QuANTUM-First: Effects of Quizartinib on RFS, OS, CIR, and MRD in Newly Diagnosed Patients With FMS-Like Tyrosine Kinase 3-Internal Tandem Duplication–Positive Acute Myeloid Leukemia Who Received Maintenance Therapy

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BACKGROUND

- The phase 3 QuANTUM-First study (NCT02668653) showed that the addition of quizartinib, a highly potent and selective type II FMS-like tyrosine kinase 3 (FLT3) inhibitor, to standard chemotherapy with or without allogeneic hematopoietic cell transplantation (allo-HCT), followed by single-agent maintenance therapy with quizartinib or placebo (according to initial randomization) for up to 3 years, resulted in a statistically significant and clinically meaningful improvement in overall survival (OS) versus standard therapy followed by placebo maintenance in adult patients with newly diagnosed *FLT3*-internal tandem duplication (ITD)–positive acute myeloid leukemia (AML; hazard ratio [HR], 0.78; 95% CI, 0.62-0.98; 2-sided *P*=0.032), with a manageable safety profile[1]
  - An OS analysis by allo-HCT, in patients who achieved complete remission (CR)/composite complete remission (CRc) by the end of induction, revealed a longer OS with quizartinib versus placebo, regardless of whether they received allo-HCT in first CR/first CRc or not[2]
- Based on QuANTUM-First data,[1] quizartinib has been approved in the United States,[3,4] European Union,[5,6] United Kingdom,[7,8] and Japan[9] in combination with chemotherapy across induction, consolidation, and as maintenance monotherapy (but not after allo-HCT in the United States) for the treatment of adult patients with newly diagnosed *FLT3*-ITD–positive AML

OBJECTIVES

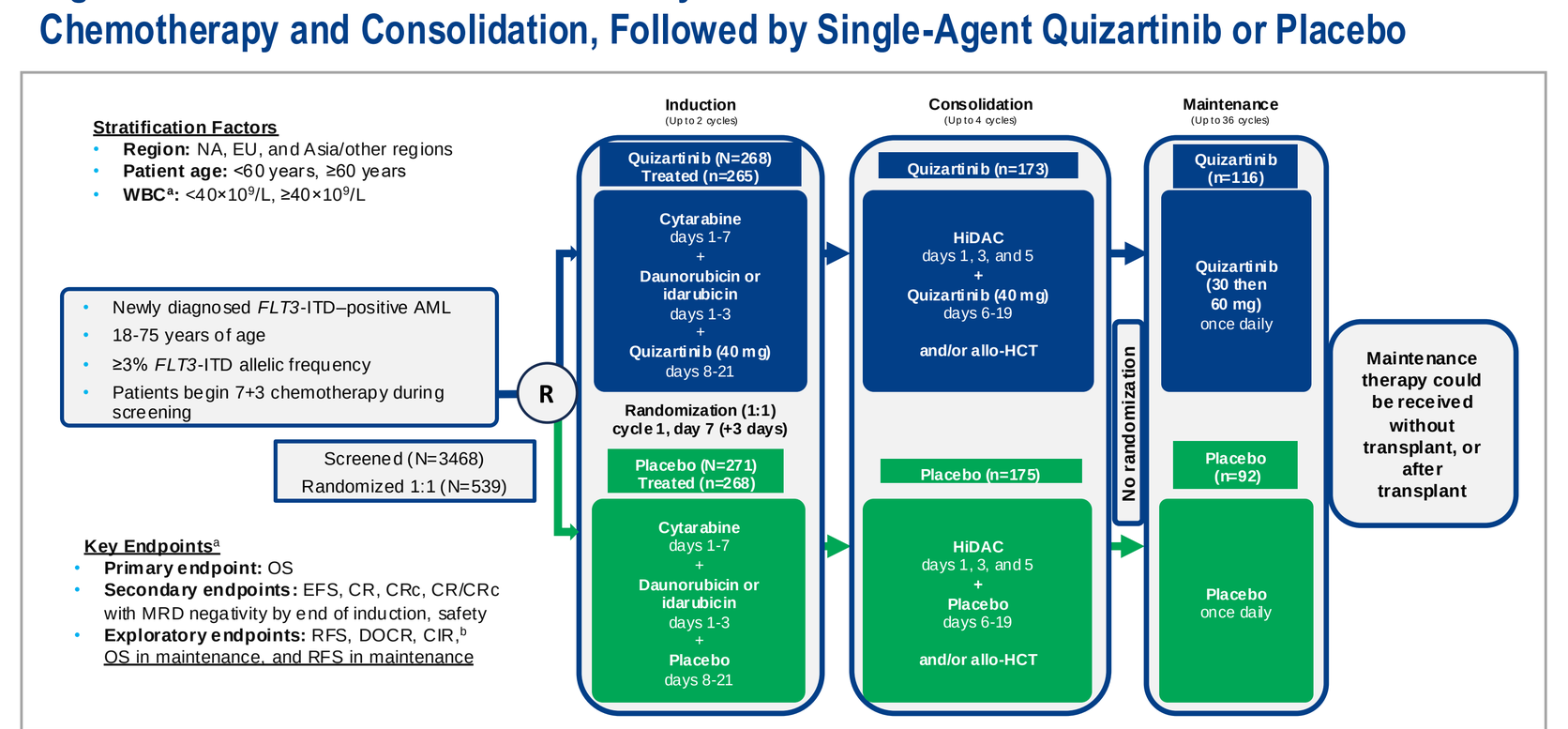
- To assess the impact of post-consolidation single-agent maintenance therapy on OS, relapse-free survival (RFS), and cumulative incidence of relapse (CIR) in patients with newly diagnosed *FLT3*-ITD–positive AML treated in the QuANTUM-First study who received maintenance, with a focus on measurable residual disease (MRD) status at the start of maintenance

METHODS

Study Design

- A detailed description of the QuANTUM-First study has been previously published (**Figure 1**)[1]
- Eligible adult patients (aged 18-75 years) with newly diagnosed *FLT3*-ITD–positive AML were randomized 1:1 to receive standard induction chemotherapy with either quizartinib (40 mg/day) or placebo combined with standard 7+3 induction chemotherapy, stratified by region, age, and white blood cell count (WBC) at diagnosis
- Patients who achieved CR or CR with incomplete hematologic recovery (CRi) received ≤4 cycles of high-dose cytarabine plus quizartinib (40 mg/day) or placebo and/or allo-HCT, followed by 36 4-week cycles (~3 years) of maintenance monotherapy with quizartinib (30-60 mg/day) or placebo
- The dose of quizartinib maintenance therapy started at 30 mg/day on days 1 to 15 of cycle 1, then increased to 60 mg/day if the average QT interval corrected with Fridericia's formula (QTcF) of the triplicate electrocardiogram (ECG) was ≤450 ms on day 15 of cycle 1. If not already increased on cycle 1 day 16, quizartinib was increased to 60 mg/day on cycle 2 day 2 if the average QTcF of the triplicate ECG was ≤450 ms on day 1 of cycle 2
- There was no rerandomization before maintenance and only patients who were randomized to induction with quizartinib were allowed to receive maintenance with quizartinib
- QuANTUM-First was not powered to detect differences within the maintenance phase

Figure 1. QuANTUM-First Phase 3 Study: Quizartinib Plus Standard Induction Chemotherapy and Consolidation, Followed by Single-Agent Quizartinib or Placebo



ClinicalTrials.gov identifier: NCT02668653.
[a]A hierarchical testing procedure was used to test the primary endpoint of OS, followed by EFS, CR, CRc, CR with *FLT3*-ITD MRD negativity, and CRc with *FLT3*-ITD MRD negativity. [b]CIR was assessed post hoc.
Allo-HCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; CIR, cumulative incidence of relapse; CR, complete remission; CRc, composite complete remission; DOCR, duration of complete remission; EFS, event-free survival; EU, European Union; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; HiDAC, high-dose cytarabine; MRD, measurable residual disease; NA, North America; OS, overall survival; R, randomized; RFS, relapse-free survival; WBC, white blood cell.

Efficacy Analyses

- OS and RFS in patients who received maintenance were prespecified exploratory analyses, and CIR was a post hoc analysis
- OS was analyzed in the intent-to-treat (ITT) population who received maintenance; CIR and RFS were analyzed in patients who achieved CR or CRi by the end of induction based on independent review committee (IRC) assessment and received maintenance
- The medians of OS and RFS were estimated based on the Kaplan-Meier method, the 2-sided 95% CIs using the method of Brookmeyer and Crowley, and the HRs with the 95% CIs using unstratified Cox regression
- Rates of CIR, calculated from randomization, were estimated by a nonparametric method, treating death from any cause as a competing risk
- Rates of OS, RFS, and CIR and 95% CIs were provided descriptively
- The median duration of follow-up was calculated by the reverse Kaplan-Meier estimate[10]
- Propensity scores were conducted based on baseline covariates (age, sex, WBC count, *NPM1* mutational status, percent of bone marrow blasts), and also allo-HCT before maintenance and type of anthracycline
- *P* values were not adjusted for multiplicity

MRD Analyses

- Samples for *FLT3*-ITD MRD analysis were collected from CRc patients ≤30 days before receiving maintenance and assessed by a polymerase chain reaction–next-generation sequencing assay
- MRD negativity was defined by no detectable *FLT3*-ITD mutation (0 cutoff)

Safety Analyses

- Safety was evaluated in patients treated with ≥1 dose of quizartinib or placebo
  - Adverse events (AE) were coded by Medical Dictionary for Regulatory Activities (MedDRA) v24.0 and assigned grades based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03

RESULTS

Baseline Demographic and Disease Characteristics in Patients Who Received Maintenance

- At the start of maintenance, the majority of the patients were MRD− in either arm
- Quizartinib-treated patients were slightly younger, had a higher rate of Eastern Cooperative Oncology Group performance status of 2, had a higher WBC count at diagnosis, had a lower rate of *NPM1* mutations, and had higher variant allele frequency for *FLT3* mutations versus placebo-treated patients (**Table 1**)
- Other parameters were generally balanced across the 2 arms

Table 1. Demographics and Disease Characteristics in Patients Who Received Maintenance by Treatment Arm

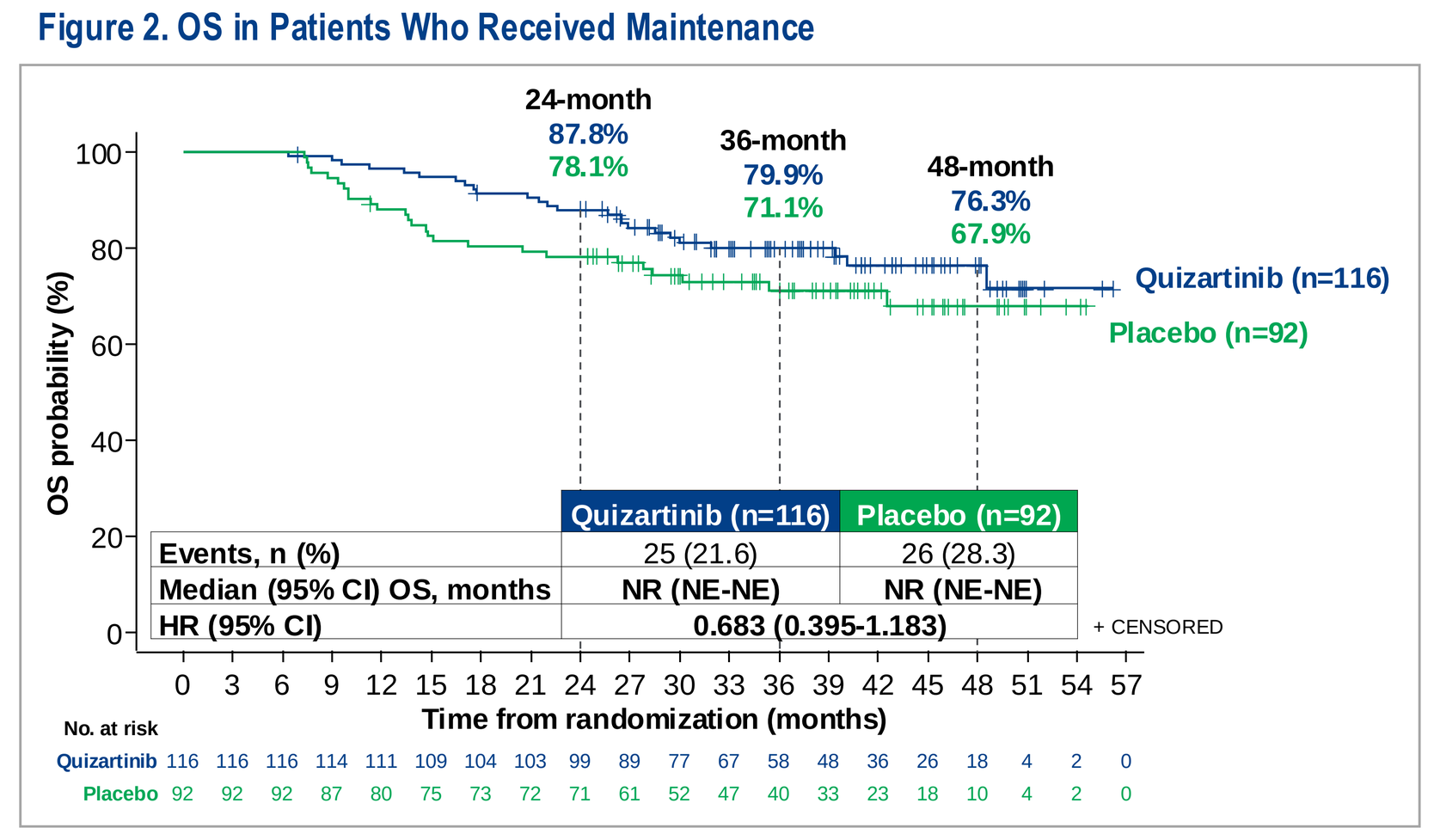
Baseline characteristics	Patients who received maintenance		ITT population	
	Quizartinib (n=116)	Placebo (n=92)	Quizartinib (n=268)	Placebo (n=271)
Age				
Median (range)	53 (23-73)	56.5 (20-74)	56 (23-75)	56 (20-75)
<60 years, %	66.4	54.3	60.1	59.8
≥60 years, %	33.6	45.7	39.9	40.2
Sex, n (%)				
Male	45.7	41.3	46.3	44.6
Female	54.3	58.7	53.7	55.4
ECOG PS, n (%)				
0	36.2	38.0	32.5	36.2
1	49.1	54.3	50.0	50.2
2	14.7	7.6	17.5	13.3
Missing	0	0	0	0.4
Cytogenetic risk status, %				
Favorable	4.3	10.9	5.2	7.0
Intermediate	72.4	65.2	73.5	71.2
Unfavorable	6.9	9.8	7.1	10.0
Unknown/Missing	16.4	14.1	14.2	11.8
Mutated *NPM1*,[a] %	59.5	65.2	53.0	51.7
***FLT3*-ITD/total *FLT3* (VAF), %**				
≥3% to ≤25%	37.9	45.7	35.1	36.2
>25% to ≤50%	50.9	45.7	53.4	50.9
>50%	10.3	8.7	11.2	12.9
>25%	61.2	54.3	64.6	63.8
Unknown	0.9	0	0.4	0
WBC count at AML diagnosis, %				
$<40\times10^9$/L	49.1	63.0	50.4	50.6
$\geq40\times10^9$/L	50.9	37.0	49.6	49.4
***FLT3*-ITD MRD Negativity (0 cutoff) at the start of maintenance,[b] n/n (%)**	73/90 (81.1)	64/80 (80.0)	NA	NA
***FLT3-ITD* MRD Negativity (0 cutoff) during maintenance,[c] n/n (%)**	67/74 (90.5)	50/59 (84.7)	NA	NA
Median (range) time from randomization to start of maintenance, months	7.28 (2.7-13.6)	6.44 (3.7-16.7)	NA	NA

[a]*NPM1* data are based on the Navigate central data. [b]MRD data collected at day 1 of maintenance cycle 1 and within 30 days before entering maintenance. [c]MRD data collected at cycle 4 day 1 of maintenance. AML, acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; ITT, intent-to-treat; MRD, measurable residual disease; NA, not applicable; *NPM1*, nucleophosmin 1; VAF, variant allele frequency; WBC, white blood cell.

OS in Patients Who Received Maintenance

- A total of 208 patients (quizartinib, n=116; placebo, n=92) received maintenance (**Figure 2**)
- Among these patients, quizartinib provided a numerical OS benefit over placebo, with an HR of 0.683, which compares numerically favorably with the HR of the primary OS analysis (0.78)[1] in all the ITT patient population (**Figure 2**)

Figure 2. OS in Patients Who Received Maintenance

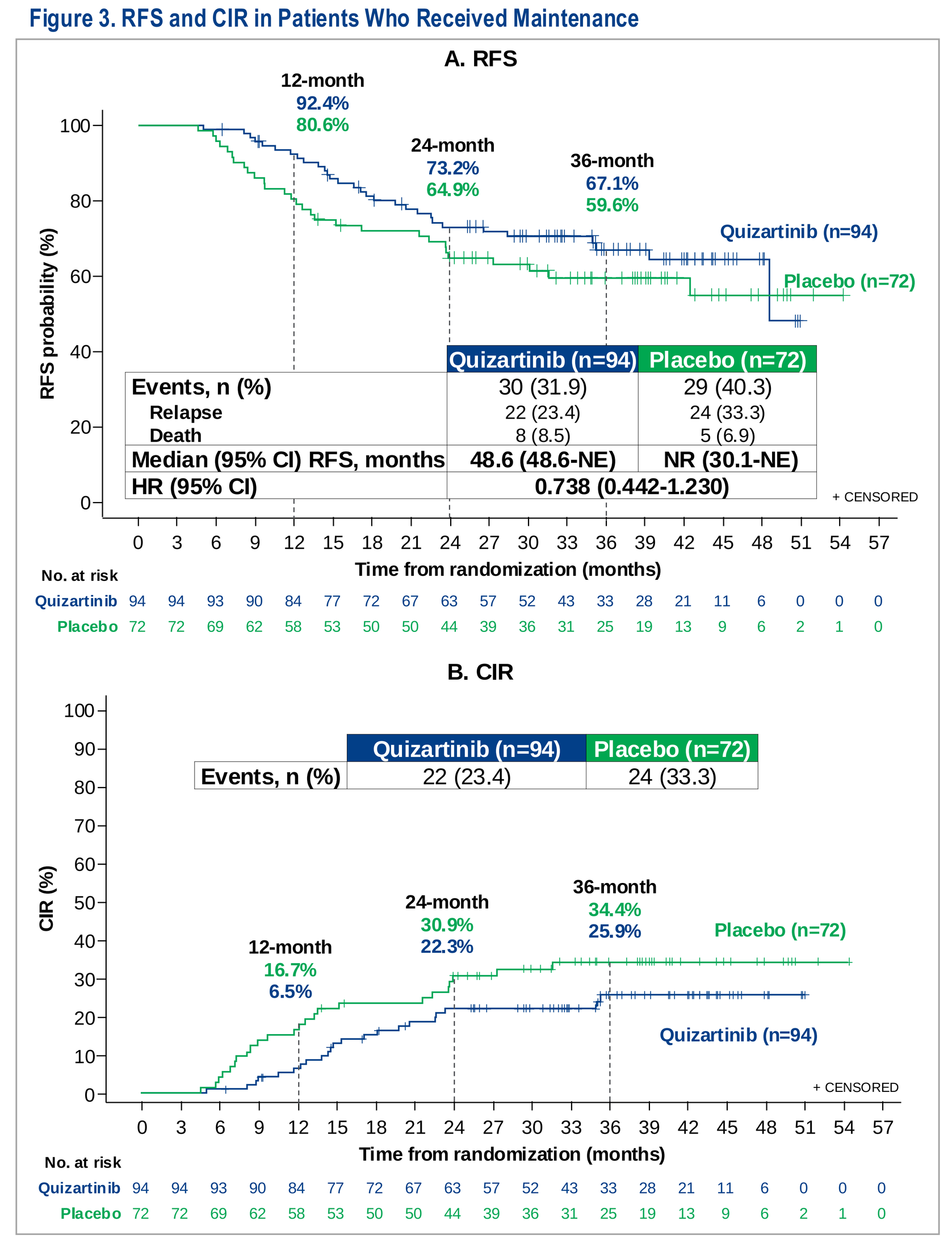


HR, hazard ratio; NE, not estimable; NR, not reached; OS, overall survival.

RFS and CIR in Patients Who Received Maintenance

- Among 166 patients (quizartinib, n=94; placebo, n=72) who achieved CR per IRC by the end of induction and received maintenance (**Figure 3**):
  - RFS rates were numerically higher at 1, 2, and 3 years in the quizartinib arm versus the placebo arm, with an HR of 0.738, favoring quizartinib (**Figure 3A**)
  - CIR rates were numerically lower at 1, 2, and 3 years in the quizartinib arm versus the placebo arm, favoring quizartinib (**Figure 3B**)
- Similar trends of RFS and CIR were found in patients who achieved CRc per IRC by the end of induction and received maintenance

Figure 3. RFS and CIR in Patients Who Received Maintenance

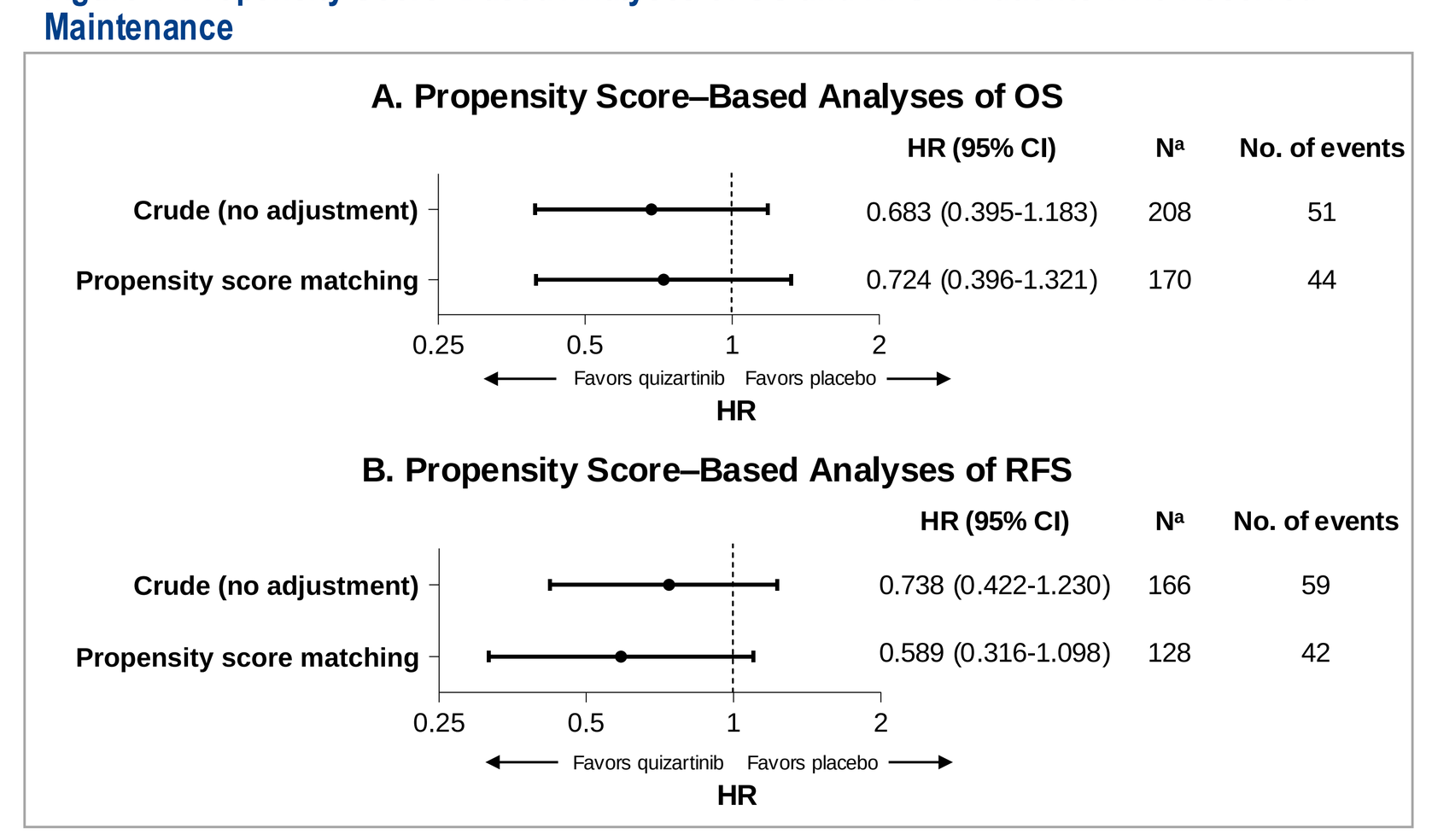


CIR, cumulative incidence of relapse; HR, hazard ratio; NE, not estimable; NR, not reached; RFS, relapse-free survival.

Propensity Score–Based Analyses of OS and RFS in Patients Who Received Maintenance

- These analyses were conducted to account for potential confounding factors and further understand the benefit of quizartinib in the maintenance phase
- The propensity score–based analyses of OS (**Figure 4A**) and RFS (**Figure 4B**) in patients who received maintenance favored quizartinib over placebo
  - All the statistical adjustments yielded similar results

Figure 4. Propensity Score–Based Analyses of OS and RFS in Patients Who Received Maintenance

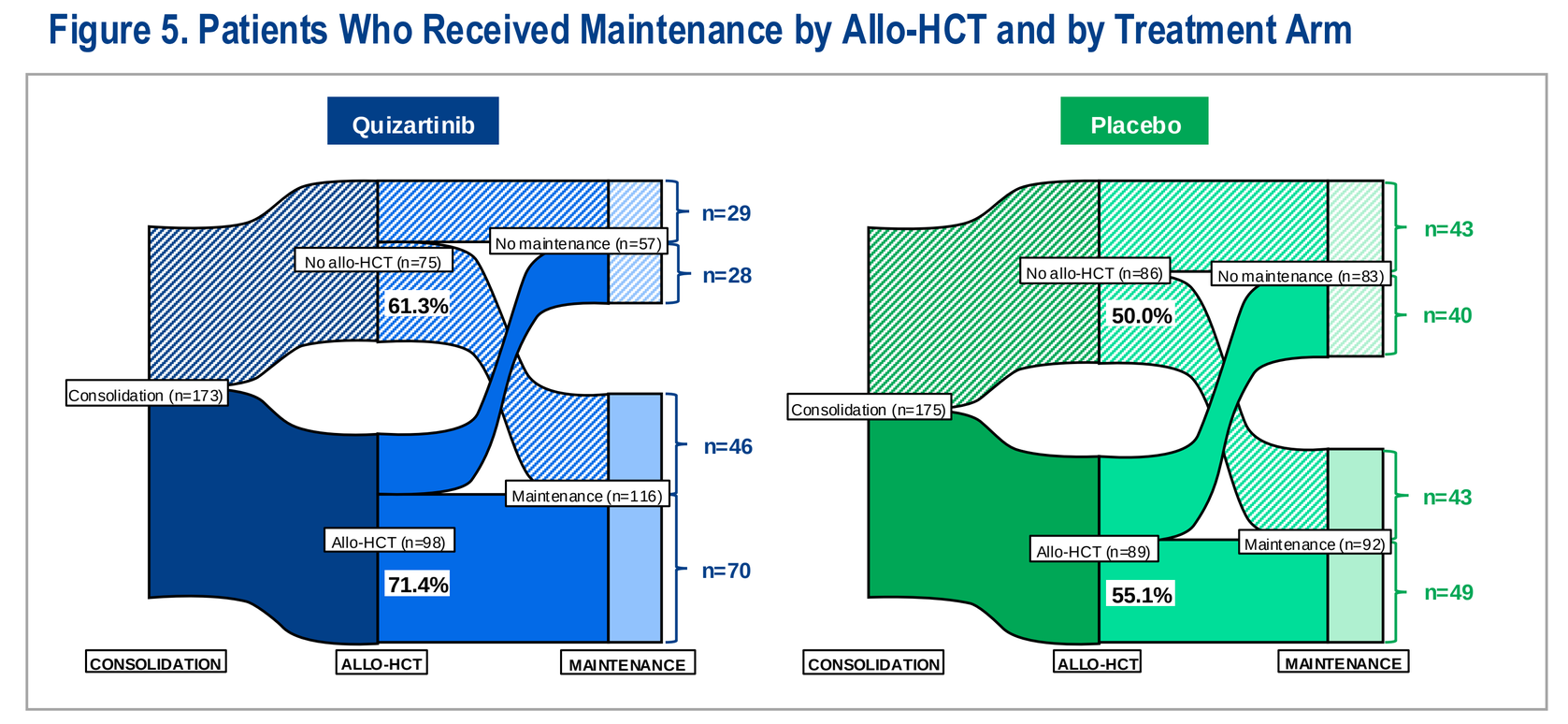


[a]Patients who are matched using the propensity score matching are included. HR, hazard ratio; OS, overall survival; RFS, relapse-free survival.

Disposition of Patients Who Received Maintenance by Allo-HCT and by Treatment Arm

- Of the 187 patients who had allo-HCT in consolidation, more patients in the quizartinib arm (71.4%) versus the placebo arm (55.1%) received maintenance (**Figure 5**)
  - More transplanted patients in the placebo arm versus the quizartinib arm (44.9% vs 28.6%) could not proceed to maintenance due to either relapse or failure to meet maintenance criteria
  - A similar proportion of patients who did not undergo allo-HCT in consolidation in the quizartinib arm (61.3%) and placebo arm (50.0%) proceeded to maintenance

Figure 5. Patients Who Received Maintenance by Allo-HCT and by Treatment Arm

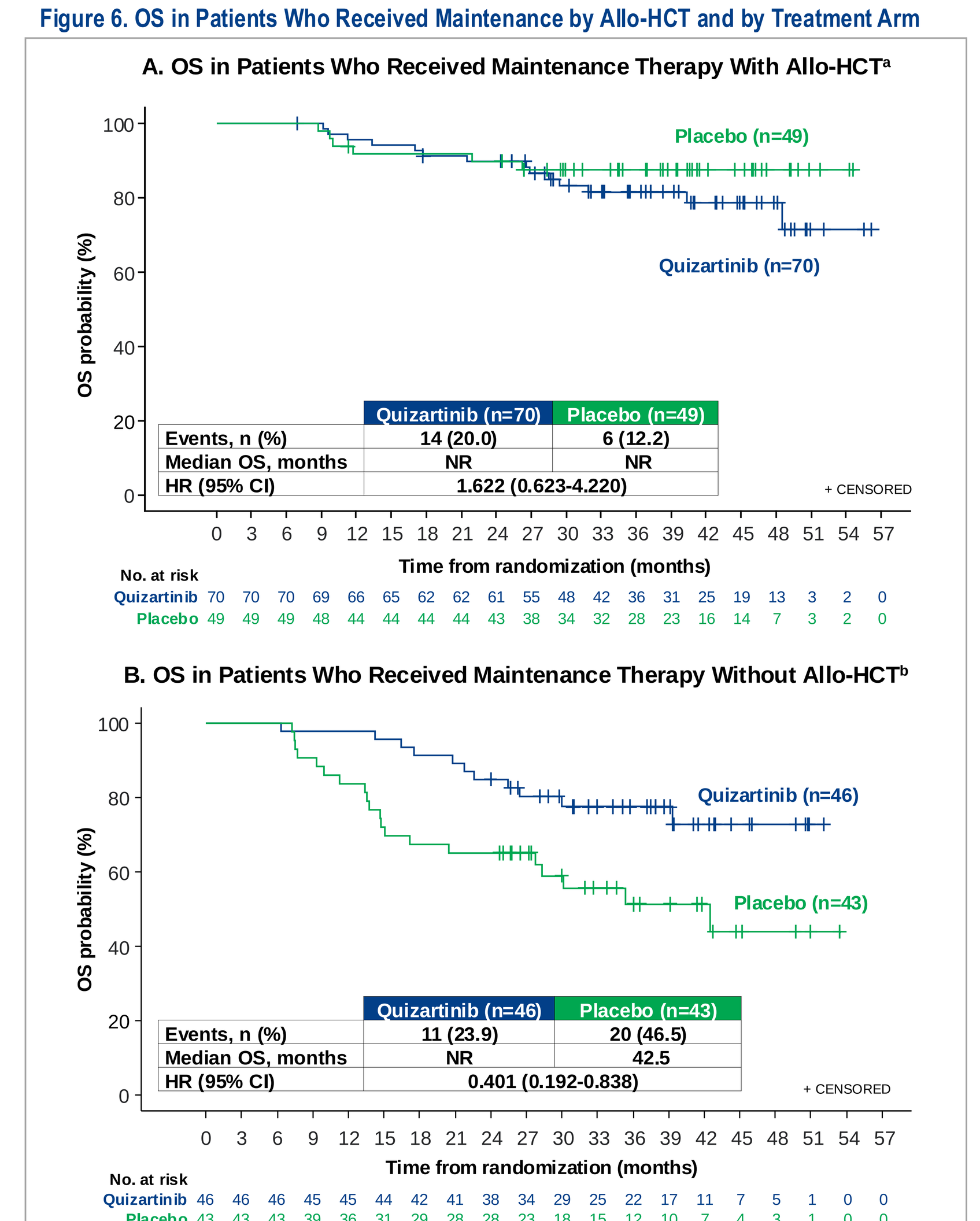


Sankey flow diagrams. The thickness of each flow path is proportional to the number of patients.
Allo-HCT, allogeneic hematopoietic cell transplantation.

OS by Allo-HCT in Patients Who Received Maintenance

- Among 119 patients who underwent allo-HCT before receiving maintenance, a survival difference between arms was not demonstrated (**Figure 6A**)
  - The number of transplanted patients proceeding to maintenance was different between arms (71.4% with quizartinib vs 55.1% with placebo; **Figure 5**)
  - The number of OS events is limited, accounting for 16.8% of the 119 patients
  - The 95% CI of the HR is wide (at 0.623-4.220)
- Among 89 patients who received maintenance without prior allo-HCT, quizartinib provided an OS benefit over placebo with a 60% reduction in the risk of death (**Figure 6B**)
  - The number of patients in the 2 arms was similar, with a similar proportion of patients without allo-HCT in both arms proceeding to maintenance (**Figure 5**), and the number of OS events accounts for 34.8% of the 89 patients (**Figure 6B**)

Figure 6. OS in Patients Who Received Maintenance by Allo-HCT and by Treatment Arm

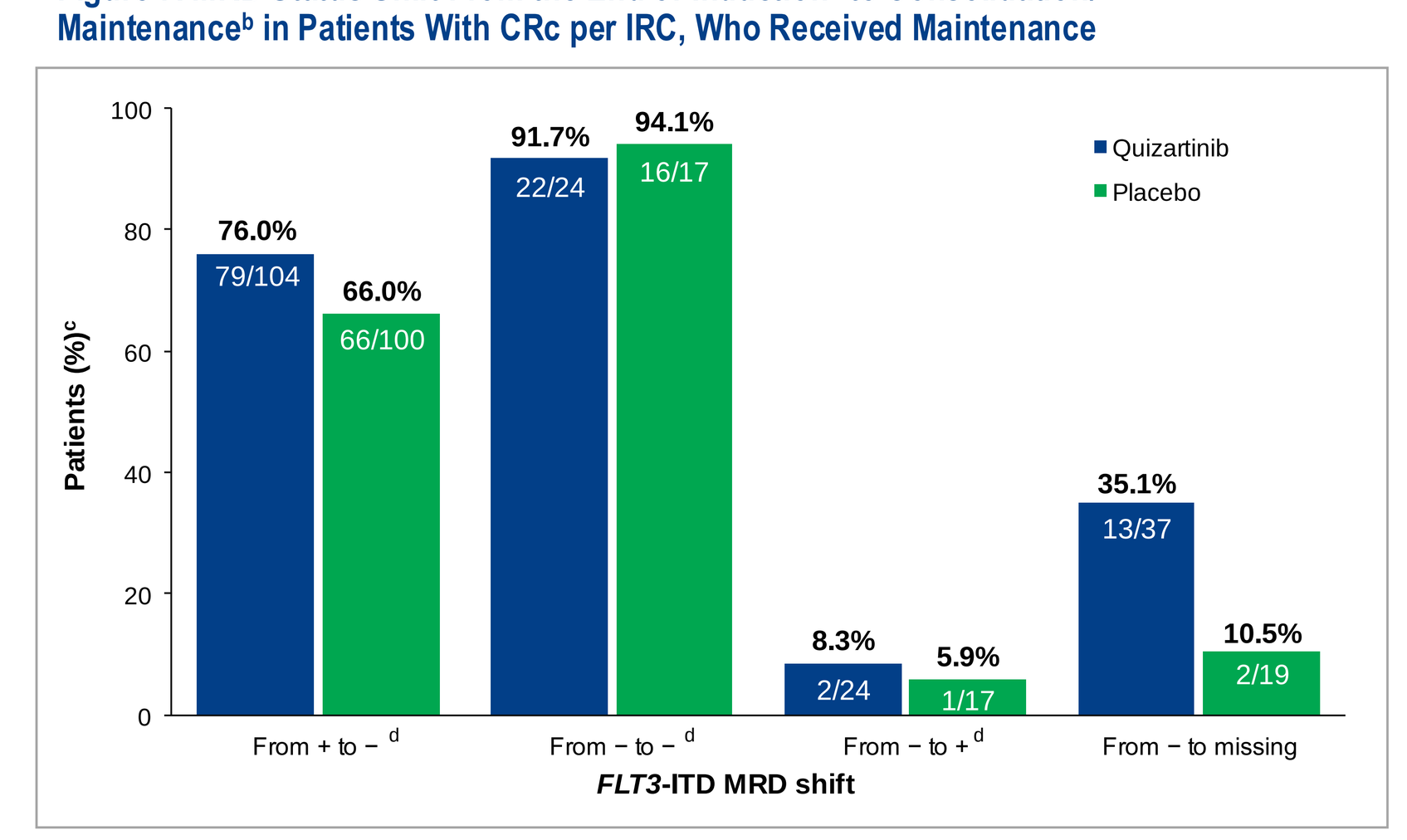


[a]Includes protocol-specified allo-HCT. [b]There were 6 patients who underwent allo-HCT during maintenance (4 in the quizartinib arm and 2 in the placebo arm); these 6 patients are included in this plot.
Allo-HCT, allogeneic hematopoietic cell transplantation; HR, hazard ratio; NR, not reached; OS, overall survival.

MRD Status Shift in Patients Who Received Maintenance

- The rate of CRc patients who were MRD-positive by the end of induction and became MRD-negative in consolidation/maintenance was higher with quizartinib (76.0%) versus placebo (66.0%; **Figure 7**)
- The rate of CRc patients who were MRD-negative by the end of induction and became MRD-positive in consolidation/maintenance was similar with quizartinib (8.3%) and placebo (5.9%; **Figure 7**)
- Among patients who were MRD-negative by the end of induction, more quizartinib-treated patients than placebo-treated patients had a missing MRD assessment in consolidation/maintenance (35.1% vs 10.5%; **Figure 7**)

Figure 7. MRD Status Shift From the End of Induction[a] to Consolidation/Maintenance[b] in Patients With CRc per IRC, Who Received Maintenance

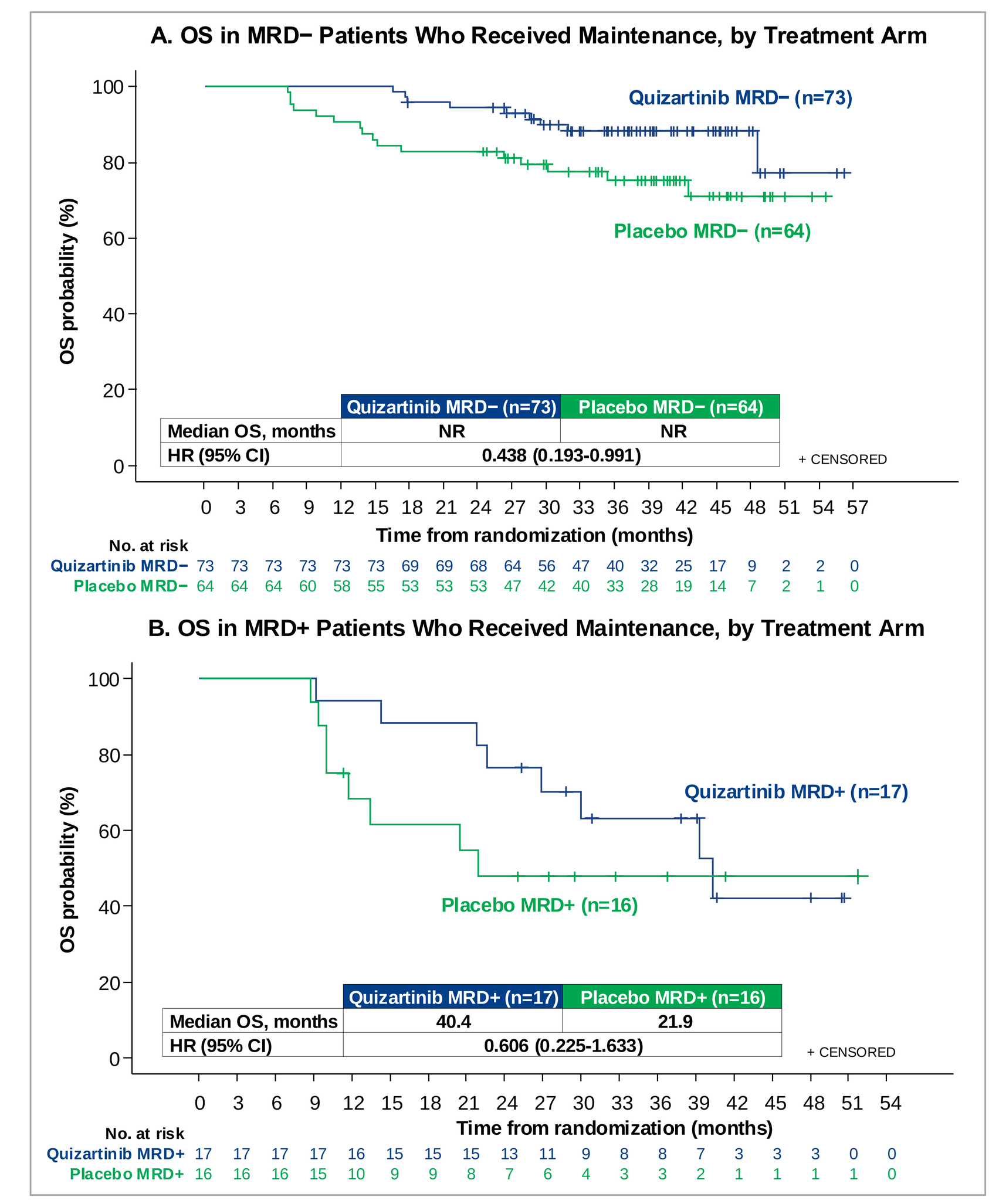


[a]Specimens were collected in induction cycle 1, day 21, up to day 56, and/or in induction cycle 2, day 21, up to day 56.
[b]Specimens were collected in consolidation cycle 1, day 21, in the last consolidation cycle, day 21, in maintenance cycle 1, day 1, and/or in maintenance cycle 4, day 1. [c]Denominators for percentages are the number of patients achieving CRc by the end of induction in the intent-to-treat population. [d]Denominators exclude patients with missing MRD data.
CRc, composite complete remission; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; IRC, independent review committee; MRD, measurable residual disease.

OS by MRD Status in Patients Who Received Maintenance

- Of the 208 patients who received maintenance, the MRD status within 30 days before entering maintenance was available for 170 (quizartinib, n=90; placebo, n=80)
  - The HR for OS favored quizartinib versus placebo in 137 MRD-negative patients (0.438; 95% CI, 0.193-0.991; **Figure 8A**) and numerically favored quizartinib in 33 MRD-positive patients (0.606; 95% CI, 0.225-1.633; **Figure 8B**)

Figure 8. OS in Patients Who Received Maintenance by MRD Status

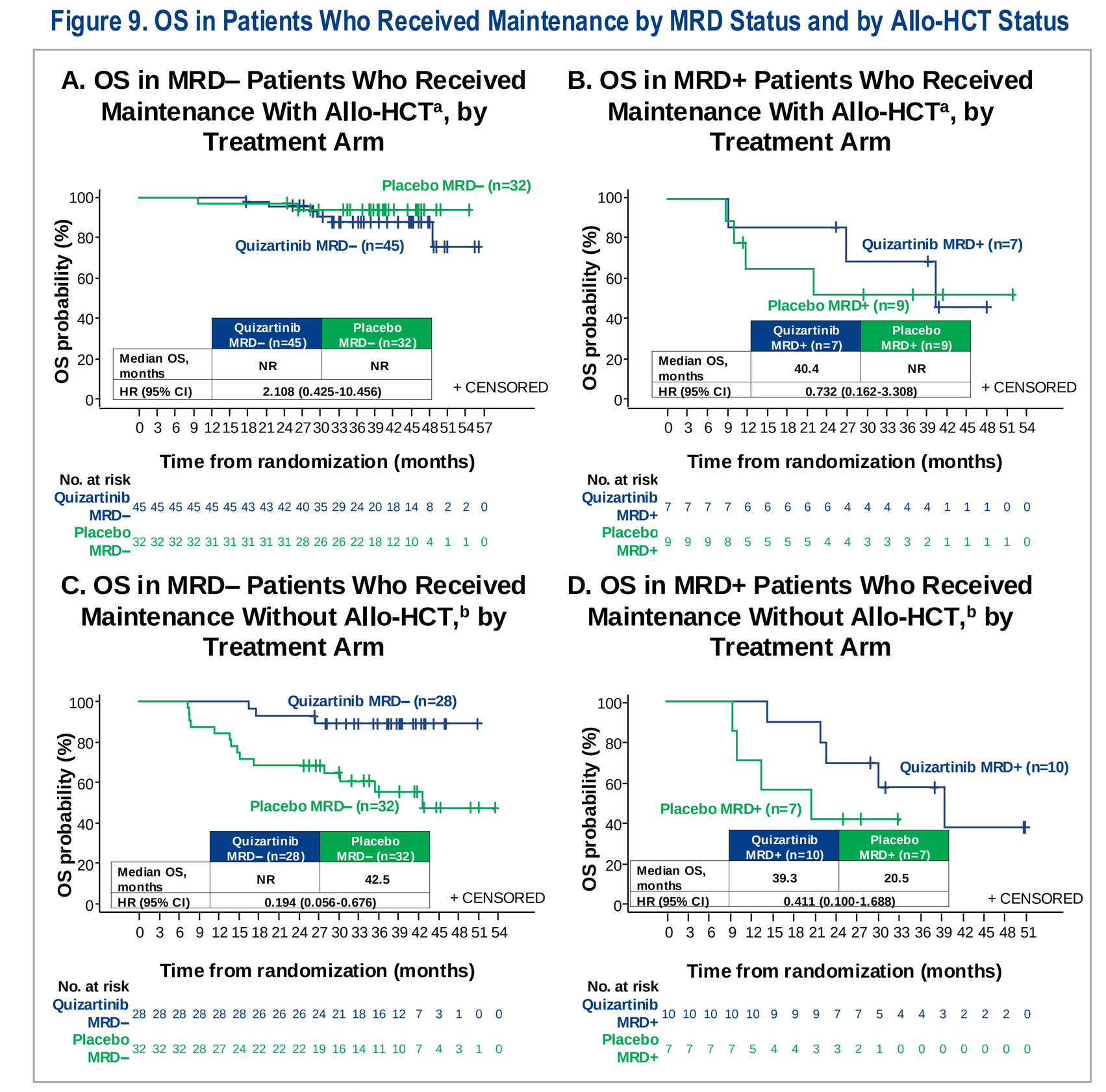


HR, hazard ratio; NR, not reached; MRD, measurable residual disease; OS, overall survival.

OS by MRD Status and by Allo-HCT in Patients Who Received Maintenance

- The benefit provided by quizartinib, regardless of MRD status, in patients who received maintenance was more evident in those without allo-HCT (**Figure 9**). The HR for OS among patients without allo-HCT was 0.194 (95% CI, 0.056-0.676) in MRD-negative patients (quizartinib, n=28; placebo, n=32; **Figure 9C**) and was 0.411 (95% CI, 0.100-1.688) in MRD-positive patients (quizartinib, n=10; placebo, n=7; **Figure 9D**)

Figure 9. OS in Patients Who Received Maintenance by MRD Status and by Allo-HCT Status



[a]Includes protocol-specified allo-HCT. [b]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.
Allo-HCT, allogeneic hematopoietic cell transplantation; HR, hazard ratio; NR, not reached; MRD, measurable residual disease; OS, overall survival.

Exposure

- The exposure during maintenance was similar in the 2 treatment arms, with a median treatment duration of 1.3 years and with over 60% of the patients receiving ≥12 cycles, in both arms (**Table 2**)

Table 2. Exposure During Maintenance

	Quizartinib (n=116)	Placebo (n=92)
Median (range) number of cycles	16 (1-36)	17 (1-36)
Median (range) adjusted treatment durations, weeks	67.36 (0.4-164.1)	67.71 (0.3-150.4)
Maintenance therapy ≥12 cycles, n (%)	75 (64.7)	59 (64.1)

Overall Safety During Maintenance

- Rates of grade ≥3 treatment-emergent AEs (TEAE) and drug-related AEs were more common in the quizartinib arm versus placebo during maintenance (**Table 3**)
- Rates of AEs leading to dose interruptions and dose reductions were more common with quizartinib versus placebo during maintenance (**Table 3**)

Table 3. Overall Safety During Maintenance

	Quizartinib (n=116)	Placebo (n=92)
AEs, n (%)		
Any TEAEs	109 (94.0)	84 (91.3)
Any TRAEs	85 (73.3)	34 (37.0)
Grade ≥3 TEAEs (including grade 5)	91 (78.4)	53 (57.6)
Grade ≥3 TRAEs (including grade 5)	62 (53.4)	16 (17.4)
Serious TEAEs	39 (33.6)	34 (37.0)
TRSAEs	8 (6.9)	5 (5.4)
AEs associated with fatal outcome	3 (2.6)[a]	7 (7.6)[b]
TRAEs associated with fatal outcome	0	0
Dose modifications, n (%)		
TEAEs associated with discontinuation	18 (15.5)	7 (7.6)
TRAEs associated with discontinuation	12 (10.3)	3 (3.3)
TEAEs associated with dose interruption	65 (56.0)	22 (23.9)
TRAEs associated with dose interruption	46 (39.7)	11 (12.0)
TEAEs associated with dose reduction	42 (36.2)	14 (15.2)
TRAEs associated with dose reduction	32 (27.6)	8 (8.7)

[a]The fatal TEAEs in the quizartinib arm were: septic shock, varicella Zoster virus infection, and GVHD in GI tract (n=1 each).
[b]The fatal TEAEs in the placebo arm were: general physical health deterioration (n=3), pneumonia, cerebrovascular accident, respiratory failure, and rectal hemorrhage (n=1 each).
AE, adverse event; GI, gastrointestinal; GVHD, graft versus host disease; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; TRSAE, treatment-related serious adverse event.

TEAEs During Maintenance

- The most common (≥15%) TEAEs of all grades during maintenance were:
  - 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%) in the quizartinib arm (**Table 4**)
  - Pyrexia and arthralgia (17.4% each) in the placebo arm (**Table 4**)

Table 4. TEAEs Occurring in ≥15% of Patients During Maintenance

TEAEs, %	Quizartinib (n=116)		Placebo (n=92)	
	All grade[a]	Grade ≥3	All grade[a]	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)
Arthralgia	13 (11.2)	0	16 (17.4)	0

[a]The 15% threshold is based on all-grade TEAEs.
TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Quizartinib is part of a treatment regimen that includes induction, consolidation, and maintenance
- For the entire study population, in patients who received maintenance, a numerically longer OS, higher RFS rates, and lower CIR rates were observed for those treated with quizartinib
- More patients in the quizartinib arm could proceed to maintenance versus placebo, especially in those who underwent transplantation
  - Among the transplanted patients, a survival difference between arms was not demonstrated, the Kaplan-Meier OS curves for quizartinib and placebo overlapped, with a wide CI and a limited number of OS events
  - Among the patients who received maintenance but did not undergo transplantation, quizartinib provided an OS benefit over placebo
- Quizartinib provides continuous clinical benefit from induction to consolidation through maintenance, regardless of MRD status, with an acceptable and manageable safety profile
  - These data indicate that quizartinib-treated patients may achieve deeper and longer remission versus placebo-treated patients
- This exploratory analysis in patients who received maintenance together with the positive benefit-risk profile in the ITT population support the use of quizartinib in patients with newly diagnosed *FLT3*-ITD–positive AML, across the whole treatment regimen

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DISCLOSURES

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