Impact of hematopoietic cell transplantation and quizartinib in newly diagnosed patients with acute myeloid leukemia and FMS-like tyrosine kinase 3-internal tandem duplications in the QuANTUM-First trial

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Abstract

QuANTUM-First (ClinicalTrials.gov identifier: NCT02668653) was a randomized phase III trial in patients with newly diagnosed *FLT3*-internal tandem duplication (ITD)-positive acute myeloid leukemia (AML) treated with quizartinib or placebo plus standard induction and consolidation chemotherapy and/or allogeneic hematopoietic cell transplantation (allo-HCT), followed by single-agent maintenance therapy. We evaluated the impact of allo-HCT performed in first complete remission (CR1) or composite CR1 (CRc1) on overall survival (OS), considering treatment randomization. *Post-hoc* extended Cox regression multivariable analyses were conducted in patients who achieved complete remission/composite complete remission by the end of induction, including allo-HCT in CR1/CRc1 as a time-dependent variable to identify prognostic and predictive factors for OS. There were 297 patients with complete remission by the end of induction (quizartinib, N=147; placebo, N=150); of these, 157 (52.9%) underwent allo-HCT in CR1 (quizartinib, N=84; placebo, N=73). There were 368 patients with composite complete remission by the end of induction (quizartinib, N=192; placebo, N=176); of these, 196 (53.3%) underwent allo-HCT in CRc1 (quizartinib, N=110; placebo, N=86). Multivariable analyses revealed quizartinib treatment and allo-HCT in either CR1 (hazard ratio [HR]=0.553, 95% confidence interval [95% CI]: 0.383-0.798, *P*=0.0015 and HR=0.527, 95% CI: 0.349-0.796, *P*=0.0023, respectively) or CRc1 (HR=0.645, 95% CI: 0.470□0.886, *P*=0.0068 and HR=0.557, 95% CI: 0.391-0.793, *P*=0.0012, respectively) as significant predictive factors for a longer OS. No new safety signals were identified. Patients who underwent protocol-specified allo-HCT in CR1/CRc1 experienced post-transplant-related complications, mostly grade ≥2 graft-*versus*-host disease, as expected. This *post-hoc* analysis further supports the use of quizartinib and allo-HCT in CR1/CRc1 as an efficacious and well-tolerated treatment strategy for newly diagnosed *FLT3*-ITD-positive AML patients fit for intensive chemotherapy.

Introduction

FMS-like tyrosine kinase 3-internal tandem duplication (*FLT3*-ITD) is among the most common genetic alterations in newly diagnosed acute myeloid leukemia (AML), with an incidence of ≈25%; it is associated with poor prognosis, high relapse rate, and inferior overall survival (OS).[1,2] Standard chemotherapy with FLT3 inhibitors followed by allogeneic hematopoietic cell transplantation (allo-HCT) is the mainstay treatment for patients with newly diagnosed *FLT3*-ITD-positive AML who are fit for intensive chemotherapy.[3,4]

According to the most recent National Comprehensive Cancer Network (NCCN)[4] and European LeukemiaNet (ELN)[3] AML guidelines, all patients with *FLT3*-ITD AML are categorized as intermediate risk, regardless of *FLT3*-ITD allelic ratio (*FLT3*-ITD/*FLT3* wild-type) or nucleophosmin 1 (*NPM1*) mutation status. Allo-HCT in first complete remission (CR1) improves OS and relapse-free survival (RFS) in patients with AML.[5,6] However, even with allo-HCT, the risk of relapse remains high in patients with newly diagnosed *FLT3*-ITD-positive AML (30%-59%), particularly in comparison to that of patients without *FLT3*-ITD (16%-19%).[7,8] Therefore, inhibiting the tyrosine kinase signaling pathway has been a successful new therapeutic strategy for these patients.[9-13] Furthermore, in patients with newly diagnosed *FLT3*-mutated AML, treatment with midostaurin in combination with standard chemotherapy, including the option to undergo allo-HCT in CR1 or complete remission (CR) with incomplete neutrophil or platelet recovery (CRi), improved survival substantially, relative to placebo. Of note, the benefit provided by midostaurin over placebo was more pronounced in patients who underwent allo-HCT than in those who did not.[12,14]

Quizartinib is a highly potent, selective, second-generation, type II FLT3 inhibitor for once-daily, oral treatment.[15-18] Based on data from the QuANTUM-First trial (ClinicalTrials.gov identifier: NCT02668653),[19] quizartinib has recently been approved in combination with chemotherapy across induction, consolidation, and as maintenance monotherapy by the United States Food and Drug Administration,[20,21] the Japanese health agency,[22] the European Medicines Agency,[23,24] and by the United Kingdom health agency,[25,26] for the treatment of adult patients with newly diagnosed *FLT3*-ITD-positive AML (but not after allo-HCT in the United States). In QuANTUM-First, the addition of quizartinib to standard induction and consolidation chemotherapy, including allo-HCT, followed by up to 36 cycles (≈3 years) of quizartinib maintenance monotherapy resulted in a statistically significant 16.8 months OS extension compared with standard therapy (placebo group) in patients with newly diagnosed *FLT3*-ITD-positive AML, with a significant reduction in the risk of death (hazard ratio [HR]=0.78, *P*=0.032), and a manageable safety profile.[19] A clinically meaningful reduction in cumulative incidence of relapse (CIR), an increased duration of CR, and a reduction in measurable residual disease contributed to the OS benefit. The objectives of this QuANTUM-First *post-hoc* analysis were to assess the impact of allo-HCT in CR1 and in composite CR1 (CRc1), with composite CR (CRc) including both CR as well as CRi and the interplay with quizartinib treatment on clinical outcomes in patients with newly diagnosed *FLT3*-ITD-positive AML.

Methods

A detailed description of the QuANTUM-First trial was previously published.[19] Per protocol, patients were permitted to undergo allo-HCT after CR or CRi had been achieved (protocol-specified allo-HCT).[19] Allo-HCT for consolidation could be performed after induction, any time during consolidation, or within the first 3 months of maintenance.[19] After engraftment, patients who received protocol-specified allo-HCT were eligible to enter maintenance and received 36 cycles (28 days per cycle) of quizartinib 60 mg daily or placebo, according to their initial study randomization. Any allo-HCT performed for other reasons (e.g., molecular relapse or without CR or CRi response) was considered as non-protocol-specified AML therapy.[19] Patients receiving non-protocol-specified AML therapy were discontinued from the allocated treatment and followed up for clinical outcome data. Any allo-HCT performed after treatment discontinuation was non-protocol-specified.[19] The trial was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines outlined by the International Council for Harmonisation. Institutional review boards or independent ethics committees approved the protocol at each participating site. Patients provided written informed consent before enrollment.

Statistical analyses of efficacy

OS was analyzed in the intent-to-treat analysis set, comprising all randomized patients. The median duration of follow-up was calculated by the reverse Kaplan-Meier estimate.[27] The effect of allo-HCT on OS as a time-dependent intervening event was tested by using the Mantel-Byar method[28] for univariable and extended Cox regression (Andersen-Gill model)[29] for multivariable analyses. The Mantel-Byar univariable OS analysis was performed in patients who achieved CR/CRc by the end of induction comparing OS for patients who underwent allo-HCT with OS for patients who did not undergo allo-HCT in each treatment arm. The multivariable extended Cox regression OS analysis was performed in patients who achieved CR/CRc by the end of induction, stratified by region, age, and white blood cell count, including allo-HCT in CR1/CRc1 as a time-dependent variable and adjusted for *FLT3*-ITD variant allele frequency (*FLT3*-ITD/total *FLT3*) and sex. The method of Simon and Makuch[30] was used to assess the time-dependent effect of allo-HCT in CR1/CRc1 on OS according to initial randomization, in patients who

achieved CR/CRc by the end of induction. The Simon and Makuch plot considers the timing of allo-HCT occurrence; therefore, once a patient undergoes allo-HCT, the patient switches from the "without allo-HCT" category to the "with allo-HCT" category and is censored at that time in the "without allo-HCT" curve. *P* values were not adjusted for multiplicity. The analyses presented are *post-hoc* analyses. RFS and CIR were analyzed in patients who achieved CR/CRc by the end of induction based on independent review committee assessment. RFS was defined as the time from randomization until documented relapse or death from any cause, whichever occurred first. The medians of OS and RFS were estimated based on the Kaplan-Meier method, the two-sided 95% confidence interval (95% CI) using the method of Brookmeyer and Crowley, and the HR (with 95% CI) using an unstratified Cox proportional hazards model.

Graft-*versus*-host disease analyses

The incidence and severity (including grading and staging)[31,32] of acute or chronic graft-*versus*-host disease (GvHD) were assessed in the safety analysis population (i.e., patients who received at least one dose of quizartinib or placebo and underwent protocol-specified allo-HCT) every 4 weeks after allo-HCT and at the following post-transplant timepoints: day 100, 6 months (±3 months), 12 months (±3 months), 18 months (±3 months), and 24 months (–3/+6 months). Details on patients, randomization, and safety analyses are provided in the *Online Supplementary Methods*.

Results

Patients' disposition

In QuANTUM-First, 539 patients were randomized to receive either quizartinib (N=268) or placebo (N=271) (Figure 1).[19] At the time the trial was conducted, the risk stratification outlined in the NCCN and ELN guidelines[33] of that time indicated that patients with a high *FLT3*-ITD allelic ratio and *NPM1* wild type had an adverse risk, those with a low *FLT3*-ITD allelic ratio and *NPM1* wild type had an intermediate risk, and those with a low *FLT3*-ITD allelic ratio and *NPM1* mutation had a favorable risk. Allo-HCT was not recommended by these guidelines for patients with low *FLT3*-ITD allelic ratio and *NPM1* mutation.

Overall, 272 (50.4%) patients of the 539 in the intent-to-treat population underwent allo-HCT (both protocol-specified and non-protocol-specified; 53.7% [144/268] of patients in the quizartinib arm and 47.2% [128/271] in the placebo arm) (Table 1). There were 83 patients who underwent non-protocol-specified allo-HCT (44 in the quizartinib arm and 39 in the placebo arm), but four of these patients (2 in each treatment arm) also underwent protocol-specified allo-HCT (Table 1). Of the intent-to-treat population, 64.6% of patients in either the quizartinib arm (173/268) or the placebo arm (175/271) entered consolidation (Figure 1). Of these, allo-HCT in CR1/CRc1 was performed in 31.3% (84/268)/41.1% (110/268) of patients in the quizartinib arm *versus* 26.9% (73/271)/31.7% (86/271) in the placebo arm (Figure 1, Table 1). In addition, there were 115 allo-HCT performed outside CR1 (22.4% [60/268] of patients in the quizartinib arm and 20.3% [55/271] in the placebo arm) (Table 1). Of the 115 allo-HCT conducted outside CR1, 93 (80.9%) occurred in patients who did not achieve CR1 (52/268 [19.4%] in the quizartinib arm and 41/271 [15.1%] in the placebo arm) and 22 (19.1%) occurred after relapse (8/268 [3.0%] in the quizartinib arm and 14/271 [5.2%] in the placebo arm) (Table 1). Of 93 patients who underwent allo-HCT not in CR1, 39 had allo-HCT in CRc1 (26/268 [9.7%] in the quizartinib arm and 13/271 [4.8%] in the placebo arm) (Table 1). Of the intent-to-treat population, 43.3% (116/268) of patients in the quizartinib arm *versus* 33.9% (92/271) in the placebo arm entered maintenance (Figure 1). Of these, allo-HCT in CR/CRc1 was performed in 22.8% (61/268)/28.4% (76/268) of patients in the quizartinib arm *versus* 13.3% (36/271)/16.6% (45/271) in the placebo arm (Figure 1). The disposition of patients who achieved CR/CRc is presented in *Online Supplementary Figure S1*.

Conditioning regimen and graft characteristics in patients undergoing allogeneic transplantation in first remission

The conditioning regimens and graft characteristics were well balanced between treatment arms in the two cohorts (Table 1). Among patients who underwent allo-HCT in CR1/CRc1 with quizartinib (N=84/N=110), those who did so with placebo (N=73/N=86), 50.0%/50.9% in the quizartinib arm received a myeloablative conditioning regimen *versus* 45.2%/47.7% in the placebo arm. Patients predominantly received grafts from unrelated donors (47.6%/49.1% in the quizartinib arm *vs*. 52.1%/50.0% in the placebo arm, respectively). The majority of patients received matched grafts (72.6%/70.9% in the quizartinib arm *vs*. 69.9%/67.4% in the placebo arm, respectively). Peripheral blood was the major source of stem cells for 78.6%/75.5% in the quizartinib arm *versus* 84.9%/83.7% in the placebo arm, respectively. In the quizartinib arm, allo-HCT was performed in CR1/CRc1 after a median time of 3.5 months; in the placebo arm, allo-HCT was performed in CR1 after a median of 3.3 months and in CRc1 after a median of 3.2 months (Table 1). For GvHD prophylaxis, patients received mainly calcineurin inhibitors (cyclosporine and tacrolimus), methotrexate, and mycophenolate mofetil.

Baseline patients' demographics and disease characteristics

Patients' demographics and disease characteristics were well balanced across the five cohorts, including patients who achieved CR (N=297), patients who underwent allo-HCT in CR1 (N=157), patients who achieved CR and did not undergo allo-HCT in CR1 (N=140), patients who achieved CRc

(N=368), and patients who underwent allo-HCT in CRc1 (N=196) (Table 2). The median age of patients achieving CR/CRc was 56 years/55 years, similar to that of the overall population of QuANTUM-First of 56 years.[19] Patients who underwent allo-HCT in CR1/CRc1 were younger (median age of 51 years) with lower rates of Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 (13.4%/11.2%, respectively) than those who did not undergo allo-HCT in CR1

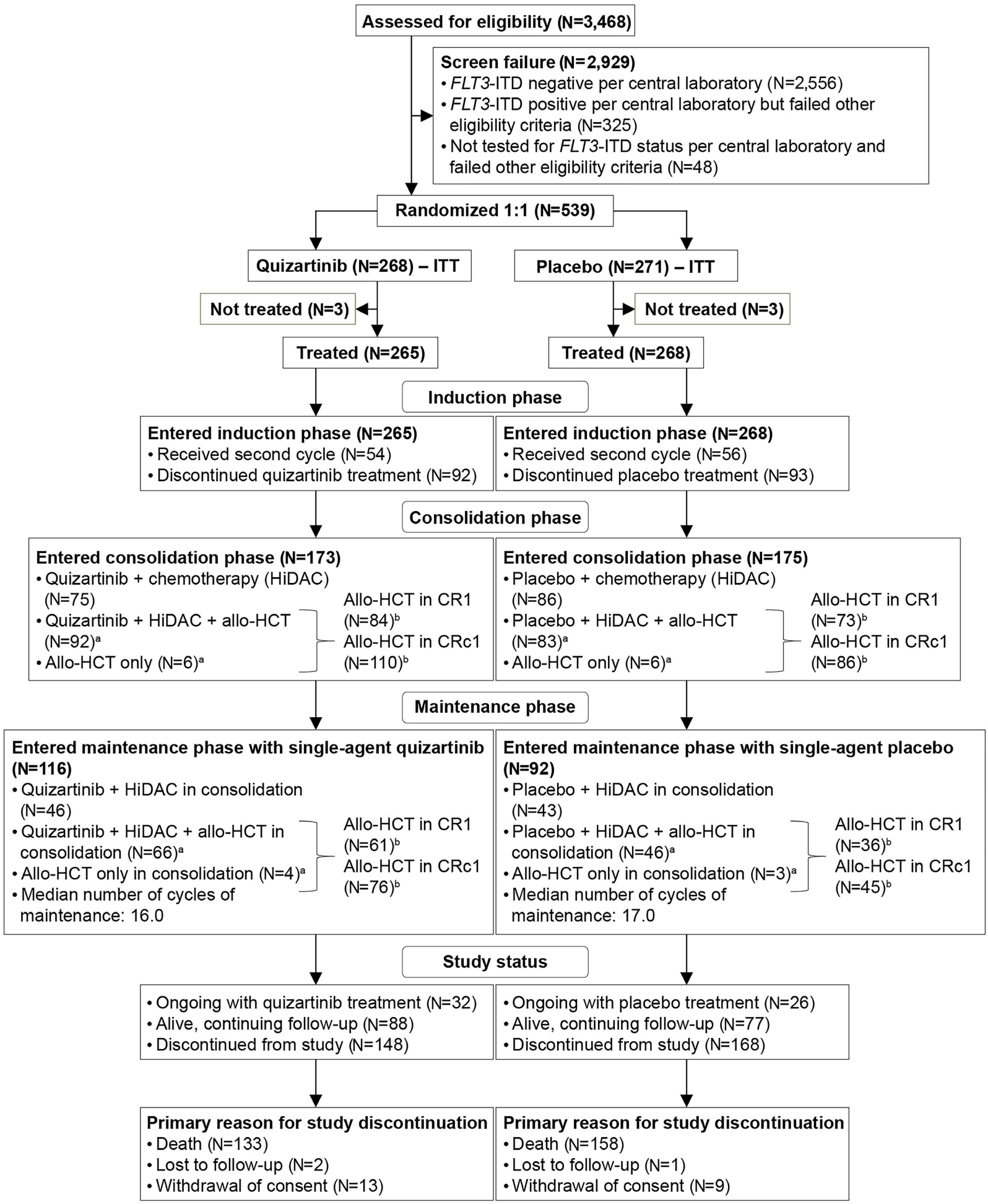


Figure 1. Diagram of the patients flow in the study. [a]Includes protocol-specified allogeneic hematopoietic cell transplantation (allo-HCT). [b]Includes protocol-specified allo-HCT and non-protocol-specified allo-HCT. *FLT3*-ITD: FMS-like tyrosine kinase 3-internal tandem duplication; ITT: intent-to-treat; HiDAC: high-dose cytarabine; CR1: first complete remission; CRc1: first composite complete remission.

Table 1. Allogeneic hematopoietic cell transplantation timing, conditioning regimens, and graft characteristics.

Characteristics	Quizartinib	Placebo
Overall allo-HCT timing		
Patients in the ITT population, N	268	271
Patients who underwent allo-HCT overall,[a] N (%) [95% CI][b]	144 (53.7) [47.6-59.8]	128 (47.2) [41.2-53.4]
In CR1,[c] N (%) [95% CI][b]	84 (31.3) [25.8-37.3]	73 (26.9) [21.7-32.6]
Time to allo-HCT in CR1 in months, median (range)	3.5 (0.6-11.2)	3.3 (0.8-11.6)
Time to allo-HCT in CR1 in months, mean (SD)	4.1 (2.1)	3.6 (1.9)
Outside CR1, N (%) [95% CI][b]	60 (22.4) [17.5-27.9]	55 (20.3) [15.7-25.6]
Without CR, N (%) [95% CI][b]	52 (19.4) [14.8-24.7]	41 (15.1) [11.1-20.0]
In CRc1, N (%) [95% CI][b]	26 (9.7) [6.4-13.9]	13 (4.8) [2.6-8.1]
After relapse,[d] N (%) [95% CI][b]	8 (3.0) [1.3-5.8]	14 (5.2) [2.9-8.5]
In CRc1,[e] N (%) [95% CI][b]	110 (41.0) [35.1-47.2]	86 (31.7) [26.2-37.6]
Time to allo-HCT in CRc1 in months, median (range)	3.5 (0.6-11.2)	3.2 (0.8-11.6)
Time to allo-HCT in CRc1 in months, mean (SD)	4.1 (2.1)	3.6 (1.8)
Outside CRc1, N (%) [95% CI][b]	34 (12.7) [8.9-17.3]	42 (15.5) [11.4-20.4]
Patients who underwent protocol-specified[f] allo-HCT, N (%) [95% CI][b]	102 (38.1) [32.2-44.2]	91 (33.6) [28.0-39.5]
After CR, N (%) [95% CI][b]	74 (27.6) [22.3-33.4]	72 (26.6) [21.4-32.2]
After CRc, N (%) [95% CI][b]	99 (36.9) [31.1-43.0]	85 (31.4) [25.9-37.3]
Patients who underwent non-protocol–specified allo-HCT, N (%) [95% CI][b]	44 (16.4) [12.2-21.4]	39 (14.4) [10.4-19.1]
Conditioning regimen and graft characteristics in patients receiving allo-HCT[a] in CR1		
N of patients	84	73
Conditioning regimen, N (%)		
Ablative, MAC	42 (50.0)	33 (45.2)
Reduced intensity/non-ablative, RIC	34 (40.5)	35 (47.9)
Reduced intensity	11 (13.1)	8 (11.0)
Non-ablative, NMA	23 (27.4)	27 (37.0)
Missing	8 (9.5)	5 (6.8)
Donors related or unrelated, N (%)		
Sibling	29 (34.5)	22 (30.1)
Other related[g]	15 (17.9)	13 (17.8)
Unrelated	40 (47.6)	38 (52.1)
Match type, N (%)		
Matched[h]	61 (72.6)	51 (69.9)
Not matched[i]	5 (6.0)	8 (11.0)
Haploidentical[j]	18 (21.4)	14 (19.2)
Source of stem cells, N (%)		
Bone marrow	15 (17.9)	9 (12.3)
Peripheral blood	66 (78.6)	62 (84.9)
Cord blood	3 (3.6)	2 (2.7)
Conditioning regimen and graft characteristics in patients receiving allo-HCT[a] in CRc1		
N of patients	110	86
Conditioning regimen, N (%)		
Ablative, MAC	56 (50.9)	41 (47.7)
Reduced intensity/non-ablative, RIC	45 (40.9)	40 (46.5)
Reduced intensity	12 (10.9)	9 (10.5)
Non-ablative, NMA	33 (30.0)	31 (36.0)
Missing	9 (8.2)	5 (5.8)
Donors related or unrelated, N (%)		
Sibling	32 (29.1)	26 (30.2)
Other related[g]	24 (21.8)	17 (19.8)
Unrelated	54 (49.1)	43 (50.0)
Match type, N (%)		
Matched[h]	78 (70.9)	58 (67.4)
Not matched[i]	6 (5.5)	9 (10.5)
Haploidentical[j]	26 (23.6)	19 (22.1)

Continued on following page.

Characteristics	Quizartinib	Placebo
Conditioning regimen and graft characteristics in patients receiving allo-HCT[a] in CRc1		
Source of stem cells, N (%)		
Bone marrow	23 (20.9)	12 (14.0)
Peripheral blood	83 (75.5)	72 (83.7)
Cord blood	3 (2.7)	2 (2.3)
Missing	1 (0.9)	0

[a]Includes protocol-specified and non-protocol-specified allogeneic hematopoietic cell transplantation (allo-HCT). Some patients had both protocol-specified and non-protocol-specified allo-HCT. [b]Based on the Clopper-Pearson method. [c]Includes protocol-specified and non-protocol-specified allo-HCT that occurred after the first complete remisssion (CR) without evidence of relapse by independent review committee (IRC) assessment. [d]Includes protocol-specified and non-protocol-specified allo-HCT that occurred after relapse post-CR by IRC assessment. [e]Includes protocol-specified and non-protocol-specified allo-HCT that occurred after the first composite CR without evidence of relapse by IRC assessment. [f]Patients who underwent allo-HCT directly after protocol treatment with no intervening acute myeloid leukemia therapy (excluding conditioning regimens). [g]Relative of the patient other than sibling. [h]Defined as at least antigen-level matching at HLA-A and HLA-B and high-resolution matching at HLA-DRB1 in 6/6 loci. [i]Any other antigen matching less than 6/6 was left to the decision of the treating investigator. [j]Half matching. ITT: intent-to-treat; CI: confidence interval; CR1: first complete remission; SD: standard deviation; CRc1: first composite complete remission; CRc: composite complete remission; MAC: myeloablative conditioning; RIC: reduced intensity conditioning; NMA: non-myeloablative conditioning; HLA: human leukocyte antigen.

(median age of 61.5 years; ECOG PS of 2 in 18.6%) (Table 2). In the overall population, 52.3% had a concomitant *NPM1* mutation, while patients who achieved CR/CRc and those who underwent allo-HCT in CR1/CRc1 had a slightly higher rate of concomitant *NPM1* mutation (65.7%, 63.9%, 64.3%, and 62.8%, respectively). Most patients across the five cohorts (roughly 52.4%-55.6%) had *FLT3*-ITD variant allele frequency values ranging from >25% to ≤50%, which was similar to that of the overall population of QuANTUM-First (52.1%) (Table 2). As expected, patients who did not undergo allo-HCT in CR1 had the highest rates of concomitant *NPM1* mutation (67.1%) as well as the highest rates of *FLT3*-ITD variant allele frequency values, ranging from >25% to ≤50% (57.9%) (Table 2). The patients' demographics and disease characteristics in these five cohorts, separated by treatment arms, are provided in *Online Supplementary Table S1.*

Efficacy analysis

A univariable Mantel-Byar OS analysis found, among patients who achieved CR by the end of induction, a statistically significant OS benefit with allo-HCT in CR1 in the quizartinib arm (P=0.0248) and in the placebo arm (P=0.0046). Similarly, among patients who achieved CR by the end of induction, an OS benefit was found with allo-HCT in CRc1 in the quizartinib arm (P=0.0234) and in the placebo arm (P=0.0008).

According to a multivariable extended Cox regression analysis conducted in patients who achieved CR by the end of induction, both quizartinib treatment (HR=0.553, 95% CI: 0.383-0.798, P=0.0015) (Figure 2A) and allo-HCT in CR1 (HR=0.527, 95% CI: 0.349-0.796, P=0.0023) (Figure 2A) were found to be predictive factors for a better OS. Similarly, in patients who achieved CRc by the end of induction, both quizartinib treatment (HR=0.645, 95% CI: 0.470-0.886, P=0.0068) (Figure 2B) and allo-HCT in CRc1 (HR=0.557, 95% CI: 0.391-0.793, P=0.0012) (Figure 2B) were predictive factors for longer OS. As expected, a *FLT3*-ITD variant allele frequency >50% was an unfavorable prognostic factor for OS (Figure 2B). Neither ECOG PS nor cytogenic risk category was a predictive factor for longer OS in patients who achieved CR/CRc by the end of induction (Figure 2A, B).

Based on this model, quizartinib-treated patients who achieved CR/CRc by the end of induction and proceeded to allo-HCT in CR1/CRc1 had an OS advantage (HR=0.292, 95% CI: 0.168-0.505 for CR1; HR=0.359, 95% CI: 0.225-0.573 for CRc1) at any given time, compared with placebo-treated patients who achieved CR/CRc by the end of induction who had not yet received allo-HCT in CR1/CRc1 by that time.

According to a Kaplan-Meier OS analysis in patients who achieved CR/CRc by the end of induction, longer OS was observed in patients treated with quizartinib *versus* placebo, irrespective of whether they received allo-HCT in CR1/CRc1 or not (Figure 3). Among patients who underwent allo-HCT in CR1, the HR was 0.591 (95% CI: 0.330-1.059) (Figure 3A). Among patients who did not undergo allo-HCT in CR1, the HR was 0.579 (95% CI: 0.353-0.949) (Figure 3B) when OS was censored at the date of starting the conditioning regimen for allo-HCT. Similar findings were obtained in the analysis by allo-HCT in CRc1 (Figure 3C, D). According to a Simon and Makuch OS analysis by allo-HCT, patients who achieved CR by the end of induction in the quizartinib arm had longer OS compared with those in the placebo arm, regardless of whether they received allo-HCT in CR1 or not (Figure 4A). Similar findings were obtained in the analysis by allo-HCT in CRc1 (Figure 4B). The time-dependent Simon and Makuch analysis of the effect of allo-HCT in CR1/CRc1 on OS was consistent with the earlier analysis conducted with the Kaplan-Meier method (Figure 3).

Similar to the OS analysis, the RFS analysis in patients who achieved CR/CRc by the end of induction and underwent allo-HCT showed a longer RFS in patients treated with quizartinib *versus* placebo, irrespective of whether they received allo-HCT in CR1/CRc1 or not (*Online Supplementary Figure S2*). Among patients who underwent

Table 2. Baseline demographics and disease characteristics of specific cohorts of patients.

Characteristics	All patients[a]	Patients who achieved CR	Patients who achieved CR and underwent allo-HCT in CR1[b]	Patients who achieved CR and did not undergo allo-HCT in CR1[c]	Patients who achieved CRc	Patients who achieved CRc and underwent allo-HCT in CRc1[d]
N of patients	539	297	157	140	368	196
Patients' demographics						
Age						
In years, median (range)	56 (20-75)	56 (20-75)	51 (20-70)	61.5 (23-75)	55 (20-75)	51 (20-70)
<60 years, N (%)	323 (59.9)	180 (60.6)	116 (73.9)	64 (45.7)	223 (60.6)	138 (70.4)
≥60 years, N (%)	216 (40.1)	117 (39.4)	41 (26.1)	76 (54.3)	145 (39.4)	58 (29.6)
60-64 years, N (%)	81 (15.0)	47 (15.8)	26 (16.6)	21 (15.0)	55 (14.9)	31 (15.8)
≥65 years, N (%)	135 (25.0)	70 (23.6)	15 (9.6)	55 (39.3)	90 (24.5)	27 (13.8)
Sex, N (%)						
Male	245 (45.5)	125 (42.1)	67 (42.7)	58 (41.4)	159 (43.2)	89 (45.4)
Female	294 (54.5)	172 (57.9)	90 (57.3)	82 (58.6)	209 (56.8)	107 (54.6)
Race, N (%)						
Asian	158 (29.3)	87 (29.3)	55 (35.0)	32 (22.9)	109 (29.6)	69 (35.2)
Black or African American	7 (1.3)	4 (1.3)	0	4 (2.9)	4 (1.1)	0
American Indian or Alaska Native	1 (0.2)	1 (0.3)	0	1 (0.7)	1 (0.3)	0
Native Hawaiian/Pacific Islander	0	0	0	0	0	0
White	322 (59.7)	176 (59.3)	88 (56.1)	88 (62.9)	220 (59.8)	110 (56.1)
Other	51 (9.5)	29 (9.8)	14 (8.9)	15 (10.7)	34 (9.2)	17 (8.7)
Region, N (%)						
North America	34 (6.3)	19 (6.4)	13 (8.3)	6 (4.3)	21 (5.7)	15 (7.7)
Europe	326 (60.5)	181 (60.9)	86 (54.8)	95 (67.9)	225 (61.1)	108 (55.1)
Asia/Other regions	179 (33.2)	97 (32.7)	58 (36.9)	39 (27.9)	122 (33.2)	73 (37.2)
Disease characteristics						
ECOG PS, N (%)[e]						
0	185 (34.3)	107 (36.0)	58 (36.9)	49 (35.0)	126 (34.2)	69 (35.2)
1	270 (50.1)	143 (48.1)	78 (49.7)	65 (46.4)	188 (51.1)	105 (53.6)
2	83 (15.4)	47 (15.8)	21 (13.4)	26 (18.6)	54 (14.7)	22 (11.2)
Cytogenetic risk, N (%)[f]						
Favorable	33 (6.1)	16 (5.4)	7 (4.5)	9 (6.4)	22 (6.0)	10 (5.1)
Intermediate	390 (72.4)	217 (73.1)	122 (77.7)	95 (67.9)	269 (73.1)	154 (78.6)
Unfavorable	46 (8.5)	23 (7.7)	13 (8.3)	10 (7.1)	27 (7.3)	13 (6.6)
Unknown	69 (12.8)	40 (13.5)	14 (8.9)	26 (18.6)	49 (13.3)	18 (9.2)
Missing	1 (0.2)	1 (0.3)	1 (0.6)	0	1 (0.3)	1 (0.5)
Mutated *NPM1*, N (%)[g]	282 (52.3)	195 (65.7)	101 (64.3)	94 (67.1)	235 (63.9)	123 (62.8)
Mutated *CEBPA*, N (%)[g]	126 (23.4)[h]	73 (24.6)	39 (24.8)	34 (24.3)	88 (23.9)	46 (23.5)
FLT3-ITD/total *FLT3*, N (%)[i,j]						
≥3% to ≤25%	192 (35.6)	96 (32.3)	54 (34.4)	42 (30.0)	127 (34.5)	72 (36.7)
>25% to ≤50%	281 (52.1)	165 (55.6)	84 (53.5)	81 (57.9)	193 (52.4)	100 (51.0)
>50%	65 (12.1)	36 (12.1)	19 (12.1)	17 (12.1)	47 (12.8)	24 (12.2)
WBC count at diagnosis of AML, N (%)						
$<40\times10^9$/L	272 (50.5)	141 (47.5)	72 (45.9)	69 (49.3)	178 (48.4)	97 (49.5)
$\geq40\times10^9$/L	267 (49.5)	156 (52.5)	85 (54.1)	71 (50.7)	190 (51.6)	99 (50.5)

[a]Three patients in the intent-to-treat set were randomized but not treated in each arm. [b]Includes protocol-specified allogeneic hematopoietic cell transplantation (allo-HCT) and non-protocol-specified allo-HCT that occurred after the first complete remission (CR) without evidence of relapse by independent review committee (IRC) assessment. [c]Includes 118 patients who achieved CR and did not undergo allo-HCT at all, and 22 patients who achieved CR and underwent allo-HCT outside first CR (after relapse). [d]Includes protocol-specified allo-HCT and non-protocol-specified allo-HCT that occurred after the first composite CR without evidence of relapse by IRC assessment. [e]For one patient in the placebo group, information on Eastern Cooperative Oncology Group performance status was not available. [f]Favorable: inv(16), t(16;16), t(8;21), t(15;17); intermediate: normal, +8, +6, –Y; unfavorable: del(5q), –5, del(7q), –7, complex karyotype. [g]Based on the Navigate BioPharma central data. [h]In a *post-hoc* analysis, 38 (7.1%) patients had *CEBPA* single mutations, and 13 (2.4%) patients had *CEBPA* double mutations. [i]Variant allele frequency was assessed by central laboratory testing. [j]One patient with unknown *FLT3*-ITD/total *FLT3* status by central laboratory testing was positive per local laboratory testing. CR1: first complete remission; CRc: composite complete remission; CRc1: first composite complete remission; ECOG PS: Eastern Cooperative Oncology Group performance status; *NPM1*: nucleophosmin 1; *CEBPA*: CCAAT enhancer-binding protein alpha; *FLT3*-ITD: FMS-like tyrosine kinase 3-internal tandem duplication; WBC: white blood cell; AML: acute myeloid leukemia.

allo-HCT in CR1, the HR was 0.607 (95% CI: 0.351-1.052) (*Online Supplementary Figure S2A*). Among patients who did not undergo allo-HCT in CR1, the HR was 0.682 (95% CI: 0.458-1.016) (*Online Supplementary Figure S2B*). Similar findings were obtained in the RFS analysis by allo-HCT in CRc1 (*Online Supplementary Figure S2C, D*). Consistently, the CIR rates were numerically lower in the quizartinib arm than in the placebo arm, irrespectively of whether the patients received allo-HCT in CR1/CRc1 or not (*Online Supplementary Figure S3*).

Safety analysis

Of the 102 patients in the quizartinib arm and 91 in the placebo arm who underwent protocol-specified allo-HCT in CR1/CRc1, 57 (55.9%)/41 (45.1%), respectively, had post-transplant–related complications (Table 3). Most complications were grade ≥2 GvHD, which affected 34 (33.3%) patients in the quizartinib arm and 22 (24.2%) patients in the placebo arm (Table 3). Among patients who underwent protocol-specified allo-HCT, acute GvHD was reported in 46 (45.1%) patients in the quizartinib arm and in 35 (38.5%) patients in the placebo arm, and the percentage of patients with grade 3/4 acute GvHD was higher in the quizartinib arm (17 [16.7%]) than in the placebo arm (6 [6.6%]) (Table 3). Chronic GvHD was reported in 30 (29.4%) patients in the quizartinib arm and 18 (19.8%) in the placebo arm (Table 3). Of the 85 patients with grade 2-4 acute GvHD and chronic GvHD, the percentage of patients who discontinued in the quizartinib arm (31/51 [60.8%]) was lower than the percentage of those who discontinued placebo (24/34 [70.6%]) (Table 3). *Online Supplementary Table S2* describes the maximum score for each organ. For patients who underwent allo-HCT, clinically relevant medical conditions that had their onset and resolution during the allo-HCT period, as well as other medical conditions that started during the allo-HCT period and were still ongoing on day 1 of the phase, were collected. The most common medical conditions in patients who underwent protocol-specified allo-HCT were gastrointestinal disorders (stomatitis, diarrhea, nausea, and vomiting), infections (cytomegalovirus infection and pneumonia), and immune system disorders (GvHD) (*Online Supplementary Table S3*). Similar proportions of patients in the quizartinib *versus* placebo groups had at least one adverse event (100%, each) and one grade 3 or worse adverse event (96.1% *vs.*

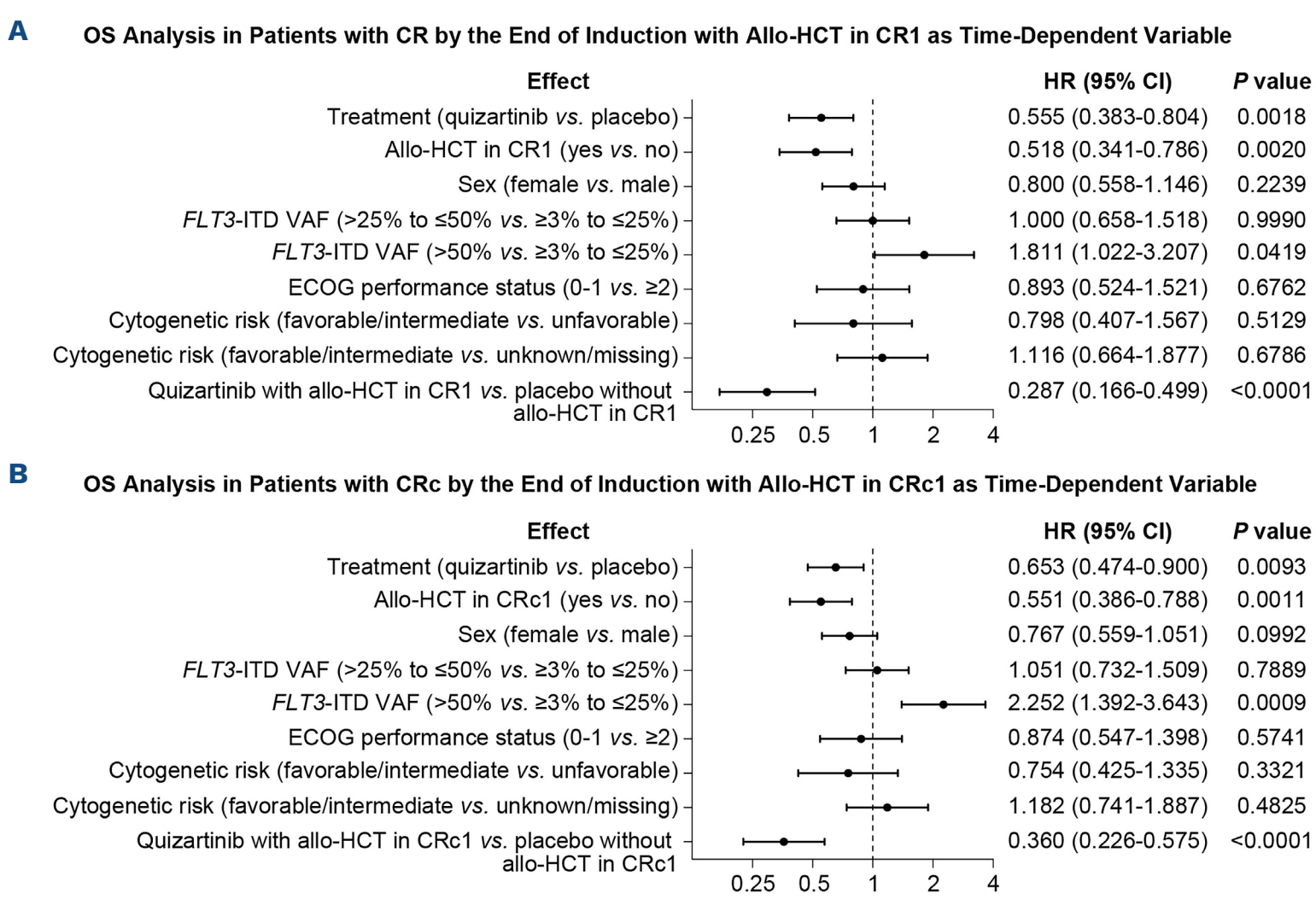
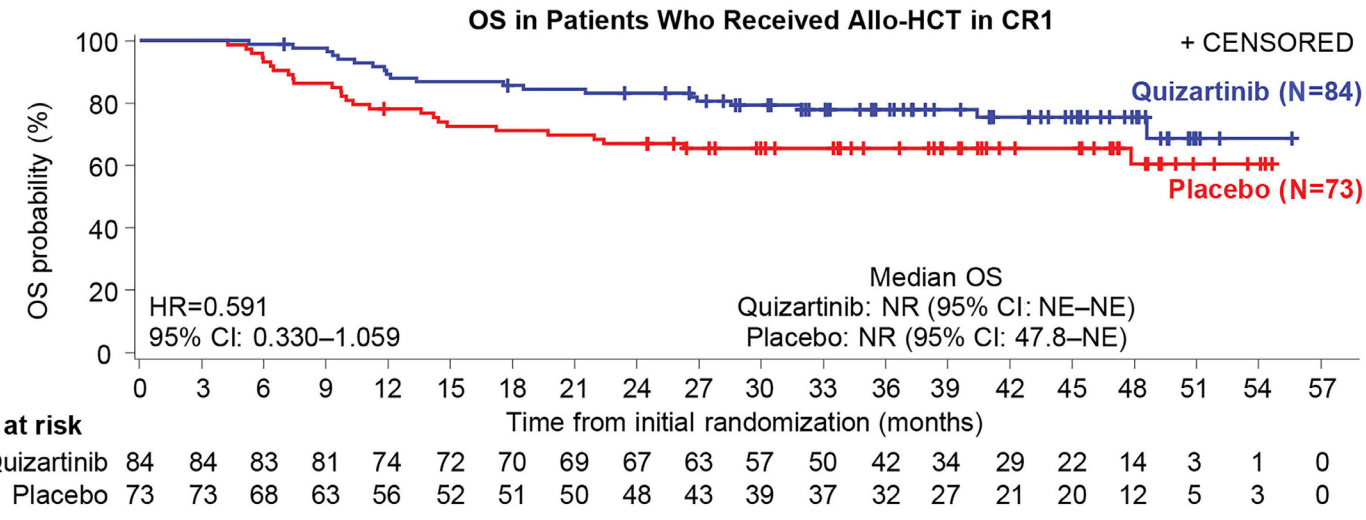


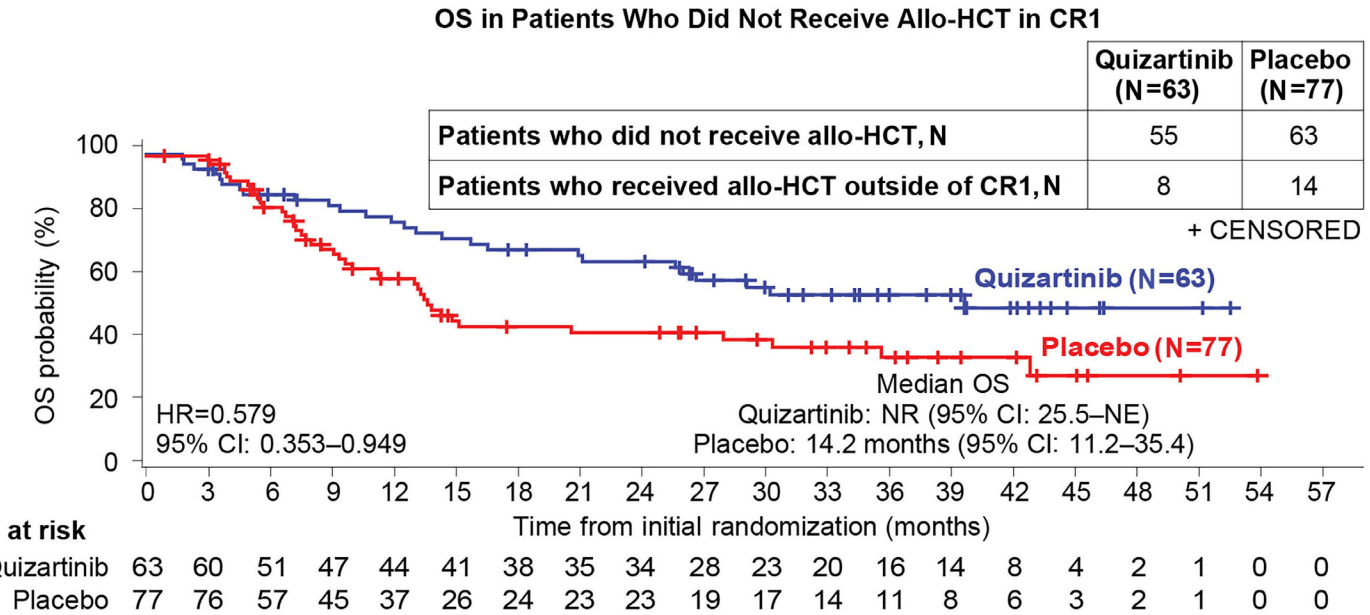
Figure 2. Extended Cox regression analysis of overall survival, stratified by region, age, and white blood cell count. (A, B) Multivariable extended Cox regression *post-hoc* analysis was conducted in patients who achieved complete remission by the end of induction (A) and in patients who achieved composite complete remission by the end of induction (B), including allogeneic hematopoietic cell transplantation in first complete remission (A) and in first composite complete remission (B) as time-dependent variables and adjusted for *FLT3*-ITD variant allele frequency and sex. OS: overall survival; CR: complete remission; allo-HCT: allogeneic hematopoietic cell transplantation; CR1: first complete remission; HR: hazard ratio; CI: confidence interval; *FLT3*-ITD: FMS-like tyrosine kinase 3 internal tandem duplication; VAF: variant allele frequency; ECOG: Eastern Cooperative Oncology Group; CRc: composite complete remission; CRc1: first composite complete remission.

A



N at risk																				
Quizartinib	84	84	83	81	74	72	70	69	67	63	57	50	42	34	29	22	14	3	1	0
Placebo	73	73	68	63	56	52	51	50	48	43	39	37	32	27	21	20	12	5	3	0

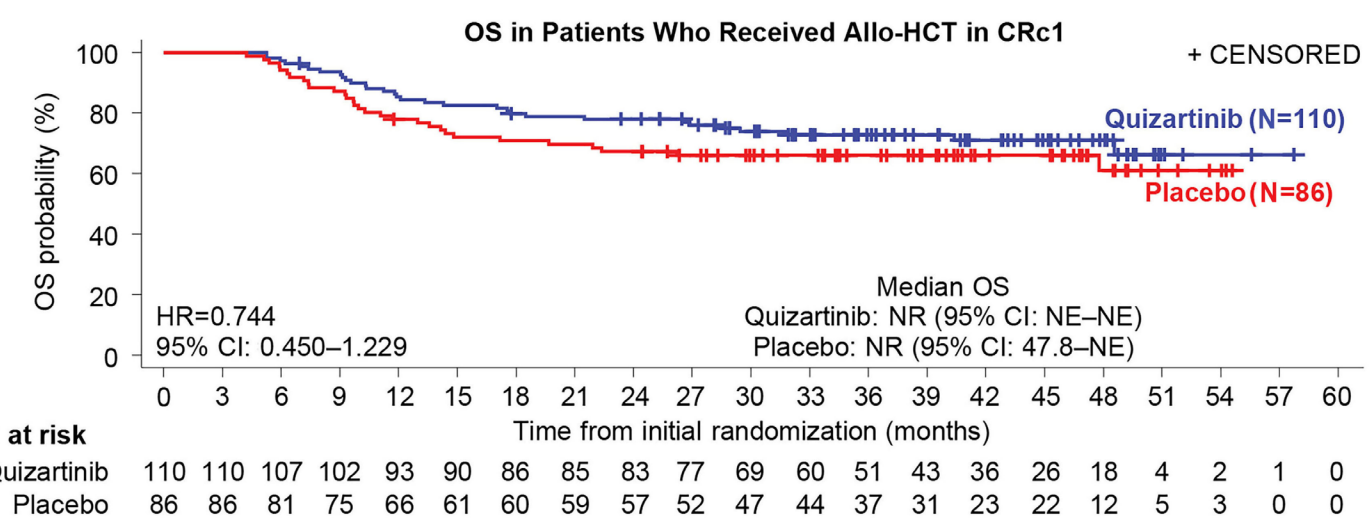
B



	Quizartinib (N=63)	Placebo (N=77)
Patients who did not receive allo-HCT, N	55	63
Patients who received allo-HCT outside of CR1, N	8	14

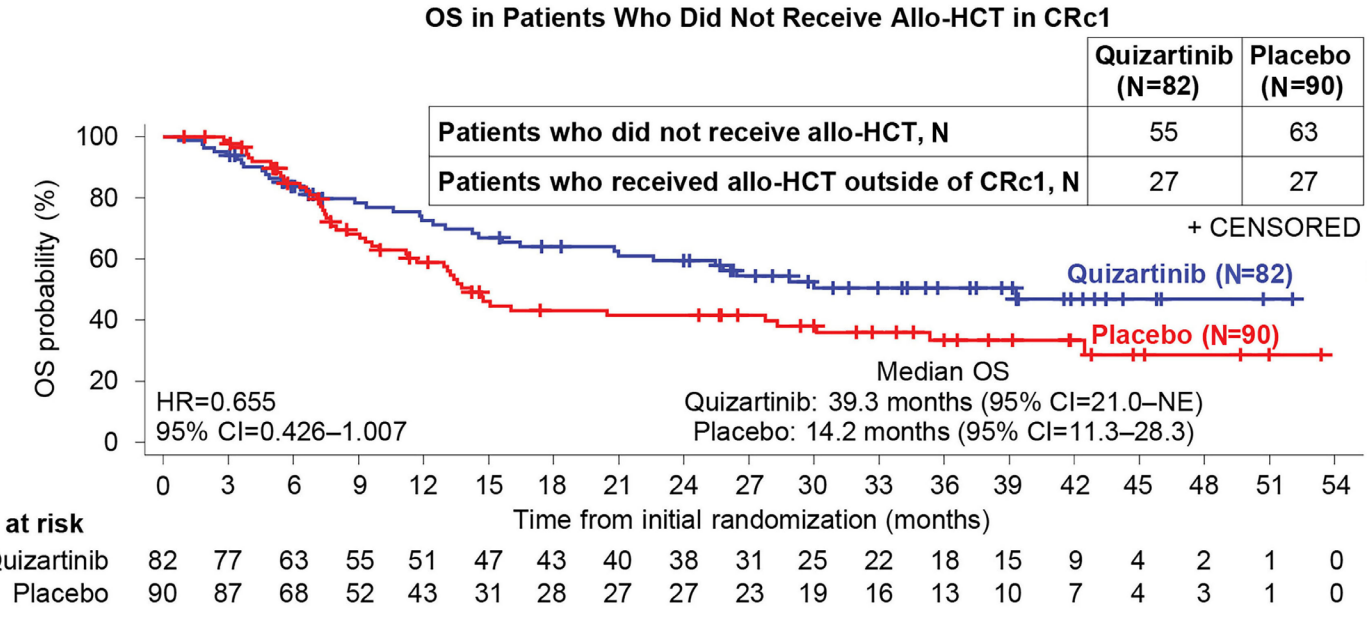
N at risk																				
Quizartinib	63	60	51	47	44	41	38	35	34	28	23	20	16	14	8	4	2	1	0	0
Placebo	77	76	57	45	37	26	24	23	23	19	17	14	11	8	6	3	2	1	0	0

C



N at risk																					
Quizartinib	110	110	107	102	93	90	86	85	83	77	69	60	51	43	36	26	18	4	2	1	0
Placebo	86	86	81	75	66	61	60	59	57	52	47	44	37	31	23	22	12	5	3	0	0

D



	Quizartinib (N=82)	Placebo (N=90)
Patients who did not receive allo-HCT, N	55	63
Patients who received allo-HCT outside of CRc1, N	27	27

N at risk																			
Quizartinib	82	77	63	55	51	47	43	40	38	31	25	22	18	15	9	4	2	1	0
Placebo	90	87	68	52	43	31	28	27	27	23	19	16	13	10	7	4	3	1	0

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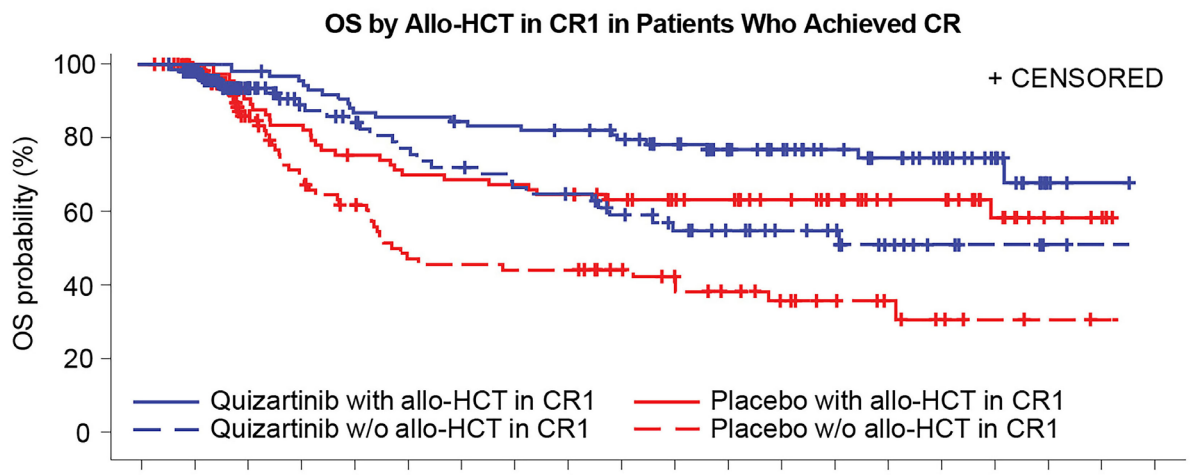
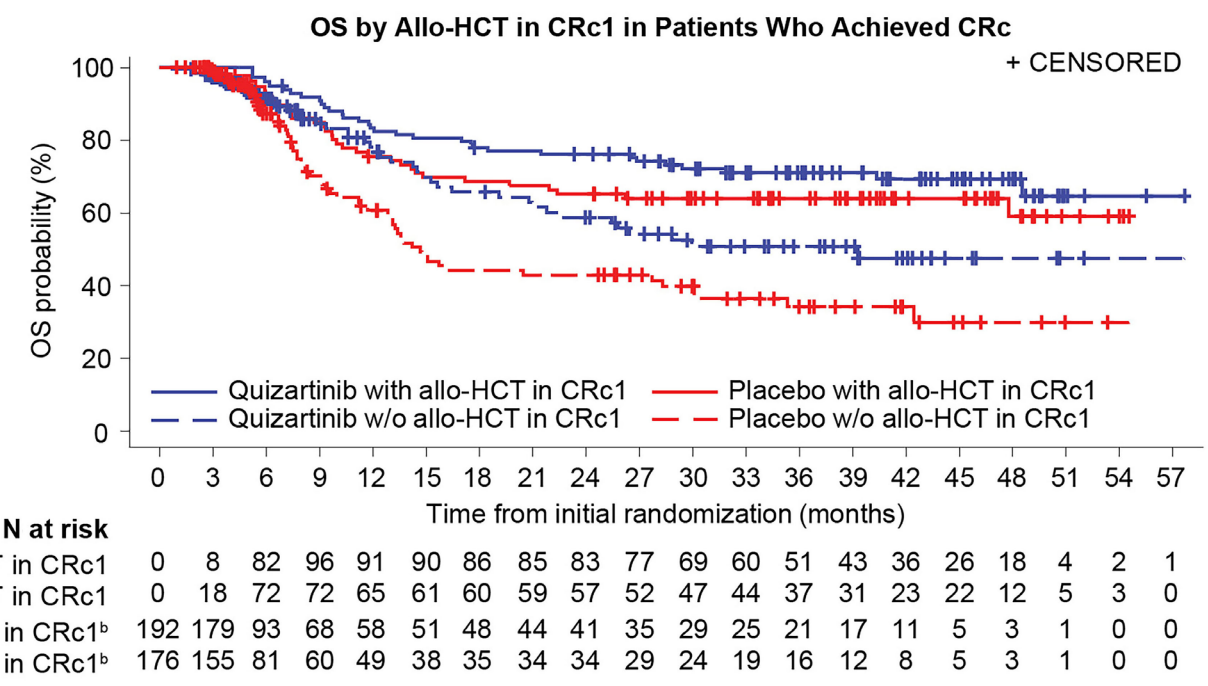
Figure 3. Kaplan-Meier plot of overall survival by treatment arm in patients who achieved complete remission (CR)/composite CR by the end of induction per independent review committee, by allogeneic hematopoietic cell transplantation in first CR/first composite CR. *Post-hoc* analysis. (A) The group of patients who underwent allogeneic hematopoietic cell transplantation (allo-HCT)[a] in first complete remission (CR1). (B) The group who did not undergo allo-HCT[a] in CR1.[b] (C) The group who underwent allo-HCT in first composite complete remission (CRc1). (D) The group who did not undergo allo-HCT in CRc1.[b] [a]Includes protocol-specified and non-protocol-specified allo-HCT. Some patients had both protocol-specified and non-protocol-specified allo-HCT. [b]Overall survival was censored at the starting date of the conditioning regimen for allo-HCT. OS: overall survival; HR: hazard ratio; 95% CI: 95% confidence interval; NR: not reached; NE: not evaluable; CRc1: first composite complete remission.

A



N at risk																				
Quizartinib with allo-HCT in CR1	0	6	63	76	72	72	70	69	67	63	57	50	42	34	29	22	14	3	1	0
Placebo with allo-HCT in CR1	0	15	60	60	55	52	51	50	48	43	39	37	32	27	21	20	12	5	3	0
Quizartinib w/o allo-HCT in CR1[a]	147	138	74	56	50	44	41	37	35	30	25	21	17	15	9	5	3	1	0	0
Placebo w/o allo-HCT in CR1[a]	150	134	69	53	43	33	31	30	30	25	22	17	14	10	7	4	2	1	0	0

B



N at risk																				
Quizartinib with allo-HCT in CRc1	0	8	82	96	91	90	86	85	83	77	69	60	51	43	36	26	18	4	2	1
Placebo with allo-HCT in CRc1	0	18	72	72	65	61	60	59	57	52	47	44	37	31	23	22	12	5	3	0
Quizartinib w/o allo-HCT in CRc1[b]	192	179	93	68	58	51	48	44	41	35	29	25	21	17	11	5	3	1	0	0
Placebo w/o allo-HCT in CRc1[b]	176	155	81	60	49	38	35	34	34	29	24	19	16	12	8	5	3	1	0	0

Figure 4. Time-dependent Simon and Makuch plot of overall survival from initial randomization by allogeneic hematopoietic cell transplantation in first complete remission (CR)/first composite CR in patients who achieved CR/composite CR by the end of induction per independent review committee. *Post-hoc* analysis. (A) The group who achieved CR by the end of induction. (B) The group who achieved composite CR by the end of induction. [a]"W/o allo-HCT in CR1" refers to patients who achieved CR without allogeneic hematopoietic cell transplantation (allo-HCT) in the study or patients who achieved CR with allo-HCT outside first CR. [b]"W/o allo-HCT in CRc1" refers to patients who achieved composite CR without allo-HCT in the study or patients who achieved composite CR with allo-HCT outside of first composite CR. OS: overall survival; CR1: first complete remission; CRc1: first composite complete remission; CRc: composite complete remission.

94.5%), with serious adverse events and adverse events associated with dose modifications being more frequent in the quizartinib group than in the placebo group (*Online Supplementary Table S4*). Among patients who underwent protocol-specified allo-HCT, the most common grade 3/4 adverse events (occurring in ≥10% of patients) were febrile neutropenia, neutropenia, hypokalemia, pneumonia, and anemia in both groups; neutrophil count decreased and

gamma-glutamyl transferase concentration increased more in the quizartinib group; and thrombocytopenia occurred more in the placebo group (Table 4).

Among 193 patients who underwent allo-HCT, 119 (quizartinib, N=70; placebo, N=49) received maintenance therapy. The exposure during maintenance therapy in these 119 patients was relatively similar between the two treatment arms, with a median adjusted treatment duration of 1.6 years in the quizartinib arm *versus* 1.7 years in the placebo arm, and with 68.6% of patients in the quizartinib arm *versus* 73.5% in the placebo arm receiving ≥12 cycles (*Online Supplementary Table S5*). Patients who underwent allo-HCT and received quizartinib maintenance had higher rates of grade ≥3 treatment-emergent adverse events and rates of adverse events associated with dose modifications than those who received maintenance with placebo (*Online Supplementary Table S6*).

Table 3. Graft-*versus*-host disease during the allogeneic hematopoietic cell transplantation period in patients who underwent protocol-specified allogeneic hematopoietic cell transplantation (safety analysis set).[a]

Characteristics	Quizartinib	Placebo
N of patients	102	91
Outcome of transplant, N (%)		
Engraftment	85 (83.3)	71 (78.0)
Relapse	0	3 (3.3)
Death	6 (5.9)	6 (6.6)
Any transplant-related complications, N (%)	57 (55.9)	41 (45.1)
Grade ≥2 GvHD	34 (33.3)	22 (24.2)
Patients with any post-allo-HCT GvHD, N (%)	57 (55.9)	43 (47.3)
Acute GvHD[b]	46 (45.1)	35 (38.5)
Onset after the start of the maintenance phase	7 (6.9)	2 (2.2)
Onset before the maintenance phase (including no maintenance phase)	39 (38.2)	33 (36.3)
Chronic GvHD[c]	30 (29.4)	18 (19.8)
Onset after the start of the maintenance phase	23 (22.5)	13 (14.3)
Onset before the maintenance phase (including no maintenance phase)	7 (6.9)	5 (5.5)
Acute GvHD		
Event onset		
N	45	34
Time in days, median (range)[d]	34.0 (1-116)	27.5 (6-155)
Patients with highest grade as, N (%)		
Grade 1	11 (10.8)	11 (12.1)
Grade 2	15 (14.7)	16 (17.6)
Grade 3	10 (9.8)	3 (3.3)
Grade 4	7 (6.9)	3 (3.3)
Not applicable[e]	3 (2.9)	2 (2.2)
Chronic GvHD[b]		
Event onset		
N	27	18
Time in days, median (range)[d]	224 (102-747)	177 (82-722)
Study drug discontinuation in patients with grade 2-4 acute GvHD or chronic GvHD, N[f]		
Study drug discontinuation at any phase, N (%)	51	34
Primary reasons for study drug discontinuation, N (%)	31 (60.8)	24 (70.6)
Adverse events	10 (19.6)	1 (2.9)
Relapse	5 (9.8)	5 (14.7)
Investigator's decision	1 (2.0)	2 (5.9)
Failure to meet maintenance criteria	3 (5.9)	3 (8.8)
Patient's decision	5 (9.8)	7 (20.6)
Other	7 (13.7)	6 (17.6)

[a]The safety analysis set includes all patients who received at least one dose of study drug or placebo (3 patients in each arm were not treated and are not included in the safety analysis set). If a patient had more than one event, the patient was counted only once; the earliest onset time is displayed. [b]Acute graft-*versus*-host disease (GvHD) generally occurs within 100 days of the transplant date, but it also includes "late acute GvHD", which occurs after day 100. [c]Chronic GvHD generally occurs after 100 days from the transplant date, but it also includes "overlap chronic GvHD", which may occur before day 100. [d]Event onset time (days) = onset date − transplant date + 1. [e]Acute GvHD present but could not be graded. [f]The primary reasons for study drug discontinuation are as follows: adverse events, death, refractory disease, relapse, non-protocol-specified acute myeloid leukemia therapy, pregnancy, patient's decision to discontinue dose, study terminated by sponsor, protocol violation, lost to follow-up, investigator's decision, patients did not meet ≥1 of the eligibility criteria for the maintenance phase, and other. If the number of patients who discontinued study treatment due to a reason was >0, the reason and the corresponding number are presented in the table. allo-HCT: allogeneic hematopoietic cell transplantation.

Table 4. Adverse events of grade 3/4 occurring in ≥5% of the patients who underwent protocol-specified allogeneic hematopoietic cell transplantation, in either treatment arm (safety analysis set).[a]

Grade 3/4 adverse events	Quizartinib	Placebo
N of patients	102	91
Adverse events, N (%)[b]	95 (93.1)	84 (92.3)
Febrile neutropenia	42 (41.2)	35 (38.5)
Neutropenia	24 (23.5)	11 (12.1)
Neutrophil count decrease	17 (16.7)	4 (4.4)
Hypokalemia	14 (13.7)	17 (18.7)
Pneumonia	12 (11.8)	12 (13.2)
Gamma-glutamyl transferase increase	12 (11.8)	5 (5.5)
Anemia	11 (10.8)	10 (11.0)
Thrombocytopenia	9 (8.8)	13 (14.3)
Platelet count decrease	8 (7.8)	2 (2.2)
Decreased appetite	8 (7.8)	0
Alanine aminotransferase increase	7 (6.9)	7 (7.7)
Hypophosphatemia	6 (5.9)	6 (6.6)
Pyrexia	5 (4.9)	6 (6.6)
Blood bilirubin increase	5 (4.9)	3 (3.3)
Hypertension	4 (3.9)	5 (5.5)
Pneumonia, fungal	3 (2.9)	5 (5.5)
Sepsis	3 (2.9)	5 (5.5)
Staphylococcal sepsis	0	5 (5.5)

[a]The safety analysis set includes all patients who received at least one dose of quizartinib or placebo (3 patients in each arm were not treated and are not included in the safety analysis set). If a patient had more than one event, the patient was counted only once. [b]Regardless of causality.

As expected, based on quizartinib's safety profile,[19] rates of blood cytopenias (including neutropenia/neutrophil count decrease, anemia, and thrombocytopenia/platelet count decrease), gastrointestinal disorders (nausea, diarrhea, and vomiting), and infections (pneumonia and herpes zoster) were higher in the quizartinib arm than in the placebo arm (*Online Supplementary Table S7*).

Discussion

These analyses of the QuANTUM-First trial[19] were focused on assessing the impact of allo-HCT in CR1/CRc1 and the interplay with quizartinib treatment compared with placebo on OS in patients with newly diagnosed *FLT3*-ITD-positive AML. The demographics and disease characteristics in the cohorts of patients who achieved CR/CRc and those who underwent allo-HCT in CR1/CRc1 were well balanced between treatment arms and generally reflective of the patient population with newly diagnosed *FLT3*-ITD-positive AML with a high burden of aggressive disease.

The multivariable extended Cox regression analysis, including allo-HCT as a time-dependent covariable, demonstrated that among patients who achieved CR/CRc, quizartinib treatment and allo-HCT in CR1/CRc1 were associated with longer OS, with estimated reductions in the risk of death of 44.7% and 47.3%, respectively, for patients who achieved CR, and 35.5% and 44.3%, respectively, for patients who achieved CRc. One of the limitations of the Kaplan-Meier plot is that it does not consider the timing of allo-HCT occurrence, as patients' categorization has to be defined since randomization; therefore, patients who have undergone allo-HCT during the course of the study are included in the "with allo-HCT" category since the beginning. A more analytically rigorous approach of the impact of allo-HCT on OS is provided by the Simon and Makuch method.[30] Therefore, we have illustrated the survival benefit provided by treatment with quizartinib, including the interplay with allo-HCT as a time-dependent intervention in patients with CR/CRc, in a Simon and Makuch plot, confirming improved OS in patients proceeding to allo-HCT in CR1/CRc1 and in patients receiving standard consolidation chemotherapy in the quizartinib arm over the placebo arm. A pre-planned sensitivity analysis of OS of the QuANTUM-First trial that censored at the starting date of the conditioning regimen for allo-HCT revealed a strong trend favoring quizartinib over placebo (HR=0.75), consistent with the primary analysis of OS (HR=0.78).[19] RFS and CIR curves revealed that quizartinib provided higher RFS rates and lower CIR rates *versus* placebo, regardless of whether patients underwent allo-HCT or not, which could be attributed to higher rates of not detectable measurable residual disease in quizartinib-treated patients than in placebo-treated patients, as previously reported.[19] In the QuANTUM-First trial, patients who underwent protocol-specified allo-HCT experienced post-transplant -related complications, mostly grade ≥2 GvHD, as expected. Rates of acute and chronic post-transplant GvHD

in this study were generally in line with those reported for allo-HCT in patients with *FLT3*-mutated AML.[34] More patients treated with quizartinib were able to undergo allo-HCT, resulting in more reporting of grade 3/4 acute GvHD in the quizartinib arm. GvHD events were reported as resolved or improved in the majority of patients. No new safety signals were identified in patients with newly diagnosed *FLT3*-ITD-positive AML who underwent allo-HCT in CRc1, and the safety profile was in agreement with QuANTUM-First safety data overall.[19]

Other studies demonstrated the value of allo-HCT as a valuable consolidation treatment that improves survival outcomes for patients with *FLT3*-ITD-positive AML, particularly when performed in CR1.[6,12,35-38] Among the patients who underwent allo-HCT in CR1 in the RATIFY trial, a remarkable improvement in OS was seen in those receiving induction and consolidation therapy with midostaurin and chemotherapy compared with those receiving placebo and chemotherapy.[12] When the OS analysis was performed starting from the time of allo-HCT, patients in the midostaurin arm had a 24% risk reduction of death (compared with 22% risk reduction, based on the primary OS analysis), although allo-HCT was not mandatory and patients were not randomized to undergo allo-HCT.[12]

The risk of relapse is still higher in patients with newly diagnosed *FLT3*-ITD-positive AML than in patients without *FLT3*-ITD, even after undergoing allo-HCT.[7] Therefore, there is still an unmet need to decrease relapse rates after consolidation. The FLT3 inhibitor gilteritinib was investigated in patients with *FLT3*-ITD AML as maintenance therapy after allo-HCT in the phase III MORPHO trial (NCT02997202).[39] The MORPHO trial did not meet its primary RFS endpoint nor its key secondary OS endpoint; hence, it did not provide a definitive answer on the role of maintenance therapy after HCT with a FLT3 inhibitor.[39] *Post-hoc* analyses from QuANTUM-First suggest that quizartinib would allow more patients to receive maintenance therapy after HCT than would placebo, but due to statistical limitations with small sample sizes and small numbers of OS events, more research is warranted.[40] Two phase III trials of FLT3 inhibitors in patients with newly diagnosed *FLT3*-mutated AML are ongoing, but their results are not yet available (ARO-021 [NCT03258931][41] and HOVON 156 AML [NCT04027309]).[42]

These unplanned *post-hoc* analyses have several limitations. The fact that allo-HCT was performed per investigator's decision adds some variability to the study. In addition, only slightly more than 50% of patients who achieved CR/CRc received allo-HCT. As a result, some analyses included a small number of patients, which could limit the generalization of the results. The *P* values were not adjusted for multiplicity; therefore, results should be interpreted appropriately.

These *post-hoc* analyses of the QuANTUM-First trial showed that quizartinib treatment and allo-HCT in CR1/CRc1 were favorable factors for longer OS for patients in the study. Patients who achieved remission on quizartinib had longer OS than patients on placebo, irrespective of whether they underwent allo-HCT in first remission. Rates of post-transplant GvHD seemed to be in line with those reported for allo-HCT in previous studies. No new safety signals were identified in patients who underwent allo-HCT. Therefore, taken together, these data further support quizartinib as an efficacious and well-tolerated treatment option for patients aged 18-75 years with newly diagnosed *FLT3*-ITD-positive AML.

Disclosures

RFS reports consulting fees from Daiichi Sankyo, AbbVie, Jazz, and Pfizer; payment for lectures/speakers' bureaus from Daiichi Sankyo, Novartis, and Pfizer; participation on an advisory board/DSMC for BerGenBio and Novartis; and having received equipment from AbbVie, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, PharmaMar, Pfizer, Recordati Rare Diseases, and Roche. PM reports research grants from AbbVie, Bristol Myers Squibb, Jazz, Menarini, Stemline, Novartis, Pfizer, and Takeda; consulting fees from AbbVie, Astellas, BeiGene, Bristol Myers Squibb, Gilead, Incyte, Jazz, Kura Oncology, Menarini, Stemline, Nerviano, Novartis, Otsuka, Pfizer, Ryvu, and Takeda; and payment for speakers' bureaus from AbbVie, Astellas, Bristol Myers Squibb, Gilead, Jazz, and Pfizer. H-JK reports research grants from BL&H; consulting fees from AbbVie, AIMS BioScience, Amgen, AMLHub, Astellas, Aston BioSciences, Bristol Myers Squibb, Celgene, Boryung, Daiichi Sankyo, GC Biopharma, Handok, Ingenium, Janssen, LG Chem, Meiji Seika, Novartis, Pfizer, Sanofi Genzyme, SL VaxiGen, Takeda, and VigenCell; payment for lectures/speakers' bureaus from AbbVie, AMLHub, Astellas, Bristol Myers Squibb, Handok, Jazz, Novartis, and Takeda; travel support from AbbVie, the APLC, Astellas, Jazz, and Takeda; being on a data safety monitoring board/advisory board for AbbVie, AMLHub, the APBMT , the APLC, Astellas, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Handok, Janssen, Novartis, Pfizer, and Sanofi Genzyme; and being a leader in other boards, societies, committees, or advocacy groups for AMLHub, the APLC, the APBMT, Bristol Myers Squibb, the KSABMT, and Novartis. RV reports consulting fees from AbbVie, Astellas, and Pfizer; and payment for lectures/speakers' bureaus from AbbVie, Astellas, Merck Sharp & Dohme, Novartis, Pfizer, PharmaS, and Servier. EP reports consulting fees from KCR US; payment for lectures/speakers' bureaus from Amgen, Angelini, Astellas, Novartis, and Servier; and travel support from Angelini, Astellas, Bristol Myers Squibb, Jazz, Novartis, Pfizer, and Servier. JC reports research grants from AbbVie, Daiichi Sankyo, Novartis, Sun, and Pfizer; consulting fees from AbbVie, Bio-Path, Daiichi Sankyo, Gilead, Forma, Novartis, Pfizer, and Takeda; payment for lectures/speakers' bureaus from Novartis, Pfizer, and Takeda; and having stock options with Bio-Path. MAS reports payment for participation on an advisory board/DSMC from Bristol Myers Squibb, Kurome, and Schrödinger; and having stock

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Contributions

Daiichi Sankyo and the study steering committee (including RFS, PM, EP, JC, MAS, HD, SA, JW, AEP, MJL, and HPE) designed the study. All authors contributed to the critical review and revision of the article and approved the decision to submit it for publication. Data were collected by the investigators and monitored by Daiichi Sankyo. All authors had full access to all the data in the study. LL and RFS directly accessed and verified the data. RFS, AEP, MJL, and HPE wrote the first draft of this article with professional medical writing and editing support. Daiichi Sankyo and all authors were responsible for data analysis and interpretation.

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Data-sharing statement

Anonymized individual participant data from completed studies and applicable supporting clinical study documents are available upon request at https://vivli.org/. Data-sharing access is provided through the Vivli data-sharing portal (https://vivli.org/ourmember/daiichi-sankyo/) after approval of a research proposal and signed data agreement from the research, legal, and intellectual property reviewers of the funder of this study and an independent review panel from the Vivli platform. If clinical study data and supporting documents are provided pursuant to company policies and procedures, Daiichi Sankyo will continue to protect the privacy of the company and clinical study participants.

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