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ORIGINAL ARTICLE

Maintenance therapy with the *FMS*-like tyrosine kinase 3 inhibitor gilteritinib in patients with *FMS*-like tyrosine kinase 3–internal tandem duplication acute myeloid leukemia: A phase 2 study

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Abstract

Background: The GOSSAMER phase 2 study assessed the *FMS*-like tyrosine kinase 3 (FLT3) inhibitor gilteritinib as maintenance therapy in patients with *FLT3*–internal tandem duplication (*FLT3*-ITD) acute myeloid leukemia (AML) in first complete remission without previous hematopoietic stem cell transplantation (HSCT).

Methods: Patients had to be within 2 months of their last consolidation cycle and have completed the recommended number of cycles per local practice. FLT3 inhibitors were allowed only during induction and/or consolidation. The primary end point was relapse-free survival (RFS). Secondary end points included overall survival (OS), event-free survival, and measurable residual disease (MRD).

This study was presented in part as a poster presentation at the Annual Meeting of the American Association for Cancer Research; April 8–13, 2022; New Orleans, Louisiana.

This study was presented in part as an oral presentation at the Annual Meeting of the Japanese Society of Hematology; October 13–15, 2023; Tokyo, Japan.

Results: In total, 98 patients were randomized (gilteritinib, $n = 63$; placebo, $n = 35$). RFS was not significantly different between the arms (hazard ratio, 0.74; 95% confidence interval, 0.41–1.34; $p = .16$). RFS rates for the gilteritinib and placebo arms were 68.5% and 55.3% at 1 year, 51.8% and 44.9% at 2 years, and 41.2% and 40.8% at 3 years, respectively. OS was not significantly different between the arms but may have been affected by subsequent AML therapies after discontinuation. In patients who received subsequent therapy (gilteritinib, 46.8%; placebo, 60.0%), a higher percentage of placebo-treated (57.1%) versus gilteritinib-treated patients (27.6%) underwent HSCT. At the end of treatment, 96.4% of gilteritinib-treated and 85.7% of placebo-treated patients had undetectable MRD. Relapsed placebo-treated (86.7%) versus gilteritinib-treated patients (34.8%) had a greater *FLT3* mutational burden. No new significant safety concerns were noted.

Conclusions: The primary end point was not achieved; however, an observed trend toward potential benefit was noted in patients with *FLT3*-ITD AML who had not undergone prior HSCT.

KEYWORDS
FLT3 inhibitor, *FMS*-like tyrosine kinase 3–internal tandem duplication acute myeloid leukemia (*FLT3*-ITD AML), gilteritinib, maintenance therapy, measurable residual disease

INTRODUCTION

Acute myeloid leukemia (AML) is a genetically heterogeneous disease with several molecular subgroups.[1] Among the most common AML mutations are aberrations in the *FMS*-like tyrosine kinase 3 (*FLT3*) gene that occur in 20%–30% of adult patients.[1–4] There are two types of *FLT3* aberrations: internal tandem duplications (ITDs), which are present in 19%–25% of patients, and tyrosine kinase domain (TKD) point mutations, which occur in 5%–6% of patients.[4,5] Aberrations of *FLT3* lead to tyrosine kinase receptor activation, which promotes hematopoietic stem cell proliferation.[6] *FLT3*-ITD AML is associated with shorter overall survival (OS) and disease-free survival (DFS) rates compared with *FLT3*–wild-type AML.[1,7] Furthermore, patients with *FLT3*-ITD AML have a significantly greater risk of relapse at 5 years compared with patients without *FLT3* aberrations (64% vs. 44%), even when some patients receive allogeneic hematopoietic stem cell transplantation (HSCT).[8]

The current AML therapy for eligible patients includes induction therapy to achieve complete remission (CR), followed by consolidation and/or maintenance therapy to maximize the duration of remission and response.[9] To prevent relapse, HSCT is recommended in the majority of patients with "intermediate-risk" AML, which includes patients with *FLT3*-ITD AML.[9] However, HSCT is still not feasible for all patients because of biological and/or socioeconomic factors.[10] Consequently, there is a need for maintenance treatment strategies for patients with *FLT3*-ITD AML who are unable to undergo allogeneic HSCT. The standard treatment for patients with newly diagnosed *FLT3*-mutated AML who are fit for intensive therapy is midostaurin (a first-generation tyrosine kinase inhibitor [TKI]) in combination with chemotherapy during induction and consolidation therapy,[9] and quizartinib (a second-generation TKI)[11] in combination with chemotherapy is also approved for patients with newly diagnosed *FLT3*-ITD AML.[12]

Midostaurin treatment may be continued as maintenance therapy in patients with *FLT3*-mutated AML but its value before and/or after allogeneic HSCT is unclear,[9,11] whereas quizartinib is approved as maintenance therapy after consolidation chemotherapy but is not approved for use after allogeneic HSCT.[12]

Gilteritinib is a second-generation, highly selective, small-molecule FLT3 TKI with an inhibitory effect against both *FLT3*-ITD and *FLT3*-TKD aberrations.[13,14] The efficacy and safety of gilteritinib have been demonstrated in patients with relapsed/refractory (R/R) *FLT3*-mutated AML,[15] and the drug received Food and Drug Administration approval as a monotherapy in 2018 for this indication.[16] However, no study to date has investigated the efficacy and safety of gilteritinib as maintenance therapy in patients with newly diagnosed *FLT3*-ITD AML in first CR (CR1) who did not proceed to allogeneic HSCT. The GOSSAMER study sought to determine whether gilteritinib might benefit these patients. The primary objective of this phase 2 study was to assess relapse-free survival (RFS) in patients with *FLT3*-ITD AML in CR1 who were not receiving HSCT and who were treated with gilteritinib or placebo.

MATERIALS AND METHODS

Study design

Original phase 3 study design

This study was originally planned as a phase 3 study with an initial target sample size of 354 patients. Patient follow-up was intended

for 3 years after an initial 30-day follow-up visit or until 80% of patients had an RFS event, whichever came first. However, because of a substantially slower enrollment rate than originally anticipated, a protocol amendment was implemented that removed the adaptive design enrollment method, reduced the target sample size, and reduced the number of RFS events expected at the time of the primary analysis. On the basis of this amendment the study was changed to a randomized phase 2 study.

Amended phase 2 study design

GOSSAMER (NCT02927262) was a phase 2, randomized, placebo-controlled, double-blind, two-arm study that compared the effect of gilteritinib as maintenance therapy versus placebo after induction and/or consolidation therapy in adult patients with *FLT3*-ITD AML in CR1 where a decision was made not to continue with allogeneic HSCT. The study was conducted at 63 centers in North America, Europe, South America, and Asia. Patients were enrolled from April 18, 2017, until June 6, 2019. Before randomization, patients entered a 14-day screening period before starting study treatment, after which patients were randomized 2:1 to receive gilteritinib or placebo.

Patients received treatment for up to 2 years or until discontinuation criteria were met. After treatment discontinuation, patients had a 30-day follow-up visit for safety before entering the long-term follow-up period (until final database lock on August 16, 2021) for data collection on subsequent AML treatment, remission status, and survival (Figure S1).

Discontinuation criteria for patients included withdrawal of consent; noncompliance with the study protocol; deviation from one or more of the inclusion or exclusion criteria; development of unacceptable toxicity; a study investigator's opinion that continuation of study treatment would be detrimental to the patient; patient relapse; the patient beginning other antileukemic therapy (including HSCT); loss of the patient to follow-up; and patient pregnancy or death. The decision to proceed with other antileukemic therapy (including HSCT) was made by the treating physician, and was not prespecified in the study protocol at the time of patient recruitment.

Ethics

The study protocol and other relevant documents were reviewed and approved by the study site Institutional Review Board/Independent Ethics Committee before the start of the study and before the authorization of drug shipment to the study site. The study was conducted in accordance with International Council for Harmonisation guidelines for Good Clinical Practice, the Declaration of Helsinki, Council for International Organizations of Medical Sciences international ethical guidelines, and applicable regulations/guidelines governing clinical study conduct and ethical principles. Written informed consent was obtained from each patient before the initiation of any study or screening procedures.

Participants

The study enrolled adults diagnosed with *FLT3*-ITD AML in CR1 (including patients in CR with incomplete platelet recovery and CR with incomplete hematologic recovery) for whom a decision not to proceed with transplantation was made or a suitable donor could not be identified. All patients received induction and consolidation treatment before enrollment.

The main inclusion criteria for patients were less than 2 months from the start of their last consolidation therapy cycle; completed the recommended number of consolidations as per local practice; not used FLT3 inhibitors except during induction and/or consolidation therapy within the 4 weeks before enrollment; met predefined clinical laboratory test criteria; and suitable for oral administration of gilteritinib or placebo. Patients who had undergone previous allogeneic HSCT were ineligible. Detailed inclusion and exclusion criteria are provided in Supplementary Methods.

Treatment procedures

Patients were instructed to take oral gilteritinib (120 mg) or placebo tablets once daily. Treatment dosing could be interrupted or reduced if necessary for patient safety. Drug doses could be reduced from 120 mg to 80 and 40 mg, and were reduced stepwise by one dose level per day. A maximum of two dose-level reductions was permitted. Treatment was interrupted if a grade 3 or greater adverse event (AE) occurred and the investigator considered the AE possibly or probably related to the treatment. National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03) was used to grade AEs. Treatment could be resumed at the next lower dose level if the AE level decreased to less than one, or at the original dose if the investigator considered the AE unrelated to the gilteritinib treatment (further details are provided in Table S1).

End points

The primary end point was RFS, which was defined as the time from randomization until relapse or death from any cause. Leukemia-specific relapse was defined as bone marrow blasts of 5% or higher, any circulating blasts, and any extramedullary blast foci, which was according to the revised International Working Group criteria.[17] The key secondary end point was OS, which was defined as the time from randomization until death from any cause.

Other secondary end points included event-free survival (EFS; defined as the time from randomization until relapse, treatment discontinuation, initiation of other antileukemic treatments, or death); measurable residual disease (MRD); and the relationship between MRD and RFS. MRD was determined with a highly sensitive next-generation sequencing platform specific to *FLT3*-ITD mutations, and was analyzed by a sponsor-designated central

laboratory by using bone marrow samples. The *FLT3*/ITD mutation ratio was measured as the proportion of *FLT3*-ITD alleles relative to the total *FLT3* alleles (including both wild-type and mutant alleles). Changes from baseline in MRD and the relationship between MRD and RFS were measured at a $\log_{10}$-transformed overall *FLT3*/ITD mutation ratio of $>-4/\leq-4$ and an additional cutoff of $>-6/\leq-6$. MRD was assessed at baseline and 3, 6, 12, and 24 months/end of treatment (EOT). The assessment of *FLT3* mutation status at relapse was an exploratory end point.

Statistical analyses

Details of the statistical plan for the original phase 3 study are provided in Supplementary Methods. Efficacy analyses were conducted with the full analysis set (FAS), which comprised all patients randomized to gilteritinib or placebo. A safety analysis set (SAS) included all randomized patients receiving at least one dose of the study treatment. The primary outcome of RFS was treated as a time-to-event variable. The median RFS in the placebo arm was assumed to be 15 months on the basis of the control arm data from patients with *FLT3* mutations achieving CR1 after induction and consolidation treatment in the RATIFY trial.[18] A total of 54 relapse or death events were determined to provide 83.2% power to detect a hazard ratio (HR) of 0.5, which corresponded to a 24% between-group difference in 2-year RFS rates.

RFS was compared between treatment arms with a stratified log-rank test performed at a one-sided 0.075 significance level. The stratified log-rank test was used to test the null hypothesis that RFS in the gilteritinib arm was worse than or equal to RFS in the placebo arm versus the alternative hypothesis that RFS in the gilteritinib arm was better than RFS in the placebo arm. The log-rank test was stratified for patient age at randomization (<60 and ≥60 years); screening MRD status (yes/no); geographic region (North America or Europe, or Asia/Pacific/South America/Central America/rest of the world); and use of FLT3-inhibiting agents during induction and/or consolidation treatment (yes/no). The presence of MRD was considered detectable if the $\log_{10}$-transformed overall *FLT3*/ITD mutation ratio was >-4; a mutation ratio of ≤-4 meant that MRD was undetectable.

OS and EFS were also analyzed with a stratified log-rank test with the same strata as the RFS analysis. A sequential multiple test procedure was used to control for overall type I error at the one-sided 0.075 significance level, and formal significance testing of OS was only conducted if the RFS comparison was statistically significant. Kaplan–Meier curves were used to estimate RFS, OS, and EFS and 95% confidence intervals (CIs). A sensitivity analysis of OS was conducted by censoring patients who initiated other antileukemic treatments (including HSCT) at the time of first HSCT or first non-HSCT antileukemic treatment, whichever occurred first. A post hoc analysis was conducted to calculate relapse rates at 6 months and 1 year.

RESULTS

Patient disposition

Of 124 screened patients, 98 (79.0%) were randomized to gilteritinib (63 of 98; 64.3%) or placebo (35 of 98; 35.7%) (Figure 1). At the end of the 2-year treatment period, 20 of 63 (31.7%) and 12 of 35 (34.3%) patients in the gilteritinib and placebo arms, respectively, completed treatment. In total, 94 of 98 patients (95.9%) reached the 30-day follow-up evaluation (gilteritinib, 59 of 63 [93.7%]; placebo, 35 of 35 [100%]). The long-term follow-up evaluation was reached by 39 of 98 patients (39.8%), with similar percentages of patients in both treatment arms. Disease relapse was the most common reason for study discontinuation (Figure 1).

Patient baseline characteristics

Overall, 47 of 98 patients (48.0%) were male, the median age was 64.0 years (range, 22–79 years), and 74 of 98 patients (75.5%) had an intermediate cytogenetic risk. Most patients had undetectable MRD at screening (84 of 98; 85.7%) and had not used FLT3 inhibitors during induction and/or consolidation (76 of 98; 77.6%) (Table 1).

The median (minimum, maximum [min, max]) disease duration from initial diagnosis to randomization was 6.5 months (0.5, 14.4 months) in the gilteritinib arm and 5.9 months (2.7, 21.7 months) in the placebo arm. Overall, 52 of 98 patients (53.1%) gave the reason for not undergoing HSCT as "other," whereas 31 of 98 patients (31.6%) did not undergo HSCT because of the patient's choice and 15 of 98 patients (15.3%) had no available donor (Table 1).

Treatment exposure

The median (min, max) treatment duration was 427.0 days (7744 days) in the gilteritinib arm and 212.0 days (1736 days) in the placebo arm. The median average daily dose of gilteritinib was 120.0 mg/day. In the gilteritinib arm, 24 of 62 patients (38.7%) had dose decreases and 28 of 62 patients (45.2%) had dose interruptions.

Subsequent AML therapies

At the end of the data cutoff date, 21 of 35 patients (60.0%) in the placebo arm had subsequent AML therapy compared with 29 of 62 patients (46.8%) in the gilteritinib arm. Of these patients, 12 (57.1%) and eight (27.6%) in the placebo and gilteritinib arms, respectively, received a subsequent allogeneic HSCT (Table S2). The most common reason for undergoing allogeneic HSCT was any molecular relapse in the gilteritinib arm (three of eight; 37.5%) and morphologic relapse in the placebo arm (two of 12; 16.7%) (Table S2).

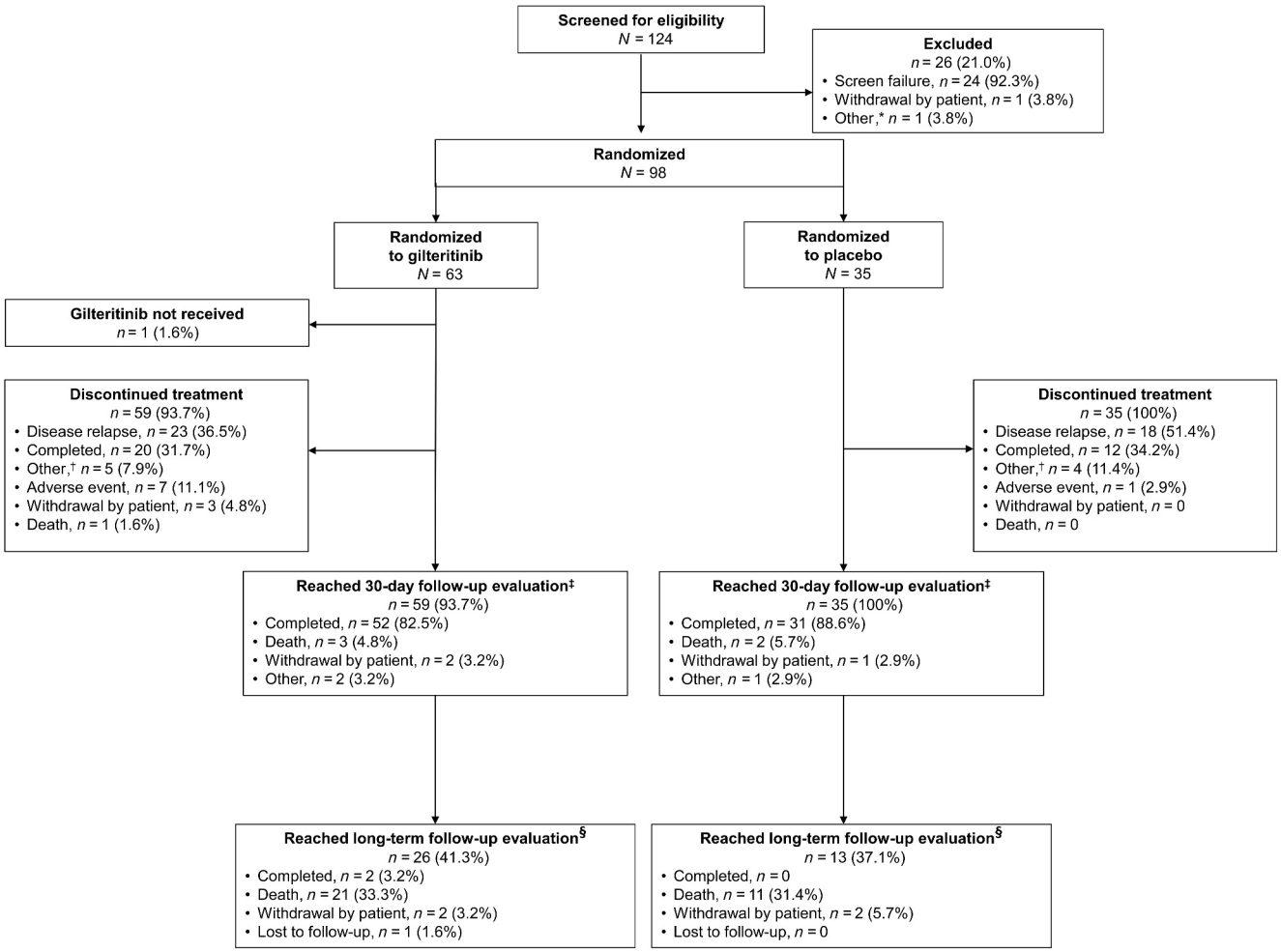

FIGURE 1 Patient disposition. *The patient's MRD status was not available in time for randomization; therefore, the patient was rescreened and given a new patient number. †In total across both treatment arms, the end-of-treatment category of "other" included physician decision ($n = 3$); the patient became eligible for transplant and proceeded to transplant ($n = 3$); the patient was not eligible for the study ($n = 1$); MRD was detected ($n = 1$); and the patient was randomized in error ($n = 1$). ‡After treatment discontinuation, patients had a 30-day follow-up visit for safety as per the study protocol. §After the 30-day safety follow-up visit, patients entered the long-term follow-up period for collection of subsequent acute myeloid leukemia treatment, remission status, and survival information as per the study protocol. Follow-up continued until the final database lock. MRD indicates measurable residual disease.

Primary end point

RFS

The primary end point of RFS was not met; there was no statistically significant difference in RFS in patients treated with gilteritinib as maintenance therapy compared with placebo (HR, 0.74; 95% CI, 0.4–1.34; $p = .16$) (Figure 2). A total of five of 29 gilteritinib-treated patients (17.2%) and three of 15 placebo-treated patients (20.0%) were censored with a new AML therapy or HSCT. In the gilteritinib arm, 34 of 63 patients (54.0%) had RFS events compared with 20 of 35 patients (57.1%) in the placebo arm. The median (95% CI) duration of RFS was 24.0 months (14.1 months to not estimable) in the gilteritinib arm and 15.8 months (3.0 months to not estimable) in the placebo arm.

In the gilteritinib versus placebo arms, the RFS rates (95% CI) at 1, 2, and 3 years were 68.5% (55.1%–78.6%) versus 55.3% (37.1%–70.2%), 51.8% (38.2%–63.8%) versus 44.9% (27.4%–61.0%), and 41.2% (27.9%–54.0%) versus 40.8% (23.6%–57.4%), respectively (Table S3).

Secondary end points

OS

The median (95% CI) follow-up of OS was 33.9 months (28.8–36.4 months) in the gilteritinib arm and 33.4 months (26.5–39.6 months) in the placebo arm. There were 21 of 63 deaths (33.3%) in the gilteritinib arm and 11 of 35 deaths (31.4%) in the placebo arm. Death without relapse was reported in three of 63 patients (8.8%) in the gilteritinib arm and no patients in the placebo arm.

There were no significant differences in OS between treatment arms (HR, 1.13; 95% CI, 0.54–2.36; $p = .63$) (Figure 3). In both arms,

TABLE 1 Patient baseline characteristics.

Characteristic	Gilteritinib (*n* = 63)	Placebo (*n* = 35)	Total (*N* = 98)
Sex, No. (%)			
Female	31 (49.2)	20 (57.1)	51 (52.0)
Male	32 (50.8)	15 (42.9)	47 (48.0)
Race, No. (%)			
White	38 (60.3)	22 (62.9)	60 (61.2)
Asian	17 (27.0)	10 (28.6)	27 (27.6)
Other	1 (1.6)	0	1 (1.0)
Not allowed to be collected	7 (11.1)	3 (8.6)	10 (10.2)
Age, years			
Mean (SD)	61.4 (11.0)	59.9 (13.9)	60.9 (12.1)
Median (min, max)	64.0 (27, 79)	64.0 (22, 79)	64.0 (22, 79)
Age group (years), No. (%)			
<60	24 (38.1)	13 (37.1)	37 (37.8)
≥60	39 (61.9)	22 (62.9)	61 (62.2)
Baseline ECOG status,[a] No. (%)			
0–1	63 (100)	35 (100)	98 (100)
BMI, kg/m^2			
Mean (SD)	25.8 (5.5)	25.8 (5.2)	25.8 (5.4)
Median (min, max)	25.1 (18, 46)	26.0 (16, 39)	25.4 (16, 46)
Cytogenetic risk status, No. (%)			
Intermediate	45 (71.4)	29 (82.9)	74 (75.5)
Unfavorable	3 (4.8)	1 (2.9)	4 (4.1)
Favorable	2 (3.2)	0	2 (2.0)
Other[b]	13 (20.6)	5 (14.3)	18 (18.4)
MRD[c] detected at screening per IRT at randomization, No. (%)			
Yes	8 (12.7)	6 (17.1)	14 (14.3)
No	55 (87.3)	29 (82.9)	84 (85.7)
Use of FLT3 inhibitor during induction and/or consolidation per IRT at randomization,[d] No. (%)			
Yes	12 (19.0)	10 (28.6)	22 (22.4)
No	51 (81.0)	25 (71.4)	76 (77.6)
Disease duration from initial diagnosis until randomization,[e] months			
Mean (SD)	6.7 (2.3)	6.8 (3.6)	6.7 (2.8)
Median (min, max)	6.5 (0.5, 14.4)	5.9 (2.7, 21.7)	6.1 (0.5, 21.7)
Reason for not undergoing HSCT, No. (%)			
Patient choice	19 (30.2)	12 (34.3)	31 (31.6)
No available donor	11 (17.5)	4 (11.4)	15 (15.3)
Other	33 (52.4)	19 (54.3)	52 (53.1)
Prior use of FLT3 inhibitor during induction and/or consolidation treatment,[d] No. (%)			
No	50 (79.4)	29 (82.9)	79 (80.6)
Yes	13 (20.6)	6 (17.1)	19 (19.4)
Midostaurin	10 (15.9)	6 (17.1)	16 (16.3)

TABLE 1 (Continued)

Characteristic	Gilteritinib (n = 63)	Placebo (n = 35)	Total (N = 98)
Quizartinib	3 (4.8)	0	3 (3.1)
Other	1 (1.6)	0	1 (1.0)
Response to treatment,[f] No. (%)			
CR	55 (87.3)	30 (85.7)	85 (86.7)
CRi	4 (6.3)	3 (8.6)	7 (7.1)
CRp	3 (4.8)	0	3 (3.1)
Not applicable	0	1 (2.9)	1 (1.0)

Abbreviations: AML, acute myeloid leukemia; BMI, body mass index; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; ECOG, Eastern Cooperative Oncology Group; FLT3, *FMS*-like tyrosine kinase 3; HSCT, hematopoietic stem cell transplantation; IRT, interactive response technology; ITD, internal tandem duplication; max, maximum; min, minimum; MRD, measurable residual disease; SD, standard deviation.

[a]If a patient was randomized but not treated, screening ECOG status was used as the baseline ECOG status.

[b]The category of "other" included those with a cytogenetic risk status that could not be categorized as favorable, intermediate, or unfavorable.

[c]Undetectable MRD was defined as a $\log_{10}$-transformed overall *FLT3*/ITD mutation ratio of ≤4.

[d]The frequency of prior use of FLT3 inhibitors varies between rows because of differences between data collected in the electronic data capture system and IRT entries undertaken for randomization and stratification.

[e]The duration of disease was calculated from initial diagnosis of AML to randomization.

[f]If a patient had multiple prior AML therapies, the patient was summarized under the last AML therapy administered before randomization.

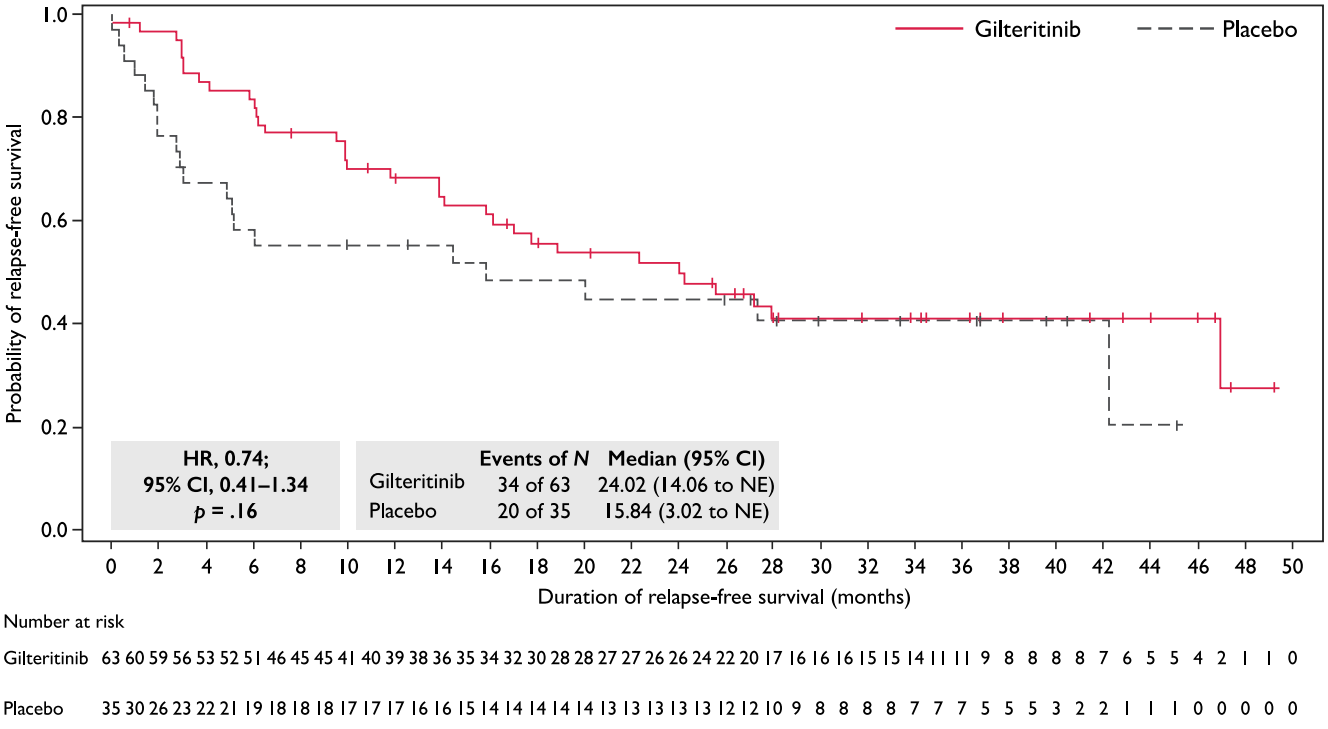

FIGURE 2 Kaplan–Meier estimate of RFS. The primary analysis of RFS was performed at a one-sided 0.075 significance level to test the null hypothesis that RFS in the gilteritinib arm is worse than or equal to RFS in the placebo arm, versus the alternative hypothesis that RFS in the gilteritinib arm is better. The p value was calculated from a stratified one-sided log-rank test. Stratification factors were age, geographic region, the presence of measurable residual disease at screening, and use of FLT3-inhibiting agents per interactive response technology. HRs were based on a Cox proportional hazards model. Assuming proportional hazards, an HR of <1 indicated a reduction in hazard in favor of the gilteritinib arm. CI indicates confidence interval; FLT3, *FMS*-like tyrosine kinase 3; HR, hazard ratio; NE, not estimable; RFS, relapse-free survival.

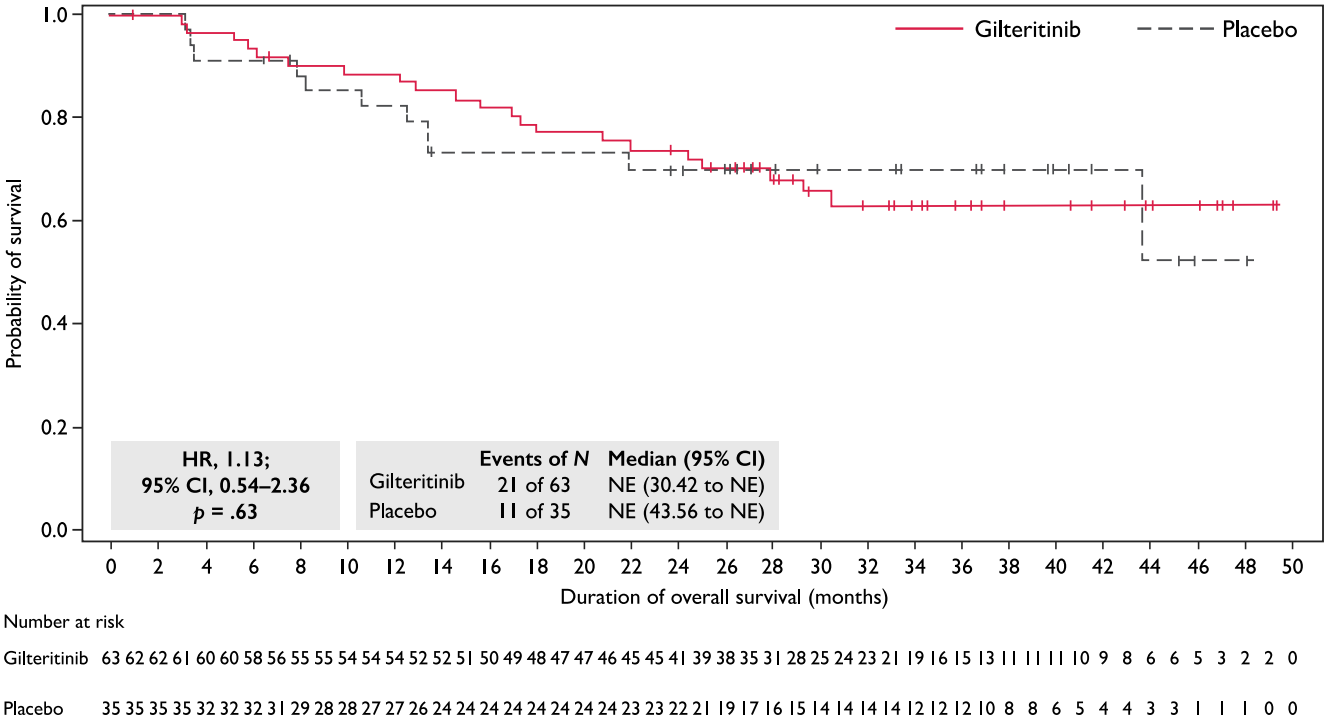

FIGURE 3 Kaplan–Meier estimate of OS. OS was analyzed in the full analysis set with a stratified log-rank test. With the sequential multiple test procedure to control for overall type I error at the one-sided 0.075 significance level, formal significance testing of OS was conducted only if the RFS comparison was statistically significant. Otherwise, OS analysis was considered exploratory. Stratification factors were age, geographic region, the presence of measurable residual disease at screening, and use of FLT3-inhibiting agents per interactive response technology. HRs were based on a Cox proportional hazards model. Assuming proportional hazards, an HR of <1 indicated a reduction in hazard in favor of the gilteritinib arm. CI indicates confidence interval; FLT3, *FMS*-like tyrosine kinase 3; HR, hazard ratio; NE, not estimable; OS, overall survival; RFS, relapse-free survival.

the OS rates at 1, 2, 3, and 4 years were similar (Table S3). A sensitivity analysis of OS that censored patients who initiated other antileukemic treatments at the time of their first antileukemic treatment was consistent with the original analysis (HR, 1.60; 95% CI, 0.33–7.75; $p = .72$).

EFS

A total of 69 of 98 patients (70.4%) had EFS events throughout the study period, with similar rates between gilteritinib-treated patients (44 of 63; 69.8%) and placebo-treated patients (25 of 35; 71.4%). There was no significant difference in EFS between treatment arms (HR, 0.86; 95% CI, 0.51–1.46; $p = .30$) (Figure 4). The rates of EFS at 1, 2, and 3 years were similar between treatment arms (Table S3). The median (95% CI) duration of EFS was 14.1 months (9.9–23.7 months) in the gilteritinib arm and 6.7 months (2.9–22.0 months) in the placebo arm.

MRD

In patients with available MRD data, the median (min, max) quantitative MRD was similar between the gilteritinib arm (−6.0 [−6.0, −1.3]) and placebo arm (−5.8 [−6.0, −1.7]) at baseline. There were no significant differences between treatment arms in the change from baseline MRD values at any time point (Figure 5).

At 24 months/EOT, 27 of 28 gilteritinib-treated patients (96.4%) and 12 of 14 placebo-treated patients (85.7%) had undetectable MRD. There were no significant differences in the detection of MRD between treatment arms at any time point (Table S4).

Relationship between MRD and RFS

In patients with undetectable MRD at baseline, the HR (95% CI) for RFS in patients treated with gilteritinib versus placebo was 0.92 (0.35–2.40) ($p = .86$), whereas for patients with detectable MRD at baseline it was 0.80 (0.39–1.65) ($p = .55$) (Figure 6).

Exploratory end points

Detection of *FLT3* mutation at relapse

In patients who discontinued treatment because of relapse and had *FLT3* sequencing performed at relapse, eight of 23 gilteritinib-treated patients (34.8%) compared with 13 of 15 placebo-treated patients (86.7%) had a *FLT3* mutation detected.

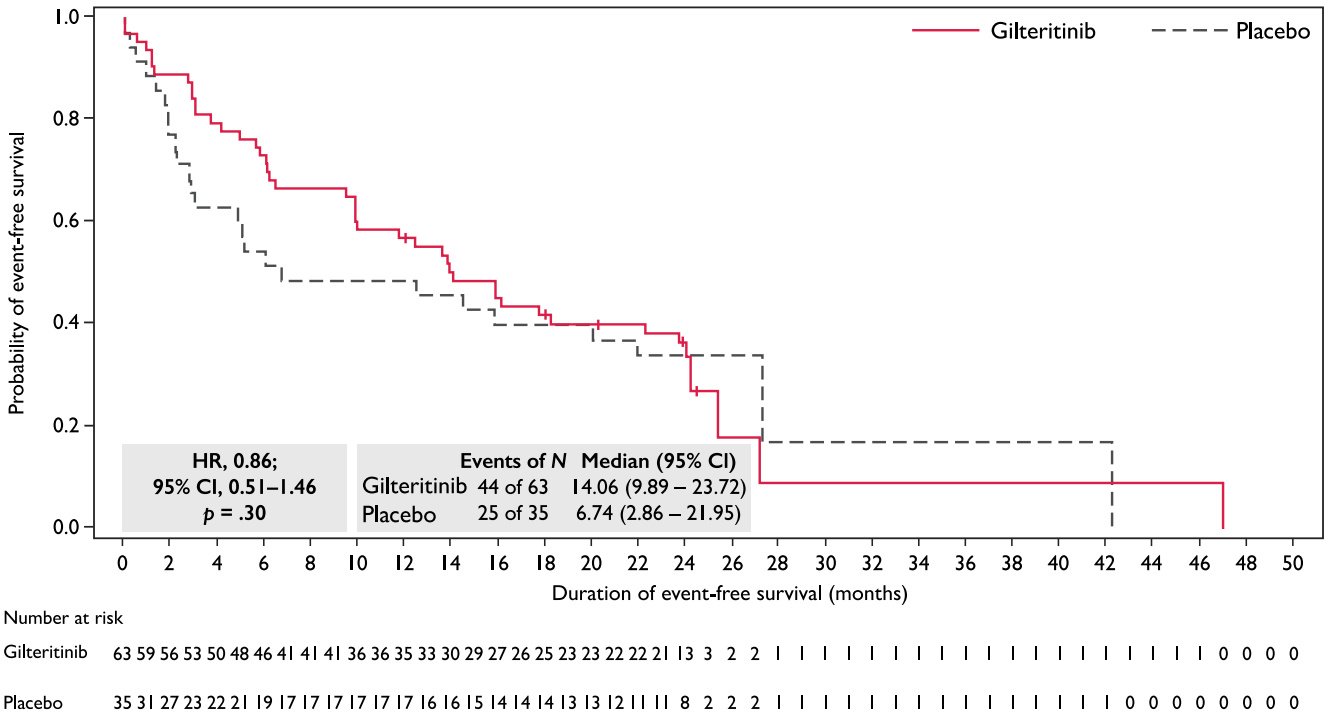

FIGURE 4 Kaplan–Meier estimate of EFS. EFS was analyzed with a stratified one-sided log-rank test with a one-sided 0.075 significance level. Stratification factors were age, geographic region, the presence of measurable residual disease at screening, and use of FLT3-inhibiting agents per interactive response technology. HRs were based on a Cox proportional hazards model. Assuming proportional hazards, an HR of <1 indicated a reduction in hazard in favor of the gilteritinib arm. CI indicates confidence interval; EFS, event-free survival; FLT3, *FMS*-like tyrosine kinase 3; HR, hazard ratio.

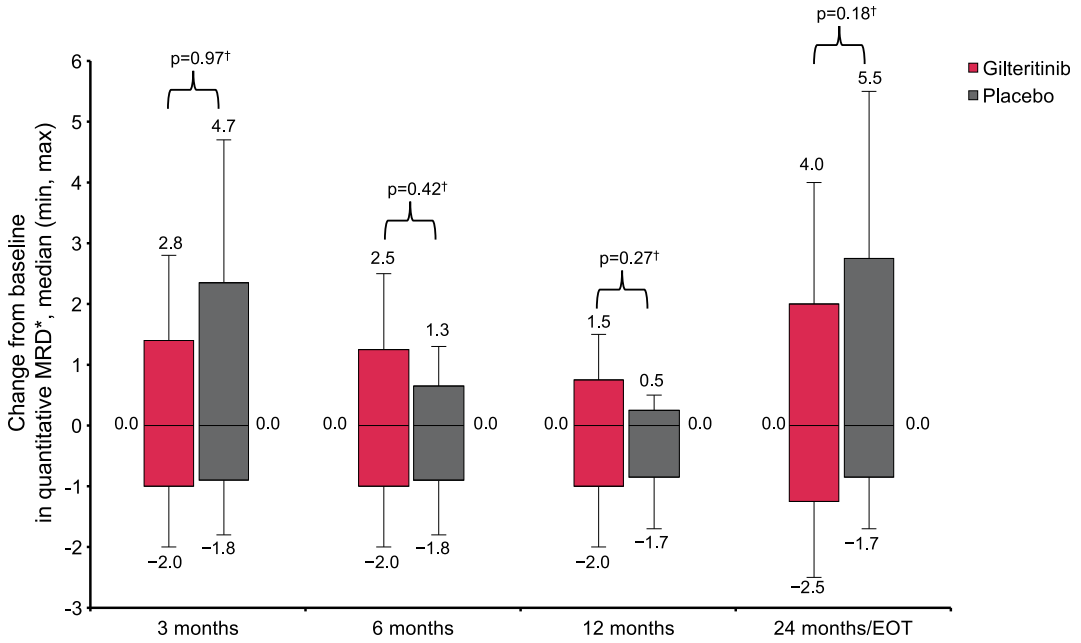

FIGURE 5 Median change from baseline in quantitative MRD as measured by a $\log_{10}$-transformed overall *FLT3*/ITD mutation ratio. Error bars represent min and max values. *MRD was measured as a $\log_{10}$-transformed overall *FLT3*/ITD mutation ratio (limit of detection, 10^{-6}). Change from baseline by ratio was defined as postbaseline value/baseline value. Median (min, max) baseline values were −6.0 (−6.0, −1.3) in the gilteritinib arm and −5.8 (−6.0, −1.7) in the placebo arm. †Two-sided *p* values from analysis of covariance including treatment, age group, geographic region, and use of FLT3-inhibiting agents per interactive response technology as fixed factors and baseline score as the covariate. EOT indicates end of treatment; FLT3, *FMS*-like tyrosine kinase 3; ITD, internal tandem duplication; max, maximum; min, minimum; MRD, measurable residual disease.

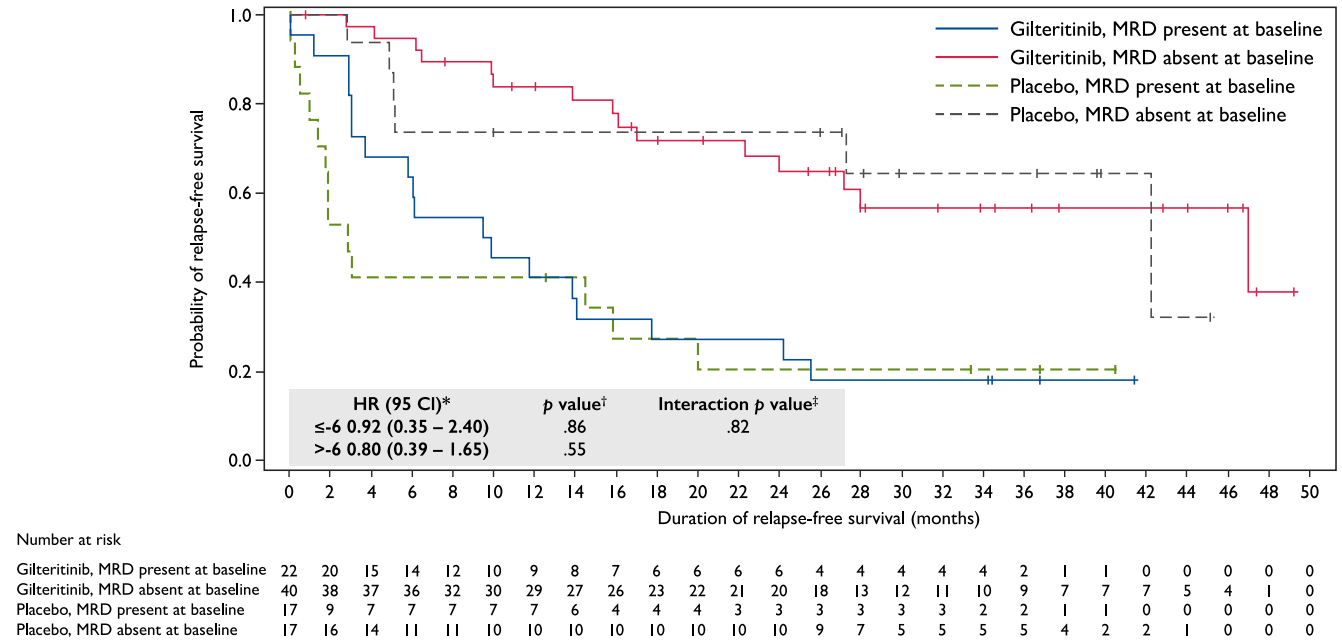

FIGURE 6 Kaplan–Meier estimate of RFS by MRD status at baseline. MRD was measured as a $\log_{10}$-transformed overall *FLT3*/ITD mutation ratio (limit of detection, 10^{-6}). MRD was considered detectable if the $\log_{10}$-tranformed FLT3/ITD mutation ratio was >-6; a mutation ratio of ≤-6 meant MRD was undetectable. *In each subgroup, the HR was estimated with an unstratified Cox proportional hazards model. Assuming proportional hazards, an HR of <1 indicated a reduction in hazard in favor of the gilteritinib arm. †Based on the Wald test. ‡For each subgroup, the interaction *p* value is from a Cox regression model, which included treatment, covariate, and treatment–covariate interaction terms. CI indicates confidence interval; FLT3, *FMS*-like tyrosine kinase 3; HR, hazard ratio; ITD, internal tandem duplication; MRD, measurable residual disease; RFS, relapse-free survival.

Post hoc analysis of relapse rates

The relapse rates (95% CI) at 6 months were 14.7% (7.9%–26.4%) and 41.6% (27.1%–60.0%) in the gilteritinib and placebo arms, respectively. At 1 year, relapse rates were 28.4% (18.7%–41.6%) in the gilteritinib arm and 44.7% (29.8%–62.9%) in the placebo arm.

Safety

AEs

In the SAS, 58 of 62 gilteritinib-treated patients (93.5%) and 33 of 35 placebo-treated patients (94.3%) experienced at least one treatment-emergent adverse event (TEAE) (Table 2). Study intervention–related TEAEs were reported in 51 of 62 patients (82.3%) in the gilteritinib arm compared with 20 of 35 patients (57.1%) in the placebo arm. Study intervention–related TEAEs leading to treatment withdrawal were similar between arms (gilteritinib, five of 62 [8.1%]; placebo, two of 35 [5.7%]). Only one patient in each treatment arm had a TEAE that led to death (Table 2). Serious TEAEs were reported by 24 of 62 patients (38.7%) in the gilteritinib arm and 14 of 35 patients (40.0%) in the placebo arm. Serious study intervention–related TEAEs were reported in 10 of 62 patients (16.1%) and three of 35 patients (8.6%) in the gilteritinib and placebo arms, respectively (Table 2). Increased blood creatine phosphokinase was the most commonly reported TEAE (≥10%) in the gilteritinib arm, whereas nausea was the most common TEAE in the placebo arm (Table S5).

DISCUSSION

To our knowledge, this is the first study to explore the use of gilteritinib as maintenance therapy in patients with *FLT3*-ITD AML in CR1 not receiving HSCT. Compared with placebo, gilteritinib treatment showed a numerical trend of improvement in RFS (8.2 months) but this was not statistically significant (HR, 0.74; 95% CI, 0.41–1.34; $p = .16$), and the primary objective was not met.

These results may have been affected by the change in trial design from a phase 3 to a phase 2 study, which led to an important power reduction. The high number of patients with undetectable baseline MRD may have also affected the results because in patients with AML, MRD negativity is associated with superior DFS and OS.[19] Patients in the gilteritinib arm demonstrated a nonsignificant improvement in median RFS (24.0 months) compared with the placebo arm (15.8 months). Furthermore, there were nonsignificant but increased RFS rates at 1 year (gilteritinib, 68.5% vs. placebo, 55.3%) and 2 years (gilteritinib, 51.8% vs. placebo, 44.9%) and numerically lower relapse rates at 6 months and 1 year in the gilteritinib arm compared with the placebo arm. These results suggest that gilteritinib may be effective in reducing the rate of early relapse because

TABLE 2 Overview of TEAEs and deaths.

	Gilteritinib[a] (*n* = 62), No. (%)	Placebo (*n* = 35), No. (%)
TEAE[b]	58 (93.5)	33 (94.3)
Study intervention–related[c] TEAE	51 (82.3)	20 (57.1)
TEAE before relapse	57 (91.9)	28 (80.0)
Study intervention–related[c] TEAE before relapse	51 (82.3)	15 (42.9)
Serious TEAE[d]	24 (38.7)	14 (40.0)
Study intervention–related[c] serious TEAE[d]	10 (16.1)	3 (8.6)
TEAE leading to death	1 (1.6)	1 (2.9)
Study intervention–related[c] TEAE leading to death	0	1 (2.9)
TEAE leading to withdrawal of treatment	15 (24.2)	6 (17.1)
Study intervention–related[c] TEAE leading to withdrawal of treatment	5 (8.1)	2 (5.7)
Grade 3 or higher TEAE[e]	42 (67.7)	18 (51.4)
Study intervention–related[c] grade 3 or higher TEAE[e]	33 (53.2)	4 (11.4)
TEAE leading to dose reduction	15 (24.2)	1 (2.9)
Study intervention–related[c] TEAE leading to dose reduction	14 (22.6)	1 (2.9)
TEAE leading to dose interruption	35 (56.5)	4 (11.4)
Study intervention–related[c] TEAE leading to dose interruption	31 (50.0)	1 (2.9)
Death[f]	20 (32.3)	11 (31.4)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; TEAE, treatment-emergent adverse event.

[a]One patient in the gilteritinib arm did not receive treatment and was not included in the safety analysis set.

[b]TEAE was defined as an adverse event observed from the start of the study intervention (gilteritinib or placebo) until 30 days from the last study treatment.

[c]Possible or probable, as assessed by the investigator, or records where the relationship was missing.

[d]Included serious adverse events upgraded by the sponsor on the basis of review of the sponsor's list of "always serious" terms, if any update was done.

[e]The patient was counted once under the maximum NCI CTCAE grade. A missing CTCAE grade was considered the maximum CTCAE grade. If a patient had at least one missing grade and at least one nonmissing grade of 5, the patient was counted in grade 5. If a patient had at least one missing grade and all nonmissing grades of <5, the patient was counted in the missing category.

[f]All reported deaths after the first study intervention administration.

FLT3-ITD AML is associated with increased relapse rates within the first 2 years.[8]

In addition, fewer patients in the gilteritinib arm compared with the placebo arm had a *FLT3* aberration detected at the time of relapse or MRD at the end of the treatment period, although this difference was not statistically significant. Together with the RFS results, this suggests that gilteritinib treatment may delay *FLT3*-ITD–related disease relapse.

Analysis of OS was considered exploratory because the primary objective was not met, and results showed no significant differences between the treatment arms. A potential confounding factor in the analysis of OS was that patients could receive additional AML treatments, including allogeneic HSCT, after discontinuing their initial treatment. Patients have improved long-term survival after undergoing HSCT, regardless of *FLT3* mutation status.[20,21] In addition, treatment with subsequent therapies after disease relapse has previously been shown to be a confounder in survival data.[22] In the present study, a greater percentage of patients in the placebo arm received subsequent AML therapy; of these patients, a larger number of placebo-treated patients received allogeneic HSCT. However, a sensitivity analysis censoring patients at the time of HSCT or other leukemic treatments was consistent with the original OS analysis.

In line with the RFS and OS results observed in this study, there was no significant difference in EFS for patients randomized to gilteritinib compared with placebo.

On the basis of the results from the RATIFY study,[18] which included patients with *FLT3*-ITD and *FLT3*-TKD AML, it is common for patients with newly diagnosed *FLT3*-mutated AML to receive midostaurin incorporated into standard induction and consolidation chemotherapy.[9] However, the RATIFY study was not designed to determine the independent effect of midostaurin maintenance therapy.[18] In the context of the present study, which included only patients with *FLT3*-ITD aberrations, analyses of the RATIFY subgroups by *FLT3* subtype showed that midostaurin maintenance therapy had some benefit in patients with *FLT3*-ITD AML compared to placebo but OS did not differ significantly according to the trial regimen within each subgroup.[18] In a post hoc exploratory analysis of the RATIFY study in patients with *FLT3*-ITD AML only, the 5-year OS

rates of patients in the midostaurin and placebo arms were 73.0% and 53.0%, respectively.[23] Similarly, in the present study, the 4-year OS rates were 63.1% and 52.6% in the gilteritinib and placebo arms, respectively. These results suggest that midostaurin and gilteritinib have broadly similar effects compared with placebo. Notably, the RATIFY trial and subsequent post hoc analysis were not powered for subgroup analyses or to show statistically significant differences between treatment groups.[18,23] Any comparisons between studies should be interpreted cautiously because the RATIFY trial included both patients with *FLT3*-ITD and *FLT3*-TKD aberrations, there were differences in sample size and trial design, and some patients in both arms of this present study had previously received midostaurin. Furthermore, the use of midostaurin as maintenance therapy remains uncertain because of reports of increased gastrointestinal toxicity and infections associated with the treatment[24] and inconclusive results on its impact on clinical outcomes.[25]

In an analysis examining the relationship between baseline MRD and RFS, it was found that in the gilteritinib and placebo arms the probability of RFS was greater in patients with undetectable MRD at baseline compared with patients with detectable MRD. These results are in line with a recent meta-analysis, which found that DFS (including RFS) was improved in patients with AML with undetectable MRD across a variety of subgroups.[19] There is also evidence that patients with *FLT3*-ITD AML with detectable MRD may benefit from the use of FLT3 inhibitors (sorafenib, gilteritinib, or quizartinib).[26] In contrast to the results presented in the present study, results from the MORPHO trial demonstrated that gilteritinib treatment led to significantly higher RFS compared with placebo in patients with detectable MRD before or after allogeneic HSCT.[27] The benefit of FLT3 inhibition in patients with detectable MRD has also been previously demonstrated.[26] The differences between the results from the present study and those of other studies may be due to the small number of patients in the placebo arm. Furthermore, in the present study, a higher proportion of patients in the placebo arm underwent subsequent HSCT, which has been shown to affect the variant allele frequency of different genes,[28] including *FLT3*,[29] and so may have acted as a confounder in this analysis. Future evaluations are needed to examine the relationship between MRD and RFS in the context of FLT3 inhibitor use.

Overall, maintenance therapy with gilteritinib was generally well tolerated over 2 years, and there were no deaths in the gilteritinib arm attributed to study intervention–related TEAEs. Although patients in the gilteritinib arm had more frequent TEAEs than in the placebo arm, a similar number of patients in both arms had study intervention–related TEAEs leading to treatment discontinuation. The TEAEs reported in this study were consistent with those in phase 1, 2, and 3 clinical trials.[15,30,31] This study contributes to the body of evidence of the efficacy and safety of gilteritinib in other populations of patients with AML, including patients with R/R *FLT3*-mutated AML[15,32] and those with newly diagnosed *FLT3*-mutated AML ineligible for intensive chemotherapy.[33]

This study's limitations include the small sample size; only a small number of patients with detectable MRD at baseline, which limited the interpretation of the results; and most patients had not previously received FLT3 inhibitors during induction and/or consolidation, and as such the patient population for this study may not accurately reflect patients with *FLT3*-ITD AML in clinical practice.

In summary, although the primary end point of improved RFS with gilteritinib compared with placebo did not reach statistical significance at the 2-year mark, some benefits and no new safety signals were observed with gilteritinib treatment. This suggests that gilteritinib may be a treatment option for patients with *FLT3*-ITD AML in CR1 who are unable to undergo allogeneic HSCT, and to bridge some patients to transplant. However, further investigation into the use of gilteritinib in this patient population is necessary.

AUTHOR CONTRIBUTIONS

Emmanuel Gyan: Investigation, formal analysis, writing–original draft, and writing–review and editing. **Mark D. Minden**: Investigation, writing–original draft, and writing–review and editing. **Kohmei Kubo**: Investigation, writing–original draft, and writing–review and editing. **Alessandro Rambaldi**: Investigation, writing–original draft, and writing–review and editing. **Gunnar Juliusson**: Investigation, writing–original draft, and writing–review and editing. **Martin Jädersten**: Investigation, writing–original draft, and writing–review and editing. **Richard J. Kelly**: Investigation, writing–original draft, and writing–review and editing. **László Szerafin**: Investigation, writing–original draft, and writing–review and editing. **Wensheng He**: Formal analysis, writing–original draft, and writing–review and editing. **Stanley C. Gill**: Formal analysis, writing–original draft, and writing–review and editing. **Jason E. Hill**: Formal analysis, writing–original draft, and writing–review and editing. **Caroline Chen**: Formal analysis, writing–original draft, and writing–review and editing. **David Delgado**: Formal analysis, writing–original draft, and writing–review and editing. **Nahla Hasabou**: Formal analysis, writing–original draft, and writing–review and editing.

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CONFLICT OF INTEREST STATEMENT

Emmanuel Gyan has received honoraria from AbbVie, Astellas Pharma Inc., Bristol Myers Squibb, Janssen, Incyte, Roche, EUSA Pharma, Jazz Pharmaceuticals, Gilead, and Sanofi; research support from Novartis, Amgen, Bristol Myers Squibb, and Roche; travel support from AbbVie; and investigator fees from Pharmacyclics and Mundipharma. Mark D. Minden has received funding from the Canadian Institutes of Health Research for studies of the *nucleophosmin 1* mutant in patients with acute myeloid leukemia, and is named on a patent related to the *LSC17* gene expression signature to assign risk in patients with newly

diagnosed acute myeloid leukemia. Kohmei Kubo and László Szerafin have nothing to disclose. Alessandro Rambaldi has received honoraria from Novartis, Amgen, Pfizer, Astellas Pharma Inc., Jazz Pharmaceuticals, Janssen, Incyte, Kite-Gilead, Roche, Otsuka, AbbVie, and Omeros; support for attending meetings and/or travel from Novartis, Amgen, Pfizer, Astellas Pharma Inc., Jazz Pharmaceuticals, Janssen, Incyte, Kite-Gilead, Roche, and Omeros; and participated on a data safety monitoring board/advisory board for Amgen and Omeros. Gunnar Juliusson has received honoraria from AbbVie, Astellas Pharma Inc., Laboratoires Delbert, and Servier. Martin Jädersten has received institutional support for arranging educational events for AbbVie, AstraZeneca, Pfizer, and Laboratoires Delbert; and participated on a data safety monitoring board/advisory board for AbbVie and CanCell Therapeutics. Richard J. Kelly has received research support from Novartis and Sobi; honoraria from Astellas Pharma Inc., AbbVie, Alexion, Jazz Pharmaceuticals, Novartis, Otsuka, Roche, and Sobi; and travel support from Sobi. Wensheng He, Stanley C. Gill, Jason E. Hill, Caroline Chen, David Delgado, and Nahla Hasabou are employees of Astellas Pharma Inc.

DATA AVAILABILITY STATEMENT

Researchers may request access to anonymized participant-level data, trial-level data, and protocols from Astellas-sponsored clinical trials at https://www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing, see https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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