MOLECULAR MEASURABLE RESIDUAL DISEASE IN PATIENTS WITH NEWLY DIAGNOSED MUTANT *IDH1* ACUTE MYELOID LEUKEMIA TREATED WITH IVOSIDENIB + AZACITIDINE

Courtney DiNardo, MD, MSc[1]; Dylan Marchione, PhD[2]; Michael Heuser, MD, PhD[3]; Jianan Hui, PhD[2]; Diego Gianolio, PhD[2]; Scott Daigle, MSc[2]; Sung Choe, PhD[2]; Prapti Patel, MD[2]; Stéphane De Botton, MD, PhD[4]; and Hartmut Döhner, MD, PhD[5]

[1]Division of Cancer Medicine, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Servier Pharmaceuticals LLC., Boston, MA, USA; [3]Department of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany; [4]Department of Hematology, Gustave Roussy Cancer Center, Villejuif, France; [5]Department of Internal Medicine III, Ulm University Hospital, Ulm, Germany

INTRODUCTION

- Ivosidenib (IVO) + azacitidine (AZA) improved complete remission (CR) rates and overall survival (OS) relative to placebo (PBO) + AZA in patients with newly diagnosed mutant isocitrate dehydrogenase 1 (*mIDH1*) acute myeloid leukemia (AML) in the pivotal AGILE study[1]
- Prior analyses showed clinical responses to IVO+AZA were associated with deep clearance of m*IDH1* (limit of detection [LOD]: 0.02–0.04% variant allele frequency [VAF]) as well as clearance of baseline co-mutations below the threshold of conventional next-generation sequencing (NGS) (LOD: 2.0% VAF)[2,3]
- Here, we present an NGS analysis of measurable residual disease (MRD) responses seen in the AGILE study

METHODS

- All AGILE patients who had a best overall response (BOR) of CR, CR with incomplete count recovery, or CR with incomplete platelet recovery, and had ≥1 on-treatment bone marrow mononuclear cell (BMMC) sample available were included
- Suggested timepoints for MRD testing included day 1 of treatment cycles 3, 5, 7, 9, 11, 14, 20, 26, and 32
- Baseline and on-treatment BMMC DNA samples were analyzed using a diagnostic 51-gene myeloid NGS panel (LOD: 3% VAF) and a 26-gene Munich Leukemia Laboratory AML MRD panel, respectively
  - For variants detected at baseline, the LOD was 0.1% VAF
  - For variants not detected at baseline (either emerging mutations or if baseline samples were unavailable), the LOD was 0.5% VAF
- All variants above the applicable LOD with known or potential clinical significance were considered evidence of MRD, aside from *DNMT3A*, *TET2*, and *ASXL1* ("DTA") mutations, which were excluded to reduce the risk of false-positive MRD due to clonal hematopoiesis of indeterminate potential (CHIP)
- To determine differences in MRD response according to baseline m*IDH1* characteristics and number of variants, a two-sided t-test was used
- A log-rank test was used to evaluate event-free survival (EFS) and OS using 0.1% and 1.0% VAF thresholds

RESULTS

- The analysis set comprised 173 samples from 33 IVO+AZA-treated patients and 10 PBO+AZA-treated patients (**Figure 1A**)
- Clinical response, MRD response and EFS data were based on a March 18, 2021, primary analysis data cut; OS and patient disposition data were based on an updated June 30, 2022, data cut
- The median number of baseline mutations was 4 (range: 1–10) per patient, median number of MRD assessments was 3 (range: 1–9) (**Figure 1B**); the median follow-up period was 189 days (range: 49–875)
- In the IVO+AZA arm, the median age was 76.0 years (range: 58–84) and most patients (72.7%) had de novo AML (**Table 1**)
- Ten (30.3%) IVO+AZA-treated patients had an MRD-negative (MRD_{neg}) response, compared with 2 (20.0%) PBO+AZA-treated patients
- No significant differences in age, sex, AML type, Eastern Cooperative Oncology Group performance status, *IDH1* variant, or European LeukemiaNet 2022 risk were observed between MRD-positive (MRD_{pos}) and MRD_{neg} patients (**Table 1**)

Figure 1. Study schema and patient disposition (A) and patient response according to the day of MRD assessment (B)

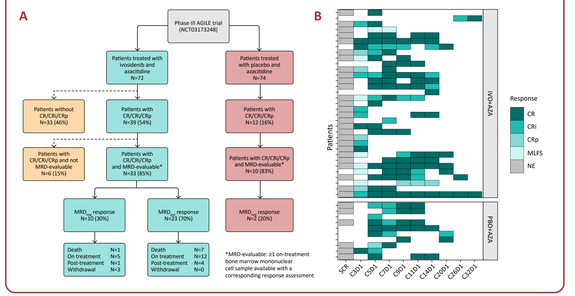


Table 1. Baseline demographics and disease characteristics in the IVO+AZA arm, overall and according to MRD response

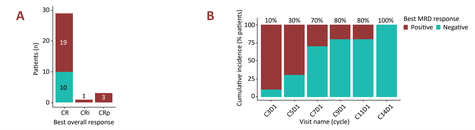
	MRD-evaluable N=33	MRD_{neg} response N=10	MRD_{pos} response N=23
Median age, years (min–max)	76.0 (58–84)	77.0 (65–84)	76.0 (58–82)
Male/female, n patients (%)	18 (54.5)/ 15 (45.5)	3 (30.0)/ 7 (70.0)	15 (65.2)/ 8 (34.8)
Disease type, n patients (%)			
De novo AML	24 (72.7)	8 (80.0)	16 (69.6)
Secondary AML	9 (27.3)	2 (20.0)	7 (30.4)
History of MDS	7 (21.2)	2 (20.0)	5 (21.7)
History of MPD	1 (3.0)	0	1 (4.3)
Other	1 (3.0)	0	1 (4.3)
ECOG PS, n patients (%)			
0	5 (15.2)	1 (10.0)	4 (17.4)
1	15 (45.5)	5 (50.0)	10 (43.5)
2	13 (39.4)	4 (40.0)	9 (39.1)

	MRD-evaluable N=33	MRD_{neg} response N=10	MRD_{pos} response N=23
IDH1 R132 variant[a], n patients (%)			
R132C	26 (78.8)	7 (70.0)	19 (82.6)
R132G	3 (9.1)	1 (10.0)	2 (8.7)
R132H	3 (9.1)	1 (10.0)	2 (8.7)
R132L	1 (3.0)	1 (10.0)	0
ELN 2022 risk, n patients (%)			
Favorable	2 (6.1)	1 (10.0)	1 (4.3)
Intermediate	6 (18.2)	3 (30.0)	3 (13.0)
Adverse	19 (57.6)	5 (50.0)	14 (60.9)
Unknown	6 (18.2)	1 (10.0)	5 (21.7)

[a]Based on central testing

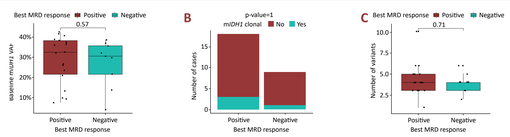
- Of the 29 IVO+AZA-treated patients achieving a BOR of CR, 10 (34.5%) had an MRD_{neg} response (**Figure 2A**)
- Seven (70.0%) of the 10 MRD_{neg} IVO+AZA-treated responding patients converted to an MRD_{neg} response by day 1 of cycle 7 (C7D1) (**Figure 2B**)

Figure 2. BOR (A; N=33) and time to MRD_{neg} response (B; N=10) with IVO+AZA



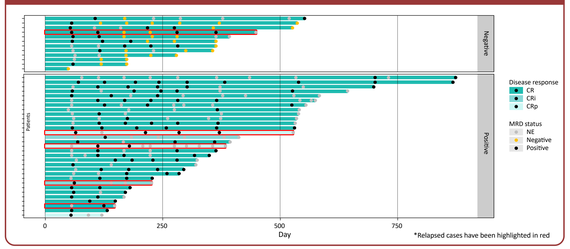
- No significant differences in MRD response were observed, according to:
  - Baseline m*IDH1* VAF in BMMCs (**Figure 3A**)
  - Whether or not m*IDH1* was "clonal" (mutation with the highest VAF) (**Figure 3B**)
  - The number of distinct variants detected at baseline (**Figure 3C**)

Figure 3. MRD response in the IVO+AZA arm, according to baseline mIDH1 characteristics (A, B) and number of variants (C) (N=33)



- All 5 (15.2%) IVO+AZA-treated patients with confirmed relapses had detectable MRD at the last completed assessment prior to relapse (**Figure 4**)
  - One patient converted from an MRD_{neg} to an MRD_{pos} response ("MRD relapse") 169 days prior to overt clinical relapse

Figure 4. Swimlane plot of MRD status over time (N=33)*



*Relapsed cases have been highlighted in red

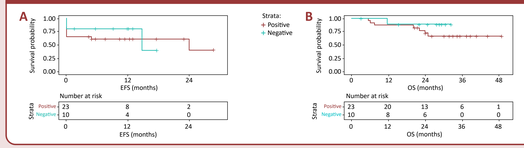
RESULTS

EFS and OS outcomes in the IVO+AZA arm, according to MRD response

- Using a 0.1% VAF threshold for clearance of baseline co-mutations, Kaplan-Meier estimates of EFS at 12 months and OS at 24 months were numerically higher in MRD_{neg} vs MRD_{pos} responders (80.0% vs 60.6% and 88.9% vs 72.3% of patients, respectively) (**Figures 7A, B**); however, no statistical significance was reached for EFS or OS when comparing MRD_{neg} and MRD_{pos} groups
  - Several patients with an MRD_{pos} response experienced prolonged OS (**Figure 8**)
- Among the 23 IVO+AZA-treated patients without an MRD_{neg} response, 16 were alive at the updated data cut off; OS ranged from 20.3–48.9 months

- Some patients in the MRD_{pos} group may have gone on to experience MRD_{neg} responses after the latest BMMC sample was collected, or after the final response data cut of March 18, 2021
  - The dataset was assembled retrospectively from available samples that were collected on an optional basis and no minimum threshold of evaluable MRD samples was set; however, restricting analysis to the subset of patients with samples available at C7D1 or later did not change the results

Figure 7. EFS (A) and OS (B) by best MRD response, using a 0.1% VAF threshold (N=33)



- Most baseline VAFs decreased over time (**Figure 5**)
- There was no single gene in which mutations were associated with a statistically significant difference in MRD response
- The most common baseline mutations in patients without an MRD_{neg} response included *ASXL1* (n=8), *SRSF2* (n=7), and *RUNX1* (n=6) (**Figure 6**)

Figure 5. Genes mutated at baseline and present in >1 patient

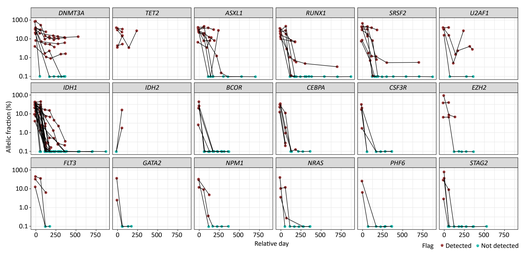


Figure 6. Heatmap of baseline variants, MRD response, and OS (N=33)

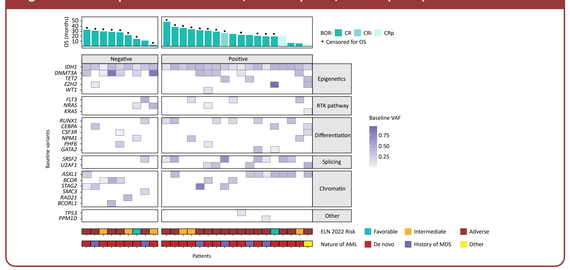
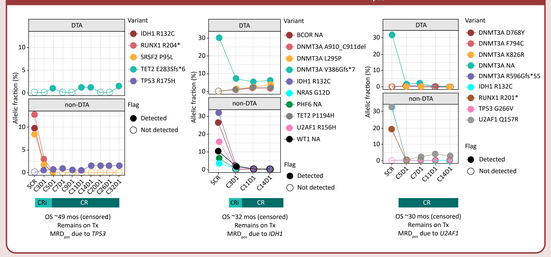
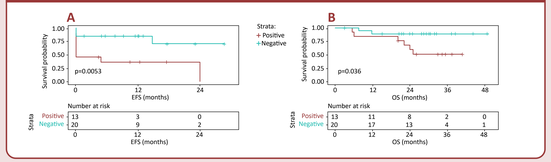


Figure 8. Three patients with durable long-term OS and MRD_{pos} responses



- Survival analyses were repeated using a 1% VAF threshold instead of 0.1% for clearance of baseline co-mutations, with the definition of emerging mutations remaining unchanged
  - Using this new threshold, 20 of 33 (60.6%) IVO+AZA-treated patients overall and 20 of 29 (69.0%) patients with CR were considered MRD_{neg}
  - Kaplan-Meier estimates of EFS at 12 months and OS at 24 months were significantly higher in MRD_{neg} vs MRD_{pos} patients (85.0% vs 36.9% [p=0.0053] and 89.5% vs 59.8% [p=0.036], respectively) (**Figure 9A, B**)
- Median time to first MRD negativity was 5.6 months (range: 1.6–12.0 months) using a 0.1% VAF threshold, and 5.2 months (range: 1.6–23.0 months) using a 1% VAF threshold

Figure 9. EFS (A) and OS (B) by best MRD response, using a 1% VAF threshold (N=33)



CONCLUSIONS

- **Ivosidenib + azacitidine induced molecular MRD negativity in approximately one third of responding patients with newly diagnosed m*IDH1* AML, with MRD_{neg} responses being most often observed on or before day 1 of cycle 7**
- **MRD_{neg} responses were observed across a range of demographic and disease characteristics and were irrespective of m*IDH1* VAF, inferred clonality, or the number of baseline variants**
- **Differences in EFS at 12 months and OS at 24 months between patients with MRD_{neg} vs MRD_{pos} responses were not significant at a 0.1% VAF threshold for clearance of baseline co-mutations but were when the threshold was increased to 1% VAF**
- **Interestingly, several patients had durable clinical responses and OS despite ongoing MRD positivity**
  - **This may have been due to persistence of non-DTA CHIP, which commonly occurs in older patients, rather than true AML MRD, thereby illustrating the complexity of interpreting NGS MRD data**

Table and figure abbreviations

AML, acute myeloid leukemia; AZA, azacitidine; BOR, best overall response; C, cycle, CHIP, clonal hematopoiesis of indeterminate potential; CR, complete remission; CRi, complete remission with incomplete hematological recovery; CRp, complete remission with incomplete platelet recovery; D, day; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ELN, European LeukemiaNet; EFS, event-free survival; *IDH1*, isocitrate dehydrogenase 1; IVO, ivosidenib; MDS, myelodysplastic syndromes; m*IDH1*, mutant isocitrate dehydrogenase 1; MLFS, morphologic leukemia-free state; mos, months; MPD, myeloproliferative disorders; MRD, measurable residual disease; MRD_{neg}, measurable residual disease-negative; MRD_{pos}, measurable residual disease-positive; NE, not evaluable; NGS, next-generation sequencing; OS, overall survival; PBO, placebo; RTK, receptor tyrosine kinase; SCR, screening; Tx, treatment; VAF, variant allele frequency

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Disclosures

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References

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