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Impact of hematopoietic cell transplantation and quizartinib in patients with newly diagnosed FLT3-internal tandem duplication-negative acute myeloid leukemia: results from the QUIWI study

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Impact of hematopoietic cell transplantation and quizartinib in patients with newly diagnosed FLT3-internal tandem duplication-negative acute myeloid leukemia: results from the QUIWI study

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Running tittle: Allogeneic hematopoietic cell transplantation in first remission and quizartinib for newly diagnosed *FLT3*-ITD–negative AML.

Key words: Acute myeloid leukemia, allogeneic hematopoietic cell transplantation, quizartinib, *FLT3*-ITD–negative

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Availability of data and material: Data and study material could be shared under reasonable proposal by contacting the corresponding author.

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Authors' contributions

Study design: PM and PLM. Data analysis and interpretation: PM, DMC, JL, and PLM. Provision of study materials or patients: All authors. Collection of and contribution to the quality of data: All authors. Manuscript revision and final approval: All authors.

ABSTRACT

QUIWI (NCT04107727) was a phase II, randomized, double-blind, placebo-controlled trial evaluating quizartinib or placebo added to induction and consolidation chemotherapy and/or allogeneic hematopoietic cell transplantation (allo-HCT), followed by maintenance, in newly diagnosed FLT3-ITD–negative acute myeloid leukemia (AML). This *post hoc* analysis assessed the impact of allo-HCT, modeled as a time-dependent variable, performed in first composite complete remission (CRc1) on overall survival (OS) and disease-free survival (DFS) according to treatment arm. Among 273 randomized patients, 32.2% in the quizartinib arm and 30.1% in the placebo arm underwent allo-HCT in CRc1. Quizartinib improved OS and DFS compared with placebo regardless of allo-HCT status. In Cox models with allo-HCT as a time-dependent covariate, quizartinib remained associated with improved OS (HR 0.59; p=0.008) and DFS (HR 0.67; p=0.03), whereas allo-HCT was not significantly associated with OS (HR 0.91; p=0.62) and showed a numerical DFS benefit (HR 0.73; p=0.08). Multivariable analyses confirmed quizartinib as an independent favorable factor for OS (HR 0.56; p=0.046) and DFS (HR 0.60; p=0.04). No additional safety signals were observed. In patients with newly diagnosed FLT3-ITD–negative AML achieving CRc1, quizartinib improved OS and DFS in the overall population. Notably, the clinical benefit of quizartinib was observed regardless of allo-HCT, and appeared more evident in patients who did not proceed to transplant.

INTRODUCTION

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy characterized by marked molecular and cytogenetic heterogeneity.[1] Among the molecular drivers implicated in AML pathobiology, the FLT3 receptor is particularly relevant, as it is frequently overexpressed in leukemic blasts and mutated in approximately one-third of newly diagnosed (ND) cases, most commonly through internal tandem duplications (ITD), which confer constitutive kinase activation and are classically associated with inferior clinical outcomes.[2–4]

Although FLT3 inhibition has demonstrated clear benefit in FLT3-mutated AML, emerging evidence indicates potential activity in FLT3–wild-type disease as well, with early-phase studies suggesting increased chemosensitivity regardless of mutation status.[5–8] On this basis, the QUIWI trial (NCT04107727) was designed by the Programa Español de Tratamientos en Hematología (PETHEMA group) to evaluate the clinical role of quizartinib, a potent and selective type II FLT3 inhibitor, in patients with ND FLT3-ITD–negative AML.[9] The QUIWI study was a phase 2, randomized, double-blind, placebo-controlled trial assessing quizartinib combined with induction and consolidation chemotherapy and/or allogeneic hematopoietic cell transplantation (allo-HCT), followed by single-agent maintenance therapy. In this FLT3-wild-type population, quizartinib significantly improved event-free survival (EFS) and overall survival (OS) compared with placebo and showed a manageable safety profile.[9]

Allo-HCT remains a key curative strategy for intermediate- and high-risk AML and is frequently offered to patients who achieve first complete remission (CR) or CR with incomplete hematologic recovery (CRi).[10–13] In the QUIWI study, allo-HCT was permitted in first CR/CRi after induction for eligible patients.[9] However, the interaction between quizartinib and subsequent allo-HCT in FLT3-ITD–negative AML has not been previously characterized. This *post hoc* analysis aimed to assess the impact of undergoing allo-HCT

in CR/CRi and to explore how quizartinib interacts with transplant to influence post-remission outcomes in patients with ND FLT3-ITD–negative AML.

METHODS

A detailed description of the QUIWI trial has been previously published.[9] Allo-HCT was permitted in first composite complete remission (CRc1; CR or CRi) for patients with an established indication and an available donor. Therefore, protocol-specified allo-HCTs were defined as those performed in CRc1. Any allo-HCT performed outside CRc1 (i.e., non-CRc, after relapse or refractory disease, or in subsequent CRc) was considered non–protocol-specified and excluded from the analyses.

Indications for allo-HCT followed PETHEMA group recommendations, which were in line with European LeukemiaNet (ELN) 2017 risk stratification and post-consolidation measurable residual disease (MRD) assessment.[9,14] Full details of the transplant criteria and transplant procedures are provided in the *Data Supplement* and summarized in Supplementary Figure 1. Maintenance with quizartinib or placebo (up to 12 cycles of 28 days) was initiated for transplanted patients between days 60 and 180 post-allo-HCT.

MRD monitoring was performed through the PETHEMA centralized platform (four central laboratories with harmonized methodologies). In patients with *NPM1*-mutated AML and *CBF* AML (i.e., *RUNX1-RUNX1T1* and *CBFB-MYH11*), MRD was assessed by standardized RT-qPCR techniques in peripheral blood (PB). In the remaining AML subtypes, MRD was evaluated in bone marrow samples (BM) using standardized multiparametric flow cytometry (MPFC). MRD negativity was defined according to protocol-specified criteria. For MPFC, MRD negativity was defined as <0.1% in BM samples. For RT-qPCR in PB, the following cut-offs were applied: ratio (NPM1/ABL) × 10^4 < 1, ratio (RUNX1-RUNX1T1/ABL) × 10^4 < 0.1, and ratio (CBFB-MYH11/ABL) × 10^4 < 1.

The study protocol was approved by the Ethics Committee of the Hospital Universitari i Politécnic La Fe and by the corresponding Ethics Committees at each participating center. The trial was conducted in accordance with the Declaration of Helsinki, applicable local regulations, and the International Council for Harmonisation Guidelines on Good Clinical Practices. All patients provided written informed consent in accordance with national, local, and institutional guidelines before enrollment.

Statistical analyses

The data cutoff date was July 27, 2024. Efficacy analyses were conducted in the intention-to-treat (ITT) population, defined as all randomized patients. The median duration of follow-up was estimated using the reverse Kaplan-Meier method.[15] The primary endpoint was OS, assessed by the independent review committee (IRC) and defined as the time from randomization to death from any cause. Additional IRC-assessed endpoints included disease-free survival (DFS), defined as time from CRc1 by the end of induction to relapse or death from any cause; duration of remission (DoR), defined as the time from randomization to relapse; and cumulative incidence of relapse (CIR), calculated from the date of CRc1 until relapse. Time-to-event endpoints (i.e., OS, DFS, and DoR) were analyzed using the Kaplan–Meier method.[16] Treatment-group comparisons were performed using the log-rank test.[17] Unstratified Cox proportional hazards models, including treatment group as a model factor, were used to estimate hazard ratios (HR) with the corresponding two-sided 95% confidence intervals (CI). CIR was analyzed using cumulative incidence methods with relapse as the event of interest and death without relapse as a competing event, and differences between groups were assessed using Gray's test.[18]

The effect of allo-HCT in CRc1 on OS and DFS was assessed using univariable Mantel-Byar method with allo-HCT as a time-dependent covariate.[19] Survival curves were also illustrated using Simon-Makuch plots, whereby patients initially contributed to the "no allo-HCT" group and switched to the "allo-HCT" group at the time of transplantation, with censoring at that time in the "no allo-HCT" curve.[20] For multivariable

analysis for OS and DFS, allo-HCT was modeled as a time-dependent covariate within an extended Cox proportional hazards model, adjusting for clinically relevant baseline characteristics.

Safety analyses were performed in the safety analysis set, defined as all patients who received at least one dose of quizartinib or placebo. Adverse events (AEs) were collected and summarized by treatment arm. For patients who underwent allo-HCT in CRc1, any AEs occurring after allo-HCT were recorded using a specific post-allo-HCT safety form. Details on study design, patients, randomization, and safety analyses are provided in the *Data Supplement.*

RESULTS

Patient disposition

In the randomized phase of the study, 273 patients with FLT3-ITD–negative AML were randomized 2:1 to receive quizartinib (n = 180) or placebo (n = 93) across 45 Spanish PETHEMA centers between September 2019 and November 2021 (Figure 1). Overall, 32.2% (58/180) of patients in the quizartinib arm and 30.1% (28/93) in the placebo arm underwent allo-HCT in CRc1. Median time to allo-HCT in CRc1 was 3.6 months in the quizartinib arm and 3.1 months in the placebo arm (Table 1).

As shown in Figure 1, among the 58 patients in the quizartinib arm who underwent allo-HCT in CRc1, transplantation was performed after one induction cycle in 7 patients (12.1%) and after a second induction cycle in 2 patients (3.4%), as well as after the first, second, third, and fourth consolidation cycles in 26 (44.8%), 15 (25.9%), 5 (8.6%), and 2 (3.4%) patients, respectively; allo-HCT was performed after the end of treatment (EOT) visit in 9 patients (15.5%). In the placebo arm, among the 28 patients who underwent allo-HCT in CRc1, transplantation was performed after two induction cycles in 2 patients (7.1%), after the first and second consolidation cycles in 14 (50%) and 11 (39.3%) patients, and after the third consolidation

in 1 patient (3.6%); one allo-HCT (3.6%) occurred after EOT. A detailed CONSORT diagram is also provided in Supplementary Figure 2.

Indications for allo-HCT performed in CRc1

Supplementary Figure 3 presents a Sankey diagram illustrating the allocation of patients who did or did not undergo allo-HCT in each treatment arm according to protocol-specified indications and ELN 2017 risk categories. Allo-HCT was performed due to MRD positivity after the second cycle of consolidation in 5 (8.6%) in the quizartinib arm and 2 (7.1%) in the placebo arm. Other protocol-defined indications, including adverse-risk disease and the need for a second induction cycle, are detailed in Supplementary Table 1. Patients transplanted in CRc1 outside predefined protocol criteria were classified as “Other”, reflecting investigator-driven decisions. As detailed in Supplementary Table 1, allo-HCT was performed in 6% vs 2% of favorable-risk patients, 11% vs 8% of intermediate-risk patients, and 15% vs 20% of adverse-risk patients in the quizartinib and placebo arms, respectively. Notably, 29% of adverse-risk patients in both arms did not proceed to allo-HCT. Despite some variation across indication categories, no statistically significant differences were observed between treatment arms in the reasons for undergoing allo-HCT ($p = 0.38$).

Conditioning regimen and graft characteristics in patients receiving allo-HCT in CRc1

Conditioning regimen and graft characteristics were well balanced between treatment arms (Table 1). Regarding transplant conditioning intensity, 31% of quizartinib patients received a reduced-intensity regimen (RIC), compared to 42.9% in the placebo group ($p = 0.40$). Donor type distribution showed that 41.4% of quizartinib patients had an unrelated donor, compared to 28.6% in the placebo group. Sibling donors accounted for 43.1% in the quizartinib and 35.7% in the placebo arm. Most patients received matched grafts (58.6% in the quizartinib arm and 53.6% in the placebo arm), with a higher proportion of

haploidentical donors in the placebo group (35.7% vs 22.4%). Peripheral blood was the predominant stem cell source in both arms.

Baseline patient demographics and disease characteristics

Table 2 summarizes patient demographics and disease characteristics overall and according to allo-HCT performance in CRc1 by the end of induction. The median age of patients achieving CRc1 was 57 years. Patients who underwent allo-HCT in CRc1 were younger (median age 55 years) and had a slightly higher proportion with favorable Eastern Cooperative Oncology Group performance status (ECOG PS 0–1, 94.2%) compared with those who did not undergo allo-HCT in CRc1 (median age 60 years, ECOG PS 0–1, 91.3%). In addition, as expected, patients who proceeded to allo-HCT in CRc1 had higher rates of adverse risk cytogenetics (30.3% vs. 15%) and ELN 2017 adverse risk (53.5% vs. 28.4%) compared to those who did not undergo allo-HCT. In the overall QUIWI population, 20.5% had a concomitant *NPM1* mutation, while patients who achieved CRc1 had a slightly higher rate of *NPM1* mutation (25.4%). As expected, patients who did not undergo allo-HCT in CRc1 had the highest prevalence of concomitant *NPM1* mutations (33.9% vs. 12.8%).

Efficacy analysis

Impact of quizartinib and allo-HCT among patients in CRc1

The median duration of follow-up was 40.5 months (95% CI 38.9–42). According to the Kaplan-Meier plots for OS and DFS in patients who achieved CRc1 by the end of induction, treatment with quizartinib was associated with longer survival outcomes compared with placebo, independent of allo-HCT status (Figure 2). Among patients who underwent allo-HCT in CRc1, quizartinib was associated with a HR for OS of 0.59 (95% CI 0.28–1.25) and numerically longer median OS (median not estimated [NE] for both arms, $p = 0.16$) (Figure 2A). In patients who did not undergo allo-HCT in CRc1, OS similarly favored quizartinib (HR 0.59,

95% CI 0.33–1.04) , with a median OS of NE vs 36 months (p = 0.06; Figure 2B). Among patients who underwent allo-HCT in CRc1, the HR for DFS was 0.80 (95% CI 0.39–1.63, p = 0.54; Figure 2C). Among patients who did not undergo allo-HCT, DFS was significantly improved with quizartinib versus placebo, with a HR of 0.61 (95% CI 0.36–0.98, p = 0.04) (Figure 2D). In line with these findings, an exploratory analysis restricted to adverse-risk patients (ELN 2017 and 2022) who did not undergo allo-HCT in CRc1 showed a consistent numerical trend toward improved OS and DFS with quizartinib compared with placebo (Supplementary Figure 4).

Consistent with OS and DFS results, a numerical improvement in DoR with quizartinib was observed among patients who did not undergo allo-HCT (HR 0.68, 95% CI 0.40–1.15, p = 0.15) (Supplementary Figure 5). Regarding CIR, quizartinib showed numerically lower CIR rates in patients who did not receive allo-HCT, whereas in those who underwent transplantation, CIR rates were comparable between arms (Supplementary Figure 6).

Impact of quizartinib and time-dependent allo-HCT in patients in CRc1

Results from the time-dependent Simon-Makuch analysis of allo-HCT in CRc1 on OS and DFS were in line with the findings of the previous Kaplan-Meier analysis (Figure 3). In the time-dependent Cox model, quizartinib treatment was significantly associated with improved OS (HR 0.59, 95% CI 0.40–0.87, p = 0.008), whereas undergoing allo-HCT in CRc1 did not have a statistically significant impact on OS (HR 0.91, 95% CI 0.62–1.33, p = 0.62) (Supplementary Table 2). OS rates were consistently higher in both quizartinib groups compared with placebo, regardless of whether patients underwent allo-HCT (Figure 3A). Regarding DFS, in the time-dependent Cox regression model, quizartinib was significantly associated with improved DFS compared with placebo (HR 0.67, 95% CI 0.48–0.95, p = 0.03). Allo-HCT performed in CRc1 was associated with a numerically improved DFS, however, this did not reach statistical significance (HR 0.73,

95% CI 0.52–1.03, *p* = 0.08) (Supplementary Table 2). The poorest outcomes were observed among placebo-treated patients who did not undergo allo-HCT (Figure 3B).

Multivariable analysis

In the multivariable extended Cox regression analysis for OS restricted to patients who achieved CRc1 after induction, treatment with quizartinib was independently associated with improved OS (HR 0.56, 95% CI 0.31–0.99, *p* = 0.046) (Figure 4A). In contrast, allo-HCT in CRc1, included as a time-dependent covariate, was not independently associated with OS (HR 0.69, 95% CI 0.32–1.50, *p* = 0.35). However, when treatment and allo-HCT were considered together, the strategy combining quizartinib with subsequent allo-HCT in CRc1 was associated with a significantly lower risk of death at any given time compared with placebo treated patients who had not received allo-HCT by that time (HR 0.47, 95% CI 0.24–0.93, *p* = 0.03). Male sex, secondary AML, and ELN 2022 adverse risk were independently associated with inferior OS (Figure 4A).

In the multivariable extended Cox for DFS, quizartinib treatment was also significantly associated with improved DFS (HR 0.60, 95% CI 0.38–0.97, *p* = 0.04). In contrast, allo-HCT performed in CRc1 was associated with a favorable trend in DFS but did not reach statistical significance (HR 0.54, 95% CI 0.26–1.12, *p* = 0.09) (Figure 4B). Similarly, male sex and ELN 2022 adverse risk were associated with inferior DFS. Again, the combination of quizartinib followed by allo-HCT in CRc1 was associated with improved outcomes compared with placebo without allo-HCT (HR 0.48, 95% CI 0.25–0.90, *p* = 0.02) (Figure 4B).

As an additional exploratory analysis, post-allo-HCT maintenance was incorporated into the multivariable extended Cox models as a time-dependent covariate. In the OS model, quizartinib maintenance was associated with a numerically lower risk of death compared with placebo maintenance (HR 0.43; 95% CI 0.18–1.05; p = 0.06). In the DFS model, no significant association was observed (HR 0.82; 95% CI 0.37–

1.79; p = 0.61). Importantly, adjustment for post-allo-HCT maintenance did not materially alter the overall treatment effect of quizartinib. Full results are provided in Supplementary Table 3.

Additional subgroup analyses were performed using multivariable extended Cox models including allo-HCT as a time-dependent covariate and assessed the interaction between treatment arm and allo-HCT status (Supplementary Table 4). No significant difference between quizartinib and placebo was observed among patients who underwent allo-HCT in CRc1, whereas quizartinib was associated with a significantly lower risk of death and relapse among patients who did not undergo allo-HCT.

Impact of treatment and allo-HCT in CRc1 according to measurable residual disease post-induction

OS and DFS were analyzed according to MRD status post-induction, stratified by allo-HCT status within each treatment arm (Supplementary Figure 7 and 8). Among patients who achieved CRc1 after induction therapy, centralized post-induction MRD assessment was available for most patients (82.4% in the quizartinib arm and 91.5% in the placebo arm). Post-induction MRD status was similarly distributed between arms (MRD-positive: 43.6% in the quizartinib arm vs 50.8% in the placebo arm; MRD-negative: 56.4% vs 49.2%, p = 0.36). To further characterize whether MRD response after induction differed according to baseline disease biology, we evaluated MRD negativity stratified by ELN-2017 risk category within each treatment arm (Supplementary Table 5). MRD negativity rates were numerically higher in the quizartinib arm across favorable (34.1% vs 27.3%) and intermediate-risk groups (78.8% vs 60.0%), and were comparable in the adverse-risk group (59.5% vs 59.3%), although none of these differences reached statistical significance.

In the OS analysis, among patients with MRD positivity post-induction undergoing allo-HCT in CRc1, the HR comparing quizartinib versus placebo was 0.23 (95% CI 0.07–0.69), and among those who did not undergo allo-HCT, the HR was 0.59 (95% CI 0.24–1.44) (Supplementary Figure 7). The treatment effect did not differ according to allo-HCT status (p for interaction = 0.34). DFS analyses showed findings consistent

with those observed for OS. In the allo-HCT subgroup, patients treated with quizartinib had longer DFS compared with placebo (HR 0.30, 95% CI 0.10–0.89). A similar, although not statistically significant, trend was seen among patients who did not undergo allo-HCT (HR 0.59, 95% CI 0.30–1.19) (Supplementary Figure 7). Again, no evidence of an interaction between treatment and allo-HCT status was observed (*p* for interaction = 0.38).

Among patients who were MRD-negative after induction, no significant differences were observed between treatment arms for either OS or DFS (Supplementary Figure 8). Within the allo-HCT subgroup, the HR for quizartinib versus placebo was 1.03 (95% CI 0.34–3.16) for OS and HR 1.38 (95% CI 0.47–4.04) for DFS. In patients who did not undergo allo-HCT, the corresponding HRs were 0.49 (95% CI 0.19–1.26) for OS and HR 0.63 (95% CI 0.27–1.48) for DFS, showing a positive trend for quizartinib. No evidence of treatment-by-transplant interaction was observed (*p* for interaction = 0.32 and 0.25, respectively).

Impact of prior allo-HCT status at start of maintenance

Among patients who underwent allo-HCT in CRc1, 25 patients (43.1%) in the quizartinib arm and 12 patients (42.9%) in the placebo arm received post-transplant maintenance therapy. Exposure during maintenance was comparable between treatment arms, with 48% and 50% of patients receiving ≥12 cycles, respectively (Supplementary Table 6). Treatment effects during maintenance were explored by prior allo-HCT in CRc1. Although the sample size was limited (allo-HCT: n = 37; no allo-HCT: n = 65), no clear or consistent differences between quizartinib and placebo were observed for OS or DFS within either the transplanted or non-transplanted subgroups, with wide confidence intervals precluding firm conclusions (Supplementary Figure 9).

To further explore the potential effect of maintenance therapy, post-allo-HCT outcomes were also summarized according to maintenance status stratified by pre-allo-HCT MRD status. Given the very small number of patients and events in each subgroup, these analyses are descriptive and formal statistical

comparisons were not feasible. Numerically, OS and DFS outcomes favored quizartinib maintenance in both MRD-positive and MRD-negative patients, with a more pronounced difference in the MRD-positive subgroup. Detailed descriptive results are provided in Supplementary Table 7.

Safety analysis

Among the 58 patients in the quizartinib arm and 28 in the placebo arm who underwent protocol-specified allo-HCT in CRc1, post-allo-HCT AEs were reported in 47 patients (81%) and 24 patients (85.7%), respectively. The incidence of post-allo-HCT AEs is summarized in Table 3. Overall, the incidence of AEs was comparable between treatment arms. An overview of post-allo-HCT safety is provided in Supplementary Table 8. Deaths related to AEs were reported in 5.2% of patients in the quizartinib arm and 10.7% in the placebo arm. In the quizartinib arm, fatal events included cytomegalovirus reactivation (n = 1) and lung infection (n = 2), whereas in the placebo arm fatal AEs included solid neoplasm (n = 1), sepsis (n = 1), and acute hepatic graft-versus-host disease (GVHD, n = 1). In patients who entered in the maintenance phase post-allo-HCT, treatment-related adverse events were more frequent in the quizartinib arm than in the placebo arm (52% vs 16.7%), although this difference did not reach statistical significance (p = 0.07) (Supplementary Table 8). The incidence of post-allo-HCT serious AEs (SAEs) was similar between treatment arms and is detailed in Supplementary Table 9.

Regarding GVHD, any grade was reported in 24.1% of patients in the quizartinib arm and 32.1% in the placebo arm. Only one case of GVHD with a fatal outcome was observed, which occurred in the placebo arm (acute hepatic GVHD). A more detailed description of GVHD during the allo-HCT period is provided in Supplementary Table 10. Acute GVHD occurred in 15.5% and 25% of patients in the quizartinib and placebo arms, respectively. The median time to onset of acute GVHD was slightly earlier in patients receiving quizartinib compared with those receiving placebo (28 days vs 40 days). Regarding severity, the distribution of the highest grade of acute GVHD was generally similar between treatment arms, with most

events being grade 1-3. The most frequently involved organ in acute GVHD was the skin (12.1% vs 10.7% in the quizartinib and placebo arms, respectively), followed by gastrointestinal (GI) involvement (5.2% vs 10.7%). Chronic GVHD was less frequently reported than acute GVHD, occurring in 8.6% of patients in the quizartinib arm and 7.1% in the placebo arm.

DISCUSSION

In this study, treatment with quizartinib was associated with improved survival outcomes compared with placebo, both in patients who underwent allo-HCT in CRc1 and in those who did not. The present analysis of the QUIWI study focuses on patients with ND FLT3-ITD wild-type AML and evaluates the impact of allo-HCT in CRc1, as well as the role of quizartinib compared with placebo within this context. Baseline characteristics were generally well balanced between patients who underwent allo-HCT and those who did not in CRc1, and were consistent with those previously reported in adult AML patients.[21–24] As expected, patients proceeding to allo-HCT were significantly younger and more frequently classified as adverse genetic risk, reflecting standard transplant selection criteria rather than treatment related imbalances.

A limitation of standard Kaplan-Meier analyses in this setting is that they do not properly account for the time-dependent nature of allo-HCT, potentially introducing immortal time bias.[25] To better assess the true impact of allo-HCT, we used the Simon-Makuch method to analyze OS and DFS.[20] When allo-HCT was modeled as a time-dependent covariate, quizartinib remained independently associated with improved OS, whereas allo-HCT performed in CRc1 did not have a statistically significant impact on OS. With respect to DFS, quizartinib was again independently associated with significantly improved outcomes, while allo-HCT in CRc1 showed a numerically favorable effect (p = 0.08). Placebo-treated patients without allo-HCT had the poorest DFS, whereas the most favorable outcomes were observed in patients receiving both

quizartinib and allo-HCT in CRc1. However, no statistically significant interaction between quizartinib and allo-HCT was identified, and thus no clear synergistic or complementary effect could be demonstrated.

Multivariable analyses incorporating allo-HCT as a time-dependent covariate confirmed these findings, identifying quizartinib as an independent factor associated with improved OS and DFS in patients achieving CRc1, whereas the effect of allo-HCT performed in CRc1 did not reach statistical significance, although a more favorable trend was observed for DFS. The differential impact of allo-HCT on DFS and OS, observed in both univariable and multivariable analyses, may be explained by the ability of allo-HCT to reduce relapse risk without necessarily translating into a clear OS advantage, as previously reported in other studies.[11,23,26,27] This may also reflect the availability of effective salvage therapies after relapse, as well as increased non-relapse mortality associated with allo-HCT.[23] Interestingly, our study shows that, through accurate selection of patients for allo-HCT indication in first CRc1 and addition of quizartinib to standard induction and consolidation chemotherapy, allo-HCT did not retain its independent protective effect for OS and DFS.

In addition, we evaluated the impact of post-induction MRD status on OS and DFS according to treatment arm and allo-HCT status. Among patients who remained MRD positive after induction, quizartinib was associated with more favorable OS and DFS compared with placebo, regardless of subsequent allo-HCT, with no evidence that transplant status modified the treatment effect. These findings suggest that quizartinib may provide clinical benefit in the setting of MRD positivity independently of allo-HCT, as previously reported in the primary analysis of the QUIWI trial.[9] Among patients who achieved MRD negativity after induction, a favorable trend was observed in non-transplanted patients treated with quizartinib. In this MRD-negative subgroup, OS curves for quizartinib-treated patients with or without allo-HCT were nearly superimposable, and survival in quizartinib-treated patients without allo-HCT was similar to that of placebo-treated patients who underwent allo-HCT, suggesting a limited additional contribution of allo-HCT to long-term outcomes in this biologically favorable population, although

confirmation in larger studies is warranted. In addition, MRD-negative rates after induction varied more across ELN 2017 risk groups than between treatment arms, suggesting that post-induction MRD may be a driver for allo-HCT decision in routine practice but also could be influenced primarily by baseline disease biology.

In the QUIWI study, a similar proportion of patients underwent allo-HCT in CRc1 in both arms. AEs observed during the post-allo-HCT period were those expected in AML patients undergoing allo-HCT. Overall, the incidence of GVHD was slightly higher in the placebo arm (32.1% vs 24.1%) and remained within the range previously observed for this setting.[28,29] Fatal outcomes attributable to GVHD were uncommon, and most events were grade 2–3 with predominantly cutaneous and GI involvement. No new safety signals were identified, and the safety profile was consistent with the overall QUIWI trial.[9]

To the best of our knowledge, published evidence specifically addressing the interaction between allo-HCT in CRc1 and FLT3 inhibitors in FLT3-ITD wild-type AML remains scarce, and QUIWI represents one of the first randomized studies to explore this setting. Moreover, data on FLT3 inhibitor maintenance after allo-HCT in FLT3-ITD–negative AML are lacking, and available evidence in FLT3-mutated AML has not shown a clear overall clinical benefit of post-allo-HCT maintenance. In the phase III MORPHO trial, gilteritinib did not show a significant improvement in efficacy endpoints in the overall population as maintenance therapy after allo-HCT; however, a significant relapse-free survival benefit was observed in patients who were MRD-positive in the pre- or early post-allo-HCT setting.[30] *Post hoc* analyses from the QuANTUM-First trial suggested that the benefit of quizartinib may be greater among patients who had not undergone allo-HCT before maintenance, although these findings were limited by small sample sizes.[31] Similarly, in the present study, no clear differences in outcomes were observed between quizartinib and placebo during the maintenance phase, irrespective of prior allo-HCT status. In addition, adjustment for post-allo-HCT maintenance in multivariable time-dependent models did not materially modify the overall treatment effect on OS or DFS. Although quizartinib maintenance was associated with a numerically lower

risk of death compared with placebo, this did not reach statistical significance. Descriptive analyses also suggested numerically improved post-allo-HCT outcomes with quizartinib maintenance, particularly among MRD-positive patients. Nevertheless, all these analyses were limited by the small number of patients and few events, precluding definitive conclusions.

Several limitations of this study should be addressed. First, although the protocol provided guidance, the decision to proceed to allo-HCT was made at the investigator's discretion, introducing variability across centers (including conditioning regimens and GVHD prophylaxis/treatment practices). Second, this was a single-country study, and some subgroup analyses included relatively few patients, limiting statistical power and generalizability.

In conclusion, these *post hoc* analyses of the QUIWI study suggest that quizartinib offers a clinically relevant benefit in ND FLT3-ITD wild-type AML, including in patients undergoing allo-HCT in CRc1. Overall, quizartinib remained independently associated with improved efficacy outcomes when controlling for receipt of allo-HCT and for baseline covariates of interest. In contrast, while allo-HCT contributed to relapse control, this did not consistently translate into a clear OS advantage in this setting. No new transplant-related safety signals were identified. Taken together, these findings provide a strong rationale for the ongoing global, randomized, double-blind, placebo-controlled phase III QuANTUM-Wild trial (NCT06578247).

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Table 1. Allo-HCT timing, conditioning regimens, and graft characteristics.

	Quizartinib	Placebo
Overall allo-HCT timing		
Patients in the ITT, n (%)	180 (100)	93 (100)
Patients who underwent allo-HCT in CRc1 (protocol-specified)[a], n (%) [95% CI][b]	58 (32.2) [25.5–39.6]	28 (30.1) [21–40.5]
Median (range) age, years	54.5 (20–70)	58.5 (30–70)
Median (range) time to allo-HCT from randomization, months	4.7 (2.6–23.7)	4.4 (2.5–7.4)
Mean (SD) time to allo-HCT from randomization, months	5.5 (3.1)	4.6 (1.3)
Median (range) time to allo-HCT from CRc1, months	3.6 (0.9–22.4)	3.1 (1.2–6.5)
Mean (SD) time to allo-HCT from CRc1, months	4.2 (3.1)	3.4 (1.4)
Patients who underwent allo-HCT in CR1 (protocol-specified)[a], n (%) [95% CI][b]	37 (20.6) [14.9–27.2]	20 (21.5) [13.7–31.2]
Conditioning regimen and graft characteristics in patients receiving allo-HCT[a] in CRc1		
Number of patients, n (%)	58 (100)	28 (100)
Conditioning regimen, n (%)		
Myeloablative (MAC)	35 (60.3)	15 (53.6)
Reduced intensity/non-ablative	19 (32.8)	13 (46.4)
Reduced intensity (RIC)	18 (31)	12 (42.9)
Non-ablative (NMA)	1 (1.7)	1 (3.6)
Missing	4 (6.9)	0
Reason for RIC regimen, n (%)		
Age	16 (88.9)	10 (83.3)
Comorbidities	1 (5.6)	1 (8.3)
Physician decision	1 (5.6)	1 (8.3)
Donors related or unrelated, n (%)		
Sibling	25 (43.1)	10 (35.7)
Other related[c]	7 (12.1)	10 (35.7)
Unrelated	24 (41.4)	8 (28.6)
Missing	2 (3.4)	0
Match type, n (%)		
Matched[d]	34 (58.6)	15 (53.6)
Not matched[f]	8 (13.8)	3 (10.7)

Haploidentical[g]	13 (22.4)	10 (35.7)
Missing	3 (5.2)	0
Source of stem cells, n (%)		
Bone marrow	6 (10.3)	3 (10.7)
Peripheral blood	48 (82.8)	25 (89.3)
Cord blood	1 (1.7)	0
Missing	3 (5.2)	0
CD34+ cell dose infused (x10^6/kg), n (%)	53 (91.4)	25 (89.3)
Median (range)	5.9 (2.3–16.2)	6.0 (2.4–17)
Mean (SD)	6.3 (2.5)	6.4 (2.9)

[a]Protocol-specified allo-HCT refers to transplants performed in CRc1 (by IRC assessment). [b]95% CIs calculated using the Clopper–Pearson exact method. [c]Relative to the patient other than sibling. [d]Defined as at least antigen-level matching at HLA-A and HLA-B and high-resolution matching at HLA-DRB1 in 6 out of 6 loci. [f]Any other antigen matching less than 6/6 was left to the decision of the treating investigator. [g]Half matching. Abbreviations: Allo-HCT: allogeneic hematopoietic cell transplantation; CRc1: first composite complete remission; CI: confidence interval; HLA: human leukocyte antigen; ITT: intent-to-treat; MAC: myeloablative conditioning; NMA: non-myeloablative conditioning; RIC: reduced-intensity conditioning; SD: standard deviation.

Table 2. Baseline demographics and disease characteristics according to allo-HCT performance in CRc1 by the end of induction.

	All patients[a]	Patients who achieved CRc1	Patients who achieved CRc1 and underwent allo-HCT[b]	Patients who achieved CRc1 and did not undergo allo-HCT[c]	p-value
Number of patients, N	273 (100)	213 (100)	86 (100)	127 (100)	
Patient demographics					
Age, years					
Median (range)	57 (19–70)	57 (19–70)	55 (20–70)	60 (19–70)	0.07
<60 years, n (%)	158 (58.1)	118 (55.4)	56 (65.1)	62 (48.8)	0.03
≥60 years, n (%)	114 (41.9)	95 (44.6)	30 (34.9)	65 (51.2)	
Sex, n (%)					
Male	157 (57.5)	118 (55.4)	43 (50)	75 (59.1)	0.24
Female	116 (42.5)	95 (44.6)	43 (50)	52 (49.9)	
Race, n (%)					
White/Caucasian	261 (95.6)	205 (96.2)	83 (96.5)	122 (96.1)	
Black or African American	0	0	0	0	0.78
Latin American	7 (2.6)	6 (2.8)	2 (2.3)	4 (3.1)	
Asian	3 (1.1)	1 (0.5)	0	1 (0.8)	
Other	2 (0.7)	1 (0.5)	1 (1.2)	0	
Disease characteristics					
AML type, n (%)					
De novo	237 (86.8)	186 (87.3)	74 (86)	112 (88.2)	0.80
Secondary	36 (13.2)	27 (12.7)	12 (14)	15 (11.8)	
ECOG PS, n (%)					
0	171 (62.6)	136 (63.9)	59 (68.6)	77 (60.6)	
1	83 (30.4)	61 (28.6)	22 (25.6)	39 (30.7)	0.46
2	19 (7)	16 (7.5)	5 (5.8)	11 (8.7)	
WBC count at diagnosis, n (%)					
<20×10^9/L	216 (79.1)	168 (78.9)	72 (83.7)	96 (75.6)	0.21
≥20×10^9/L	57 (20.9)	45 (21.1)	14 (16.3)	31 (24.4)	

Cytogenetic risk, n (%)[d]					
Low	14 (5.1)	14 (6.6)	2 (2.3)	12 (9.4)	
Intermediate	155 (56.8)	130 (61)	48 (55.8)	82 (64.6)	0.02
High	76 (27.8)	45 (21.1)	26 (30.3)	19 (15)	
Missing	28 (10.3)	24 (11.3)	10 (11.6)	14 (11)	
Genetic risk per IRC ELN 2017, n (%)					
Favorable	76 (27.5)	73 (34.3)	12 (13.9)	61 (48)	<0.001
Intermediate	72 (26.4)	58 (27.2)	28 (32.6)	30 (23.6)	
Adverse	125 (46.2)	82 (38.5)	46 (53.5)	36 (28.4)	
Genetic risk per IRC ELN 2022, n (%)					
Favorable	78 (28.2)	76 (35.7)	13 (15.1)	63 (49.6)	<0.001
Intermediate	35 (12.8)	32 (15)	17 (19.8)	15 (11.8)	
Adverse	160 (58.9)	105 (49.3)	56 (65.1)	49 (38.6)	
Mutated *NPM1*, n (%)[e]	56 (20.5)	54 (25.4)	11 (12.8)	43 (33.9)	<0.001
Mutated *FLT3*-TKD, n (%)[e]	19 (7)	19 (8.9)	9 (10.5)	10 (7.9)	0.69
Mutated *IDH1*, n (%)[e]	25 (9.2)	22 (10.3)	6 (7)	16 (12.6)	0.27
Mutated *IDH2*, n (%)[e]	49 (17.9)	37 (17.4)	13 (15.1)	24 (18.9)	0.60
Mutated *TP53*, n (%)[e]	33 (12.1)	15 (7)	8 (9.3)	7 (5.5)	0.43

[a]Three patients in the ITT set (two in quizartinib and one in placebo) were randomized but not treated in each arm. [b]Includes protocol-specified allo-HCT (transplants performed in CRc1 by IRC assessment). [c]Includes 123 patients who achieved CRc after induction and did not undergo allo-HCT at all, and 4 patients who underwent allo-HCT outside CRc1. [d]According to MRC 2010 cytogenetics risk by IRC assessment. [e]Data based on central NGS testing performed at diagnosis in PETHEMA reference laboratories. Abbreviations: Allo-HCT: allogeneic hematopoietic cell transplantation; AML: acute myeloid leukemia; CRc1: first composite complete remission; ECOG PS: Eastern Cooperative Oncology Group performance status; ELN: European LeukemiaNet; *FLT3*-TKD: FMS-like tyrosine kinase 3, tyrosine kinase domain; *IDH1/2*: isocitrate dehydrogenase 1/2; IRC: independent review committee; ITT: intent-to-treat; MRC: Medical Research Council; *NPM1*: nucleophosmin 1; *TP53*: tumor protein 53; WBC: white blood cell.

Table 3. Adverse events occurring in ≥5% of patients who underwent protocol-specified allo-HCT in CRc1 in either treatment arm.

	Quizartinib (n = 58)		Placebo (n = 28)	
Adverse event[a]	**All grades, n (%)**	**Grade ≥3, n (%)**	**All grades, n (%)**	**Grade ≥3, n (%)**
Mucositis	19 (32.8)	13 (22.4)	13 (46.4)	6 (21.4)
Graft versus host disease	14 (24.1)	5 (8.6)	9 (32.1)	5 (17.9)
Febrile neutropenia	12 (20.7)	3 (5.2)	4 (14.3)	1 (3.6)
Neutrophil count decreased	11 (19)	9 (15.5)	2 (7.1)	2 (7.1)
Fatigue	11 (19)	0 (0)	3 (10.7)	1 (3.6)
Cytomegalovirus infection reactivation	11 (19)	2 (3.5)	3 (10.7)	1 (3.6)
Nausea and vomiting	11 (19)	0 (0)	3 (10.7)	1 (3.6)
Diarrhea	10 (17.2)	1 (1.7)	5 (17.9)	0 (0)
Infections and infestations (other)	10 (17.2)	3 (5.2)	6 (21.4)	3 (10.7)
Skin and subcutaneous tissue disorders	9 (15.5)	1 (1.7)	4 (14.3)	0 (0)
Fever	9 (15.5)	0 (0)	10 (35.7)	0 (0)
Rash	9 (15.5)	0 (0)	2 (7.1)	0 (0)
Anemia	9 (15.5)	3 (5.2)	3 (10.7)	1 (3.6)
Sepsis	9 (15.5)	9 (15.5)	4 (14.3)	4 (14.3)
Lung infection	8 (13.8)	3 (5.2)	1 (3.6)	1 (3.6)
Platelet count decreased	8 (13.8)	4 (6.9)	1 (3.6)	1 (3.6)
COVID-19 infection	8 (13.8)	1 (1.7)	3 (10.7)	0 (0)
Metabolism and nutrition disorders	7 (12.1)	1 (1.7)	2 (7.1)	1 (3.6)
Bleeding	7 (12.1)	0 (0)	2 (7.1)	0 (0)
Investigations	6 (10.3)	2 (3.5)	1 (3.6)	0 (0)
QT corrected interval prolonged	6 (10.3)	0 (0)	2 (7.1)	0 (0)
Respiratory, thoracic and mediastinal disorders	6 (10.3)	0 (0)	2 (7.1)	0 (0)
Edema limbs	6 (10.3)	0 (0)	3 (10.7)	0 (0)
Pain	6 (10.3)	0 (0)	4 (14.3)	0 (0)
Enterocolitis	5 (8.6)	2 (3.5)	0 (0)	0 (0)
Nervous system disorders	5 (8.6)	0 (0)	2 (7.1)	0 (0)

Headache	5 (8.6)	0 (0)	2 (7.1)	0 (0)
Acute kidney injury	5 (8.6)	0 (0)	2 (7.1)	2 (7.1)
Urinary tract infection	5 (8.6)	0 (0)	6 (21.4)	3 (10.7)
Gastrointestinal hemorrhage	4 (6.9)	1 (1.7)	0 (0)	0 (0)
Anorexia	4 (6.9)	1 (1.7)	0 (0)	0 (0)
Hepatobiliary disorders	4 (6.9)	1 (1.7)	1 (3.6)	1 (3.6)
Eye disorders	4 (6.9)	0 (0)	1 (3.6)	0 (0)
Injury, poisoning and procedural complications	4 (6.9)	1 (1.7)	2 (7.1)	1 (3.6)
Abdominal pain	4 (6.9)	0 (0)	3 (10.7)	0 (0)
Endocrine disorders	3 (5.2)	0 (0)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders	3 (5.2)	1 (1.7)	0 (0)	0 (0)
Cardiac disorders	3 (5.2)	1 (1.7)	0 (0)	0 (0)
Peripheral sensory neuropathy	3 (5.2)	0 (0)	0 (0)	0 (0)
Dizziness	3 (5.2)	0 (0)	0 (0)	0 (0)
Vascular disorders	3 (5.2)	0 (0)	1 (3.6)	0 (0)
Pancytopenia	3 (5.2)	3 (5.2)	1 (3.6)	1 (3.6)
Alanine aminotransferase increased	3 (5.2)	2 (3.5)	1 (3.6)	0 (0)
General disorders and administration site conditions	3 (5.2)	0 (0)	1 (3.6)	0 (0)
Pruritus	3 (5.2)	0 (0)	1 (3.6)	0 (0)
Hemorrhoids	3 (5.2)	0 (0)	2 (7.1)	0 (0)
Hypertension	2 (3.5)	0 (0)	2 (7.1)	0 (0)
Reproductive system and breast disorders	1 (1.7)	0 (0)	2 (7.1)	0 (0)

If a patient had more than one event, the patient was counted only once. [a]Regardless of causality. Abbreviations: AE: adverse event; allo-HCT: allogeneic hematopoietic cell transplantation; CRc1: first composite complete remission.

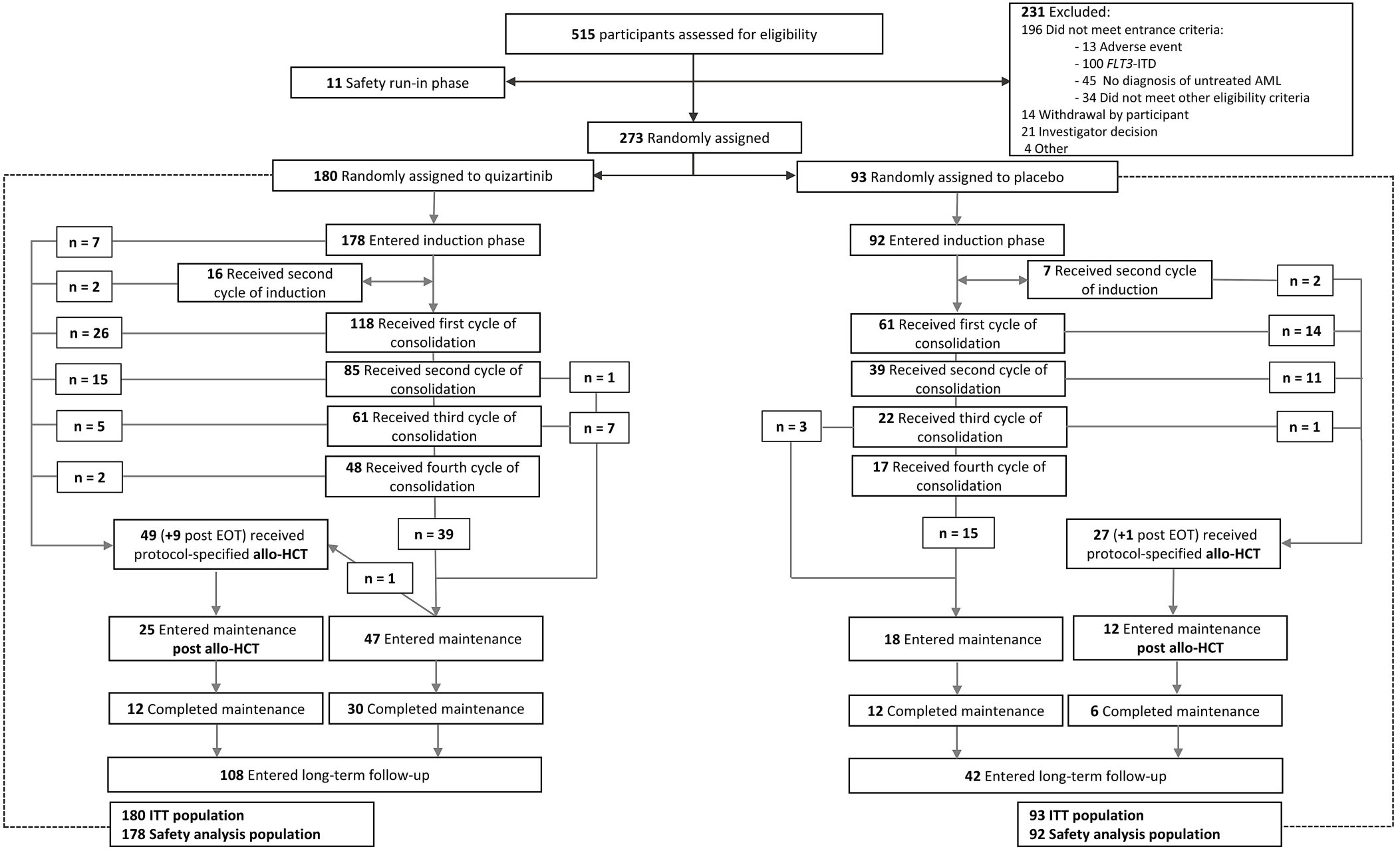
Figure Legends

Figure 1. Diagram of patients flow. Abbreviations: Allo-HCT: allogeneic hematopoietic cell transplantation; EOT: end of treatment; FLT3-ITD: FMS-like tyrosine kinase 3-internal tandem duplication; ITT: intent-to-treat.

Figure 2. Kaplan-Meier plots of OS and DFS according to treatment arm and allo-HCT status in patients who achieved CRc1 after induction per IRC. (A) OS in patients who received allo-HCT in CRc1. (B) OS in patients who did not receive allo-HCT in CRc1. (C) DFS in patients who received allo-HCT in CRc1. (D) DFS in patients who did not receive allo-HCT in CRc1. Abbreviations: Allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; CRc1: first composite complete remission; DFS: disease-free survival; HR: hazard ratio; IRC: independent review committee; NE: not estimated; OS: overall survival.

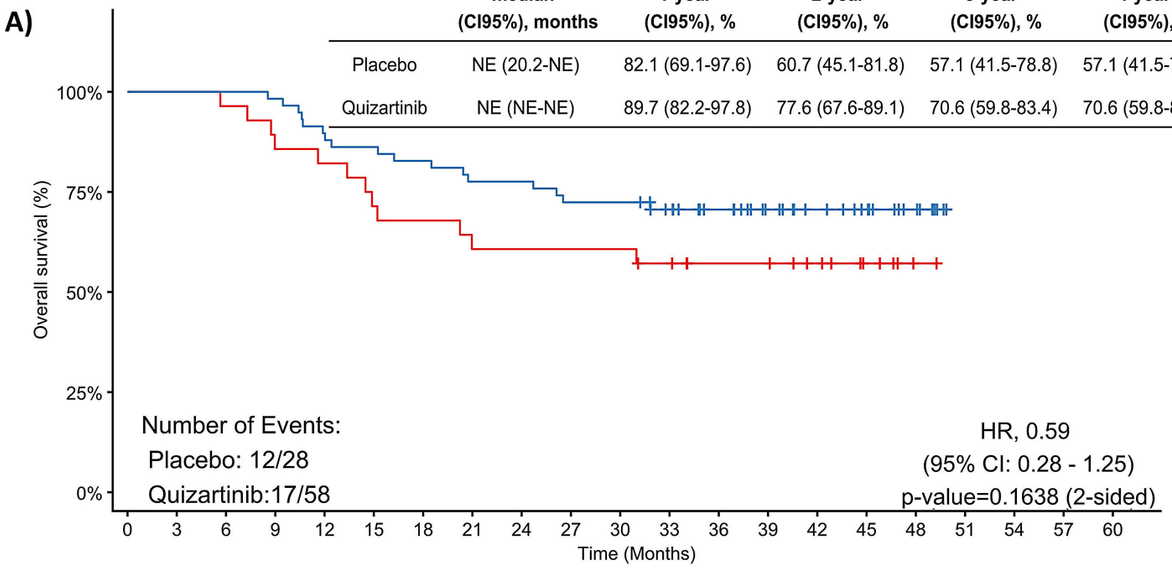
Figure 3. Time-dependent Simon-Makuch plots of OS and DFS according to allo-HCT in patients who achieved CRc1 by the end of induction per IRC. (A) Time-dependent Simon-Makuch plot of OS from randomization by allo-HCT in patients who achieved CRc1 by the end of induction per IRC. (B) Time-dependent Simon-Makuch plot of DFS by allo-HCT in patients who achieved CRc1 by the end of induction per IRC. Abbreviations: Allo-HCT: allogeneic hematopoietic cell transplantation; CRc1: first composite complete remission; DFS: disease-free survival; IRC: independent review committee; NE: not estimated; OS: overall survival.

Figure 4. Multivariable extended Cox regression models for OS and DFS including allo-HCT in CRc1 as a time-dependent covariate. (A) Multivariable extended Cox regression model for OS including allo-HCT in CRc1 as a time-dependent covariate. (B) Multivariable extended Cox regression model for DFS including allo-HCT in CRc1 as a time-dependent covariate. Abbreviations: Allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; CRc1: first composite complete remission; DFS: disease-free survival; ELN: European LeukemiaNet; ECOG: Eastern Cooperative Oncology Group; FLT3-TKD: FMS-like tyrosine kinase 3 tyrosine kinase domain; HR: hazard ratio; OS: overall survival; WBC: white blood cell.


515 participants assessed for eligibility
231 Excluded:
196 Did not meet entrance criteria:
- 13 Adverse event
- 100 FLT3-ITD
- 45 No diagnosis of untreated AML
- 34 Did not meet other eligibility criteria
14 Withdrawal by participant
21 Investigator decision
4 Other
11 Safety run-in phase
273 Randomly assigned
180 Randomly assigned to quizartinib
93 Randomly assigned to placebo
n = 7
178 Entered induction phase
92 Entered induction phase
n = 2
16 Received second cycle of induction
7 Received second cycle of induction
n = 2
n = 26
118 Received first cycle of consolidation
61 Received first cycle of consolidation
n = 14
n = 15
85 Received second cycle of consolidation
n = 1
39 Received second cycle of consolidation
n = 11
n = 5
61 Received third cycle of consolidation
n = 7
n = 3
22 Received third cycle of consolidation
n = 1
n = 2
48 Received fourth cycle of consolidation
17 Received fourth cycle of consolidation
49 (+9 post EOT) received protocol-specified allo-HCT
n = 39
n = 15
27 (+1 post EOT) received protocol-specified allo-HCT
n = 1
25 Entered maintenance post allo-HCT
47 Entered maintenance
18 Entered maintenance
12 Entered maintenance post allo-HCT
12 Completed maintenance
30 Completed maintenance
12 Completed maintenance
6 Completed maintenance
108 Entered long-term follow-up
42 Entered long-term follow-up
180 ITT population
178 Safety analysis population
93 ITT population
92 Safety analysis population

A)

	median (CI95%), months	1-year (CI95%), %	2-year (CI95%), %	3-year (CI95%), %	4-year (CI95%), %
Placebo	NE (20.2-NE)	82.1 (69.1-97.6)	60.7 (45.1-81.8)	57.1 (41.5-78.8)	57.1 (41.5-78.8)
Quizartinib	NE (NE-NE)	89.7 (82.2-97.8)	77.6 (67.6-89.1)	70.6 (59.8-83.4)	70.6 (59.8-83.4)

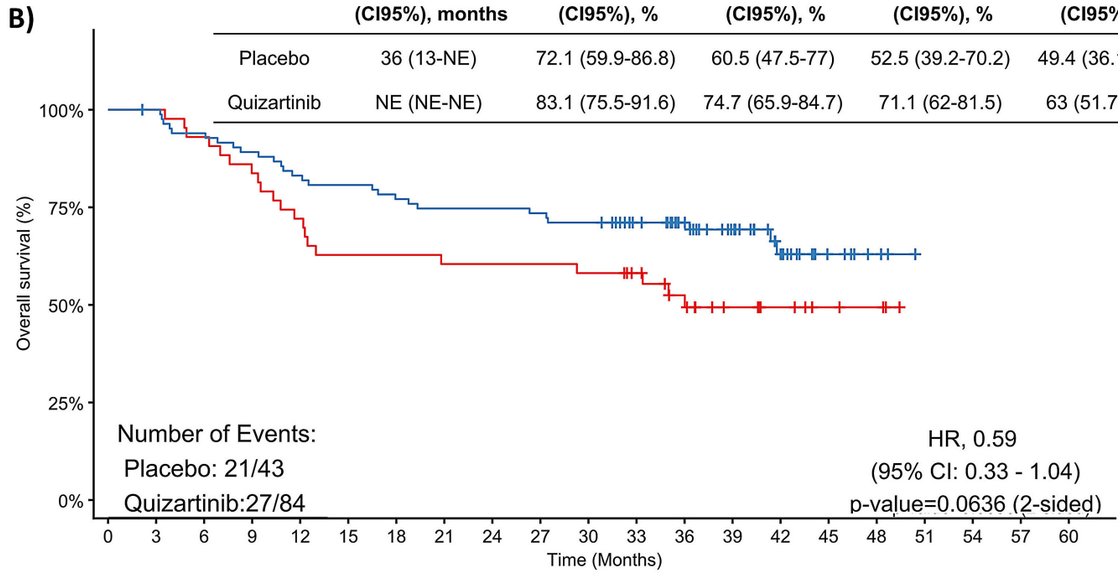


Number at risk

Placebo	28	28	27	24	23	20	19	17	17	17	17	15	12	12	9	5	1	0	0	0
Quizartinib	58	58	58	57	52	50	48	45	45	42	42	37	31	24	19	14	8	0	0	0

B)

	median (CI95%), months	1-year (CI95%), %	2-year (CI95%), %	3-year (CI95%), %	4-year (CI95%), %
Placebo	36 (13-NE)	72.1 (59.9-86.8)	60.5 (47.5-77)	52.5 (39.2-70.2)	49.4 (36.1-67.6)
Quizartinib	NE (NE-NE)	83.1 (75.5-91.6)	74.7 (65.9-84.7)	71.1 (62-81.5)	63 (51.7-76.7)

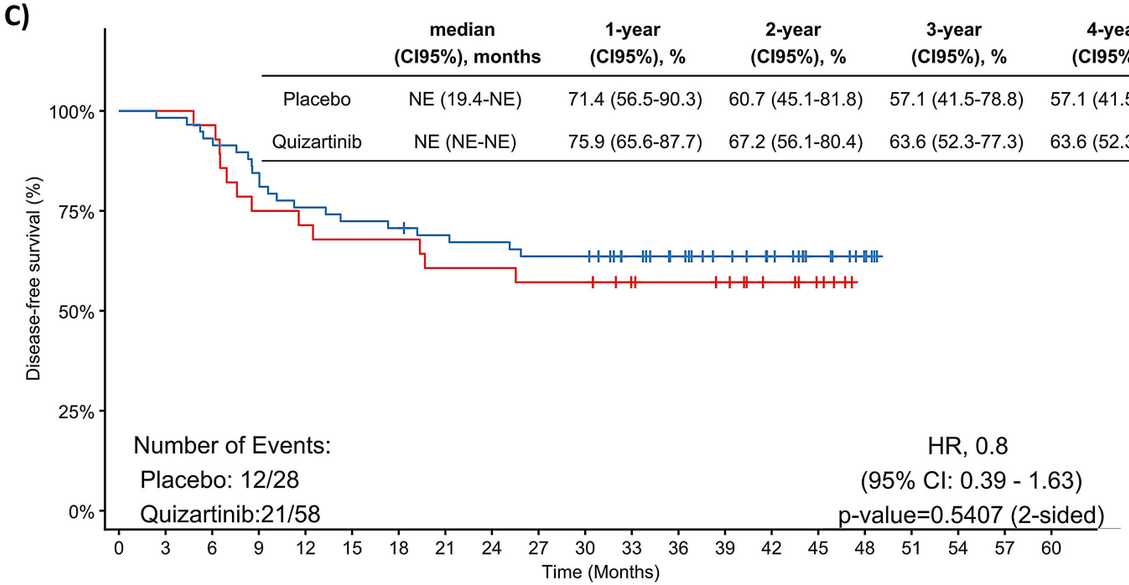


Number at risk

Placebo	43	43	40	36	31	27	27	26	26	26	25	22	17	11	7	4	3	0	0	0
Quizartinib	84	83	78	74	69	67	64	62	62	61	59	50	41	31	18	8	3	0	0	0

C)

	median (CI95%), months	1-year (CI95%), %	2-year (CI95%), %	3-year (CI95%), %	4-year (CI95%), %
Placebo	NE (19.4-NE)	71.4 (56.5-90.3)	60.7 (45.1-81.8)	57.1 (41.5-78.8)	57.1 (41.5-78.8)
Quizartinib	NE (NE-NE)	75.9 (65.6-87.7)	67.2 (56.1-80.4)	63.6 (52.3-77.3)	63.6 (52.3-77.3)

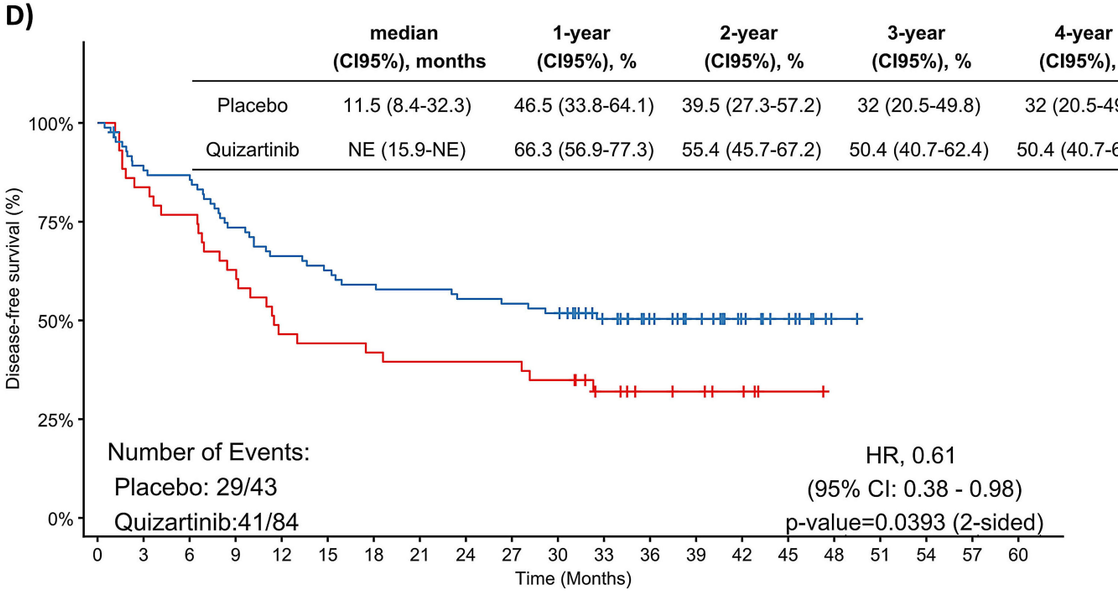


Number at risk

Placebo	28	28	27	21	20	19	19	17	17	16	16	13	12	11	7	4	0	0	0	0
Quizartinib	58	57	54	49	44	42	41	39	38	36	36	30	25	20	16	9	4	0	0	0

D)

	median (CI95%), months	1-year (CI95%), %	2-year (CI95%), %	3-year (CI95%), %	4-year (CI95%), %
Placebo	11.5 (8.4-32.3)	46.5 (33.8-64.1)	39.5 (27.3-57.2)	32 (20.5-49.8)	32 (20.5-49.8)
Quizartinib	NE (15.9-NE)	66.3 (56.9-77.3)	55.4 (45.7-67.2)	50.4 (40.7-62.4)	50.4 (40.7-62.4)

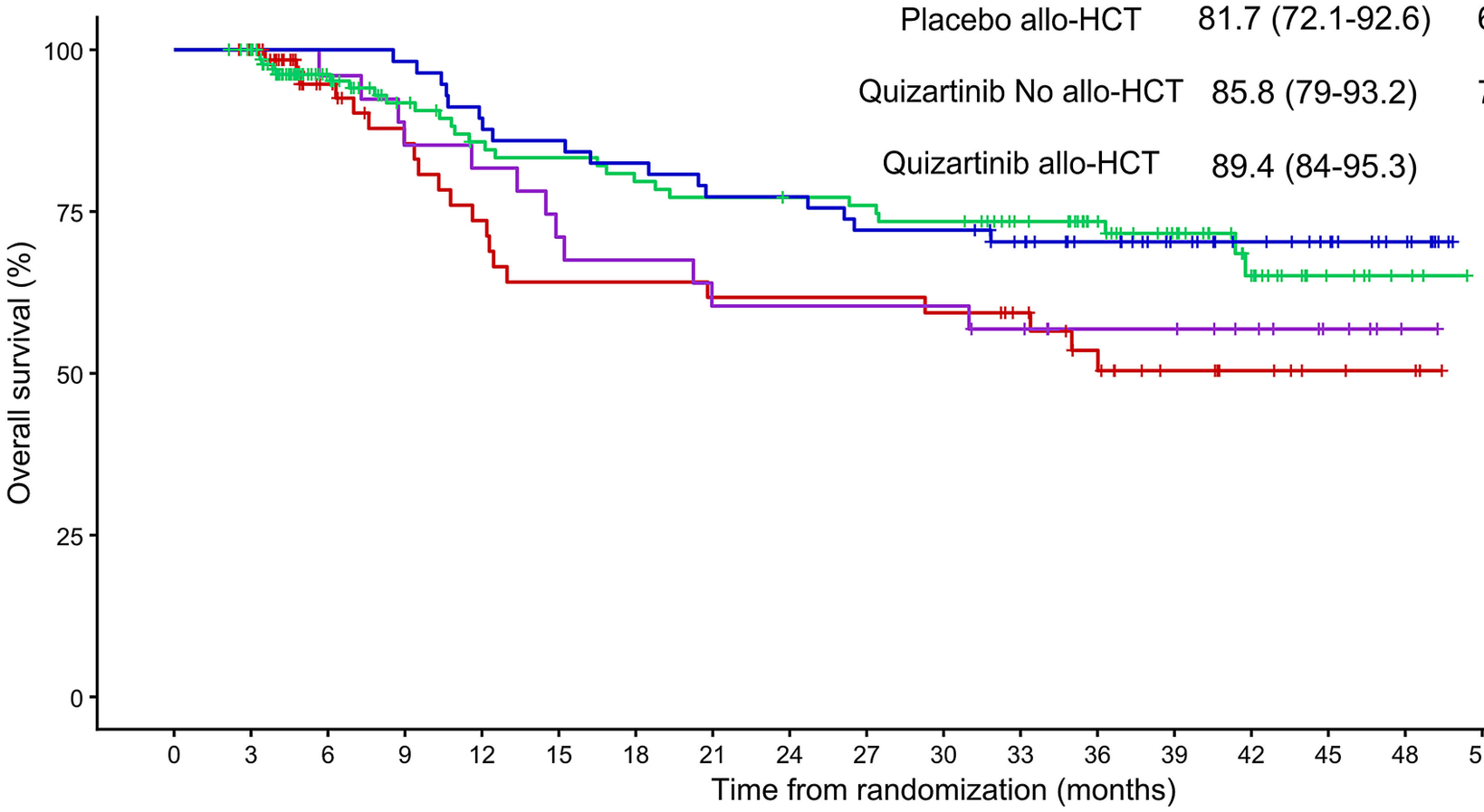


Number at risk

Placebo	43	36	33	27	20	19	18	17	17	17	15	10	7	6	4	1	0	0	0	0
Quizartinib	84	73	72	61	55	52	49	48	46	45	43	34	25	20	12	8	1	0	0	0

A)

Group	1-year	2-year	3-year	4-year
Placebo No allo-HCT	73.6 (61.7-87.8)	61.7 (48.8-78)	53.6 (40.3-71.2)	50.4 (37-68.6)
Placebo allo-HCT	81.7 (72.1-92.6)	60.4 (48.8-74.7)	56.8 (45.2-71.4)	56.8 (45.2-71.4)
Quizartinib No allo-HCT	85.8 (79-93.2)	77.2 (68.9-86.5)	73.5 (64.7-83.4)	65.1 (53.8-78.7)
Quizartinib allo-HCT	89.4 (84-95.3)	77.3 (70-85.3)	70.3 (62.4-79.2)	70.3 (62.4-79.2)

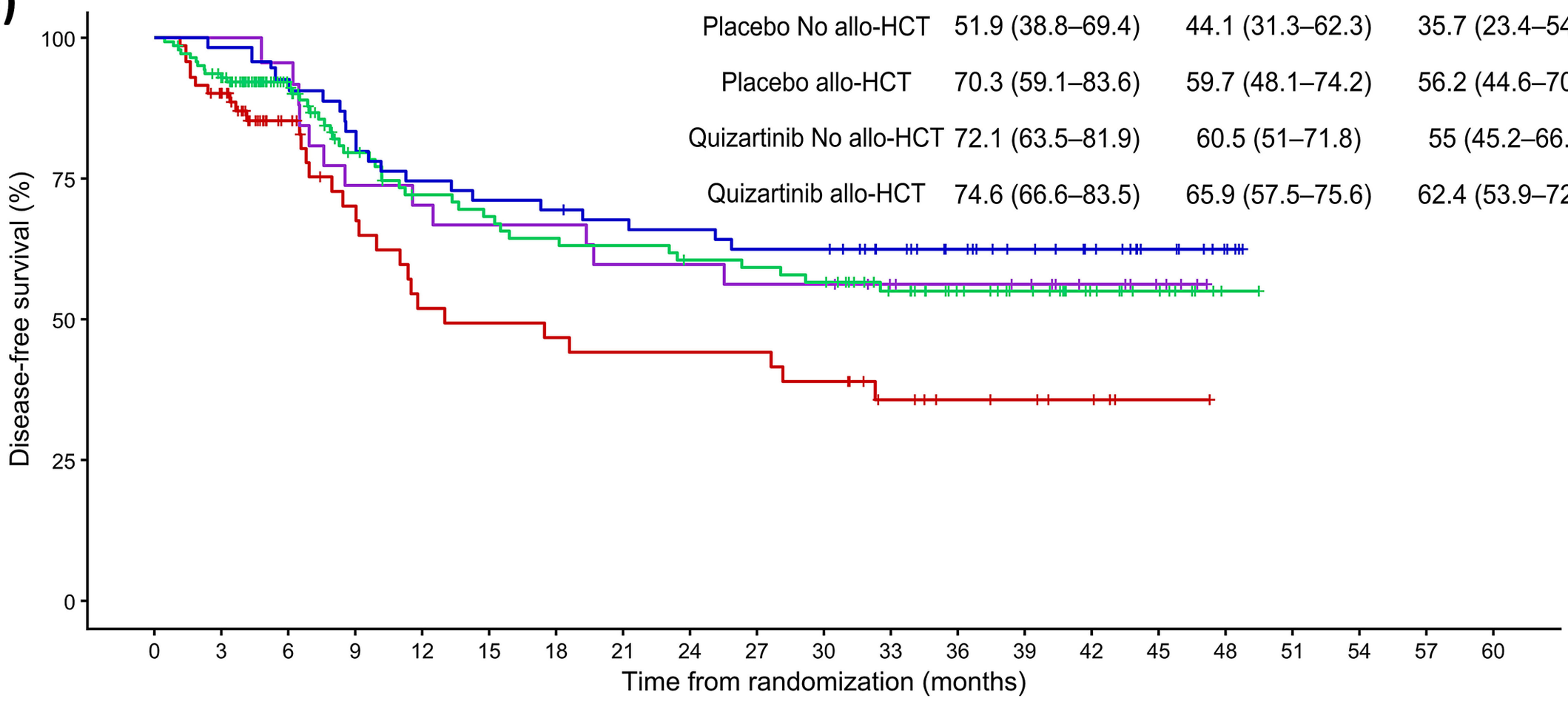


Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Placebo No allo-HCT	71	57	41	36	31	27	27	26	26	26	25	22	17	11	7	4	3	0	0	0	0
Placebo allo-HCT	0	14	26	24	23	20	19	17	17	17	17	15	12	12	9	5	1	0	0	0	0
Quizartinib No allo-HCT	142	120	87	77	70	68	65	63	62	61	59	50	41	31	18	8	3	0	0	0	0
Quizartinib allo-HCT	0	21	49	54	51	49	47	44	45	42	42	37	31	24	19	14	8	0	0	0	0

B)

Group	1-year	2-year	3-year	4-year
Placebo No allo-HCT	51.9 (38.8–69.4)	44.1 (31.3–62.3)	35.7 (23.4–54.4)	35.7 (23.4–54.4)
Placebo allo-HCT	70.3 (59.1–83.6)	59.7 (48.1–74.2)	56.2 (44.6–70.9)	56.2 (44.6–70.9)
Quizartinib No allo-HCT	72.1 (63.5–81.9)	60.5 (51–71.8)	55 (45.2–66.9)	55 (45.2–66.9)
Quizartinib allo-HCT	74.6 (66.6–83.5)	65.9 (57.5–75.6)	62.4 (53.9–72.3)	62.4 (53.9–72.3)

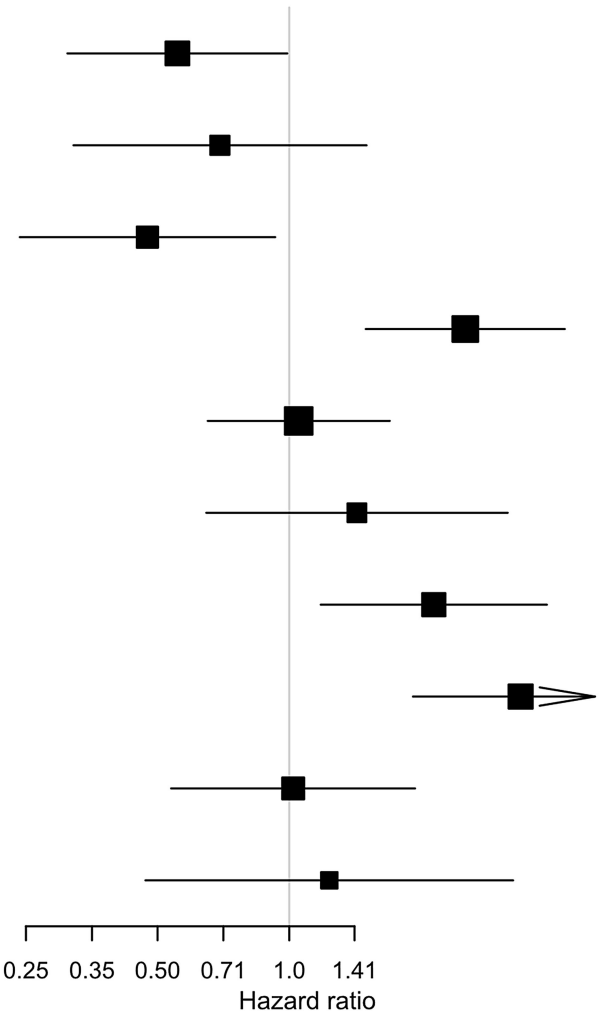


Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Placebo No allo-HCT	71	53	34	28	23	19	19	17	17	17	15	12	8	6	4	1	1	0	0	0	0
Placebo allo-HCT	0	14	26	23	21	19	19	17	17	17	16	15	12	12	9	5	1	0	0	0	0
Quizartinib No allo-HCT	142	116	81	67	58	55	50	49	48	46	44	37	28	22	15	8	3	0	0	0	0
Quizartinib allo-HCT	0	21	47	49	44	43	41	39	39	37	37	33	27	22	18	13	8	0	0	0	0

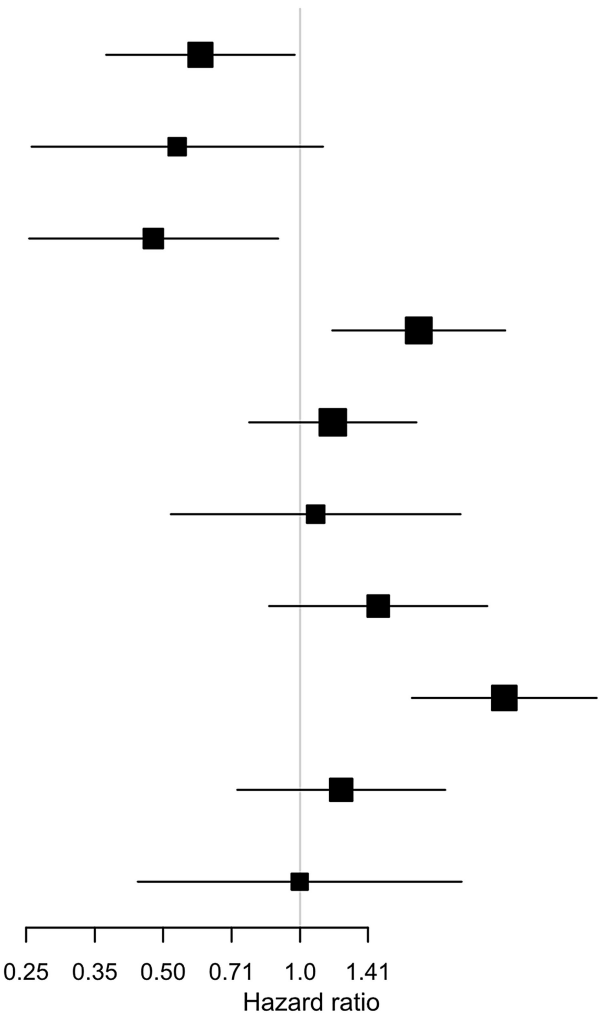
A)

Effect	HR (95% CI)	p-value
Treatment (quizartinib vs placebo)	0.555 (0.311–0.990)	0.0463
Allo-HCT in CRc1 (yes vs no)	0.694 (0.321–1.503)	0.3543
Quizartinib with allo-HCT in CRc1 vs placebo without allo-HCT in CRc1	0.474 (0.242–0.929)	0.0297
Sex (male vs female)	2.527 (1.496–4.267)	<0.001
Age (≥60 years vs <60 years)	1.051 (0.651–1.698)	0.8373
ECOG performance status (2 vs 0–1)	1.428 (0.646–3.159)	0.3790
AML type (secondary vs de novo)	2.141 (1.180–3.883)	0.0122
ELN 2022 risk (adverse vs favorable/intermediate)	3.382 (1.918–5.963)	<0.001
WBC (≥20 vs <20 ×10⁹/L)	1.021 (0.537–1.940)	0.9500
FLT3-TKD (positive vs negative)	1.235 (0.469–3.251)	0.6686



B)

Effect	HR (95% CI)	p-value
Treatment (quizartinib vs placebo)	0.604 (0.375–0.973)	0.0382
Allo-HCT in CRc1 (yes vs no)	0.537 (0.257–1.123)	0.0984
Quizartinib with allo-HCT in CRc1 vs placebo without allo-HCT in CRc1	0.476 (0.254–0.895)	0.0211
Sex (male vs female)	1.823 (1.177–2.823)	0.0072
Age (≥60 years vs <60 years)	1.180 (0.773–1.801)	0.4436
ECOG performance status (2 vs 0–1)	1.082 (0.520–2.252)	0.8331
AML type (secondary vs de novo)	1.485 (0.855–2.578)	0.1603
ELN 2022 risk (adverse vs favorable/intermediate)	2.810 (1.761–4.484)	<0.001
WBC (≥20 vs <20 ×10⁹/L)	1.231 (0.728–2.084)	0.4379
FLT3-TKD (positive vs negative)	0.998 (0.440–2.264)	0.9971



SUPPLEMENTARY MATERIAL

Contents

SUPPLEMENTARY METHODS

Study design

QUIWI was a randomized, double-blind, placebo-controlled, phase II trial conducted at Spanish PETHEMA group centers, evaluating quizartinib in combination with standard intensive induction and consolidation chemotherapy in adult patients with newly diagnosed FLT3 wild-type acute myeloid leukemia (AML). The study included an initial open-label safety run-in phase to assess tolerability and determine the recommended dose, followed by the randomized phase. After induction therapy, patients achieving remission could proceed to consolidation, allogeneic hematopoietic cell transplantation when indicated, and maintenance therapy according to the study protocol. Additional details of the study design and methodology are provided in the main study publication.[1]

Patients

Eligible patients were adults with newly diagnosed AML considered candidates for intensive induction chemotherapy. Key eligibility criteria included a confirmed diagnosis of newly diagnosed AML according to the World Health Organization 2008 and 2016 classification criteria, age ≥18 and ≤70 years at the time of screening, and absence of FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD; allelic ratio <0.03) at diagnosis. Patients with acute promyelocytic leukemia or other protocol-specified exclusion criteria were not eligible. All patients provided written informed consent prior to study enrollment, in accordance with local and institutional regulations.

The analyses presented in this report focus on patients randomized to quizartinib or placebo who achieved a first composite complete remission (CRc1) by the end of induction, defined as complete remission (CR) or CR with incomplete hematologic recovery (CRi), as assessed by the independent review committee (IRC). For analyses evaluating the impact of allogeneic hematopoietic cell transplantation (allo-HCT), only allo-HCT procedures performed in CRc1 were considered protocol-specified and included.

Randomization and masking

Patients were randomly assigned in a 2:1 ratio to receive quizartinib or placebo, in combination with standard induction and consolidation chemotherapy, according to the study protocol. Randomization was stratified by age at diagnosis (<60 vs ≥60 years) and was managed through an Interactive Web Response System (IWRS). Patients, investigators, and study personnel remained blinded to treatment assignment throughout the randomized phases of the trial. Matching placebo tablets were used to ensure masking.

Allo-HCT indications and transplant procedures

Allo-HCT was recommended for (i) NPM1-mutated or intermediate-risk cytogenetics AML with persistent MRD positivity after second consolidation, (ii) high-risk cytogenetics irrespective of MRD status (as per ELN 2017 but excluding NPM1 mutated), and (iii) non-CBF, non–NPM1-mutated AML requiring a second induction to achieve CRc1.

Allo-HCT was generally not recommended for CBF or biallelic CEBPA-mutated AML. These indications were protocol-recommended but not mandatory, and transplant decisions were ultimately made according to institutional practice and investigator criteria. Conditioning regimens, stem cell source, and graft-versus-host disease (GVHD) prophylaxis were used according to institutional practice at each participating center.

Safety analyses

Safety was evaluated in the safety analysis population, defined as all patients who received at least one dose of quizartinib or placebo. Adverse events were assessed in terms of incidence, severity (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], version 5.0), duration, seriousness, and relationship to investigational therapy (quizartinib or placebo) and/or chemotherapy. Safety analyses were descriptive in nature.

SUPPLEMENTARY TABLES AND FIGURES

Supplementary Table 1. Indications for allo-HCT according treatment arm and ELN 2017 risk. [a]ELN 2017 risk was assessed by the IRC. [b]MRD-positive refers to MRD status after second cycle of consolidation. [c]Other refers to investigator-driven decision to proceed with allo-HCT in CRc1 despite not meeting the predefined protocol criteria. Note: Percentages displayed in the table refer to the proportion within each treatment arm (quizartinib n = 180; placebo n = 93). Abbreviations: allo-HCT: allogeneic hematopoietic cell transplantation; CRc1: first composite complete remission; Second induction: need for a second induction cycle to achieve CRc1; ELN: European LeukemiaNet; IRC: independent review committee; MRD+: measurable residual disease positivity.

	Allo-HCT in CRc1, n (%) n = 86					No allo-HCT, n (%) n = 187
	ELN 2017 risk[a]	**Adverse risk**	**MRD+[b]**	**Second induction**	**Other[c]**	
Quizartinib (n = 180)	Favorable	0 (0)	3 (2)	0 (0)	7 (4)	42 (23)
	Intermediate	0 (0)	2 (1)	4 (2)	15 (8)	28 (16)
	Adverse	27 (15)	0 (0)	0 (0)	0 (0)	52 (29)
Placebo (n = 93)	Favorable	0 (0)	2 (2)	0 (0)	0 (0)	22 (24)
	Intermediate	0 (0)	0 (0)	0 (0)	7 (8)	16 (17)
	Adverse	19 (20)	0 (0)	0 (0)	0 (0)	27 (29)

Supplementary Table 2. Cox regression model for OS and DFS including treatment arm and time-dependent allo-HCT in CRc1. Abbreviations: allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; DFS: disease-free survival; HR: hazard ratio; OS: overall survival.

Time-dependent Cox model	**HR (95% CI)**	**p-value**
Overall survival		
Quizartinib vs placebo	0.59 (0.40 – 0.87)	0.0078
Allo-HCT (time-dependent)	0.91 (0.62 – 1.33)	0.618
Disease-free survival		
Quizartinib vs placebo	0.67 (0.48–0.95)	0.025
Allo-HCT (time-dependent)	0.73 (0.52–1.03)	0.076
Allo-HCT (time-dependent) – Placebo arm	0.61 (0.35–1.06)	0.078
Allo-HCT (time-dependent) – Quizartinib arm	0.82 (0.52–1.28)	0.378

Supplementary Table 3. Multivariable time-dependent Cox models for OS and DFS including post–allo-HCT quizartinib maintenance. Abbreviations: allo-HCT: allogeneic hematopoietic cell transplantation; AML: acute myeloid leukemia; CI: confidence interval; DFS: disease-free survival; ECOG: Eastern Cooperative Oncology Group; ELN: European LeukemiaNet; FLT3-TKD: FMS-like tyrosine kinase 3 tyrosine-kinase domain; HR: hazard ratio; OS: overall survival; WBC: white blood cell count.

Multivariable time-dependent Cox model for OS				
Effect	**HR**	**Lower CI**	**Upper CI**	**p-value**
Treatment (quizartinib vs placebo)	0.56	0.31	0.99	0.046
Allo-HCT in CRc1 (yes vs no)	0.94	0.42	2.10	0.87
Quizartinib with allo-HCT in CRc1 vs placebo without allo-HCT in CRc1	0.61	0.301	1.22	0.16
Post-allo-HCT maintenance (quizartinib vs placebo)	0.43	0.18	1.05	0.062
Sex (male vs female)	2.52	1.49	4.26	<0.001
Age (≥60 years vs <60 years)	1.07	0.66	1.73	0.78
ECOG performance status (2 vs 0–1)	1.33	0.60	2.95	0.48
AML type (secondary vs de novo)	2.28	1.25	4.14	0.007
ELN 2022 risk (adverse vs favorable/intermediate)	3.35	1.90	5.93	<0.001
WBC (≥20 vs <20 $\times 10^9$/L)	1.08	0.56	2.063	0.82
FLT3-TKD (positive vs negative)	1.26	0.48	3.306	0.65
Multivariable time-dependent Cox model for DFS				
Effect	**HR**	**Lower CI**	**Upper CI**	**p-value**
Treatment (quizartinib vs placebo)	0.60	0.38	0.97	0.038
Allo-HCT in CRc1 (yes vs no)	0.58	0.26	1.27	0.17
Quizartinib with allo-HCT in CRc1 vs placebo without allo-HCT in CRc1	0.51	0.26	0.99	0.047
Post-allo-HCT maintenance (quizartinib vs placebo)	0.82	0.37	1.79	0.61
Sex (male vs female)	1.83	1.18	2.84	0.007
Age (≥60 years vs <60 years)	1.18	0.77	1.81	0.44
ECOG performance status (2 vs 0–1)	1.07	0.51	2.23	0.86
AML type (secondary vs de novo)	1.50	0.86	2.62	0.15
ELN 2022 risk (adverse vs favorable/intermediate)	2.81	1.76	4.48	<0.001
WBC (≥20 vs <20 $\times 10^9$/L)	1.24	0.73	2.11	0.42
FLT3-TKD (positive vs negative)	1.0	0.44	2.26	0.99

Supplementary Table 4. Multivariable subgroup Cox analyses comparing quizartinib versus placebo according to allo-HCT status. Subgroup analyses were performed using multivariable Cox proportional hazards models including allo-HCT as a time-dependent covariate, treatment arm, and their interaction. Models were adjusted for age category, AML type, ECOG performance status, ELN 2022 risk category, baseline white blood cell count, FLT3-TKD mutation status, and sex. Abbreviations: allo-HCT: allogeneic hematopoietic cell transplantation; AML: acute myeloid leukemia; CI: confidence interval; DFS: disease-free survival; ECOG: Eastern Cooperative Oncology Group; ELN: European LeukemiaNet; HR: hazard ratio; OS: overall survival.

Time-dependent Cox model	HR (95% CI)	p-value
Overall survival		
Quizartinib + allo-HCT vs placebo + allo-HCT	0.68 (0.32–1.45)	0.32
Quizartinib without allo-HCT vs placebo without allo-HCT	0.56 (0.31–0.99)	0.046
Disease-free survival		
Quizartinib + allo-HCT vs placebo + allo-HCT	0.89 (0.43–1.85)	0.75
Quizartinib without allo-HCT vs placebo without allo-HCT	0.60 (0.38–0.97)	0.038

Supplementary Table 5. MRD status after induction according to ELN 2017 risk and treatment arm.

	Quizartinib (n = 116)[a]		Placebo (n = 64)[a]		
ELN 2017 risk	**MRD-negative n (%)**	**MRD-positive n (%)**	**MRD-negative n (%)**	**MRD-positive n (%)**	**p-value**
Favorable	14 (34.1)	27 (65.9)	6 (27.3)	16 (72.7)	0.78
Intermediate	26 (78.8)	7 (21.2)	9 (60)	6 (40)	0.29
Adverse	25 (59.5)	17 (40.5)	16 (59.3)	11 (40.7)	1.00

[a]Patients in CRc1 with centrally assessed MRD status available after induction. Abbreviations: CRc1: first composite complete remission; ELN: European LeukemiaNet; MRD: measurable residual disease.

Supplementary Table 6. Exposure to quizartinib or placebo during maintenance therapy in patients who underwent protocol-specified allo-HCT in CRc1.

	Quizartinib	Placebo
Number of patients, n	**25**	**12**
Median (range), months	10.87 (0.66–13.83)	10.36 (0.46–12.48)
<12 cycles, n (%)	13 (52)	6 (50)
Completed 12 cycles, n (%)	12 (48)	6 (50)
Dose intensity, median (range), mg/day[a]	47.14 (25–58.94)	53.62 (44.9–58.92)
Relative dose intensity, median (range), %[b]	64.29 (29.52–99.74)	86.09 (71.43–97.7)

[a]Dose intensity was defined as the cumulative dose received divided by the adjusted treatment duration, and expressed as mg/day. [b]Relative dose intensity was defined as the ratio between dose intensity and the planned daily dose, expressed as a percentage. Abbreviations: allo-HCT: allogeneic hematopoietic cell transplantation; CRc1: first composite complete remission.

Supplementary Table 7. Post–allo-HCT OS and DFS outcomes according to pre–allo-HCT MRD status and post–allo-HCT quizartinib maintenance. Abbreviations: allo-HCT: allogeneic hematopoietic cell transplantation; DFS: disease-free survival; MRD: measurable residual disease; OS: overall survival.

MRD status Pre–allo-HCT	Maintenance	n	OS events	DFS events	Median OS	Median DFS	OS (%) at 1/2/3/4-year	DFS (%) at 1/2/3/4-year
MRD-positive	**Quizartinib maintenance**	6	1	2	Not reached	Not reached	83 / 83 / 83 / 83	83 / 67 / 67 / 67
	No maintenance	6	4	4	24.8 months	2.8 months	83 / 50 / 25 / 25	33 / 33 / 33 / 33
MRD-negative	**Quizartinib maintenance**	13	2	3	Not reached	Not reached	92 / 85 / 85 / 85	77 / 77 / 77 / 77
	No maintenance	10	3	4	Not reached	Not reached	80 / 70 / 70 / 70	70 / 60 / 60 / 60

Supplementary Table 8. Overview of overall safety in patients who underwent protocol-specified allo-HCT in CRc1.

	Quizartinib n (%)	Placebo n (%)
Type of AE	**58 (100)**	**28 (100)**
Any AE[a]	47 (81)	24 (85.7)
SAE	17 (29.3)	10 (35.7)
AESI[b]	6 (10.3)	2 (7.1)
Outcome of AEs		
Resolved / resolving	45 (77.6)	21 (75)
Resolved with sequelae	2 (3.5)	1 (3.6)
Not resolved	15 (25.9)	6 (21.4)
Death	3 (5.2)	3 (10.7)
Maintenance phase post-allo-HCT[c]	**25 (100)**	**12 (100)**
Treatment-related AEs[d]	13 (52)	2 (16.7)
Dose modifications due to AE[e]		
Delay	7 (28)	2 (16.7)
Dose reduction	4 (16)	0 (0)
Discontinuation	3 (12)	3 (25)

If a patient had more than one event, the patient was counted only once. [a]Regardless of causality. [b]AESI included QTc prolongation and other ventricular arrhythmias, and combined elevations of transaminases and bilirubin (ALT/AST >3xULN with total bilirubin >2xULN), assessed by the IRC. [c]Treatment-related AEs and dose modifications due to AEs are reported only for patients who initiated maintenance therapy post-allo-HCT (n = 25 in the quizartinib arm; n = 12 in the placebo arm). [d]Based on investigator-reported causality. [e]Patients may be included in more than one category.
Abbreviations: AE: adverse event; AESI: adverse event of special interest; allo-HCT: allogeneic hematopoietic cell transplantation; CRc1: first composite complete remission; IRC: independent review committee; SAE: serious adverse event.

Supplementary Table 9. Summary of SAEs in all patients who underwent protocol-specified allo-HCT in CRc1 in either treatment arm.

	Quizartinib (n = 58)		Placebo (n = 28)	
SAE[a]	**All grades, n (%)**	**Grade ≥3, n (%)**	**All grades, n (%)**	**Grade ≥3, n (%)**
Sepsis	5 (8.6)	5 (8.6)	1 (3.6)	1 (3.6)
Lung infection	3 (5.2)	3 (5.2)	1 (3.6)	1 (3.6)
Febrile neutropenia	2 (3.5)	1 (1.7)	1 (3.6)	1 (3.6)
Graft versus host disease	2 (3.5)	2 (3.5)	3 (10.7)	3 (10.7)
Infections and infestations	2 (3.5)	2 (3.5)	2 (7.1)	2 (7.1)
Enterocolitis	2 (3.5)	1 (1.7)	0 (0)	0 (0)
Fever	1 (1.7)	0 (0)	1 (3.6)	0 (0)
Injury, poisoning and procedural complications	1 (1.7)	1 (1.7)	1 (3.6)	1 (3.6)
COVID-19 Infection	1 (1.7)	1 (1.7)	1 (3.6)	0 (0)
Febrile neutropenia	2 (3.5)	1 (1.7)	1 (3.6)	1 (3.6)
Acute kidney injury	0 (0)	0 (0)	1 (3.6)	1 (3.6)
Psychiatric disorders	0 (0)	0 (0)	1 (3.6)	0 (0)
Nausea and vomiting	0 (0)	0 (0)	1 (3.6)	1 (3.6)
Neoplasms benign and malignant	0 (0)	0 (0)	1 (3.6)	1 (3.6)
Gastrointestinal hemorrhage	1 (1.7)	1 (1.7)	0 (0)	0 (0)
Urinary tract infection	0 (0)	0 (0)	1 (3.6)	1 (3.6)
Cytomegalovirus infection reactivation	1 (1.7)	1 (1.7)	0 (0)	0 (0)
Pancytopenia	1 (1.7)	1 (1.7)	0 (0)	0 (0)
Cardiac disorders	1 (1.7)	1 (1.7)	0 (0)	0 (0)

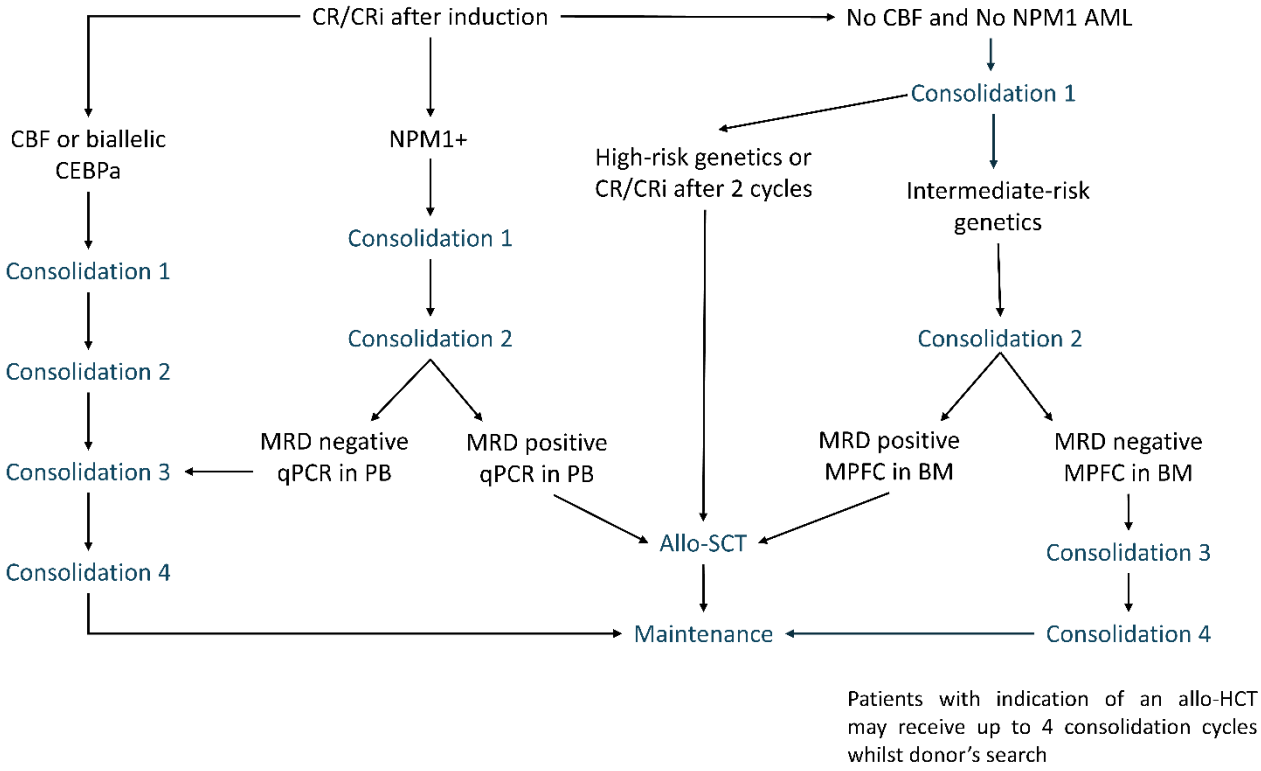
If a patient had more than one event, the patient was counted only once. [a]Regardless of causality. Abbreviations: allo-HCT: allogeneic hematopoietic cell transplantation; CRc1: first composite complete remission; SAE: serious adverse event.

Supplementary Table 10. GVHD during the allo-HCT period in patients who underwent protocol-specified allo-HCT in CRc1.

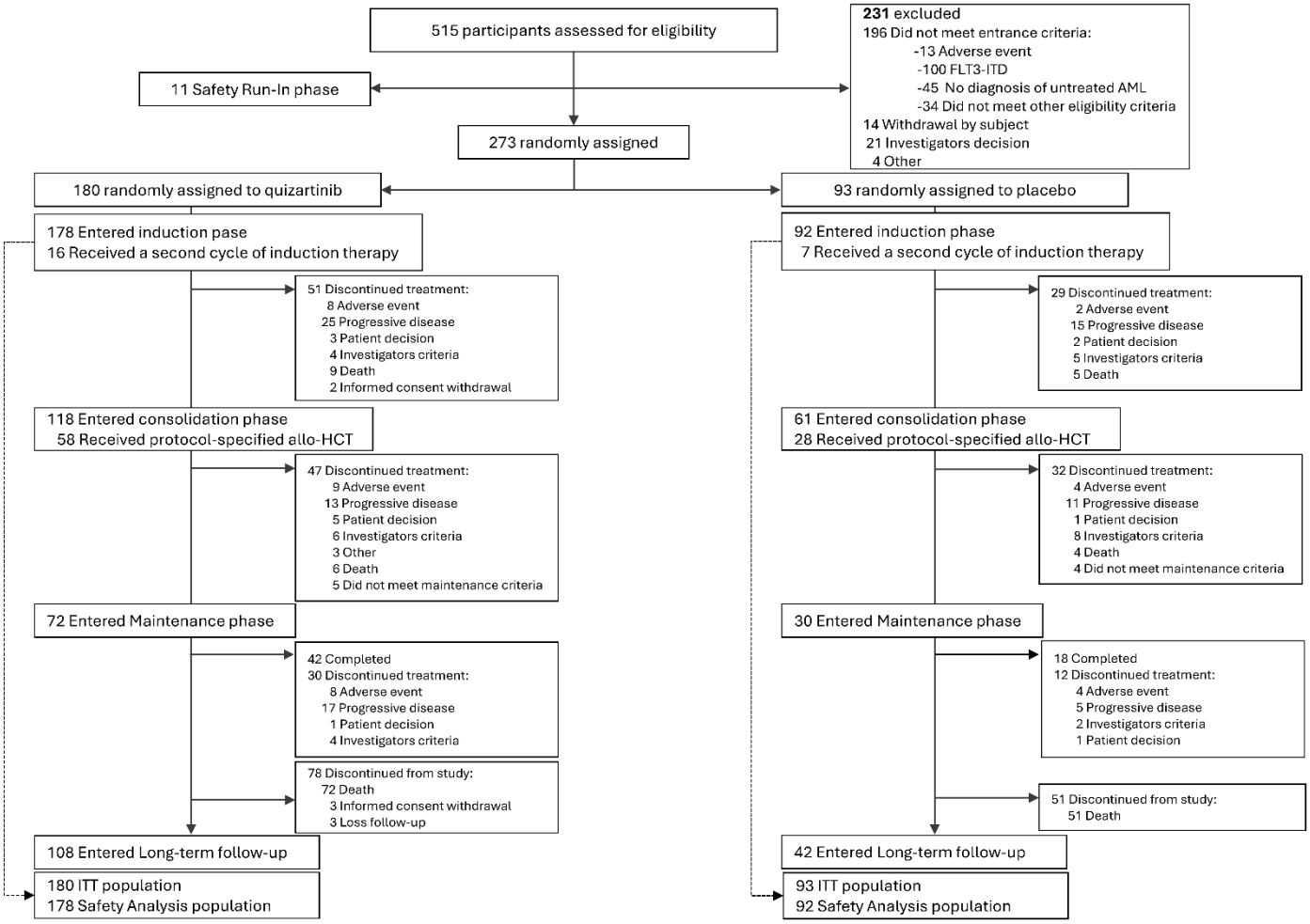
	Quizartinib (n = 58) n (%)	Placebo (n = 28) n (%)
Acute GVHD[a]	9 (15.5)	7 (25)
Time to onset, median (range), days[b]	28 (19–91)	40 (16–189)
Highest grade acute GVHD[c]		
Grade 1	3 (5.2)	1 (3.6)
Grade 2	3 (5.2)	3 (10.7)
Grade 3	3 (5.2)	1 (3.6)
Grade 4	0 (0)	1 (3.6)
Not applicable	0 (0)	1 (3.6)
Location[d]		
Skin involvement	7 (12.1)	3 (10.7)
GI involvement	3 (5.2)	3 (10.7)
Liver involvement	0 (0)	1 (3.6)
Eye involvement	0 (0)	0 (0)
Unknown	1 (1.7)	2 (7.1)
Chronic GVHD[a]	5 (8.6)	2 (7.1)
Time to onset, median (range), days[b]	258 (111–501)	186 (129–243)
Highest grade chronic GVHD[c]		
Grade 1	1 (1.7)	0 (0)
Grade 2	3 (5.2)	0 (0)
Grade 3	1 (1.7)	2 (7.1)
Grade 4	0 (0)	0 (0)
Not applicable	0 (0)	0 (0)

[a]GVHD subtype (acute vs. chronic) and organ involvement were classified based on investigator assessment. When this information was not available, acute GVHD was defined as onset within 100 days after allo-HCT, and chronic GVHD as onset occurring beyond day 100. [b]Event onset time (days) was calculated as the number of days from allo-HCT to the first documented GVHD onset (onset date – transplant date + 1). [c]GVHD severity was defined using the highest grade per patient (Grades 1-4). Grade 5 corresponds to a fatal outcome in CTCAE and was not considered a GVHD severity grade (not applicable). [d]A patient may present GVHD involvement in more than one organ, and such cases were counted in all applicable organ categories. Abbreviations: allo-HCT: allogeneic hematopoietic cell transplantation; CRc1: first composite complete remission; GI: gastrointestinal; GVHD: graft-versus-host disease.

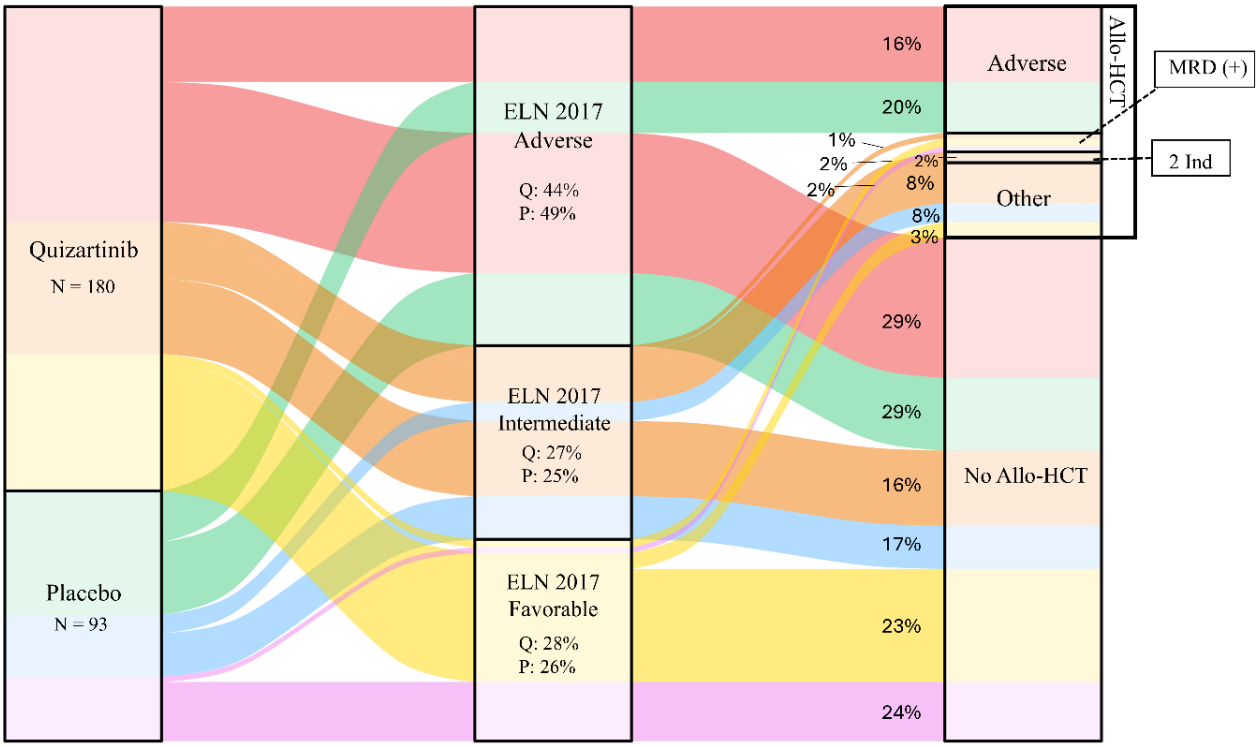
Supplementary Figure 1. Post-remission therapy flowchart and allo-SCT indications. Abbreviations: allo-HCT: allogeneic hematopoietic cell transplantation; BM: bone marrow; CBF: core-binding factor; CEBPa: CCAAT/enhancer-binding protein alpha; CR/CRi: complete remission/complete remission with incomplete hematologic recovery; MPFC: multiparameter flow cytometry; MRD: measurable residual disease; NPM1: nucleophosmin 1; PB: peripheral blood; qPCR: quantitative polymerase chain reaction.



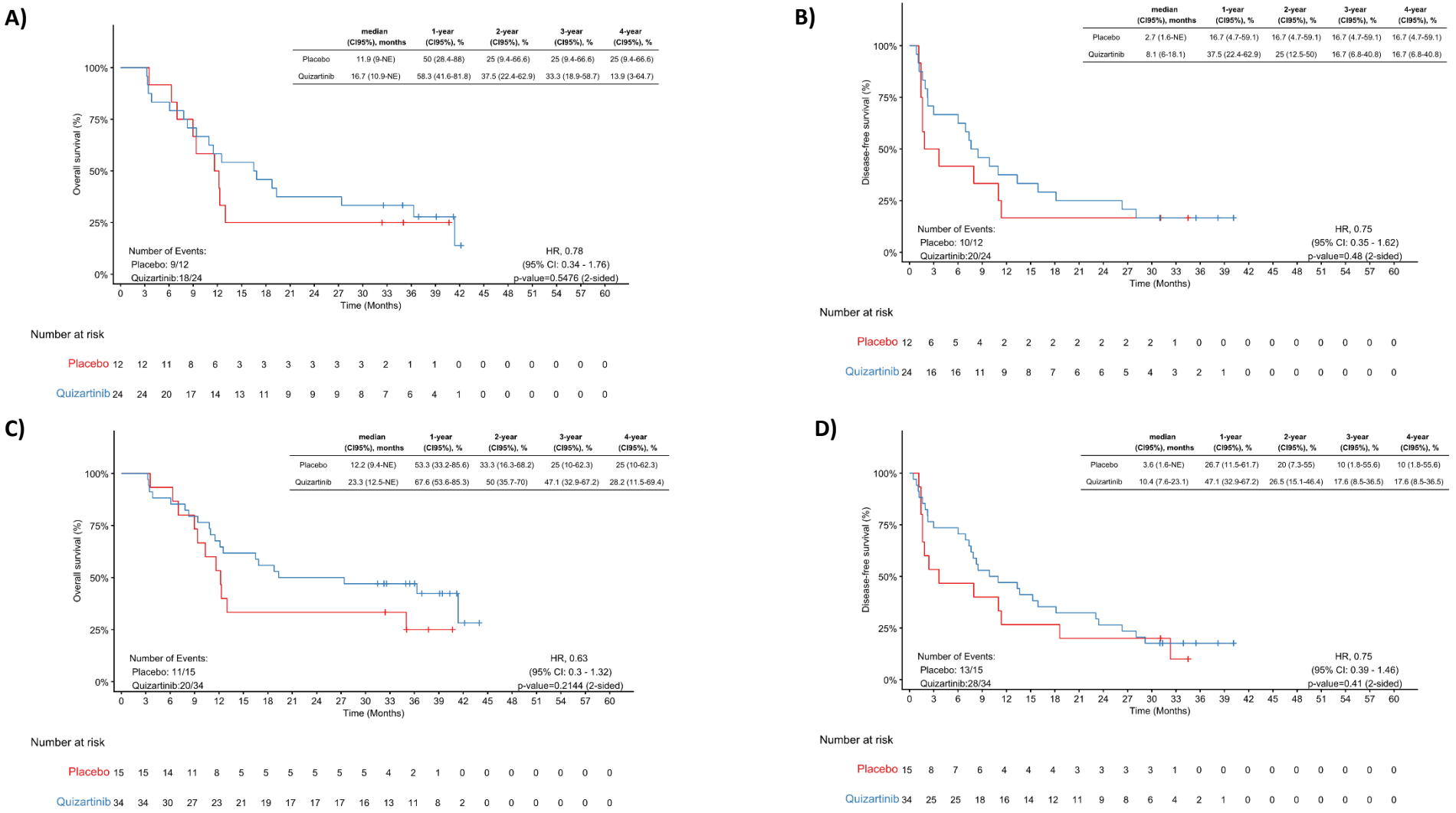
Supplementary Figure 2. CONSORT diagram of patient flow. Abbreviations: FLT3-ITD: FMS-like tyrosine kinase 3-internal tandem duplication; ITT: intent-to-treat.



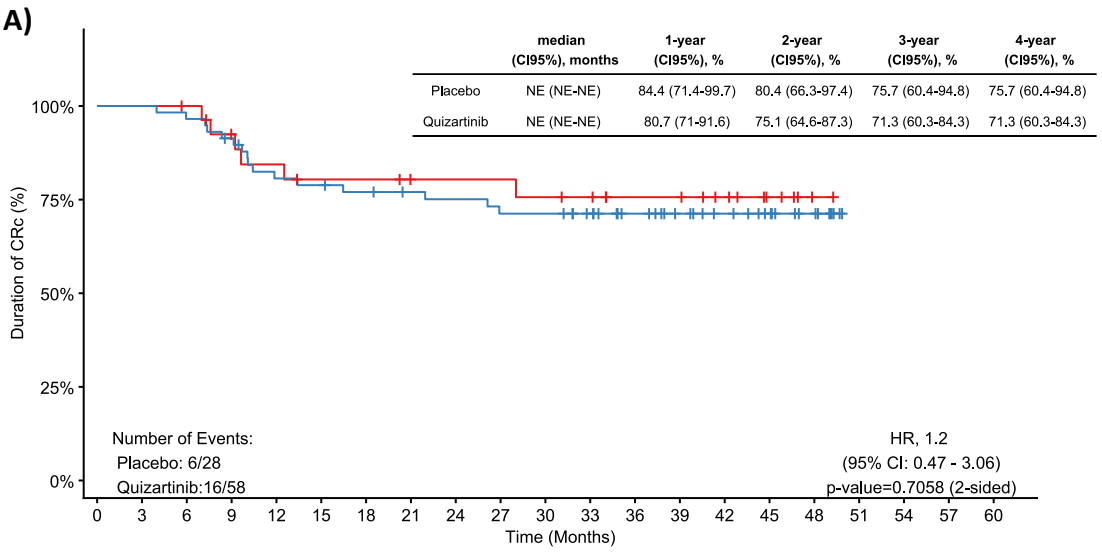
Supplementary Figure 3. Sankey diagram of allo-HCT according to protocol-specified indications. ELN 2017 risk was assessed by the IRC. MRD-positive refers to MRD status after second cycle of consolidation. "Other" refers to investigator-driven decision to proceed with allo-HCT in CR1c despite not meeting the predefined protocol criteria. Percentages displayed in the Sankey diagram refer to the proportion within each treatment arm (quizartinib n = 180; placebo n = 93). Abbreviations: 2 Ind: need for a second induction cycle to achieve CRc1; allo-HCT: allogeneic stem cell transplantation; CRc1: first composite complete remission; ELN: European LeukemiaNet; IRC: independent review committee; MRD (+): measurable residual disease positivity; P: placebo; Q: quizartinib.



Supplementary Figure 4. Kaplan-Meier plots of OS and DFS by treatment arm in patients with ELN 2017 (A and B) and ELN 2022 (C and D) adverse-risk AML who achieved CRc1 after induction per IRC and did not undergo allo-HCT. Abbreviations: allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; CRc1: first composite complete remission; DFS: disease-free survival; HR: hazard ratio; NE: not estimated; OS: overall survival.

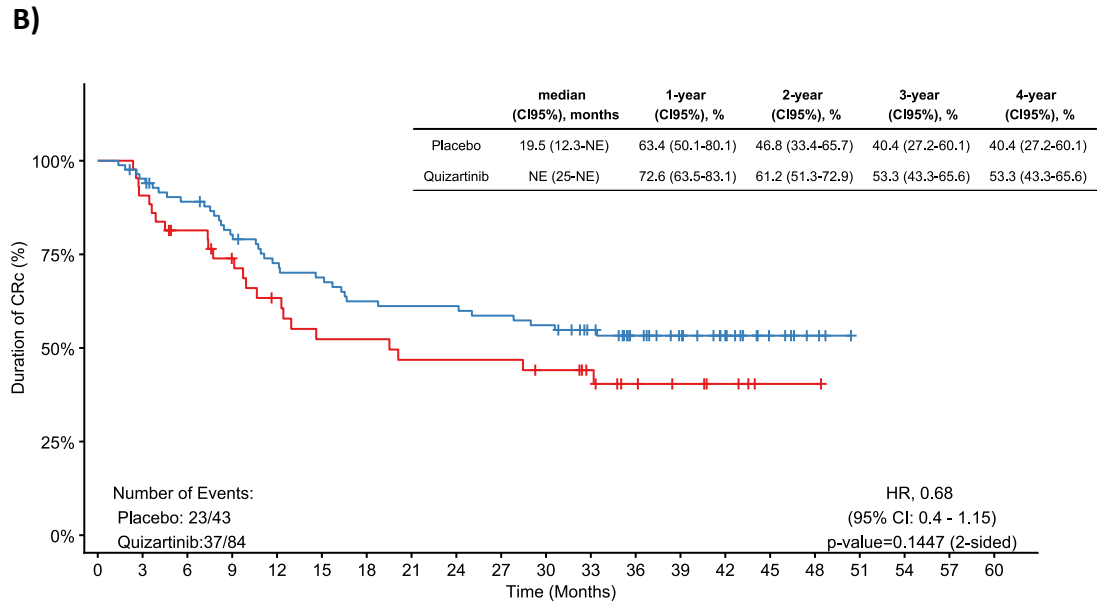


Supplementary Figure 5. Kaplan-Meier plot of DoR by treatment arm in patients who achieved CRc1 after induction per IRC by allo-HCT. A) DoR in patients who received allo-HCT in CRc1. B) DoR in patients who did not receive allo-HCT in CRc1. Abbreviations: allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; CRc1: first composite complete remission; DoR: Duration of response; HR: hazard ratio; IRC: independent review committee; NE: not estimated.



Number at risk

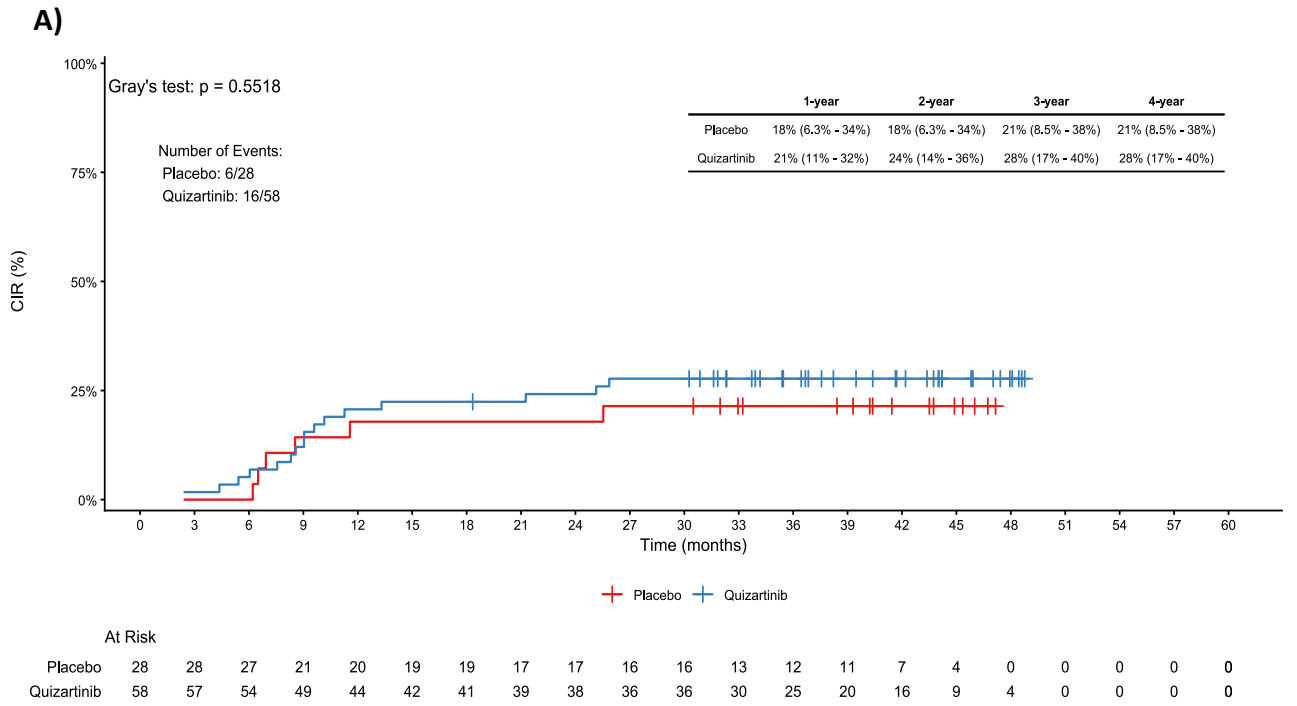
Placebo	28	28	27	23	21	19	19	17	17	17	16	15	12	12	9	5	1	0	0	0	0
Quizartinib	58	58	56	52	45	44	42	40	39	37	37	33	27	22	18	13	8	0	0	0	0

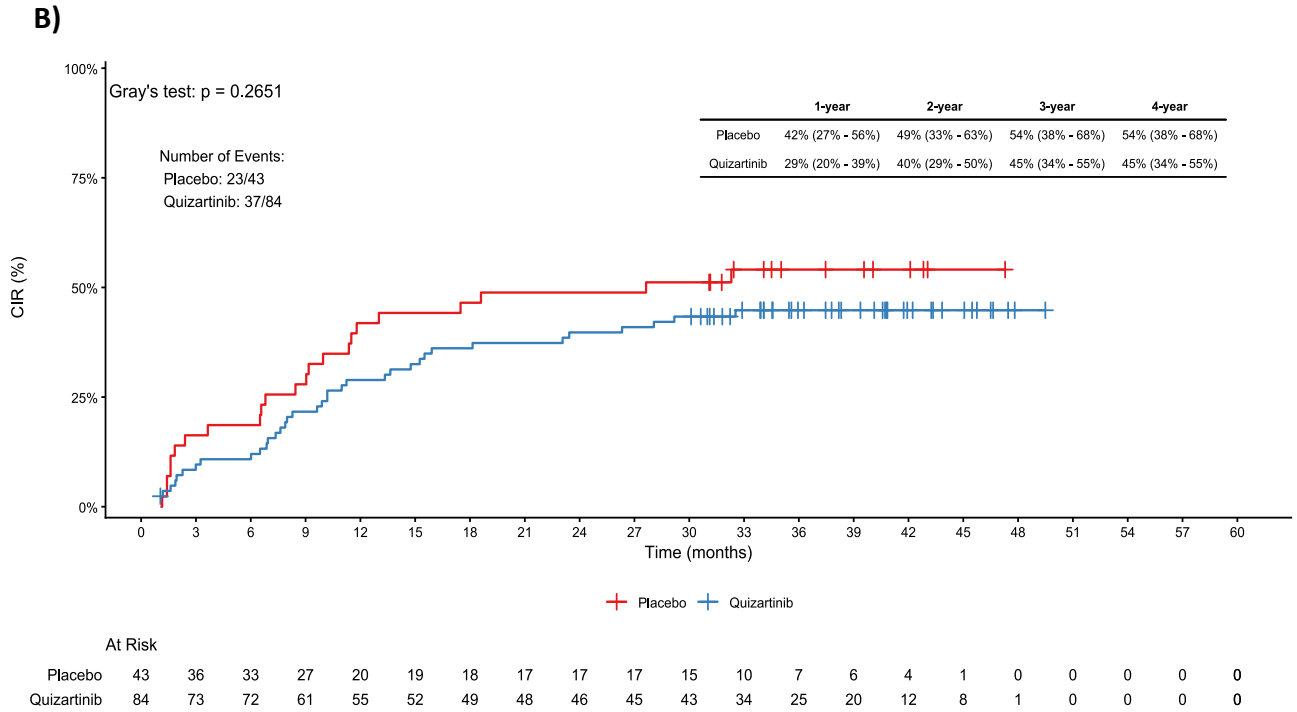


Number at risk

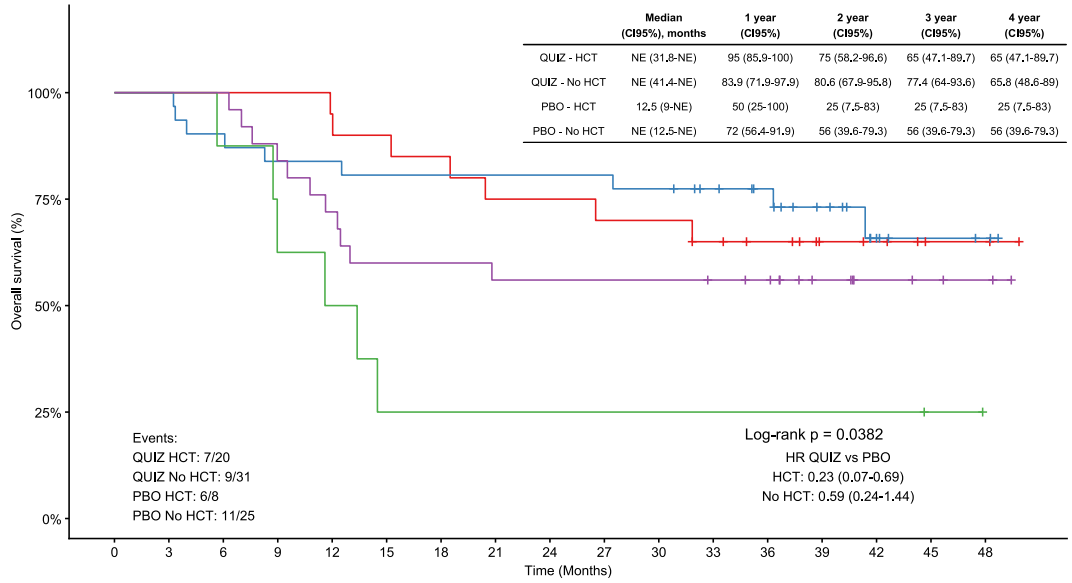
Placebo	43	39	33	28	23	19	19	17	17	17	15	12	8	6	4	1	1	0	0	0	0
Quizartinib	84	79	72	64	57	54	49	48	48	46	44	37	28	22	15	8	3	0	0	0	0

Supplementary Figure 6. CIR by treatment arm in patients who achieved CRc1 after induction per IRC by allo-HCT. A) CIR in patients who received allo-HCT in CRc1. B) CIR in patients who did not receive allo-HCT in CRc1. Abbreviations: allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; CIR: cumulative incidence of relapse CRc1: first composite complete remission; IRC: independent review committee.



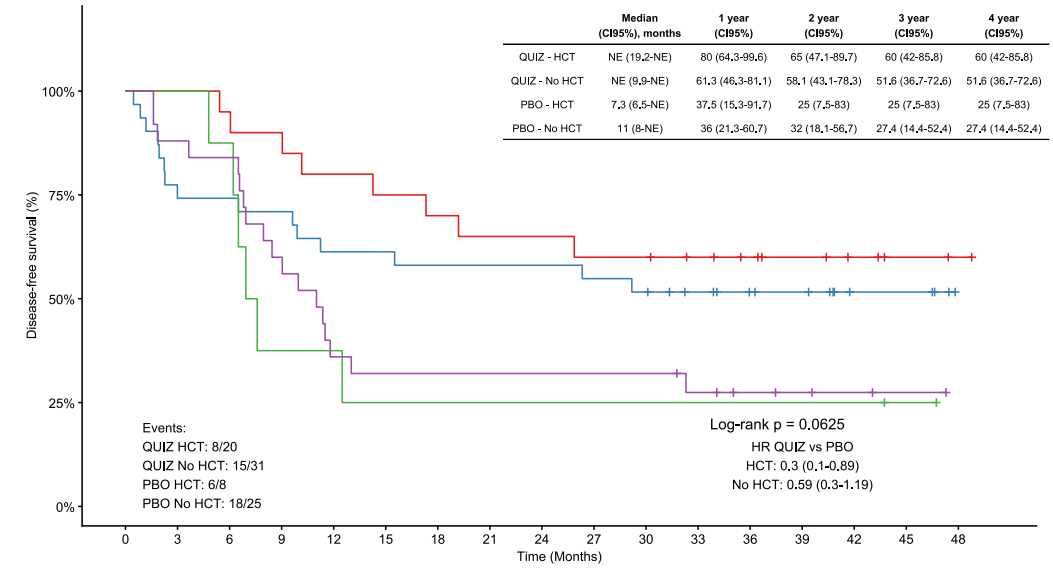


Supplementary Figure 7. Kaplan-Meier plot of OS and DFS by treatment arm among patients in CRc1 with MRD positivity after induction, stratified by allo-HCT status. Abbreviations: allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; CRc1: first composite complete remission; DFS: disease-free survival; HR: hazard ratio; IRC: independent review committee; NE: not estimated; MRD: measurable residual disease; OS: overall survival; PBO: placebo; QUIZ: quizartinib.



Number at risk

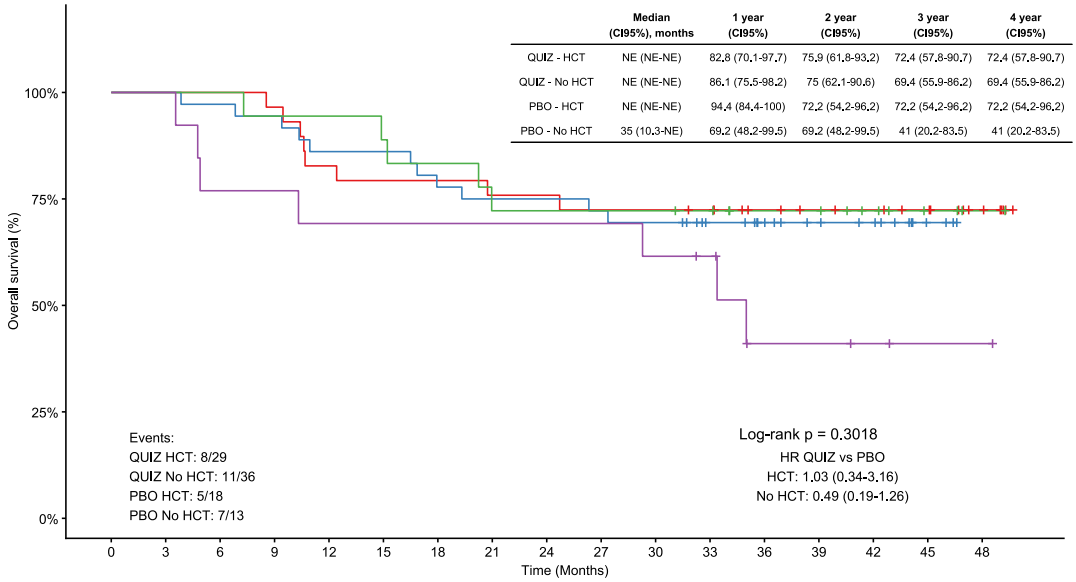
QUIZ- HCT	20	20	20	20	19	18	17	15	15	14	14	12	10	6	5	2	2
QUIZ- No HCT	31	31	28	26	26	25	25	25	25	25	24	21	18	13	6	4	2
PBO - HCT	8	8	7	5	4	2	2	2	2	2	2	2	2	2	2	1	0
PBO - No HCT	25	25	25	21	18	15	15	14	14	14	14	13	12	7	4	3	2



Number at risk

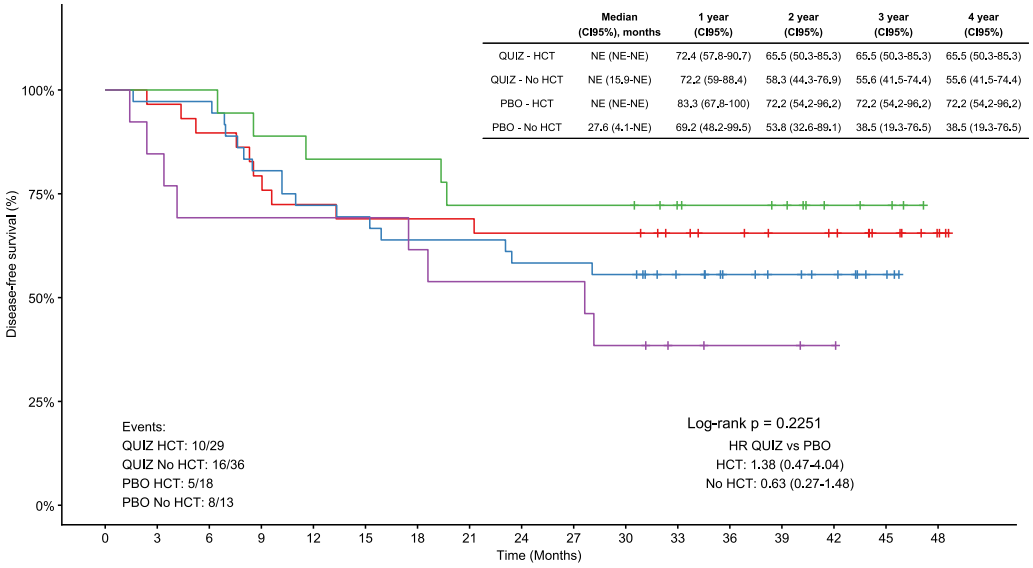
QUIZ - HCT	20	20	19	18	16	15	14	13	13	12	12	10	8	6	4	2	1
QUIZ - No HCT	31	23	23	22	19	19	18	18	18	17	16	13	10	9	4	4	0
PBO - HCT	8	8	7	3	3	2	2	2	2	2	2	2	2	2	2	1	0
PBO - No HCT	25	22	21	15	9	8	8	8	8	8	8	6	4	3	2	1	0

Supplementary Figure 8. Kaplan-Meier plot of OS and DFS by treatment arm among patients in CRc1 with MRD negativity after induction, stratified by allo-HCT status. Abbreviations: allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; CRc1: first composite complete remission; DFS: disease-free survival; HR: hazard ratio; IRC: independent review committee; NE: not estimated; MRD: measurable residual disease; OS: overall survival; PBO: placebo; QUIZ: quizartinib.



Number at risk

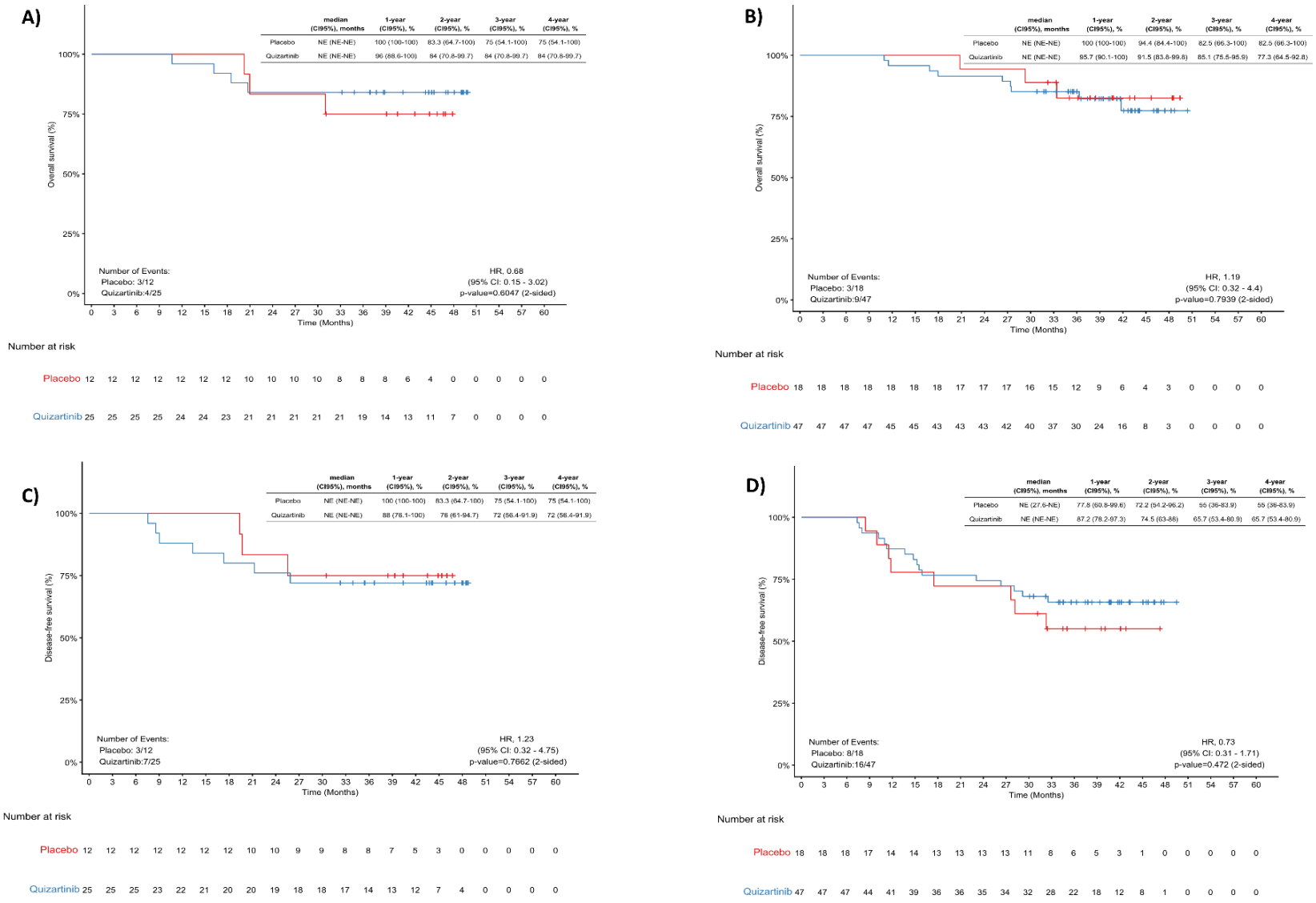
QUIZ- HCT	29	29	29	28	24	23	23	22	22	21	21	20	16	14	13	11	6
QUIZ- No HCT	36	36	35	34	31	31	28	27	27	26	25	20	16	12	10	3	0
PBO - HCT	18	18	18	17	17	16	15	13	13	13	13	12	9	9	6	3	1
PBO - No HCT	13	13	10	10	9	9	9	9	9	9	8	7	3	3	2	1	1



Number at risk

QUIZ - HCT	29	28	26	23	21	20	20	20	19	19	19	16	14	12	11	7	3
QUIZ - No HCT	36	35	35	29	26	25	23	23	21	21	20	15	11	9	7	3	0
PBO - HCT	18	18	18	16	15	15	15	13	13	13	13	10	9	8	4	3	0
PBO - No HCT	13	11	9	9	9	9	8	7	7	7	5	3	2	2	1	0	0

Supplementary Figure 9. Kaplan-Meier plot of OS and DFS by prior allo-HCT status at start of maintenance. A) OS in patients who received allo-HCT in CRc1 prior to start maintenance. B) OS in patients who did not receive allo-HCT in CRc1 prior to start maintenance. C) DFS in patients who received allo-HCT in CRc1 prior to start maintenance. D) DFS in patients who did not receive allo-HCT in CRc1 prior to start maintenance. Abbreviations: allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; CRc1: first composite complete remission; DFS: disease-free survival; HR: hazard ratio; NE: not estimated; OS: overall survival.



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