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Gilteritinib as Post-Transplant Maintenance for AML With Internal Tandem Duplication Mutation of *FLT3*

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ABSTRACT

PURPOSE Allogeneic hematopoietic cell transplantation (HCT) improves outcomes for patients with AML harboring an internal tandem duplication mutation of *FLT3* (*FLT3-ITD*) AML. These patients are routinely treated with a FLT3 inhibitor after HCT, but there is limited evidence to support this. Accordingly, we conducted a randomized trial of post-HCT maintenance with the FLT3 inhibitor gilteritinib (ClinicalTrials.gov identifier: NCT02997202) to determine if all such patients benefit or if detection of measurable residual disease (MRD) could identify those who might benefit.

METHODS Adults with *FLT3-ITD* AML in first remission underwent HCT and were randomly assigned to placebo or 120 mg once daily gilteritinib for 24 months after HCT. The primary end point was relapse-free survival (RFS). Secondary end points included overall survival (OS) and the effect of MRD pre- and post-HCT on RFS and OS.

RESULTS Three hundred fifty-six participants were randomly assigned post-HCT to receive gilteritinib or placebo. Although RFS was higher in the gilteritinib arm, the difference was not statistically significant (hazard ratio [HR], 0.679 [95% CI, 0.459 to 1.005]; two-sided $P = .0518$). However, 50.5% of participants had MRD detectable pre- or post-HCT, and, in a prespecified subgroup analysis, gilteritinib was beneficial in this population (HR, 0.515 [95% CI, 0.316 to 0.838]; $P = .0065$). Those without detectable MRD showed no benefit (HR, 1.213 [95% CI, 0.616 to 2.387]; $P = .575$).

CONCLUSION Although the overall improvement in RFS was not statistically significant, RFS was higher for participants with detectable *FLT3-ITD* MRD pre- or post-HCT who received gilteritinib treatment. To our knowledge, these data are among the first to support the effectiveness of MRD-based post-HCT therapy.

ACCOMPANYING CONTENT

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View Online Article

INTRODUCTION

AML is stratified into different molecular subtypes to guide therapy.[1] Internal tandem duplication mutations of *FLT3* (*FLT3-ITD*) are common in AML and confer an increased relapse risk.[2] Allogeneic hematopoietic stem cell transplantation (HCT) in first remission is considered the standard of care for these patients when feasible.[1,3]

Guidelines from the National Comprehensive Cancer Network recommend post-HCT maintenance with FLT3 inhibitors to reduce the risk of relapse[4] on the basis of results from small randomized trials of sorafenib and midostaurin.[5-8] However, this practice is controversial[9] as patients in these trials were not treated with FLT3 inhibitors pre-HCT (the current standard practice) and two of the trials[6,8] were nonblinded and allowed only myeloablative conditioning (MAC). Treatment with FLT3 inhibitors can be toxic and often needs to be interrupted or halted because of adverse events (AEs).[8,10-13] For patients treated with current induction standards for *FLT3-ITD* AML undergoing HCT in first remission, the question remains if the benefits of

CONTEXT

Key Objective

To determine if all patients with internal tandem duplication mutation of *FLT3* (*FLT3-ITD*) AML undergoing allogeneic hematopoietic stem-cell transplantation (HCT) benefit from post-HCT maintenance with the FLT3 inhibitor gilteritinib or if benefit is restricted to those patients who have *FLT3-ITD* measurable residual disease (MRD) at the time of HCT.

Knowledge Generated

Patients with AML with *FLT3-ITD* MRD detectable in the peri-HCT period benefit from post-HCT gilteritinib, whereas those without detectable MRD do not. These prospective results establish *FLT3-ITD* mutations as essential markers of MRD and illustrate how molecular MRD can be used to guide the therapy of patients with AML undergoing HCT.

Relevance *(C.F. Craddock)*

Post-transplant gilteritinib maintenance represents a significant therapeutic advance in patients allografted for *FLT3-ITD* AML who have evidence of peri-transplant MRD. MRD-negative patients derive no benefit from gilteritinib maintenance but instead may be exposed to unnecessary toxicity.*

*Relevance section written by *JCO* Associate Editor Charles F. Craddock, MD.

maintenance with FLT3 inhibition outweigh the risks of toxicity. Despite the risk of post-HCT relapse, at least half of patients with *FLT3-ITD* AML transplanted in first remission are cured without further treatment,[4] which means that many patients treated with post-HCT FLT3 inhibition are subjected to an unnecessary therapy.

The presence of measurable residual disease (MRD) pre- or post-HCT is highly predictive of outcomes.[14-17] Because of their apparent instability during the course of the disease, *FLT3-ITD* mutations have not historically been regarded as useful markers of MRD, but recent data suggest otherwise.[18-20] Highly sensitive assays using sequential polymerase chain reaction (PCR) and next-generation sequencing (NGS) detect low levels of *FLT3-ITD* mutations in patients in remission, and retrospective studies suggest that the presence of these mutations correlates with relapse.[18,19,21,22]

Gilteritinib is a potent, well-tolerated oral FLT3 inhibitor approved as monotherapy for relapsed or refractory *FLT3*-mutated AML.[23] The randomized, double-blinded, placebo-controlled Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 1506 (MORPHO) trial was designed to determine (1) if post-HCT maintenance with gilteritinib provided benefit for patients with *FLT3-ITD* AML in first remission undergoing HCT and (2) if *FLT3-ITD* MRD detection could be used to identify the patients who benefit.

METHODS

Patients

Eligible patients were adults with *FLT3-ITD* AML (diagnosed with local mutation testing) who were in continuous first remission achieved with not more than two cycles of intensive therapy (with or without a FLT3 inhibitor and including any investigational regimens) and intended to undergo allogeneic HCT after induction and any consolidation within 1 year of achieving remission. Any donor source, conditioning regimen, and graft-versus-host disease (GVHD) prophylaxis were permitted.

Trial Design and Treatment

Participants were registered before HCT, and a bone marrow (BM) aspirate was obtained to confirm remission and for MRD analysis. Once engrafted (defined by absolute neutrophil count ≥500/mm^3, platelet count ≥20,000/mm^3, and platelet transfusion–independent) and provided that they were free of grade II-IV GVHD (and requiring not more than 0.5 mg/kg prednisone per day), participants were randomly assigned between days 30 and 90 after HCT to placebo or 120 mg per day gilteritinib for 24 months. Immediately before random assignment, a second BM aspirate was obtained to confirm ongoing remission and for MRD analysis. Random assignment was double-blinded at a ratio of 1:1 between the treatment arm and the placebo arm using permuted blocks of random sizes, stratified by conditioning regimen intensity (myeloablative *v* reduced intensity/nonmyeloablative), time from transplantation to random assignment (30-60 *v* 61-90 days), and the presence of *FLT3-ITD* MRD at a level of 1×10^{-4} or greater (present *v* absent/indeterminate) on the basis of the pre-HCT BM aspirate.

MRD Assay

The first 2 mL of any study marrow aspirate was reserved for MRD analysis. For the MRD assay,[21] 700 ng of genomic DNA was amplified by 25 cycles of PCR using primers flanking

exons 14 and 15 of *FLT3* and the amplicons were analyzed by NGS. The limit of blank (LOB) was two variant reads, and the lower limit of detection was estimated to be the *FLT3-ITD* variant allele frequency of 5×10^{-5}. However, any level of *FLT3-ITD* mutation (minimum of three variant reads) above the LOB (quantified as low as 1×10^{-6}), irrespective of whether it was the same mutation reported at diagnosis, was considered detectable MRD. The pre-HCT level used for stratification was 1×10^{-4} or higher. Investigators were blinded to the results of MRD analyses.

End Points and Assessments

The primary end point was relapse-free survival (RFS) as assessed by a blinded end point review committee (BERC), measured from the time of random assignment to either morphological relapse or death, using the intention-to-treat (ITT) population. Morphological relapse was defined as BM blasts 5% or higher, any circulating blasts, or any extramedullary blast foci as per published criteria.[24] Overall survival (OS) was a key secondary objective. Other secondary objectives included nonrelapse mortality (NRM) and examining the effect of MRD on RFS and OS in the gilteritinib and placebo arms and the effect of gilteritinib versus placebo separately in patients with and without MRD. Additional details on end points and assessments are provided in the Data Supplement (Appendix, online only).

Trial Conduct and Oversight

This trial was conducted in accordance with the Declaration of Helsinki. Institutional review boards at each site approved the trial protocol, and all investigators obtained informed consent from each participant or each participant's guardian. The trial was funded by grant Nos. U10HL069294 and U24HL138660 to the BMT CTN from the National Heart Lung and Blood Institute (NHLBI) and the National Cancer Institute and by Astellas Pharma Global Development, Inc. The trial was designed by the BMT CTN and approved by the NHLBI and Astellas. The Emmes Company monitored North American sites, and Parexel monitored non–North American sites. All investigators and the industry sponsor were blinded to outcomes. Data collection and monitoring procedures are provided in the Data Supplement (Appendix). The investigators had full access to the data at study closure. The study cochairs (M.J.L. and Y.-B. C.) reviewed the data and wrote the manuscript with editorial input from coauthors and without assistance from nonauthors.

Statistical Analysis

The sample size was based on estimates of RFS in the control group of 67% at 1 year, 59% at 2 years, and 55% at 3 years derived from Center for International Blood and Marrow Transplant Research data on participants with *FLT3-ITD* mutation transplanted in first remission. A total of 122 events would provide 85% power to detect a hazard ratio (HR) of 0.57 (corresponding to a 15% difference in 2-year RFS) with a two-sided significance level of 0.05. The analysis was scheduled for when 122 events were observed or 2.5 years after the last patient was randomly assigned, whichever came first. The primary end point of RFS was summarized using Kaplan-Meier curves and compared between arms using stratified log-rank tests, with the random assignment factors used as stratification variables. A stratified Cox proportional hazards model was used to provide HR estimates and CIs. To maintain the overall two-sided type I error rate at 0.05, formal significance testing of

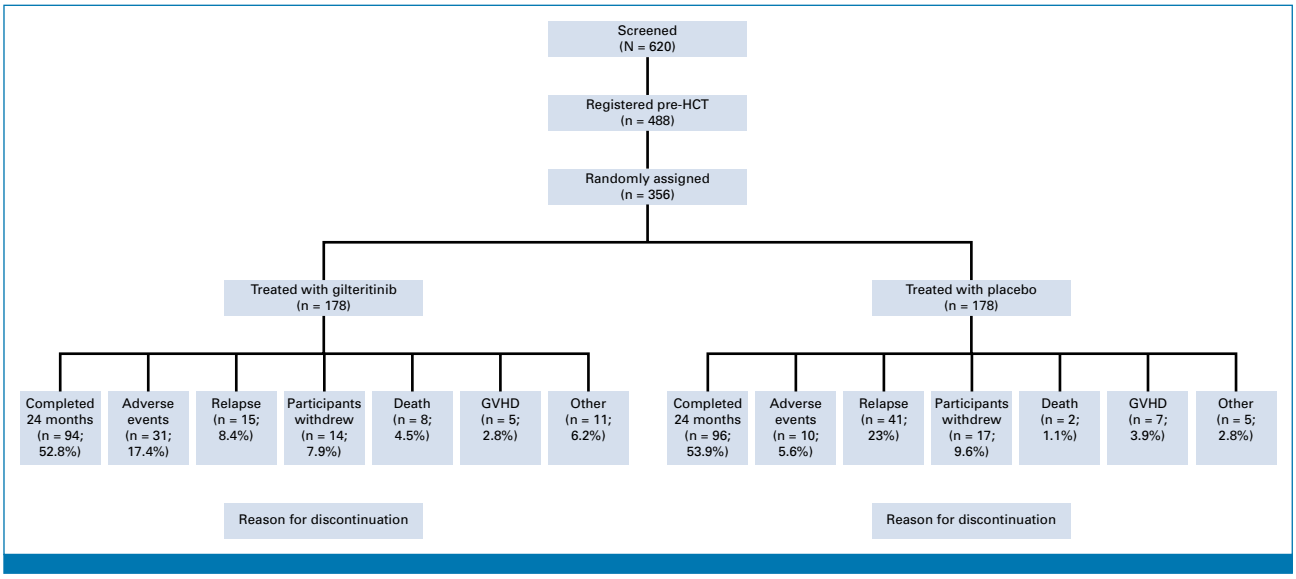

FIG 1. Screening, registration, random assignment, and reasons for discontinuing study treatment. GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation.

OS using a gatekeeping approach was to be conducted if the RFS comparison was statistically significant. Otherwise, OS analysis would be considered exploratory. OS was analyzed in the ITT population in the same manner as RFS. Competing risk end points (relapse, NRM, acute GVHD [aGVHD], chronic GVHD [cGVHD], eradication or detection of MRD) were summarized using the cumulative incidence function and compared between arms using Gray's test, with subdistribution HRs obtained using the Fine-Gray model. Prespecified subgroup analyses of MRD status were conducted using interaction testing between treatment and subgroup, and forest plots of the treatment effect within subgroups were drawn. No formal multiplicity adjustment for secondary end points or subgroup analyses was used.

RESULTS

Participants

Between August 17, 2017, and July 8, 2020, 620 patients at 122 centers in 16 countries were screened for eligibility, 488 participants were registered, and 356 were randomly assigned, 178 in each arm (Fig 1). The last participant finished treatment in July 2022. The primary analysis is based on a data cutoff on January 7, 2023 (2.5 years after the last participant was randomly assigned). Of 488 participants registered, 132 (27%) participants were not randomly assigned for the following reasons: 68 (51.5%) failed to meet random assignment criteria (including GVHD and failure to engraft); 26 (19.7%) for patient/physician decision; 16 (12.1%) for early death; 10 (7.6%) for relapse; and 12 (9.1%) for other reasons. The safety analysis set (SAF) comprised 355 participants (178 in the gilteritinib arm and 177 in the placebo arm) who took at least one dose of study drug (one participant randomly assigned to placebo received gilteritinib, and one participant randomly assigned to gilteritinib did not take study drug). The most common reasons for early discontinuation were an AE in the gilteritinib arm (17.4%) and relapse (23%) in the placebo arm (Fig 1).

Participant characteristics are displayed in Table 1. There were more than 30 unique conditioning regimens used worldwide. NPM1 mutations were reported in 34.6% of participants. Information on other comutations or *FLT3-ITD* allelic ratio was not available, and so classification according to the European LeukemiaNet 2022 system was not possible.[1] Marrow aspirates for MRD analysis were available from 350 of 356 (98%) participants pre-HCT and 347 of 356 (97.5%) post-HCT (before random assignment). MRD was detected at the stratification level (1×10^{-4} or higher) in 75 of 356 (21.1%) participants and at a level of 1×10^{-6} or higher in 164 of 356 (46.1%) pre-HCT. Post-HCT, MRD was detected at a level of 1×10^{-6} or higher in 71 of 356 (19.9%), including 16 (4.5%) participants with detectable MRD post-HCT but not pre-HCT. Therefore, a total of 180 ([164 + 16 of 356]; 50.6%) participants had detectable MRD in the peri-HCT period.

TABLE 1. Participant Characteristics at Baseline (ITT population)

Parameter	Gilteritinib (n = 178)	Placebo (n = 178)
Age, years, median (range)	53 (20-78)	53 (18-76)
Sex, No. (%)		
Male	91 (51.1)	92 (51.7)
Female	87 (48.9)	86 (48.3)
Race, No. (%)		
White	114 (64)	106 (59.6)
African American	6 (3.4)	3 (1.7)
Asian	47 (26.4)	56 (31.5)
Other/missing	11 (6.2)	13 (7.3)
Geographic, No. (%)		
North America	77 (43.3)	77 (43.3)
Europe	49 (27.5)	43 (24.2)
Asia/Pacific	52 (29.2)	58 (32.6)
Genetic results at AML diagnosis, No. (%)		
Favorable karyotype	9 (5.1)	4 (2.2)
Intermediate karyotype	119 (66.9)	90 (50.6)
Adverse karyotype	7 (3.9)	7 (3.9)
Unknown	29 (16.3)	51 (28.7)
Other	14 (7.9)	26 (14.6)
FLT3 inhibitor pre-HCT, No. (%)	110 (61.8)	103 (57.9)
HCT-specific comorbidity index, No. (%)		
0	79 (44.4)	70 (39.3)
1-2	49 (27.5)	51 (28.7)
3+	49 (27.5)	57 (32)
Conditioning regimen intensity, No. (%)		
MAC	106 (59.6)	107 (60.1)
RIC/nonmyeloablative	72 (40.4)	71 (39.9)
Stem-cell donor, No. (%)		
Matched sibling	55 (30.9)	48 (27)
Haploidentical	22 (12.4)	38 (21.3)
Matched unrelated	71 (39.9)	65 (36.5)
Mismatched unrelated	15 (8.4)	17 (9.6)
Cord blood	11 (6.2)	8 (4.5)
Stem-cell source, No. (%)		
Peripheral blood	140 (78.7)	140 (78.7)
Marrow	27 (15.2)	30 (16.9)
Cord blood	11 (6.2)	8 (4.5)
GVHD prophylaxis, No. (%)		
Calcineurin inhibitor + methotrexate	98 (55.1)	96 (53.9)
Calcineurin inhibitor + mycophenolate mofetil	43 (24.2)	51 (28.7)
Other	37 (20.8)	30 (16.9)
Missing	0 (0)	1 (0.6)
Time from HCT to random assignment, No. (%)		
30-60 days	95 (53.4)	97 (54.5)
61-90 days	83 (46.6)	81 (45.5)
MRD, No. (%)		
Pre-HCT MRD ≥ 10^{-4}	39 (21.9)	36 (20.2)
Pre-HCT MRD ≥ 10^{-6}	82 (46.1)	82 (46.1)
Pre- or post-HCT MRD ≥ 10^{-6}	89 (50)	91 (51.1)

Abbreviations: GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; ITT, intention-to-treat; MAC, myeloablative conditioning; MRD, measurable residual disease; RIC, reduced-intensity conditioning.

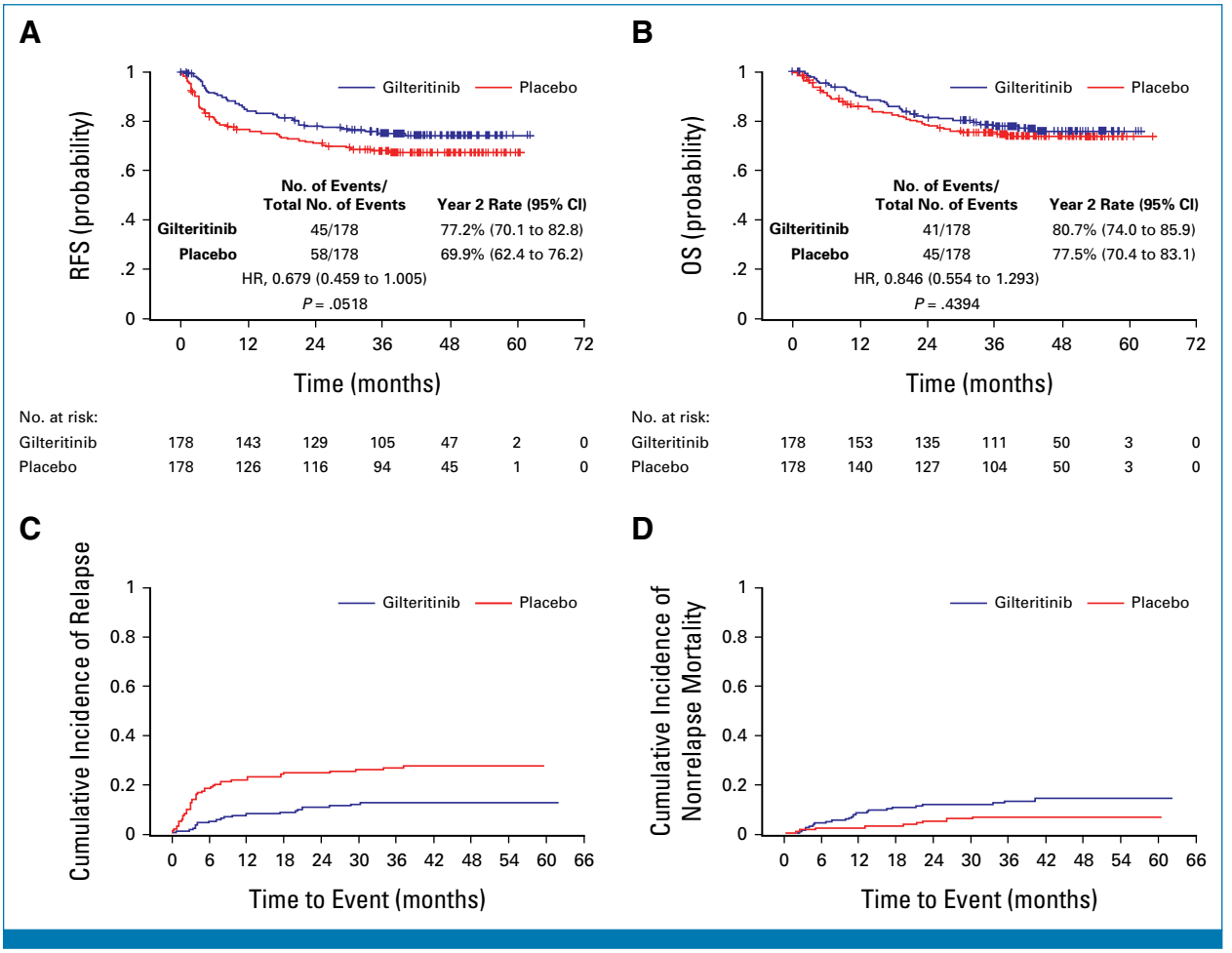

FIG 2. Survival, relapse, and nonrelapse mortality (ITT population). (A) Relapse-free survival, (B) overall survival for the gilteritinib and placebo groups, (C) cumulative incidence of relapse for the gilteritinib group versus placebo group, and (D) cumulative incidence of nonrelapse mortality (defined as death without documentation of morphological relapse). HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; RFS, relapse-free survival.

Efficacy

Among the 270 participants who survived at data cutoff, the median follow-up was 43.8 months. A total of 103 RFS events (by BERC) were observed in the primary analysis, which led to an approximate reduction in power to 78.6% instead of 85.0%. Longer follow-up would not have increased the number of events measurably because of very low event rates beyond 2 years post-HCT. While there was improved RFS in the gilteritinib arm compared with that in the placebo arm (Fig 2A), the difference did not meet the predetermined threshold for significance (HR, 0.679 [95% CI, 0.459 to 1.005]; two-sided $P = .0518$). The 2-year RFS rate by BERC (95% CI) was 77.2% (CI, 70.1 to 82.8) for participants receiving gilteritinib and 69.9% (CI, 62.4 to 76.2) for those receiving placebo. OS (Fig 2B) was analyzed by ITT in the primary analysis (which included a total of 86 deaths) and did not show a statistically significant difference (HR, 0.846 in favor of gilteritinib [95% CI, 0.554 to 1.293]; two-sided $P = .4394$). The incidence of relapse was lower and NRM was higher in the gilteritinib arm compared with the placebo arm (Figs 2C and 2D). Of 47 participants who relapsed in the placebo arm, 20 (42.6%) were treated with a FLT3 inhibitor (gilteritinib-13, quizartinib-4, sorafenib-3) after relapse. The cumulative incidence of relapse by geographic region is displayed in the Data Supplement (Fig 1).

MRD at a level of 1×10^{-6} or greater was associated with decreased RFS and OS (Figs 3A and 3B) irrespective of the treatment arm. Subgroup analysis of RFS and OS performed on MRD and other prespecified subgroups is displayed in the Data Supplement (Figs 2 and 3). Participants with detectable MRD pre- or post-HCT had a significantly improved RFS if they were on gilteritinib compared with the placebo arm, whereas MRD-negative participants in both arms had similar RFS (Figs 3C and 3D). This was the case for participants with detectable MRD pre-HCT ($P = .0105$), post-HCT ($P = .0143$), or either pre- or post-HCT ($P = .0065$). Similarly, participants with pre- or post-HCT MRD at a level of 1×10^{-6} or greater had improved OS when treated with gilteritinib

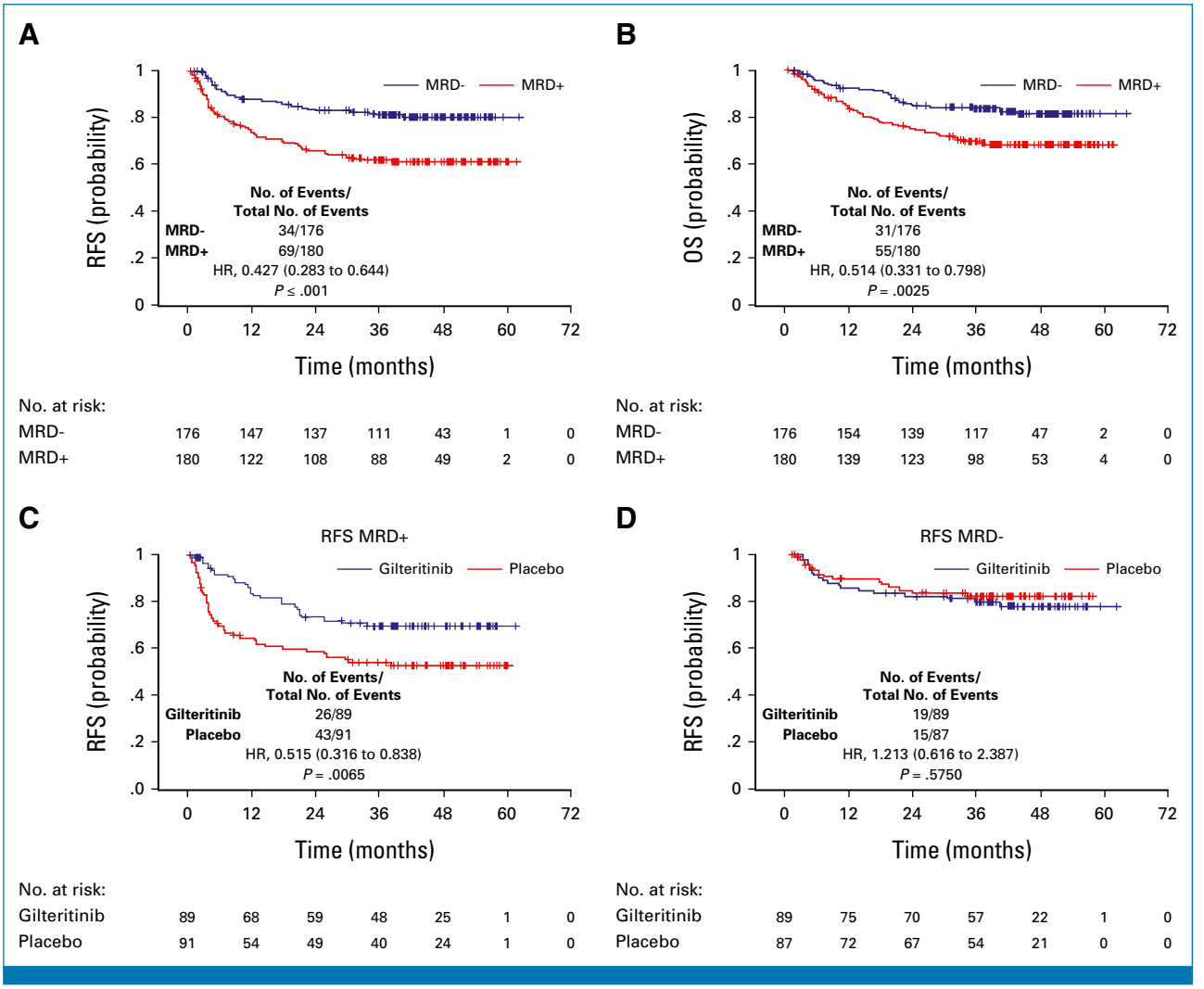

FIG 3. The impact of measurable residual disease on relapse-free survival (ITT population). (A) Relapse-free survival, (B) overall survival for all participants irrespective of the treatment arm according to whether any (eg, *FLT3-ITD* variant allele frequency of 1×10^{-6} or above) MRD was detectable peri-HCT, (C) relapse-free survival in participants with any (eg, *FLT3-ITD* variant allele frequency of 1×10^{-6} or above) detectable peri-HCT MRD according to the treatment arm, and (D) relapse-free survival in participants with no detectable peri-HCT MRD, according to the treatment arm. *FLT3-ITD*, internal tandem duplication mutation of *FLT3*; HCT, hematopoietic cell transplantation; HR, hazard ratio; ITT, intention-to-treat; MRD, measurable residual disease; OS, overall survival; RFS, relapse-free survival.

(Data Supplement, Fig 4) although this did not reach statistical significance (P = .0731).

For participants who received a FLT3 inhibitor pre-HCT (60%), gilteritinib conferred a RFS benefit compared with placebo (HR, 0.598; P = .0436) although there was no difference between those who did and did not receive pre-HCT FLT3 inhibition in the rate of detectable pre-HCT MRD (48.3% *v* 52.1%). Participants who received MAC had improved OS compared with those who received reduced-intensity conditioning (RIC) (HR, 0.529; P = .0027), irrespective of MRD status (Data Supplement, Fig 5). The effect of gilteritinib versus placebo in participants receiving MAC and RIC separately is shown in the Data Supplement (Fig 6).

Subgroup analysis revealed differences in outcomes according to the geographic region. Gilteritinib was beneficial in North America, was of minimal benefit in Asia/rest of world (ROW), and had a mildly negative effect in Europe (Fig 4). However, there were distinct geographic differences in study populations and practice patterns, such as the time from diagnosis to HCT, number of induction and consolidation courses, pre-HCT FLT3 inhibitor use, conditioning regimen, and concomitant azole use (Data Supplement, Table 1).

Safety

The SAF consisted of 178 gilteritinib and 177 placebo participants. In the gilteritinib arm, 94 of 178 (52.8%) participants completed 24 months of maintenance compared with 96 of 178 (53.9%) on placebo. Treatment-emergent grade II-IV aGVHD occurred in 33 of 178 (18.5%) participants on gilteritinib versus 36 of 177 (20.3%) on placebo (P = .6157),

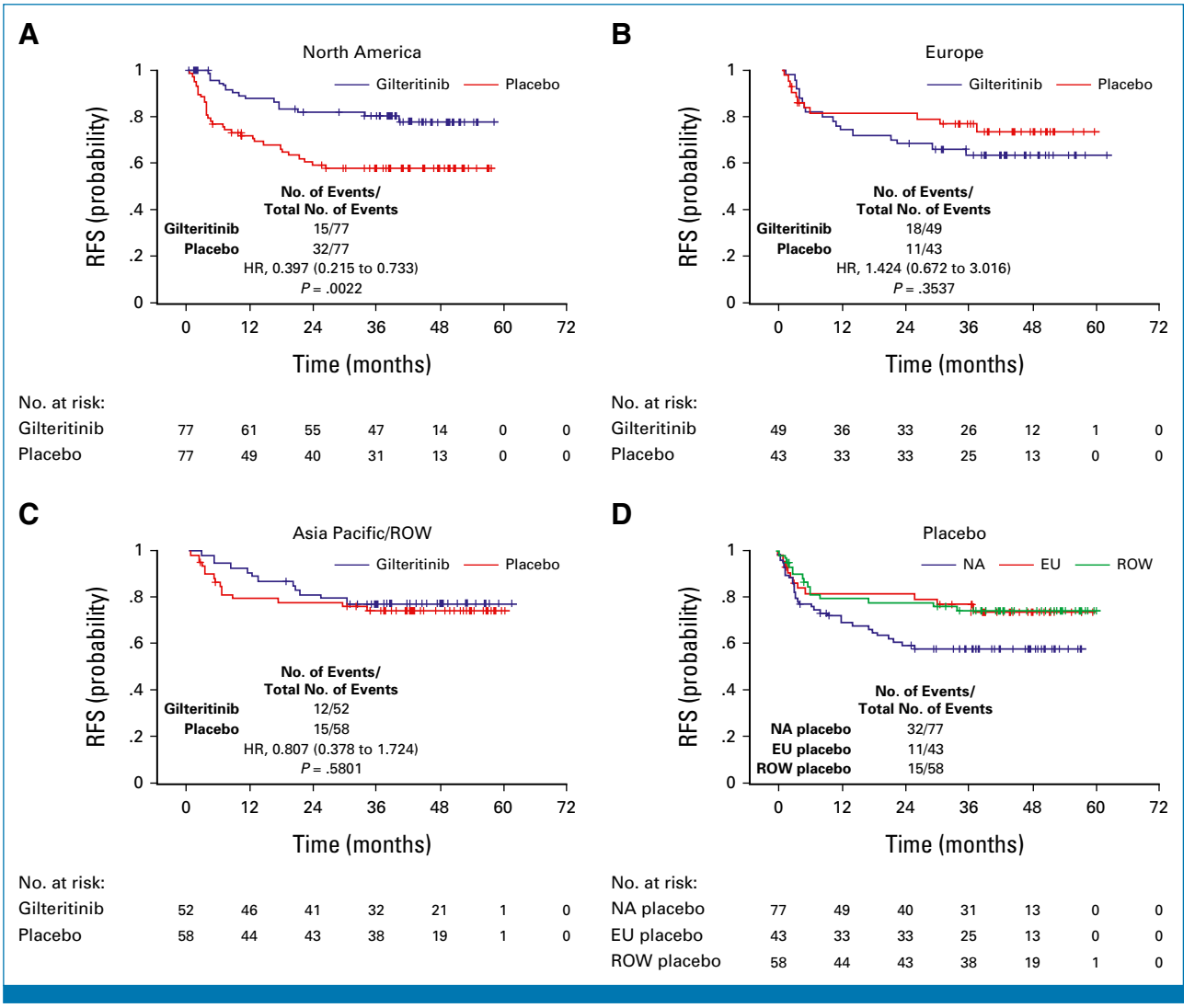

FIG 4. Relapse-free survival by treatment arm according to the geographic region: (A) North America (United States and Canada), (B) Europe (Greece, Belgium, France, Spain, Italy, United Kingdom, Denmark, Poland, Germany), (C) Asia Pacific and ROW (Japan, Korea, Taiwan, Australia, New Zealand), and (D) Relapse-free survival of placebo arms only from the three regions (NA, EU, and ROW). EU, Europe; HR, hazard ratio; NA, North America; ROW, rest of world.

whereas treatment-emergent cGVHD occurred in 93 of 178 (52.2%) on gilteritinib versus 75 of 177 (42.4%) on placebo (P = .181).

Treatment-emergent AEs (TEAEs) ≥grade 3 occurred in 146 of 178 (82%) participants on gilteritinib compared with 94 of 177 (53.1%) on placebo. Both treatment-emergent myelosuppression and infection were more common in the gilteritinib arm compared with placebo, and myelosuppression was the most common reason for early withdrawal from study treatment. Table 2 lists grade 3 or greater TEAEs occurring in 5% or more of participants, and TEAEs leading to drug interruption, dose reduction, or withdrawal from treatment are summarized in the Data Supplement (Table 2). TEAEs leading to drug discontinuation by geographic region are displayed in the Data Supplement (Table 3).

Because of a previously noted association between azole use, gilteritinib trough levels, and myelosuppression,[25] we examined gilteritinib pharmacokinetics using plasma collected at regular intervals. A total of 67.8% of participants were treated with concomitant azoles (fluconazole, itraconazole, posaconazole, voriconazole, and isavuconazonium), with considerable geographic variation. Concomitant azole use was associated with higher median gilteritinib concentrations, but there was wide interparticipant variability (Data Supplement, Fig 7A). Concomitant azole use was more common outside of North America (Data Supplement, Fig 7B).

DISCUSSION

These data show that the improvement in RFS conferred by gilteritinib over placebo did not reach the predetermined

TABLE 2. Grade 3 or Greater Treatment-Emergent Adverse Events Occurring in 5% or More of Participants (SAF population)

	Gilteritinib (n = 178)	Placebo (n = 177)	Total (n = 355)
Adverse Event	No. of Patients (%)		
Hematologic			
Neutrophil count decreased	64 (36)	23 (13)	87 (24.5)
Platelet count decreased	38 (21.3)	20 (11.3)	58 (16.3)
Anemia	17 (9.6)	14 (7.9)	31 (8.7)
WBC count decreased	18 (10.1)	3 (1.7)	21 (5.9)
Nonhematologic			
ALT increased	11 (6.2)	8 (4.5)	19 (5.4)
AST increased	11 (6.2)	6 (3.4)	17 (4.8)
Hypertension	11 (6.2)	6 (3.4)	17 (4.8)
Creatine phosphokinase elevation	14 (7.9)	1 (0.6)	15 (4.2)

Abbreviation: SAF, safety analysis set.

level of significance. However, in secondary analysis, consistent with the pretrial hypothesis, participants with *FLT3-ITD* AML who undergo HCT in first remission with peri-HCT detectable *FLT3-ITD* MRD benefit from post-HCT gilteritinib. By contrast, participants in deep remissions did not benefit from maintenance gilteritinib and were therefore exposed unnecessarily to its potential toxicity.

Our data suggest that FLT3 inhibition during induction and/or consolidation may select for participants who are more likely to benefit from post-HCT FLT3 inhibition, which was somewhat unexpected. It is possible that in many cases, pre-HCT FLT3 inhibition serves to control, but not eliminate, FLT3-driven AML clones, and continuous inhibition is necessary until an allogeneic effect can eradicate the disease. In the absence of FLT3 inhibition during induction, many participants with these FLT3-driven clones presumably relapse before HCT.

Although *FLT3-ITD* mutations detected by standard PCR have generally been considered unreliable markers of MRD,[26] recent studies have established the value of PCR-NGS *FLT3-ITD* MRD.[18-20] Using that assay (currently available in the United States),[21] we found a high correlation between detection of a *FLT3-ITD* mutation (at any level) and benefit from a drug specifically targeting that mutation. A post hoc analysis of a recent study using a similar MRD assay suggested that a level of 10^{-4} was an important survival discriminator, but this was postinduction rather than peri-HCT.[20] Our prospective findings establish *FLT3-ITD* mutations as reliable and actionable markers of MRD in the peri-HCT setting.

The principal toxicity observed in this study was myelosuppression, a known effect of potent FLT3 inhibitors.[23,27] The mechanism is likely inhibition of wild-type FLT3 on multipotent progenitor cells.[28] A study of gilteritinib combined with intensive chemotherapy reported an association between higher gilteritinib plasma concentrations and concomitant azole use and myelosuppression.[25] Azole use was much more common outside North America, and given that myelosuppression led to drug interruption, reduction, or withdrawal, variations in azole use might have contributed to the geographic variation in efficacy we observed.

A single cause of the observed regional differences was not identified in efficacy end points. Participants in the placebo arm in North America, in contrast to those in Europe or Asia/ROW, displayed a 2-year RFS very close to the 59% that was predicted from Center for International Blood and Marrow Transplant Research data used in the statistical analysis plan (Fig 4D). In contrast to the other participants, most North American participants received FLT3 inhibitors pre-HCT and, in general, were bridged more rapidly to HCT (Data Supplement, Table 1). *FLT3-ITD* AML is a molecularly heterogeneous disease, with responsiveness to FLT3 inhibition clearly influenced by comutations.[29,30] It is possible that, outside of North America, patients with disease in which FLT3 was a more prominent driver were less likely to remain in remission long enough to enroll on this study because of lack of FLT3 inhibition, a longer time from diagnosis to transplant, or both. These differences might have selected for a different patient population in North America, one more likely to benefit from post-HCT FLT3 inhibition. At the 110 different centers on this study, the variation in number and intensity of induction and consolidation regimens, azole use, availability of FLT3 inhibitors, time to transplantation, conditioning regimens, and GVHD prophylaxis platforms all were reflections of local clinical practice. They might have contributed to such regional differences, but no single practice or group of practices explaining the differences could be identified in multivariate regression models.

We conducted this study to challenge the assumption that all patients with *FLT3-ITD* AML worldwide, regardless of those variations, should receive a FLT3 inhibitor post-HCT, and our results have indeed invalidated that assumption. In summary, we found that post-HCT maintenance with gilteritinib does confer a benefit for patients with *FLT3-ITD*

AML, but only for those with peri-HCT *FLT3-ITD* MRD. At the same time, we have validated the utility of *FLT3-ITD* mutations as useful markers of MRD with clear implications for intervention. These findings are practice-changing, and further study of the data from this trial is likely to yield more insights into the biology and management of this disease.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

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

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The BMT-CTN 1506/MORPHO Study Investigators are presented in Appendix Table A1 (online only).

REFERENCES

1. Dohner H, Wei AH, Appelbaum FR, et al: Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood 140:1345-1377, 2022
2. Levis M, Small D: FLT3: ITDoes matter in leukemia. Leukemia 17:1738-1752, 2003
3. Tallman MS, Wang ES, Altman JK, et al: Acute myeloid leukemia, version 3.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 17:721-749, 2019
4. Deol A, Sengsayadeth S, Ahn KW, et al: Does FLT3 mutation impact survival after hematopoietic stem cell transplantation for acute myeloid leukemia? Cancer 122:3005-3014, 2016

5. NCCN Guidelines: NCCN Clinical Practice Guidelines in Oncology for Guideline for AML. 2023. http://NCCN.org
6. Xuan L, Wang Y, Huang F, et al: Sorafenib maintenance in patients with FLT3-ITD acute myeloid leukaemia undergoing allogeneic haematopoietic stem-cell transplantation: An open-label, multicentre, randomised phase 3 trial. Lancet Oncol 21:1201-1212, 2020
7. Burchert A, Bug G, Fritz LV, et al: Sorafenib maintenance after allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia with FLT3-internal tandem duplication mutation (SORMAIN). J Clin Oncol 38:2993-3002, 2020
8. Maziarz RT, Levis M, Patnaik MM, et al: Midostaurin after allogeneic stem cell transplant in patients with FLT3-internal tandem duplication-positive acute myeloid leukemia. Bone Marrow Transpl 56:1180-1189, 2021
9. Levis MJ, Chen YB, Hamadani M, et al: FLT3 inhibitor maintenance after allogeneic transplantation: Is a placebo-controlled, randomized trial ethical? J Clin Oncol 37:1604-1607, 2019
10. Chen YB, Li S, Lane AA, et al: Phase I trial of maintenance sorafenib after allogeneic hematopoietic stem cell transplantation for fms-like tyrosine kinase 3 internal tandem duplication acute myeloid leukemia. Biol Blood Marrow Transpl 20:2042-2048, 2014
11. Pratz KW, Rudek MA, Smith BD, et al: A prospective study of peritransplant sorafenib for patients with FLT3-ITD acute myeloid leukemia undergoing allogeneic transplantation. Biol Blood Marrow Transpl 26:300-306, 2020
12. Dohner H, Weber D, Krzykalla J, et al: Midostaurin plus intensive chemotherapy for younger and older patients with AML and FLT3 internal tandem duplications. Blood Adv 6:5345-5355, 2022
13. Morin S, Giannotti F, Mamez AC, et al: Real-world experience of sorafenib maintenance after allogeneic hematopoietic stem cell transplantation for FLT3-ITD AML reveals high rates of toxicity-related treatment interruption. Front Oncol 13:1095870, 2023
14. Dillon LW, Gui G, Page KM, et al: DNA sequencing to detect residual disease in adults with acute myeloid leukemia prior to hematopoietic cell transplant. JAMA 329:745-755, 2023
15. Walter RB, Buckley SA, Pagel JM, et al: Significance of minimal residual disease before myeloablative allogeneic hematopoietic cell transplantation for AML in first and second complete remission. Blood 122:1813-1821, 2013
16. Zhou Y, Othus M, Araki D, et al: Pre- and post-transplant quantification of measurable ("minimal") residual disease via multiparameter flow cytometry in adult acute myeloid leukemia. Leukemia 30: 1456-1464, 2016
17. Hourigan CS, Dillon LW, Gui G, et al: Impact of conditioning intensity of allogeneic transplantation for acute myeloid leukemia with genomic evidence of residual disease. J Clin Oncol 38:1273-1283, 2020
18. Loo S, Dillon R, Ivey A, et al: Pretransplant FLT3-ITD MRD assessed by high-sensitivity PCR-NGS determines posttransplant clinical outcome. Blood 140:2407-2411, 2022
19. Grob T, Sanders MA, Vonk CM, et al: Prognostic value of FLT3-internal tandem duplication residual disease in acute myeloid leukemia. J Clin Oncol 41:756-765, 2023
20. Erba HP, Montesinos P, Kim HJ, et al: Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 401:1571-1583, 2023
21. Levis MJ, Perl AE, Altman JK, et al: A next-generation sequencing-based assay for minimal residual disease assessment in AML patients with FLT3-ITD mutations. Blood Adv 2:825-831, 2018
22. Blatte TJ, Schmalbrock LK, Skambraks S, et al: getITD for FLT3-ITD-based MRD monitoring in AML. Leukemia 33:2535-2539, 2019
23. Perl AE, Martinelli G, Cortes JE, et al: Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. N Engl J Med 381:1728-1740, 2019
24. Cheson BD, Bennett JM, Kopecky KJ, et al: Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 21:4642-4649, 2003
25. Pratz KW, Cherry M, Altman JK, et al: Gilteritinib in combination with induction and consolidation chemotherapy and as maintenance therapy: A phase IB study in patients with newly diagnosed AML. J Clin Oncol, 41:426-4246, 2023
26. Heuser M, Freeman SD, Ossenkoppele GJ, et al: 2021 Update on MRD in acute myeloid leukemia: A consensus document from the European LeukemiaNet MRD Working Party. Blood 138: 2753-2767, 2021
27. Cortes JE, Khaled S, Martinelli G, et al: Quizartinib versus salvage chemotherapy in relapsed or refractory FLT3-ITD acute myeloid leukaemia (QuANTUM-R): A multicentre, randomised, controlled, open-label, phase 3 trial. Lancet Oncol 20:984-997, 2019
28. Beaudin AE, Boyer SW, Forsberg EC: Flk2/Flt3 promotes both myeloid and lymphoid development by expanding non-self-renewing multipotent hematopoietic progenitor cells. Exp Hematol 42: 218-229.e4, 2014
29. Dohner K, Thiede C, Jahn N, et al: Impact of NPM1/FLT3-ITD genotypes defined by the 2017 European LeukemiaNet in patients with acute myeloid leukemia. Blood 135:371-380, 2020
30. Smith CC, Levis MJ, Perl AE, et al: Molecular profile of FLT3-mutated relapsed/refractory patients with AML in the phase 3 ADMIRAL study of gilteritinib. Blood Adv 6:2144-2155, 2022

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Gilteritinib as Post-Transplant Maintenance for AML With Internal Tandem Duplication Mutation of *FLT3*

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APPENDIX

TABLE A1. BMT-CTN 1506/MORPHO Study Investigators

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(continued in next column)

TABLE A1. BMT-CTN 1506/MORPHO Study Investigators (continued)

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(continued on following page)

TABLE A1. BMT-CTN 1506/MORPHO Study Investigators (continued)

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Olalekan Oluwole	Vanderbilt University Medical Center
Masahiro Onozawa	Hokkaido University Hospital
Jeremy Pantin	Augusta University, Georgia Regents University
Esperanza B. Papadopoulos	Memorial Sloan-Kettering Cancer Center
Kristjan Paulson	CancerCare Manitoba
Lucy Pemberton	Dunedin Hospital
Travis Perera	Wellington Hospital
Alexander E. Perl	University of Pennsylvania
Beata Piatkowska-Jakubas	Szpital Uniwersytecki w Krakowie
Xavier Poire	Cliniques Universitaires Saint-Luc
Rachel Protheroe	University Hospitals Bristol NHS Foundation Trust
Alessandro Rambaldi	Ospedale Papa Giovanni XXIII
David Ritchie	Royal Melbourne Hospital
Kelly Ross	West Virginia University Medicine

(continued in next column)

TABLE A1. BMT-CTN 1506/MORPHO Study Investigators (continued)

Investigator	Institution
Marie-Therese Rubio	CHRU Brabois—Service Hématologie et Medecine Interne
Stella Santarone	Ospedale Civile Santo Spirito
Jaime Sanz Caballer	H. U. Politecnico La Fe
Masashi Sawa	Anjo Kosei Hospital
Dale Schaar	Rutgers Cancer Institute
Christoph Scheid	Medical University of Cologne
Jeffrey Schriber	Cancer Transplant Institute at Virginia G. Piper Cancer Center
Stuart Seropian	Yale University
Nilay Shah	West Virginia University Medicine
Nirav Shah	Medical College of Wisconsin
Tsiporah Shore	NYP/Weill Cornell Medical Center
Jorge Sierra Gil	Hospital de la Santa Creu i Sant Pau
Anurag Singh	The University of Kansas Health System
Ronald Sobecks	Cleveland Clinic Foundation
Gerard Socie	Hopital Saint Louis
Robert Soiffer	Dana Farber Cancer Institute
Melhem Solh	Northside Hospital
Kellie Sprague	Tufts Medical Center
Alexandros Spyridonidis	University General Hospital of Patras
Matthias Stelljes	Universitatsklinikum Muenster
Patrick Stiff	Loyola University Medical Center
Robert Stuart	Medical University of South Carolina
Masatsugu Tanaka	Kanagawa Cancer Center
Anand Tandra	Indiana Blood and Marrow Transplant
Eleni Tholouli	Central Manchester University Hospital NHS Foundation Trust
Xavier Thomas	Centre Hospitalier Lyon Sud
Kirsty Thomson	University College London Hospital NHS Foundation Trust
Mario Tiribelli	Azienda Ospedaliero-Universitaria di Udine
Benjamin Tomlinson	University Hospitals Cleveland Medical Center
Panagiotis Tsirigotis	University Hospital Attikon
Dimitrios Tzachanis	University of California San Diego
Naoyuki Uchida	KKR Toranomon Hospital
Masumi Ueda	Fred Hutchinson Cancer Research Center
Celalettin Ustun	University of Minnesota
Geoffrey L. Uy	Washington University in St Louis
David Valcarcel Ferreiras	Hospital Universitario Vall D'Hebron
Sumithra Vasu	Ohio State University Hospital
Eva Wagner	Johannes-Gutenberg-Universitat, Universitätsklinik Mainz
Edmund K. Waller	Emory University
Anne-Marie Watson	Liverpool Hospital
Daniel Weisdorf	University of Minnesota
John R. Wingard	University of Florida

(continued on following page)

TABLE A1. BMT-CTN 1506/MORPHO Study Investigators (continued)

Investigator	Institution
Christine Wolschke	Universitatsklinikum Hamburg-Eppendorf
Tomasz Wrobel	Uniw Szpital Kliniczny im Jana Mikulicza-Radeckieg we Wrocla
Ibrahim Yakoub-Agha	CHRU de Lille
Takuji Yamauchi	Kyushu University Hospital
Jean Yared	University of Maryland Medical Center
Su-Peng Yeh	China Medical University Hospital
Sung-Soo Yoon	Seoul National University Hospital
Satoshi Yoshihara	Hyogo College of Medicine, College Hospital