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Quizartinib in older patients (aged ≥60 years) with newly diagnosed *FLT3*-ITD-positive acute myeloid leukemia: subgroup analyses from QuANTUM-First

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Author Contributions

Daiichi Sankyo and the study steering committee (including PM, MJL, EP, JC, AEP, MAS, HD, SA, JW, RFS, and HPE) designed the study. All authors contributed to critical review and revision of the article and approved the decision to submit for publication. Data were collected by the investigators and monitored by Daiichi Sankyo. All authors had full access to all the data

in the study. LL and PM directly accessed and verified the data. Daiichi Sankyo and all authors were responsible for data analysis and interpretation.

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Data availability statement

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

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Abstract

The QuANTUM-First trial (NCT02668653) showed quizartinib significantly improved overall survival (OS) *versus* placebo when added to standard chemotherapy and as maintenance monotherapy in patients with newly diagnosed, FMS-related tyrosine kinase 3-internal tandem duplication (*FLT3*-ITD)–positive acute myeloid leukemia. These post hoc analyses further evaluated clinical outcomes in older patients (≥ 60 years). Median OS was 17.5 and 14.2 months with quizartinib (n=107) and placebo (n=109), respectively (hazard ratio [HR], 0.91; 95% confidence interval [CI]: 0.66–1.26). Complete remission rates were similar (quizartinib, 53%; placebo, 55%), but median duration of complete response was numerically longer with quizartinib (15.9 vs. 9.0 months; HR, 0.92; 95% CI: 0.59–1.42). Cumulative incidence of relapse at 24 months was lower (quizartinib, 44%; placebo, 51%) and relapse-free survival was numerically longer (median, 16.6 vs. 9.7 months; HR, 0.91; 95% CI: 0.59–1.42) with quizartinib. *NPM1* (quizartinib 62%, placebo 61%) and *DNMT3A* (51% and 50%) mutations were common and often co-mutated together (*NPM1*+*DNMT3A*; 38% and 38%), with each mutation or combination associated with numerically longer median OS with quizartinib (vs. placebo): 25.8 *versus* 15.4 (*NPM1*), 15.6 *versus* 11.5 (*DNMT3A*), and 21.8 *versus* 9.7 months (*NPM1*+*DNMT3A*), respectively. Quizartinib showed manageable tolerability for older patients, with safety generally similar to the placebo arm. Higher frequency of gastrointestinal treatment-emergent adverse events and a longer time to hematologic recovery were observed with quizartinib. ClinicalTrials.gov Identifier: NCT02668653.

Introduction

In acute myeloid leukemia (AML), older age is associated with poorer clinical outcomes and worse tolerance for intensive treatment regimens.^{1,2} Approximately 30% of patients with AML have FMS-related tyrosine kinase 3 (*FLT3*) gene alterations, the majority (75%–80%) of which are *FLT3*-internal tandem duplications (ITDs).³⁻⁵ Patients with *FLT3*-ITD alterations have higher risk of relapse and shorter duration of remission, with worse overall survival (OS) outcomes.⁶ Along with *FLT3*-ITD, *NPM1*, and *DNMT3A* mutations are the most common molecular alterations in AML; they frequently co-occur with *FLT3*-ITD and can further impact prognosis and outcomes.^{7,8} *DNMT3A*, *NPM1*, and *FLT3*-ITD are the most common three-gene mutation co-occurrence in AML, and are associated with particularly poor outcomes in patients treated with conventional intensive regimens.⁸

For patients with newly diagnosed (ND) *FLT3*-ITD–positive AML who are fit for intensive chemotherapy, clinical guidelines recommend using a FLT3 inhibitor in combination with standard cytarabine-based induction and consolidation chemotherapy, followed by single-agent FLT3-inhibitor maintenance therapy for patients achieving remission.^{9,10} Allogeneic hematopoietic cell transplantation (allo-HCT) is given to appropriate candidates. Midostaurin was the first FLT3 inhibitor approved for use with intensive chemotherapy in this frontline setting, based on results from the pivotal, phase III RATIFY trial, which was limited to patients aged <60 years and included patients with *FLT3*-ITD (77.4%) and *FLT3*-tyrosine kinase domain (TKD) (22.6%) mutations.¹¹ In the single-arm AMLSG 16-10 trial of midostaurin combined with intensive chemotherapy in a broader age range, including older patients aged >60 years, midostaurin demonstrated a superior event-free survival (EFS) and OS relative to the historical control cohort.¹² However, this cohort contained patients from other AMLSG trials conducted between 1993 and 2009, limiting meaningful interpretation *versus* the AMLSG 16-10 study

which enrolled patients between June 2012 and February 2018. In the AMLSG 16-10 trial, overall grade ≥ 3 treatment-emergent adverse events (TEAEs) rates between older and younger patients were generally similar. Grade ≥ 3 TEAEs by Medical Dictionary for Regulatory Activities defined system organ classes that were significantly more frequent in older patients (≥ 60 years) *versus* younger patients included metabolism and nutrition disorders (38% vs. 23%; $P=0.003$) and vascular disorders (21% vs. 13%; $P=0.04$). In all patients, the most common TEAEs resulting in discontinuation were thrombocytopenia, nausea/vomiting, graft-*versus*-host disease, hepatobiliary disease/increase of transaminases, and infections.

Quizartinib is a second-generation, highly potent, oral, selective, type II FLT3 inhibitor that was investigated in patients aged 18 to 75 years with ND, FLT3-ITD–positive AML in the pivotal, phase III, randomized, double-blind, placebo-controlled QuANTUM-First trial (NCT02668653).¹³ Quizartinib, when added to standard induction and consolidation chemotherapy, with or without allo-HCT, followed by up to 36 cycles of single-agent maintenance therapy, resulted in a statistically significant and clinically meaningful improvement in OS compared with placebo in the overall study population (hazard ratio [HR], 0.78; 95% confidence interval [CI]: 0.62–0.98; two-sided $P=0.032$).¹³ In a prespecified subgroup analysis, the OS benefit of quizartinib was pronounced among patients aged <60 years (HR vs. placebo, 0.68; 95% CI: 0.49–0.95) but modest among those aged ≥ 60 years (HR, 0.91; 95% CI: 0.66–1.26).¹³ Here we report exploratory post hoc subgroup analyses further evaluating clinical outcomes in older patients aged ≥ 60 with ND FLT3-ITD–positive AML receiving quizartinib or placebo in the QuANTUM-First trial, building upon prespecified OS analyses by age group.

Methods

Ethics approval and consent to participate

The QuANTUM-First trial was approved by the relevant institutional review boards and independent ethics committees and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Patients

The design, methods, and primary findings of the QuANTUM-First trial have been previously reported.¹³ Briefly, eligible patients were aged 18 to 75 years with ND *FLT3*-ITD–positive AML (defined by a *FLT3*-ITD variant allelic frequency [VAF] of $\geq 3\%$) and were considered fit for standard induction chemotherapy. Participants were randomized 1:1 to quizartinib (40 mg/day [equivalent to 35.4 mg free base]); during standard cytarabine-based “7+3” induction chemotherapy and received quizartinib or placebo for 14 days starting on Day 8. Patients achieving complete remission (CR) or CR with incomplete neutrophil or platelet recovery (CRi) after induction received up to four cycles of standard consolidation therapy (cytarabine 3 g/m² for those <60 years; 1.5 g/m² for those ≥ 60 years) plus quizartinib or placebo for 14 days starting on Day 6, with an option for allo-HCT per investigator discretion, followed by single-agent maintenance therapy with quizartinib (30 mg [equivalent to 26.5 mg free base], increasing to 60 mg [equivalent to 53 mg free base] if QT intervals were ≤ 450 ms on Day 15) or placebo once daily for up to 36 cycles.¹³

Mutation analysis

Gene mutations were analyzed in blood or marrow samples collected at screening (prior to initiation of induction chemotherapy) and assessed in a central reference laboratory using the

Archer VARIANTPlex Core Myeloid panel (IDT; Coralville, IA, USA) comprising 38 AML-related genes. A gene was considered mutated if it exhibited ≥ 1 somatic mutation with a VAF of $\geq 2.7\%$.

Study endpoints

The primary efficacy endpoint was OS, defined as the time from randomization until death from any cause. Secondary efficacy endpoints included EFS, CR rate, composite CR rate (CRc; CR + CRi), and rates of measurable residual disease (MRD) negativity. Other efficacy endpoints included durability of remission, cumulative incidence of relapse (CIR) using competing risk analysis, and relapse-free survival (RFS). For patients achieving remission (CRc), MRD was assessed at the end of induction using an amplicon-based *FLT3*-ITD polymerase chain reaction next-generation sequencing assay with a 0.01% (10^{-4}) MRD-positivity threshold. Safety evaluations included rates of TEAEs, hematologic recovery, and dose modification and treatment discontinuations due to adverse events. Detailed statistical methods are provided in the *Online Supplementary Methods*.

Results

Patients

Screening and enrollment for the QuANTUM-First study occurred between September 27, 2016, and August 14, 2019, and the data cutoff date was August 13, 2021. Of the 539 randomized patients in QuANTUM-First, 216 (40%) were aged ≥ 60 years (quizartinib, 107/268 [40%]; placebo, 109/271 [40%]) (*Online Supplementary Figure S1*). Baseline characteristics other than age were generally similar between older patients and the overall patient population. However, compared with the overall patient population, older patients were more likely to have an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 1-2 (72% vs. 65%

overall), and had a higher frequency of gene mutations in *NPM1* (61% vs. 52%, respectively) and *DNMT3A* (50% vs. 42%). Baseline characteristics of older patients were generally similar between treatment arms (Table 1). Most patients in the quizartinib and placebo groups had an ECOG PS score of 1-2 (quizartinib 72% and placebo 73%), *NPM1* mutations (quizartinib 62% and placebo 61%), and *DNMT3A* mutations (quizartinib 51% and placebo 50%). While no statistical comparisons of baseline characteristics were conducted, a numerically greater proportion of patients in the placebo group had de novo AML (93%; quizartinib, 87%), whereas greater proportions of patients in the quizartinib group had prior myelodysplastic syndromes (10%; placebo, 4%) and AML with myelodysplasia-related changes (11%; placebo, 8%).

In the quizartinib arm, 106 (99%), 62 (58%), and 39 (36%) patients entered the induction, consolidation, and maintenance phases, respectively. In the placebo arm, 108 (99%), 70 (64%), and 42 (39%) patients entered the induction, consolidation, and maintenance phases, respectively. In total, 93 patients in the quizartinib arm and 89 patients in the placebo arm discontinued treatment, most commonly due to relapse (20% and 28%, respectively), refractory disease (16% and 26%), or TEAEs (27% and 11%).

Remission rates and durations

Among patients aged ≥ 60 years, similar proportions of patients achieved CR in the quizartinib (53%, n=57) and placebo (55%, n=60) groups (*Online Supplementary Table S1*). Among the 117 patients achieving CR by the end of induction, median duration of CR was numerically longer with quizartinib (15.9 months vs. 9.0 months with placebo; HR, 0.92; 95% CI: 0.59–1.42; Figure 1A; *Online Supplementary Table S1*). Among the 117 patients achieving CR by the end of induction, CIR rates were numerically lower in the quizartinib arm at 1 year (27% vs. 44% in the placebo arm), 2 years (44% vs. 51%, respectively), and 3 years (50% vs. 55%) from

randomization (Figure 1B). A total of 41 patients aged ≥ 60 years received allo-HCT in CR, with a similar rate in the quizartinib and placebo groups (both 19%; *Online Supplementary Table S2*). The CIR was numerically lower at the 1-, 2-, and 3-year landmarks for patients receiving quizartinib regardless of allo-HCT status in CR (Figure 2).

A numerically greater proportion of patients receiving quizartinib achieved CRc (69%, n=74) compared with placebo (65%, n=71; *Online Supplementary Table S1*). The median duration of CRc was numerically longer with quizartinib *versus* placebo (15.3 vs. 9.0 months, respectively; HR, 0.94; 95% CI: 0.63–1.40; *Online Supplementary Table S1 and Figure S2A*), and fewer patients in CRc receiving quizartinib experienced AML relapse at the 1-, 2-, or 3-year landmarks (*Online Supplementary Figure S2B*). Among patients who achieved CRc and had available MRD assessment at the end of induction, MRD negativity was achieved in 39.1% of patients (25/64) in the quizartinib arm, compared with 31.8% of patients (21/66) in the placebo arm. A total of 58 patients received allo-HCT in CRc; rate of allo-HCT was numerically higher in the quizartinib group (30% [n=32], vs. 24% [n=26] with placebo; *Online Supplementary Table S2*).

OS

As reported previously, median OS was 17.5 *versus* 14.2 months (HR, 0.91; 95% CI: 0.66–1.26) for the quizartinib and placebo arms in the older patient population, respectively,¹³ with a median OS follow-up of 40.8 months (95% CI: 36.4–43.1). A numerical median OS benefit was observed for older patients receiving quizartinib who did not undergo allo-HCT in CR (median, 25.5 vs. 14.2 months with quizartinib vs. placebo, respectively; HR, 0.82; 95% CI: 0.45–1.50; Figure 3) and CR (median 25.5 vs. 14.7 months; HR, 0.79; 95% CI: 0.45–1.38; *Online Supplementary Figure S3A*). Among the small subgroup (n=41) of older patients who underwent allo-HCT, OS was similar between treatment arms in CR (median 48.6 months with quizartinib

and not reached [NR] with placebo; HR, 0.92; 95% CI: 0.36–2.32; Figure 3) and CRc (median 48.6 months vs. NR; HR, 1.24; 95% CI: 0.56–2.74; *Online Supplementary Figure S3B*). Results from a stratified Cox proportional hazards model, demonstrated numerically longer OS for quizartinib *versus* placebo (HR 0.82; 95% CI: 0.59–1.15; *Online Supplementary Figure S4*).

To understand the effect of quizartinib in the setting of baseline molecular alterations in addition to *FLT3*-ITD, OS was evaluated for patients with co-mutations of *NPM1* (n=132 [61%]; n=66 in each treatment arm), *DNMT3A* (n=108 [50%]; 54 in each arm), which were the two most common co-mutations at baseline in the overall population and older-patient subgroups, or both *NPM1* and *DNMT3A* (n=82 [38%]; n=41 in each arm). Quizartinib provided a numerically longer median OS compared with placebo among those with *NPM1* (median 25.8 months with quizartinib vs. 15.4 months with placebo; HR, 0.83; 95% CI: 0.53–1.31; Figure 4A) or *DNMT3A* (15.6 vs. 11.5 months, respectively; HR, 0.77; 95% CI: 0.48–1.22; Figure 4B) co-mutations. Median OS was numerically longer with quizartinib among patients with both *NPM1* and *DNMT3A* co-mutations (21.8 vs. 9.7 months; HR, 0.67; 95% CI: 0.38–1.19; Figure 4C). The survival advantage of quizartinib *versus* placebo was more pronounced in the subgroup of patients with *NPM1*+*DNMT3A* co-mutations who did not proceed to allo-HCT in CR (median not estimable vs. 8.5 months; HR, 0.57; 95% CI: 0.22–1.51; *Online Supplementary Figure S5*).

TET2, an epigenetic regulatory gene, was the third most common baseline co-mutation (quizartinib n=28 [26%], placebo n=30 [28%]) in the QuANTUM-First older patient population and was associated with a median OS of 21.0 *versus* 14.7 months in the quizartinib and placebo arms, respectively (HR, 0.89; 95% CI: 0.45–1.77; Figure 4D). As *TET2* is part of a broader group of genes with overlapping epigenetic functions in chromatin methylation, including *DNMT3A*, *WT1*, *IDH1*, and *IDH2*,¹⁴ co-mutations in *NPM1* and at least one of these epigenetic regulator genes were assessed. The majority of older patients in QuANTUM-First (n=123 [57%]; quizartinib: 60 [56%], placebo: 63 [58%]) had this mutation profile, which, as

observed with *NPM1+DNMT3A*, was also associated with numerically longer OS with quizartinib (median 26.6 vs. 14.8 months; HR 0.71, 95% CI: 0.44–1.13; Figure 4E).

EFS and RFS

The primary EFS analysis (induction treatment failure [ITF] defined as no CR by Day 42 from the start of the last induction cycle) showed similar EFS between patients receiving quizartinib or placebo (median 0.1 vs. 1.0 months; HR, 1.02; 95% CI: 0.77–1.37), with refractory disease/ITF comprising the majority of events in both treatment arms (Table 2). The sensitivity analysis of EFS (no CR by up to Day 56 from the start of the last induction cycle) also showed a similar EFS between quizartinib and placebo arms (3.2 vs. 2.9 months; HR, 0.97; 95% CI: 0.72–1.29; Table 2).

Median RFS was numerically longer with quizartinib compared with placebo among patients who achieved CR (16.6 vs. 9.7 months; HR, 0.91; 95% CI: 0.59–1.42; Figure 5) or CRc (16.5 vs. 9.7 months; HR, 0.94; 95% CI: 0.63–1.40) during induction. This nominal RFS benefit persisted irrespective of whether patients received allo-HCT (median RFS, 35.3 months with quizartinib vs. NR with placebo; HR, 0.91; 95% CI: 0.38–2.19; *Online Supplementary Figure S6*) or did not (11.6 vs. 6.9 months; HR; 0.93; 95% CI: 0.56–1.55).

Safety

A total of 214 older patients were included in the safety analysis set (quizartinib, n=106; placebo, n=108). Overall study drug and chemotherapy exposures in induction and consolidation were similar for patients receiving quizartinib or placebo (*Online Supplementary Tables S3 and S4*). The median dose intensity of quizartinib was lower than placebo during the maintenance phase with a similar median number of cycles (*Online Supplementary Table S3*). Nearly all patients experienced a TEAE during the study (quizartinib, 99%; placebo, 98%), with

drug-related TEAEs occurring in 61% and 40% of those receiving quizartinib or placebo, respectively (Table 3). Similar proportions of patients receiving quizartinib or placebo experienced grade ≥ 3 TEAEs (93% and 91%, respectively) and drug-related TEAEs associated with fatal outcome (2% and 1%). A greater proportion of patients receiving quizartinib experienced TEAE-associated dose interruption (33% and 26%) or dose reduction (15% and 7%) (Table 3). Incidences of gastrointestinal TEAEs, neutropenia, and QT prolongation were more common in the quizartinib arm than in the placebo arm (*Online Supplementary Table S5*), with most incidences of QT prolongation ≤ 480 ms in both treatment arms. Among patients who achieved CR, median time to cell count recovery was numerically longer with quizartinib compared with placebo, at 34 *versus* 29 days to recover from grade 3 neutropenia, respectively, and 31 *versus* 29 days for grade 1 thrombocytopenia (*Online Supplementary Table S6*). In all patients aged ≥ 60 years, TEAEs leading to death at any time during the study period occurred in 16 (15%) and 14 (13%) patients receiving quizartinib and placebo, respectively (Table 3), most commonly due to infections in the quizartinib arm (n=11 [10%]), and infections (n=4 [4%]) and general physical health deterioration (n=4 [4%] in the placebo arm). In these older patients, early mortality rate (death within 30 days from the first dose of chemotherapy) was 8% (9/106) in the quizartinib arm and 6% (6/108) in the placebo arm.

Discussion

These exploratory post hoc subgroup analyses from the phase 3 QuANTUM-First trial revealed numerical trends toward improvements in the rate and duration of remission, with a higher proportion of patients achieving MRD negativity by the end of induction and numerically lower rates of relapse, with quizartinib *versus* placebo in older patients aged ≥ 60 years with ND *FLT3*-ITD–positive AML, irrespective of whether they received allo-HCT during consolidation. The safety and tolerability of quizartinib among these older patients were consistent with the overall

QuANTUM-First population, with gastrointestinal events, neutropenia, and low-grade QT prolongation being more common with quizartinib. Overall, no unexpected safety signals were identified in the older subgroup, with similar overall drug and chemotherapy exposure in induction and consolidation therapy between the quizartinib and placebo groups, and a lower dose intensity of quizartinib in maintenance therapy.¹³

As previously reported, in QuANTUM-First the OS HR for older patients receiving quizartinib *versus* placebo was 0.91 (95% CI: 0.66–1.26).¹³ In the sensitivity analysis reported here, which adjusted for geographic region, white blood count at diagnosis, and age, a trend towards favorable OS was observed in favor of quizartinib *versus* placebo. Likewise, a similar trend towards favorable OS with quizartinib was also observed among patients aged ≥ 60 years who did not receive allo-HCT in first remission, and survival outcomes were similar between arms for those who did undergo transplant.

While the primary OS analysis did not achieve statistical significance in the older-patients subgroup, an important clinical benefit of quizartinib emerged in the durability of remissions. Among patients who achieved CR, the rates of CIR were consistently numerically lower with quizartinib compared with placebo across the 1-, 2-, and 3-year landmark time points, and persisted regardless of allo-HCT status. This trend of persistent reduction in relapse, while not reaching statistical significance, suggests that quizartinib could improve leukemic control in older patients. These findings suggest that, in addition to the limited sample size, the lack of OS benefit may be related to factors other than leukemic control, such as treatment-related toxicities associated with high-intensity regimens, receipt of allo-HCT during remission, or comorbidities in this older population.

Co-mutations of *DNMT3A* and *NPM1* are associated with adverse outcomes in patients with *FLT3*-ITD AML receiving conventional intensive chemotherapy regimens.⁸ Conversely, older patients in QuANTUM-First with *FLT3*-ITD and *NPM1*+*DNMT3A* co-mutations receiving quizartinib showed a trend toward prolonged OS compared with placebo as well as those with individual *NPM1* or *DNMT3A* mutations, though none of these findings achieved statistical significance in these exploratory analyses. Although based on small patient numbers, the subgroup of older patients with baseline *NPM1*+*DNMT3A* co-mutations who did not receive allo-HCT in CR showed a numerically longer median OS with quizartinib. Older patients with co-mutations in *NPM1* and the epigenetic regulatory gene group (comprising *DNMT3A*, *TET2*, *WT1*, *IDH1*, or *IDH2*) showed a similar favorable trend in OS from quizartinib compared with placebo as those with *NPM1*+*DNMT3A* mutations. These exploratory observations may suggest a biological mechanism beyond age that drives quizartinib sensitivity in patients with this molecular profile.

While midostaurin combined with intensive chemotherapy has improved historical treatment response rates in older patients fit for intensive chemotherapy with ND *FLT3*-mutated AML, it is also associated with substantial toxicity.^{15,16} In the AMLSG 16-10 study, including patients aged >60 years, most patients required midostaurin dose reductions (84%), and dose interruptions were also frequent (40%), primarily due to toxicity (74% and 73%, respectively).¹² Therefore, there remains an unmet need for more tolerable treatment options in older patients.¹⁵ The subgroup analyses reported here represent exploratory investigations in older patients aged ≥60 years with ND *FLT3*-ITD–positive AML, and while numerical trends favored quizartinib, particularly in those not suitable for or unwilling to undergo allo-HCT in CR/CRC, statistical significance was not achieved and these findings require prospective validation. The ongoing phase III HOVON 156 AML study in adult patients with *FLT3*-mutant ND AML including older patients aged ≥60 years, evaluating gilteritinib *versus* midostaurin in combination with induction

and consolidation therapy, followed by 1 year of remission maintenance (NCT04027309), will provide more insights regarding the addition of a FLT3 inhibitor to standard chemotherapy in this setting.¹⁷

The use of quizartinib in combination with intensive cytarabine-based chemotherapy was also recently investigated in the phase II randomized, placebo-controlled QUIWI trial, which enrolled patients aged 18 to 70 years with ND, *FLT3*-ITD–negative AML (NCT04107727).¹⁸ The challenges in demonstrating a significant survival benefit in a heterogeneous older patient population are evident in a subgroup analysis from QUIWI in which patients aged ≥60 years showed a numerically longer median OS with quizartinib *versus* placebo of 41.8 *versus* 13.4 months, respectively (HR, 0.65; 95% CI: 0.39–1.1), though the QUIWI patient population differed by *FLT3* mutation status and fitness criteria.

Quizartinib was well tolerated in QUIWI, with infrequent discontinuation due to TEAEs (14.6%) and a low, comparable rate of early deaths (within 30 days of randomization) between treatment arms (quizartinib, 2.8% vs. placebo, 3.2%). In the overall patient population of the QuANTUM-First study, early mortality rates were higher in the quizartinib arm than the placebo arm (6% vs. 3%, respectively),¹³ and this trend persisted within the older patient subgroup (8% vs. 6%). Detailed analyses of early deaths in QuANTUM-First are ongoing and will be reported in a future safety-focused publication. Based on the positive results from the QUIWI trial, the global, randomized, double-blind, placebo-controlled, phase III, QuANTUM-Wild trial (NCT06578247) in patients aged 18 to 70 years with *FLT3*-ITD–negative ND AML is ongoing, and will further elucidate the potential benefit of quizartinib in this setting.

Lower-intensity regimens, notably venetoclax in combination with a hypomethylating agent, have emerged as the standard of care for patients deemed “unfit” for intensive chemotherapy

regimens, typically due to older age and poor performance status, but have not shown a survival advantage in the *FLT3*-ITD–positive population.^{19,20} As a consequence of this lack of survival advantage, trials investigating quizartinib in combination with lower intensity backbone regimens have been initiated. Early data have been reported from studies evaluating quizartinib in combination with venetoclax-based lower-intensity regimens for older, more-frail patients with comorbidities or poor performance status; populations fundamentally different from the older patients in the QuANTUM-First subgroup who were prospectively selected as suitable candidates for intensive chemotherapy. A phase I/II study (NCT03661307) of venetoclax, decitabine, and quizartinib in older patients (age ≥ 75 years, or age < 75 years with comorbidities) with ND *FLT3*-ITD AML ineligible for intensive chemotherapy, median OS was 36.5 months, with 86% of patients (36/42) achieving CRc.²¹ In the phase I/II VEN-A-QUI trial (NCT04687761), which investigated quizartinib with venetoclax plus azacitidine or venetoclax plus low-dose cytarabine in older (> 65 years) unfit patients, demonstrated a favorable CR rate and median OS in patients with *FLT3*-ITD ND AML of 91% and 29 months, respectively.²² These outcomes are broadly consistent with the efficacy observed with lower-intensity regimens in less-fit populations with significant comorbidities, but they differ substantially from the intensive chemotherapy-based outcomes observed in fit older patients in QuANTUM-First, highlighting the importance of appropriate patient selection and treatment intensity stratification. While these early triplet data support the potential utility of quizartinib in unfit populations, direct cross-trial comparisons between intensive-chemotherapy-based and lower-intensity-based quizartinib regimens should be avoided given the important differences in patient fitness, eligibility criteria, and backbone regimen intensity. The safety, tolerability, and efficacy of quizartinib in combination with lower-intensity treatment regimens *versus* intensive chemotherapy regimens will be evaluated in future trials prospectively designed and adequately powered to compare distinct treatment approaches and patient populations.

While these exploratory QuANTUM-First post hoc analyses provide important contextual information for treatment considerations in older patients, it should be noted that these subgroup analyses were not powered to show conclusive outcomes. Some analyses included a small subset of patients from the overall QuANTUM-First population, limiting statistical power and the generalizability of findings. Nonetheless, these findings may provide useful insight for point-of-care and population health decisions and should prompt further evaluation of targeted therapies in patients aged ≥ 60 years.

QuANTUM-First was the first randomized, controlled clinical trial to demonstrate the efficacy and safety of targeted therapy in a population of patients up to 75 years old with ND *FLT3*-ITD–positive AML fit to receive intensive chemotherapy. These subgroup analyses of QuANTUM-First patients aged ≥ 60 years showed a generally consistent trend of favorable clinical outcomes for quizartinib in this setting, including numerically greater proportions of patients achieving treatment response with a longer response duration, and fewer relapses over 3 years, as well as a numerically longer OS compared with placebo. These findings further elucidate the use of quizartinib in patients aged ≥ 60 years with ND *FLT3*-ITD–positive AML.

References

1. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447.
2. Appelbaum FR. Impact of allogeneic hematopoietic cell transplantation on the outcome of older patients with acute myeloid leukemia. *Best Pract Res Clin Haematol*. 2017;30(4):320-326.
3. Daver N, Schlenk RF, Russell NH, Levis MJ. Targeting FLT3 mutations in AML: review of current knowledge and evidence. *Leukemia*. 2019;33(2):299-312.
4. Levis M. FLT3 mutations in acute myeloid leukemia: what is the best approach in 2013? *Hematology Am Soc Hematol Educ Program*. 2013;2013(1):220-226.
5. Naseem S, Binota J, Varma N, Virk H, Varma S, Malhotra P. *NPM1* and *FLT3-ITD/TKD* gene mutations in acute myeloid leukemia. *Int J Hematol Oncol Stem Cell Res*. 2021;15(1):15-26.
6. Molica M, Perrone S, Rossi M. Gilteritinib: the story of a proceeding success into hard-to-treat *FLT3*-mutated AML patients. *J Clin Med*. 2023;12(11):3647.
7. Othman J, Potter N, Ivey A, et al. Molecular, clinical, and therapeutic determinants of outcome in *NPM1*-mutated AML. *Blood*. 2024;144(7):714-728.
8. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016;374(23):2209-2221.
9. Bacher U, Kern W, Schnittger S, Hiddemann W, Haferlach T, Schoch C. Population-based age-specific incidences of cytogenetic subgroups of acute myeloid leukemia. *Haematologica*. 2005;90(11):1502-1510.
10. Short NJ, Nguyen D, Ravandi F. Treatment of older adults with FLT3-mutated AML: emerging paradigms and the role of frontline FLT3 inhibitors. *Blood Cancer J*. 2023;13(1):142.

11. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med*. 2017;377(5):454-464.
12. Döhner H, Weber D, Krzykalla J, et al. Midostaurin plus intensive chemotherapy for younger and older patients with AML and FLT3 internal tandem duplications. *Blood Adv*. 2022;6(18):5345-5355.
13. Erba HP, Montesinos P, Kim HJ, et al. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2023;401(10388):1571-1583.
14. Wang Y, Xiao M, Chen X, et al. WT1 recruits TET2 to regulate its target gene expression and suppress leukemia cell proliferation. *Mol Cell*. 2015;57(4):662-673
15. Sierra J, Montesinos P, Thomas X, et al. Midostaurin plus daunorubicin or idarubicin for young and older adults with FLT3-mutated AML: a phase 3b trial. *Blood Adv*. 2023;7(21):6441-6450.
16. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. 2022;140(12):1345-1377.
17. National Library of Medicine (U.S.). A study of gilteritinib versus midostaurin in combination with induction and consolidation therapy followed by one-year maintenance in patients with newly diagnosed acute myeloid leukemia or myelodysplastic syndromes with excess blasts-2 with FLT3 mutations eligible for intensive chemotherapy (HOVON 156 AML). <https://clinicaltrials.gov/study/NCT04027309>. Accessed April 10, 2026.
18. Montesinos P, Rodríguez-Veiga R, Bergua JM, et al. Quizartinib for newly diagnosed *FLT3*-internal tandem duplication-negative AML: the randomized, double-blind, placebo-controlled, phase II QUIWI study. *J Clin Oncol*. 2026;44(1):42-53.

19. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-629.
20. Fathi A, Perl A, Fell G, et al. Results from paradigm-a phase 2 randomized multi-center study comparing azacitidine and venetoclax to conventional induction chemotherapy for newly diagnosed fit adults with acute myeloid leukemia. *Blood*. 2025;146(Supplement 1):6.
21. Yilmaz M, Muftuoglu M, DiNardo CD, et al. Quizartinib in combination with decitabine and venetoclax for newly diagnosed and relapsed/refractory FLT3-mutated AML. *J Clin Oncol*. 2026;44(16_suppl):6504.
22. Burgues JMB, Rodríguez-Veiga R, Ferri IC, et al. Final results of VEN A QUI trial: a phase I-II trial comparing venetoclax with low dose cytarabine or azacitidine combined with quizartinib in non-fit patients with acute myeloid leukemia. *Hemasphere*. 2025;9(Suppl 1):PF480.

Tables

Table 1. Baseline demographic and disease characteristics in patients aged ≥60 years.

	Quizartinib (n=107)	Placebo (n=109)
Age, years, median (range)	66 (60–75)	66 (60–75)
ECOG PS score, n (%)		
0	30 (28.0)	30 (27.5)
1	59 (55.1)	63 (57.8)
2	18 (16.8)	16 (14.7)
Type of AML, n (%)		
De novo	93 (86.9)	101 (92.7)
Secondary	14 (13.1)	8 (7.3)
AML with myelodysplasia-related changes, n (%)	12 (11.2)	9 (8.3)
Prior MDS/MPN, n (%)	11 (10.3)	4 (3.7)
Cytogenetic risk status, n (%)		
Favorable	3 (2.8)	5 (4.6)
Intermediate	82 (76.6)	79 (72.5)
Unfavorable	7 (6.5)	10 (9.2)
Unknown	15 (14.0)	15 (13.8)
Co-mutations, n (%)		
<i>NPM1</i>	66 (61.7)	66 (60.6)
<i>DNMT3A</i>	54 (50.5)	54 (49.5)
<i>NPM1</i> and <i>DNMT3A</i>	41 (38.3)	41 (37.6)
<i>FLT3</i> -ITD/total <i>FLT3</i> , n (%)		
≥3% to ≤25%	41 (38.3)	38 (34.9)
>25% to ≤50%	56 (52.3)	57 (52.3)
>50%	9 (8.4)	14 (12.8)
>25%	65 (60.7)	71 (65.1)
Unknown	1 (0.9)	0

AML: acute myeloid leukemia; ECOG PS: Eastern Cooperative Oncology Group performance status;
MDS: myelodysplastic syndromes; MPN: myeloproliferative neoplasm.

Table 2. EFS in patients aged ≥60 years.

	Quizartinib (n=107)	Placebo (n=109)
Primary analysis: ITF based on no CR by Day 42 ^a		
Events, n (%)	91 (85.0)	92 (84.4)
Refractory disease	53 (49.5)	52 (47.7)
Relapse	18 (16.8)	28 (25.7)
Death	20 (18.7)	12 (11.0)
Median (95% CI) EFS, months	0.1 (0.0–1.9)	1.0 (0.0–3.8)
Unstratified HR (95% CI)	1.023 (0.766–1.368)	
Sensitivity analysis: ITF based on no CR by Day 56 ^b		
Events, n (%)	89 (83.2)	90 (82.6)
Refractory disease	40 (37.4)	45 (41.3)
Relapse	26 (24.3)	32 (29.4)
Death	23 (21.5)	13 (11.9)
Median (95% CI) EFS, months	3.2 (0.3–6.8)	2.9 (0.0–6.0)
Unstratified HR (95% CI)	0.965 (0.719–1.294)	

EFS was defined as the time from randomization to lack of complete remission based on independent review committee assessment, relapse, or death from any cause, whichever occurred first.

^aITF definition: not achieving complete remission by Day 42 from the start of the last induction cycle. ^bITF definition: not achieving complete remission by the end of induction, up to Day 56 from the start of the last induction cycle. CI: confidence interval; CR: complete remission; EFS: event-free survival; HR: hazard ratio; ITF: induction treatment failure.

Table 3. TEAEs in the overall population and patients aged ≥60 years (safety analysis set).

	Overall (N=533)		Patients ≥60 years (n=214)	
	Quizartinib (n=265)	Placebo (n=268)	Quizartinib (n=106)	Placebo (n=108)
TEAEs, n (%)				
Any TEAE	264 (99.6)	265 (98.9)	105 (99.1)	106 (98.1)
Drug-related	160 (60.4)	97 (36.2)	65 (61.3)	43 (39.8)
Grade ≥3 TEAE	244 (92.1)	240 (89.6)	99 (93.4)	98 (90.7)
Drug-related	118 (44.5)	65 (24.3)	49 (46.2)	32 (29.6)
TESAE	143 (54.0)	123 (45.9)	59 (55.7)	59 (54.6)
Drug-related	41 (15.5)	29 (10.8)	17 (16.0)	12 (11.1)
TEAE associated with fatal outcome	30 (11.3)	26 (9.7)	16 (15.1)	14 (13.0)
Drug-related	4 (1.5)	4 (1.5)	2 (1.9)	1 (0.9)
Dose modifications, n (%)				
TEAE associated with discontinuation	54 (20.4)	23 (8.6)	28 (26.4)	12 (11.1)
Drug-related	23 (8.7)	7 (2.6)	11 (10.4)	3 (2.8)
TEAE associated with study dose interruption	90 (34.0)	54 (20.1)	35 (33.0)	28 (25.9)
Drug-related	57 (21.5)	25 (9.3)	25 (23.6)	14 (13.0)
TEAE associated with dose reduction	50 (18.9)	17 (6.3)	16 (15.1)	7 (6.5)
Drug-related	35 (13.2)	9 (3.4)	12 (11.3)	4 (3.7)
QTcF interval prolongation, n (%)				
>450 ms	91 (34.3)	48 (17.9)	36 (34.0)	27 (25.0)
>480 ms	20 (7.5)	6 (2.2)	9 (8.5)	5 (4.6)
>500 ms	6 (2.3)	2 (0.7)	5 (4.7)	2 (1.9)

QTcF QT: interval corrected using Fridericia's formula; TEAE: treatment-emergent adverse event;

TESAE: treatment-emergent serious adverse event.

Figure legends

Figure 1. Duration of CR (A) and CIR for patients who achieved CR (B) in patients aged ≥60 years.

CI: confidence interval; CIR: cumulative incidence of relapse; CR: complete remission; HR: hazard ratio.

Figure 2. CIR in patients aged ≥60 years who achieved CR^a according to allo-HCT status.

^aFor patients who did not receive allo-HCT, the analysis includes patients who did not undergo allo-HCT at all during the study and those who underwent allo-HCT outside CR. Allo-HCT outside CR was censored at the start date of the conditioning regimen for allo-HCT. Allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; CIR: cumulative incidence of relapse; CR: complete remission; HR: hazard ratio; NRM: non-relapse mortality.

Figure 3. OS of patients aged ≥60 years who achieved CR^a according to allo-HCT status.

^aFor patients who did not receive allo-HCT, the analysis includes patients who did not undergo allo-HCT at all during the study and those who underwent allo-HCT outside CR. Allo-HCT outside CR was censored at the start date of the conditioning regimen for allo-HCT. Allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; CR: complete remission; HR: hazard ratio; NR: not reached; OS: overall survival.

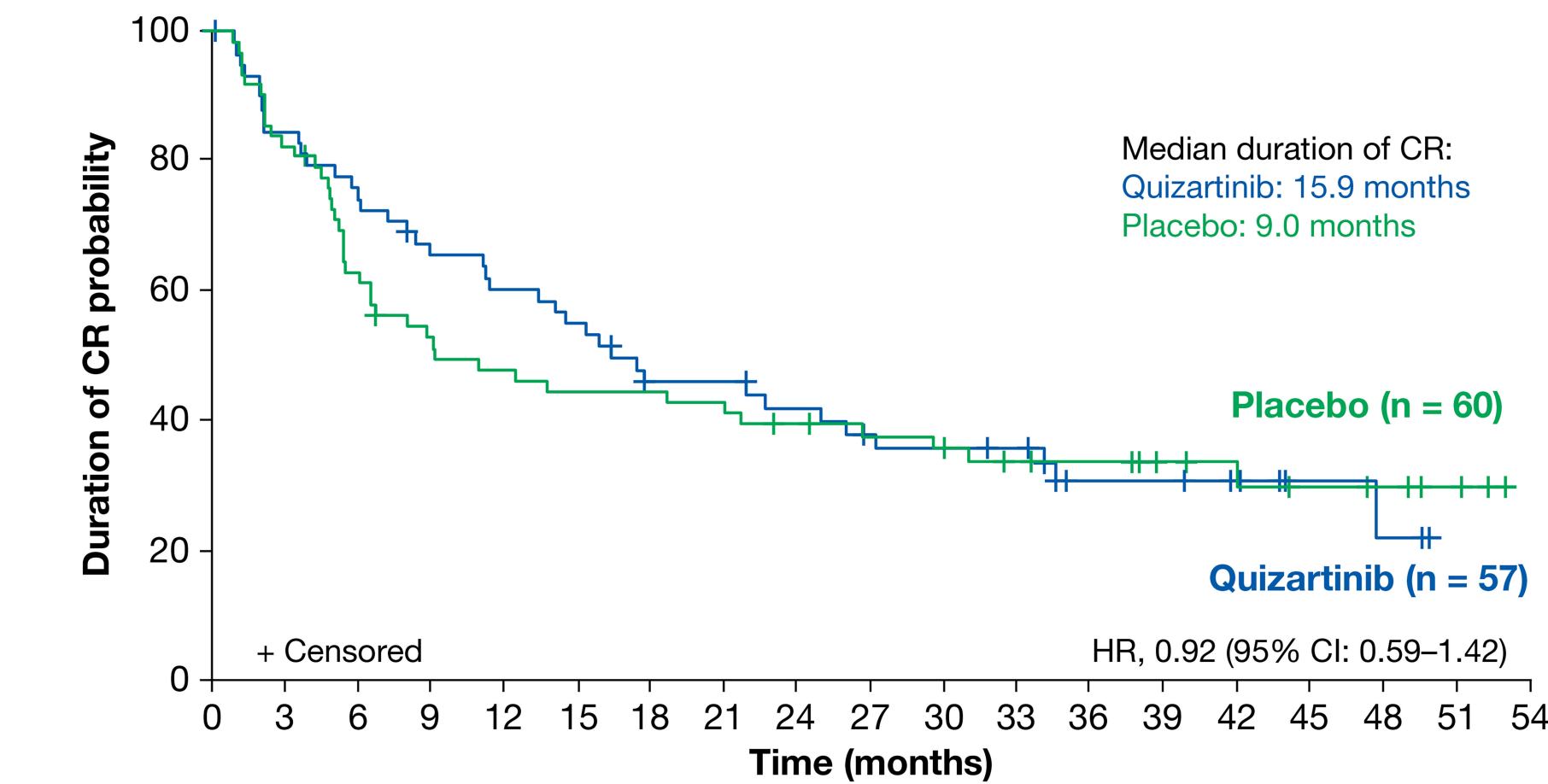
Figure 4. OS in patients aged ≥60 years with *FLT3*-ITD and baseline co-mutations in *NPM1* (A), *DNMT3A* (B), *NPM1* and *DNMT3A* (C), *TET2* (D), and *NPM1* plus ≥1 mutation in *DNMT3A*, *TET2*, *WT1*, *IDH1*, or *IDH2* (E).

CI: confidence interval; CR: complete remission; HR: hazard ratio; OS overall survival.

Figure 5. RFS for patients aged ≥60 years who achieved CR.

CI: confidence interval; CR: complete remission; HR: hazard ratio; RFS: relapse-free survival.

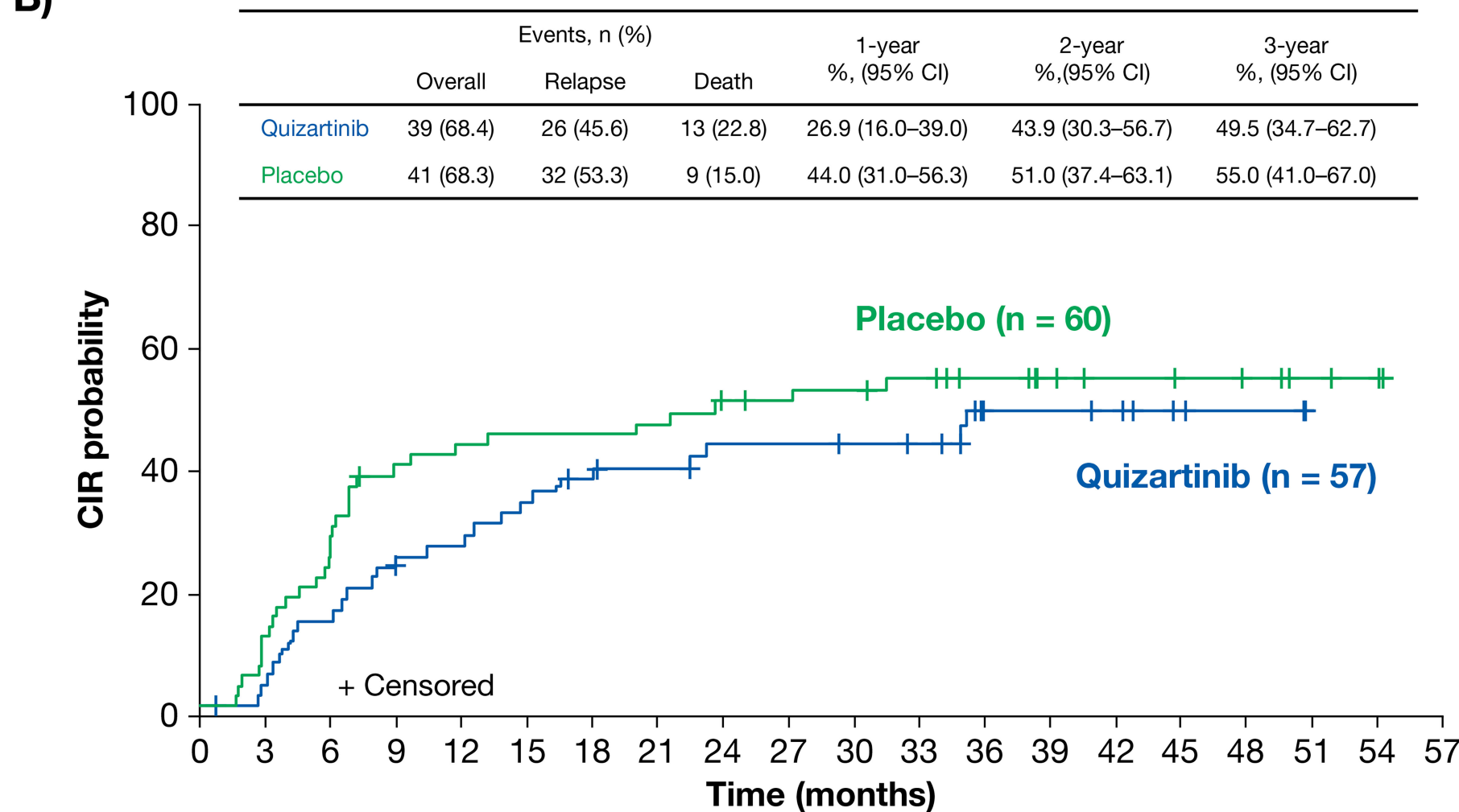
A)



No. at risk

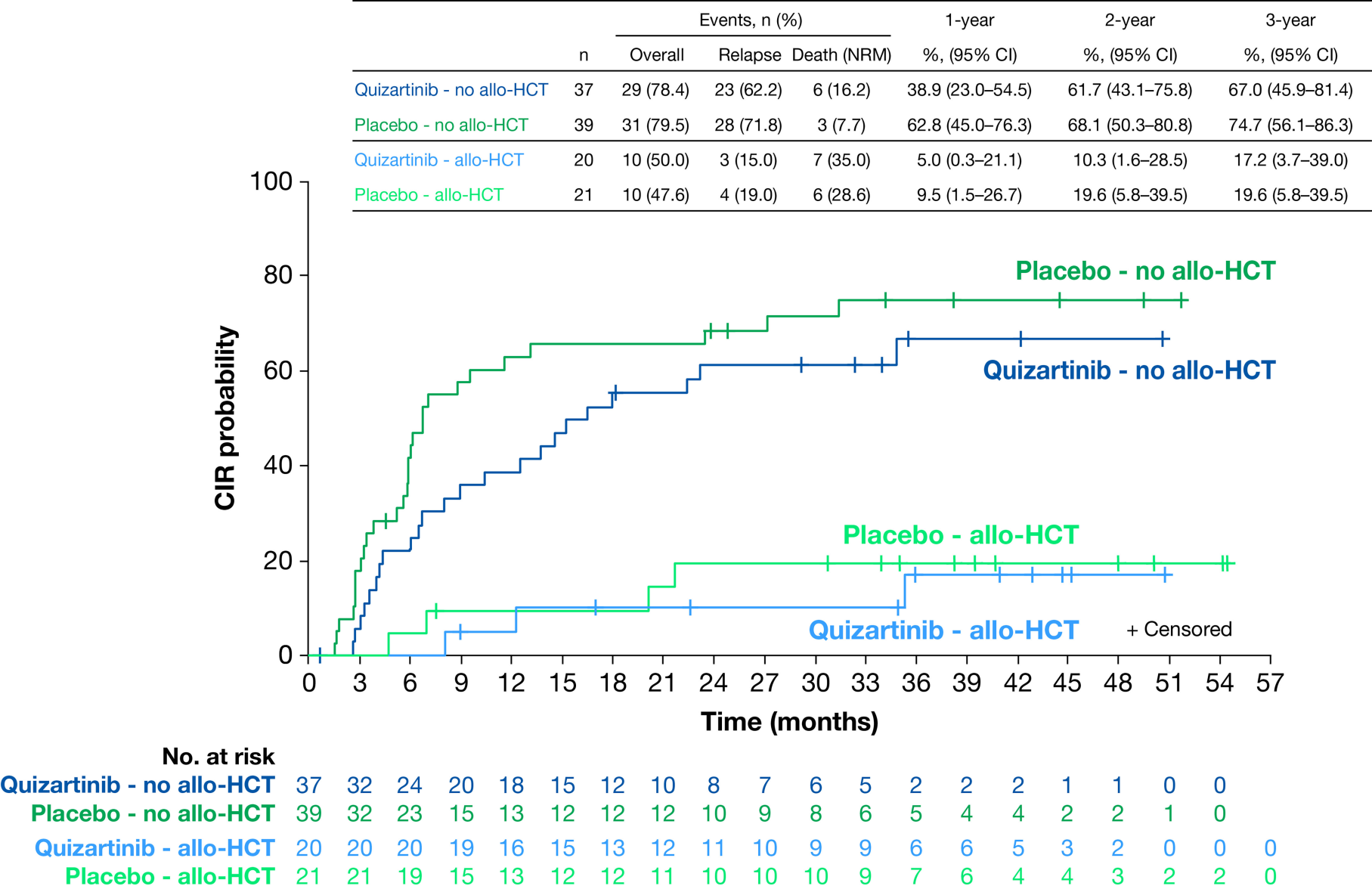
Quizartinib	57	47	42	35	32	29	22	22	19	16	15	14	8	8	6	3	2	0	0
Placebo	60	49	36	29	26	24	24	22	20	18	16	14	12	9	7	6	5	3	0

B)

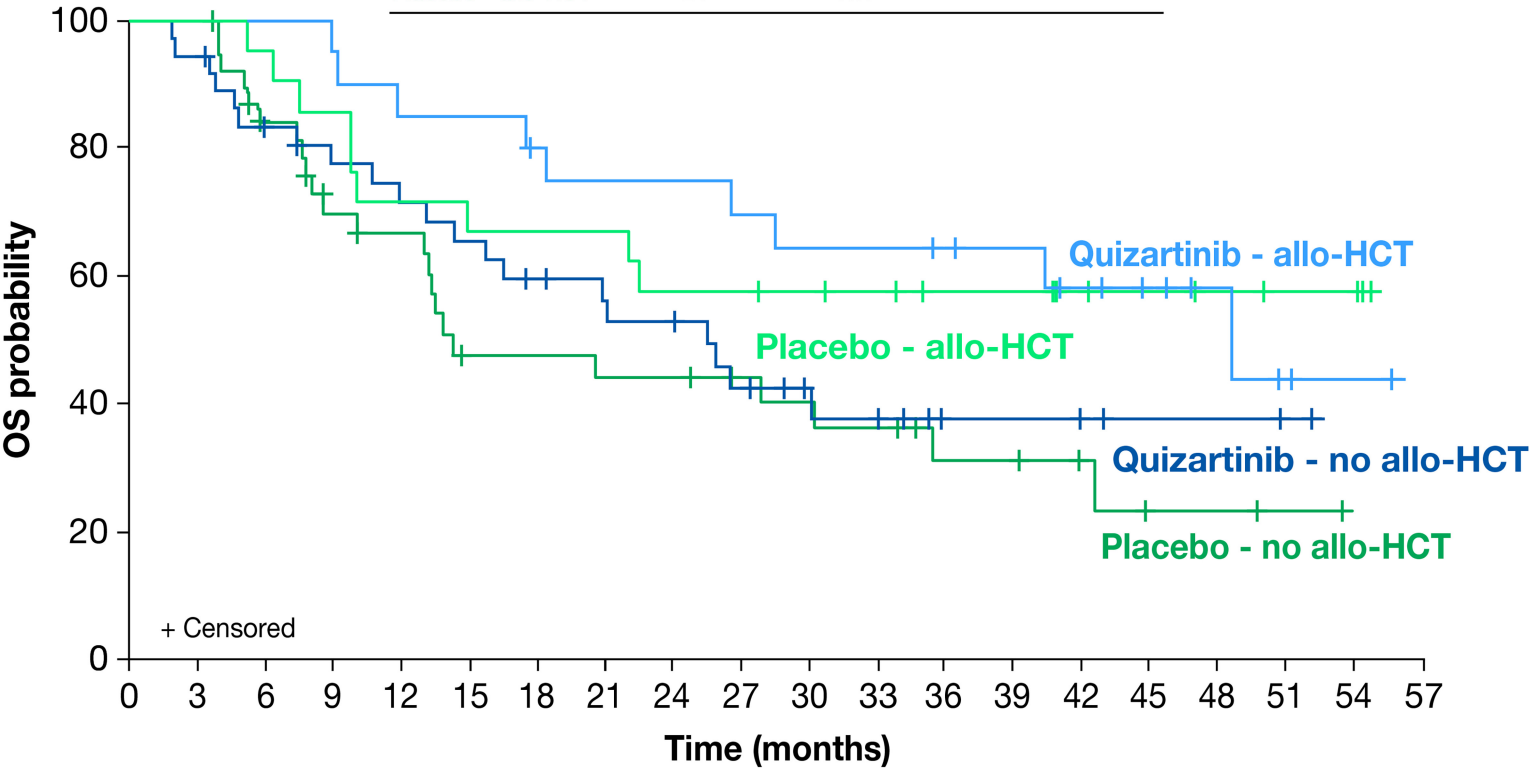


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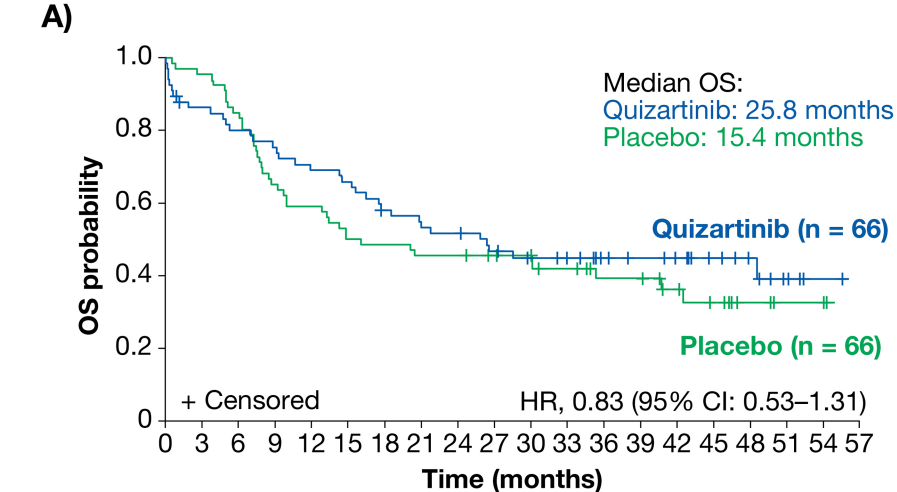
Quizartinib	57	52	44	39	34	30	25	22	19	17	15	14	8	8	7	4	3	0	0	0
Placebo	60	53	42	30	26	24	24	23	20	19	18	15	12	10	8	6	5	3	2	0



	n	Median OS, months	HR (95% CI)
Quizartinib - no allo-HCT	37	25.5	0.82 (0.45–1.50)
Placebo - no allo-HCT	39	14.2	
Quizartinib - allo-HCT	20	48.6	0.92 (0.36–2.32)
Placebo - allo-HCT	21	NR	

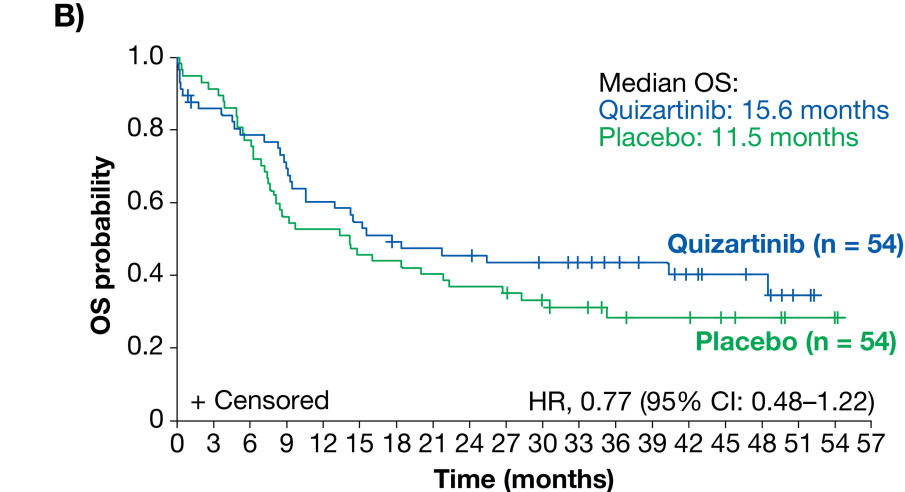


No. at risk		0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Quizartinib - no allo-HCT	37	35	29	26	24	22	19	16	15	12	8	7	4	4	3	2	2	1	0		
Placebo - no allo-HCT	39	39	30	23	21	14	14	13	13	11	10	9	6	6	4	2	2	1	0		
Quizartinib - allo-HCT	20	20	20	20	17	17	15	14	14	13	12	12	11	10	8	6	4	2	1	0	
Placebo - allo-HCT	21	21	20	18	15	14	14	14	12	12	11	10	8	8	6	5	4	3	3	0	



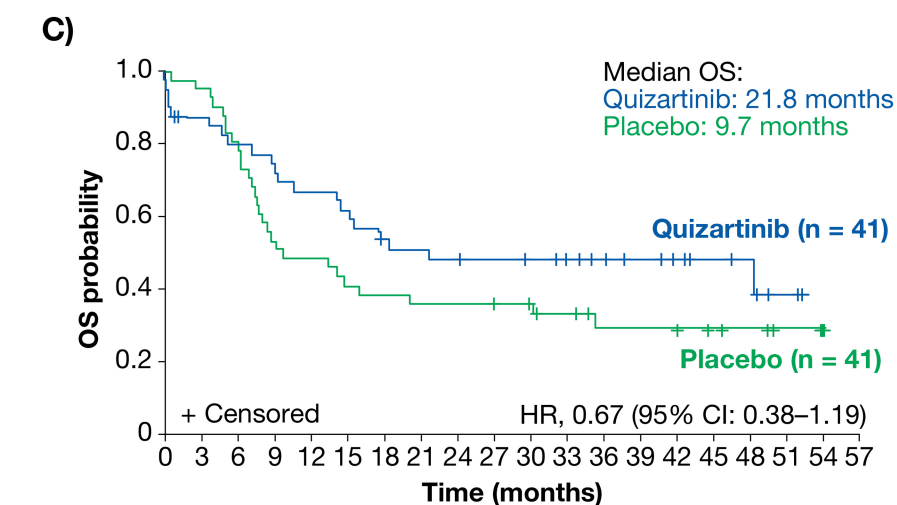
No. at risk

Time (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Quizartinib	66	55	51	48	44	42	36	33	32	28	25	23	19	17	15	11	8	4	1	0
Placebo	66	63	56	43	39	33	32	30	30	28	26	21	15	15	11	8	4	2	2	0



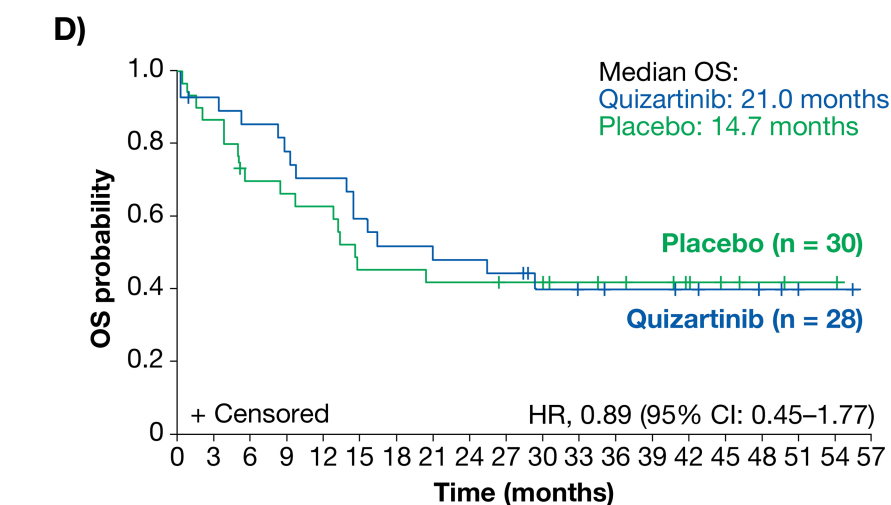
No. at risk

Time (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Quizartinib	54	44	40	36	30	27	23	22	21	19	18	16	14	12	9	7	6	2	0	0
Placebo	54	49	41	29	27	23	22	20	18	17	14	12	8	7	7	5	4	2	2	0



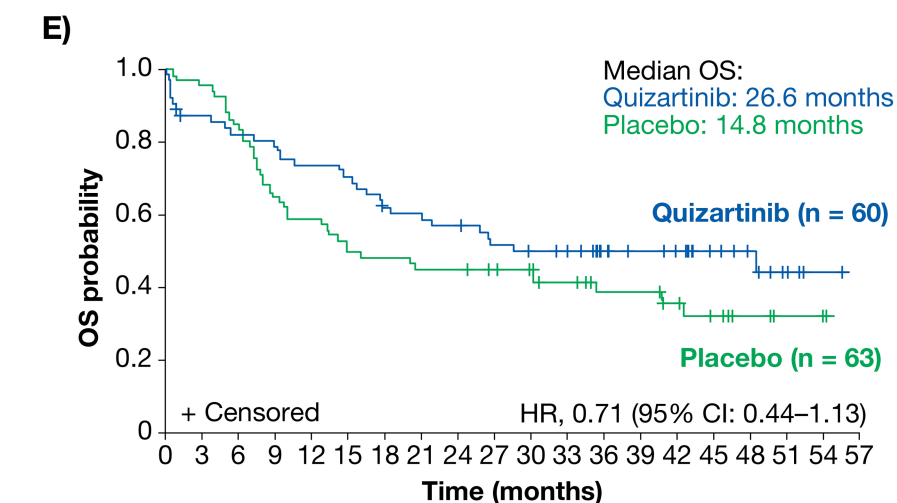
No. at risk

Time (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Quizartinib	41	34	31	29	26	24	20	19	18	17	16	14	12	10	8	6	5	2	0	0
Placebo	41	38	30	21	16	14	13	12	11	10	9	9	8	7	7	6	4	1	0	0



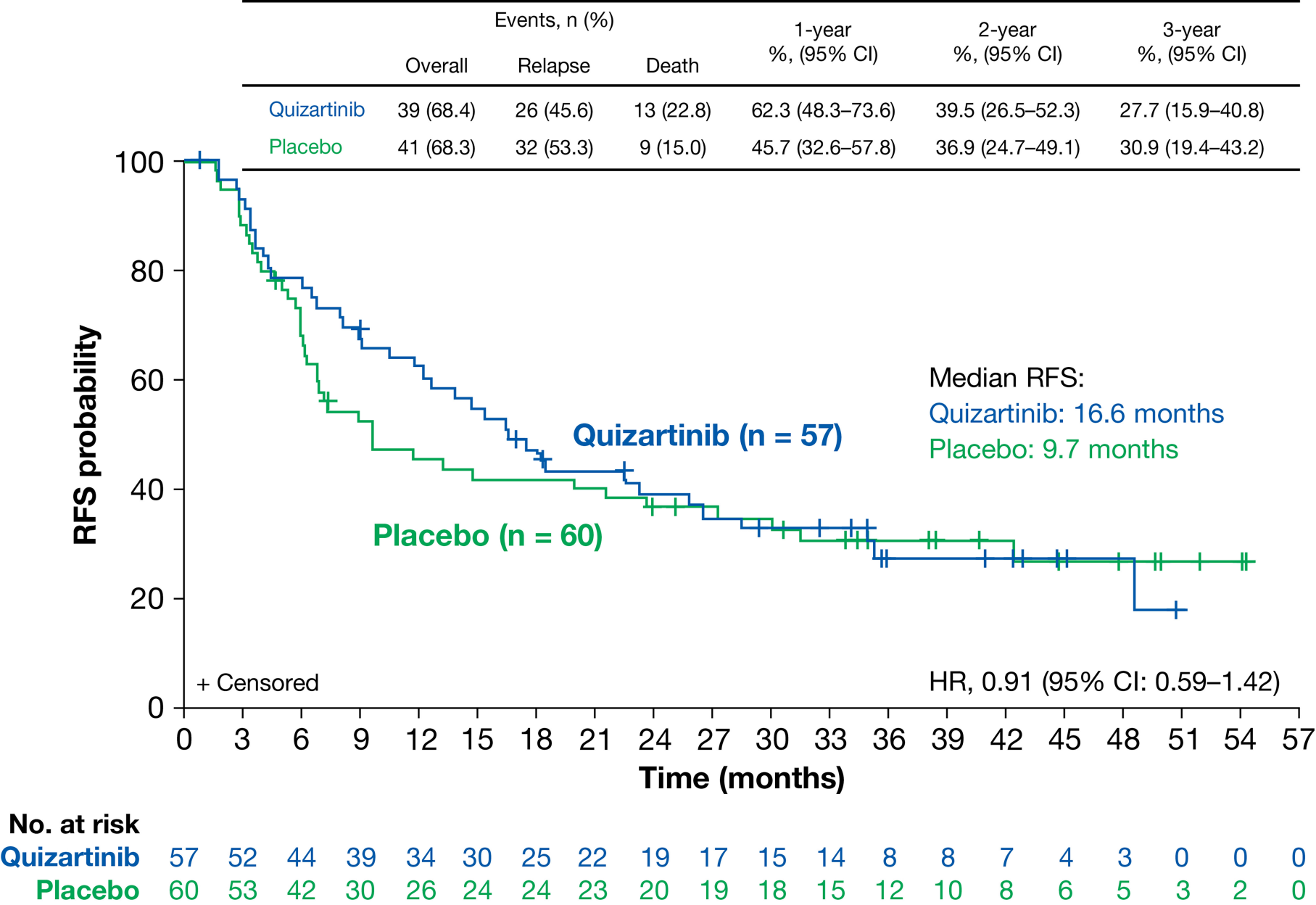
No. at risk

Time (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Quizartinib	28	25	23	21	19	16	14	13	13	12	9	8	7	7	6	4	3	2	1	0
Placebo	30	26	20	19	18	13	13	12	12	11	11	9	8	7	5	3	2	1	1	0



No. at risk

Time (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Quizartinib	60	50	47	45	42	40	34	32	31	27	25	23	19	17	15	11	8	4	1	0
Placebo	63	60	53	40	36	30	29	27	27	25	23	18	13	13	10	7	4	2	2	0



Quizartinib in older patients (aged ≥ 60 years) with newly diagnosed *FLT3*-ITD–positive acute myeloid leukemia: subgroup analyses from QuANTUM-First

Supplementary Materials

Methods

Statistical analysis

Rates of complete remission (CR) and composite complete remission (CRc; defined as CR or CR with incomplete neutrophil or platelet recovery [CRi] after induction), and duration of CR or CRc were evaluated. Duration of CR/CRc was defined as the time from the first documented CR/CRc until relapse or death from any cause, whichever occurred first. CR and CRc rates between treatment arms were summarized by treatment arm along with the two-sided 95% confidence intervals (CIs) using the Clopper-Pearson method. Durations of CR/CRc were estimated using Kaplan-Meier methods and compared between treatment groups using unstratified Cox proportional hazard models with hazard ratios (HRs) and 95% CIs. The cumulative incidence of relapse (CIR) was estimated for patients achieving CR/CRc by the end of induction using a competing risk analysis (with all-cause death as the competing risk).

Overall survival (OS) was defined as the time from randomization until death from any cause, and event free survival (EFS) was defined as the time from randomization to refractory disease (lack of CR or CRc by the end of induction), relapse, or death from any cause, whichever occurred first. An OS sensitivity analysis was also performed within the older population, including stratification factors of region (North America, Europe, or Asia/Other Regions), white blood cell count at the time of AML diagnosis (<40 or $\geq 40 \times 10^9/L$), and age ≥ 60 to <65 *versus* ≥ 65 years. The primary EFS analysis defined induction treatment failure as not achieving CR by

42 days after the start of the last induction cycle, and a sensitivity analysis of EFS defined induction treatment failure as not achieving CR by up to Day 56 from the start of the last induction cycle.

Relapse-free survival (RFS) was defined as the time from randomization until documented relapse or death from any cause, whichever occurred first. OS, EFS, and RFS were estimated using Kaplan-Meier methods and compared between treatment groups using unstratified Cox proportional hazard models, with HRs and corresponding 95% CIs. Analyses by allogeneic hematopoietic cell transplantation (allo-HCT) status in CR or CRc were also performed.

Treatment-emergent adverse events (TEAEs) were summarized descriptively in the safety analysis set, which comprised all patients receiving ≥ 1 dose of study drug, and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. TEAEs were defined as new or worsening events that occurred after the first dose of study drug until 30 days after the last dose. Hematologic recovery was defined as a neutrophil count $\geq 1,000/\text{mm}^3$ and a platelet count $\geq 100,000/\text{mm}^3$.

Tables

Table S1. Rates and durations of CR in patients aged ≥60 years.

Parameter	Overall (N = 539)		Aged ≥60 years (n = 216)	
	Quizartinib (n = 268)	Placebo (n = 271)	Quizartinib (n = 107)	Placebo (n = 109)
CR, n (%) [95% CI] ^a	147 (54.9) [48.7–60.9]	150 (55.4) [49.2–61.4]	57 (53.3) [43.4–63.0]	60 (55.0) [45.2–64.6]
CRc (CR+CRi), n (%) [95% CI] ^a	192 (71.6) [65.8–77.0]	176 (64.9) [58.9–70.6]	74 (69.2) [59.5–77.7]	71 (65.1) [55.4–74.0]
Median CR duration, ^b months (n) ^c [95% CI] ^d	38.6 (147) [21.9–NE]	12.4 (150) [8.8–22.7]	15.9 (57) [11.1–26.0]	9.0 (60) [5.4–21.6]
Median CRc duration, ^b months (n) ^c [95% CI] ^d	27.2 (192) [17.7–NE]	12.4 (176) [8.7–22.7]	15.3 (74) [11.1–22.7]	9.0 (71) [6.0–21.6]

^aBased on the Clopper-Pearson method. ^bDuration of CR defined as the time from the first documented CR until documented relapse or death from any cause, whichever occurred first. Duration of CR was not censored at the time of allo-HCT. ^cNumber of patients who achieved CR by IRC by the end of induction.

^dBased on unstratified Cox regression analysis. Allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; CR: complete remission; CRc: composite complete remission; CRi: complete remission with incomplete neutrophil or platelet recovery; IRC: independent review committee; NE: not estimable.

Table S2. Rates of allo-HCT overall and among patients aged ≥60 years in CR or CRc.

Parameter	Overall (N = 539)		Aged ≥60 years (n = 216)	
	Quizartinib (n = 268)	Placebo (n = 271)	Quizartinib (n = 107)	Placebo (n = 109)
Allo-HCT ^a in CR, n (%) [95% CI] ^b	84 (31.3) [25.8–37.3]	73 (26.9) [21.7–32.6]	20 (18.7) [11.8–27.4]	21 (19.3) [12.3–27.9]
Allo-HCT ^a in CRc, n (%) [95% CI] ^b	110 (41.0) [35.1–47.2]	86 (31.7) [26.2–37.6]	32 (29.9) [21.4–39.5]	26 (23.9) [16.2–33.0]

^aIncludes protocol-specified and non-protocol-specified allo-HCT. Some patients had both protocol-specified and non-protocol-specified allo-HCT. ^bBased on the Clopper-Pearson method. Allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; CR: complete remission; CRc: composite complete remission.

Table S3. Drug exposure in patients aged ≥60 years (safety analysis set).

	Quizartinib (n = 106)	Placebo (n = 108)
Overall		
Median (range) number of cycles	3 (1–40)	3 (1–41)
Median (range) duration of adjusted therapy, weeks ^a	6.00 (0.1–170.1)	6.00 (0.3–155.9)
Median (range) relative dose intensity, % ^b	100.00 (39.15–162.46)	100.00 (40.46–200.00)
Induction		
Number of patients	106	108
Median (range) number of cycles	1 (1–2)	1 (1–2)
Median (range) duration of adjusted therapy, weeks ^c	2.0 (0.1–4.0)	2.0 (0.3–4.0)
Median (range) relative dose intensity, % ^b	100.00 (50.00–200.00)	100.00 (50.00–200.00)
Consolidation		
Number of patients	62	70 ^d
Median (range) number of cycles	2 (1–4)	2 (1–4)
Median (range) duration of adjusted therapy, weeks ^c	4.0 (1.6–8.0)	4.0 (1.7–8.0)
Median (range) relative dose intensity, % ^b	100.00 (50.00–200.00)	100.00 (50.00–107.14)
Maintenance		
Number of patients	39	42
Median (range) number of cycles	12 (1–36)	12 (1–36)
Median (range) duration of adjusted therapy, weeks ^c	47.57 (2.0–164.1)	49.43 (2.0–146.0)
Median (range) relative dose intensity, % ^b	69.36 (36.26–170.24)	100.00 (39.35–168.29)

^aAdjusted treatment duration = sum of treatment duration minus the planned off-drug days across the three treatment phases. ^bRelative dose intensity (%) = actual dose intensity / planned dose intensity × 100. ^cAdjusted treatment duration for each phase = treatment duration minus the planned off-drug days in each phase. ^dData available for 66 patients.

Table S4. Chemotherapy exposure in patients aged ≥60 years (safety analysis set).

Parameter	Quizartinib (n = 106)	Placebo (n = 108)
Induction		
Cytarabine relative dose intensity, %, median (range) [n] ^a	100.00 (83.33–100.00) [106]	100.00 (57.14–100.00) [108]
Daunorubicin relative dose intensity, %, median (range) [n] ^a	100.00 (62.50–100.00) [47]	100.00 (52.94–100.00) [37]
Idarubicin relative dose intensity, %, median (range) [n] ^a	100.00 (86.67–100.00) [59]	100.00 (51.40–100.00) [70]
Consolidation		
Cytarabine relative dose intensity, %, median (range) [n] ^a	100.00 (62.75–100.12) [62]	100.00 (66.75–100.00) [66]

^aRelative dose intensity (%) = actual cumulative dose of chemotherapy / planned cumulative dose of chemotherapy. Planned cumulative dose of chemotherapy for each phase = sum of protocol planned doses over all treatment cycles within that treatment phase.

Table S5. Most common TEAEs among patients aged ≥60 years (safety analysis set).

	Quizartinib (n = 106)	Placebo (n = 108)
Any TEAE, n (%)	105 (99.1)	106 (98.1)
Diarrhea	48 (45.3)	39 (36.1)
Pyrexia	47 (44.3)	46 (42.6)
Febrile neutropenia	45 (42.5)	42 (38.9)
Nausea	40 (37.7)	29 (26.9)
Hypokalemia	38 (35.8)	39 (36.1)
Vomiting	27 (25.5)	20 (18.5)
Constipation	26 (24.5)	31 (28.7)
Decreased appetite	26 (24.5)	15 (13.9)
Headache	25 (23.6)	22 (20.4)
Stomatitis	23 (21.7)	28 (25.9)
Rash	22 (20.8)	29 (26.9)
Abdominal pain	22 (20.8)	16 (14.8)
Neutropenia	21 (19.8)	10 (9.3)
Electrocardiogram QT prolonged	21 (19.8)	6 (5.6)
Epistaxis	18 (17.0)	11 (10.2)
Pneumonia	17 (16.0)	16 (14.8)
Any grade 3/4 TEAE, n (%)	83 (78.3)	84 (77.8)
Febrile neutropenia	44 (41.5)	42 (38.9)
Hypokalemia	23 (21.7)	20 (18.5)
Neutropenia	20 (18.9)	8 (7.4)
Pneumonia	13 (12.3)	13 (12.0)
Select TEAEs, any grade, n (%)		
Platelet count decreased	6 (5.7)	2 (1.9)
Leukopenia	4 (3.8)	3 (2.8)
Pancytopenia	3 (2.8)	0
Myelosuppression	3 (2.8)	0
White blood cell count decreased	1 (0.9)	4 (3.7)
Lymphocyte count decreased	1 (0.9)	1 (0.9)
Lymphopenia	0	2 (1.9)
Select grade 3/4 TEAEs, n (%)		
Leukopenia	3 (2.8)	3 (2.8)
Pancytopenia	3 (2.8)	0
Myelosuppression	2 (1.9)	0
Lymphocyte count decreased	1 (0.9)	1 (0.9)
Lymphopenia	0	2 (1.9)
Grade 3/4 hematology findings, n (%)		
Anemia	6 (5.7)	4 (3.7)
Platelet count decreased	6 (5.7)	1 (0.9)

	Quizartinib (n = 106)	Placebo (n = 108)
Neutrophil count decreased	5 (4.7)	2 (1.9)
Any serious TEAE, n (%)	59 (55.7)	59 (54.6)
Serious TEAEs reported in ≥3% of patients		
MedDRA SOC: Infections and infestations	30 (28.3)	34 (31.5)
Febrile neutropenia	13 (12.3)	7 (6.5)
Pneumonia	7 (6.6)	8 (7.4)
Septic shock	7 (6.6)	3 (2.8)
Sepsis	5 (4.7)	7 (6.5)
Pyrexia	4 (3.8)	3 (2.8)
Klebsiella sepsis	4 (3.8)	1 (0.9)
Neutropenia	1 (0.9)	4 (3.7)
Thrombocytopenia	1 (0.9)	3 (2.8)

The safety analysis population included all patients who received ≥1 dose of quizartinib or placebo. Three patients in each group were not treated and were not included in the safety analysis population. If a patient had more than one event of the same TEAE, that patient was counted only once. MedDRA: Medical Dictionary for Regulatory Activities; QT: interval between the start of the Q wave and the end of the T wave; SOC: system organ class; TEAE: treatment-emergent adverse event.

Table S6. Times to hematologic recovery among patients aged ≥ 60 years (safety analysis set).

Time to hematologic recovery in patients achieving CR from C1D1 of chemotherapy, days, median (range)	Quizartinib (n = 57)	Placebo (n = 60)
Time to recovery to ANC $\geq 1,000$ cells/mm ³	34 (22–55)	29 (21–72)
Time to recovery to PLT $\geq 100,000$ cells/mm ³	31 (22–70)	29 (21–72)

The safety analysis population included all patients who received ≥ 1 dose of quizartinib or placebo. Three patients in each group were not treated and were not included in the safety analysis population. ANC: absolute neutrophil count; C1D1: Cycle 1 Day 1; CR: complete remission; PLT platelet count.

Table S7. CONSORT 2025 checklist of information to include when reporting a randomized trial.

Section / Topic	No	CONSORT 2025 checklist item description	Reported on page no.
Title and abstract			
Title and structured abstract	1a	Identification as a randomized trial	8
	1b	Structured summary of the trial design, methods, results, and conclusions	5
Open science			
Trial registration	2	Name of trial registry, identifying number (with URL) and date of registration	5
Protocol and statistical analysis plan	3	Where the trial protocol and statistical analysis plan can be accessed	N/A
Data sharing	4	Where and how the individual de-identified participant data (including data dictionary), statistical code, and any other materials can be accessed	2
Funding and conflicts of interest	5a	Sources of funding and other support (e.g., supply of drugs), and role of funders in the design, conduct, analysis, and reporting of the trial	2, 3
	5b	Financial and other conflicts of interest of the manuscript authors	3,4
Introduction			
Background and rationale	6	Scientific background and rationale	6–7
Objectives	7	Specific objectives related to benefits and harms	7
Methods			
Patient and public involvement	8	Details of patient or public involvement in the design, conduct, and reporting of the trial	N/A

Trial design	9	Description of trial design including type of trial (e.g., parallel group, crossover), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)	8
Changes to trial protocol	10	Important changes to the trial after it commenced including any outcomes or analyses that were not prespecified, with reason	N/A
Trial setting	11	Settings (e.g., community, hospital) and locations (e.g., countries, sites) where the trial was conducted	Primary publication ^a
Eligibility criteria	12a	Eligibility criteria for participants	8
	12b	If applicable, eligibility criteria for sites and for individuals delivering the interventions (e.g., surgeons, physiotherapists)	N/A
Intervention and comparator	13	Intervention and comparator with sufficient details to allow replication. If relevant, where additional materials describing the intervention and comparator (e.g., intervention manual) can be accessed	8
Outcomes	14	Pre-specified primary and secondary outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome	Primary publication ^a
Harms	15	How harms were defined and assessed (e.g., systematically, non-systematically)	Primary publication ^a
Sample size	16a	How sample size was determined, including all assumptions supporting the sample size calculation	Primary publication ^a
	16b	Explanation of any interim analyses and stopping guidelines	N/A
Randomization:			
Sequence generation	17a	Who generated the random allocation sequence and the method used	Primary publication ^a
	17b	Type of randomization and details of any restriction (e.g., stratification, blocking, and block size)	Primary publication ^a

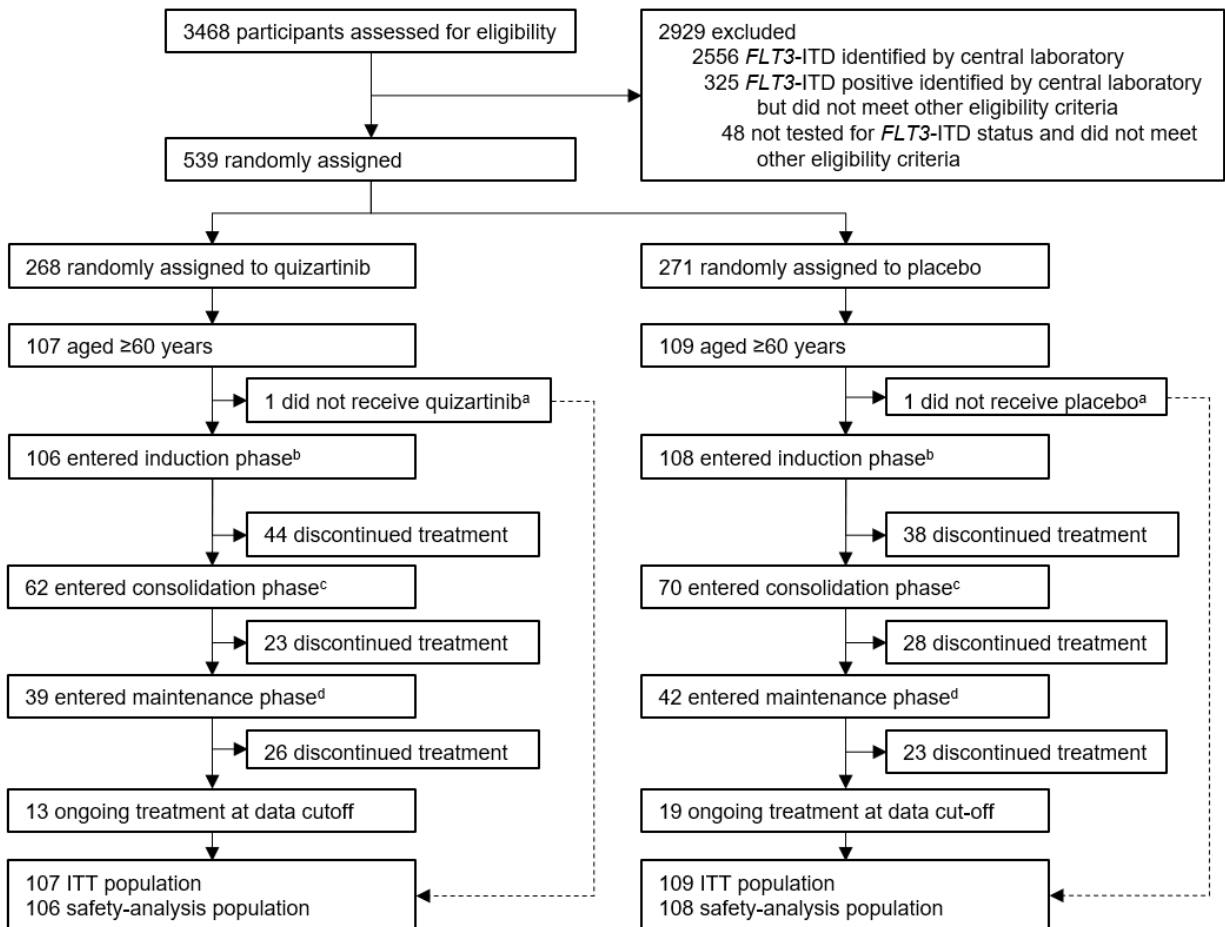
Allocation concealment mechanism	18	Mechanism used to implement the random allocation sequence (e.g., central computer/telephone; sequentially numbered, opaque, sealed containers), describing any steps to conceal the sequence until interventions were assigned	Primary publication ^a
Implementation	19	Whether the personnel who enrolled and those who assigned participants to the interventions had access to the random allocation sequence	Primary publication ^a
Blinding	20a	Who was blinded after assignment to interventions (e.g., participants, care providers, outcome assessors, data analysts)	Primary publication ^a
	20b	If blinded, how blinding was achieved and description of the similarity of interventions	Primary publication ^a
Statistical methods	21a	Statistical methods used to compare groups for primary and secondary outcomes, including harms	Supplement pp.1–2
	21b	Definition of who is included in each analysis (e.g., all randomized participants), and in which group	Primary publication ^a
	21c	How missing data were handled in the analysis	Primary publication ^a
	21d	Methods for any additional analyses (e.g., subgroup and sensitivity analyses), distinguishing prespecified from post-hoc	9, Supplement pp.1–2
Results			
Participant flow, including flow diagram	22a	For each group, the numbers of participants who were randomly assigned, received intended intervention, and were analyzed for the primary outcome	9, Supplement p.10
	22b	For each group, losses and exclusions after randomization, together with reasons	Supplement p.10
Recruitment	23a	Dates defining the periods of recruitment and follow-up for outcomes of benefits and harms	9
	23b	If relevant, why the trial ended or was stopped	N/A
Intervention and comparator delivery	24a	Intervention and comparator as they were actually administered (e.g., where appropriate, who delivered the intervention/comparator, how participants adhered, whether they were delivered as intended [fidelity])	Primary publication ^a

	24b	Concomitant care received during the trial for each group	Primary publication ^a
Baseline data	25	A table showing baseline demographic and clinical characteristics for each group	Table 1 (p.22)
Numbers analyzed, outcomes and estimation	26	For each primary and secondary outcome, by group: <ul style="list-style-type: none"> the number of participants included in the analysis the number of participants with available data at the outcome time point result for each group, and the estimated effect size and its precision (such as 95% confidence interval) for binary outcomes, presentation of both absolute and relative effect size 	10–12 + Table 2 + Figures 1 & 5 + Tables S1–S4
Harms	27	All harms or unintended events in each group	13–14 + Table 3 + Tables S5–S6
Ancillary analyses	28	Any other analyses performed, including subgroup and sensitivity analyses, distinguishing pre-specified from post-hoc	10–13 + Figures 2–4 + Figures S1–S5
Discussion			
Interpretation	29	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14–26
Limitations	30	Trial limitations, addressing sources of potential bias, imprecision, generalizability, and, if relevant, multiplicity of analyses	15–26

^aErba HP, et al. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2023;401:1571–1583. N/A: not applicable

Figures

Figure S1. CONSORT diagram for the QuANTUM-First trial.

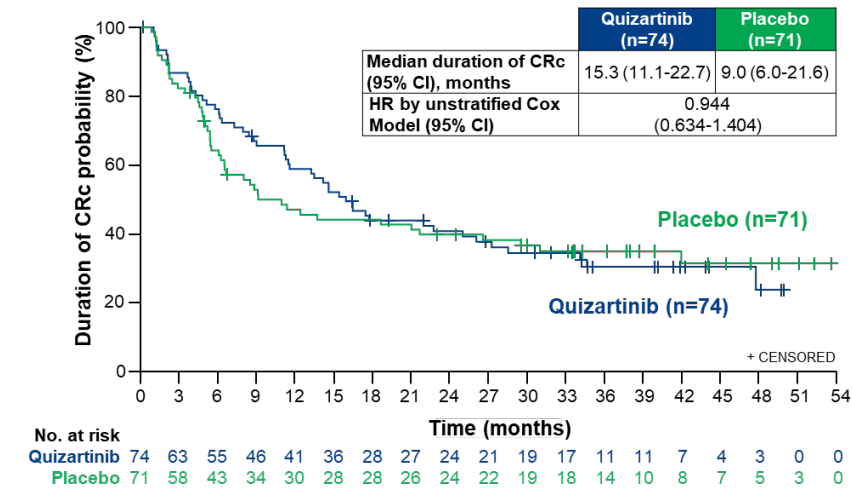


^aNot included in safety-analysis population. ^bMedian number of cycles of induction was 1 (range 1–2). ^cMedian number of cycles of consolidation was 2 (range 1–4). ^dMedian number of cycles of continuation was 12 (range 1–36).

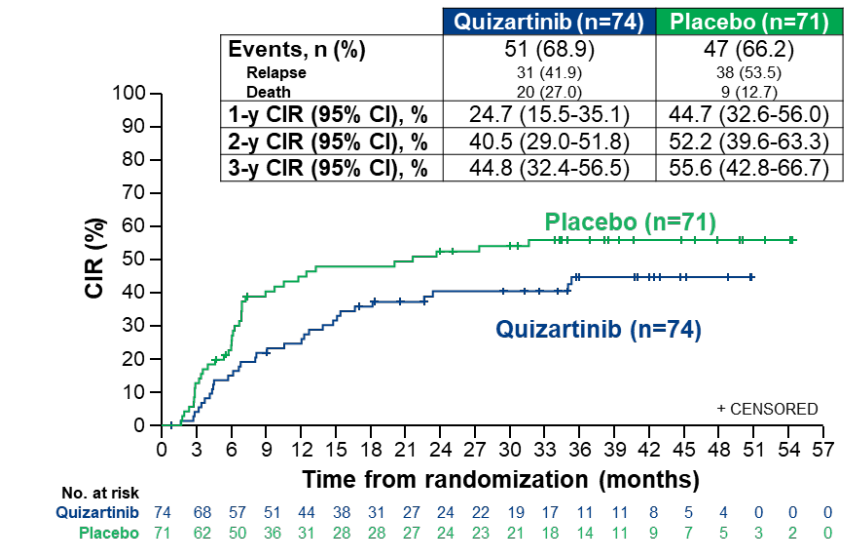
Allo-HCT: allogeneic hematopoietic cell transplantation; AML: acute myeloid leukemia; FLT3-ITD FMS-related receptor tyrosine kinase 3–internal tandem duplication; ITT: intention-to-treat.

Figure S2. For older patients aged ≥60 years achieving CRc (n = 145): duration of CRc (A) and CIR after CRc (B).

A



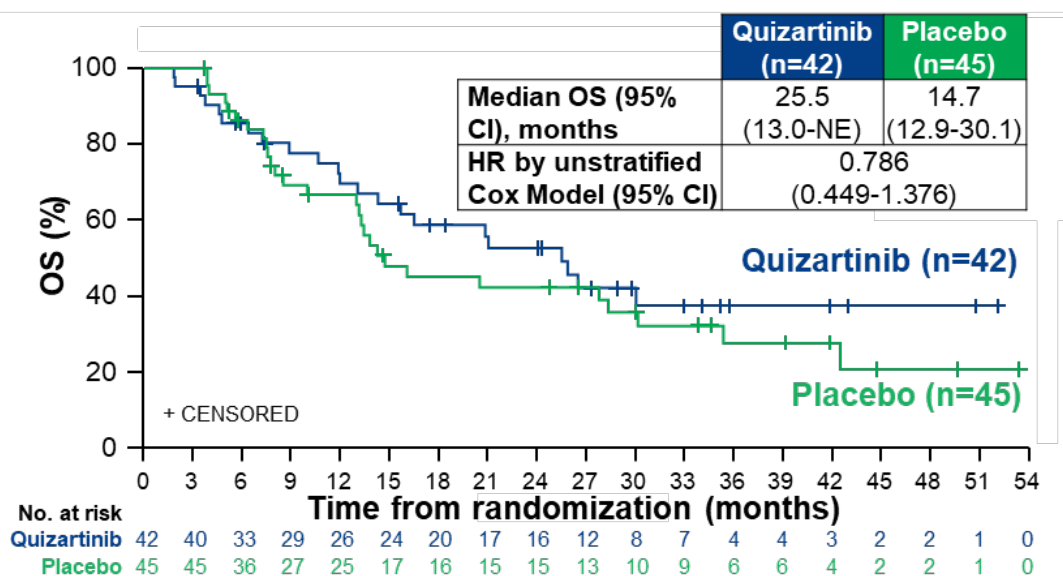
B



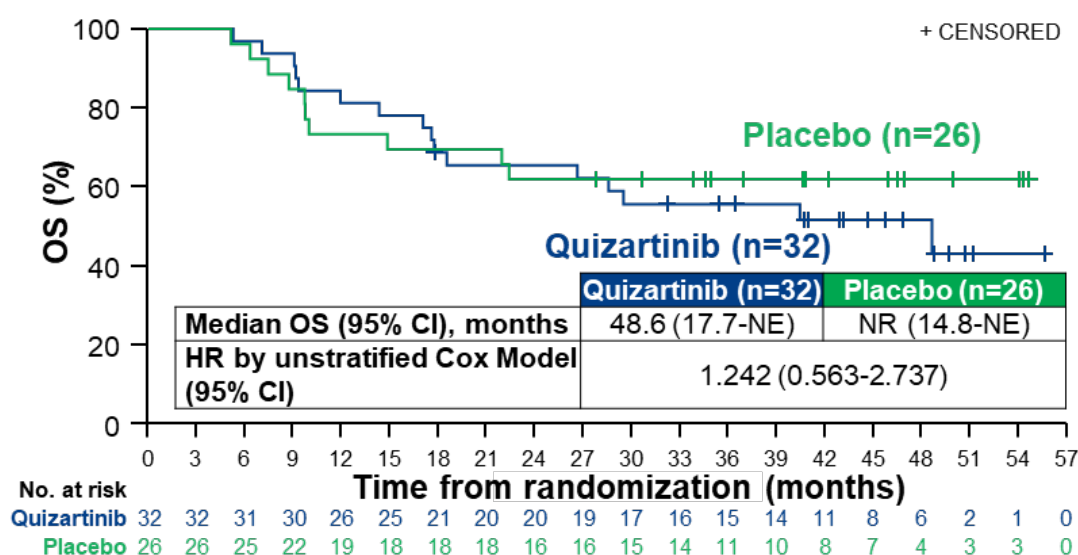
CI: confidence interval; CIR: cumulative incidence of relapse; CRc: composite complete remission; HR: hazard ratio.

Figure S3. OS for older patients who achieved CRc^a without (A) or with allo-HCT (B).

A

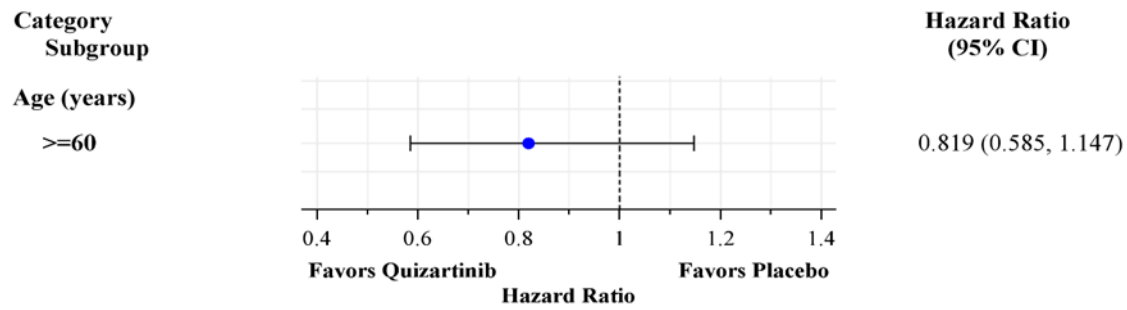


B



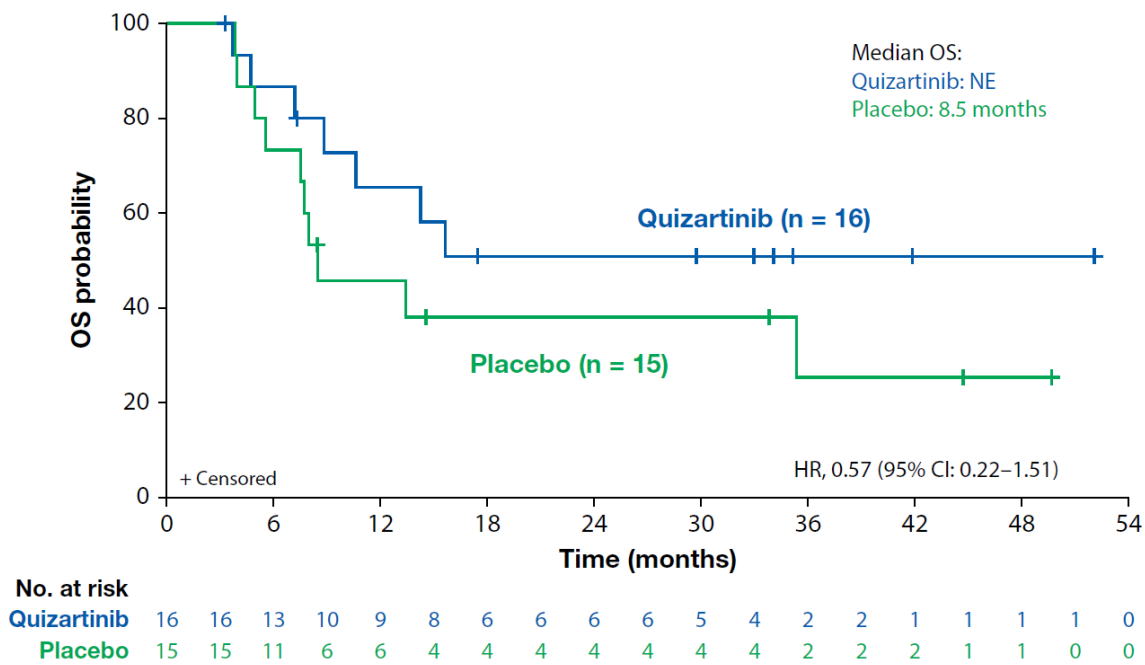
^aIncludes patients who did not undergo allo-HCT at all during the study and those who underwent allo-HCT outside CRc. Allo-HCT outside CRc was censored at the start date of the conditioning regimen for allo-HCT. Allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; CRc: composite complete remission; HR: hazard ratio; NE: not estimable; NR: not reached; OS: overall survival.

Figure S4. Sensitivity analysis of OS based on stratified Cox model.



Hazard ratio is obtained from stratified Cox proportional hazard model. Stratification factors include region (North America, Europe, Asia/Other Regions), White blood cell count at the time of diagnosis of AML ($< 40 \times 10^9/L$, $\geq 40 \times 10^9/L$), and age (≥ 60 to < 65 vs. ≥ 65). AML: acute myeloid leukemia; CI: confidence interval; OS: overall survival.

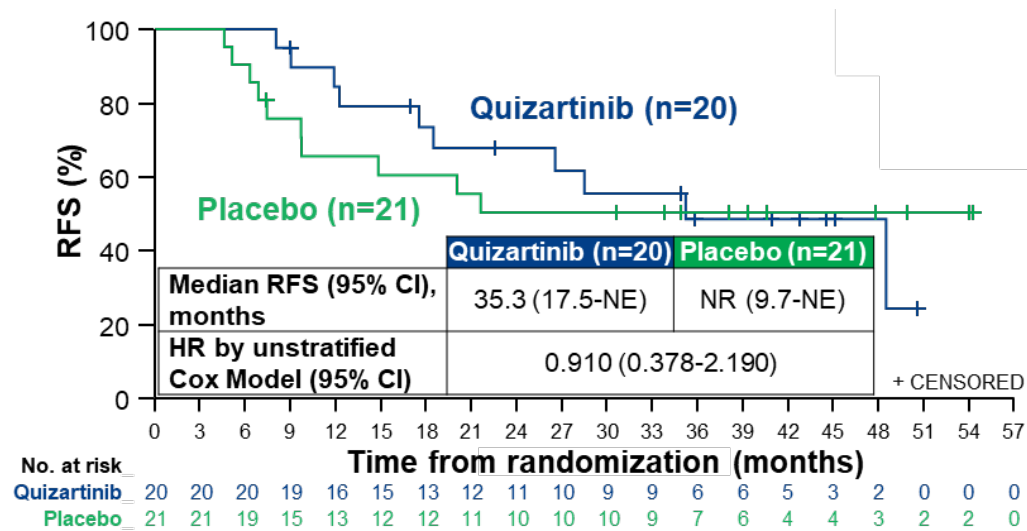
Figure S5. OS for older patients with *FLT3*-ITD, *NPM1*, and *DNMT3A* co-mutations who achieved CR but did not receive allo-HCT.



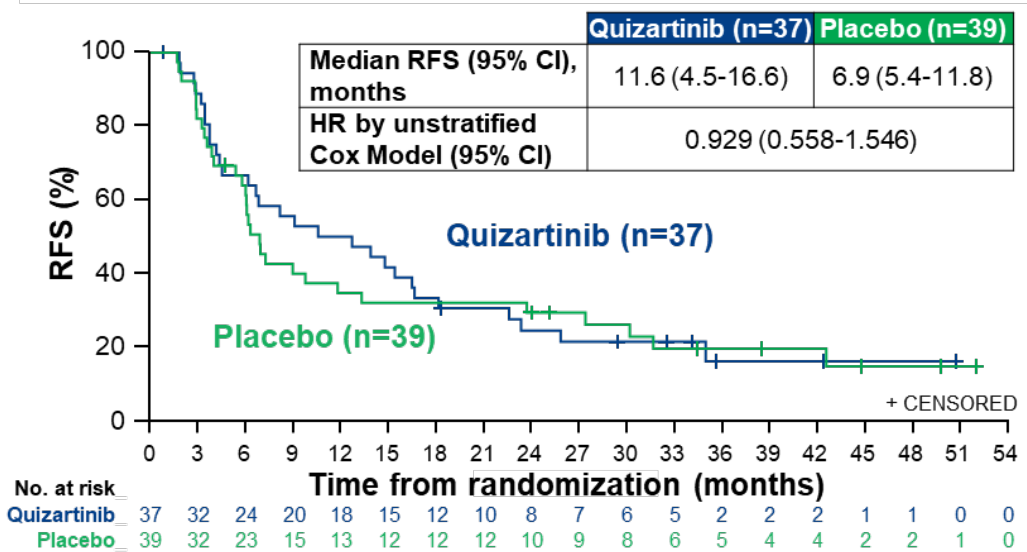
Allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; CR: complete remission; HR: hazard ratio; NE: not estimable; OS: overall survival.

Figure S6. RFS for older patients who achieved CR with (A) or without allo-HCT^a (B).

A



B



^aIncludes patients who did not undergo allo-HCT at all during the study and those who underwent allo-HCT outside CR. Allo-HCT outside CR was censored at the start date of the conditioning regimen for allo-HCT. Allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; CR: complete remission; HR: hazard ratio; NE: not estimable; NR: not reached; OS: overall survival; RFS: relapse-free survival.