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Real-World Outcomes of Midostaurin Plus Intensive Chemotherapy in *FLT3*-Mutated AML: The PETHRATIFY Study

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ABSTRACT

Mutations in *FLT3* are present in approximately 30% of patients with AML. The addition of midostaurin (MIDO) to intensive chemotherapy (IC) became standard of care following the RATIFY trial, but comprehensive real-world data spanning the full adult age spectrum and including both *FLT3*-ITD and *FLT3*-TKD mutations remain limited. We retrospectively analyzed 1658 adults aged 14–85 years with newly diagnosed *FLT3*-mutated AML from 129 PETHEMA registry centers: 469 received IC + MIDO and 1189 IC alone. Composite complete remission was higher with IC + MIDO than IC (81.4% vs. 71.7%; $p < 0.001$) and Day 30 mortality was substantially lower (2.1% vs. 7.1%; $p < 0.001$). Median overall survival was 47.2 versus 19.3 months (HR 0.64; 95% CI, 0.53–0.76; $p < 0.001$), and the benefit was sustained after multivariable adjustment (HR 0.73; $p = 0.017$). In 261 propensity score–matched pairs, the effect was attenuated, remaining significant for event-free survival (HR 0.77; $p = 0.029$) and showing a nonsignificant trend for OS (HR 0.77; $p = 0.06$). Allogeneic hematopoietic stem cell transplantation in first remission was more frequent in the IC + MIDO cohort (48.9% vs. 41.3%; $p = 0.023$). Time-dependent analyses showed the largest MIDO effect among autologous and non-transplanted patients (OS HR 0.45; $p = 0.138$, and HR 0.69; $p = 0.014$, respectively). The benefit of MIDO was consistent irrespective of *FLT3* mutation type, *FLT3*-ITD allelic burden, cytogenetic risk, and gender, while less improvement occurred among *NPM1* wild type and secondary AML patients. This large real-world cohort confirms the survival benefit of MIDO plus IC across the full adult age spectrum, supporting its standard-of-care status in *FLT3*-mutated AML.

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1 | Introduction

FLT3 mutations are among the most frequent genetic alterations in acute myeloid leukemia (AML), identified in approximately 30% of newly diagnosed adults [1, 2]. Internal tandem duplications (ITD) are associated with increased relapse rate and inferior overall survival (OS), particularly, in patients with high mutant-to-wild-type allelic ratios (ARs) [3–5]. Point mutations in the tyrosine kinase domain (TKD) occur in approximately 5%–8% of patients; their prognostic significance remains uncertain [1, 6].

Midostaurin (MIDO), a Type I multikinase inhibitor with activity against both *FLT3*-ITD and TKD mutations [7], was the first FLT3 inhibitor to demonstrate a survival benefit in combination with intensive chemotherapy (IC), improving OS and event-free survival (EFS) in patients aged 18–59 years with newly diagnosed *FLT3*-mutated AML [8]. These results led to regulatory approval of MIDO with no upper age limit. Moreover, the AMLSG 16–10 Phase 2 trial demonstrated efficacy in patients up to 70 years using daunorubicin-based chemotherapy [9], and the Sierra et al. Phase 3b study confirmed feasibility and high response rates across age groups with both daunorubicin- and idarubicin-based backbones [10]. More recently, we reported improved survival with MIDO plus IC in elderly patients (≥ 60 years) across three European registries [11]. However, comprehensive real-world data encompassing the full adult age spectrum and including both *FLT3*-ITD and TKD mutations remain limited.

The therapeutic landscape for *FLT3*-mutated AML has further evolved with the approval of quizartinib, a potent and selective Type II FLT3 inhibitor, for *FLT3*-ITD-positive AML based on the QuANTUM-First trial [12]. While second-generation inhibitors offer higher selectivity for *FLT3*-ITD, MIDO remains the only approved agent with demonstrated activity across both ITD and TKD mutations. Defining the real-world effectiveness of MIDO across the entire *FLT3*-mutated population and subsets is, therefore, of particular clinical relevance.

The aim of the PETHRATIFY study was to evaluate the real-world outcomes of MIDO combined with IC in a large, unselected cohort of adult patients with newly diagnosed *FLT3*-mutated AML (ITD and TKD) from the PETHEMA registry, compared with a historical control cohort treated with IC alone, with no upper age restriction.

2 | Materials and Methods

2.1 | Patients

This retrospective, multicenter study included adult patients registered in the multinational PETHEMA (*Programa Español de Tratamientos en Hematología*) registry (NCT02607059), which collects clinical, biological, and outcome data from patients with AML. Patients were eligible if they had newly diagnosed AML according to the World Health Organization (WHO) 2016 classification [13], harbored a *FLT3* mutation (ITD, TKD, or both), and received IC with or without MIDO. Patients with acute promyelocytic leukemia and those enrolled in interventional clinical trials ($n = 63$) were excluded. No upper age limit was applied.

The inclusion period spanned March 1999 to February 2025; database lock and follow-up cut-off were April 2025. Patients were classified into IC plus MIDO (IC + MIDO; recruited February 2017–February 2025) and IC alone (IC; March 1999–December 2024) cohorts. Ten IC + MIDO patients diagnosed in early 2017, prior to MIDO approval, accessed the drug through early-access or compassionate-use programs. The study was conducted in accordance with the Declaration of Helsinki. The PETHEMA registry protocol was approved by the institutional review boards or ethics committees of the participating centers, and written informed consent for data collection and anonymized research use was obtained from all patients at registration.

2.2 | Genetic and Cytogenetic Analysis

FLT3-ITD and *FLT3*-TKD mutations were identified during standard diagnostic workup at the time of patient inclusion, using either polymerase chain reaction (PCR)-based fragment analysis or next-generation sequencing (NGS) methods, according to the platforms available at each center and time period. The *FLT3*-ITD AR was categorized at a threshold of ≥ 0.5 versus < 0.5, consistent with the European LeukemiaNet (ELN) 2017 risk stratification [14]. *NPM1* and *IDH1*/*IDH2* mutational status were assessed by PCR or NGS as part of routine diagnostics. Cytogenetic risk was stratified according to the Medical Research Council (MRC) classification [15]. A comprehensive NGS panel was not systematically applied across the cohort, and the full ELN 2022 genetic risk classification was not assigned.

2.3 | Study Design and Treatment

The overall design and patient flow are illustrated in the CONSORT-style diagram (Figure 1). Because MIDO was administered from Day 8 of induction onward, a Day 8 landmark was applied, excluding 44 patients of the IC cohort from all analyses, yielding a final analytic population of 1658 patients (IC, $n = 1189$; IC + MIDO, $n = 469$).

2.3.1 | Induction Chemotherapy

IC + MIDO patients received a standard 3 + 7 induction (idarubicin 12 mg/m^2/day intravenously on Days 1–3 and cytarabine 200 mg/m^2/day continuous infusion on Days 1–7), combined with midostaurin at 50 mg orally twice daily on Days 8–21; the anthracycline was idarubicin in 91.0% and daunorubicin in 6.0%, while a minority (3.0%) received cytarabine-based or other intensive regimens with midostaurin. In the IC cohort, induction regimens were heterogeneous and reflected the evolving standard of care across the study period: a 3 + 7 backbone (with idarubicin or daunorubicin) was used in 75.4%, with the remainder comprising 3 + 7 plus etoposide, 3 + 7 plus gemtuzumab ozogamicin, FLAG-based regimens, CPX-351, and other schedules (Table S1).

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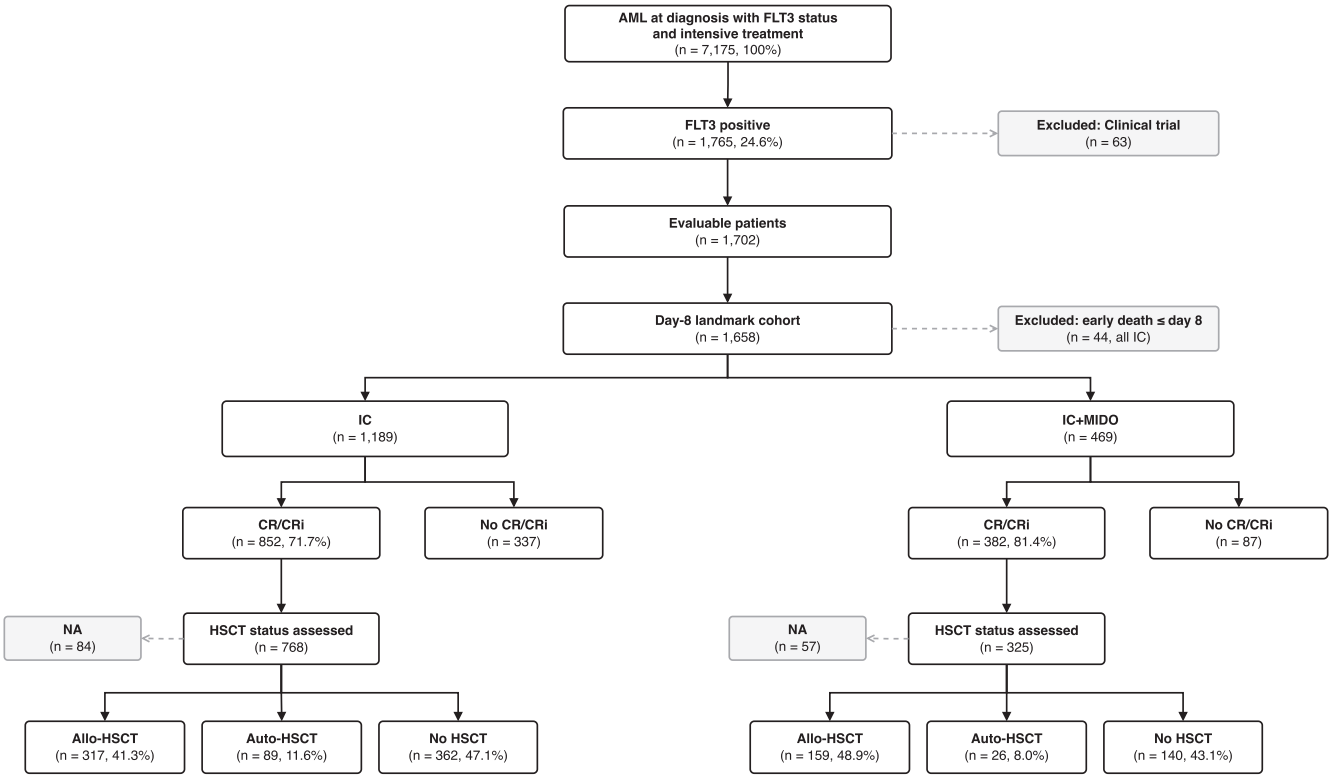

FIGURE 1 | Study flow diagram (CONSORT). A total of 7175 adult patients with newly diagnosed AML, available FLT3 mutation status, intensive treatment, and response assessment were identified in the PETHEMA registry. Of these, 1765 (24.6%) harbored FLT3 mutations. After excluding 63 patients enrolled in clinical trials, 1702 evaluable patients were identified. To mitigate guarantee-time bias, a Day 8 landmark was applied, excluding 44 patients who died within the first 8 days from treatment initiation (all in the IC arm), yielding a landmark cohort of 1658 patients: 1189 received intensive chemotherapy alone (IC) and 469 received intensive chemotherapy plus midostaurin (IC + MIDO). Composite complete remission (CR/CRi) was achieved by 852 (71.7%) and 382 (81.4%) patients, respectively. Among patients achieving CR/CRi, HSCT status was assessable in 768 (IC) and 325 (IC + MIDO); allogeneic HSCT was performed in 317 (41.3%) and 159 (48.9%), autologous HSCT in 89 (11.6%) and 26 (8.0%), and 362 (47.1%) and 140 (43.1%) did not undergo transplantation. NA, patients in CR/CRi with no available HSCT status ($n = 84$ and 57, respectively); percentages for transplant categories are calculated over patients with assessable HSCT status. NA, not available.

2.3.2 | Consolidation Therapy

Patients achieving complete remission (CR) or CR with incomplete recovery (CRi) were eligible for cytarabine-based consolidation at high dose (3 g/m^2 every 12 h intravenously Days 1–3 or 1, 3, 5) in patients aged < 60 years, or intermediate dose (1.5 g/m^2 every 12 h) in those aged ≥ 60 years. The number of consolidation cycles was determined according to institutional practice. IC + MIDO also received midostaurin 50 mg twice daily on Days 8–21 during consolidation cycles.

2.3.3 | Hematopoietic Stem Cell Transplantation

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) was considered for eligible patients in first composite complete remission (CRc), based on individual risk assessment, donor availability, and institutional guidelines. Autologous HSCT was performed in selected patients (e.g., low- or intermediate-risk with negative measurable residual disease and/or when an allo-HSCT was not possible). The transplant decision was non-protocolized and made by the treating physician case-by-case.

2.3.4 | Maintenance Therapy

Postconsolidation or posttransplantation maintenance was administered at physician discretion and as per access availability but was not systematically captured in the registry.

2.4 | Definition of Response Criteria and Survival Endpoints

Response was assessed per ELN 2022 recommendations [16]. CR required bone marrow blasts < 5%, absence of circulating blasts and extramedullary disease, an absolute neutrophil count ≥ 1.0×10^9/L, and platelets ≥ 100×10^9/L. CRi met CR criteria except for residual neutropenia or thrombocytopenia. CRc comprised CR or CRi. Primary refractory AML was defined as failure to achieve CRc after one induction cycle, or after two cycles in patients receiving two identical cycles per institutional protocol. Relapse was defined as ≥ 5% bone marrow blasts, reappearance of peripheral blood blasts, or extramedullary disease after remission. Death during induction was defined as death without evidence of disease or remission during the induction phase. Days 30 and 60 mortality were

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defined as death from any cause within 30 and 60 days of AML diagnosis, respectively.

OS was measured from AML diagnosis to death from any cause; censoring patients alive at last contact. EFS was measured from diagnosis to the first of induction failure, relapse, or death from any cause; censoring patients in continuous remission at last contact. Cumulative incidence of relapse (CIR) was estimated among patients achieving CRc, with relapse as the event of interest and nonrelapse mortality (NRM) as the competing event. NRM was defined as death in the absence of prior relapse among CRc patients, with relapse as the competing event.

2.5 | Statistical Analysis

Categorical variables were summarized as numbers and frequencies (of nonmissing data) and continuous variables as medians with ranges and comparisons made using the χ^2 test (or Fisher's exact test when appropriate) for categorical and the Mann–Whitney *U* test for continuous variables.

OS and EFS were estimated by the Kaplan–Meier method and compared using the log-rank test. Survival curves were truncated at 60 months for display only, with no administrative censoring applied to the underlying analyses. Survival probabilities were reported with 95% confidence intervals. CIR and NRM were estimated in a competing-risks framework and compared using Gray's test [17].

Prespecified univariate subgroup analyses for OS and EFS used Cox proportional hazards models across: age (<60 vs. ≥ 60 years), sex, ECOG (0–2 vs. 3–4), AML type (de novo vs. secondary), white blood cell count (WBC) at diagnosis (<20 vs. $\geq 20\times10^9$/L), MRC cytogenetic risk, *NPM1* status, *FLT3*-ITD status, *FLT3*-ITD AR (<0.5 vs. ≥ 0.5), and *FLT3*-TKD status, displayed as forest plots.

The independent prognostic impact of MIDO on OS and EFS was assessed using a full multivariable Cox model including all prespecified covariates without stepwise selection. Missing covariate data were handled by multiple imputation using chained equations with predictive mean matching (five imputed datasets), with pooled estimates obtained per Rubin's rules. The proportional hazards assumption was tested with scaled Schoenfeld residuals; non-proportional effects were interpreted as time-averaged hazard ratios.

To assess the joint effect of MIDO and HSCT while avoiding immortal-time bias, Simon–Makuch curves were constructed among CRc with HSCT modeled as a time-dependent covariate [18]. Six treatment–transplant strata were analyzed (No SCT + IC, No SCT + IC + MIDO, Auto-SCT + IC, Auto-SCT + IC + MIDO, Allo-SCT + IC, Allo-SCT + IC + MIDO), with hazard ratios estimated by time-dependent Cox regression using No SCT + IC as reference. Pairwise comparisons stratified by transplant modality were referenced to the corresponding IC group within each stratum. In an exploratory analysis, the same six-state time-dependent framework was applied separately within *NPM1*-mutated and *NPM1* wild-type patients. Midostaurin × subgroup and allo-HSCT × *NPM1* interactions were tested by likelihood ratio, and interaction *p* values across the 10 subgroups were corrected for multiple testing using the Benjamini–Hochberg procedure.

A propensity score–matched (PSM) analysis mitigated baseline imbalance between cohorts. Propensity scores were estimated by complete-case logistic regression across the prespecified covariates and matched 1:1 by nearest neighbor without replacement, using a caliper of 0.1 standard deviations of the logit; balance was assessed by standardized mean differences (SMDs), with SMD <0.1 considered adequate; matched outcomes were compared using stratified Cox regression and log-rank tests accounting for the matched-pair structure.

All analyses used R version 4.5.2. All *p*-values are two-sided, with $p<0.05$ considered significant.

3 | Results

3.1 | Patients Characteristics

A total of 1658 adult patients with newly diagnosed *FLT3*-mutated AML who received IC at 129 PETHEMA centers between March, 1999 and February, 2025 were included. Of these, 469 (28.3%) received MIDO in addition to IC (IC + MIDO cohort) and 1189 (71.7%) were treated with IC alone (IC cohort). The CONSORT-style flow diagram is depicted in Figure 1.

Baseline characteristics of the two cohorts are summarized in Table **1**. The median age at diagnosis was 55 years (range, 14–85) with no significant difference between groups (54 vs. 56 years; $p=0.35$). Overall, 36.1% of patients were aged ≥ 60 years (35.4% in the IC cohort vs. 38.0% in the IC + MIDO cohort; $p=0.34$), and 52.5% were female ($p=0.95$). Most patients had ECOG 0–2 (96.3%) and de novo AML (87.2%), with no significant differences between groups. Extramedullary disease was more frequent in the IC cohort (25.6% vs. 15.4%; $p<0.001$). The median WBC count was 43×10^9/L ($p=0.91$), and the median bone marrow blast percentage was 79% (80% in the IC cohort vs. 75% in the IC + MIDO cohort; $p=0.030$). Cytogenetic risk distribution by MRC classification showed 83.4% intermediate-risk, 10.5% high-risk, and 6.1% low-risk karyotypes, with a significantly higher proportion of low-risk cytogenetics in the IC cohort (7.8% vs. 1.7%; $p<0.001$).

FLT3-ITD was the predominant mutation type (77.8%), followed by *FLT3*-TKD (17.1%) and concurrent ITD/TKD (5.1%); although *FLT3*-ITD positivity was identical between cohorts (77.8% in both), the overall mutation-type distribution differed ($p=0.001$), reflecting a higher frequency of concurrent ITD/TKD in the IC + MIDO group (7.9% vs. 4.0%). The median *FLT3*-ITD AR was 0.46 overall (0.41 in the IC cohort vs. 0.50 in the IC + MIDO cohort; $p=0.058$). *NPM1* mutations were detected in 58.4% of patients (56.8% IC vs. 62.3% IC + MIDO; $p=0.051$), while *IDH1* and *IDH2* mutations were identified in 9.6% and 14.4%, respectively, without significant differences between groups. The overall proportion of missing data across imputed variables was 7.05%.

Reflecting the extended study period and the chronology of MIDO approval, the temporal distribution of patients was unbalanced: 42.4% of the overall cohort was diagnosed before

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TABLE 1 | Demographic and baseline characteristics in the overall study population according to treatment cohort.

Characteristic	Overall ($N=1658$)	IC ($n=1189$)	IC + MIDO ($n=469$)	p
Age, years—median (range)	55 (14–85)	54 (14–85)	56 (17–78)	0.35
≥ 60 years	599 (36.1)	421 (35.4)	178 (38.0)	0.34
Sex	1656 (100)	1188 (100)	468 (100)	
Male	786 (47.5)	565 (47.6)	221 (47.2)	0.95
Female	870 (52.5)	623 (52.4)	247 (52.8)	
ECOG—median (range)	1 (0–4)	1 (0–4)	1 (0–4)	0.78
0–2	1340 (96.3)	921 (95.8)	419 (97.2)	0.27
3–4	52 (3.7)	40 (4.2)	12 (2.8)	
AML type	1638 (100)	1177 (100)	461 (100)	
De novo	1429 (87.2)	1026 (87.2)	403 (87.4)	0.96
Secondary	209 (12.8)	151 (12.8)	58 (12.6)	
AML diagnosis year	1658 (100)	1189 (100)	469 (100)	
≤ 2017	703 (42.4)	693 (58.3)	10 (2.1)	< 0.001
> 2017	955 (57.6)	496 (41.7)	459 (97.9)	
FAB subtype	1122 (100)	868 (100)	254 (100)	
M0/M6/M7	85 (7.6)	67 (7.7)	18 (7.1)	0.88
M1/M2	459 (40.9)	357 (41.1)	102 (40.2)	
M4/M5	578 (51.5)	444 (51.2)	134 (52.8)	
Extramedullary disease	1233 (100)	902 (100)	331 (100)	
Yes	282 (22.9)	231 (25.6)	51 (15.4)	< 0.001
WBC, $\times 10^9$/L—median (range)	43 (0.1–800)	43 (0.1–434)	42 (0.3–800)	0.91
< 20	532 (33.4)	367 (32.4)	165 (35.9)	0.20
≥ 20	1059 (66.6)	765 (67.6)	294 (64.1)	
Hemoglobin, g/dL—median (range)	8.8 (1.9–16.4)	8.9 (1.9–16.4)	8.7 (2.8–15.1)	0.61
Platelet count, $\times 10^9$/L—median (range)	56 (3–939)	56 (3–939)	55 (3–907)	0.56
BM blasts, %—median (range)	78 (0–100)	79 (0–100)	75 (1–100)	0.030
Creatinine, mg/dL—median (range)	0.83 (0.07–10.9)	0.84 (0.07–6.8)	0.83 (0.24–10.9)	0.72
Uric acid, mg/dL—median (range)	4.9 (0–70)	5.0 (0–70)	4.7 (0–51)	0.38
Alkaline phosphatase, U/L—median (range)	76 (11–753)	78 (11–753)	71 (12–543)	0.11
Albumin, g/dL—median (range)	3.6 (0.04–8.5)	3.6 (0.04–8.5)	3.6 (0.4–5.4)	0.83
LDH, U/L—median (range)	666 (13–13 741)	690 (13–13 741)	594 (21–11 488)	< 0.001
MRC cytogenetic risk	1423 (100)	1018 (100)	405 (100)	
Low	88 (6.2)	81 (8.0)	7 (1.7)	< 0.001
Intermediate	1186 (83.3)	830 (81.5)	356 (87.9)	
High	149 (10.5)	107 (10.5)	42 (10.4)	
NPM1	1516 (100)	1062 (100)	454 (100)	
Negative	630 (41.6)	459 (43.2)	171 (37.7)	0.051
Positive	886 (58.4)	603 (56.8)	283 (62.3)	

(Continues)

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TABLE 1 | (Continued)

Characteristic	Overall ($N=1658$)	IC ($n=1189$)	IC + MIDO ($n=469$)	p
FLT3 mutation type	1658 (100)	1189 (100)	469 (100)	
ITD	1290 (77.8)	925 (77.8)	365 (77.8)	0.001
TKD	284 (17.1)	217 (18.3)	67 (14.3)	
ITD + TKD	84 (5.1)	47 (4.0)	37 (7.9)	
FLT3-ITD allelic ratio—median (range)	0.46 (0–43.9)	0.41 (0–43.9)	0.50 (0–12)	0.058
< 0.5	668 (51.6)	471 (53.2)	197 (48.0)	0.094
≥ 0.5	627 (48.4)	414 (46.8)	213 (52.0)	
IDH1	826 (100)	454 (100)	372 (100)	
Positive	79 (9.6)	46 (10.1)	33 (8.9)	0.62
IDH2	826 (100)	454 (100)	372 (100)	
Positive	119 (14.4)	66 (14.5)	53 (14.2)	0.99

Note: Data are presented as *n* (%) for categorical variables and median (range) for continuous variables. Percentages are calculated from nonmissing data. Patients who died within the first 8 days of induction ($n=44$, all in the IC group) were excluded to establish a Day 8 landmark, since midostaurin is administered from Day 8 onward. *p* values were calculated using the χ^2 or Fisher's exact test for categorical variables and the Mann–Whitney *U* test for continuous variables.
Abbreviations: BM, bone marrow; ECOG, Eastern Cooperative Oncology Group performance status; FAB, French-American-British; IC, intensive chemotherapy; IC + MIDO, intensive chemotherapy plus midostaurin; ITD, internal tandem duplication; LDH, lactate dehydrogenase; MRC, Medical Research Council; TKD, tyrosine kinase domain; WBC, white blood cell count.

2018, 58.3% in the IC versus 2.1% in the IC + MIDO groups; $p < 0.001$.

3.2 | Induction Response and Early Mortality

Induction regimens are detailed in Table S1. In the IC + MIDO cohort, 461 patients (98.3%) received a standard 3 + 7 backbone combined with midostaurin. In the IC cohort, the most common regimen was 3 + 7 (967 patients; 81.3%), followed by 3 + 7 plus etoposide ($n=94$; 7.9%), 3 + 7 plus gemtuzumab ozogamicin ($n=25$; 2.1%), FLAG-based regimens ($n=44$; 3.7%), CPX-351 ($n=20$; 1.7%), and other intensive regimens ($n=30$; 2.5%).

CRc after induction was achieved in 81.4% of the IC + MIDO cohort versus 71.7% of the IC cohort ($p < 0.001$). Detailed response categories are depicted in Figure 2. Primary refractory disease occurred in 11.3% of IC + MIDO patients (53/469) compared with 13.5% of IC patients (161/1189). Death during induction occurred in 12 IC + MIDO patients (2.6%) versus 99 IC patients (8.3%) ($p < 0.001$).

Mortality at day 30 was 2.1% (10/469) in the IC + MIDO cohort versus 7.1% (84/1189) in the IC cohort, and at day 60 was 3.8% (18/469) versus 9.6% (114/1189), respectively (both $p < 0.001$) (Table 2). The distribution of causes of death during induction was similar between cohorts, with infection/sepsis predominating in each (50.0% and 50.5%, respectively; Table S2). Among patients achieving CR/CRi after the first induction cycle ($n=1163$), median times to neutrophil and platelet recovery were comparable between cohorts, with only a marginal delay in neutrophil recovery to $\geq 0.5 \times 10^9$/L in the IC + MIDO group (26 vs. 25 days; $p=0.041$; Table S3).

3.3 | Postremission Therapy

Among the 1234 patients who achieved CRc, postremission strategies included consolidation chemotherapy with or without subsequent allo-HSCT. Consolidation regimens varied across centers and time periods according to evolving institutional protocols. Transplantation data were available for 1093 patients (88.6% of CRc).

Allo-HSCT in first CRc was performed in 476 patients (43.6%), with a significantly higher rate in the IC + MIDO compared with the IC cohort (159/325, 48.9% vs. 317/768, 41.3%; $p=0.023$). Autologous HSCT was performed in 115 patients (10.5%; 8.0% IC + MIDO vs. 11.6% IC), and 502 patients (45.9%) did not undergo any transplant procedure (43.1% IC + MIDO vs. 47.1% IC). Postconsolidation or posttransplantation maintenance therapy with MIDO or other FLT3 inhibitors was not analyzed in this study.

3.4 | Survival Outcomes

Overall, the median follow-up was 35.8 months (95% CI, 32.9–38.7): 46.5 months (95% CI, 43.2–52.3) for the IC cohort and 21.5 months (95% CI, 19.4–25.1) for the IC + MIDO cohort. Median OS was 47.2 months (95% CI, 36.1–NR) in the IC + MIDO vs. 19.3 months (95% CI, 17.0–22.2) in the IC cohort (HR 0.64; 95% CI, 0.53–0.76; $p < 0.001$) (Figure 3). One- and 3-years OS rates were 74.7% (95% CI, 70.5–79.2), and 55.8% (95% CI, 50.3–61.8) in the IC + MIDO, compared with 61.0% (95% CI, 58.2–64.0), and 40.4% (95% CI, 37.4–43.7) in the IC cohort. Median EFS was 14.8 months (95% CI, 11.7–20.5) in the IC + MIDO versus 9.2 months (95% CI, 8.2–10.2) in the IC cohort (HR 0.73; 95% CI, 0.63–0.84; $p < 0.001$), with 1- and

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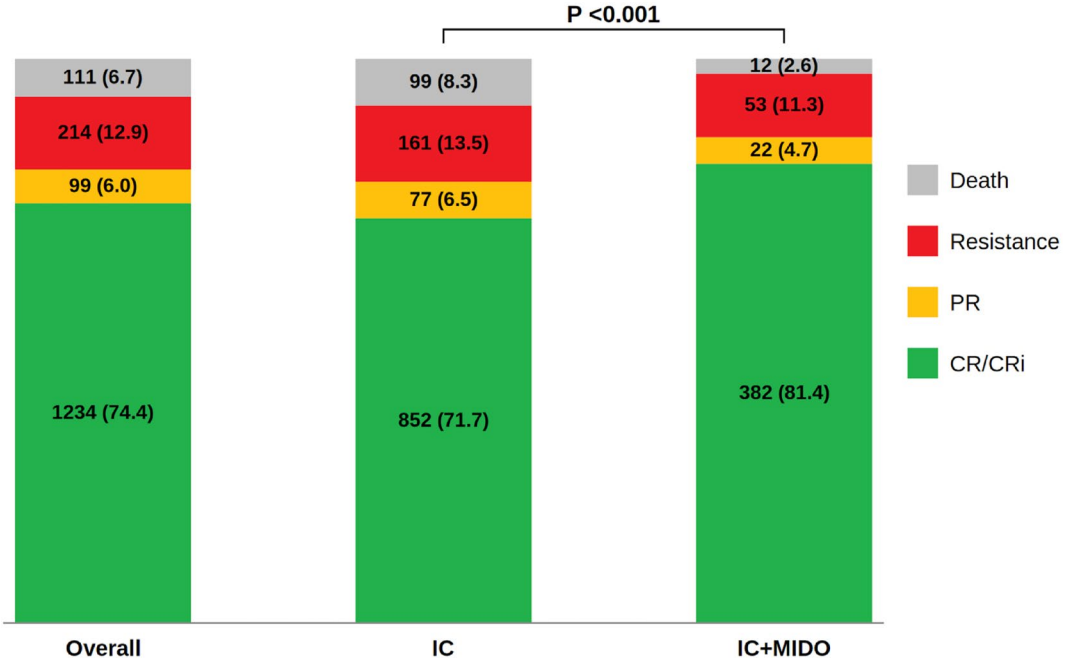

FIGURE 2 | Response to induction chemotherapy in the overall study population and according to midostaurin use. Stacked bar chart depicting the distribution of induction response categories in the over all cohort ($n = 1658$) and stratified by treatment with intensive chemotherapy alone (IC; $n = 1189$) versus intensive chemotherapy plus midostaurin (IC + MIDO; $n = 469$). Bar segments display the absolute number of patients and the corresponding proportion (%) for each response category: composite complete remission (CR/CRi, green), partial response (PR, yellow), primary refractory disease (resistance, red), and death during induction prior to response assessment (death, grey). Response categories were defined according to the ELN 2022 recommendations. The overall distribution of response categories differed significantly between cohorts (χ^2 test, $p < 0.001$), driven by a higher rate of CR/CRi (81.4% vs. 71.7%) and a substantially lower rate of induction death (2.6% vs. 8.3%) in the IC + MIDO cohort. Abbreviations: CR, complete remission; CRi, complete remission with incomplete hematologic recovery; IC, intensive chemotherapy; IC + MIDO, intensive chemotherapy plus midostaurin; PR, partial response. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 | Early mortality during induction in the overall study population and according to midostaurin use.

Outcome	Overall ($N = 1658$)	IC ($n = 1189$)	IC + MIDO ($n = 469$)	p
Death during induction, *n* (%)	111 (6.7)	99 (8.3)	12 (2.6)	< 0.001
Mortality at Day 30, *n* (%)	94 (5.7)	84 (7.1)	10 (2.1)	< 0.001
Mortality at Day 60, *n* (%)	132 (8.0)	114 (9.6)	18 (3.8)	< 0.001
Time to induction death, median (IQR), days	19 (15–23)	19 (15–23)	20 (19–23)	0.224

Note: Data are presented as *n* (%) or median (interquartile range). Death during induction was defined as death without response assessment during the first induction cycle. Days 30 and 60 mortality were defined as death from any cause within 30 and 60 days from AML diagnosis, respectively. Time to induction death was calculated from the start of induction chemotherapy to the date of death.
p Values were calculated using the χ^2 or Fisher's exact test for categorical variables and the Mann–Whitney *U* test for continuous variables.
Abbreviations: IC, intensive chemotherapy; IC + MIDO, intensive chemotherapy plus midostaurin; IQR, interquartile range.

3-year EFS rates of 54.5% (95% CI, 49.9–59.6), and 39.3% (95% CI, 34.3–45.1) in the IC + MIDO vs. 43.3% (95% CI, 40.5–46.3), and 29.4% (95% CI, 26.7–32.3) in the IC cohort.

Among the 1234 patients who achieved CRc, the CIR showed a trend favoring the IC + MIDO cohort (Gray's test $p = 0.054$; Figure 3C), with 3-year CIR estimates of 42% (95% CI, 35–48) in the IC + MIDO vs. 47% (95% CI, 43–50) in the IC cohort. NRM was comparable between cohorts (3-year NRM: 11% [95% CI, 7.3–15] in IC + MIDO vs. 12% [95% CI, 9.7–14] in IC; Gray's test $p = 0.568$; Figure 3D).

3.5 | Subgroup and Prognostic Factor Analyses

Univariate subgroup analyses for OS and EFS were performed across clinical and molecular factors (Figure S1). The benefit of MIDO on OS was consistent across the majority of subgroups, including age (< 60 and ≥ 60 years), sex (male and female), ECOG performance status 0–2, de novo AML, WBC count (< 20 and ≥ 20×10^9/L), MRC intermediate- and high-risk cytogenetics, *NPM1* positive, *FLT3*-ITD positive, and both categories of *FLT3*-ITD AR (< 0.5 and ≥ 0.5). The magnitude of benefit was particularly pronounced in patients with

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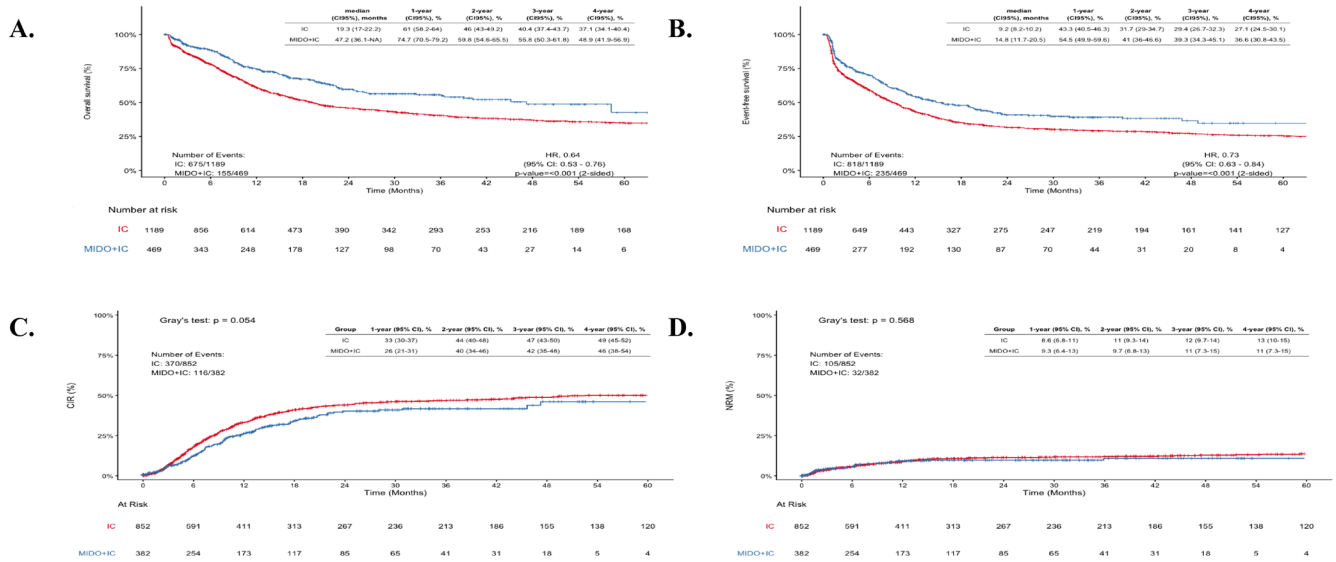

FIGURE 3 | Survival outcomes according to midostaurin use in the overall study population. Kaplan–Meier curves for overall survival (A) and event-free survival (B) and cumulative incidence curves for cumulative incidence of relapse (C) and nonrelapse mortality (D) in patients treated with intensive chemotherapy plus midostaurin (IC + MIDO; blue, $n = 469$) versus intensive chemotherapy alone (IC; red, $n = 1189$). Median OS was 47.2 months (95% CI, 36.1–not reached) versus 19.3 months (95% CI, 17.0–22.2; HR 0.64; 95% CI, 0.53–0.76; $p < 0.001$). Median EFS was 14.8 months (95% CI, 11.7–20.5) versus 9.2 months (95% CI, 8.2–10.2; HR 0.73; 95% CI, 0.63–0.84; $p < 0.001$). The CIR showed a trend favoring the IC + MIDO cohort without reaching statistical significance (Gray's test $p = 0.054$). NRM did not differ significantly between groups (Gray's test $p = 0.568$). Numbers at risk are shown below each panel. CI, confidence interval; CIR, cumulative incidence of relapse; EFS, event-free survival; HR, hazard ratio; IC, intensive chemotherapy; NRM, nonrelapse mortality; OS, overall survival. [Color figure can be viewed at wileyonlinelibrary.com]

MRC high-risk cytogenetics (OS: HR 0.39; 95% CI, 0.21–0.72; $p = 0.003$) and *NPM1*-mutated patients (OS: HR 0.55; 95% CI, 0.43–0.70; $p < 0.001$). Four subgroups did not reach statistical significance for OS: MRC low-risk (HR 1.12; 95% CI, 0.26–4.78; $p = 0.878$), *FLT3*-TKD-positive (HR 0.78; 95% CI, 0.50–1.20; $p = 0.257$), *NPM1* negative (HR 0.79; 95% CI, 0.61–1.04; $p = 0.096$), and secondary AML (HR 0.76; 95% CI, 0.47–1.21; $p = 0.249$). Results for EFS paralleled those for OS across all subgroups. Kaplan–Meier curves for OS and EFS according to midostaurin use within each subgroup—age, AML type, MRC cytogenetic risk, *NPM1* status, *FLT3* mutation type, and *FLT3*-ITD AR—are provided in Figures S2–S7, respectively.

In the multivariable analyses, IC + MIDO remained independently associated with improved OS (adjusted HR 0.73; 95% CI, 0.56–0.94; $p = 0.017$) and EFS (adjusted HR 0.76; 95% CI, 0.61–0.94; $p = 0.012$), after adjustment for age, sex, ECOG performance status, AML type, WBC count, MRC cytogenetic risk, *NPM1*, *FLT3*-ITD, *FLT3*-ITD AR, and *FLT3*-TKD status (Figure 4). Other independent adverse prognostic factors for OS were age ≥ 60 years (HR 2.44; 95% CI, 1.90–3.13; $p < 0.001$), WBC $\geq 20 \times 10^9$/L (HR 1.37; 95% CI, 1.04–1.79; $p = 0.024$), and *FLT3*-ITD AR ≥ 0.5 (HR 1.43; 95% CI, 1.06–1.93; $p = 0.019$). For EFS, the same adverse factors retained significance, whereas *NPM1* positivity (HR 0.70; 95% CI, 0.56–0.87; $p = 0.001$) and intermediate/low MRC cytogenetic risk (HR 0.67; 95% CI, 0.49–0.92; $p = 0.013$) emerged as favorable prognostic factors. Scaled Schoenfeld residuals indicated nonproportional hazards for the midostaurin effect (OS, $p = 0.030$; EFS, $p = 0.020$); adjusted HRs represent time-averaged effects.

3.6 | Impact of Allogeneic HSCT and Midostaurin Use on Survival

To account for the time-dependent nature of HSCT and avoid immortal time bias, a Simon–Makuch analysis was performed in the 1035 patients who achieved CRc with assessable transplant status, using HSCT modality (no HSCT, auto-HSCT, or allo-HSCT) combined with MIDO exposure as a time-dependent covariate. Six mutually exclusive groups were defined, and patients receiving neither HSCT nor MIDO (No SCT + IC) served as the reference category (Figure 5). The benefit of MIDO was consistent across all transplant status strata when compared with the No HSCT + IC reference. Among patients who did not undergo HSCT, the addition of MIDO was associated with significantly improved OS (HR 0.69; 95% CI, 0.51–0.92; $p = 0.012$) and EFS (HR 0.78; 95% CI, 0.61–0.99; $p = 0.045$). Within the auto-HSCT and allo-HSCT strata, MIDO use further enhanced outcomes (auto-HSCT + IC + MIDO OS HR 0.32, 95% CI 0.13–0.78, $p = 0.012$; allo-HSCT + IC + MIDO OS HR 0.51, 95% CI 0.35–0.73, $p < 0.001$), with parallel findings for EFS.

Pairwise within-stratum comparisons of IC + MIDO versus IC were performed using separate Cox models restricted to each transplant modality (Figure S8). The largest MIDO treatment effect was observed in patients who did not undergo HSCT, with significantly improved OS (HR 0.69; 95% CI, 0.52–0.93; $p = 0.014$) and a trend toward improved EFS (HR 0.79; 95% CI, 0.62–1.00; $p = 0.053$). In auto-HSCT recipients, MIDO was associated with a significant improvement in EFS (HR 0.45; 95% CI, 0.20–1.00; $p = 0.049$), while OS showed a non-significant

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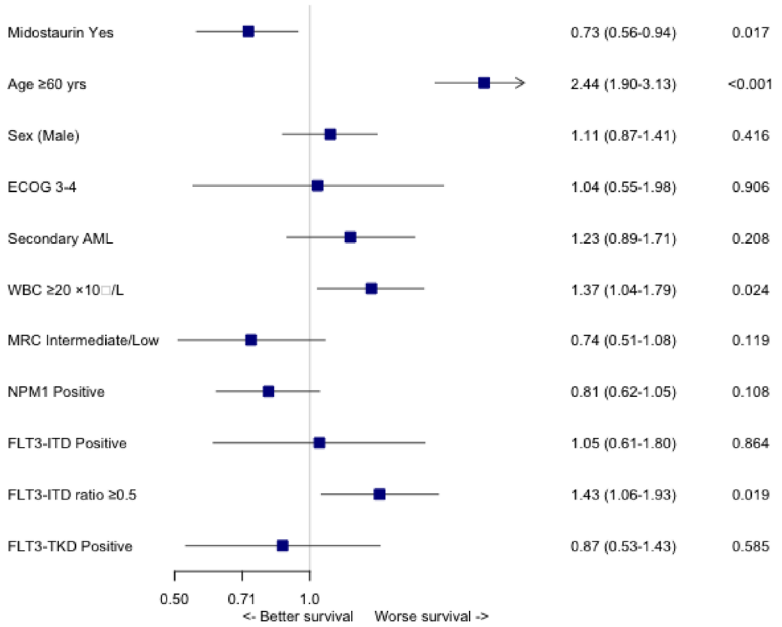
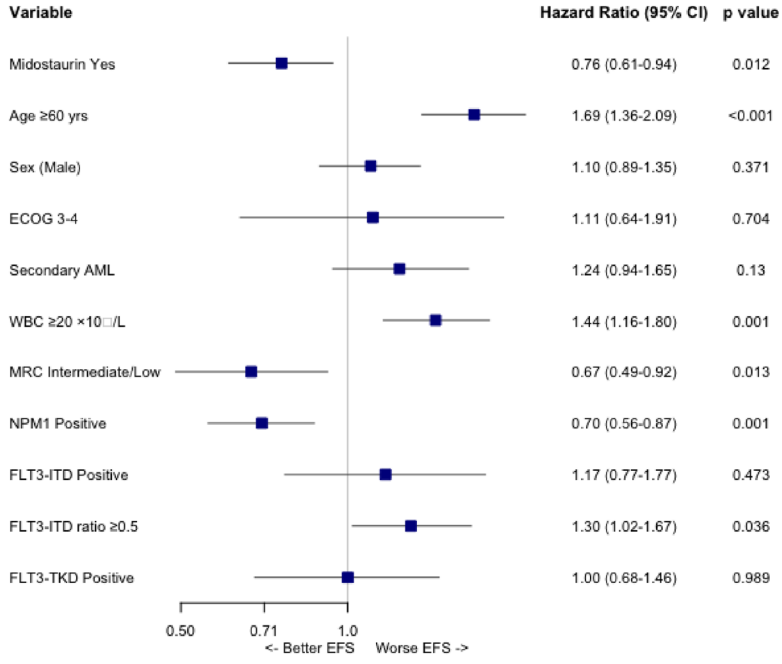
A.



Variable	HR	95% CI	p-value
FLT3 inh No (Ref)	1.00	–	–
Midostaurin Yes	0.73	0.56 – 0.94	0.017
Age <60 years (Ref)	1.00	–	–
Age ≥60 years	2.44	1.90 – 3.13	<0.001
Sex Female (Ref)	1.00	–	–
Sex Male	1.11	0.87 – 1.41	0.416
ECOG 0–2 (Ref)	1.00	–	–
ECOG 3–4	1.04	0.55 – 1.98	0.906
AML de novo (Ref)	1.00	–	–
Secondary AML	1.23	0.89 – 1.71	0.208
WBC <20 ×10⁹/L (Ref)	1.00	–	–
WBC ≥20 ×10⁹/L	1.37	1.04 – 1.79	0.024
MRC 2010 risk Adverse (Ref)	1.00	–	–
MRC 2010 risk Intermediate/Low	0.74	0.51 – 1.08	0.119
NPM1 Negative (Ref)	1.00	–	–
NPM1 Positive	0.81	0.62 – 1.05	0.108
FLT3-ITD Negative (Ref)	1.00	–	–
FLT3-ITD Positive	1.05	0.61 – 1.80	0.864
FLT3-ITD ratio <0.5 (Ref)	1.00	–	–
FLT3-ITD ratio ≥0.5	1.43	1.06 – 1.93	0.019
FLT3-TKD Negative (Ref)	1.00	–	–
FLT3-TKD Positive	0.87	0.53 – 1.43	0.585

B.



Variable	HR	95% CI	p-value
Midostaurin No (Ref)	1.00	–	–
Midostaurin Yes	0.76	0.61 – 0.94	0.012
Age <60 years (Ref)	1.00	–	–
Age ≥60 years	1.69	1.36 – 2.09	<0.001
Sex Female (Ref)	1.00	–	–
Sex Male	1.10	0.89 – 1.35	0.371
ECOG 0–2 (Ref)	1.00	–	–
ECOG 3–4	1.11	0.64 – 1.91	0.704
AML de novo (Ref)	1.00	–	–
Secondary AML	1.24	0.94 – 1.65	0.130
WBC <20 ×10⁹/L (Ref)	1.00	–	–
WBC ≥20 ×10⁹/L	1.44	1.16 – 1.80	0.001
MRC 2010 risk Adverse (Ref)	1.00	–	–
MRC 2010 risk Intermediate/Low	0.67	0.49 – 0.92	0.013
NPM1 Negative (Ref)	1.00	–	–
NPM1 Positive	0.70	0.56 – 0.87	0.001
FLT3-ITD Negative (Ref)	1.00	–	–
FLT3-ITD Positive	1.17	0.77 – 1.77	0.473
FLT3-ITD ratio <0.5 (Ref)	1.00	–	–
FLT3-ITD ratio ≥0.5	1.30	1.02 – 1.67	0.036
FLT3-TKD Negative (Ref)	1.00	–	–
FLT3-TKD Positive	1.00	0.68 – 1.46	0.989

FIGURE 4 | Multivariable Cox proportional hazards analysis of overall survival and event-free survival. Forest plots depicting adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) from multivariable Cox proportional hazards models for overall survival (A) and event-free survival (B). The models included the following covariates: midostaurin use (yes vs. no [reference]), age (≥60 vs. <60years [reference]), sex (male vs. female [reference]), ECOG performance status (3–4 vs. 0–2 [reference]), AML type (secondary vs. de novo [reference]), white blood cell count (≥20 vs. $<20\times10^9$/L [reference]), MRC cytogenetic risk (intermediate/low vs. adverse [reference]), NPM1 mutation status (positive vs. negative [reference]), FLT3-ITD (positive vs. negative [reference]), FLT3-ITD allelic ratio (≥0.5 vs. <0.5 [reference]), and FLT3-TKD (positive vs. negative [reference]). Missing data were handled using multiple imputation. Midostaurin use was independently associated with improved OS (HR 0.73; 95% CI, 0.56–0.94; $p=0.017$) and EFS (HR 0.76; 95% CI, 0.61–0.94; $p=0.012$). Other independent adverse prognostic factors included age ≥60 years (OS HR 2.44; $p<0.001$), WBC ≥20×10^9/L (OS HR 1.37; $p=0.024$), and FLT3-ITD allelic ratio ≥0.5 (OS HR 1.43; $p=0.019$). Testing of scaled Schoenfeld residuals indicated a departure from the proportional hazards assumption for the midostaurin effect (OS, $p=0.030$; EFS, $p=0.020$) and for the global models (OS, $p=0.017$; EFS, $p=0.019$); accordingly, the reported HRs should be interpreted as time-averaged effects over the follow-up period. [Color figure can be viewed at wileyonlinelibrary.com]

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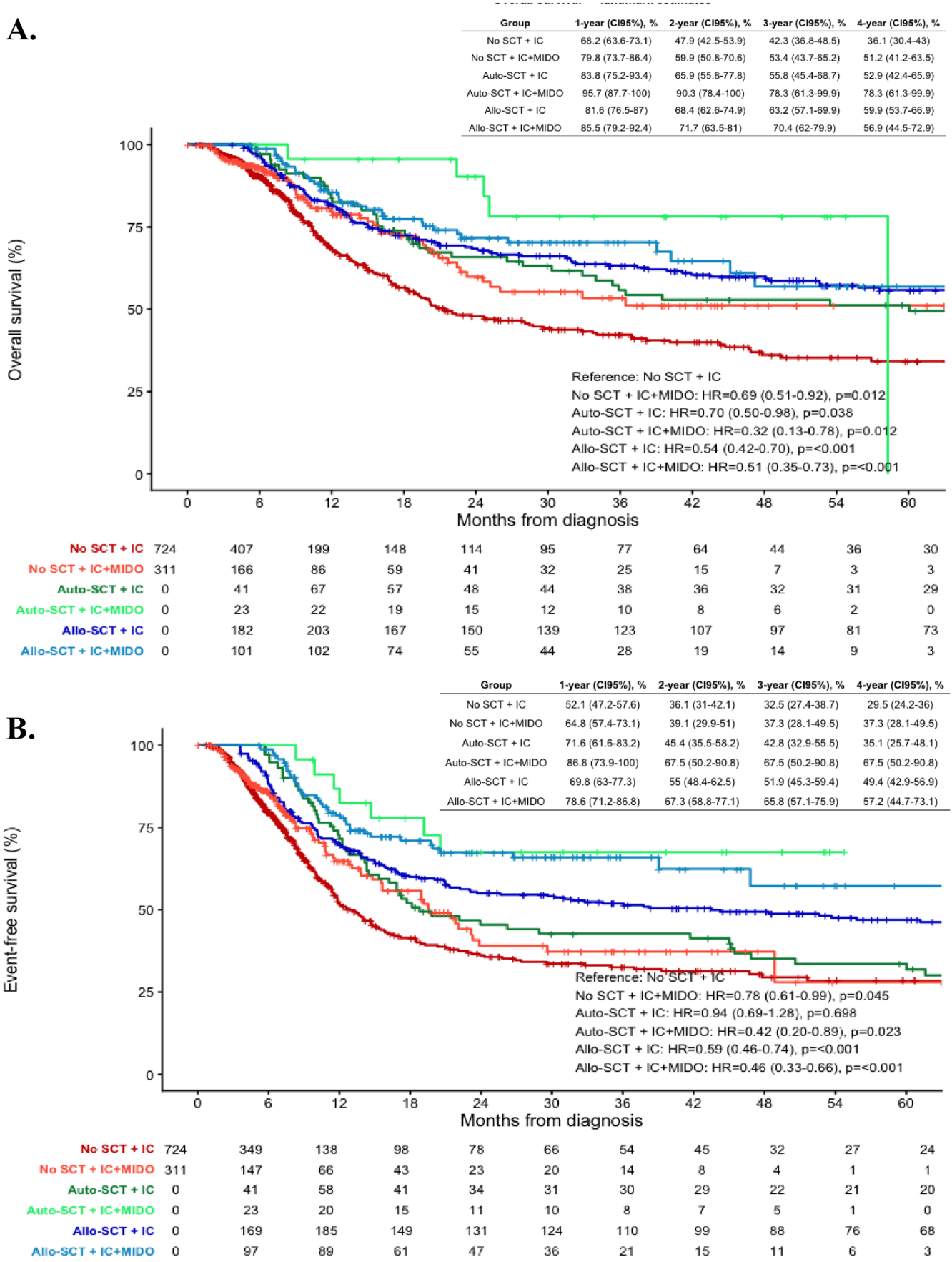

FIGURE 5 | Legend on next page.

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FIGURE 5 | Simon–Makuch analysis of overall survival and event-free survival according to allogeneic HSCT and midostaurin use. Simon–Makuch curves for overall survival (A) and event-free survival (B) among patients achieving composite complete remission (CRc), using auto or allo-SCT as a time-dependent covariate. Patients were classified into six groups based on transplant modality (allo-SCT, auto-SCT, or No SCT) and midostaurin exposure (IC + MIDO vs. IC). The No SCT without midostaurin (No SCT + IC) group served as the reference group. Patients contributed observation time to their pre-SCT group until the date of transplantation, at which point they were reassigned to the corresponding SCT group, thereby avoiding immortal time bias. Hazard ratios (HRs) and 95% confidence intervals (CIs) are shown relative to the reference group and were estimated using time-dependent Cox proportional hazards models. For OS (A), patients who received neither SCT nor midostaurin had the worst outcome, while patients treated with midostaurin without SCT had significantly better outcomes compared with the reference group (HR 0.69; 95% CI, 0.51–0.92; $p = 0.012$). The most favorable outcomes were observed in transplanted patients, with allogeneic HSCT conferring the greatest benefit irrespective of midostaurin exposure (Allo-SCT + IC: HR 0.54; 95% CI, 0.42–0.70; Allo-SCT + IC + MIDO: HR 0.51; 95% CI, 0.35–0.73; both $p < 0.001$). A similar pattern was observed for EFS (B), where the No SCT +IC group had markedly inferior outcomes, and midostaurin use in the absence of SCT was associated with improved EFS compared with the reference group (HR 0.78; 95% CI, 0.61–0.99; $p = 0.045$); allogeneic HSCT was again associated with the greatest benefit (Allo-SCT + IC: HR 0.59; 95% CI, 0.46–0.74; Allo-SCT + IC + MIDO: HR 0.46; 95% CI, 0.33–0.66; both $p < 0.001$). [Color figure can be viewed at wileyonlinelibrary.com]

trend in the same direction (HR 0.49; 95% CI, 0.19–1.26; $p = 0.138$). In contrast, no significant difference between cohorts was observed within the allo-HSCT subgroup for either OS (HR 0.89; 95% CI, 0.60–1.31; $p = 0.547$) or EFS (HR 0.75; 95% CI, 0.52–1.10; $p = 0.138$).

When the analysis was repeated within *NPM1* strata (Figure S9), allo-HSCT was associated with a comparable survival benefit in both *NPM1* strata (HR 0.60 and 0.57 in mutated and wild-type patients, respectively, versus No SCT + IC), and the allo-HSCT × *NPM1* interaction was not significant (OS $p = 0.799$). In contrast, the midostaurin effect differed: among nontransplanted patients, OS improved in *NPM1*-mutated (HR 0.60; 95% CI, 0.42–0.86; $p = 0.005$) but not in wild-type patients (HR 1.07; 95% CI, 0.61–1.85; $p = 0.822$), and this pattern persisted after adjustment for time-dependent allo-HSCT (Table S5). The midostaurin × *NPM1* interaction was the smallest of the 10 subgroup interactions tested (OS $p = 0.041$; EFS $p = 0.010$) but did not remain significant after correction for multiple testing (Benjamini–Hochberg-adjusted $p = 0.296$ and $p = 0.098$, respectively), nor after adjustment for transplant (OS $p = 0.096$).

3.7 | Propensity Score–Matched Analysis

To mitigate residual baseline imbalance between cohorts and reduce confounding by indication, a 1:1 nearest-neighbor propensity score matching was performed, yielding 261 matched pairs (261 IC and 261 IC + MIDO). Adequate balance (SMD < 0.1) was achieved across all covariates included in the propensity model (Table S4 and Figure S10), with the exception of diagnosis year.

In the matched cohorts, MIDO use was associated with significantly improved EFS and a consistent, non-significant trend toward improved OS compared with IC alone (Figure 6). Median OS was 58.3 months (95% CI, 39.0–NR) in the IC + MIDO cohort versus 37.0 months (95% CI, 25.8–97.5) in the IC cohort (HR 0.77; 95% CI, 0.58–1.01; $p = 0.06$), with 1- and 3-year OS rates of 78.1%, and 58.7% versus 69.2%, and 50.4%, respectively. Median EFS was 19.9 months (95% CI, 12.9–48.9) versus 13.6 months (95% CI, 10.2–19.3) (HR 0.77; 95% CI, 0.62–0.97; $p = 0.029$), with corresponding 1- and 3-years EFS rates of 58.7%, and 45.3% in the IC + MIDO vs. 52.7%, and 37.1% in the IC cohort.

Overall, the magnitude of the treatment effect was attenuated in the PSM analysis compared with the unadjusted comparison (OS: HR 0.77 vs. 0.64; EFS: HR 0.77 vs. 0.73).

4 | Discussion

This large real-world study shows that the addition of MIDO to IC was associated with improved OS in the unadjusted analysis and after multivariable adjustment, with a similar magnitude of effect after PSM as compared with the RATIFY randomized trial comparing as well IC versus IC + MIDO (HR 0.77 in PETHRATIFY and 0.78 in RATIFY). The consistency of these effect estimates across progressively adjusted models supports the conclusion that MIDO confers a clinically meaningful advantage in routine practice beyond the controlled environment of clinical trials [8].

To our knowledge, our study represents the largest single-registry real-world cohort of *FLT3*-mutated AML patients treated with MIDO plus IC reported to date. We analyzed 1658 adults across the full adult age spectrum (14–85 years), with no upper age restriction. Our cohort, extending to patients older than 70 and 80 years and including those with secondary AML and poor performance status, underscores the feasibility and activity of MIDO-based regimens outside of clinical trials. Notably, the predominant use of idarubicin-based induction in our cohort—in contrast to the daunorubicin-based backbone of the RATIFY trial—extends the evidence of MIDO efficacy to alternative anthracycline partners, consistent with AMLSG 16–10 (idarubicin plus cytarabine and etoposide) and Sierra et al., in which 55.1% of patients received idarubicin [10]. In our IC + MIDO cohort median OS and EFS were 47.2 and 14.8 months. These results compare favorably with most published real-world series of midostaurin plus IC, which often comprise smaller patient numbers, single-center designs, or selected age subgroups [19, 20].

The CRc rate of 81.4% observed in our IC + MIDO cohort is favorable when contextualized with prior reports. The pivotal RATIFY trial, limited to patients aged 18–59 years, reported a CR rate of 58.9% in the midostaurin arm [8], although CR and CRi were not combined as a primary endpoint. The AMLSG 16–10 trial reported a CR/CRi rate of 77.9% in older patients (61–70 years) [9], while the Sierra et al. Phase 3b study reported a CR/

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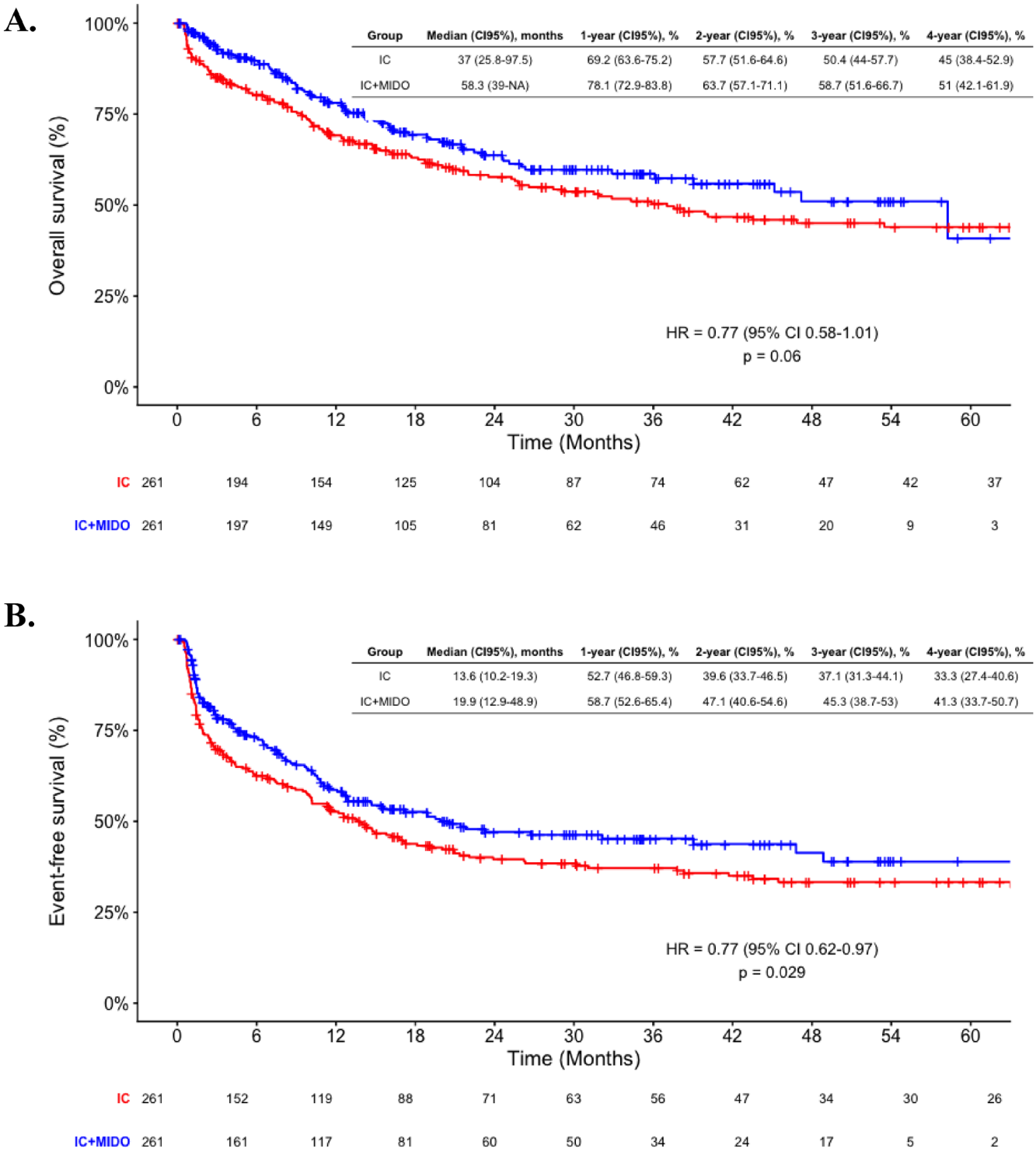

FIGURE 6 | Overall survival and event-free survival in the propensity score–matched cohorts. Kaplan–Meier estimates of overall survival (A) and event-free survival (B) comparing the IC + MIDO ($n = 261$) and IC ($n = 261$) cohorts after 1:1 nearest-neighbor propensity score matching. Inset tables display median survival and landmark estimates at 1, 2, 3, and 4 years with 95% confidence intervals. In the matched analysis, midostaurin use was associated with a treatment effect of similar magnitude for both endpoints that did not reach statistical significance for OS (median 58.3 vs. 37.0 months; HR 0.77; 95% CI, 0.58–1.01; $p = 0.060$) but was significant for EFS (median 19.9 vs. 13.6 months; HR 0.77; 95% CI, 0.62–0.97; $p = 0.029$). Four-year OS rates were 51.0% (95% CI, 42.1–61.9) for IC + MIDO versus 45.0% (95% CI, 38.4–52.9) for IC; 4-year EFS rates were 41.3% (95% CI, 33.7–50.7) versus 33.3% (95% CI, 27.4–40.6), respectively. [Color figure can be viewed at wileyonlinelibrary.com]

CRi of 80.7%, including 82.5% in patients aged > 60–≤ 70 years [10], consistent with our registry study of *FLT3*-mutated AML patients aged ≥ 60 years (CRc 78.9%) [11].

A marked global reduction in early mortality was observed in our IC + MIDO cohort, in line with the MIDOLAM study analyzing patients aged > 59 years old, where Day 60 induction

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death was 8.2% with IC + MIDO versus 21.4% with IC alone [11], and is consistent with the AMLSG 16–10 trial, in which induction death in older patients dropped from 15.7% to 2.4% with midostaurin [9]. These data suggest that, in routine practice, the addition of MIDO is not necessarily associated with increased toxicity of induction phase (i.e., no relevant delay of neutrophil and platelet count recovery was observed), but is also possibly reflecting refinements in supportive care and patient selection that cannot be directly assessed in this retrospective cohort. In fact, the IC cohort was diagnosed in an early period, and showed higher LDH levels which have been associated with increased risk of induction mortality.

Subgroup analyses revealed that the benefit of MIDO was preserved across most clinical and molecular categories. We confirm the benefit across age groups (< 60 and ≥ 60) [12], but we do not confirm the preferential benefit of midostaurin among females observed in the RATIFY. Our analysis also shows that secondary AML (underrepresented in the RATIFY) could have less benefit of adding MIDO; however, a substantial increase in OS and EFS was observed among the high-risk MRC group. Of note, no benefit of MIDO appeared among low-risk cytogenetics, where patients received since 2019 the combination of 3 + 7 and mylotarg. Interestingly, while the sensitivity analyses of the RATIFY showed the best HR for OS and EFS among *FLT3*-TKD patients, in our study the benefit was more pronounced in the *FLT3*-ITD subgroup. The therapeutic benefit of MIDO was preserved across both *FLT3*-ITD AR categories (< 0.5; HR 0.68) and high (≥ 0.5; HR 0.62), with substantial improvements in OS and EFS. This is concordant with prior real-world data showing that midostaurin attenuates the prognostic weight of *FLT3*-ITD AR [19] and with the ELN 2022 decision to exclude AR from genetic risk stratification [16]. However, in our multivariable analysis, an AR ≥ 0.5 retained independent adverse prognostic value for both OS and EFS, suggesting that, even in the era of FLT3-targeted therapy, allelic burden continues to inform prognosis. On the other hand, *NPM1* mutation identified patients with the greatest benefit (OS HR 0.55), possibly reflecting the cooperative pathogenesis and heightened FLT3 signaling dependence typical of *FLT3*-ITD/*NPM1*-mutated AML.

The time-dependent analyses revealed that the survival benefit of MIDO was most pronounced in patients who did not undergo allo-HSCT. We can hypothesize that: (1) the allogeneic graft-versus-leukemia effect may supersede the incremental contribution of midostaurin in those patients, (2) that nonselective toxicity related to allo-HSCT may equalize outcomes irrespective of upfront therapy, and (3) the use of sorafenib or other maintenance strategies after allo-HSCT could affect outcomes as well in the IC alone group [21, 22]. Conversely, midostaurin conferred a substantial survival advantage in nontransplanted patients, of particular relevance for elderly or transplant-ineligible patients. Interestingly, the QuANTUM-First trial showed that non allo-HSCT patients were particularly benefitting from the addition of quizartinib to 3 + 7, especially when they received the maintenance phase (up to 36 cycles) [23].

Stratification by *NPM1* status indicated that allo-HSCT retained a similar benefit in both mutated and wild-type patients, whereas the midostaurin effect was confined to the *NPM1*-mutated subgroup. Transplant is unlikely to account for this difference: allo-HSCT was in fact performed more frequently in the IC + MIDO arm among wild-type patients (66.7% vs. 43.9%), which would have favored rather than obscured detection of a benefit. This observation should nonetheless be regarded as hypothesis-generating: although the *NPM1* interaction was the smallest of the 10 subgroup interactions tested, it did not remain significant after correction for multiple testing, was attenuated after adjustment for time-dependent transplant, and has not been formally evaluated in randomized trials, in which *NPM1* status has been analyzed only in combination with the *FLT3*-ITD AR within ELN risk categories [24]. Prospective evaluation is warranted. Importantly, since allo-HSCT was associated with a comparable benefit in both *NPM1* strata, these findings do not alter transplant recommendations in *NPM1* wild-type AML.

In our cohort, the addition of midostaurin was associated with a substantially higher CRc rate (81.4% vs. 71.7%; $p < 0.001$), expanding the pool of patients eligible for allogeneic HSCT in first remission. Among patients achieving CRc, the proportion proceeding to allogeneic HSCT was significantly higher in the IC + MIDO group than in the IC group (48.9% vs. 41.3%; $p = 0.023$). This bridging effect is consistent with the AMLSG 16–10 trial, in which 72.4% of patients achieving CR proceeded to allogeneic HSCT in first CR [9], and aligns with contemporary treatment algorithms recommending the integration of FLT3 inhibitors during induction with early consideration for allogeneic HSCT in eligible patients [25].

We performed a PSM analysis to account for baseline imbalances between groups. The progressive attenuation of the OS HR from the unadjusted (0.64) to the multivariable-adjusted (0.73) and matched (0.77) estimates is expected and informative, indicating that part of the crude benefit reflects residual confounding, including temporal factors and selection bias, while the effect remained consistent in direction across all models. Similar patterns have been reported in other retrospective series: the MIDOLAM study reported a PSM OS HR of 0.46 (118 matched pairs) [11], while the AMLSG 16–10 study reported a propensity score–weighted EFS HR of 0.58 [9].

Our findings should be contextualized within the evolving FLT3-targeted landscape. QuANTUM-First showed that quizartinib improved OS in *FLT3*-ITD AML aged 18–75 years (HR 0.78 [95% CI: 0.62–0.98]; $p = 0.032$; median OS 31.9 vs. 15.1 months), leading to regulatory approval [12]. Direct comparison with our results is precluded by differences in design, population (*FLT3*-ITD only vs. ITD and TKD), and comparator (placebo vs. historical control without FLT3 inhibition); nonetheless, our cohort's survival benefit (propensity-matched HR 0.77) provides a pragmatic real-world benchmark. Notably, the QuANTUM-First subgroup analysis showed OS benefit only in patients < 60 years (HR 0.68 [95% CI: 0.49–0.95]), with no significant effect in those ≥ 60 years (HR 0.91 [95% CI: 0.66–1.26]) [12], reflecting the ongoing debate on FLT3 inhibitors in older adults [26]. Further studies will inform about the safety and efficacy of quizartinib in the real-world setting.

Several limitations of this study merit consideration. First, the retrospective design with a historical control cohort inherently introduces selection bias and residual confounding that cannot be fully eliminated by multivariable or propensity score-based methods.

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Second, temporal changes in standards of care (the so-called era effect)—advances in supportive therapy, broader molecular diagnostics, and evolving transplant practices—may partially account for improved outcomes in the MIDO era. Third, 41.7% of controls were diagnosed after 2017, reflecting heterogeneous adoption of MIDO across centers and introducing a temporal confounder with the MIDO cohort. Fourth, the absence of a comprehensive NGS panel precluded the complete ELN 2022 risk classification and limited the analysis of comutations such as *DNMT3A, ASXL1*, and *TP53*. Fifth, maintenance therapy was not systematically captured, preventing assessment of its contribution to postremission outcomes. Sixth, the effect of MIDO on MRD kinetics could not be demonstrated, as standardized MRD monitoring was not consistently available across centers, and *NPM1*-mutant transcript monitoring by RT-qPCR was not collected in the registry, precluding an exploratory analysis of whether molecular MRD negativity modifies the benefit of allo-HSCT in first remission.

In conclusion, our findings from the largest single-registry series of *FLT3*-mutated AML treated with MIDO in routine practice—without upper age restriction—support a clinically meaningful and independent survival benefit of adding MIDO to IC. The benefit was particularly pronounced among non-allografted patients, while MIDO also increased allo-HSCT rates in patients achieving CRc, supporting FLT3 inhibition as both an autonomous treatment component and a bridge-to-transplant strategy. Significantly improved outcomes were observed in *FLT3*-ITD and *NPM1*-comutated patients, consistent with modern risk classifications for these subgroups. These results complement the RATIFY trial data and support the standard-of-care status of MIDO across all adult age groups, while serving as a benchmark for future studies addressing real-world outcomes of IC plus quizartinib.

Author Contributions

Mónica Alejandra Romero Riquelme: conceptualization, data curation, investigation, methodology, writing – original draft, writing – review and editing. **Gaspar Aspas Requena:** conceptualization, data curation, investigation, methodology, writing – original draft, writing – review and editing. **Pilar Lloret-Madrid:** formal analysis, methodology, data curation, investigation, visualization, writing – review and editing. **Pau Montesinos:** conceptualization, data curation, investigation, methodology, supervision, project administration, writing – review and editing. Remaining authors: investigation, resources, data curation, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data underlying this study are available from the PETHEMA registry upon reasonable request to P.M. (montesinos_pau@gva.es), subject to institutional approval and data sharing agreements. Individual patient-level data are not publicly available because of privacy and ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** ajh70488-sup-0001-Supplementary_Figure_Legends.docx. **Figure S1:** Univariate subgroup analysis of overall survival and event-free survival according to midostaurin use. **Figure S2:** Overall survival and event-free survival according to midostaurin use in patients aged <60 and ≥60 years. **Figure S3:** Overall survival and event-free survival according to midostaurin use in de novo and secondary AML. **Figure S4:** Overall survival and event-free survival according to midostaurin use by MRC cytogenetic risk category. **Figure S5:** Overall survival and event-free survival according to midostaurin use by NPM1 mutation status. **Figure S6:** Overall survival and event-free survival according to midostaurin use by FLT3 mutation type (ITD vs. TKD). **Figure S7:** Overall survival and event-free survival according to midostaurin use by FLT3-ITD allelic ratio (<0.5 vs. ≥0.5). **Figure S8:** Overall survival and event-free survival according to midostaurin use stratified by transplant modality. **Figure S9:** Simon–Makuch analysis of overall survival and event-free survival according to transplant modality and midostaurin use, by *NPM1* mutational status. **Figure S10:** Propensity score distribution before and after matching. **Table S1:** Induction regimens in the overall study population and according to midostaurin use. **Table S2:** Causes of death during induction in the overall study population and according to midostaurin use. **Table S3:** Hematologic recovery after induction chemotherapy among patients achieving complete remission, according to midostaurin use. **Table S4:** Baseline characteristics of the propensity score-matched cohorts. **Table S5:** Midostaurin and allo-HSCT effects within *NPM1* strata, and midostaurin × subgroup interaction tests across the 10 subgroups with correction for multiple testing.

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