia with IVO+AZA compared with PBO+AZA. Grade ≥3 febrile neutropenia occurred in 28% of patients treated with IVO+AZA and 34% treated with PBO+AZA (Figure 6)
- There were also fewer reports of all grade or grade ≥3 pneumonia and infections in patients treated with IVO+AZA than with PBO+AZA

Figure 6: Hematologic adverse events



CONCLUSIONS

- **In the primary analysis, IVO+AZA demonstrated clinically meaningful activity in the key efficacy endpoints of EFS, OS, and CR+CRh**
- **In these sub-analyses, compared with PBO+AZA, IVO+AZA:**
  - **Blood counts recovered more rapidly**
  - **Outcomes were associated with a durable clearance of the m*IDH1* clone**
  - **Was associated with statistically significant and clinically meaningful improvements in multiple HRQoL domains**
  - **Had an acceptable safety profile with fewer neutropenic fever events or infections**

Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine; BM, bone marrow; BMA, bone marrow aspirate; BMMC, bone marrow mononuclear cell; CI, confidence interval; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete platelet recovery; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EFS, event-free survival; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire; HR, hazard ratio; HRQoL, health-related quality of life; HSCT, hematopoietic stem cell transplant; IDH1, isocitrate dehydrogenase 1; *IDH1*-MC, isocitrate dehydrogenase 1 mutation clearance; IV, intravenous; IVO, ivosidenib; m*IDH1*, mutant isocitrate dehydrogenase 1; MLFS, morphologic leukemia-free state; NA, not available; NE, not evaluable; ORR, objective response rate; OS, overall survival; PB, peripheral blood; PBMC, peripheral blood mononuclear cell; PBO, placebo; PCR, polymerase chain reaction; PD, progressive disease; PO, orally; PR, partial response; QD, every day; SC, subcutaneous; SD, stable disease; VAF, variant allele frequency; WHO, World Health Organization.

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