

ORIGINAL ARTICLE

Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a *FLT3* Mutation

R.M. Stone, S.J. Mandrekar, B.L. Sanford, K. Laumann, S. Geyer, C.D. Bloomfield, C. Thiede, T.W. Prior, K. Döhner, G. Marcucci, F. Lo-Coco, R.B. Klisovic, A. Wei, J. Sierra, M.A. Sanz, J.M. Brandwein, T. de Witte, D. Niederwieser, F.R. Appelbaum, B.C. Medeiros, M.S. Tallman, J. Krauter, R.F. Schlenk, A. Ganser, H. Serve, G. Ehninger, S. Amadori, R.A. Larson, and H. Döhner

ABSTRACT

BACKGROUND

Patients with acute myeloid leukemia (AML) and a *FLT3* mutation have poor outcomes. We conducted a phase 3 trial to determine whether the addition of midostaurin — an oral multitargeted kinase inhibitor that is active in patients with a *FLT3* mutation — to standard chemotherapy would prolong overall survival in this population.

METHODS

We screened 3277 patients, 18 to 59 years of age, who had newly diagnosed AML for *FLT3* mutations. Patients were randomly assigned to receive standard chemotherapy (induction therapy with daunorubicin and cytarabine and consolidation therapy with high-dose cytarabine) plus either midostaurin or placebo; those who were in remission after consolidation therapy entered a maintenance phase in which they received either midostaurin or placebo. Randomization was stratified according to subtype of *FLT3* mutation: point mutation in the tyrosine kinase domain (TKD) or internal tandem duplication (ITD) mutation with either a high ratio (>0.7) or a low ratio (0.05 to 0.7) of mutant to wild-type alleles (ITD [high] and ITD [low], respectively). Allogeneic transplantation was allowed. The primary end point was overall survival.

RESULTS

A total of 717 patients underwent randomization; 360 were assigned to the midostaurin group, and 357 to the placebo group. The *FLT3* subtype was ITD (high) in 214 patients, ITD (low) in 341 patients, and TKD in 162 patients. The treatment groups were well balanced with respect to age, race, *FLT3* subtype, cytogenetic risk, and blood counts but not with respect to sex (51.7% in the midostaurin group vs. 59.4% in the placebo group were women, $P=0.04$). Overall survival was significantly longer in the midostaurin group than in the placebo group (hazard ratio for death, 0.78; one-sided $P=0.009$), as was event-free survival (hazard ratio for event or death, 0.78; one-sided $P=0.002$). In both the primary analysis and an analysis in which data for patients who underwent transplantation were censored, the benefit of midostaurin was consistent across all *FLT3* subtypes. The rate of severe adverse events was similar in the two groups.

CONCLUSIONS

The addition of the multitargeted kinase inhibitor midostaurin to standard chemotherapy significantly prolonged overall and event-free survival among patients with AML and a *FLT3* mutation. (Funded by the National Cancer Institute and Novartis; ClinicalTrials.gov number, NCT00651261.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Stone at the Dana-Farber Cancer Institute, 450 Brookline Ave., D-2053, Boston, MA 02115, or at richard_stone@dfci.harvard.edu.

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ACUTE MYELOID LEUKEMIA (AML) IS A heterogeneous disease that remains challenging to treat because of patient factors (age and coexisting diseases) and intrinsic biological factors.¹ Cytogenetic² and mutational³ data are used to divide patients into subgroups defined according to prognostic factors⁴⁻⁷ and factors that dictate whether allogeneic hematopoietic stem-cell transplantation should be performed during an initial remission.⁸ Mutations in the *fms*-related tyrosine kinase 3 gene (*FLT3*) are present in 30% of adults with newly diagnosed AML.⁹ Approximately three quarters of these patients have a *FLT3* internal tandem duplication mutation (ITD subtype), which results in duplication of between 3 and more than 100 amino acids located in the juxtamembrane region; ITD mutations are associated with a poor prognosis owing to a high relapse rate,¹⁰ particularly when there is a high ratio of mutant to wild-type *FLT3* alleles.^{11,12} Approximately 8% of patients with newly diagnosed AML have a *FLT3* point mutation in the tyrosine kinase domain (TKD subtype); the effect of TKD mutations on prognosis is uncertain.^{13,14} Both subtypes of *FLT3* mutation yield proteins that spontaneously dimerize (bypassing ligand-mediated activation), cause factor-independent growth when they are transfected into murine cell lines, and lead to a fatal myeloproliferative neoplasm in a mouse model.^{15,16} Small-molecule inhibitors of activated *FLT3* specifically inhibit proliferation of leukemia cells in preclinical models. However, clinical trials investigating the use of single-agent, first-generation *FLT3* inhibitors in patients with relapsed–refractory AML and a *FLT3* mutation showed transient reductions in the number of blasts in blood, marrow, or both but rarely showed complete remission.^{17,18} More specific *FLT3* inhibitors, such as quizartinib¹⁹ and gilteritinib,²⁰ yielded higher response rates than the first-generation inhibitors among patients with advanced disease.

Midostaurin, a multitargeted kinase inhibitor, was originally developed as a protein kinase C inhibitor for treatment of patients with solid tumors.²¹ On the basis of preclinical studies, which showed synergy between chemotherapy and midostaurin, a phase 1b study involving patients with newly diagnosed AML was conducted; the study established that oral midostaurin could be administered safely (with an acceptable side-effect profile) at a dose of 50 mg twice daily for 14 days,

beginning on the eighth day after the start of treatment during courses of induction and consolidation chemotherapy, and that this regimen had encouraging efficacy in patients with a *FLT3* mutation.²²

To determine the effect of the addition of midostaurin to standard chemotherapy in patients with AML and a *FLT3* mutation, we conducted the Cancer and Leukemia Group B (CALGB) 10603 (RATIFY) trial, a multi-institutional, multinational, randomized, double-blind, placebo-controlled trial. The CALGB is now part of the Alliance for Clinical Trials in Oncology.

METHODS

PATIENTS

Patients 18 to 59 years of age who had newly diagnosed AML and had not previously received antineoplastic therapy (except for limited urgent treatment for the current disease) were screened for *FLT3* mutations. The patients provided written informed consent that allowed preregistration, and then a diagnostic bone marrow sample was obtained and submitted to one of nine academic laboratories for testing for *FLT3* mutations.

Patients were registered in the trial if they had a *FLT3* mutation and met the following other eligibility criteria: a diagnosis of AML (excluding acute promyelocytic leukemia) that was not therapy-related, a bilirubin level of less than 2.5 times the upper limit of the normal range, and the absence of other major coexisting illnesses. Hydroxyurea therapy was allowed for 5 days before the start of the trial therapy.

SCREENING FOR *FLT3* MUTATIONS

The presence of a *FLT3* mutation of either the TKD subtype or the ITD subtype was reported to investigators within 48 hours after the sample was received in the laboratory. A ratio of mutant to wild-type alleles of at least 0.05 indicated that the patient was positive for *FLT3*. (For further details about assay validation and performance, see the Supplementary Appendix, available with the full text of this article at NEJM.org.)

RANDOMIZATION AND TREATMENTS

Enrolled patients were randomly assigned, in a 1:1 ratio, to receive standard chemotherapy plus either midostaurin or placebo. Randomization was performed with a block size of 6 and was

stratified according to the subtype of *FLT3* mutation: TKD, or ITD with either a high ratio (>0.7) or a low ratio (0.05 to 0.7) of mutant to wild-type alleles (ITD [high] and ITD [low], respectively).

Therapy consisted of induction therapy with daunorubicin (at a dose of 60 mg per square meter of body-surface area per day, administered by rapid intravenous injection on days 1, 2, and 3) and cytarabine (at a dose of 200 mg per square meter, administered by continuous intravenous infusion on days 1 through 7). Midostaurin or placebo was administered in a double-blind fashion, at a dose of 50 mg orally twice daily, on days 8 through 21. Midostaurin or placebo was not administered if the patient had a corrected QT interval above 500 msec or a grade 3 or 4 non-hematologic toxic effect (for further details, see the Supplementary Appendix). A missed dose of midostaurin or placebo was not made up. A bone marrow examination was to be performed on day 21. If there was definitive evidence of clinically significant residual leukemia, a second cycle of induction therapy that was identical to the first, including midostaurin or placebo, was administered.

Patients who achieved complete remission after induction therapy received four 28-day cycles of consolidation therapy with high-dose cytarabine (at a dose of 3000 mg per square meter, administered over a period of 3 hours every 12 hours on days 1, 3, and 5). Midostaurin or placebo was administered at a dose of 50 mg orally twice daily on days 8 through 21. Patients who remained in remission after completion of consolidation therapy entered a maintenance phase in which they received midostaurin or placebo, administered at a dose of 50 mg orally twice daily, for twelve 28-day cycles. Complete remission was defined as the presence of less than 5% blasts in the marrow or extramedullary leukemia, an absolute neutrophil count of more than 1000 per microliter, a platelet count of more than 100,000 per microliter, and the absence of blasts in the peripheral blood; in addition, per protocol, the complete remission had to have occurred by day 60. Transplantation was not mandated in the protocol but was performed at the discretion of the investigator.

TRIAL DESIGN AND OVERSIGHT

The trial was conducted at 225 sites in 17 countries. The institutional review board at each participating center reviewed and approved the trial

protocol, available at NEJM.org. The trial was conducted in accordance with the provisions of the Declaration of Helsinki.

The trial was funded at North American sites by the Cancer Therapy Evaluation Program of the National Cancer Institute and at non-North American sites (i.e., sites in Europe and Australia) by Novartis. The trial was designed by the CALGB and approved by the Cancer Therapy Evaluation Program and Novartis. The data were gathered by the investigators, and case-report forms were sent to the Alliance Statistics and Data Center for data analysis. Novartis performed monitoring of data at the non-North American sites and performed monitoring of data in a limited fashion at the North American sites; the CALGB performed audits at the North American sites (not specifically for this trial). Data collection and monitoring procedures are fully described in the Supplementary Appendix. The investigators had full access to the data. The authors vouch for the accuracy and completeness of the data and the fidelity of the study to the protocol. The principal investigator reviewed complete case-report forms for 250 patients, in accordance with CALGB policy, and wrote the manuscript without assistance from nonauthors. All the authors made the decision to submit the manuscript for publication.

STATISTICAL ANALYSIS

The primary end point was overall survival, which was defined as the time from randomization to death from any cause. The original enrollment goal was 514 patients with 374 events; however, the trial was expanded to 714 patients in 2010, after the proportion of patients who had undergone allogeneic hematopoietic stem-cell transplantation was higher than expected (anticipated rate of transplantation, 15%; rate observed at the time of amendment, 25%) and the proportion of patients who had a *FLT3* mutation of the TKD subtype was also higher than expected (anticipated rate of TKD mutation, 14%; rate observed at the time of amendment, 26%). Assuming a hazard ratio for death (midostaurin vs. placebo) of 0.71 among patients who did not undergo transplantation and 1.0 among patients who underwent transplantation, we expected that the median overall survival would be 20.9 months in the midostaurin group and 16.3 months in the placebo group, corresponding to an overall hazard ratio for death of 0.78. We estimated that a

total sample size of 714 patients with an expected 509 deaths (with a constant enrollment rate and a follow-up of 19 months after the end of enrollment) would give the trial 84% power, at a one-sided significance level of 0.025 by a stratified log-rank test, to detect a hazard ratio for death of 0.78. One planned interim efficacy analysis was to be performed after 50% of the events (255) had occurred; this analysis took place in May 2012, and the Alliance data and safety monitoring board made the decision to continue the trial. We anticipated that 396 of the 509 deaths would occur in patients who did not undergo transplantation; thus we estimated that an overall survival analysis in which data for patients who underwent transplantation were censored would have 88% power to detect a hazard ratio for death of 0.71. P values for the primary efficacy analyses of overall and event-free survival are one-sided, in accordance with the trial design. Event-free survival was defined as the time from randomization to relapse, death from any cause, or failure to achieve protocol-specified complete remission. Disease-free survival was defined as the time from protocol-specified complete remission to relapse or death from any cause. P values for all secondary analyses are two-sided. Information about the secondary end points, as well as the complete statistical analysis plan and the amended plan to account for a lower-than-expected event rate, are provided in the Supplementary Appendix.

RESULTS

ENROLLMENT AND PATIENT CHARACTERISTICS

Data for this analysis were locked as of March 7, 2016. From May 2008 through October 2011, a total of 3277 patients were preregistered for the trial. Of the 896 patients who had a *FLT3* mutation, 717 were enrolled in the trial. The reasons that patients with AML and a *FLT3* mutation were not enrolled in the trial were not addressed prospectively but probably included patient decision and rapid disease progression. The nonenrollment rate among patients who had a *FLT3* mutation was similar across *FLT3* subtypes, including the ITD (high) subtype. At the time of this analysis, no patients were receiving the trial treatment; the trial treatment was discontinued in the last patient in August 2013.

Patients had high white-cell counts (median,

34,900 per microliter), and 375 of the 547 patients for whom the results of a cytogenetic analysis were available (68.6%) had normal karyotypes. The percentage of patients who had a *FLT3* mutation of the TKD subtype was 22.6%. Patient age, race, white-cell count, and European Leukemia-Net classification were well balanced between the two groups, but sex was not; 51.7% of the midostaurin group versus 59.4% of the placebo group were women ($P=0.04$ by chi-square test) (Table 1).

Figure 1 shows details regarding patient disposition throughout the trial. A second course of induction therapy was administered in 182 patients overall; the administration of a second course was more common among patients in the placebo group than among those in the midostaurin group (occurring in 101 and 81 patients, respectively). In 38 patients, trial treatment was discontinued immediately after a complete remission was achieved, for the following reasons: receipt of alternative therapy (in 11 patients), early disease progression (6), an adverse event (10), patient withdrawal from the trial (8), and other (3). Of these 38 patients, 29 underwent transplantation, including the 11 who received alternative therapy. A maintenance regimen was administered in more patients in the midostaurin group than in the placebo group (120 and 85 patients, respectively) and was administered for the full 12 cycles in 120 patients (69 in the midostaurin group, and 51 in the placebo group).

ADVERSE EVENTS

No unexpected adverse events were observed, although we noted adverse events that are typically associated with intensive chemotherapy for AML. Few significant differences were observed between the two treatment groups in the rates of adverse events of grade 3, 4, or 5 (combined) (Table 2). The rate of grade 3, 4, or 5 anemia was higher in the midostaurin group than in the placebo group (92.7% vs. 87.8%, $P=0.03$), as was the rate of grade 3, 4, or 5 rash (14.1% vs. 7.6%, $P=0.008$). The rate of nausea was higher in the placebo group than in the midostaurin group (9.6% vs. 5.6%, $P=0.05$). Among patients who had a protocol-defined complete remission, the median time to recovery of the absolute neutrophil count (to >500 per microliter) was 26 days (interquartile range, 24 to 30) in the midostaurin group and 26 days (interquartile range, 22 to 31)

Table 1. Baseline Characteristics of the Patients.

Characteristic	All Patients (N = 717)	Midostaurin Group (N = 360)	Placebo Group (N = 357)	P Value*
Age at trial entry — yr				0.22
Median	47.9	47.1	48.6	
Range	18.0–60.9	19.0–59.8	18.0–60.9	
Female sex — no. (%)	398 (55.5)	186 (51.7)	212 (59.4)	0.04
Race — no./total no. (%)†				0.74
White	275/309 (89.0)	147/165 (89.1)	128/144 (88.9)	
Other	34/309 (11.0)	18/165 (10.9)	16/144 (11.1)	
Subtype of <i>FLT3</i> mutation — no. (%)‡				1.00
TKD	162 (22.6)	81 (22.5)	81 (22.7)	
ITD with low allelic ratio	341 (47.6)	171 (47.5)	170 (47.6)	
ITD with high allelic ratio	214 (29.8)	108 (30.0)	106 (29.7)	
Modified European LeukemiaNet classification — no./total no. (%)§				0.15
Favorable	29/547 (5.3)	16/269 (5.9)	13/278 (4.7)	
Normal	375/547 (68.6)	172/269 (63.9)	203/278 (73.0)	
Intermediate II	104/547 (19.0)	59/269 (21.9)	45/278 (16.2)	
Adverse	39/547 (7.1)	22/269 (8.2)	17/278 (6.1)	
White-cell count per μl ¶				0.72
Median	34,900	35,600	33,000	
Range	600–421,800	600–421,800	800–329,800	
Platelet count per μl				0.58
Median	50,000	50,000	50,000	
Range	2000–461,000	2000–461,000	8000–444,000	
Absolute neutrophil count per mm^3 **				0.65
Median	2.2	2.2	2.3	
Range	0–55.9	0–55.9	0–55.9	

* All P values are two-sided. P values for continuous variables were calculated with the use of Kruskal–Wallis tests, and P values for categorical variables were calculated with the use of chi-square tests.

† Race was reported by the patients. Race was not reported for European patients (195 in the midostaurin group, and 213 in the placebo group); the P value excludes these patients.

‡ The subtypes of the *FLT3* mutation are point mutation in the tyrosine kinase domain (TKD) or internal tandem duplication (ITD) mutation with either a high ratio (>0.7) or a low ratio (0.05 to 0.7) of mutant to wild-type alleles.

§ Cytogenetic data according to a modified European LeukemiaNet classification were available for 547 patients (269 in the midostaurin group, and 278 in the placebo group). Data on mutations in the nucleophosmin gene (*NPM1*) or the CCAAT/enhancer binding protein alpha gene (*CEBP α*) are not included. A classification of favorable indicated the presence of t(8;21) and inv(16) or t(16;16), normal the presence of a normal karyotype, intermediate II the presence of cytogenetic abnormalities that were not classified as favorable or adverse, and adverse the presence of adverse-risk cytogenetic abnormalities.

¶ Data were available for 707 patients (355 in the midostaurin group, and 352 in the placebo group).

|| Data were available for 702 patients (351 in the midostaurin group, and 351 in the placebo group).

** Data were available for 673 patients (339 in the midostaurin group, and 334 in the placebo group).

in the placebo group, and the median time to recovery of the platelet count (to >100,000 per microliter) was 21 days (interquartile range, 19 to 23) in the midostaurin group and 21 days (interquartile range, 19 to 24) in the placebo group.

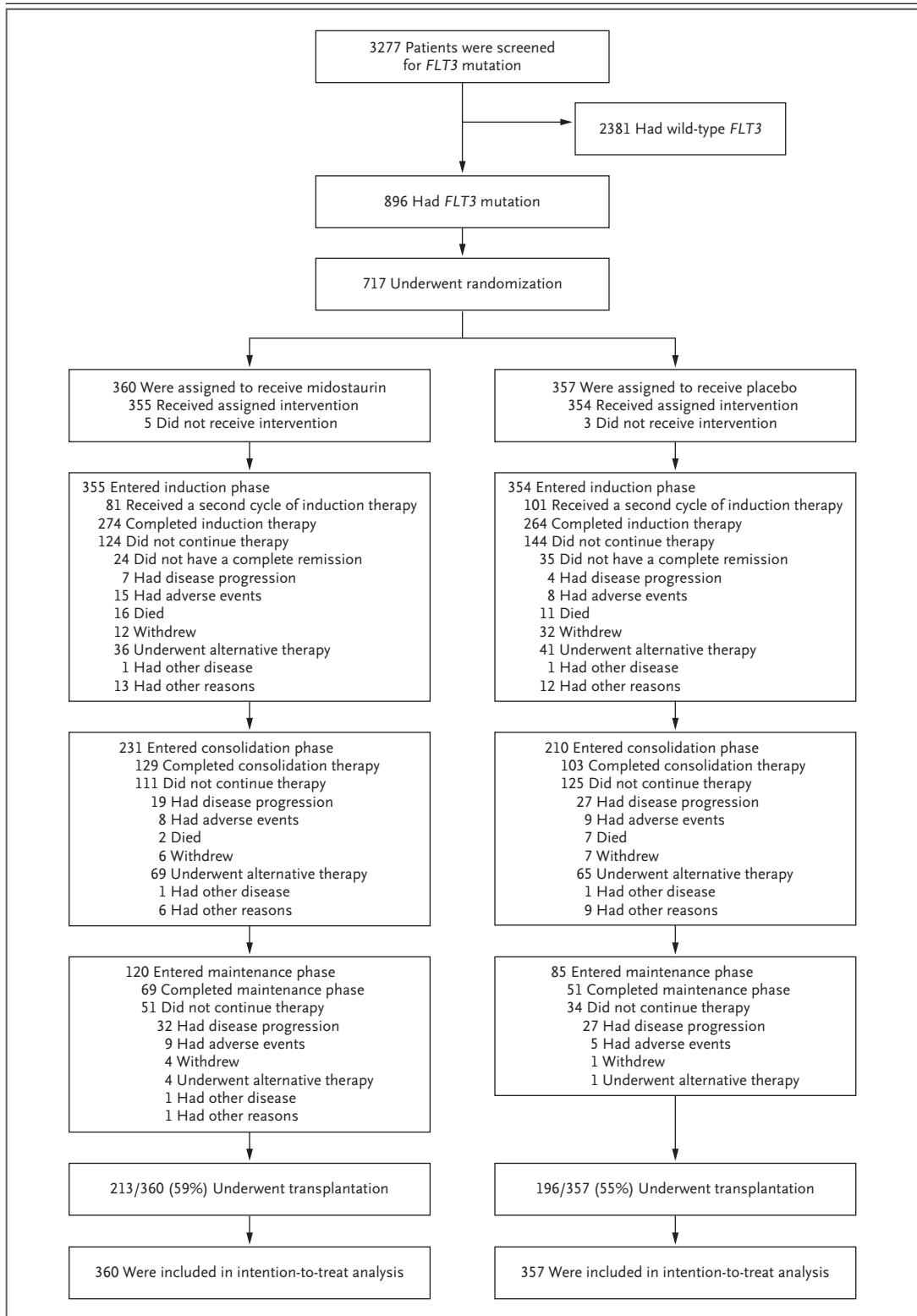


Figure 1. Screening, Randomization, and Treatment.

Four patients who had wild-type *FLT3* at screening were registered in the trial, underwent randomization, and received the trial treatment because of a site error. In accordance with the rules for intention-to-treat analysis, these patients were included in all analyses.

EFFICACY OUTCOMES

Among the 359 patients who survived, the median follow-up was 59 months. Median overall survival was 74.7 months (95% confidence interval [CI], 31.5 to not reached) in the midostaurin group and 25.6 months (95% CI, 18.6 to 42.9) in the placebo group (one-sided $P=0.009$ by stratified log-rank test). The difference between groups in median overall survival may be large because of the inflection points on the Kaplan–Meier curves; however, the corresponding hazard ratio for death of 0.78 (95% CI, 0.63 to 0.96; one-sided $P=0.009$ by stratified score test) more accurately reflects the magnitude of benefit (Fig. 2A). The 4-year overall survival rate was 51.4% in the midostaurin group and 44.3% in the placebo group. Analyses of subgroups according to *FLT3* subtype showed that midostaurin had some benefit, but overall survival did not differ significantly according to trial regimen within each subgroup (Fig. 2B). The rate of complete remission was 58.9% (95% CI, 53.6 to 64.0) in the midostaurin group and 53.5% (95% CI, 48.2 to 58.8) in the placebo group ($P=0.15$ by Fisher's exact test) (Table 3).

For the analysis of event-free survival, 536 events were observed: 298 failures to achieve protocol-specified complete remission, 181 relapses, and 57 deaths without relapse. Median event-free survival was 8.2 months (95% CI, 5.4 to 10.7) in the midostaurin group and 3.0 months (95% CI, 1.9 to 5.9) in the placebo group (one-sided $P=0.002$ by stratified log-rank test). Patients assigned to the midostaurin group had a 21.6% lower likelihood of having an event than patients assigned to the placebo group (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; one-sided $P=0.002$ by stratified score test), with 4-year event-free survival rates of 28.2% in the midostaurin group and 20.6% in the placebo group. The benefit of midostaurin with respect to event-free survival was consistent across the *FLT3* subtypes. Many patients were classified as having an early event because they did not achieve protocol-specified complete remission; 213 (29.7%) never achieved complete remission, and 101 (14.0%) achieved complete remission after more than 60 days of follow-up. Median disease-free survival was 26.7 months (95% CI, 19.4 to not reached) in the midostaurin group and 15.5 months (95% CI, 11.3 to 23.5) in the placebo group ($P=0.01$ by stratified log-rank test), a difference that is due in part to a lower risk of relapse in the midostaurin group. (For more de-

Table 2. Summary of Grade 3, 4, or 5 Adverse Events.

Adverse Event	Midostaurin Group (N=355)	Placebo Group (N=354)	P Value*
	no. of patients (%)		
Hematologic			
Thrombocytopenia	346 (97)	342 (97)	0.52
Neutropenia	338 (95)	339 (96)	0.86
Anemia	329 (93)	311 (88)	0.03
Leukopenia	93 (26)	105 (30)	0.32
Lymphopenia	68 (19)	78 (22)	0.35
Other blood or bone marrow event	1 (<1)	4 (1)	0.22
Bone marrow hypocellularity	0	1 (<1)	0.50
Nonhematologic			
Febrile neutropenia	290 (82)	292 (82)	0.84
Infection	186 (52)	178 (50)	0.60
Lymphopenia	68 (19)	78 (22)	0.35
Diarrhea	56 (16)	54 (15)	0.92
Hypokalemia	49 (14)	60 (17)	0.25
Pain	47 (13)	44 (12)	0.82
Increased alanine aminotransferase	45 (13)	33 (9)	0.19
Rash or desquamation	50 (14)	27 (8)	0.008
Fatigue	32 (9)	37 (10)	0.53
Pneumonitis or pulmonary infiltrates	28 (8)	29 (8)	0.89
Nausea	20 (6)	34 (10)	0.05
Hyponatremia	31 (9)	23 (6)	0.32
Hyperbilirubinemia	25 (7)	28 (8)	0.67
Mucositis or stomatitis	22 (6)	28 (8)	0.38
Hypophosphatemia	19 (5)	29 (8)	0.14
Hypocalcemia	24 (7)	21 (6)	0.76

* P values are two-sided and were calculated with the use of Fisher's exact test.

tails, see Table S1 and Figs. S1 and S2 in the Supplementary Appendix.)

Transplantation was performed at some point during the disease course in 57.0% of the patients; it was performed during the first complete remission in 28.1% of the patients in the midostaurin group and in 22.7% in the placebo group ($P=0.10$ by Fisher's exact test). At North American sites, transplantation was performed in 48.3% of the patients, whereas at non-North American sites, transplantation was performed in 61.3% of the patients ($P=0.001$ by Fisher's exact test). A total of 101 patients in the midostaurin group and 81 patients in the placebo group underwent allogeneic transplantation dur-

Table 3. Summary of Complete Remission.*

Variable	Midostaurin Group (N=360)	Placebo Group (N=357)	P Value†
Protocol-specified complete remission — no. (%)	212 (59)	191 (54)	0.15
Kaplan–Meier estimate of time to complete remission — days			
Median	35	35	
Range	20–60	20–60	

* Complete remission was defined as the presence of less than 5% blasts in the marrow or extramedullary leukemia, an absolute neutrophil count of more than 1000 per microliter, a platelet count of more than 100,000 per microliter, and the absence of blasts in the peripheral blood; in addition, per protocol, complete remission had to occur by day 60.

† P value is two-sided and was calculated with the use of Fisher's exact test.

ing the first complete remission; median overall survival was not reached in either group, with a 95% confidence interval of 69.8 months to not reached in the midostaurin group and 21.8 months to not reached in the placebo group ($P=0.07$ by log-rank test). In addition, among the 227 patients who underwent transplantation after the first complete remission, no treatment effect was observed ($P=0.85$). Because allogeneic transplantation was an important alternative therapy, we performed a sensitivity analysis of the primary end point in which data were censored at the time patients underwent transplantation. In this analysis, there was a 24.3% lower risk of death in the midostaurin group than in the placebo group; the 4-year overall survival rate was 63.7% in the midostaurin group and 55.7% in the placebo group, but the difference between groups was not significant ($P=0.08$ by log-rank test). (For further details, including results of post-hoc analyses, see Tables S2 and S3 and Figs. S3 and S4 in the Supplementary Appendix.)

DISCUSSION

The CALGB 10603 (RATIFY) trial showed that among patients 18 to 59 years of age who had AML and a *FLT3* mutation, the addition of midostaurin to chemotherapy resulted in a 22% lower risk of death than that among patients who received chemotherapy plus placebo. Although the trial was not powered for subgroup analyses, overall survival was longer in the midostaurin group than in the placebo group among patients with a *FLT3* mutation of the TKD subtype and among those with a *FLT3* mutation of the ITD subtype with either a high ratio or a low ratio of mutant to wild-type alleles. Since exposure to the

FLT3 inhibitor was relatively brief (median duration of trial treatment, 3 months), it is probable that the major effect of the inhibitor was the early reduction of disease burden, although other potential explanations are possible. The trial was not designed to determine the independent effect of maintenance therapy. Given that there was a benefit among patients with an ITD mutation with a low allelic burden and that the disease in such patients might be largely due to mutations other than *FLT3*, it is possible that the benefit of midostaurin, which is a multitargeted kinase inhibitor, might lie beyond its ability to inhibit *FLT3*. For example, midostaurin is known to inhibit *KIT* and has activity as a single agent in patients with wild-type *FLT3*²³ and in patients with systemic mastocytosis.²⁴ Treatment with another nonspecific *FLT3* inhibitor, sorafenib, resulted in longer event-free survival (but not overall survival) when it was added to chemotherapy in unselected younger adults with AML.²⁵

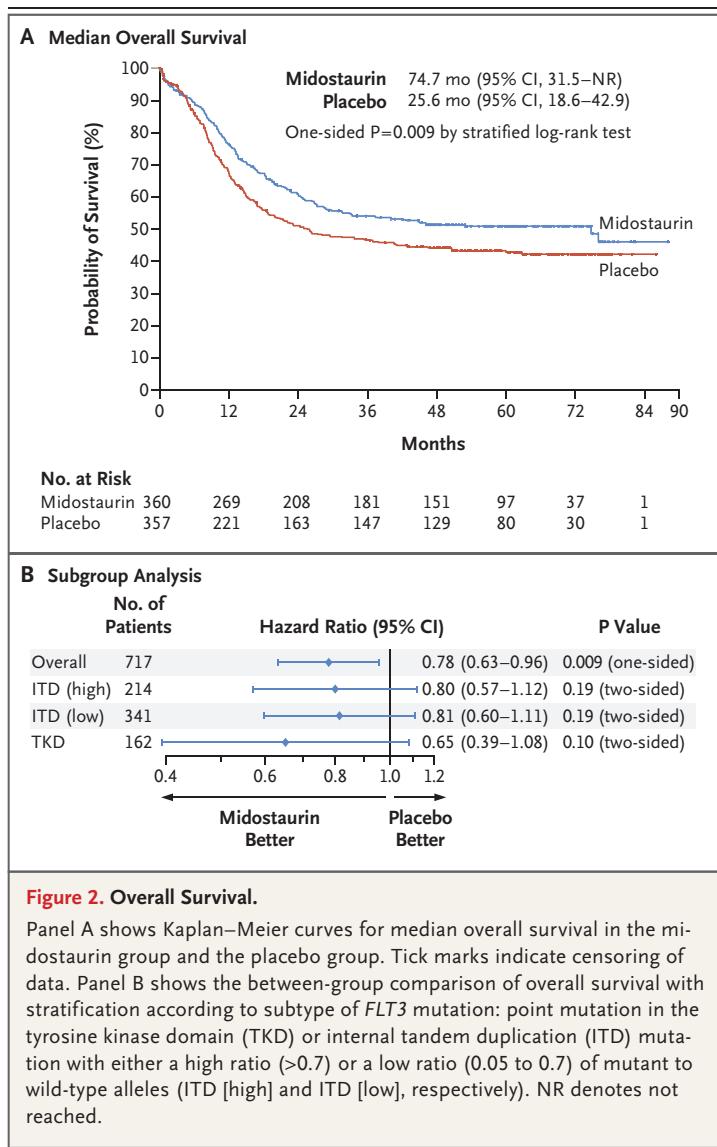
After trial enrollment began, an increasing number of investigators decided, on the basis of data from a retrospective series,⁸ that the best way to treat patients with a *FLT3* mutation of the ITD subtype was to perform allogeneic transplantation during the first remission. This strategy, coupled with the knowledge that the only way to achieve long-term survival in a patient who had a relapse was to perform transplantation,²⁶ probably led to the overall transplantation rate in this trial of 57%. Although rates of transplantation varied by region, transplantation was performed during the first remission in more patients in the midostaurin group than in the placebo group. The trial therapy was discontinued at the time of transplantation. Thus, an early transplantation could have limited exposure to midostau-

rin and thus limited its effect. However, in an analysis of the primary end point (overall survival) that was performed after censoring of data at the time of transplantation, a lower risk was nonetheless observed among patients in the midostaurin group than among those in the placebo group. The benefit of midostaurin was observed among patients who underwent transplantation during the first remission but not among those who underwent transplantation at a later time. After an overt relapse and additional chemotherapy, particularly if that treatment is followed by effective transplantation, there is probably little effect remaining from early randomization to an active drug versus placebo. However, there may be a role for *FLT3* inhibitors after transplantation.²⁷⁻²⁹

The biologic and logistic challenges of this trial are further described in the Supplementary Appendix. Despite these challenges, in this large collaborative effort, we determined that midostaurin, a multitargeted kinase inhibitor, led to improved outcomes among younger adults with AML and a *FLT3* mutation, a population with a poor prognosis that represents approximately one fourth of all patients with AML. It remains unclear whether agents with different target profiles, including more specific *FLT3* inhibitors, would also improve outcomes if they were added to usual therapy for younger adults with AML and a *FLT3* mutation and whether chemotherapy plus midostaurin might be beneficial for older adults or for those with wild-type *FLT3*.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Richard M. Stone, M.D., Sumithra J. Mandrekar, Ph.D., Ben L. Sanford, M.S., Kristina Laumann, B.A., Susan Geyer, Ph.D., Clara D. Bloomfield, M.D., Christian Thiede, M.D., Thomas W. Prior, Ph.D., Konstanze Döhner, M.D., Guido Marcucci, M.D., Francesco Lo-Coco, M.D., Rebecca B. Klisovic, M.D., Andrew Wei, M.B., B.S., Ph.D., Jorge Sierra, M.D., Ph.D., Miguel A. Sanz, M.D., Ph.D., Joseph M. Brandwein, M.D., Theo de Witte, M.D., Dietger Niederwieser, M.D., Frederick R. Appelbaum, M.D., Bruno C. Medeiros, M.D., Martin S. Tallman, M.D., Jürgen Krauter, M.D., Richard F. Schlenk, M.D., Arnold Ganser, M.D., Hubert Serve, M.D., Gerhard Ehninger, M.D., Sergio Amadori, M.D., Richard A. Larson, M.D., and Hartmut Döhner, M.D.

The authors' affiliations are as follows: the Department of Medical Oncology, Dana–Farber Cancer Institute, Boston (R.M.S.); the Division of Biomedical Statistics and Informatics (S.J.M., K.L.) and the Alliance Statistics and Data Center (S.J.M., K.L., S.G.), Mayo Clinic, Rochester, MN; the Alliance Statistics and Data Center, Duke University, Durham, NC (B.L.S.); the Ohio State University Comprehensive Cancer Center, Columbus (S.G., C.D.B., T.W.P., G.M., R.B.K.); Medizinische Klinik und Poliklinik I, Universitätsklinikum Carl Gustav Carus der TU Dresden, Dresden (C.T., G.E.), Department of Internal Medicine III, University Hospital of Ulm, Ulm (K.D., R.F.S., H.D.), Hematology and Oncology, University of Leipzig, Leipzig (D.N.), Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover (J.K., A.G.), and Department of Medicine II, Hematology–Oncology,

Goethe University Hospital Frankfurt, Frankfurt am Main (H.S.) — all in Germany; the Department of Biomedicine and Prevention, University Tor Vergata, Rome (F.L.-C., S.A.); the Department of Clinical Haematology, Alfred Hospital and Monash University, Melbourne, VIC, Australia (A.W.); Hospital de la Santa Creu i Sant Pau, Hematology Department, Autonomous University of Barcelona, Barcelona (J.S.), and Hospital Universitario la Fe, Hematology Department, Department of Medicine, University of Valencia, Valencia (M.A.S.) — both in Spain; the Department of Medical Oncology and Hematology, Princess Margaret Hospital, Toronto (J.M.B.); Radboud Institute Molecular Studies, Radboud University Medical Center, Nijmegen, the Netherlands (T.W.); the Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle (F.R.A.); the Division of Hematology–Oncology, Stanford Comprehensive Cancer Center, Stanford University, Stanford, CA (B.C.M.); the Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York (M.S.T.); and the Department of Medicine, University of Chicago, Chicago (R.A.L.).

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