

Midostaurin in patients with acute myeloid leukemia and *FLT3*-TKD mutations: a subanalysis from the RATIFY trial

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Key Points

- Midostaurin significantly improves event-free survival in patients with *FLT3*-TKD mutated AML.
- *NPM1* mutations and CBF rearrangements were favorable independent predictors of OS and EFS in the multivariable analysis.

The results from the RATIFY trial (ClinicalTrials.gov: NCT00651261; CALGB 10603) showed that midostaurin combined with standard chemotherapy significantly improved outcomes in patients with FMS-like tyrosine kinase 3 (*FLT3*)-mutated acute myeloid leukemia (AML), compared with placebo. In this post hoc subgroup analysis from the trial, we evaluated the impact of midostaurin in 163 patients with *FLT3*-tyrosine kinase domain (TKD) mutations. At a median follow-up of 60.7 months (95% CI, 55.0-70.8), the 5-year event-free survival (EFS) rate was significantly higher in patients treated with midostaurin than in those treated with placebo (45.2% vs 30.1%; $P = .044$). A trend toward improved disease-free survival was also observed with midostaurin (67.3% vs 53.4%; $P = .089$), whereas overall survival (OS) was similar in the 2 groups. Patients with AML and *NPM1*^{mut}/*FLT3*-TKD^{mut} or core binding factor (CBF)-rearranged/*FLT3*-TKD^{mut} genotypes had significantly prolonged OS with or without censoring at hematopoietic cell transplantation (HCT), compared with *NPM1*^{WT}/CBF-negative AMLs. The multivariable model for OS and EFS adjusted for allogeneic HCT in first complete remission as a time-dependent covariable, revealed *NPM1* mutations and CBF rearrangements as significant favorable factors. These data show that *NPM1* mutations or CBF rearrangements identify favorable prognostic groups in patients with *FLT3*-TKD AMLs, independent of other factors, also in the context of midostaurin treatment.

Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease with unsatisfactory long-term outcomes, despite significant progress in its diagnosis, monitoring, and treatment.¹ Major advances in genomic

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Table 1. Characteristics of patients with a *FLT3*-TKD^{mut} AML included in the RATIFY trial (n = 163)

	Total patient population (N = 163)	Midostaurin (n = 83)	Placebo (n = 80)	P, mido vs placebo
Sex, males/females, n	79/84	45/38	34/46	.180
Age, median (range), y	48.8 (19.3-59.9)	48.0 (19.8-59.8)	49.4 (19.3-59.9)	.827
ECOG PS 2, %	13 (8)	6 (7.2)	7 (8.8)	.945
WBC count, median (range), × 10 ⁹ /L	28.80 (1.20-300.00)	29.70 (1.20-298.40)	28.15 (1.30-300.00)	.480
Platelet count, median (range), × 10 ⁹ /L	49.00 (10.00-328.00)	53.00 (11.00-328.00)	46.50 (10.00-237.00)	.430
Bone marrow blasts, median (range), %	75.00 (0.00-100.00)	75.00 (0.00-100.00)	77.00 (0.00-100.00)	.817
Peripheral blood blasts, median (range), %	55.00 (0.00-99.00)	56.50 (0.00-99.00)	55.00 (0.00-98.00)	.594
Prior myelodysplastic syndrome, n (%)	4 (2.5)	2 (2.4)	2 (2.5)	>.99
Extramedullary disease, n (%)	31 (19.0)	13 (15.7)	18 (22.5)	.362
<i>NPM1</i>, n (%) (n = 134)				
Mutated	79 (59.0)	45 (64.3)	34 (53.1)	.256
WT	55 (41)	25 (35.7)	30 (46.9)	
Karyotype, n (%) (n = 135)				
CBF*	20 (14.8)	10 (15.6)	10 (14.1)	.140
Normal	74 (54.8)	39 (60.9)	35 (49.3)	
Other†	41 (30.4)	15 (23.4)	26 (36.6)	
CR after induction, n (%)	105 (64.4)	57 (68.6)	48 (60)	.321
Allogeneic HCT in first CR, n (%)	62 (38.0)	32 (38.6)	30 (37.5)	>.99
Midostaurin maintenance, n (%)	58 (35.6)	32 (38.6)	26 (32.5)	.52

Mido, midostaurin; ECOG-PS, Eastern Cooperative Oncology Group performance status; WBC, white blood cell.

*CBF rearrangements: inv(16), n = 11, and t(8;21), n = 9

†Includes 8 patients with adverse and 7 with intermediate karyotype in the midostaurin arm, vs 7 and 19 patients, respectively, in the placebo arm.

characterization have recently improved patient stratification and led to the identification of molecular targets to help individualized treatment approaches. A paradigm for this are activating mutations in FMS-like tyrosine kinase 3 (*FLT3*), which characterize ~35% of AML cases and have a decreasing prevalence in elderly patients.²⁻⁴ *FLT3* mutations include internal tandem duplications (ITDs), present in about 25% to 30% of younger patients with AML, and tyrosine kinase domain (TKD) mutations (eg, point mutations in D835 and I836 or deletion of codon I836), present in ~8% of patients.²⁻⁴

FLT3-ITD mutations are a known unfavorable prognostic marker associated with poor overall survival (OS) and relapse-free survival⁵⁻⁷; as such, testing for these mutations is part of the routine workup for patients with AML and is recommended by current guidelines at the time of diagnosis and at relapse.^{8,9} The leukemogenic relevance and prognostic impact of *FLT3*-TKD mutations are more uncertain, with conflicting evidence observed across studies.¹⁰⁻¹⁵ Other common mutations often co-occurring with *FLT3* affect the nucleophosmin 1 (*NPM1*) gene; these are present in ~30% of patients with AML and are associated with a favorable to intermediate prognosis, depending on the presence of concomitant *FLT3*-ITD mutations.^{7,8,16} Core binding factor (CBF) rearrangements are also frequent in *FLT3*-TKD^{mut} AML, and occur in ~15% of patients.^{3,10}

Midostaurin is a multikinase inhibitor, originally developed for the treatment of solid tumors. In AML, it inhibits *FLT3*-kinase in patients with both ITD and TKD mutations, as well as other targets involved in the disease pathogenesis.¹⁷ In the Cancer and Leukemia Group B (CALGB) 10603/RATIFY trial, which enrolled patients with a *FLT3*-mutated (*FLT3*^{mut}) AML, midostaurin in combination with

standard induction and consolidation chemotherapy, followed by single-agent maintenance therapy, significantly improved outcomes vs placebo.¹⁷ In this study, patients were stratified according to the presence of TKD mutations and ITD allelic ratios (AR). Benefits of midostaurin were seen across all *FLT3* stratification subgroups, with a significantly longer survival for patients treated with midostaurin as compared with those receiving placebo (median, 74.7 months vs 25.6 months, *P* = .009).¹⁷ The data from this trial led to the approval of midostaurin in 2017 for the treatment of adults with newly diagnosed, *FLT3*^{mut} AML.

In this post hoc analysis from the RATIFY trial, we further investigated the role of midostaurin in the treatment of *FLT3*-TKD^{mut} AML, also taking into account karyotype and *NPM1* mutation status.

Patients and methods

Study design

Results from the RATIFY trial were published previously.¹⁷ In brief, patients aged 18 to 59 years with newly diagnosed AML and a *FLT3* mutation were randomly assigned 1:1 to receive midostaurin or placebo together with standard induction and consolidation therapy. Randomization was stratified by *FLT3* mutation subtype: TKD, ITD^{low} with AR between 0.05 and 0.7, and ITD^{high} with AR >0.7. During induction and the 4 28-day cycles of consolidation therapy, 50 mg midostaurin or placebo were administered orally twice per day on days 8 to 21. Patients who remained in remission after consolidation therapy received 12 28-day cycles of maintenance therapy, with 50 mg oral midostaurin or placebo twice per day daily. The RATIFY study (ClinicalTrials.gov number: NCT00651261) was

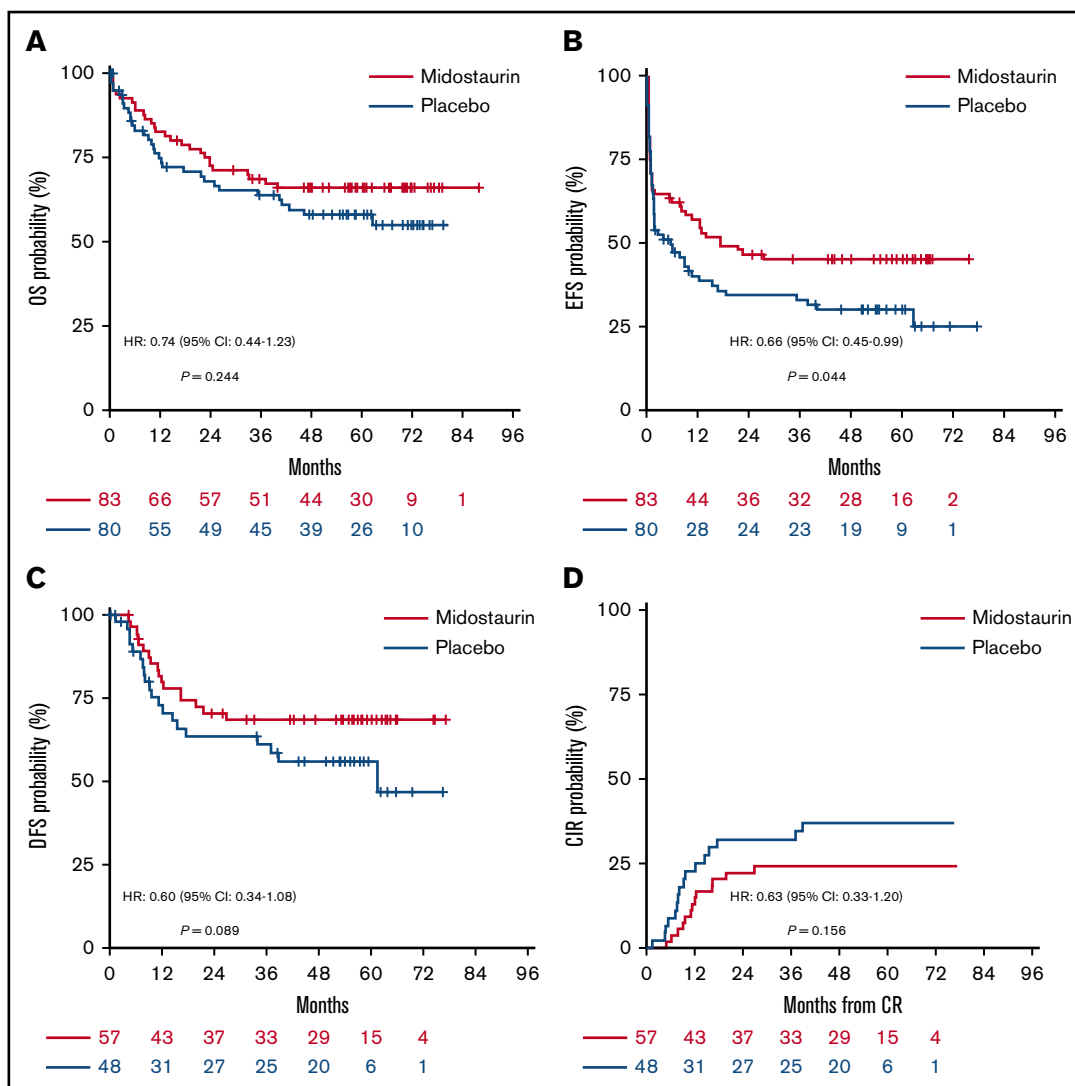


Figure 1. Survival in patients with *FLT3*-TKD^{mut} AML, according to treatment arm (n = 163 patients). HR and 95% CI are shown. OS (A), EFS (B), DFS (C), CIR (D).

approved by the ethics committees of all participating centers. Patients gave written informed consent for participating in the study.

FLT3-TKD mutations were detected by polymerase chain reaction (PCR) followed by *EcoRV* digestion and capillary electrophoresis.¹⁸ A TKD mutation-to-wild-type signal ratio of 0.05 was required for positivity.

A total of 162 patients with a *FLT3*-TKD^{mut} AML were included in the original RATIFY report,¹⁷ on the basis of randomization stratum, whereas 163 patients are included in this analysis, on the basis of the actual *FLT3*-TKD mutation status. None of the cases had a concomitant *FLT3*-ITD as tested by capillary electrophoresis. A total of 134 patients gave informed consent for additional *NPM1* mutation analysis and are considered in this report. *NPM1* mutation status was analyzed at the participating reference laboratories, according to published methods, and after inter-laboratory crossvalidation procedures. Analysis of PCR products allowed us to distinguish between wild-type (WT) (236 bp) and mutated *NPM1* (*NPM1*^{mut}), which is characterized by an insertion of 4 nucleotides.^{7,19,20} Conventional karyotyping for recurrent

translocations was performed in patients at the time of initial diagnosis.

Statistical analysis

Demographic and baseline data including disease characteristics were summarized descriptively by treatment group. Categorical data are presented as frequencies and percentages. For continuous data, median and interquartile range are shown.

Complete remission (CR) was defined by standard criteria,⁸ and assessed after 1 to 2 induction cycles. Definitions of OS and event-free survival (EFS) were as recommended,⁸ and were calculated from the date of randomization. Disease-free survival (DFS) and cumulative incidence of relapse (CIR) were calculated from the date of CR. Additional sensitivity analyses were performed censoring OS, EFS, and DFS at the time of transplantation. The median follow-up for survival and the distribution of time-to-event endpoints (OS, DFS, and EFS) were estimated using the Kaplan-Meier method.²¹ Differences between the groups were analyzed using 2-sided log-rank tests. Kaplan-Meier rates at 5 years with 95% confidence

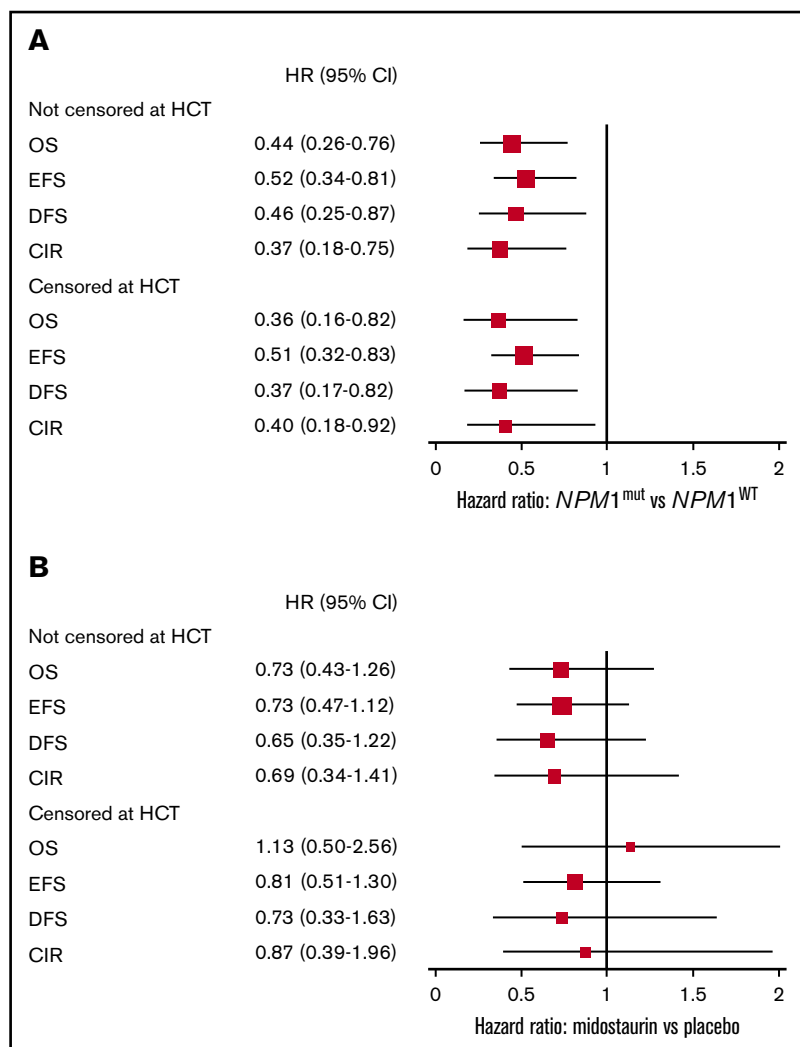


Figure 2. Estimated prognostic effect of $NPM1$ status and treatment effect. The figures show HR and 95% CI, censored at allogeneic HCT or not, for 134 $FLT3$ -TKD mutated patients, grouped for $NPM1$ mutation status (mutated vs WT) (A) and according to treatment (midostaurin vs placebo) (B). The size of the boxes indicates the precision of the estimates.

interval (CI) are presented. Hazard ratios (HR) with 95% CI were estimated using the Cox proportional hazards model. CIR was evaluated using the cumulative incidence method, considering death in CR as a competing risk. The aforementioned analyses were repeatedly performed to evaluate treatment effect (midostaurin vs placebo) and the prognostic effect of $NPM1$ mutation status (mutated vs WT). To examine the effect of allogeneic hematopoietic cell transplantation (HCT), univariable and multivariable Cox models with allogeneic HCT as a time-dependent variable were applied.²¹

Multivariable analyses for OS and EFS were performed using the Cox model, and included the following covariates: $NPM1$ vs CBF rearrangements vs other genetic alterations, treatment, sex, age (numeric variable), white blood cell counts (numeric variable), cytogenetics (normal karyotype vs CBF or vs other abnormalities), and allogeneic HCT as time-dependent covariate.

Results

Patient demographics and baseline characteristics

In total, 717 patients with AML and a $FLT3$ mutation were enrolled in the RATIFY trial.¹⁷ Of these, 163 were $FLT3$ -TKD^{mut}. Table 1 shows baseline characteristics of the 163 patients. Median $FLT3$ -TKD AR

was 0.44. Of 135 patients with available cytogenetic data, 74 (55%) had a normal karyotype and 20 (15%) had a CBF-AML, including 11 patients with $inv(16)$ and 9 with $t(8;21)$.

$NPM1$ mutation status was available for 134 patients: 79 (59%) had $NPM1^{mut}$, and 55 (41%) had $NPM1^{WT}$. Patient characteristics according to $NPM1$ mutation status are shown in supplemental Table 1. The median white blood cell count was higher in patients with $NPM1^{mut}$ (median, $34.1 \times 10^9/L$; range, $16.5 \times 10^9/L$ to $76.0 \times 10^9/L$) than in those with $NPM1^{WT}$ (median, $15.5 \times 10^9/L$; range, $8.5 \times 10^9/L$ to $34.9 \times 10^9/L$; $P = .003$). As expected, normal karyotype was significantly more frequent in patients with $NPM1^{mut}$ (90.5% vs 20.0%; $P < .001$), whereas 28.0% percent of patients with $NPM1^{WT}$ had a CBF-AML (supplemental Table 1).

Outcome analysis

The median follow-up for the $FLT3$ -TKD^{mut} patient cohort was 60.7 months (95% CI, 55.0-70.8 months; $n = 163$ patients). After induction chemotherapy, CR rates were similar in patients treated with midostaurin and in those treated with placebo (68.6% vs 60.0%; $P = .321$) (Table 1). Similarly, 5-year OS rates were comparable between the 2 treatment arms (65.9% vs 58.0%; HR, 0.74; 95% CI, 0.44-1.23; $P = .244$; Figure 1A). However, the 5-year EFS rate was

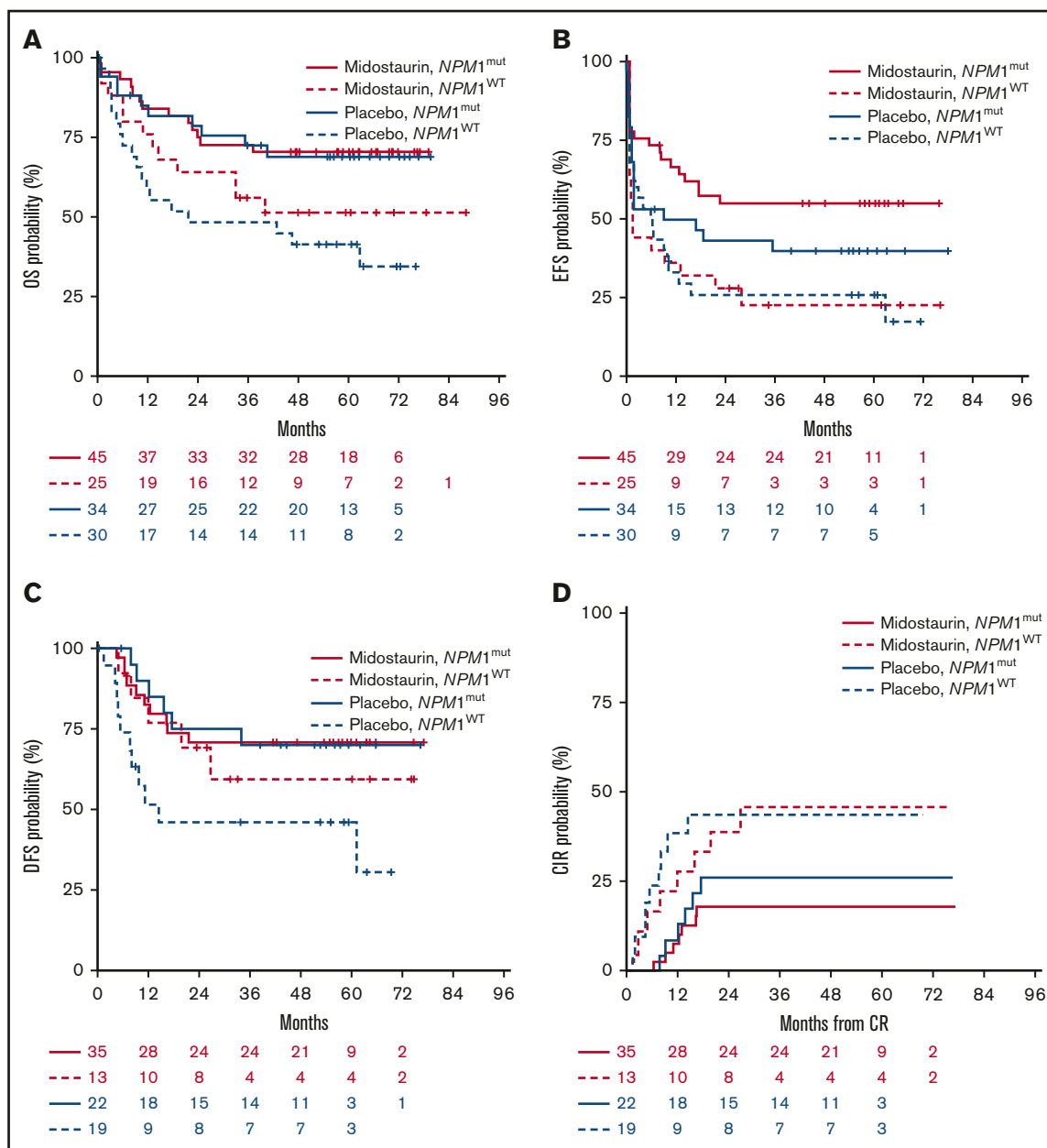


Figure 3. Survival outcomes (not censored at allogeneic HCT) by *NPM1* mutation status and treatment arm ($n = 134$ patients). OS (A), EFS (B), DFS (C), CIR (D).

significantly higher in patients treated with midostaurin than in those treated with placebo (45.2% vs 30.1%; HR, 0.66; 95% CI, 0.45-0.99; $P = .044$), and there was a trend toward improved DFS at

5 years (67.3% vs 53.4%; HR, 0.60; 95% CI, 0.34-1.08; $P = .089$) (Figure 1B-C), as well as a trend for reduced CIR (26.5% with midostaurin vs 38.5% with placebo; HR, 0.63; 95% CI, 0.33-1.20;

Table 2. Five-year survival outcomes by *NPM1* mutation status ($n = 134$ patients)

	Overall			Censored at HCT in 1st CR		
	<i>NPM1</i> ^{mut} ($n = 79$)	<i>NPM1</i> ^{WT} ($n = 55$)	<i>P</i>	<i>NPM1</i> ^{mut} ($n = 79$)	<i>NPM1</i> ^{WT} ($n = 55$)	<i>P</i>
OS, estimates at 5 y (95% CI), %	69.8 (60.2-80.9)	45.7 (34.1-61.3)	.003	82.6 (72.9-93.5)	56.8 (38.0-84.8)	.015
EFS, estimates at 5 y (95% CI), %	48.4 (38.4-61)	24.6 (15.3-39.4)	.003	50.7 (39.7-64.6)	26.4 (15.3-45.5)	.007
DFS, estimates at 5 y (95% CI), %	69.5 (58.9-81.9)	50.3 (36.6-69.1)	.001	70.5 (57.8-86.1)	44.9 (27.2-74.1)	.015
CIR, estimates at 5 y (95% CI), %	21.0 (20.1-21.9)	44.5 (43.1-45.9)	.006	22.0 (21.3-22.6)	34.8 (33.2-36.3)	.030

Significant differences are indicated in bold.

Table 3. Five-year survival outcomes in patients with a *FLT3*-TKD mutation, by *NPM1* mutation status and treatment

	<i>NPM1</i> ^{mut} (n = 79)			<i>NPM1</i> ^{WT} (n = 55)		
	Placebo	Midostaurin	HR (95% CI)	Placebo	Midostaurin	HR (95% CI)
OS						
n	34	45		30	25	
Estimates at 5 y (95% CI), %	68.9 (54.5-87.0)	70.5 (58.2-85.3)	0.94 (0.41-2.15)	41.4 (26.8-63.8)	51.3 (34.9-75.6)	0.70 (0.34-1.46)
EFS						
n	34	45		30	25	
Estimates at 5 y (95% CI), %	39.7 (26.0-60.7)	55.0 (42.1-71.8)	0.63 (0.34-1.18)	25.7 (13.8-47.8)	22.4 (10.4-48.2)	1.04 (0.57-1.92)
DFS						
n	18	34		18	11	
Estimates at 5 y (95% CI), %	65.3 (48.5-88.0)	71.9 (59.2-87.5)	0.81 (0.32-2.01)	46.4 (29.1-74.2)	54.3 (35.2-83.9)	0.64 (0.26-1.57)
CIR						
n	18	34		18	11	
Estimates at 5 y (95% CI), %	26.1 (24.4-27.9)	17.9 (17.2-18.7)	0.67 (0.23-1.94)	43.7 (41.1-46.2)	45.7 (42.6-48.8)	0.93 (0.37-2.34)

Estimated Kaplan-Meier rates at 5 years (with 95% CI) and corresponding HR. This analysis was not censored at allogeneic hematopoietic cell transplant. HR < 1 indicates a benefit with midostaurin.

$P = .156$; Figure 1D). *FLT3*-TKD AR, grouping patients according to the median value (<0.4 vs ≥ 0.4), did not play a significant prognostic role for survival or CIR (data not shown).

We then analyzed the activity of midostaurin in 134 patients with a TKD mutation and available *NPM1* mutation status (supplemental Table 1). Patients with *FLT3*-TKD/*NPM1*^{mut} represented a prognostically favorable subgroup, with a significant survival advantage in all endpoints (Table 2; Figure 2A) compared with *NPM1*^{WT} patients. In patients with *NPM1*^{mut}, the OS rate was 69.8%, the EFS rate was 48.4%, the DFS rate was 69.5%, and the CIR rate was 21.0% at 5 years. The corresponding values in patients with *NPM1*^{WT} were 45.7%, 24.6%, 50.3%, and 44.5% (OS, $P = .003$; EFS, $P = .003$; DFS, $P = .001$; CIR, $P = .006$). Relative to treatment, there were no differences in CR rates between patients with *NPM1*^{mut} (77.8% with midostaurin, vs 64.7% with placebo; $P = .303$), and those with *NPM1*^{WT} (52.0% vs 63.3%, respectively; $P = .566$). Figure 3 shows survival outcomes in 134 patients according to *NPM1* mutation status and treatment arm. The impact of midostaurin on all survival endpoints was not significant (Figures 2B and 3; Table 3).

Allogeneic HCT in first CR was performed in 51 patients, including 28 of 79 with *NPM1*^{mut} (35.4%) and 23 of 55 with *NPM1*^{WT} (41.8%, $P = .571$). In the sensitivity analyses, patients were censored at HCT, confirming significantly improved outcomes for all survival endpoints in the *NPM1*^{mut} group across the 2 treatment arms, with survival rates exceeding 80% at 5 years (Figure 2; Table 2).

Multivariable analyses validated the independent prognostic role of the *NPM1*^{mut} genotype in OS ($P = .0007$) and EFS ($P = .0005$) and of CBF rearrangements (OS, $P = .0180$; EFS, $P = .0037$), whereas midostaurin treatment had no prognostic impact on OS and EFS (Table 4). Other factors analyzed (age, sex, white blood cell count at baseline, HCT as time-dependent covariate) did not reach significance in the Cox model. A prior history of myelodysplastic syndrome, extramedullary disease, and Eastern Cooperative Oncology Group performance status of 2 were not included in the analysis, because of the low numbers of patients with these

characteristics. Figure 4 shows the Kaplan-Meier estimates for OS, EFS, DFS, and CIR, grouping patients according to *NPM1*^{mut}, CBF rearrangements, and other genotypes.

Discussion

This post hoc analysis from the RATIFY trial confirms the advantage in EFS and DFS of the addition of midostaurin to standard chemotherapy in patients with a *FLT3*-TKD^{mut} AML. At a median follow-up of 5 years, the EFS rate was 45% with midostaurin vs 30% with placebo, whereas the DFS rate was 67% vs 53%, respectively. However, this did not translate into improved OS. The ability to salvage patients after relapse in this chemoresponsive group could explain the discrepancy between the benefit in EFS and the lack of survival benefit. Also, allogeneic HCT performed in first CR in about 38% of patients and midostaurin maintenance may be confounding factors in this setting and will be the subject of

Table 4. Multivariable analysis for survival

	OS			EFS*		
	P	HR	95% CI	P	HR	95% CI
Age†	.969	1.001	0.972-1.030	.683	1.005	0.983-1.027
Male vs female	.498	0.809	0.440-1.491	.095	0.666	0.413-1.074
WBC count, $\times 10^9/L^\ddagger$.827	1.001	0.993-1.009	.246	0.996	0.989-1.003
<i>NPM1</i> ^{mut} vs other genotypes	.0007	0.282	0.135-0.586	.0005	0.343	0.189-0.624
CBF vs other genotypes	.0180	0.253	0.081-0.790	.0037	0.268	0.110-0.652
Midostaurin vs placebo	.6212	0.859	0.470-1.569	.7693	0.930	0.570-1.515
Allogeneic HCT in first CR as a time-dependent covariate	.9282	0.968	0.476-1.969	.3652	0.639	0.243-1.683

FLT3-ITD mutation status was available for 107 patients; 10 were *NPM1*^{mut}/*FLT3*-ITD^{mut} and 11 were *NPM1*^{WT}/*FLT3*-ITD^{mut}. Significant differences are indicated in bold.

*EFS, considering complete remission within 1 or 2 induction cycles (n = 134).

†Age and WBC were considered as continuous variables.

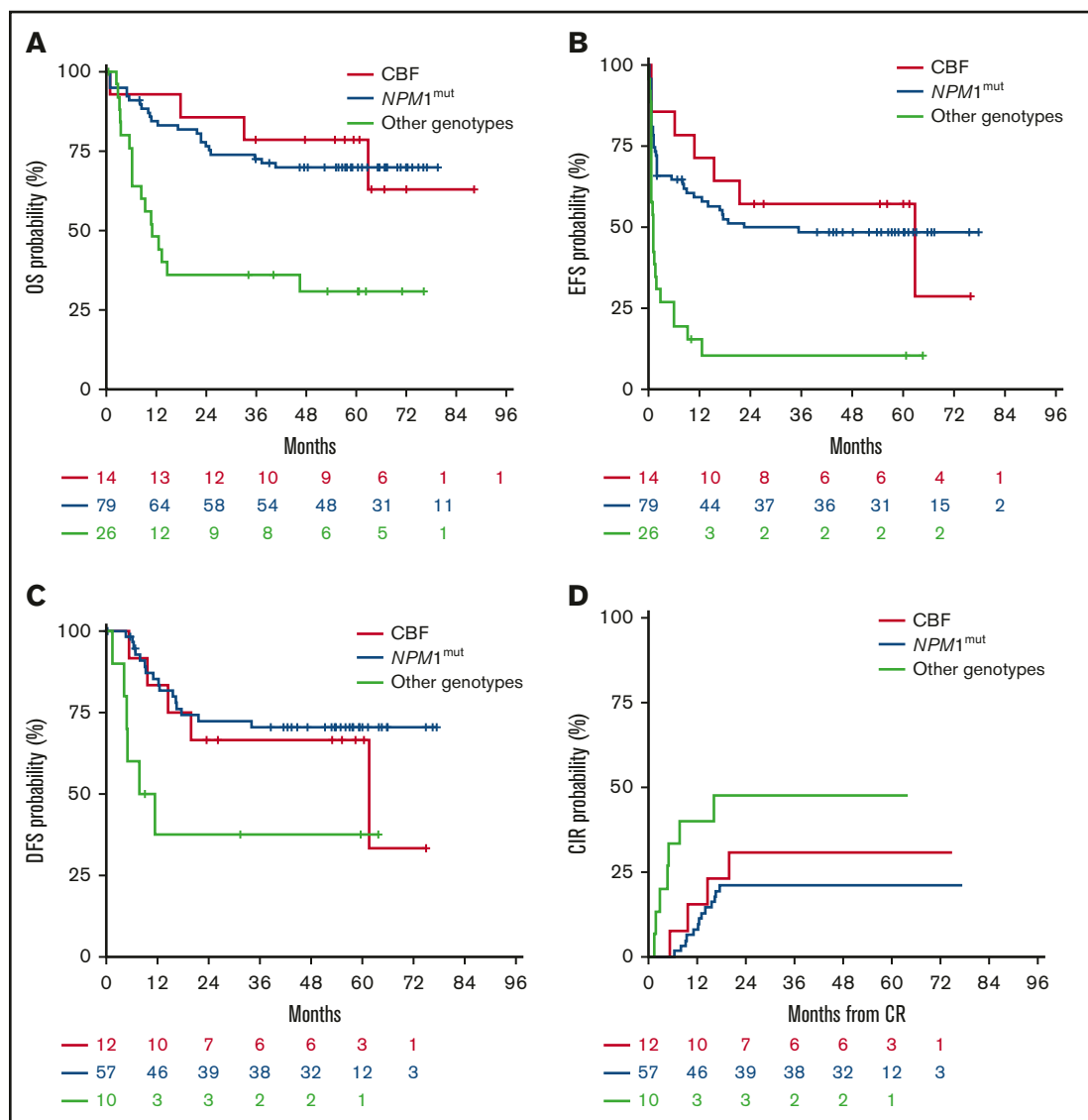


Figure 4. Survival outcomes, according to CBF rearrangements (n = 20 patients), *NPM1*^{mut} (n = 79 patients), and other genotypes (n = 26 patients). Other genotypes includes patients with intermediate (n = 11) and adverse karyotypes (n = 15 patients). OS (A), EFS (B), DFS (C), CIR (D).

a separate analysis. Results of the AMLSG 16-10 trial showed that the addition of midostaurin as single-agent maintenance after allogeneic HCT or after high-dose cytarabine improved EFS, compared with a historical control patient cohort that received similar treatment combinations without tyrosine-kinase inhibitor maintenance.²²

NPM1 mutations are a known favorable prognostic factor in AML and are associated with *FLT3*-ITD mutations in ~50% of patients. *NPM1* mutations mitigate the negative prognostic effect of *FLT3*-ITD mutations, and, according to the 2017 European LeukemiaNet (ELN) recommendations, these 2 mutations when combined define favorable- or intermediate-risk AML, depending on low (<0.5) or high (≥0.5) ITD AR.⁸ The prognostic role of *FLT3*-TKD mutations is established less clearly and appears to be diminished relative to karyotype or concomitant mutations of other genes.^{4,10-15} Actually, the favorable impact of the combined *NPM1*^{mut}/*FLT3*-TKD or

CEBPA^{mut}/*FLT3*-TKD genotypes has been previously reported in a study of 3082 patients with newly diagnosed AML treated with conventional chemotherapy, with the strongest effects seen in de novo and normal karyotype AML, after excluding *FLT3*-ITD-positive patients.²³ These data were confirmed by a retrospective study conducted in France in 126 patients with newly diagnosed AML, in which patients with the *NPM1*^{mut}/*FLT3*-TKD^{mut} profile had a high survival probability overall, and after censoring at the time of HCT.²⁴

The results from our study confirm the favorable prognostic impact of the *NPM1*^{mut}/*FLT3*-TKD genotype, with a 5-year OS rate of ~70%. In this study, we identified another favorable prognostic subgroup, represented by patients with a CBF-AML exhibiting a *FLT3*-TKD mutation. Following AML with an *NPM1* mutation, CBF-AML was the second most frequent disease entity, representing 28% of *NPM1*^{wt} patients. In the multivariable analysis, both *NPM1*^{mut}/*FLT3*-TKD and CBF/*FLT3*-TKD genotypes were independent prognostic

factors for prolonged survival when including allogeneic HCT performed in first CR as a time-dependent covariate, whereas treatment arm did not play a significant role.

Although the trial was not designed to compare the role of different postconsolidation strategies and did not include assessment of measurable residual disease, in patients with a molecular marker, allogeneic HCT could reasonably be considered in cases with persistent or increasing measurable residual disease levels, as previously proposed.¹⁵ Treatment decisions in these situations can rely on the quantification of *NPM1*^{mut} transcripts by quantitative PCR, which has been shown to consistently predict outcome, with persistent negativity being associated with prolonged remission status and cure.^{25,26} Similarly, in the context of CBF-AML, levels of *RUNX1-RUNX1T1* and *CBFB-MYH11* transcripts, overall or as log reduction in transcript number after consolidation therapy, were shown to be predictive of relapse.^{27,28}

Evaluation of other disease features may further guide treatment stratification, as the characterization mutations of the *CEBPA* gene, which have been reported in 7% to 8% of patients with TKD mutations.^{4,15,23,29} Data deriving from the ongoing genomic profiling of *FLT3*-mutated AML included in the RATIFY trial may further improve the stratification model.

Relative to treatment, midostaurin had no significant impact on achievement of CR after in the overall group, or in *NPM1*^{mut} patients. Similarly, in the recently published subanalysis of the RATIFY trial, in 318 patients with *NPM1*^{mut}/*FLT3*-ITD mutation grouped according to the 2017 ELN classification, we found that rates of CR were similar and independent of treatment arm in the favorable- and intermediate-risk categories, which include most patients with *NPM1* mutations.^{6,7} Neither *FLT3*-ITD nor *FLT3*-TKD mutations had an impact on achievement of CR in a large patient series treated with conventional chemotherapy followed by allogeneic HCT in about 20% of the patients.³⁰

The major limitation of our analysis was the relatively low number of patients with a *FLT3*-TKD mutation derived from the RATIFY trial, which was not powered for subgroup analyses. In this patient subgroup, midostaurin showed a beneficial effect in terms of EFS. Patients with combined *NPM1*^{mut}/*FLT3*-TKD and CBF/*FLT3*-TKD genotypes were identified as prognostically favorable patient subgroups, with an overall significant survival advantage, when compared with patients with *NPM1*^{WT} AML or to those with other karyotype abnormalities.

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Authorship

Contribution: M.T.V., H.D., C.D.B., and F.L.-C. analyzed data and wrote the paper; R.A.L., D.J., G.M., T.P., J.K., M.H., S.L., J.N., S.M.G., A.W., A.W., J.S., M.A.S., J.M.B., T.M.d.W., J.H.J., D.N., F.R.A., B.C.M., M.S.T., R.F.S., A.G., S.A., G.E., J.B., C.T., K.D., and R.M.S. performed research and reviewed the paper; and Y.C., Y.M.C., C.P., L.D., and A.P. analyzed data and reviewed the paper.

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