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Genotype-guided comparison of VEN/HMA versus intensive chemotherapy in newly diagnosed intermediate-risk AML: a multicenter real-world study

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TO THE EDITOR:

Approximately 30–40% of newly diagnosed acute myeloid leukemia (ND-AML) patients were categorized as intermediate-risk according to the 2022 European LeukemiaNet (ELN) classification, who exhibit heterogeneity in biological and clinical manifestations [1]. Although standard induction ("7 + 3" regimen) achieves complete remission (CR) rates of 50–70%, outcomes remain suboptimal due to variable molecular profiles and treatment-related toxicities such as profound myelosuppression, infections, and hemorrhage [2].

Venetoclax (VEN), a selective BCL-2 inhibitor, in combination with hypomethylating agents (HMAs), has been established as a standard frontline therapy for elderly or unfit AML patients, demonstrating promising efficacy and safety [3]. Recent studies have reported encouraging remission rates with VEN/HMA in younger patients [4] and in those with myelodysplasia-related gene mutations [5]. However, comparative real-world data between VEN/HMA and intensive chemotherapy (IC), particularly across distinct molecular subtypes within newly diagnosed AML patients with intermediate-risk, remains scarce. Here, we conducted a multicenter, retrospective matched cohort analysis to compare the efficacy and safety of VEN/HMA and IC in this population, with particular focus on response heterogeneity across genetic subgroups and long-term survival outcomes.

We collected data of 229 newly diagnosed non-APL AML patients classified as intermediate-risk according to the 2022 ELN criteria [1], treated at four tertiary hospitals in Hunan Province, China, between January 2016 and February 2025 (Fig. S1). All patients underwent standardized diagnostic evaluation, including targeted next-generation sequencing, cytogenetics, and fusion gene testing. Among the included patients, 88 received VEN/HMA, while 141 received IC. Treatment decisions were made jointly by clinicians and patients based on clinical fitness, comorbidities and drug accessibility. VEN/HMA regimen was defined as concurrent administration of VEN with any HMA; IC was identified as a cytarabine-based regimen at a minimum dose of 100 mg/m^2/day. To account for baseline differences, propensity score matching was performed using a 1:2 nearest-neighbor algorithm based on age. Treatment responses were assessed using ELN 2022 criteria, allowing up to 14 days for count recovery in the VEN/HMA group [1]. MRD was measured by flow cytometry with a positivity threshold of 0.1%. Overall survival (OS) was tabulated from the time of therapy initiation to death or last follow-up and progression-free survival (PFS) was defined as the time from diagnosis to an assessment that the patient was refractory to treatment (defined as a failure to respond to at least two IC regimens or at least one course of VEN/HMA), progressed after responding, or died. The study was approved by the Ethics Committee of the Third Xiangya Hospital of Central South University (approval number: 25479), and written informed consent was obtained from all patients.

In the unmatched cohort, patients in the VEN/HMA group were older and less likely to undergo allo-HSCT compared to those receiving IC (Table S1). After 1:2 propensity score matching for age, 72 patients in the VEN/HMA group and 112 in the IC group were included in the final analysis, with balanced baseline characteristics (Table 1), and cytogenetic risk profiles are shown in Fig. S2. Following 1–2 cycles of induction, VEN/HMA achieved a higher overall response rate (ORR) (80.6% vs. 62.5%, $P = 0.009$) and CR rate (76.4% vs. 50%, $P < 0.001$) compared to IC. MRD negativity at best response was also more frequent in the VEN/HMA group (78.6% vs. 57.8%, $P = 0.027$) (Fig. 1A). Subgroup analyses revealed that patients aged ≥60 years or harboring *FLT3-ITD*, *DNMT3A*, or *TET2* mutations exhibited superior responses to VEN/HMA (Fig. 1B).

VEN/HMA was associated with reduced hematologic toxicity and transfusion requirements. Compared with IC, the VEN/HMA group had significantly lower rates of febrile neutropenia (36.1% vs. 56.3%, $P = 0.008$) and platelet transfusion (50.0% vs. 72.3%, $P = 0.002$), with similar average transfusion volumes (Fig. 1C). Early mortality did not differ between groups (Table S2).

After a median follow-up of 13.3 months, VEN/HMA was associated with significantly improved OS (not reached vs 15.6 months, $P = 0.016$) and PFS (22.3 months vs 15.4 months, $P = 0.044$) (Fig. 1D, E). In patients who did not undergo allo-HSCT, VEN/HMA remained associated with significantly longer OS and PFS ($P < 0.001$ for both; Fig. S3A, B). Among patients who underwent allo-HSCT, no significant difference in 3-year OS was observed between the two treatment groups (Fig. S3C). Among MRD-negative patients without transplantation, those treated with VEN/HMA had superior OS compared to those receiving IC ($P < 0.001$; Fig. S3D). In multivariable analysis, VEN/HMA and allo-HSCT were an independent predictor of improved OS and PFS (Fig. 1F, G).

We retrospectively analyzed newly diagnosed AML patients with intermediate risk who received VEN/HMA or IC to compare response, long-term outcomes, recognize mutation-specific predictors of response. This multicenter real-world retrospective study present the first direct comparison of VEN/HMA and IC as induction therapy in newly diagnosed intermediate-risk AML. VEN/HMA achieved a comparable remission rate with IC regimens, with significantly fewer transfusion requirements and infection-related complications, underscoring its favorable safety profile. Notably, patients harboring *FLT3-ITD*, *DNMT3A*, or

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Table 1. Baseline characteristics of patients in the propensity score–matched VEN/HMA and IC cohorts.

Variable	IC ($n = 112$)	VEN/HMA ($n = 72$)	P (IC vs VEN/HMA)
Median age, years (range)	48 (17–70)	50 (15–70)	0.154
Male sex, *n* (%)	52 (46.6)	34 (47.2)	0.916
Hematological parameters			
Median WBC, $\times 10^9$/L (range)	4.94 (0.46–381.61)	3.6 (0.43–251)	0.833
Median Hb, g/L (range)	77 (36–139)	77 (50–113)	0.237
Median Plt, $\times 10^9$/L (range)	154 (4–1660)	66 (8–587)	**0.002**
Median bone marrow blast (range), %	67 (8–98)	45 (8–94)	0.233
Disease type, *n* (%)			
De novo AML	108 (96.4)	69 (95.8)	1.000
S-AML/T-AML	4 (3.6)	3 (4.2)	1.000
FAB classification			
M0/1	15 (13.4)	4 (5.6)	0.088
M5	32 (28.6)	15 (20.8)	0.240
Allo-HSCT, *n* (%)	39 (34.8)	11 (15.3)	**0.004**
Gene fusion, *n* (%)			
MLLT3::KMT2A	0 (0)	1 (1.4)	0.391
HOX11	1 (0.9)	4 (5.6)	0.078
Mutations, *n* (%)			
FLT3	36 (32.1)	23 (31.9)	1.000
FLT3-ITD	29 (25.9)	16 (22.2)	0.603
DNMT3A	22 (19.6)	20 (27.8)	0.199
TET2	10 (8.9)	18 (25.0)	**0.004**
RAS	20 (17.9)	23 (31.9)	**0.033**
NRAS	20 (17.9)	15 (20.8)	0.701
KRAS	3 (2.7)	7 (9.7)	0.050
WT1	16 (14.3)	11 (15.3)	0.835
KIT	4 (3.6)	2 (2.8)	1.000
GATA2	10 (8.9)	7 (9.7)	1.000
PTPN11	9 (8.0)	5 (6.9)	1.000
IDH	26 (23.2)	22 (30.6)	0.268
IDH1	7 (6.3)	8 (11.1)	0.276
IDH2	13 (11.6)	15 (20.8)	0.097
CSF3R	4 (3.6)	3 (4.2)	0.563
KMT2D	3 (2.7)	1 (1.4)	1.000

Bold values indicates statistical significant *P* values ($P < 0.05$).

TET2 mutations exhibited enhanced responses to VEN/HMA. Durable long-term survival appeared to rely on subsequent allo-HSCT, emphasizing the importance of post-remission strategies.

Regarding safety, compared with IC, patients receiving VEN/HMA required fewer red blood cell and platelet transfusions, and had a lower incidence of febrile neutropenia, consistent with the VEN/DEC study by Jing Lu et al., which reported a significantly decreased rate of grade ≥3 infections in the VEN group (32%), as well as reduced rates of neutropenic fever (10%) and sepsis (7%) [4]. Additionally, a meta-analysis of nine trials confirmed a significant reduction in 30-day mortality (OR = 0.23) with VEN-based regimens, without increasing overall adverse event rates [6]. Reduced toxicity may improve treatment adherence, facilitate completion of post-remission therapy, and support VEN-HMA as a viable first-line option.

Given the observed difference in ORR between VEN/HMA and IC, we further explored mutation-specific response patterns through subgroup analysis. Our findings suggest that *FLT3-ITD, DNMT3A*, and *TET2* mutations may predict better responses to VEN/HMA. For instance, *FLT3-ITD* mutations may confer greater BCL-2 dependency, thereby enhancing VEN responsiveness [7], while *DNMT3A* mutations might promote VEN/HMA efficacy by regulating the NRF2/NQO1 pathway, a mechanism implicated in daunorubicin resistance in AML cells [8]. In contrast, *KIT and KRAS/NRAS* mutations appeared to predict inferior response to VEN-based regimens [9–11], highlighting potential resistance mechanisms to BCL-2 inhibition in these molecular subtypes. This underscores the importance of tailoring induction therapy based on individual genomic profiles. Taken together, these findings support a paradigm shift from age-based to genotype-driven induction strategies [12]. Current clinical frameworks, such as the Mayo Clinic VEN score [13] and the ELN 2024 low-intensity treatment guidelines [10], have begun to incorporate genomic stratification to inform personalized treatment approaches in AML.

MRD is a validated prognostic marker in AML [14], yet its interpretation across different regimens in intermediate-risk patients remains unclear. In our cohort, non-transplanted patients who achieved MRD negativity had significantly better OS when treated with VEN/HMA compared to IC, suggesting a deeper molecular remission. VEN's ability to target leukemic stem/progenitor cells and its milder hematopoietic suppression may contribute to improved MRD responses and improved survival [15]. Nevertheless, we observed a convergence of survival curves beyond 600 days, potentially reflecting the emergence of VEN resistance during long-term follow-up. Data from our center further indicate that VEN-based therapy alone may be insufficient for durable disease control, reinforcing the need for consolidation strategies such as IC or allo-HSCT to maintain long-term remission. These findings highlight the importance of optimizing post-remission interventions and underscore the necessity of tailoring treatment strategies based on patients' genetic profiles.

Our results offer preliminary evidence supporting the use of VEN/HMA as a frontline induction regimen in the intermediate-risk AML population. However, given the retrospective nature and limited sample size, these findings should be interpreted with caution. Prospective, large-scale clinical trials are warranted to validate the efficacy and safety of VEN/HMA in intermediate-risk AML, clarify mutation-specific response patterns, and refine individualized treatment strategies to achieve deeper remission and extend survival outcomes.

In summary, this multicenter real-world study supports VEN/HMA as a safe and effective induction strategy for intermediate-risk AML, particularly in patients harboring BCL-2 inhibitor-sensitive mutations such as *FLT3-ITD*, *DNMT3A*, and *TET2*. Consolidation with allo-HSCT remains essential for achieving durable remissions. These findings underscore the value of genotype-guided treatment selection in intermediate-risk AML and warrant validation in prospective, biomarker-driven clinical trials.

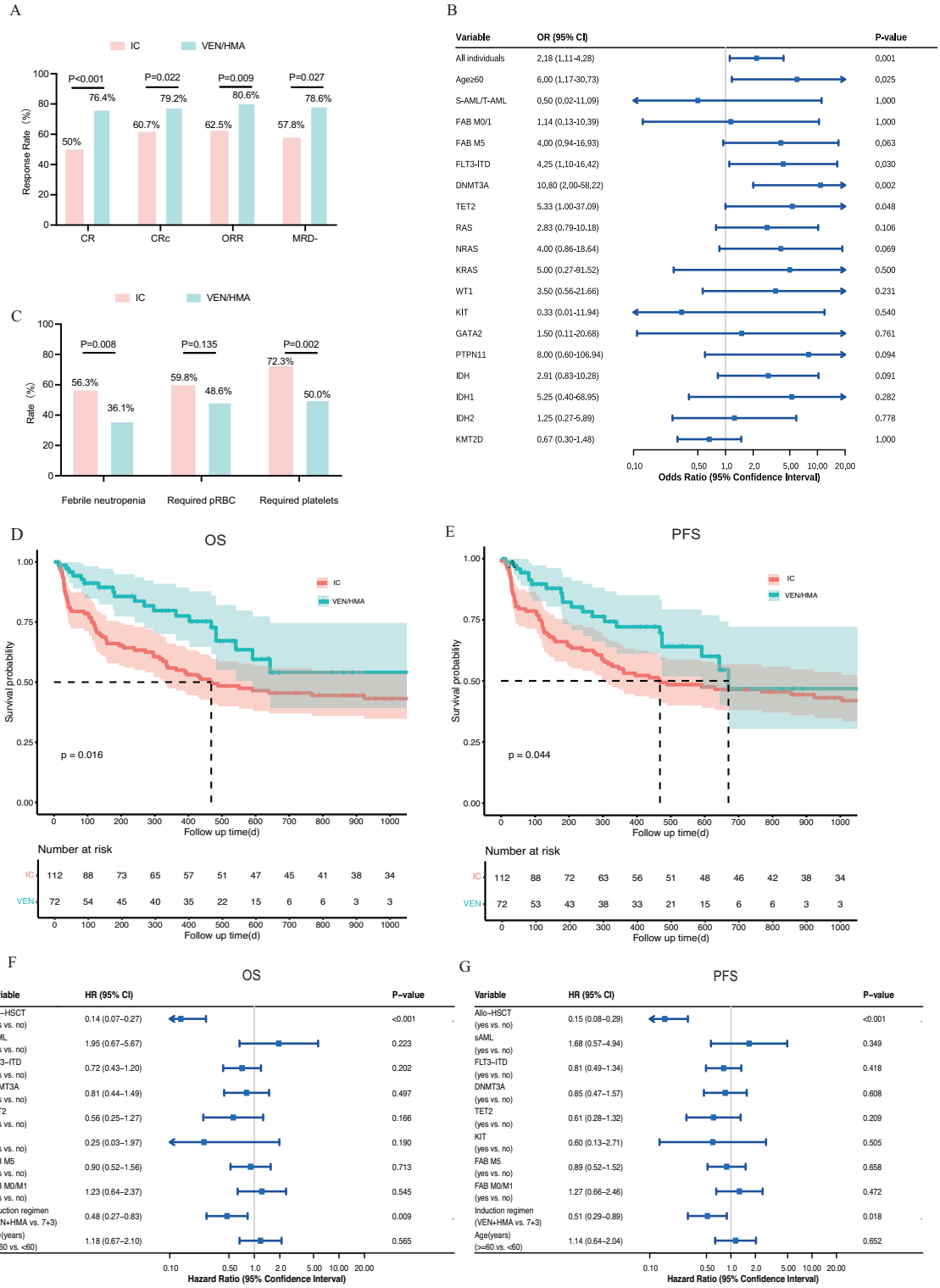

Fig. 1 Response, safety, and survival outcomes in propensity score–matched intermediate-risk AML patients treated with VEN/HMA or IC. A Response rates in matched cohorts. **B** Baseline variables predicting differential response to VEN/HMA or IC. **C** Incidence of myelosuppression-related toxicities in VEN/HMA and IC. **D, E** Overall survival (OS) and progression-free survival (PFS) in VEN/HMA versus IC groups. **F, G** Multivariable Cox regression analysis for predictors of OS and PFS.

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DATA AVAILABILITY

Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. Data are available from the corresponding author (email: lixiner1975@163.com) upon reasonable request.

REFERENCES

1. Dohner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140:1345–77.
2. Ohtake S, Miyawaki S, Fujita H, Kiyoi H, Shinagawa K, Usui N, et al. Randomized study of induction therapy comparing standard-dose idarubicin with high-dose daunorubicin in adult patients with previously untreated acute myeloid leukemia: the JALSG AML201 Study. Blood. 2011;117:2358–65.
3. Xie J, Bao X, Xue SL, Shen H, Cen J, Yao L, et al. Venetoclax with decitabine as frontline treatment in younger adults with newly diagnosed ELN adverse-risk AML. Blood. 2023;142:1323–7.
4. Lu J, Xue SL, Wang Y, He XF, Hu XH, Miao M, et al. Venetoclax and decitabine vs intensive chemotherapy as induction for young patients with newly diagnosed AML. Blood. 2025;145:2645–55.
5. Wan CL, Liu YQ, Liu FT, Huang YH, Cao HY, Huang SM, et al. Venetoclax with hypomethylating agents versus intensive chemotherapy in newly diagnosed acute myeloid leukemia with myelodysplasia-related changes: a propensity score-matched analysis based on International Consensus Classification. Blood Cancer J. 2024;14:144.
6. Wang Y, Chen Y, Ji D, Ge L, Zhang Y, Liu L, et al. Meta-analysis on the effectiveness and safety of venetoclax-based combination therapy with hypomethylation in acute myeloid leukemia. Eur J Med Res. 2025;30:330.
7. Zhu R, Li L, Nguyen B, Seo J, Wu M, Seale T, et al. FLT3 tyrosine kinase inhibitors synergize with BCL-2 inhibition to eliminate FLT3/ITD acute leukemia cells through BIM activation. Signal Transduct Target Ther. 2021;6:186.
8. Chu X, Zhong L, Dan W, Wang X, Zhang Z, Liu Z, et al. DNMT3A R882H mutation drives daunorubicin resistance in acute myeloid leukemia via regulating NRF2/NQO1 pathway. Cell Commun Signal. 2022;20:168.
9. Shu W, Yang Q, He D, Li Y, Le J, Cai Q, et al. Impact of KIT mutation on efficacy of venetoclax and hypomethylating agents in newly diagnosed acute myeloid leukemia. Eur J Med Res. 2025;30:354.
10. Dohner H, DiNardo CD, Appelbaum FR, Craddock C, Dombret H, Ebert BL, et al. Genetic risk classification for adults with AML receiving less-intensive therapies: the 2024 ELN recommendations. Blood. 2024;144:2169–73.
11. Zhang Q, Riley-Gillis B, Han L, Jia Y, Lodi A, Zhang H, et al. Activation of RAS/MAPK pathway confers MCL-1 mediated acquired resistance to BCL-2 inhibitor venetoclax in acute myeloid leukemia. Signal Transduct Target Ther. 2022;7:51.
12. Lin TL. Are you ready for it? VEN-HMA for younger patients with AML. Blood. 2025;145:2543–4.
13. Gangat N, Elbeih A, Ghosoun N, McCullough K, Aperna F, Johnson IM, et al. Mayo genetic risk models for newly diagnosed acute myeloid leukemia treated with venetoclax + hypomethylating agent. Am J Hematol. 2025;100:260–71.
14. Short NJ, Zhou S, Fu C, Berry DA, Walter RB, Freeman SD, et al. Association of measurable residual disease with survival outcomes in patients with acute myeloid leukemia: a systematic review and meta-analysis. JAMA Oncol. 2020;6:1890–9.
15. Dillon LW, Gui G, Page KM, Ravindra N, Wong ZC, Andrew G, et al. DNA sequencing to detect residual disease in adults with acute myeloid leukemia prior to hematopoietic cell transplant. JAMA. 2023;329:745–55.

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AUTHOR CONTRIBUTIONS

XC, YHY, QC, YL, EHW, JZ, HX, and LWW followed study patients. QZ supervised and performed molecular analysis; XC, YHY and YST collected data and interpreted the results; XC and YST performed statistical analysis; XC wrote the manuscript; XL supervised the project; XC, YHY, QC, YST, HX, and XL revised the manuscript. All authors approved the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Review Board of the Third Xiangya Hospital of Central South University (No. 25479). All methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all participants according to the Declaration of Helsinki.

ADDITIONAL INFORMATION

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