Time to resolution of myelosuppression and associated hospitalization in patients with newly diagnosed acute myeloid leukemia treated with ivosidenib+azacitidine compared with placebo+azacitidine

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INTRODUCTION

- Severe/prolonged myelosuppression is a common toxicity associated with hypomethylating agent (HMA)-containing treatment regimens for acute myeloid leukemia (AML) ineligible for intensive chemotherapy (IC).
- A recent study assessed myelosuppression recovery in 64 newly diagnosed (ND) responders to venetoclax plus HMA.[1]
  - In that study, which evaluated the induction period only, median time to absolute neutrophil count (ANC) recovery ≥0.5x10^9/L was 34 days (range to ≥1.0, 19–129 days), and median hospitalization was 32 days (range, 8–62), >100% of cycle 1 time.[1]
  - That retrospective analysis included patients from a single site who received the HMAs decitabine or azacitidine (AZA), assessed a limited timeframe, did not include a control arm, and looked at responders only.[1]
- The phase 3 AGILE study (NCT03173248) evaluated ivosidenib (IVO) plus AZA compared with placebo (PBO) plus AZA in patients with ND AML with mutant isocitrate dehydrogenase 1 (m*IDH1*) ineligible for IC (**Figure 1**).[2]
- The favorable outcomes of AGILE (see Poster AML-469 for an updated analysis) led to the 2022 US FDA approval of IVO+AZA for this population.

OBJECTIVES

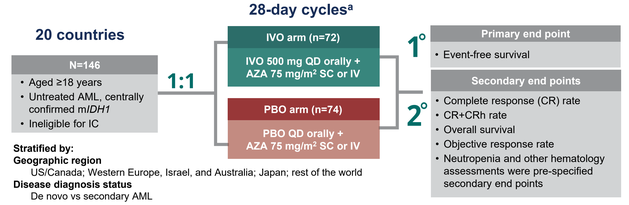
- To evaluate time to recovery from myelosuppression in the AGILE study.

METHODS

Myelosuppression and associated outcomes

- ANC was assessed weekly (cycle 1), biweekly (cycle 2–4), then per cycle.
- Hospitalization days were recorded and calculated per days alive.
- The pivotal data cutoff of 18 March 2021 was used for these analyses.

Figure 1: IVO+AZA combination therapy in first-line IC-ineligible AML patients with an *IDH1* mutation: a global phase 3 trial



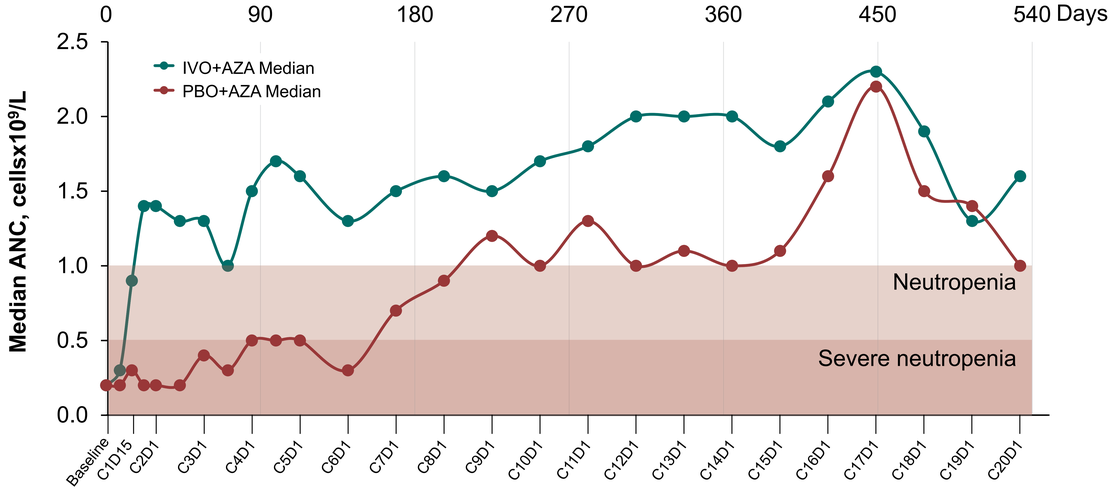
In May 2021, study enrollment was prematurely stopped based on independent data monitoring committee recommendation due to a difference in the number of deaths favoring IVO+AZA. After May 2021, crossover to IVO+AZA was permitted for eligible patients in the PBO+AZA group

[a]Patients received granulocyte colony-stimulating factor (GCSF) at investigator discretion
CRh, complete response with partial hematologic recovery; IV, intravenous; QD, once daily; SC, subcutaneous

RESULTS

Patients receiving IVO+AZA for ND mIDH1 AML had brisk and sustained neutrophil recovery

Figure 2: Neutropenia recovery in AGILE



Shading denotes neutropenia (<1.0x10^9) and severe neutropenia (<0.5x10^9)
Median is presented to avoid the potential masking influence of outliers resulting from differentiation/leukocytosis possible with reporting the mean
C, cycle

Table 1: Select concomitant medications and adverse events

Event	Patients receiving IVO+AZA n=71	Patients receiving PBO+AZA n=73
GCSF use, %	25.4	30.1
Neutropenic fever, grade 3 or higher, %	28.2	34.2
Infections, any grade, %	28.2	49.3
Relative risk (CI)	0.57 (0.37–0.89)	

One patient in each arm was randomized but did not receive treatment and are therefore not included in the safety analysis set
Relative risk is the ratio of the risk of patients having the event in the IVO+AZA group compared to the risk of patients having the event in the PBO+AZA group. The asymptotic Wald confidence limits are based on a log transformation of the relative risk.

- Primary end point result of event-free survival hazard ratio of 0.33 (*P*=0.002) favoring IVO+AZA vs PBO+AZA was previously reported.[2]

Myelosuppression

- Baseline median ANC was 0.2x10^9/L in both arms.
- With IVO+AZA (total n=71), median ANC increased to 0.9x10^9/L by cycle 1 day 15 and was sustained between 1.3–2.0 x10^9/L days 21–365 (one excursion to 1.0x10^9/L at week 10) and thereafter (**Figure 2**).
- With IVO+AZA, ANC recovery was significantly more rapid compared with PBO+AZA (total n=73) (*P*<0.025 for cycle 1 day 15/cycle 8 by two-sided Wilcoxon rank sum test). For PBO+AZA, ANC did not surpass 0.5x10^9/L for two consecutive readings until cycle 7, and similarly for 1.0x10^9/L until cycle 15.

Selected safety and associated end points

- GCSF use and neutropenic fever were similar in patients receiving IVO+AZA or PBO+AZA; infections were reduced with IVO+AZA (**Table 1**).
- Hospital days during days 1–28 averaged 42.9% vs 33.7% of days alive for IVO+AZA compared with PBO+AZA, respectively, and during days 1–90 averaged 30.9% vs 33.9% of days alive.

CONCLUSIONS

- **Patients receiving IVO+AZA for ND m*IDH1* AML had brisk and sustained neutrophil recovery.**
- **Most patients receiving AZA alone had severe neutropenia for 12 weeks and remained neutropenic for 6–12 months.**
- **Hospital days were <50% of days alive in cycle 1, then improved to <35% of days alive cycles 1–3, in both arms.**
- **These safety advantages complement the efficacy advantage of IVO+AZA.**
- **The rapid recovery from severe myelosuppression and relatively low hospitalization seen with IVO+AZA are especially encouraging in the context of prolonged cytopenia and hospitalization reported with other combination regimens for ND AML ineligible for intensive chemotherapy; direct comparisons would be worthy of study.**

Acronyms: AML, acute myeloid leukemia; ANC, absolute neutrophil count; AZA, azacitidine; C, cycle; CRh, complete response with partial hematologic recovery; GCSF, granulocyte colony-stimulating factor; HMA, hypomethylating agent; IC, intensive chemotherapy; IV, intravenous; IVO, ivosidenib; *mIDH1*, mutant isocitrate dehydrogenase 1; ND, newly diagnosed; PBO, placebo; SC, subcutaneous; QD, once a day

References: 1. Rausch CR et al. *Cancer*. 2021;127(14):2489–2499. 2. Montesinos P et al. *NEJM*. 2022;386:1519–1531.

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