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RESEARCH

Comparative efficacy of venetoclax and hypomethylating agents in acute myeloid leukemia treatment: a meta-analysis of clinical trials and Real-World outcomes

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Abstract

This meta-analysis, comprising 24 studies, evaluated the efficacy of venetoclax (VEN) in combination with hypomethylating agents (HMAs), including azacitidine (AZA) and decitabine (DEC), in untreated patients with acute myeloid leukemia (AML), comparing outcomes from clinical trials and real-world practice. No significant difference in composite complete response (CRc) rates was observed between clinical trials (52%, 95% CI: 39–65%) and real-world studies (67%, 95% CI: 47–87%). However, overall survival (OS) was significantly longer in clinical trials (13.98 months, 95% CI: 11.89–16.07) compared to real-world cohorts (9.35 months, 95% CI: 8.46–10.23; $p<0.005$). In real-world studies, the VEN+HMA combination was associated with a significantly higher CRc rate (67%, 95% CI: 48–85%) compared to HMA monotherapy (17%, 95% CI: 13–21%; $p<0.005$), although no significant difference in OS was observed between these groups (9.35 vs. 9.38 months; $p=0.964$). These findings highlight the need to optimize the implementation of VEN+HMA regimens in clinical practice, as real-world outcomes remain inferior to those reported in clinical trials.

Introduction

Acute myeloid leukemia (AML) is a clonal hematological malignancy that originates from aberrant genetic changes within hematopoietic progenitor cells. These alterations lead to excessive proliferation and accumulation of immature myeloid stem cells, resulting in bone marrow failure and infiltration of extramedullary tissues [1, 2]. AML predominantly affects older adults, with a median age at diagnosis near 68 years, and its incidence increases progressibely with advancing age [3]. In the absence of treatment, AML tipically follows an aggressive course, leading to death within weeks [4].

For fit patients, the standard induction regimen combines an anthracycline with cytarabine, commonly referred to as "3+7" protocol [5, 6]. However, this approach is often not suitable for elderly patients or those with significant comorbidities, owing to its high toxicity. In such cases, lower intensity strategies based on hypomethylating agents (HMAs) – azacitidine (AZA) or decitabine (DEC) - have allowed more elderly AML patients to be treated [4], and have shown overall survival (OS) benefits compared to low-dose cytarabine (in monotherapy or combined with other chemotherapeutic agents) or best supportive care [7–9].

More recently, the addition of venetoclax (VEN), a selective BCL-2 inhibitor, with either AZA or DEC, has transformed the therapeutic landscape for patients unfit for intensive chemotherapy. Several clinical trials have shown that VEN in combination with AZA or DEC significantly improves remission rates and OS compared to HMA monotherapy [10, 11]. Despite these encouraging findings, translating the efficacy observed in trials to routine clinical

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practice remains challenging [12]. Eligibility criteria in clinical trials are often restrictive, and real-world patients tend to present with more heterogeneous characteristics, including comorbidities, poor performance status, or unfavorable disease biology [13].

Given these discrepancies, real-world evidence is essential to determine whether the benefits of VEN + HMA combinations are reproducible outside controlled trial settings. To this end, we conducted a meta-analysis comparing the efficacy of VEN + HMA regimens in untreated AML patients across clinical trials and real-world studies. Additionally, we evaluated whether the addition of VEN to HMAs offers meaningful clinical advantage over HMA monotherapy in real-world cohorts.

Materials and methods

Study design and eligibility criteria

This meta-analysis included both randomized controlled trials and real-world observational studies evaluating the use of AZA or DEC, with or without VEN, in adult patients with newly diagnosed AML. Only studies reporting first-line treatment data were considered. Data from relapsed or refractory AML populations were excluded to maintain consistency in the clinical context evaluated.

Search strategy

A comprehensive literature search was conducted to identify relevant publications evaluating the efficacy of HMAs (AZA or DEC), with or without VEN, either in clinical trials or as standard of care regimens in real worlds cohorts. The search was performed using MEDLINE and PubMed and was last updated on March 17, 2023. Additionally, the reference lists of selected studies and relevant reviews were screened manually to ensure completeness.

The following search terms were applied: "Acute Myeloid Leukemia" OR "Acute Myeloid Leukaemia" OR "AML" AND "hypomethylating" OR "Azacitidine" OR "Vidaza" AND "Venetoclax".

A parallel search was conducted for HMA monotherapy using the same AML-related terms and replacing "venetoclax" with "monotherapy." To maintain methodological consistency and avoid data duplication, the search was limited to studies published between May 1, 2021, and March 17, 2023. Publications prior to this period were extracted from a previously conducted and published meta-analysis by our group, which applied the same eligibility criteria and search strategy [14].

Study selection

Titles and abstracts were independently screened by two reviewers (A.S.-S. and J.L.) to determine eligibility based on predefined criteria. Full texts of potentially relevant studies were assessed, and data were extracted using standardized forms developed on "Abstrackr" platform and subsequently transferred to Microsoft Excel 2010 [15]. Discrepancies were resolved through consensus or, when necessary, consultation with additional authors (R.A., M.S.-R, S.C.-S., B.C., and M.-V.C.).

Eligibility studies met the following criteria: [1] enrolled untreated AML patients receiving AZA or DEC, with or without VEN; and [2] reported efficacy outcomes including complete remission (CR), composite complete remission (CRc), minimal residual disease (MRD), and/or median OS.

Data extraction and variables collected

These following variables were systematically extracted.

- PMID.
- First author and year of publication.
- Sample size (N).
- Median age (years) and age range.
- Sex distribution (male/female).
- Eastern Cooperative Oncology Group (ECOG) performance status (0/1, 2, ≥3).
- Cytogenetics risk (proportion with poor-risk cytogenetics).
- Treatment duration (days).
- Baseline bone marrow blasts percentage (median).
- Percentage of molecular mutations (*FLT3*, *IDH1/2*, *NPM1* and *TP53*).
- Complete remission (CR) rate (%).
- Composite complete remission (cCR) rate (%):CR plus CR with incomplete recovery (CRi).
- Minimal Residual Disease (MRD) negativity (as defined by each study).
- Median OS (in months).

Outcome definitions

Complete remission (CR) was defined uniformly as bone marrow blasts < 5%, absence of peripheral blasts and Auer rods, no extramedullary disease, absolute neutrophil count > 1.0×10^9/L, and platelet count > 100×10^9/L. CRc included patients meeting criteria for CR and those achieving CRi, defined by persistent neutropenia and/or thrombocytopenia. OS was calculated by considering all deaths from any cause.

Assessment of methodological quality and risk of bias

Risk of bias was evaluated independently by two reviewers (A.S.-S. and M.S.-R.) using the Cochrane Collaboration's methodology [16], which assesses domains such as creation of random sequences, concealment of allocation, selective reporting, blinding (of participants, staff, and outcome assessment), inadequate outcome data, and other sources of bias. Discrepancies were resolved through consensus or adjudication by a third reviewer (J.L.). Risk of bias for each domain was classified as low, high or uncertain.

Statistical analysis

The meta-analysis included comparisons between clinical trials and those from real-world studies, as well as comparisons between different treatment strategies within real-world cohorts. Specifically, we evaluated the efficacy of VEN+AZA versus VEN+DEC in clinical trials, and subsequently compared clinical trial results of VEN+AZA with those reported in real-world practice. Additionally, within real-world setting, we conducted two separated analyses: one comparing patients treated with VEN+HMAs (either AZA or DEC) versus HMA monotherapy, and another comparing VEN+AZA specifically against AZA alone.

All statistical analyses were performed using STATA version 15.1 [17]. Heterogeneity was assessed through estimation of inter-study variance, intra-study variance, and inter-study coefficient of variation. The I^2 coefficient, representing the proportion of total variance attributable to heterogeneity between studies, was used as the primary measure of variability, with values > 50% indicating substantial heterogeneity. A random-effects model was applied for between-study differences in the assessment of MRD, CRc, and OS. Results were reported as point estimates with corresponding 95% confidence intervals (CI). For OS, median values and associates CI were converted to means and standard deviations (SD) using the method described by Hozo et al. [18]. All analyses conducted according to the intention-to-treat (ITT) principle.

Results

Study selection

A total of 280 citations were initially identified for combination therapy and 72 for HMA monotherapy. After removing duplicates and applying eligibility criteria, a final set of 24 studies was included. The study selection process, along with the primary reasons for exclusion, is depicted in the flow diagram (Fig. 1).

Study characteristics

This meta-analysis included 5998 patients across 31 cohorts derived from 24 individual studies. The main characteristics of the included studies are detailed in Supplementary Table 1, while Table 1 summarizes the primary efficacy outcomes.

Outcomes

Efficacy of VEN + HMA in clinical trials vs. Real world studies

No statistically significant difference in CRc rates was observed between clinical trials (61%, 95% CI: 52–70%) and real-world studies (61%, 95% CI: 34–88%) (Figs. 2A). However, a trend toward lower CR rates was observed in real-world cohorts (33%, 95% CI: 24–41%) compared to clinical trials (41%, 95% CI: 32–49%) (Supplementary Fig. 1 A).

Median OS was significantly longer in clinical trials (14.07 months; 95% CI: 11.71–16.42) compared to real-world settings (9.35 months; 95% CI: 8.46–10.23), ($p < 0.005$; Fig. 2B).

MRD negativity was also evaluated. Clinical trial participants exhibited a MRD negativity rate of 26% (95% CI: 18–33%) whereas real-world cohorts showed a higher rate of 41% (95% CI: 31–51%), with statistical significance ($p = 0.018$) (Supplementary Fig. 1B).

Efficacy of VEN + AZA vs. VEN + DEC in clinical trials

In the comparison between VEN+AZA and VEN+DEC within clinical trials, no statistically significant differences were observed in CRc rates (65%; 95% CI: 35–75% vs. 53%; 95% CI: 38–68%, respectively; $p = 0.186$) (Supplementary Fig. 2A). CR rates were also similar between groups (Supplementary Fig. 2B).

Median OS was 15.31 months (95% CI: 13.58–17.05 months) in the VEN+AZA group and 11.18 months (95% CI: 5.15–17.21 months) in the VEN+DEC group, without statistical significance ($p = 0.1987$) (Supplementary Fig. 2C).

MRD negativity rate was 29% (95% CI: 22–36%) in the VEN+AZA group and 24% (95% CI: 13–34%) in the VEN+DEC group, also without statistical significant differences.

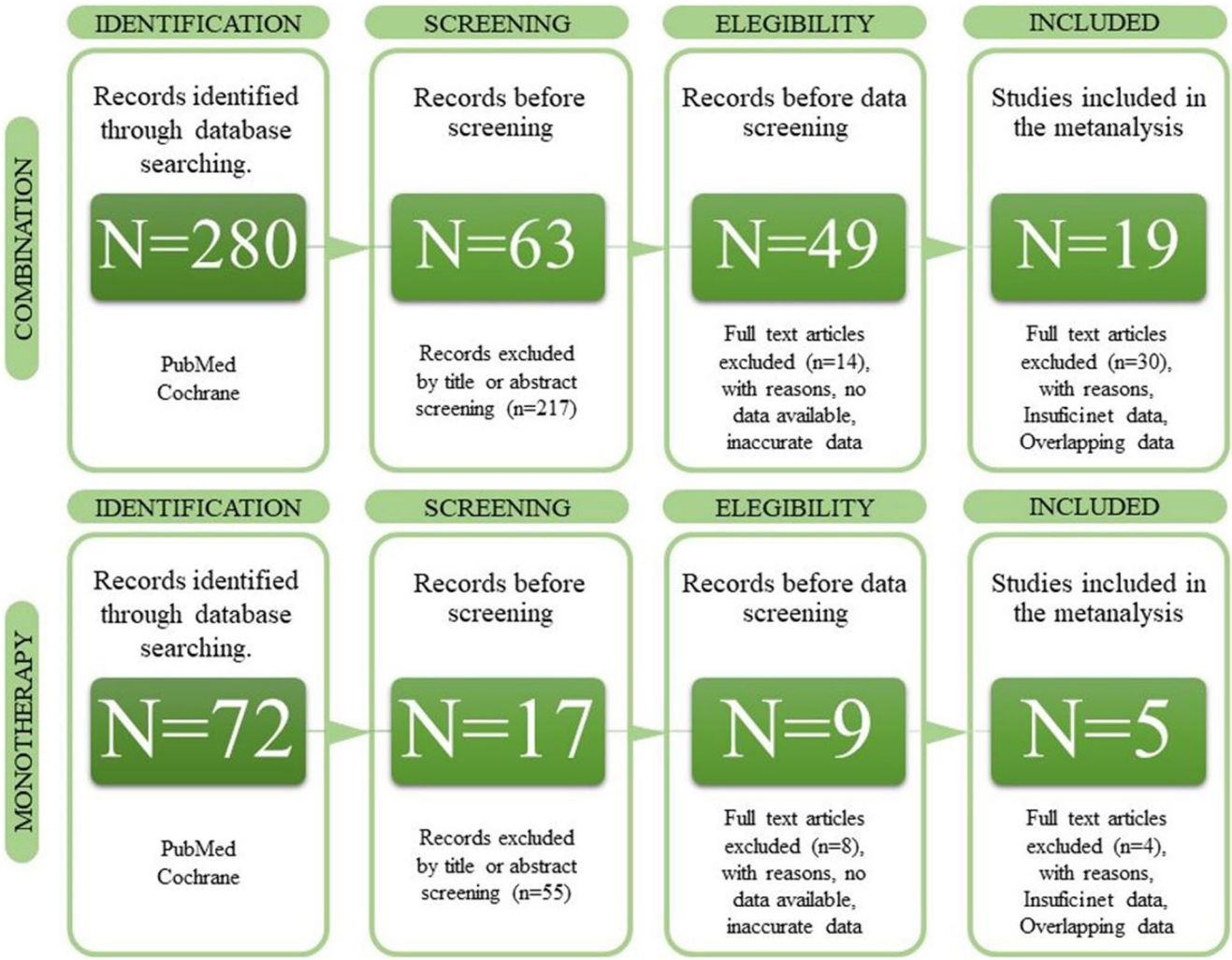


Fig. 1 Flowchart showing the primary criteria for article exclusion in the research selection process

Efficacy of VEN + AZA in clinical trial vs. real-world studies

CRc rates did not differ significantly between clinical trials (65%; 95% CI: 55–75%) and real-world studies (61%; 95% CI: 34–88%) (Supplementary Fig. 3A). CR rates were higher in the clinical trial group (44%; 95% CI: 34–54%) compared to the real-world population (33%; 95% CI: 24–41%) (Supplementary Fig. 3B).

Median OS was significantly longer in clinical trials (15.31 months; 95% CI: 13.58–17.05) compared to real-world studies (10.06 months; 95% CI: 6.53–13.59 months) ($p=0.009$) (Supplementary Fig. 3C).

Efficacy of VEN + HMA vs. HMA monotherapy in real world studies

In real-world settings, the combination of VEN + HMA was associated with significantly higher CRc rates (61%; 95% CI: 34–88%) compared to HMA monotherapy (20%; 95% CI: 17–23%) ($p<0.005$) (Fig. 3A). In contrast, CR rates were 33% (95% CI: 24–41%) in the VEN + HMA group versus 23% (95% CI: 17–29%) in the monotherapy group, without statistical significant difference.

Median OS was similar between both groups: 9.35 months (95% CI: 8.46–10.23) for VEN + HMA and 9.00 months (95% CI: 7.72–10.28) for HMA alone ($p=0.964$) (Fig. 3B).

Efficacy of VEN + AZA vs. AZA in real world studies

A separate comparison focusing exclusively on AZA was conducted. CRc data were not available for this analysis. Median OS in the VEN + AZA group was 10.06 months (95% CI: 6.53–13.59), compared to 9.69 months (95% CI: 8.31–11.06) in the AZA monotherapy group, with no significant difference (Supplementary Fig. 4).

Table 1 Table of information included in the study

Study			CR	CR+CRI	Median DOR (CI 95%)	MRD	Median OS (CI 95%)
	PMID	Study	*n*	*n*	months	*n*	months
Assay VEN+DEC *n*=311	30361262	DiNardo et al. (2019) [10]	22	22		11	
	33119898	DiNardo et al. (2020) [19]	17	23	15 (7,2–30)	9	16,2 (9,1–27,8)
	29339097	D. DiNardo, et al. (2018) [20]		14			14,2 (9,3-NR)
	35433414	K Mustafa Ali, et al. (2022) [21]		12			2.23 (1,53 − 11,3)
	36529771	Kwag, et al. (2022) [21]		37		22	13,4 (8,7-NR)
	36529771	Kwag, et al. (2022) [22]		22			13,4 (8.7-NA)
	34899303	Lucia Gozzo, et al. (2021) [23]		3			
Assay VEN+AZA *n*=1016	32786187	DiNardo, et al. (2020) [11]	105	190			14,7 (11.9–18.7)
	30361262	D. DiNardo et al. (2019) [10]	22	22		17	17,5 (12.3-NR)
	34610123	M. Cherry et al. (2021) [24]	89	102			15,87 (11–20,96)
	33119898	Daniel A Pollyea. Al (2020) [19]	37	60	21,9 (15,1–30,2)	29	16,4 (11,3–24,5)
	29339097	D. DiNardo, et al. (2018) [20]	6	13			15,2 (8,0-NR)
	34739075	Yamamoto, et al. (2022) [25]	11	16			NR (10.6-NR)
	31648312	C. Winters, et al. (2019) [26]	20	28			28,91 (12,61-NR)
	35433414	K Mustafa Ali, et al. (2022) [21]		14			12.3 (9.2-NC)
	36646889	Aiba, et al. (2023) [27]	6	10			8,34 (0,99-NR)
	35046058	Daniel A. Pollyea et al. (2022) [28]		43	29,5		Not available
	34899303	Lucia Gozzo, et al. (2021) [23]		5			14,7
Real World VEN+AZA *n*=871	31648312	C. Winters, et al. (2019) [26]		19		14	12,52 (5,72-NR)
	35861016	E Jensen, et al. (2023) [29]		26			9,1 (3,4–11,9)
	36925388	Gershon, et al. (2023) [30]					9,3 (8–10,8)
	36482507	Louise Laloi, et al. (2023) [31]		14			
	36622759	Rong-Hua Hu, et al. (2023) [32]		3			7,7
	35892834	Shin Yeu Ong, et al. (2022) [33]		57		24	Not available
	35892834	Shin Yeu Ong, et al. (2022) [33]		57			
Real World AZA n(3655)	36925388	Anda Gershon, et al. (2023) [30]					5,9 (4,8 − 6,8)
	36276561	Volkan Karakus, et al. (2022) [34]		9			7,5 (2–17)
	35565471	Jorge Labrador, et al. (2021) [35]		35			8,8 (6,7–11)
	35565471	Jorge Labrador, et al. (2021) [35]		100			10,4 (9,2–11,7)
	35565471	Jorge Labrador, et al. (2021) [35]		135			10 (8,9–11,2)
	34775483	Christian Récher, et al. (2022) [36]		211			9,2 (8,3–10,2)
	35147482	Miyamoto, et al. (2021) [37]		157			9,86 (8,9–10,8)

CR+CRI Complete Response + Complete Response Incomplete, *DOR* Duration of Response, *MRD* Minimal Residual Disease, *n* number of people, *OS* Overall Survival

Risk of bias

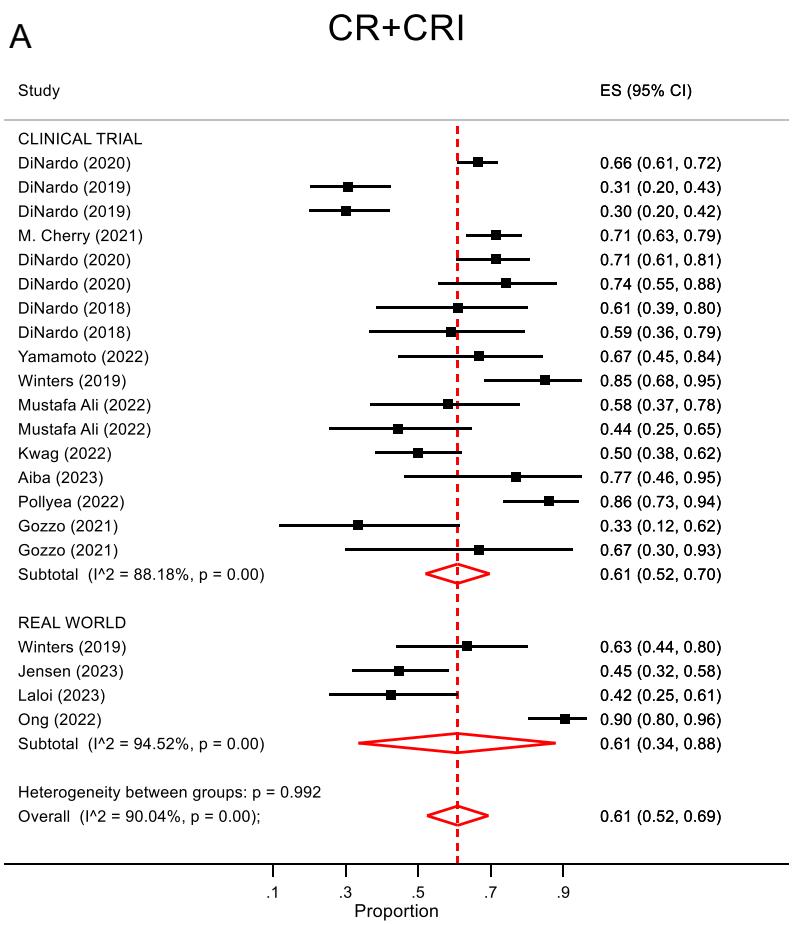
The overall risk of bias across the included studies ranged from unclear to high. Detailed assessments for each individual studies are presented in Fig. 4.

Discussion

Integrating evidence from both clinical trials and real-world studies is essential to fully understand the efficacy and safety of therapeutic strategies in hematological malignancies. While clinical trials are conducted under strictly controlled conditions, real-world studies reflect the complexity of routine clinical practice, encompassing a broader and more heterogeneous patient population. Combining insights from both contexts not only improves the external validity of findings but also helps elucidate the impact of variables such as comorbidities, treatment adherence, and supportive care on therapeutic outcomes.

The present meta-analysis corroborates the results of previous systematic reviews, which reported median overall survival (mOS) values of 9.8 and 10.3 months for patients receiving VEN+HMA regimens in real-world settings [38, 39] lending additional robustness to our observations.

Notably, our analysis found no statistically difference in CRc rates between clinical trials and real-world cohorts. However, a substantial discrepancy in OS was observed,



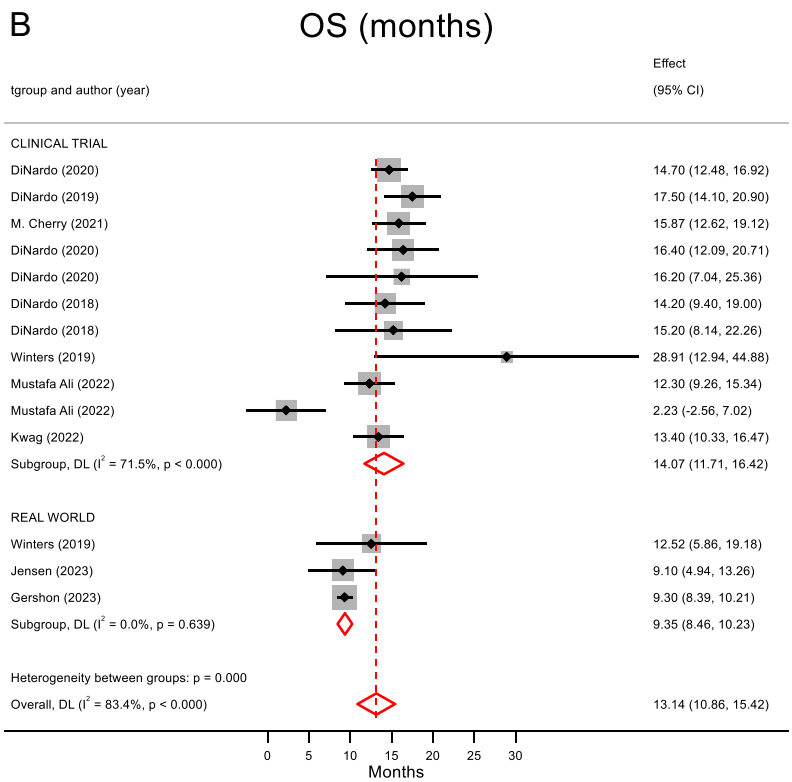


Fig. 2 **A** Composite complete response of VEN + HMA in Clinical Trials vs. real world studies. **B** Overall survival of VEN + HMA in clinical trials vs. real world studies

with a survival advantage of nearly 5 months in favor of clinical trials participants. While similar CRc rates suggest comparable efficacy of VEN+HMA regimens across settings, the lower OS in real-world populations likely reflects differences in baseline characteristics, comorbidity burden, treatment intensity, post-remission strategies or supportive care. Also, bridging the gap between trial results and clinical practice is essential to ensure equitable and effective care for patients with AML. The influence of post-remission therapy, including allogenic transplantation and the use of novel agents in clinical trials, could elucidate the discrepancy in overall survival between clinical trials and real-world settings. These factors, often not fully captured in trials protocols, may have a considerable impact on outcomes in clinical practice. Similar trends were reported by Winters, et al., underscoring the influence of real-world variables on survival [26].

Interesting, MRD negativity rates were higher in real-world studies than in clinical trials, a finding that may reflect inconsistences in MRD definition, methodology (e.g., flow cytometry vs. molecular techniques), timing of assessment, or reporting. These discrepancies highlight the need for standardization in MRD evaluation across studies.

Subgroup analysis of patients receiving VEN+AZA showed similar trends: comparable response rates between clinical trials and real-world data, but lower OS in real-world cohorts. These findings may be related to increased comorbidities, reduced adherence, or a higher rate of treatment-related complications in real-world cohorts. Notably, Candoni et al. reported that infectious mortality was a major contributor to reduced survival in patients treated outside of clinical trial settings [40].

Regarding the choice of HMA backbone, our analysis did not identify statistically significant differences in response or survival between VEN+AZA and VEN+DEC, aligning with prior reports that showed comparable efficacy between the two agents when used in monotherapy [14, 35]. These findings suggest that, in the context of VEN-based combinations, the choice between AZA and DEC may not be a major determinant of clinical outcome.

When comparing VEN+HMA with HMA monotherapy in real-world settings, combination therapy was associated with a significantly higher CRc rate, consistent with studies such as that by Baba, et al. [41]. However, in contrast to earlier analyses that reported an OS benefit with VEN-based combinations [41, 42], our findings did not demonstrate a statistically significant difference in survival. This may be attribute to treatment-related toxicity, heterogeneity in VEn dosing schedules, and differences in patient selection. In fact, our results suggest that AZA monotherapy produced survival outcomes comparable to those of VEN+AZA in some real-world cohorts.

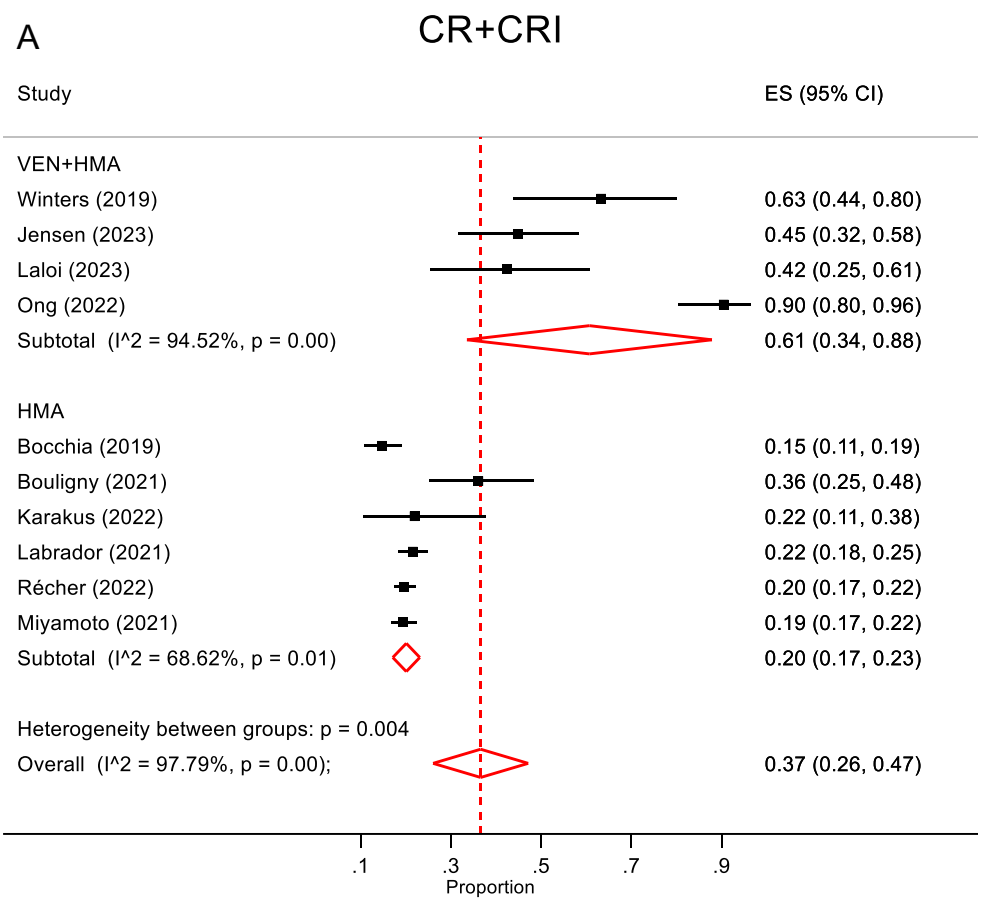
These observations underscore the persistent gap between the efficacy demonstrated in clinical trials and the effectiveness observed in real-world practice. Factors such as treatment delay, dose modifications, institutional variability, or disease characteristics may all contribute to this disparity. Moreover, outcomes may vary substantially between high-volume academic centers and smaller or community-based institutions, where therapeutic optimization may be less standardized. Bridging this gap will require careful implementation and monitoring of VEN-based regimens in routine clinical practice.

Despite the valuable insights provided, several limitations must be acknowledged. The included studies varied in design, patient characteristics, treatment protocols and outcome definitions, which likely contribute to the observed heterogeneity and may limit generalizability. Additionally, potential overlap in study populations may have led to over-representation of certain clinical profiles, particularly in real-world datasets. Many of the real-world studies were observational in nature and subject to inherent limitations, including selection bias, variability in follow-up, and lack of standardization in response assessment.

The absence of uniform risk stratification using the European LeukemiaNet (ELN) classification, or emerging molecular prognostic tools such as the mPRS developed by Bataller et al. [43], further limits the ability to compare outcome subgroups across studies. Incomplete reporting of key endpoints such as MRD or median OS in some studies also weakness the statistical power of pooled analyses. Discrepancies in MRD assessment and reporting further complicate interpretation, particularly regarding patients achieving morphological remission but lacking standardized MRD evaluation.

In clinical settings, variations in cycle length (14-, vs. 21-, vs. 28-day cycles), and differences in administration protocols between trial and real-world settings, may have influenced both, safety and efficacy outcomes. Finally, it is imperative to address the disparities in strategies employed in clinical trials compared to real-world practice.

Moreover, the retrospective nature of many real-world studies introduces potential bias in data collection and completeness. For these reasons, while our results offer relevant clinical implications, they should be cautious and serve as a basis for future prospective investigations.


A
CR+CRI
Study
ES (95% CI)
VEN+HMA
Winters (2019)
0.63 (0.44, 0.80)
Jensen (2023)
0.45 (0.32, 0.58)
Laloi (2023)
0.42 (0.25, 0.61)
Ong (2022)
0.90 (0.80, 0.96)
Subtotal (I^2 = 94.52%, p = 0.00)
0.61 (0.34, 0.88)
HMA
Bocchia (2019)
0.15 (0.11, 0.19)
Bouligny (2021)
0.36 (0.25, 0.48)
Karakus (2022)
0.22 (0.11, 0.38)
Labrador (2021)
0.22 (0.18, 0.25)
Récher (2022)
0.20 (0.17, 0.22)
Miyamoto (2021)
0.19 (0.17, 0.22)
Subtotal (I^2 = 68.62%, p = 0.01)
0.20 (0.17, 0.23)
Heterogeneity between groups: p = 0.004
Overall (I^2 = 97.79%, p = 0.00);
0.37 (0.26, 0.47)
.1
.3
.5
.7
.9
Proportion

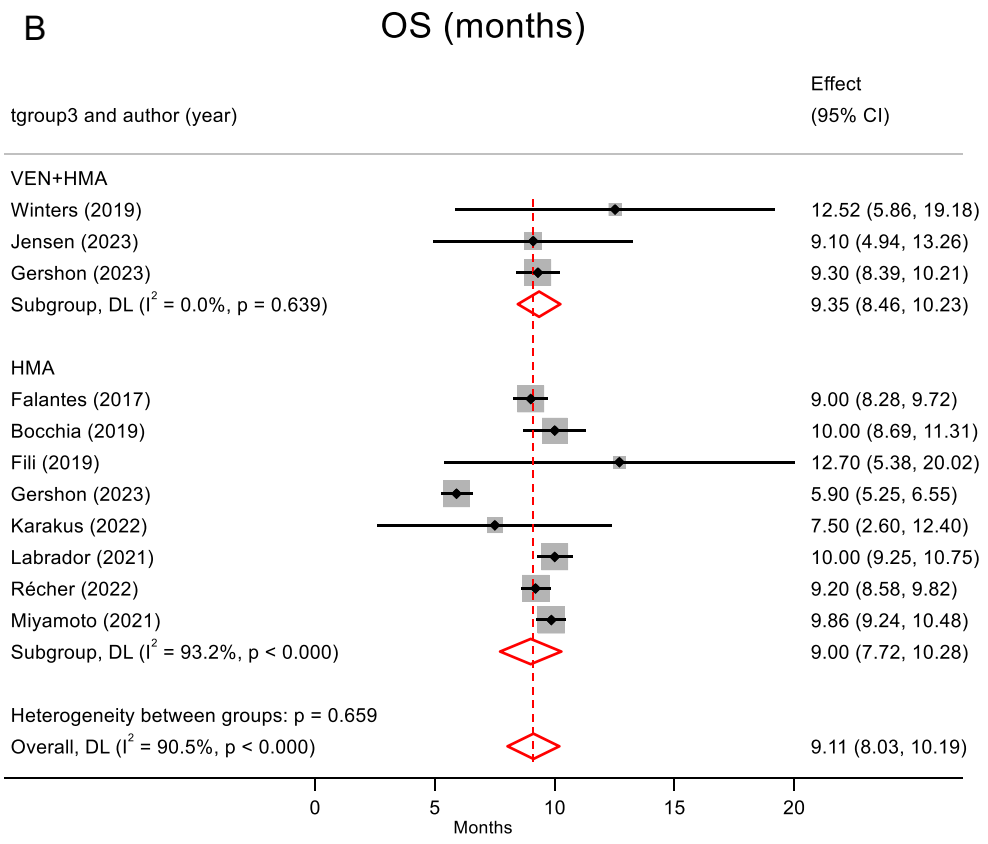
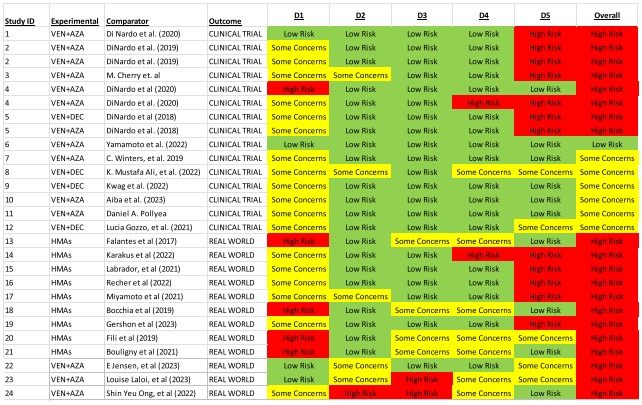

B
OS (months)
tgroup3 and author (year)
Effect
(95% CI)
VEN+HMA
Winters (2019)
12.52 (5.86, 19.18)
Jensen (2023)
9.10 (4.94, 13.26)
Gershon (2023)
9.30 (8.39, 10.21)
Subgroup, DL (I² = 0.0%, p = 0.639)
9.35 (8.46, 10.23)
HMA
Falantes (2017)
9.00 (8.28, 9.72)
Bocchia (2019)
10.00 (8.69, 11.31)
Fili (2019)
12.70 (5.38, 20.02)
Gershon (2023)
5.90 (5.25, 6.55)
Karakus (2022)
7.50 (2.60, 12.40)
Labrador (2021)
10.00 (9.25, 10.75)
Récher (2022)
9.20 (8.58, 9.82)
Miyamoto (2021)
9.86 (9.24, 10.48)
Subgroup, DL (I² = 93.2%, p < 0.000)
9.00 (7.72, 10.28)
Heterogeneity between groups: p = 0.659
Overall, DL (I² = 90.5%, p < 0.000)
9.11 (8.03, 10.19)
0
5
10
15
20
Months

Fig. 3 **A** Composite complete response of VEN + HMA vs. HMA in real world. **B** Overall survival of VEN + HMA vs. HMA in real world studies studies



Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
1	VEN+AZA	Di Nardo et al. (2020)	CLINICAL TRIAL	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	High Risk
2	VEN+AZA	DiNardo et al. (2019)	CLINICAL TRIAL	Some Concerns	Low Risk	Low Risk	Low Risk	High Risk	High Risk
2	VEN+AZA	DiNardo et al. (2019)	CLINICAL TRIAL	Some Concerns	Low Risk	Low Risk	Low Risk	High Risk	High Risk
3	VEN+AZA	M. Cherry et. al	CLINICAL TRIAL	Some Concerns	Some Concerns	Low Risk	Low Risk	High Risk	High Risk
4	VEN+AZA	DiNardo et al (2020)	CLINICAL TRIAL	High Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk
4	VEN+AZA	DiNardo et al. (2020)	CLINICAL TRIAL	Some Concerns	Low Risk	Low Risk	High Risk	High Risk	High Risk
5	VEN+DEC	DiNardo et al (2018)	CLINICAL TRIAL	Some Concerns	Low Risk	Low Risk	Low Risk	High Risk	High Risk
5	VEN+AZA	DiNardo et al. (2018)	CLINICAL TRIAL	Some Concerns	Low Risk	Low Risk	Low Risk	High Risk	High Risk
6	VEN+AZA	Yamamoto et al. (2022)	CLINICAL TRIAL	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
7	VEN+AZA	C. Winters, et al. 2019	CLINICAL TRIAL	Some Concerns	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns
8	VEN+DEC	K. Mustafa Ali, et al. (2022)	CLINICAL TRIAL	Some Concerns	Some Concerns	Low Risk	Some Concerns	Some Concerns	Some Concerns
9	VEN+DEC	Kwag et al. (2022)	CLINICAL TRIAL	Some Concerns	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns
10	VEN+AZA	Aiba et al. (2023)	CLINICAL TRIAL	Some Concerns	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns
11	VEN+AZA	Daniel A. Pollyea	CLINICAL TRIAL	Some Concerns	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns
12	VEN+DEC	Lucia Gozzo, et al. (2021)	CLINICAL TRIAL	Some Concerns	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
13	HMAs	Falantes et al (2017)	REAL WORLD	High Risk	Low Risk	Some Concerns	Some Concerns	Low Risk	High Risk
14	HMAs	Karakus et al (2022)	REAL WORLD	Some Concerns	Low Risk	Low Risk	High Risk	High Risk	High Risk
15	HMAs	Labrador, et al (2021)	REAL WORLD	Some Concerns	Low Risk	Low Risk	Low Risk	High Risk	High Risk
16	HMAs	Recher et al (2022)	REAL WORLD	Some Concerns	Low Risk	Low Risk	Low Risk	High Risk	High Risk
17	HMAs	Miyamoto et al (2021)	REAL WORLD	Some Concerns	Some Concerns	Low Risk	Low Risk	High Risk	High Risk
18	HMAs	Bocchia et al (2019)	REAL WORLD	High Risk	Low Risk	Some Concerns	Some Concerns	Low Risk	High Risk
19	HMAs	Gershon et al (2023)	REAL WORLD	Some Concerns	Low Risk	Low Risk	Low Risk	High Risk	High Risk
20	HMAs	Fili et al (2019)	REAL WORLD	High Risk	Low Risk	Some Concerns	Some Concerns	Some Concerns	High Risk
21	HMAs	Bouligny et al (2021)	REAL WORLD	High Risk	Low Risk	Some Concerns	Some Concerns	Low Risk	High Risk
22	VEN+AZA	E Jensen, et al (2023)	REAL WORLD	Low Risk	Some Concerns	Low Risk	Low Risk	Some Concerns	High Risk
23	VEN+AZA	Louise Lalol, et al (2023)	REAL WORLD	Low Risk	Some Concerns	High Risk	Some Concerns	Some Concerns	High Risk
24	VEN+AZA	Shin Yeu Ong, et al (2022)	REAL WORLD	Some Concerns	High Risk	High Risk	Some Concerns	Low Risk	High Risk

Fig. 4 Risk of bias clinical trials and real word trials; D1: Randomization process; D2: Deviations from the intended interventions; D3: Missing outcome data; D4: Measurement of the outcome; D5: Selection of the reported result

Conclusions

This meta-analysis highlights the disparity in treatment outcomes between clinical trials and real-world practice for treatment-naïve patients with AML receiving VEN in combination with HMAs. While CRc rates were comparable across both settings, OS was significantly longer among patients treated in clinical trials. These findings emphasize the need for optimized implementation of VEN-based regimens in routine practice, with greater attention to supportive management, standardization of protocols to improve the effectiveness of this therapeutic approach in real-world populations.

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Declarations

Competing interests The authors declare no competing interests.

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