REGULAR ARTICLE

blood advances

Quizartinib for patients with newly diagnosed *FLT3*-ITD–positive AML who received maintenance therapy in QuANTUM-First

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Key Points

- Quizartinib maintenance therapy provided a clear clinical benefit vs placebo in patients who did not undergo allo-HCT.
- Patients entering quizartinib maintenance with no detectable *FLT3*-ITD MRD had a 3-year survival of 89.1% without allo-HCT.

QuANTUM-First demonstrated improved overall survival (OS) in patients with newly diagnosed acute myeloid leukemia with FMS-like receptor tyrosine kinase 3–internal tandem duplication (*FLT3*-ITD) treated with quizartinib + standard chemotherapy. Herein, we evaluated the impact of postconsolidation/posttransplant single-agent maintenance therapy on clinical outcomes in patients receiving maintenance, focusing on measurable residual disease (MRD) status at maintenance onset. OS, event-free survival, and relapse-free survival were prespecified exploratory analyses. Cumulative incidence of relapse, analyses by allogeneic hematopoietic cell transplant (allo-HCT), and analyses by MRD status were post hoc and not powered for statistical significance. Samples for *FLT3*-ITD MRD analysis were collected from patients with composite complete remission ≤30 days before receiving maintenance and assessed using an ultrasensitive amplicon-based assay. More patients who had received an allo-HCT and quizartinib treatment received maintenance (71%) vs placebo (55%); OS benefit was not demonstrated among these patients. In patients who did not undergo allo-HCT, quizartinib maintenance was associated with a significant OS benefit (hazard ratio [HR], 0.401; 95% confidence interval [CI], 0.192-0.838), including a benefit in patients who were MRD negative at the start of maintenance (OS HR, 0.194; 95% CI, 0.056-0.676). Patients who were MRD negative at the completion of consolidation achieved 89.1% (95% CI, 70.0-96.4) survival at 3 years with quizartinib maintenance in the absence of allo-HCT. These data suggest that for patients who achieve *FLT3*-ITD MRD negativity after induction and consolidation with quizartinib, maintenance with quizartinib provides a significant survival benefit and, in some patients, may eliminate the need for allo-HCT. This trial was registered at www.clinicaltrials.gov as NCT02668653.

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Anonymized individual participant data from completed studies and applicable supporting clinical study documents are available on request at https://vivli.org/. Data sharing access is provided via the Vivli data sharing portal (https://vivli.org/ourmember/daiichi-sankyo/) after approval of a research proposal and a 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 patients.

The full-text version of this article contains a data supplement.

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Introduction

Patients with newly diagnosed acute myeloid leukemia (ndAML) with FMS-like receptor tyrosine kinase 3–internal tandem duplication (*FLT3*-ITD) mutations have a higher risk of relapse and shorter overall survival (OS) vs those without *FLT3*-ITD mutations.[1-6] Based on the QuANTUM-First data,[7] quizartinib received regulatory approval in several countries for combination with chemotherapy across induction/consolidation and as single-agent maintenance therapy (not after allogeneic hematopoietic cell transplant [allo-HCT] in the United States) for adults with *FLT3*-ITD–positive ndAML. The phase 3 QuANTUM-First study (ClinicalTrials.gov identifier: NCT02668653) demonstrated that adding the highly potent, oral, selective, type II FLT3 inhibitor quizartinib to standard induction/consolidation chemotherapy with/without allo-HCT, followed by quizartinib maintenance for up to 36 cycles, resulted in a statistically significant and clinically meaningful OS improvement vs standard therapy followed by placebo maintenance in patients aged between 18 and 75 years with *FLT3*-ITD–positive ndAML (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.62-0.98; 2-sided $P = .032$), with a manageable safety profile.[7] Another analysis revealed a longer OS with quizartinib vs placebo in patients achieving complete remission (CR) or composite CR (CRc; CR + CR with incomplete neutrophil or platelet recovery [CRi]) by the end of induction, regardless of allo-HCT status in first CR/CRc.[8]

Here, we assessed the impact of postconsolidation single-agent maintenance therapy on OS, event-free survival (EFS), relapse-free survival (RFS), and cumulative incidence of relapse (CIR) in patients with *FLT3*-ITD–positive ndAML in the QuANTUM-First study receiving maintenance, focusing on *FLT3*-ITD measurable residual disease (MRD) status at maintenance onset. These analyses are exploratory and not powered for statistical significance.

Methods

Patients

A previous publication detailed the QuANTUM-First study.[7] The study was conducted in compliance with the Declaration of Helsinki and approved by institutional review boards at each site. All patients provided informed consent. Eligible patients with *FLT3*-ITD–positive ndAML aged 18 to 75 years were randomized 1:1 to quizartinib (40 mg/d) or placebo with standard 7 + 3 induction chemotherapy. Patients achieving CRc received standard consolidation chemotherapy + quizartinib (40 mg/d) or placebo and/or allo-HCT, followed by single-agent maintenance with quizartinib (30-60 mg/d) or placebo (according to initial randomization) for up to 36 cycles (~3 years).[7] Patients achieving CRc could undergo allo-HCT after induction, anytime during consolidation, or within the first 3 months of maintenance.[7] Quizartinib maintenance started at 30 mg/d, potentially increasing to 60 mg/d in the absence of QT prolongation.[7] There was no rerandomization before maintenance. Only patients randomized to induction with quizartinib could receive quizartinib as maintenance.[7] QuANTUM-First was not powered to detect treatment effect differences during maintenance.

Statistical analyses of efficacy

OS, EFS, and RFS in patients receiving maintenance were prespecified exploratory analyses, and CIR was a post hoc analysis. Analyses by transplant and MRD status were post hoc. OS and EFS were analyzed in the intent-to-treat (ITT) population receiving maintenance. RFS and CIR were analyzed in patients achieving CR/CRc by the end of induction based on the independent review committee (IRC) assessment of those who received maintenance. OS was defined as the time from randomization until death from any cause. EFS was defined as the time from randomization to refractory disease or induction treatment failure (ITF; ie, not achieving CR/CRc per IRC assessment by the end of induction), relapse, or death from any cause, whichever occurred first. For the primary EFS analysis, ITF was defined as not achieving CR by day 42 from the start of the last induction cycle. For the sensitivity EFS analyses, ITF was defined as not achieving CR/CRc by the end of induction, up to day 56 from the start of the last induction cycle. RFS was defined as the time from randomization until documented relapse/death, whichever occurred first.

Medians of OS, EFS, and RFS were calculated using the Kaplan-Meier method, 2-sided 95% CIs using the Brookmeyer and Crowley method, and HRs with 95% CIs using unstratified Cox regression. CIR rates were estimated from randomization by a nonparametric method, treating death from any cause as a competing risk. Rates of OS, EFS, RFS, and CIR, and 95% CIs were reported descriptively at 12, 24, and 36 months. The median duration of follow-up was calculated by reverse Kaplan-Meier estimate.[9]

Propensity score–based OS and RFS analyses were conducted to account for potential confounding factors and further understand the quizartinib benefit during maintenance. The methods applied included propensity score stratification, inverse probability treatment weighting, propensity score matching, and covariate adjustment. Covariates included age, sex, white blood cell count at AML diagnosis, nucleophosmin 1 (*NPM1*) mutational status, bone marrow blast percentage, allo-HCT before maintenance, and anthracycline type. *P* values were not adjusted for multiplicity.

MRD analyses

Samples for *FLT3*-ITD MRD were collected from patients who had achieved CRc (IRC or investigator assessed) within 30 days before receiving maintenance and analyzed by an ultrasensitive amplicon-based assay, as described elsewhere,[10] with a lower limit of quantification of 10^{-4} and estimated lower limit of detection of ~2×10^{-6} *FLT3*-ITD mutations. MRD negativity was defined by 2 cutoffs: no detectable *FLT3*-ITD mutation (MRD 0 cutoff) and MRD 10^{-4} cutoff (0.01% variant allele frequency [*FLT3*-ITD/total *FLT3*]).

Safety analyses

Adverse events (AE) were analyzed in the safety analysis set (patients receiving ≥1 dose of study drug). AE grading and management were as per the investigator. AEs were coded by Medical Dictionary for Regulatory Activities version 24.0, and grades were assigned by the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.03.

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During maintenance, quizartinib/placebo doses could be reduced per the investigator's discretion for myelosuppression. Dosing could decrease from 60 to 40 to 30 mg/d. For patients experiencing myelosuppression requiring dose reduction while on 30 mg/d (20 mg/d with a strong CYP3A4 inhibitor), dosing was temporarily interrupted.

Additional details are provided in the supplemental Methods.

Results

Patient disposition

Of the 539 randomized patients in QuANTUM-First (quizartinib, n = 268; placebo, n = 271), 533 were treated (quizartinib, n = 265; placebo, n = 268; Figure 1). Among these, a similar proportion of patients on quizartinib (173/265) and on placebo (175/268) received consolidation (65.3% each). However, a higher proportion of patients on quizartinib (116/265 [43.8%]) received maintenance vs placebo (92/268 [34.3%]) because more patients on placebo (49/175 [28.0%]) than quizartinib (24/173 [13.9%]) could not enter maintenance because of relapse or failure to meet maintenance criteria.

Of the 208 patients receiving maintenance (quizartinib, n = 116; placebo, n = 92), 201 had achieved CR/CRi by the end of induction per IRC, and 7 had achieved CR/CRi per investigator (Figure 1). The most common reasons for treatment discontinuation during maintenance were relapse (47/208 [22.6%] overall; 23/116 [19.8%] with quizartinib vs 24/92 [26.1%] with placebo) and AEs (26/208 [12.5%] overall; 19/116 [16.4%] with quizartinib vs 7/92 [7.6%] with placebo).

To better understand the reason why fewer patients treated with placebo entered maintenance compared with those treated with quizartinib, we analyzed the reasons for discontinuation during consolidation by arm and by allo-HCT status. Among the 187 patients who received allo-HCT in consolidation, 70 of the 98 (71.4%) on quizartinib vs 49 of the 89 (55.1%) on placebo received maintenance (supplemental Figure 1). More patients who received allo-HCT on placebo than allo-HCT recipients on quizartinib (40/89 [44.9%] vs 28/98 [28.6%]) could not enter maintenance because of relapse or failure to meet maintenance criteria (supplemental Table 1). A similar proportion of patients who did not undergo allo-HCT on quizartinib (46/75 [61.3%]) and placebo (43/86 [50.0%]) entered maintenance (supplemental Figure 1; supplemental Table 1). The most common reasons for treatment discontinuation during consolidation in patients who had undergone allo-HCT were relapse (15/187 [8.0%] overall; 5/98 [5.1%] with quizartinib vs 10/89 [11.2%] with placebo) and failure to meet maintenance criteria (14/187 [7.5%] overall; 5/98 [5.1%] with quizartinib vs 9/89 [10.1%] with placebo; supplemental Table 1). For those who did not receive allo-HCT, the most common reasons were relapse (42/161 [26.1%] overall; 14/75 [18.7%] with quizartinib vs 28/86 [32.6%] with placebo) and AEs (15/161 [9.3%] overall; 11/75 [14.7%] with quizartinib vs 4/86 [4.7%] with placebo). There were 6 patients who underwent allo-HCT during maintenance (4 in the quizartinib arm and 2 in the placebo arm). These 6 patients are included in the group of patients who received maintenance without allo-HCT.

Baseline demographics and disease characteristics in patients receiving maintenance

The baseline demographics and disease characteristics of the 208 patients who entered maintenance (quizartinib, n = 116; placebo, n = 92) are displayed in Table 1. The median time from randomization to maintenance onset was 26 days longer for patients treated with quizartinib. Other parameters were generally balanced across arms. At maintenance onset, most patients were MRD negative in both arms, using either MRD 0 as a cutoff (81.1% with quizartinib and 80.0% with placebo) or MRD 10^{-4} as a cutoff (92.2% with quizartinib and 90.0% with placebo). The baseline demographics and disease characteristics of the 208 patients who received maintenance according to whether or not they received allo-HCT are displayed in supplemental Table 2.

Among patients who received maintenance and underwent allo-HCT, more than half of the patients (57.0% in patients with CR; 57.3% in those achieving CRc) had a myeloablative conditioning (MAC) regimen (supplemental Table 3). The proportion of patients who received a MAC regimen was similar between arms. Similarly, the proportion of patients who received a reduced-intensity conditioning (RIC) regimen was similar between arms. Among patients who achieved CR, MAC accounted for 56.1% in the quizartinib arm vs 58.3% in the placebo arm, and RIC accounted for 43.9% in the quizartinib arm vs 41.7% in the placebo arm. Similarly, among patients who achieved CRc, MAC accounted for 55.6% in the quizartinib arm vs 60.0% in the placebo arm, and RIC accounted for 44.4% in the quizartinib arm vs 40.0% in the placebo arm.

Efficacy analysis

Overall, the median follow-up was 39.2 months. For the maintenance period, the median follow-up was 31.7 months (interquartile range [IQR], 24.2-39.5), which was similar between arms (quizartinib, 32.1 months [IQR, 24.3-39.1]; placebo, 31.1 months [IQR, 24.0-40.3]). OS was longer in the quizartinib arm compared with placebo (HR, 0.683; 95% CI, 0.395-1.183; Figure 2A), and although the HR compares favorably with that found in the primary OS analysis (HR, 0.78; 95% CI, 0.62-0.98) in the ITT population,[7] with only 208 patients in the maintenance arm, this was not statistically significant. The median OS was not reached for either arm, with a 3-year OS rate of 79.9% (quizartinib) vs 71.1% (placebo). According to the primary EFS analysis, with ITF defined as not achieving CR by day 42 from the start of the last induction cycle, the median EFS was similar in both arms (HR, 0.951; 95% CI, 0.658-1.375; supplemental Figure 2). Sensitivity analyses of EFS, without the day-42 restriction, showed a trend toward EFS improvement with quizartinib, with an HR of 0.786 (95% CI, 0.532-1.162) when ITF was defined as not achieving CR, and an HR of 0.760 (95% CI, 0.490-1.179) when ITF was defined as not achieving CRc.

Among 166 patients with CR by the end of induction receiving maintenance (quizartinib, n = 94; placebo, n = 72), RFS rates trended higher at 1, 2, and 3 years with quizartinib vs placebo (Figure 2B), but these differences did not reach statistical significance. Three-year RFS was 67.1% with quizartinib vs 59.6% placebo, and the HR for RFS was 0.738 (95% CI, 0.442-1.230), again trending in favor of quizartinib. CIR rates were lower at 1, 2, and 3 years with quizartinib vs placebo (Figure 2C). Three-year CIR was 25.9% with quizartinib vs 34.4% placebo. Similar

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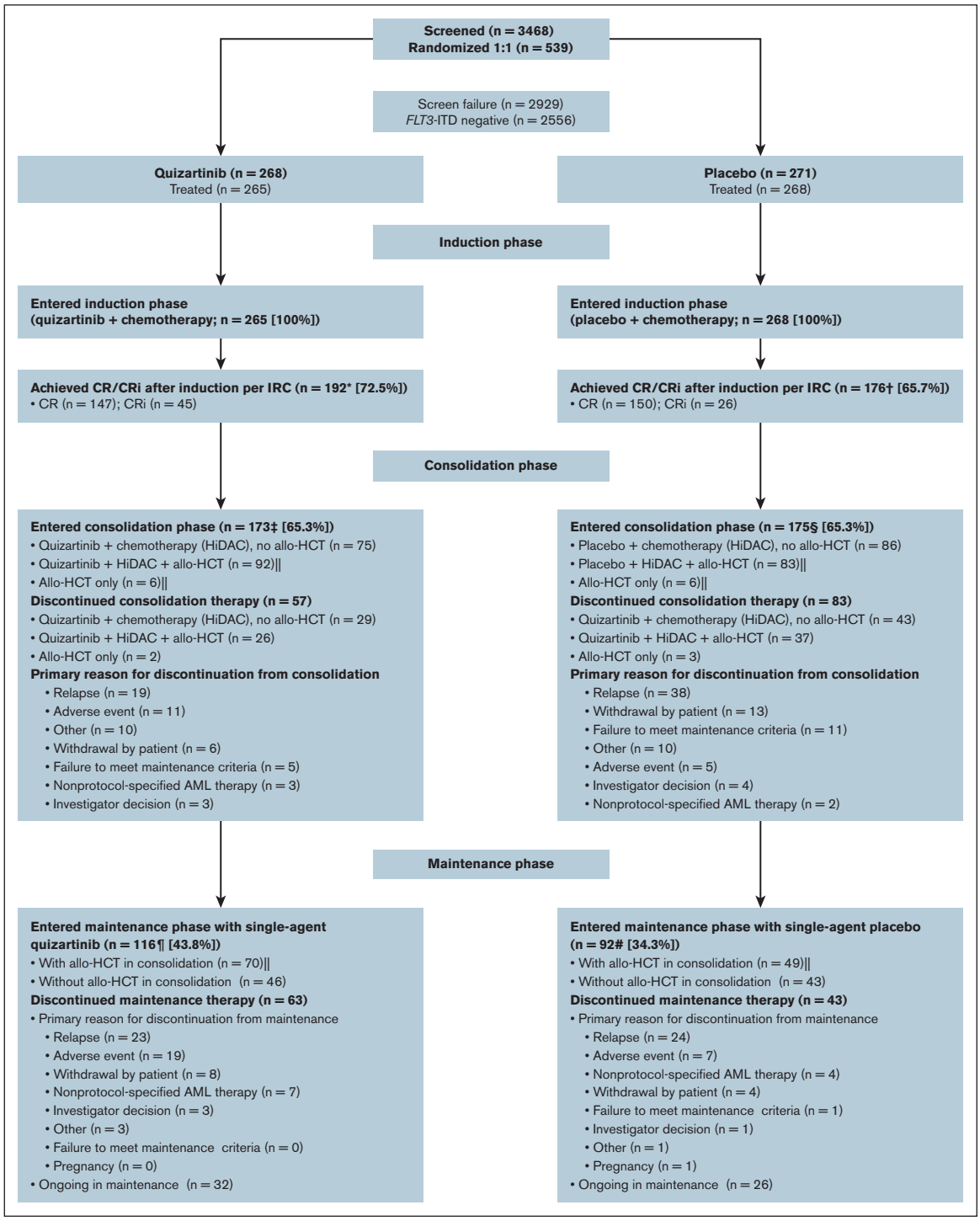


Figure 1. Diagram of patient flow. *Of the 192 patients, 25 discontinued during induction; therefore, 167 with CR or CRi per IRC entered consolidation. †Of the 176 patients, 12 discontinued during induction; therefore, 164 with CR or CRi per IRC entered consolidation. ‡Of the 173 patients, 167 had achieved CR or CRi per IRC, and 6 had achieved CR or CRi per the investigator's assessment. §Of the 175 patients, 164 had achieved CR or CRi per IRC, and 11 had achieved CR or CRi per the investigator's assessment. ||Includes protocol-specified allo-HCT. ¶Of the 116 patients, 114 had achieved CR or CRi per IRC, and 2 had achieved CR or CRi per the investigator's assessment. #Of the 92 patients, 87 had achieved CR or CRi per IRC, and 5 had achieved CR or CRi per the investigator's assessment. HiDAC, high-dose cytarabine.

trends in RFS and CIR were found among patients with CRc by the end of induction receiving maintenance (quizartinib, n = 114; placebo, n = 87; supplemental Figure 3).

The propensity score–based OS and RFS analyses in patients receiving maintenance favored quizartinib over placebo (supplemental Figure 4). Analyses of treatment effects on OS and

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Table 1. Demographics and disease characteristics in patients who received maintenance therapy by treatment arm

	Patients who received maintenance therapy			ITT population		
Baseline characteristics	**Quizartinib (n = 116)**	**Placebo (n = 92)**	**Total (N = 208)**	**Quizartinib (n = 268)**	**Placebo (n = 271)**	**Total (N = 539)**
Age, y						
Median (range)	53 (23-73)	56.5 (20-74)	54 (20-74)	56 (23-75)	56 (20-75)	56 (20-75)
<60, n (%)	77 (66.4)	50 (54.3)	127 (61.1)	161 (60.1)	162 (59.8)	323 (59.9)
≥60, n (%)	39 (33.6)	42 (45.7)	81 (38.9)	107 (39.9)	109 (40.2)	216 (40.1)
Sex, n (%)						
Male	53 (45.7)	38 (41.3)	91 (43.8)	124 (46.3)	121 (44.6)	245 (45.5)
Female	63 (54.3)	54 (58.7)	117 (56.3)	144 (53.7)	150 (55.4)	294 (54.5)
ECOG PS, n (%)						
0	42 (36.2)	35 (38.0)	77 (37.0)	87 (32.5)	98 (36.2)	185 (34.3)
1	57 (49.1)	50 (54.3)	107 (51.4)	134 (50.0)	136 (50.2)	270 (50.1)
2	17 (14.7)	7 (7.6)	24 (11.5)	47 (17.5)	36 (13.3)	83 (15.4)
Missing	0	0	0	0	1 (0.4)	1 (0.2)
Cytogenetic risk status, n (%)						
Favorable	5 (4.3)	10 (10.9)	15 (7.2)	14 (5.2)	19 (7.0)	33 (6.1)
Intermediate	84 (72.4)	60 (65.2)	144 (69.2)	197 (73.5)	193 (71.2)	390 (72.4)
Unfavorable	8 (6.9)	9 (9.8)	17 (8.2)	19 (7.1)	27 (10.0)	46 (8.5)
Unknown/missing	19 (16.4)	13 (14.1)	32 (15.4)	38 (14.2)	32 (11.8)	70 (13.0)
Mutated *NPM1*,* n (%)	69 (59.5)	60 (65.2)	129 (62.0)	142 (53.0)	140 (51.7)	282 (52.3)
***FLT3*-ITD/total *FLT3* (VAF), n (%)**						
≥3% to ≤25%	44 (37.9)	42 (45.7)	86 (41.3)	94 (35.1)	98 (36.2)	192 (35.6)
>25% to ≤50%	59 (50.9)	42 (45.7)	101 (48.6)	143 (53.4)	138 (50.9)	281 (52.1)
>50%	12 (10.3)	8 (8.7)	20 (9.6)	30 (11.2)	35 (12.9)	65 (12.1)
>25%	71 (61.2)	50 (54.3)	121 (58.2)	173 (64.6)	173 (63.8)	346 (64.2)
Unknown	1 (0.9)	0	1 (0.5)	1 (0.4)	0	1 (0.2)
WBC count at AML diagnosis, n (%)						
<40 × 10^9/L	57 (49.1)	58 (63.0)	115 (55.3)	135 (50.4)	137 (50.6)	272 (50.5)
≥40 × 10^9/L	59 (50.9)	34 (37.0)	93 (44.7)	133 (49.6)	134 (49.4)	267 (49.5)
FLT3-ITD MRD negativity (MRD 0 cutoff) at the start of maintenance,† n/n (%)	73/90 (81.1)	64/80 (80.0)	137/170 (80.6)	NA	NA	NA
FLT3-ITD MRD negativity (MRD 0 cutoff) during maintenance,‡ n/n (%)	67/74 (90.5)	50/59 (84.7)	117/133 (88.0)	NA	NA	NA
FLT3-ITD MRD negativity (MRD 0 cutoff) in induction, n/n (%)	NA	NA	NA	37/162 (22.8)	19/159 (11.9)	56/321 (17.4)
FLT3-ITD MRD negativity (MRD 10^{-4} cutoff) at the start of maintenance,† n/n (%)	83/90 (92.2)	72/80 (90.0)	155/170 (91.2)	NA	NA	NA
FLT3-ITD MRD negativity (MRD 10^{-4} cutoff) during maintenance,‡ n/n (%)	71/74 (95.9)	53/59 (89.8)	124/133 (93.2)	NA	NA	NA
FLT3-ITD MRD negativity (MRD 10^{-4} cutoff) in induction, n/n (%)	NA	NA	NA	78/162 (48.1)	61/159 (38.4)	139/321 (43.3)
Time from randomization to start of maintenance therapy, median (range), mo	7.28 (2.7-13.6)	6.44 (3.7-16.7)	6.85 (2.7-16.7)	NA	NA	NA

ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not applicable; VAF, variant allele frequency; WBC, white blood cell.
**NPM1* data are based on the Navigate central data.
†MRD data collected on day 1 of maintenance cycle 1 and within 30 days before receiving maintenance.
‡MRD data collected at cycle 4 day 1 of maintenance.

RFS based on propensity score stratification, inverse probability treatment weighting, propensity score matching, and covariate adjustment yielded similar results favoring quizartinib.

Among the 119 patients who received allo-HCT before maintenance, no survival difference between arms was demonstrated (2-year OS rates, 89.8% [quizartinib] vs 89.7% [placebo];

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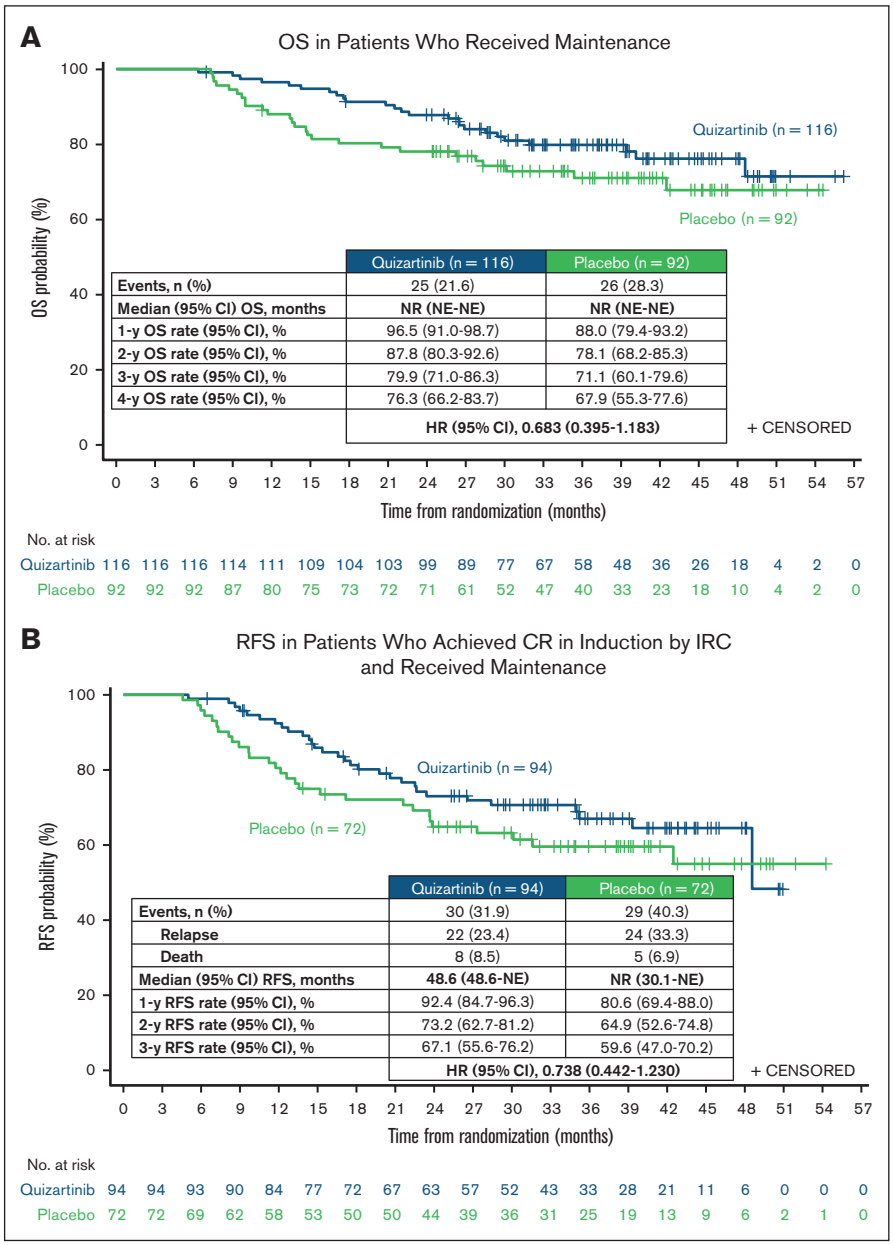


Figure 2. Efficacy analysis in patients who received maintenance therapy. (A) OS in patients who received maintenance, by treatment arm. (B) RFS in patients who achieved CR in induction by IRC and received maintenance, by treatment arm. (C) CIR in patients who achieved CR in induction by IRC and received maintenance, by treatment arm. NE, not estimable; NR, not reached.

Figure 3A). It should be noted that the number of patients by arm was different because 71.4% of the patients who received allo-HCT and were on quizartinib entered maintenance vs 55.1% on placebo (Figure 3A; supplemental Figure 1) because more patients in the placebo arm experienced disease relapse after transplant before being able to start maintenance. Moreover, the number of OS events in the quizartinib arm is limited (20/119 [16.8%]), and the 95% CI for the HR is wide (0.623-4.220; Figure 3A).

Among the 89 patients who did not receive allo-HCT and received maintenance, quizartinib provided an OS benefit over placebo, with 60% reduction in the risk of death (HR, 0.401; 95% CI, 0.192-0.838), and median OS was not reached with quizartinib vs 42.5 months with placebo (Figure 3B). A similar proportion of patients who did not receive allo-HCT in both arms entered maintenance (supplemental Figure 1), and the number of OS events accounts for 34.8% (31/89) of the patients. When focusing on patients who underwent allo-HCT, including those who proceeded to maintenance and those who did not, both OS and RFS starting from allo-HCT were greater in the quizartinib arm than in the placebo arm (Figure 3C-D), but this did not reach statistical significance.

Among the 127 patients aged <60 years receiving maintenance (quizartinib, n = 77; placebo, n = 50), the OS HR for quizartinib

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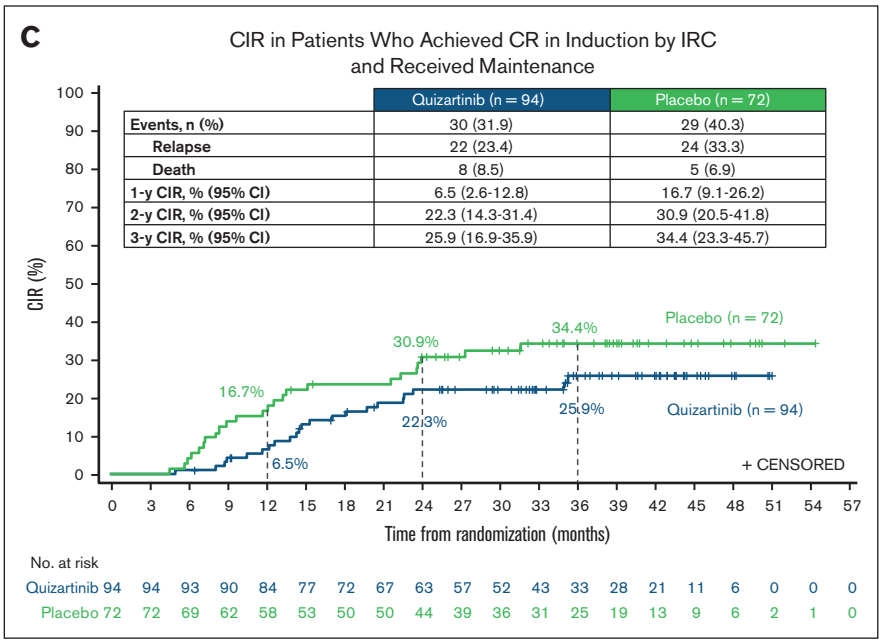


Figure 2 (continued)

compared with placebo was 0.603 (95% CI, 0.226-1.607), although the median OS was not reached in either arm (supplemental Figure 5A). Among the 81 patients aged ≥60 years receiving maintenance (quizartinib, n = 39; placebo, n = 42), the HR for OS was 0.921 (95% CI, 0.475-1.789; supplemental Figure 5B).

The RFS analysis showed no difference between arms among patients achieving CR/CRc by the end of induction with allo-HCT before maintenance (HR, 1.196 [patients with CR]; HR, 1.254 [patients with CRc]; supplemental Figure 6A,C). Among patients who did not undergo allo-HCT but received maintenance, those in the quizartinib arm had a higher RFS compared with those on placebo, but this difference in RFS did not reach statistical significance (HR, 0.626, 95% CI, 0.336-1.169 [patients with CR]; HR, 0.711, 95% CI, 0.400-1.262 [patients with CRc]; supplemental Figure 6B,D). Similar trends were observed in the CIR analysis in patients receiving maintenance by allo-HCT (supplemental Figure 7).

MRD analyses

The MRD status shift from the end of induction to consolidation as well as from the end of consolidation to maintenance in patients with CRc or CR who received maintenance therapy is provided in supplemental Tables 4-7.

MRD status within 30 days before receiving maintenance was available for 170 of the 208 patients (quizartinib, n = 90; placebo, n = 80; Figure 4). At this time point, 80.6% of the patients (quizartinib, 81.1%; placebo, 80.0%) achieved MRD-negative status, whereas 19.4% (quizartinib, 18.9%; placebo, 20.0%) achieved MRD-positive status, using MRD 0 as a cutoff (Figure 4A-B). This MRD analysis showed an HR for OS favoring quizartinib vs placebo in 137 patients with MRD-negative status (0.438 [95% CI, 0.193-0.991]). The HR for OS also favored quizartinib vs placebo in 33 patients with MRD-positive status (0.606 [95% CI, 0.225-1.633]), using MRD 0 as a cutoff, although this did not reach statistical significance. Similar trends were found using MRD 10^{-4} as a cutoff (Figure 4C-D).

A similar overall picture was seen with 134 patients with CRc who were either MRD negative (quizartinib, n = 72; placebo, n = 62) or MRD positive (quizartinib, n = 16; placebo, n = 13) within 30 days before receiving maintenance. The HR for RFS favored quizartinib vs placebo in patients with MRD-negative status (0.642 [95% CI, 0.345-1.198]) and in patients with MRD-positive status (0.692 [95% CI, 0.281-1.706]), using MRD 0 as a cutoff (supplemental Figure 8A-B) but without reaching statistical significance. Similar trends were found using MRD 10^{-4} as a cutoff (supplemental Figure 8C-D).

Among the 29 patients with CRc who achieved MRD-positive status within 30 days before receiving maintenance, using MRD 0 as a cutoff, more patients treated with quizartinib achieved MRD-negative status than those treated with placebo (66.7% vs 33.3%; supplemental Table 8).

OS for patients receiving maintenance therapy with quizartinib or placebo according to MRD status at the start of maintenance is shown in Figure 5. The OS benefit for patients in the quizartinib arm was particularly striking for those who did not undergo allo-HCT (Figure 5C). Patients who were MRD negative (MRD 0 cutoff) after completion of induction and consolidation and before entering maintenance had a 3-year survival of 89.1% (95% CI, 70.0%-96.4%) by Kaplan-Meier estimate, with an HR of 0.194 (95% CI, 0.056-0.676) relative to patients in the placebo arm. There was no statistically significant effect of quizartinib maintenance for patients entering maintenance who were MRD negative after allo-HCT (Figure 5A). For patients who were MRD positive (MRD 0 cutoff) entering maintenance, HR values were in favor of

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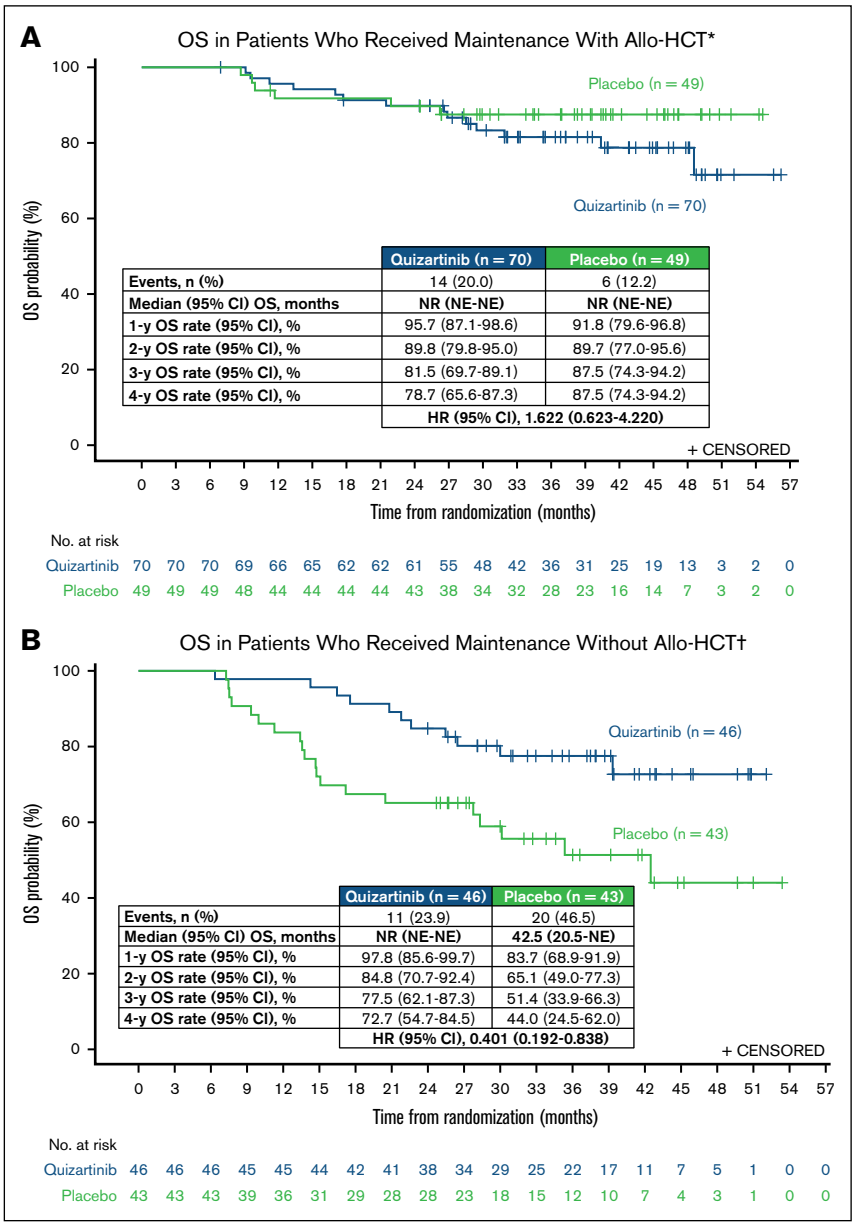


Figure 3. OS and RFS analyses by allo-HCT status. (A) OS in patients who underwent allo-HCT and received maintenance, by treatment arm. (B) OS in patients who did not undergo allo-HCT and received maintenance, by treatment arm. (C) OS in patients who underwent allo-HCT and received or did not receive maintenance, by treatment arm. (D) RFS in patients who achieved CRc in induction by IRC and underwent allo-HCT, with or without maintenance, by treatment arm. *Includes protocol-specified allo-HCT. †There were 6 patients who underwent allo-HCT during maintenance (4 in the quizartinib arm and 2 in the placebo arm); these 6 patients are included in this plot. NE, not estimable; NR, not reached.

quizartinib regardless of transplant status, but the number of such patients was too small for any statistically meaningful conclusion (Figures 5B,D). Similar trends were found using MRD 10^{-4} as a cutoff (supplemental Figure 9). RFS analysis by allo-HCT status in patients with CRc receiving maintenance yielded similar results as the OS analysis, using either MRD 0 or MRD 10^{-4} as a cutoff (supplemental Figures 10 and 11).

Safety analysis during maintenance

Maintenance exposure was similar across arms, with a median treatment duration of 1.3 years, and >60% of the patients received ≥12 cycles (supplemental Table 9). Rates of grade ≥3 AEs and rates of AEs leading to dose interruptions/reductions were greater with quizartinib vs placebo (supplemental Table 10). Treatment-emergent AEs (TEAEs) associated with fatal outcomes occurred in 3 (2.6%) patients treated with quizartinib and 7 (7.6%) patients treated with placebo (Table 2). Although electrocardiogram QT prolongation was more common with quizartinib (11.2%) vs placebo (2.2%), all these events were grade 1/2, with no QT interval corrected using Fridericia's formula interval of >500 (Table 2; supplemental Table 10). The most common TEAEs (≥15%) of all grades occurring in patients treated with quizartinib were

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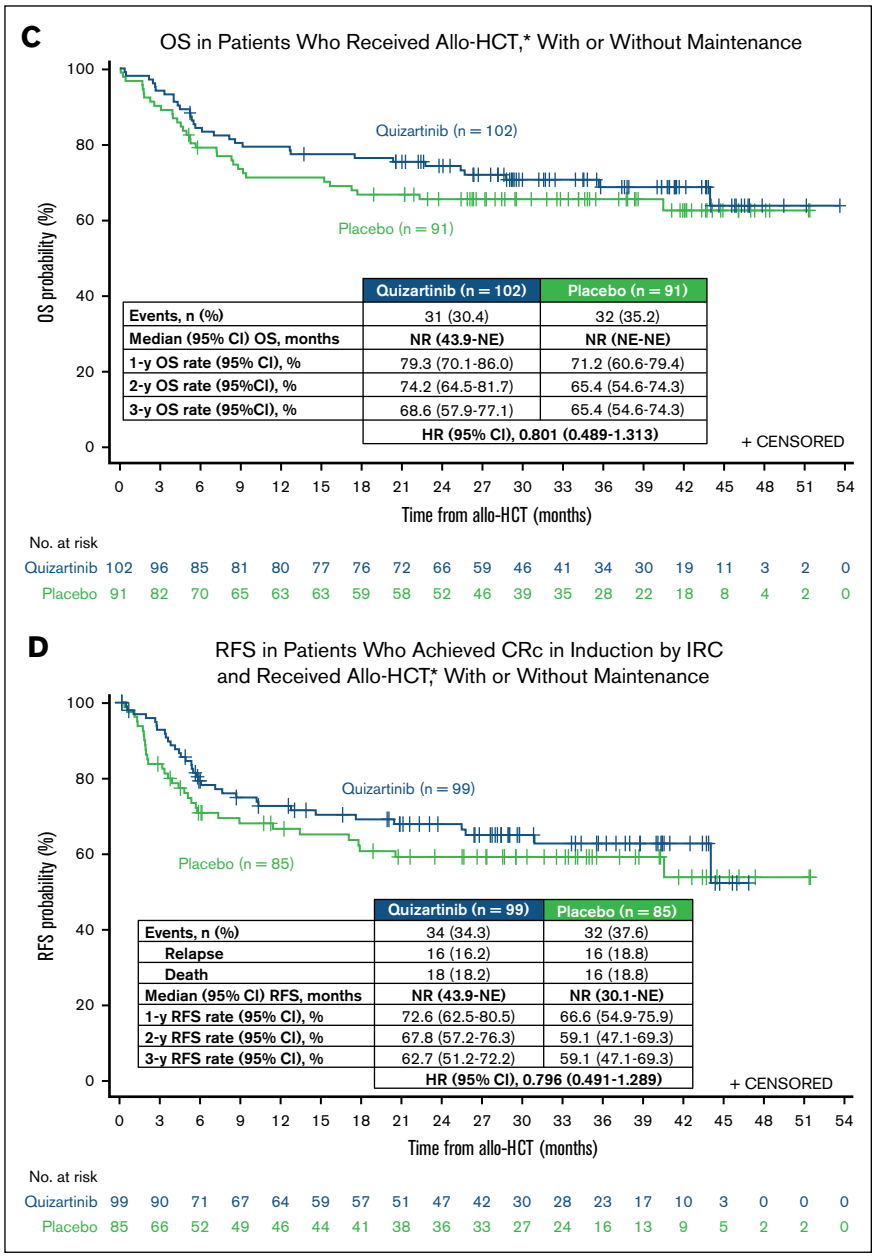


Figure 3 (continued)

neutropenia (36.2%), nausea (23.3%), diarrhea (20.7%), thrombocytopenia (17.2%), upper respiratory tract infection (17.2%), anemia (16.4%), and cough (16.4%). Pyrexia and arthralgia (17.4% each) were the most common TEAEs in patients treated with placebo (Table 2). The most common treatment-related AEs (≥10%) of all grades occurring in patients treated with quizartinib were neutropenia (32.8%), thrombocytopenia (12.9%), decrease in neutrophil count (11.2%), and prolonged electrocardiogram QT (11.2%) (supplemental Table 11).

Among patients treated with quizartinib, those who received allo-HCT experienced more TEAEs of any grade, TEAEs of grade ≥3, and serious TEAEs than those who did not undergo allo-HCT, a trend not seen with placebo (supplemental Table 12). AEs associated with treatment modifications were more common with quizartinib than placebo and in patients who received allo-HCT than those who did not in both arms. Consistent with overall study data, blood cytopenias, gastrointestinal disorders (nausea, diarrhea, and vomiting), and infections (pneumonia and herpes zoster virus) were reported more frequently with quizartinib than placebo, and they were more common in patients who underwent allo-HCT than those who did not (supplemental Table 13).

Cytopenias were more common in patients who underwent allo-HCT vs those who did not in both arms (supplemental Table 14). In the quizartinib arm, the most common grade ≥3 cytopenias were neutropenia (30.0% quizartinib vs 4.1% placebo)

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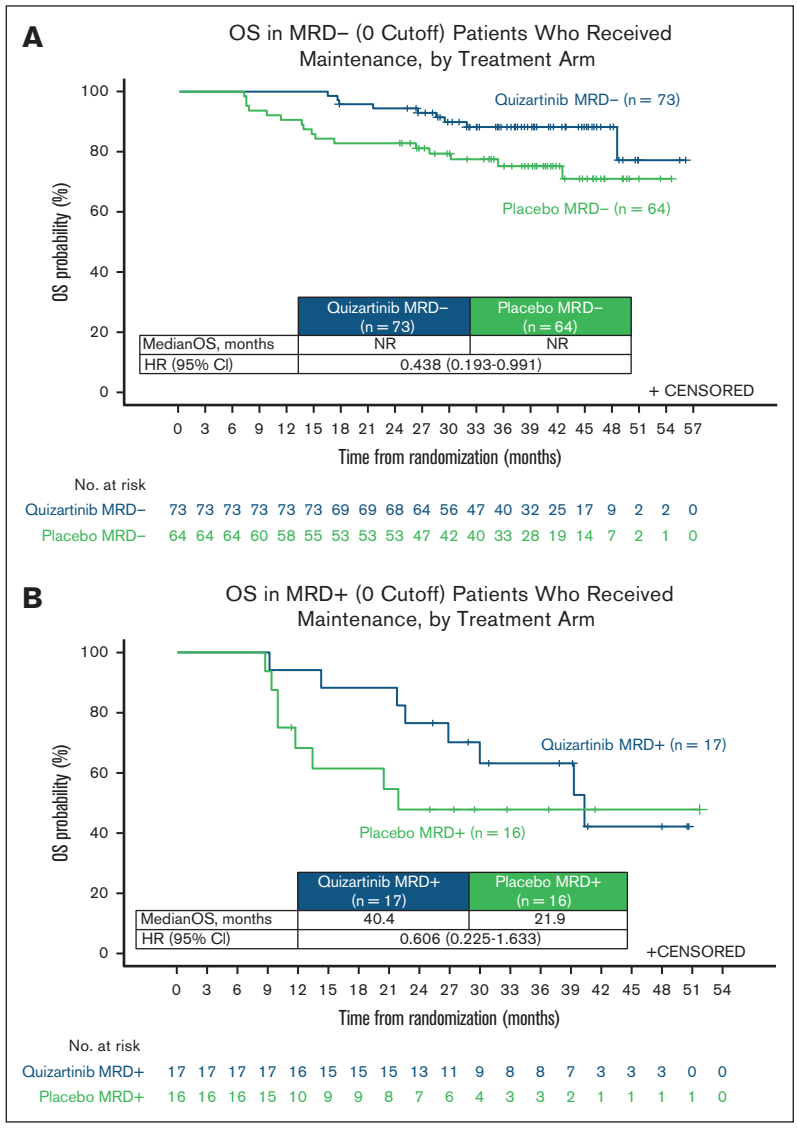


Figure 4. OS in patients who received maintenance therapy by MRD status.* (A) OS in patients with MRD-negative status (based on 0 cutoff) who received maintenance, by treatment arm. (B) OS in patients with MRD-positive status (based on 0 cutoff) who received maintenance, by treatment arm. (C) OS in patients with MRD-negative status (based on 10^{-4} cutoff) who received maintenance, by treatment arm. (D) OS in patients with MRD-positive status (based on 10^{-4} cutoff) who received maintenance, by treatment arm. *MRD data was not available in 38 patients of the 208 who received maintenance (18.3%). NR, not reached.

and decreased neutrophil count (17.1% quizartinib vs 0% placebo) among those who underwent allo-HCT and neutropenia (32.6% quizartinib vs 4.7% placebo) and febrile neutropenia (15.2% quizartinib vs 11.6% placebo) among those who did not undergo allo-HCT.

Posttrial therapies after maintenance

Overall, 43 of the 209 (20.7%) patients received posttrial anticancer therapy after maintenance, with more patients on placebo (27.2%) than on quizartinib (15.5%; supplemental Table 15). Few patients received other FLT3 inhibitors, with more patients receiving gilteritinib (3 in the quizartinib arm and 3 in the placebo arm) than midostaurin (none in the quizartinib arm and 2 in the placebo arm).

Discussion

Outcomes for patients with *FLT3*-ITD–positive AML have significantly improved over the past 2 decades because of the incorporation of FLT3 inhibitors[11,12] into treatment regimens, more widespread use of allo-HCT, and improvements in supportive care. Although randomized trials, including QuANTUM-First,[7] have demonstrated the benefit of FLT3 inhibition in combination with intensive chemotherapy for *FLT3*-ITD–positive ndAML, the value of maintenance therapy with those inhibitors, with or without allo-HCT, remains a controversial issue.[13,14]

Studies on FLT3 inhibitors in patients with *FLT3*-ITD–positive AML in the postremission maintenance setting include the midostaurin phase 3 RATIFY trial (ClinicalTrials.gov identifier: NCT00651261),[13]

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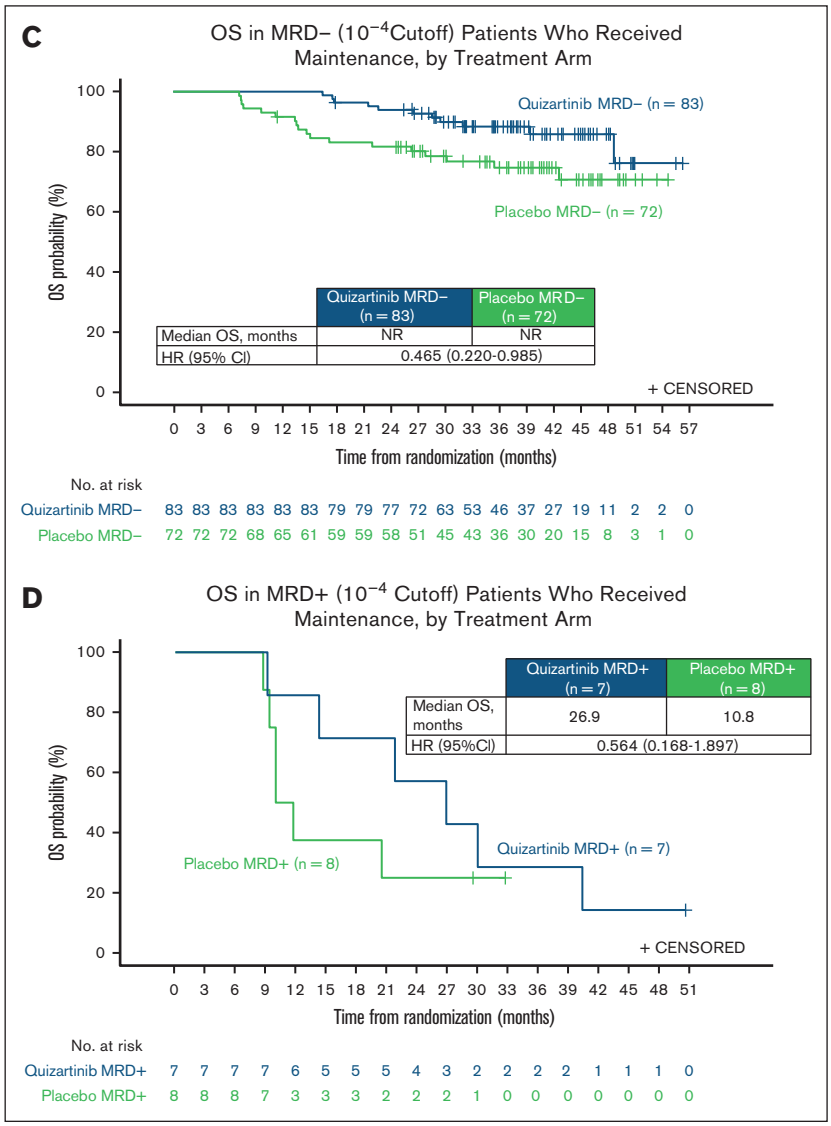


Figure 4 (continued)

the gilteritinib randomized phase 2 GOSSAMER trial (NCT02927262),[15] and the gilteritinib MORPHO study.[14,16] An analysis of the patients in the RATIFY trial achieving CR who received midostaurin maintenance for up to 1 year was inconclusive on the clinical benefit, with no significant difference between the risks of relapse between arms when considering transplant as a competing risk.[13] In the GOSSAMER study, patients in first CR receiving gilteritinib maintenance for up to 2 years experienced an improved RFS with no statistical significance, with no OS difference between treatment arms (HR, 1.13; 95% CI, 0.54-2.36).[15] The BMT-CTN 1506/MORPHO study (ClinicalTrials.gov identifier: NCT02997202) was conducted in patients with *FLT3*-ITD–positive AML in first remission who underwent allo-HCT and, between 30 and 90 days after transplantation, were randomized to gilteritinib or placebo maintenance.[14] Based on the results of the MORPHO study, post–allo-HCT maintenance with gilteritinib conferred an RFS benefit only for patients with peri–allo-HCT *FLT3*-ITD MRD-positive disease.[16] In the aforementioned study,[16] the *FLT3*-ITD MRD assay used was similar to the assay used in QuANTUM-First.[7]

Of the 539 randomized patients in QuANTUM-First, 297 (55.1%) achieved CR by the end of induction (quizartinib, n = 147; placebo, n = 150); of these, 157 (52.9%) underwent allo-HCT in first CR (quizartinib, n = 84; placebo, n = 73).[8] The results from the MORPHO trial indicate that for patients with *FLT3*-ITD–positive AML undergoing allo-HCT, only those with peritransplant *FLT3*-ITD MRD benefited from post–allo-HCT maintenance with the FLT3 inhibitor gilteritinib.[16] However, the data presented in this post hoc analysis of the QuANTUM-First trial provide evidence of the benefit of maintenance with quizartinib for all patients not undergoing allo-HCT, irrespective of *FLT3*-ITD MRD status. For those undergoing allo-HCT, our findings regarding the benefit of quizartinib maintenance are limited by small patient numbers, but the findings seem similar to those of the MORPHO trial[16] in that only those patients with MRD benefited from maintenance.

There are 2 striking implications of these findings and, in particular, the results shown in Figure 5C, consisting of patients who entered maintenance without having undergone allo-HCT. First, for

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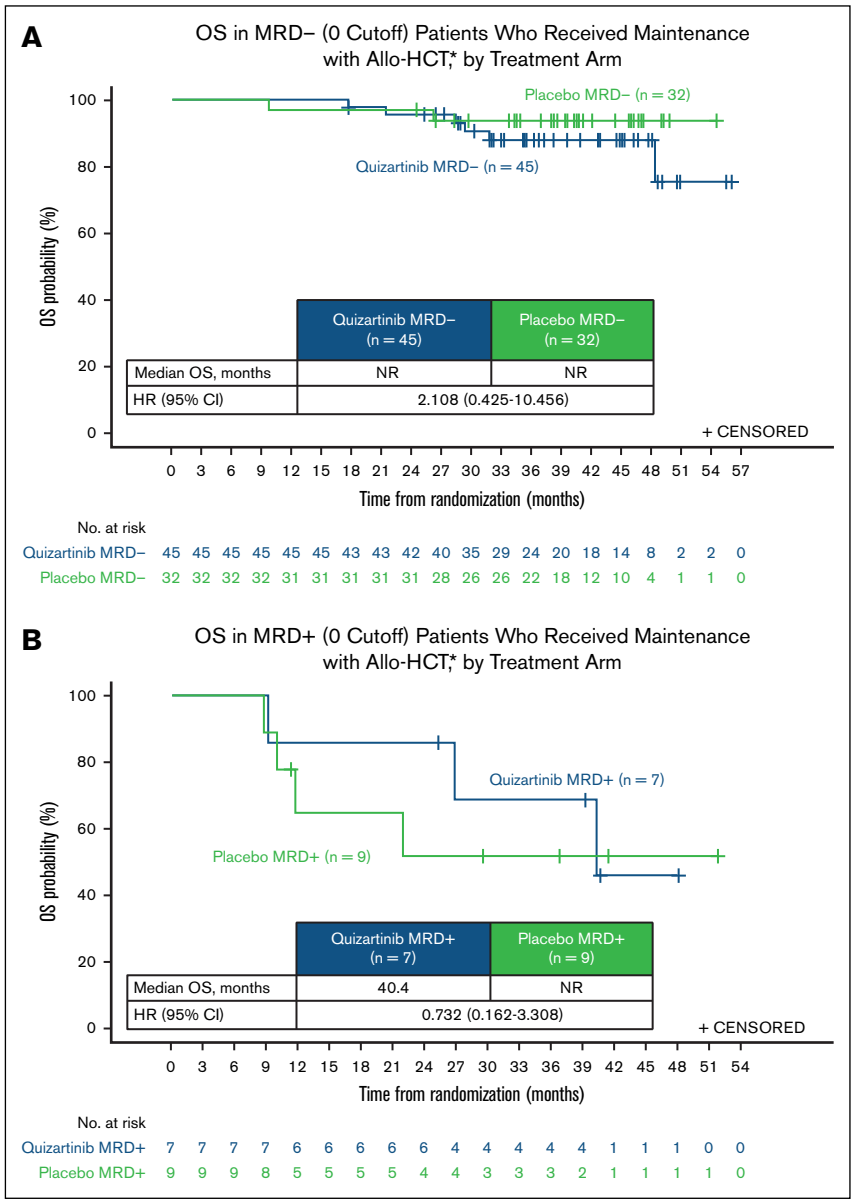


Figure 5. OS in patients who received maintenance therapy by MRD status (0 cutoff) and by allo-HCT status. (A) OS in patients with MRD-negative status (based on 0 cutoff) who underwent allo-HCT and received maintenance, by treatment arm. (B) OS in patients with MRD-positive status (based on 0 cutoff) who underwent allo-HCT and received maintenance, by treatment arm. (C) OS in patients with MRD-negative status (based on 0 cutoff) who did not undergo allo-HCT and received maintenance, by treatment arm. (D) OS in patients with MRD-positive status (based on 0 cutoff) who did not undergo allo-HCT and received maintenance, by treatment arm. *Includes protocol-specified allo-HCT. There were 6 patients who underwent allo-HCT during maintenance (4 in the quizartinib arm and 2 in the placebo arm); these 6 patients are included in panels C and D. NR, not reached.

patients who completed consolidation without undergoing allo-HCT and entered maintenance with no detectable *FLT3*-ITD MRD, there appears to have been a clear benefit conferred by quizartinib maintenance, implying that there can be clinically significant residual AML below the limit of detection of the MRD assay. Second, for those same patients with MRD-negative status who did not undergo allo-HCT, randomized to quizartinib maintenance, OS was remarkably high. This implies that for those patients who are MRD negative after consolidation, allo-HCT is not necessary to achieve long-term survival. This raises the possibility that MRD can identify patients for whom quizartinib maintenance could potentially substitute for allo-HCT. More than half of the patients achieving remission on QuANTUM-First underwent allo-HCT, but the implication here is that many could have achieved long-term survival with quizartinib maintenance to an equal or perhaps greater degree than they achieved by undergoing allo-HCT. A prospective trial would be required to confirm the validity of such an approach.

Post–allo-HCT maintenance, of course, is a very different issue. There was no suggestion of benefit of quizartinib maintenance after allo-HCT for those who were MRD negative (Figure 5A), but

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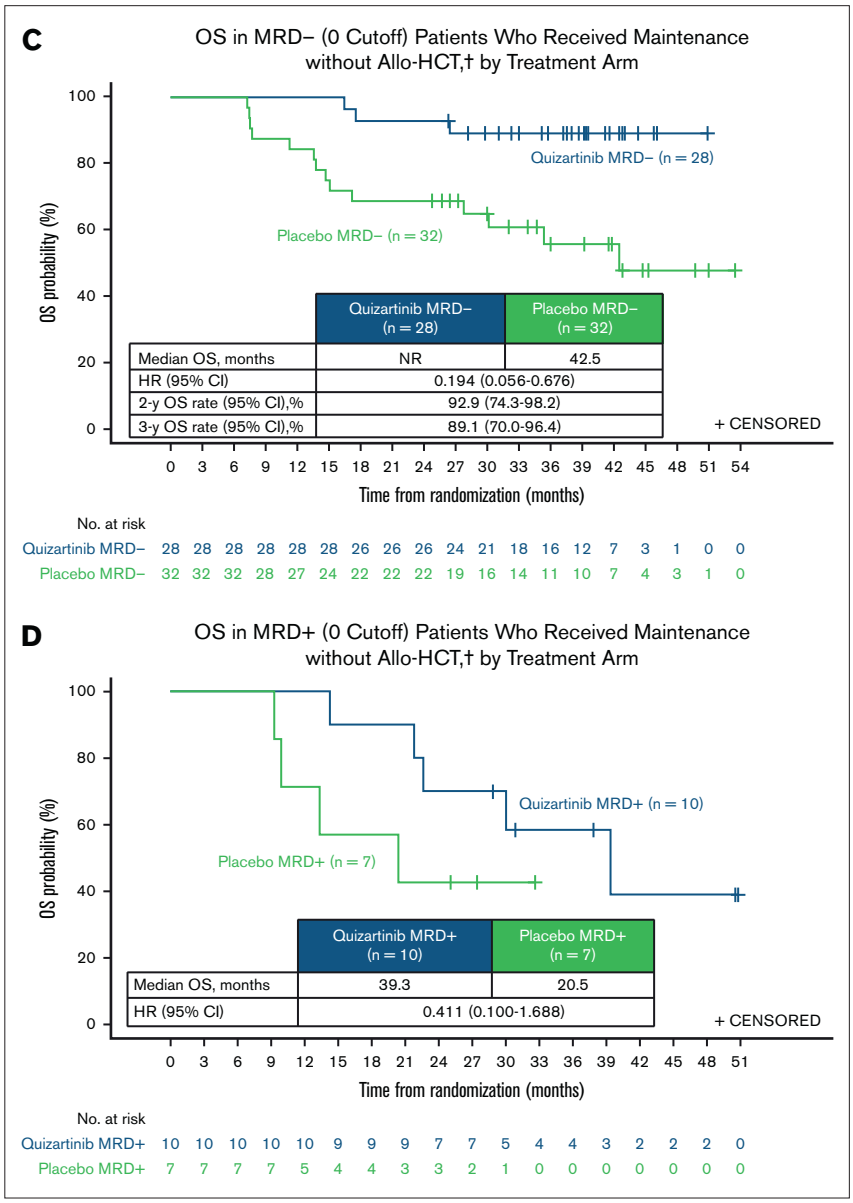


Figure 5 (continued)

these results were likely confounded by the fact that more patients in the placebo arm relapsed after allo-HCT before they could even start maintenance (supplemental Figure 1; supplemental Table 1). Therefore, the most straightforward conclusion on this issue from these data that we can make is similar to what was found in the MORPHO trial,[16] namely that *FLT3*-ITD MRD status, when available, should be used to determine the potential benefit of post–allo-HCT maintenance with quizartinib.

These data are, to our knowledge, the first to provide evidence from a randomized trial for the benefit of FLT3 inhibitor maintenance in the postremission setting. These analyses have a number of limitations because of their exploratory and post hoc nature. QuANTUM-First was not powered to detect treatment effect differences during maintenance. There was no second randomization before maintenance that would have allowed assessment of the benefit of quizartinib maintenance separately from the benefit of quizartinib during induction/consolidation. Because QuANTUM-First was not designed specifically to assess the effect of quizartinib maintenance, the results presented here are inconclusive, and a prospective study would be needed to assess the benefit-risk profile of quizartinib maintenance. Additionally, some analyses included a few patients, potentially limiting the generalization of the results. Because most patients were MRD negative before maintenance, and few patients were MRD positive (only 33 patients in total), conclusions on the role of maintenance in the MRD-positive subgroup should be interpreted appropriately; allo-HCT was performed per the investigator's decision, introducing variability. *P* values were not adjusted for multiplicity; therefore, results should be interpreted appropriately.

In conclusion, the favorable benefit-risk profile previously demonstrated in the ITT population and results in patients receiving maintenance support the use of quizartinib for patients with *FLT3*-

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Table 2. TEAEs occurring in 10% or more of patients in either arm during maintenance therapy

	Quizartinib (n = 116)		Placebo (n = 92)	
TEAEs, n (%)	All grades*	Grade ≥3	All grades*	Grade ≥3
Any TEAEs	109 (94.0)	91 (78.4)	84 (91.3)	53 (57.6)
Neutropenia	42 (36.2)	36 (31.0)	6 (6.5)	4 (4.3)
Nausea	27 (23.3)	2 (1.7)	8 (8.7)	1 (1.1)
Diarrhea	24 (20.7)	3 (2.6)	10 (10.9)	1 (1.1)
Thrombocytopenia	20 (17.2)	10 (8.6)	8 (8.7)	4 (4.3)
Upper respiratory tract infection	20 (17.2)	1 (0.9)	9 (9.8)	0
Anemia	19 (16.4)	6 (5.2)	4 (4.3)	2 (2.2)
Cough	19 (16.4)	1 (0.9)	11 (12.0)	0
Neutrophil count decreased	17 (14.7)	14 (12.1)	4 (4.3)	0
Vomiting	17 (14.7)	0	7 (7.6)	0
Pyrexia	16 (13.8)	0	16 (17.4)	2 (2.2)
Alanine aminotransferase increased	15 (12.9)	3 (2.6)	7 (7.6)	3 (3.3)
Arthralgia	13 (11.2)	0	16 (17.4)	0
Rash	14 (12.1)	2 (1.7)	11 (12.0)	0
Edema peripheral	14 (12.1)	1 (0.9)	8 (8.7)	2 (2.2)
Headache	14 (12.1)	0	8 (8.7)	1 (1.1)
Decreased appetite	13 (11.2)	4 (3.4)	5 (5.4)	0
ECG QT prolonged	13 (11.2)	0	2 (2.2)	0
Fatigue	12 (10.3)	1 (0.9)	8 (8.7)	0

ECG, electrocardiogram.
*The 10% threshold is based on all-grade TEAEs.

ITD–positive ndAML across the whole treatment regimen for patients not undergoing allo-HCT. In those undergoing allo-HCT, these data preclude any firm conclusions because of small patient numbers and the lack of rerandomization after allo-HCT but are probably consistent with the findings of the MORPHO trial.[16] The results highlight the importance of using an FLT3 inhibitor with intensive chemotherapy and continuing, if indicated, with maintenance therapy to maximize clinical benefit.

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Authorship

Contribution: R.F.S., P.M., E.P., J.C., M.A.S., H.D., S.A., J.W., A.E.P., M.J.L., and H.P.E. designed the study; data were collected by the investigators: M.J.L., H.P.E., P.M., E.P., J.C., A.E.P., H.D., S.A., J.W., R.F.S., and M.A.S.; L.L. and M.J.L. directly accessed and verified the data; M.J.L. and M.A.S. wrote the first draft of the manuscript with professional medical writing and editing support; and all authors had full access to all data in this study, were responsible for data analysis and interpretation, contributed to the critical review and revision of the manuscript, and approved the decision to submit for publication.

Conflict-of-interest disclosure: M.J.L. served as a consultant or in an advisory role for Daiichi Sankyo, Amgen, Astellas Pharma, Bristol Myers Squibb, AbbVie/Genentech, GSK, Syndax, and Takeda; provided expert testimony for Novartis; received research funding from Astellas Pharma (institutional); and funding for travel, accommodations, and expenses from Astellas Pharma. H.P.E. served as a consultant or in an advisory role for AbbVie, Agios Pharmaceuticals, Astellas Pharma, Bristol Myers Squibb, Celgene (a Bristol Myers Squibb company), Daiichi Sankyo, Genentech, GlycoMimetics, ImmunoGen, Incyte, Jazz Pharmaceuticals, Kura Oncology, MacroGenics, Novartis, Pfizer, Servier, Syros Pharmaceuticals, Takeda, and Trillium Therapeutics; served on speakers bureaus for AbbVie, Agios Pharmaceuticals, Bristol Myers Squibb, Celgene (a Bristol Myers Squibb company), Incyte, Jazz Pharmaceuticals, Novartis, and Servier; received research funding from AbbVie, Agios Pharmaceuticals, ALX Oncology, Amgen, Ascentage Pharma, Celgene (a Bristol Myers Squibb company), Daiichi Sankyo, Forma Therapeutics, Forty Seven, Gilead, GlycoMimetics, ImmunoGen, Jazz Pharmaceuticals, Kura Oncology, MacroGenics, Novartis, PTC Therapeutics, Servier, and Sumitomo Dainippon Pharma; and additional disclosures include steering committee member for GlycoMimetics, chair of the Myeloid Neoplasms

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Repository study for Bristol Myers Squibb and Celgene (a Bristol Myers Squibb company), and chair of the independent review committee of the VIALE-A and VIALE-C studies for AbbVie. P.M. served as a consultant or in an advisory role for AbbVie, Astellas, BeiGene, Bristol Myers Squibb, Gilead, Incyte, Jazz Pharmaceuticals, Kura Oncology, Menarini Group, Stemline Therapeutics, Nerviano Medical Sciences, Novartis, Otsuka Pharmaceutical, Pfizer, Ryvu Therapeutics, and Takeda; served on speakers bureaus for AbbVie, Astellas Pharma, Bristol Myers Squibb, Gilead, Jazz Pharmaceuticals, and Pfizer; and received research funding from AbbVie, Bristol Myers Squibb, Jazz Pharmaceuticals, Menarini Group, Stemline Therapeutics, Novartis, Pfizer, and Takeda. E.P. served as a consultant or in an advisory role for KCR US; received payment for lectures from Amgen, Angelini Pharma, Astellas Pharma, Novartis, Pfizer, and Servier; and funding for travel, accommodations, and expenses from Angelini Pharma, Astellas Pharma, Bristol Myers Squibb, Jazz Pharmaceuticals, Novartis, Pfizer, and Servier. J.C. served as a consultant or in an advisory role for AbbVie, Bio-Path Holdings, Daiichi Sankyo, Gilead, Forma Therapeutics, Novartis, Pfizer, and Takeda; received payment for lectures from Novartis, Pfizer, and Takeda; research funding from AbbVie, Daiichi Sankyo, Novartis, Sun Pharma, and Pfizer; and stock options from Bio-Path Holdings. A.E.P. received honoraria for Astellas Pharma and Daiichi Sankyo; served as a consultant or in an advisory role for AbbVie, Actinium Pharmaceuticals, Astellas Pharma, Daiichi Sankyo, Forma Therapeutics, Sumitomo Dainippon Pharma, Bristol Myers Squibb, Celgene (a Bristol Myers Squibb company), Syndax, Genentech, BerGenBio, ImmunoGen, Foghorn Therapeutics, Rigel Pharmaceuticals, and Curis; received research funding from Astellas Pharma (institutional), Bayer (institutional), Daiichi Sankyo (institutional), Fujifilm (institutional), AbbVie (institutional), and Syndax (institutional); and funding for travel, accommodations, and expenses from Daiichi Sankyo. H.D. served as a consultant or in an advisory role for Incyte and Servier. J.W. served as a consultant or in an advisory role for AbbVie; and participated on a data safety monitoring committee for AstraZeneca. R.F.S. reports consulting fees from Daiichi Sankyo for participation on a steering committee, and from AbbVie, Jazz Pharmaceuticals, and Pfizer for participation on advisory boards; received payment for lectures from Daiichi Sankyo, Novartis, and Pfizer; serves on a data safety monitoring board or advisory board for BerGenBio and Novartis; and received research funding from AbbVie, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, PharmaMar, Pfizer, and Roche. M.A.S. served as a consultant or in an advisory role for Bristol Myers Squibb, Kurome Therapeutics, and Novartis; and received stock options from Kurome Therapeutics. L.L., K.I., A.L., and K.B. are employees of Daiichi Sankyo. Y.M.K. is a former employee of Daiichi Sankyo; reports grants or contracts from Bexon Clinical Consulting and Stemline Therapeutics; and consulting fees from Stemline Therapeutics. S.A. declares no competing financial interests.

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