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Venetoclax plus Hypomethylating Agents versus Intensive Chemotherapy as Induction Therapy for Newly Diagnosed AML Patients with NPM1/FLT3-ITD/DNMT3A Triple Mutations: A Real-World, Multicenter Analysis Run title: VEN-HMA vs IA as induction therapy for AML patients with NPM1, FLT3-ITD and DNMT3A mutations

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Run title: VEN-HMA vs IA as induction therapy for AML patients with NPM1, FLT3-ITD and DNMT3A mutations

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Abstract

Acute myeloid leukemia (AML) harboring concurrent NPM1, FLT3-ITD and DNMT3A mutations (triple-mutated AML) has a dismal prognosis. Venetoclax combined with hypomethylating agent (VEN-HMA) is superior to conventional chemotherapy in some AML subsets, but its specific efficacy in this triple-mutated subgroup remains unclear. Therefore, we conducted a multicenter retrospective study including 79 newly diagnosed triple-mutated AML patients from three Chinese institutions between June 2018 and June 2023, comparing first-line induction idarubicin/cytarabine (IA, n=45) and VEN-HMA (n=34). The VEN-HMA group was older (median 55 vs 48 years, $P < 0.001$) and had poorer performance status (ECOG ≥2: 73.5% vs 4.4%, $P < 0.001$). CRc rate was significantly higher with VEN-HMA (71.9% vs 44.2%, $P = 0.017$). A ≥1-log reduction in NPM1 transcript levels occurred more frequently in the VEN-HMA group (56.7% vs 31.6%, $P = 0.038$). Grade ≥3 treatment-related serious adverse events (SAEs) were less common with VEN-HMA (51.6% vs. 83.3%, $P = 0.005$). Three-year overall survival (OS) and event-free survival (EFS) did not differ significantly (OS: 60.0% vs 39.5%, $P = 0.104$; EFS: 45.4% vs 30.6%, $P = 0.219$). In conclusion, VEN-HMA induction was associated with higher remission rates, deeper molecular responses and a favorable safety profile than IA in this real-world cohort of triple-mutated AML, supporting its potential role as an effective induction option in this high-risk subset and underscoring the prognostic value of early NPM1 MRD kinetics.

Keywords: Acute myeloid leukemia; NPM1/FLT3-ITD/DNMT3A co-mutation; Venetoclax; Hypomethylating agents; IA

Introduction

Acute myeloid leukemia with NPM1 mutation (NPM1^{mut} AML) accounts for approximately one-third of adult AML cases and represents the most common molecular subtype of the disease [1-3]. NPM1^{mut} AML is recognized as a unique subtype of leukemia by the International Consensus Classification (ICC) of AML in 2022 [4]. The outcome of NPM1^{mut} AML is closely associated with the mutation status of FLT3-ITD. According to the European leukemia network (ELN) 2022 and 2024 guidelines, AML patients harboring concurrent NPM1 and FLT3-ITD mutations are stratified into the intermediate-risk category [5-6].

However, NPM1/FLT3-ITD-mutated AML patients displayed marked inter-individual heterogeneity. Co-mutation was one of the important prognostic factors for NPM1/FLT3-ITD-mutated AML patients, and DNMT3A mutation was the most common co-mutation of this subtype of patients [7]. A large-scale prospective multicenter clinical study revealed that FLT3-ITD and DNMT3A mutations were the independent risk factors for measurable residual disease (MRD) positivity of NPM1^{mut} AML, and NPM1/FLT3-ITD/DNMT3A-mutated AML patients had a higher 3-year cumulative incidence of relapse (CIR) and worse 3-year overall survival (OS) [8]. Some researchers divided NPM1^{mut} AML patients into four subgroups according to the FLT3-ITD and DNMT3A mutation status, and also found that NPM1/FLT3-ITD/DNMT3A triple mutants showed poor OS and event-free survival (EFS) among four groups [9]. Additionally, FLT3-ITD/DNMT3A-mutated AML patients had lower complete remission (CR) rate and poorer clinical outcomes compared to those with FLT3-ITD or DNMT3A mutations alone [10,11].

The VIALE-A study has conclusively demonstrated that, in comparison to azacitidine monotherapy, the addition of the BCL2 inhibitor venetoclax to azacitidine not only improved clinical response rates but also prolonged median overall survival, and this landmark finding has thus established the combination regimen as the new standard induction for elderly and unfit patients with acute myeloid leukemia [12]. Meanwhile, a prospective randomized controlled clinical trial demonstrated that a composite CR (CRc) rate was higher in young adult fit NPM1^{mut} AML patients who received venetoclax plus decitabine (VEN-DEC) than in those administered with the IA regimen [13]. However, some studies showed that the survival was better in older fit AML patients treated with IA (“7+3” regimen) compared with those receiving venetoclax plus hypomethylating agents

(VEN-HMA) [14]. It remains unclear whether VEN-HMA or IA regimen is more effective in AML patients with concurrent NPM1, FLT3-ITD and DNMT3A triple mutations.

Given that DNMT3A mutations confer sensitivity to hypomethylating agents and NPM1 mutations enhance BCL-2 dependence, we hypothesized that VEN-HMA might be particularly effective in triple-mutated AML. Therefore, we performed a multicenter retrospective analysis to directly compare VEN-HMA and IA as induction therapy in this molecularly defined population.

Methods

Patients

We retrospectively analyzed 405 consecutive patients with de novo NPM1^{mut} AML diagnosed between June 2018 and June 2023 at three Chinese hospitals: the First Affiliated Hospital of Soochow University, Suzhou Hongci Hematology Hospital and the First People's Hospital of Yancheng. De novo NPM1^{mut} AML patients were diagnosed according to 2022 ICC criteria. Among them, 120 patients (29.6%) harbored concurrent FLT3-ITD and DNMT3A mutations. Twenty-six patients received priming regimen induction therapy, 10 patients with early death before induction, and 5 patients lost to follow-up were excluded. The remaining 79 eligible patients were assigned to the IA group (n=45) and the VEN-HMA group (n=34) according to their initial induction therapy regimen. The patient selection process is shown in **Fig. S1**.

Patients in the IA group received intravenous idarubicin at 12 mg/m² on days 1-3 and cytarabine at 100mg/m² on days 1-7. In the VEN-HMA group, venetoclax was administered orally, starting at 100 mg on day 1, escalating to 400 mg on day 3, and maintained until days 21-28 of the first cycle. HMA component comprised either intravenous decitabine at 20 mg/m² daily on days 1-5, or subcutaneous azacitidine at 75 mg/m² daily on days 1-7 of each 28-day cycle. Consolidation treatments involved intermediate-dose cytarabine-based chemotherapy, VEN-HMA and allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Assessments

Responses were defined according to International Working Group criteria. Overall response included CRc, CR and CR with incomplete hematological recovery (CRi). MRD was measured in bone marrow (BM) by quantitative PCR (qPCR; sensitivity, 0.001%) for NPM1 mutations (types A/B/D) before each cycle of chemotherapy or after treatment upon hematopoietic recovery. MRD negativity

was defined as absence of the NPM1 transcript. Treatment efficacy was assessed by CRc rate and MRD reduction level.

Adverse events (AEs) were assessed by investigators per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0. AEs were defined as occurring from the first dose of induction therapy to 30 days post-induction or prior to consolidation therapy. Early death was defined as any death occurring within 30 days of diagnosis.

The definition of hematologic recovery after induction chemotherapy was consistent with CR with partial hematologic recovery (CRh). Time to neutrophil and platelet recovery was defined as the number of days from the start of induction chemotherapy to the day when absolute neutrophil count (ANC) reached 0.5×10^9/L and platelet count (PLT) reached 50×10^9/L, respectively.

Statistical analyses

The data were processed and analyzed using R, SAS 9.4 and GraphPad Prism 10.0 statistical software packages. Associations between mutation persistence and clinical parameters were analyzed using Wilcoxon rank-sum test for continuous and Fisher's exact test for categorical variables, and the t-test was used if the data were normally or approximately normally distributed, with non-parametric tests used otherwise. OS was measured from the date of diagnosis to the date of death or the last follow-up. EFS was measured from the date of diagnosis to the date of primary refractory disease, or relapse from CR or CRi, or death. Survival curves were generated using the Kaplan-Meier method. Survival rates of different groups were compared by the log-rank (Mantel-Cox) test. Uni- and multivariable analyses were performed using a Cox proportional hazards model. $P < 0.05$ was defined as statistically significant. The deadline for follow-up was December 1, 2025, with a median follow-up time of 39.5 (1.2-88.4) months.

Results

Patient characteristics

We enrolled 79 patients with de novo NPM1/FLT3-ITD/DNMT3A-mutated AML, including 45 patients in the IA group and 34 patients in the VEN-HMA group. All patients did not receive FLT3 inhibitors (such as sorafenib, midostaurin, and gilteritinib) during the initial induction. Patients' baseline features were summarized in **Table 1**. Compared with the IA group, the VEN-HMA group was older (median 55 vs 48 years, $P < 0.001$), had worse ECOG performance status (ECOG ≥2: 73.5%

vs 4.4%, $P < 0.001$), and included more males (61.8% vs 37.8%, $P = 0.035$). Other characteristics, including white blood cell count, bone marrow blasts, and co-mutational profiles (e.g., TET2, WT1, RAS, PTPN11), were balanced between groups (**Table 1 and Fig. 1**).

Response and MRD Reduction

Four patients experienced early death before efficacy evaluation and were excluded from the efficacy analysis. The CRc rate after induction therapy was significantly higher in the VEN-HMA group than in the IA group (71.9% vs. 44.2%; $P = 0.017$, **Fig. 2A** and **Table 2**). Moreover, the rate of CR was also higher in the VEN-HMA group (62.5% vs. 39.5%; $P = 0.004$, **Table 2**).

A total of 68 patients were available for MRD assessment after initial induction therapy, including 38 patients in the IA group and 30 patients in the VEN-HMA group. Among these patients, a ≥1-log reduction in NPM1 transcript levels was achieved in a significantly higher proportion of patients in the VEN-HMA group than in the IA group (56.7% vs. 31.6%, $P = 0.038$, **Fig. 2B** and **Table 2**).

Safety

A total of 67 patients were available for the safety evaluation, with 36 patients in the IA group and 31 patients in the VEN-HMA group. All patients experienced at least one AE (**Table S1**). The incidence of hematologic AEs (grade ≥3) was similar between VEN-HMA and IA, including neutropenia (100% vs. 100%, $P = 1.000$), thrombocytopenia (90.3% vs. 100%, $P = 0.188$) and anemia (93.5% vs. 100%, $P = 0.210$). In addition, no significant differences were observed between the two groups in platelet transfusion volume or red blood cell transfusion volume during the induction period.

With respect to non-hematological AEs, the incidence of pyrexia was significantly higher in the IA group than in the VEN-HMA group (86.1% vs. 54.8%, respectively; $P = 0.010$). The incidence of treatment-related serious adverse events (SAEs) of grade ≥3 febrile neutropenia was significantly lower in the VEN-HMA group than in the IA group (51.6% vs 83.3%, $P = 0.005$). The incidence of other grade ≥3 SAEs and the early death rate during induction were similar between the two groups. Additionally, patients with hyperleukocytosis were treated with hydroxyurea or leukapheresis before starting induction treatment, and no cases of tumor lysis syndrome (TLS) were observed in our study.

Hematologic recovery

There was no significant difference in the use of Granulocyte-stimulating factor (76.7% vs. 68.8%, $P = 0.439$) and thrombopoietic agents (such as thrombopoietin, thrombopoietin receptor agonists or IL-11, 65.1% vs. 53.1%, $P = 0.294$) between the two groups. No significant difference was observed

between the two groups in the time to hematologic recovery (**Fig. 3A, B**). The median time to neutrophil recovery was 33 (95% CI, 28-35) days in the VEN-HMA group compared to 23 (95% CI, 22-27) days in the IA group (P = 0.337). Similarly, the median time to platelet recovery was 32 (95% CI, 24-38) days in the VEN-HMA group and 25 (95% CI, 23-37) days in the IA group (P = 0.664).

Survival

The median follow-up was 39.5 months (range 1.2-88.4). At the time of data cutoff, 28/43 (65.1%) patients in the IA group and 19/32 (59.4%) patients in the VEN-HMA group underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT, P = 0.134). The median OS of patients was not reached in the VEN-HMA group versus 24.6 months in the IA group. 3-year OS rates were 39.5% in the IA group and 60.0% in the VEN-HMA group. Although the VEN-HMA regimen demonstrated a numerically superior OS, the difference did not reach statistical significance (HR=1.75, 95% CI 0.92-3.31, P = 0.104, **Fig. 4A**). On multivariate analysis, the WT1 co-mutation at diagnosis (HR=2.85, 95% CI 1.31 - 6.21, P = 0.009) and failure to achieve a ≥1 log reduction in NPM1 transcript levels after induction therapy (HR=2.47, 95% CI 1.16 - 6.46, P = 0.022) were associated with inferior OS, whereas ECOG ≥2 (vs. 0-1; HR=0.26, 95% CI 0.10-0.72, P = 0.009), FLT3 inhibitors therapy (HR=0.29, 95% CI 0.11 - 0.78, P = 0.015) and allo-HSCT (HR=0.20, 95% CI 0.10 - 0.41, P < 0.001) were protective (**Table S2**).

The median EFS was 10.4 months in the IA group and 18.0 months in the VEN-HMA group, with corresponding 3-year EFS rate was 30.6% and 45.4%, respectively. Similar to OS, no significant difference in EFS was observed between the two groups either (HR=1.45, 95% CI 0.81-2.59, P = 0.219, **Fig. 4B**). In the multivariate analysis, WT1 co-mutation (HR = 2.76, 95% CI 1.36–5.60, P = 0.005) and suboptimal NPM1 response (HR = 3.33, 95% CI 1.44–7.68, P = 0.005) remained adverse predictors, while ECOG ≥2 (vs. 0-1; HR = 0.38, 95% CI 0.17–0.84, P = 0.016) and allo-HSCT (HR = 0.24, 95% CI 0.11–0.50, P < 0.001) were protective (**Table S2**).

Discussion

This multicenter real-world study is the first to attempt to directly compare VEN-HMA and IA induction in AML patients with the adverse NPM1/FLT3-ITD/DNMT3A triple-mutational profile. Our findings suggested that VEN-HMA was associated with favorable response rates in these triple-mutated AML patients, including improved the CR rate and induced deeper molecular remission. This aligns

with preclinical evidence that DNMT3A mutations sensitize leukemic cells to hypomethylating agents and that NPM1 mutations create BCL-2 dependence, rendering the combination synthetically lethal [15-18]. Both VEN-HMA and IA exhibited safety profiles that aligned with their predefined toxicological profiles, and VEN-HMA was associated with a lower incidence of AEs, which was consistent with previous reports [13-14]. However, as a retrospective study with a small cohort size, baseline imbalances in age and performance status were present between the two groups. Moreover, VEN-HMA was not identified as an independent favorable factor of remission and survival in multivariate analysis (**Figure S2-S3, Table S2**). The lack of survival benefit may reflect the small sample size, baseline imbalances, and the confounding effect of subsequent allogeneic transplantation. Therefore, larger registry retrospective studies and well-designed prospective clinical trials are needed to further validate the efficacy of VEN-HMA in this high-risk subset.

In addition, we have identified a <1 log reduction in NPM1 transcript levels following initial induction therapy as a powerful independent predictor of poor OS and EFS. A significantly higher proportion of patients in the VEN-HMA group achieved a ≥1-log reduction in NPM1 transcripts compared with the IA group. Despite a higher median age and inferior performance status in the VEN-HMA group, this regimen still yielded a higher CRc rate and a greater reduction in MRD. Meanwhile, our multivariate analysis showed that failure to achieve a ≥1 log reduction in NPM1 transcript levels was an independent adverse risk factor for OS and EFS (**Table S2**). It suggested that VEN-HMA may be more suitable for elderly or unfit AML patients, thereby providing clinical evidence for individualized treatment decision-making [19]. However, it is important to recognize that MRD may lie on the causal pathway between treatment and survival. As mediation effects were not formally evaluated in this study, the prognostic interpretation of MRD reduction should be made with caution, which reprensts a limitation of the present analysis.

Given the high cost of FLT3 inhibiors in China, few patients received these agents during the first treatment cycle, and none of the 79 study patients were treated with FLT3 inhibitors during initial induction. A total of 12 patients received FLT3 inhibitors after induction. Among them, 9 received them after failing to achieve remission following first induction, 1 received FLT3 inhibitors during consolidation to attain molecular remission before transplantation, and 2 received them at relapse. Although only 16% of patients in our cohort received FLT3 inhibitors, their use was associated with favorable OS (Table S2). This finding aligns with previous reports demonstrating that FLT3 inhibitors

facilitate deeper molecular remissions [20] and serve as a key prognostic and therapeutic determinant in triple-mutated AML [7,21-24].

In respect to the prognostic impact of co-mutation, although a higher incidence rate of *TET2* mutation which was defined as clonal hematopoiesis-related gene mutation in the VEN-HMA group, VEN-HMA did not delay neutrophil or platelet recovery [25-27]. Consistent with previous reports [9], IDH2 co-mutation showed a favorable trend toward improved survival in our multivariate analysis (**Table S2**), although the difference did not reach statistical significance. More importantly, in line with the RATIFY trial [28], we found that WT1 co-mutation at diagnosis was an independent adverse prognostic factor for OS in this triple-mutated cohort (**Table S2**). This finding was further supported by the NCRI MRD study, which revealed that WT1 mutation was associated with MRD positivity and poor survival in $NPM1^{mut}$ AML [8]. Here we demonstrated a complex interaction between WT1, FLT3-ITD, and DNMT3A, with particularly poor outcomes if WT1 mutation was present along with either FLT3-ITD or DNMT3A mutations.

The counterintuitive association between ECOG ≥2 and improved OS (HR = 0.38, P = 0.016) is likely explained by selection bias and the complex interplay between treatment and post-remission outcomes. The IA group, despite being younger and fitter, had a higher transplant rate (65.1%), potentially exposing more patients to transplant-related mortality and graft-versus-host disease (GVHD), which may have offset the expected survival benefit of favorable performance status. In contrast, the VEN-HMA group, enriched for poor ECOG status, achieved comparable outcomes without intensive chemotherapy or transplant-related risks.

There is no doubt that allo-HSCT is an independent favorable prognostic factor for OS (**Table S2**), consistent with previous reports [25,29-30]. Some studies showed that AML patients with triple mutations exhibited comparable post-transplant outcomes to patients with NPM1/FLT3-ITD or FLT3-ITD/DNMT3A co-mutations [25,29]. A multicenter retrospective analysis in China further demonstrated that allo-HSCT could overcome the adverse prognosis of NPM1/FLT3-ITD/DNMT3A-mutated AML patients [30]. Collectively, combination therapy consisting of VEN-HMA induction, serial MRD-guided allo-HSCT, and FLT3 inhibitor maintenance may serve as a promising therapeutic strategy for these triple-mutated AML patients.

This study has several important limitations. First, its retrospective and non-randomized design introduces inevitable selection bias, as reflected by significant baseline imbalances in age and ECOG

status (both $P < 0.001$); the VEN-HMA group comprised significantly older patients with poorer performance status. Multivariate adjustment cannot fully eliminate confounding by indication, and propensity score-based balancing was precluded by the small sample size. Second, the sample is relatively small, and survival comparisons are underpowered. This limitation should be considered when interpreting the present results. Finally, owing to the small proportion of patients who received FLT3 inhibitors, the analysis was underpowered, and no definitive conclusion could be drawn regarding their impact on survival. Accordingly, prospective randomized controlled trials comparing VEN-HMA ± FLT3 inhibitor versus intensive chemotherapy in this molecularly defined subset are urgently needed.

In conclusion, in patients with newly diagnosed NPM1/FLT3-ITD/DNMT3A triple-mutated AML, VEN-HMA induction was associated with higher remission rates and deeper molecular responses than IA, with a more favorable safety profile. Although survival benefit was not demonstrated in this real-world analysis, the favorable early response supports the potential role of VEN-HMA as a reasonable treatment alternative for this high-risk subset. Early NPM1 MRD reduction appears to be a reliable prognostic marker and may facilitate risk-adapted strategies.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

Linlin Wang: Writing - original draft, Methodology, Investigation, Funding acquisition, Data curation.

Yanan Ma and Xueqing Dou: Formal analysis, Data curation, Resources, Methodology.

Ke Shi, Li Wang, Mingkai Shu and Rui Jiang: data collection.

Xiaofei Yang, Yuexin Cheng, Depei Wu and Suning Chen: collected samples and treated the patients.

Zhao Zeng and Peng Ke: Writing - review & editing, Supervision, Conceptualization.

Suning Chen: Writing - review & editing, Visualization, Validation, Supervision, Data curation, Conceptualization.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval

This study was approved by the Research Ethics Committees of the First Affiliated Hospital of Soochow University (Approval No.: 2026102), which also covered its affiliate Suzhou Hongci Hematology Hospital, and the First People‘s Hospital of Yancheng (Approval No.: 2026-K032). Informed consent was waived due to the retrospective design, and all procedures complied with the Declaration of Helsinki.

Consent to participate

The requirement for informed consent was waived by the Ethics Committee of the First Affiliated Hospital of Soochow University and the First People's Hospital of Yancheng due to the retrospective study design.

Table 1. Patient demographic and clinical characteristics.

Characteristic	Total cohort (n=79)	IA Group (n=45)	VEN-HMA Group (n=34)	P value
Male/Female	38/41	17/28	21/13	0.035
Median age (years)	52 (19-74)	48 (19-62)	55 (22-74)	<0.001
ECOG performance status, n (%)				<0.001
0-1	52 (65.8)	43 (95.6)	9 (26.5)	
2-3	27 (34.2)	2 (4.4)	25 (73.5)	
WBC ($\times10^9$/l)	86.8 (1.4-346.1)	84.6 (10.5-346.1)	86.8 (1.4-212.9)	0.651
HB (g/l)	79 (53–139)	86 (56–134)	75 (53–139)	0.108
PLT ($\times10^9$/l)	57 (10–448)	51.5 (19–448)	62 (10–341)	0.620
BM blast (%)	73 (14.8–94)	70 (29–92)	74 (14.8–94)	0.834
Patients with gene mutations detected in pretreatment sample, n (%)				
FLT3-TKD	15 (19.0)	7 (15.6)	8 (23.5)	0.371
K/NRAS	14 (17.7)	6 (13.3)	8 (23.5)	0.240
PTPN11	13 (16.5)	8 (17.8)	5 (14.7)	0.715
TET2	12 (15.2)	5 (11.1)	7 (20.6)	0.245
WT1	11 (13.9)	5 (11.1)	6 (17.6)	0.615
IDH2	7 (8.9)	2 (4.4)	5 (14.7)	0.234
IDH1	3 (3.8)	2 (4.4)	1 (2.9)	1.000
Early death*, n (%)	4 (5.1)	2 (4.4)	2 (5.9)	1.000
Allo-HSCT, n (%)	47/75 (62.7)	28/43 (65.1)	19/32 (59.4)	0.134
Disease stage pre-SCT				0.367
CR/CRi	26	17	9	
Relapse/refractory	21	11	10	
FLT3 inhibitors using after induction therapy†, n (%)	12/75 (16.0)	6/43 (14.0)	6/32 (18.8)	0.575

Abbreviation: IA, idarubicin + cytarabine; VEN-HMA, venetoclax combined with hypomethylating agent; ECOG, Eastern Cooperative Oncology Group; WBC, white blood cell; HB, hemoglobin; PLT, platelet; BM, bone marrow; allo-HSCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission, CRi, CR with incomplete hematological recovery.

*The causes of early death in the 4 patients were cerebral hemorrhage (2 patients), pneumorrhagia (1 patient) and gastrointestinal bleeding (1 patient).

† A total of 12 patients received FLT3 inhibitors after induction. Among them, 9 received them after failing to achieve remission following first induction, 1 received FLT3 inhibitors during consolidation to attain molecular remission before transplantation, and 2 received them at relapse.

Table 2. Overall Response.

Variable	IA Group (n=43)	VEN-HMA Group (n=32)	P value
CRc, n (%)	19/43 (44.2)	23/32 (71.9)	0.017
CR, n (%)	17/43 (39.5)	20/32 (62.5)	0.004
CRi, n (%)	2/43 (4.7)	3/32 (9.4)	
MRD			0.038
≥1 log reduction, n (%)	12/38 (31.6)	17/30 (56.7)	
MRD negative, n (%)	2/38 (5.3)	3/30 (10.0)	
3-4 log reduction, n (%)	3/38 (7.9)	4/30 (13.3)	
2-3 log reduction, n (%)	3/38 (7.9)	6/30 (20.0)	
1-2 log reduction, n (%)	4/38 (10.5)	4/30 (13.3)	
<1 log reduction, n (%)	26/38 (68.4)	13/30 (43.3)	

Abbreviation: IA, idarubicin + cytarabine; VEN-HMA, venetoclax combined with hypomethylating agent; CRc, composite complete remission; CRi, CR with incomplete hematological recovery; MRD, measurable residual disease.

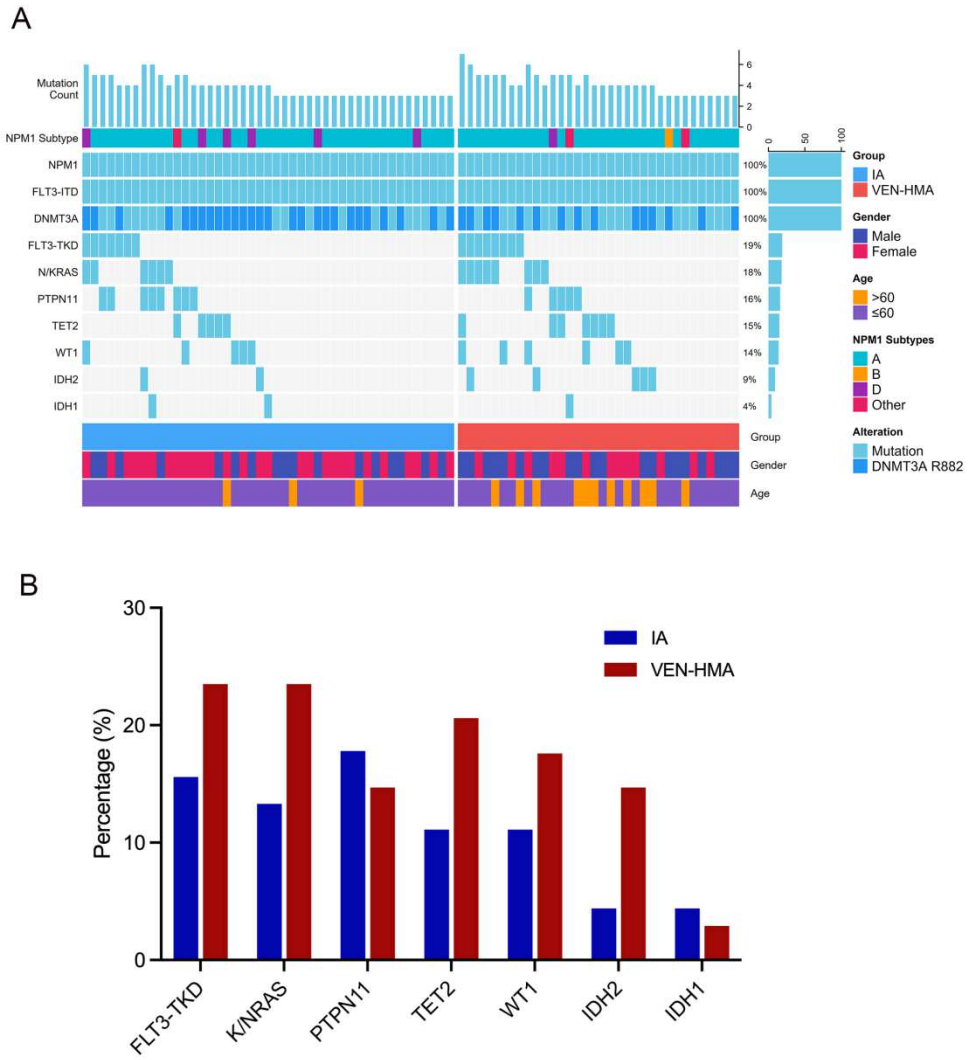


Fig. 1 Comparison of gene mutations at diagnosis. A. Mutational landscape in the IA and the VEN-HMA group. Each column represents one patient. B. Frequency of mutations identified at diagnosis.

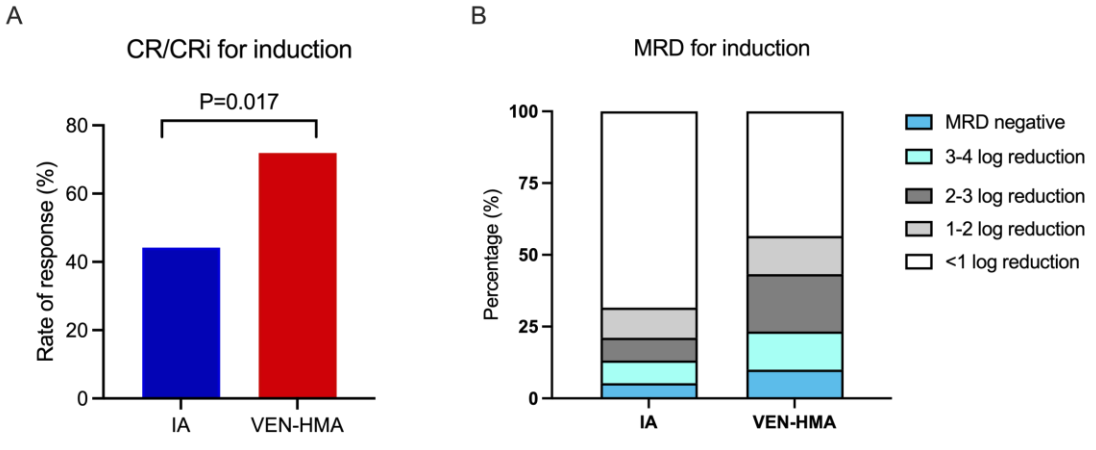
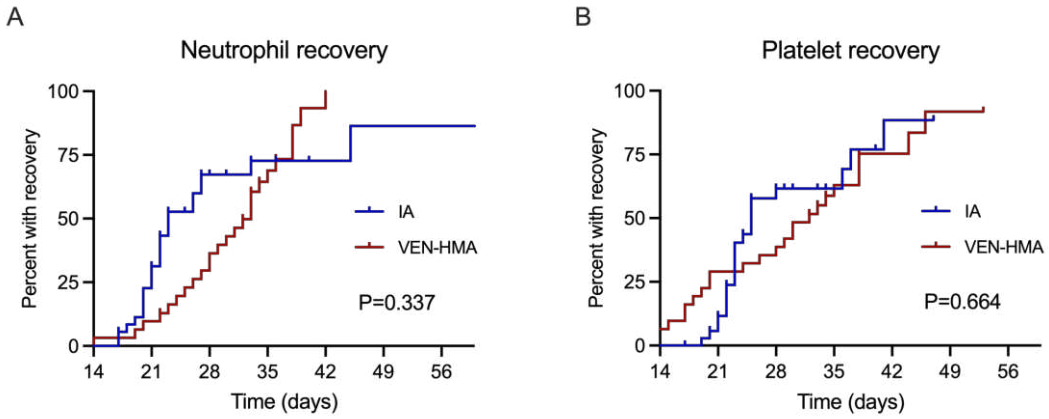


Fig. 2 Comparison of CRc (A) and MRD (B) for induction therapy.

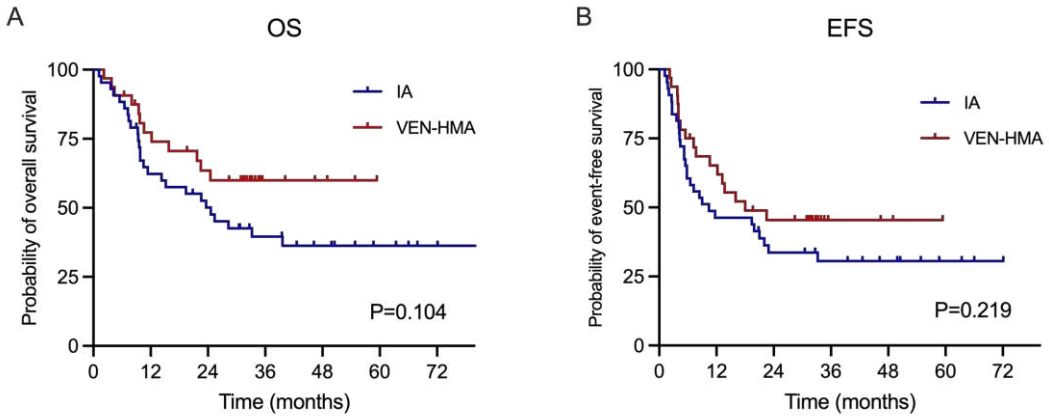


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436 **Fig. 3** Comparison of neutrophil (A) and platelet (B) recovery after induction chemotherapy between

437 two induction treatment groups.

438



439

440 **Fig. 4** Kaplan-Meier survival curves for overall survival (OS) and event-free survival (EFS) in patients

441 with triple-mutated AML. (A,B) OS and EFS comparisons between the two induction groups.

Supplementary Files

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