Title

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Journal

Blood, 132(6)

ISSN

0006-4971

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Publication Date

2018-08-09

DOI

10.1182/blood-2018-01-821629

Peer reviewed

Phase 2b study of two dosing regimens of quizartinib monotherapy in *FLT3*-ITD mutated, relapsed or refractory AML

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Short Title:

Quizartinib in *FLT3*-ITD–mutated AML

Statement of prior presentation

Presented in poster form at the 2014 American Society of Clinical Oncology 50th Annual Meeting, Chicago, IL, June 2, 2014 (Schiller GJ, Tallman MS, Goldberg SL. Final results of a randomized phase 2 study showing the clinical benefit of quizartinib (AC220) in patients with *FLT3*-ITD positive relapsed or refractory acute myeloid leukemia [poster]. *J Clin Oncol*. 2014;(suppl): abstr 7100) and the 58th American Society of Hematology Annual Meeting, San Diego, CA, December 3, 2016 (Levis MJ, Cortes JE, Gammon GM, et al. Laboratory and clinical investigations to identify the optimal dosing strategy for quizartinib (AC220) monotherapy in *FLT3*-ITD—positive (+) relapsed/refractory (R/R) acute myeloid leukemia (AML) [abstract]. *Blood*. 2016;128: abstract 4042).

Word Counts:

Title = 112 characters

Short title = 35 characters

Text only = 3930 words; max allowed 4000

Abstract = 249 words – maximum allowed 250 words

Figures + Tables (limit: 7; CONSORT flowchart is counted) =

7 (2 figures + 5 tables); plus 3 online-only supplemental (appendix) tables

References = 30

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Key Points

- Quizartinib at 60-mg/day (vs 30-mg/day) was associated with higher overall response, survival, and bridge to transplant.
- The benefit-risk profile of quizartinib monotherapy in relapsed or refractory *FLT3*-ITD–mutated AML demonstrated in this study suggests further evaluation of the 60-mg once daily dose in future studies is warranted.

Abstract – current word count 249; max allowed 250

This randomized, open-label, phase 2b study (NCT01565668) evaluated efficacy and safety of two dosing regimens of quizartinib monotherapy in patients with relapsed/refractory (R/R) *FLT3*-internal tandem duplication (ITD)–mutated acute myeloid leukemia (AML) who previously underwent transplant or one second-line salvage therapy. Patients (N=76) were randomized to 30- or 60-mg/day doses (escalations to 60 or 90 mg/day, respectively, permitted for lack/loss of response) of single-agent oral quizartinib dihydrochloride. Allelic frequency ≥10% was defined as *FLT3*-ITD mutated disease. Co-primary endpoints were composite complete remission (CRc) rates, and incidence of QT interval corrected by Fridericia's formula (QTcF) >480 msec (grade 2 or greater). Secondary endpoints included overall survival (OS), duration of CRc, bridge to transplant, and safety. CRc rates were 47% in both arms, similar to earlier reports with higher quizartinib doses. Incidence of QTcF >480 msec was 11% and 17% and QTcF >500 msec was 5% and 3% in 30-mg and 60-mg arms, respectively; less than earlier reports with higher doses of quizartinib. Median OS (20.9 and 27.3 weeks), duration of CRc (4.2 and 9.1 weeks), and bridge to transplant rates (32% and 42%) were higher in 60-mg arm than in 30-mg arm. Dose escalation occurred in 61% and 14% of patients in 30-mg and 60-mg arms, respectively. This high clinical activity of quizartinib at the evaluated doses is consistent with previous reports with an improved safety profile. Need to dose-escalate more than half of patients who received quizartinib 30 mg also supports further investigation of treatment with quizartinib 60 mg/day.

Text word count 3930; max allowed 4000

Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease with multiple factors influencing long-term outcome.[1,2] *FLT3* mutations (predominantly internal tandem duplication [ITD]; reported in ~25% of patients with AML)[3,4,5] are common molecular abnormalities in AML. *FLT3*-ITD mutations are a key oncogenic driver[6,7,8,9] and patients with *FLT3* mutated AML have poorer outcomes, lower response rates to chemotherapy, increased risk for relapse, and shorter survival, compared with patients without *FLT3* mutation.[4,10,11,12,13] Consequently, the therapeutic potential of kinase inhibitors targeting *FLT3* has been investigated. The recent approval of midostaurin, a first-generation multi-kinase (including *FLT3*) inhibitor, in combination with chemotherapy in newly diagnosed *FLT3*-mutated AML, based on outcomes from the RATIFY trial,[14] provides support for *FLT3* as a viable target in AML. However, there remains a large unmet need for effective treatment options in patients with relapsed or refractory (R/R) *FLT3*-ITD mutated AML.

Quizartinib is an orally administered, highly potent and selective next-generation tyrosine kinase inhibitor that inhibits *FLT3* and is active against ITD mutants.[15,16,17] Accumulated clinical experience in phase 1 and 2 clinical trials has shown quizartinib to be highly active in R/R *FLT3*-ITD mutated AML.[18,19]

In a first-in-human phase 1 study, the maximum tolerated dose of quizartinib was 200 mg orally daily in patients with R/R AML with QT interval corrected using Fridericia's formula (QTcF) prolongation as the dose-limiting toxicity.[18] Quizartinib demonstrated encouraging clinical activity and was associated with a manageable safety profile. Results also suggested the potential for complete and sustained inhibition of *FLT3*

phosphorylation.[18] In a subsequent phase 2 study (NCT00989261), efficacy and safety of quizartinib monotherapy was evaluated in 2 independent cohorts: patients ≥60 years of age with R/R AML within 1 year after first-line therapy (Cohort 1), and those ≥18 years of age with R/R disease following salvage chemotherapy or allogeneic hematopoietic stem cell transplant (HSCT) (Cohort 2).[19] Initial treatment with 200 mg/day yielded a higher rate of QTcF prolongation than expected therefore lower doses (90 and 35 mg/day) were explored. QTcF prolongation was reversible and successfully managed by treatment interruption and/or dose reductions. QTcF> 500 msec was reported in 15% and 17% of patients treated with 90 and 135 mg/day, respectively.[19] These results demonstrated that single-agent quizartinib was highly active (CRc rate 46% in *FLT3*-ITD positive patients with 35% of patients bridging to HSCT [cohort 2]) and generally well-tolerated in patients with R/R AML (particularly those with *FLT3*-ITD mutations).

The study reported here evaluated two different dosing regimens of single-agent quizartinib to determine if the same clinical activity could be achieved while improving the safety profile in patients with R/R *FLT3*-ITD–mutated AML who had previously received hematopoietic stem cell transplant (HSCT) or one second-line salvage therapy.

Methods

Study design

NCT01565668 was a Phase 2b open-label, randomized study in adult (age ≥18 years) patients with morphologically documented primary AML or AML secondary to myelodysplastic syndrome as defined by the World Health Organization criteria and confirmed by pathology review at the treating institution. Patients were randomly assigned to one of 2 dosing regimens with quizartinib dihydrochloride monotherapy: a 30-mg once-daily starting-dose arm (equivalent to 26.5 mg free base) or a 60-mg once-daily starting-dose arm (equivalent to 53 mg free base). Each arm allowed protocol-specified dose escalation for lack/loss of response and dose reduction/interruption for adverse events (AEs). Patients received quizartinib oral solution daily in 28-day cycles until disease progression, intolerance, or HSCT. Quizartinib dihydrochloride powder was reconstituted in sterile water at a concentration of 5 mg/mL with a final volume of 6 mL or 12 mL (for 30-mg and 60-mg doses, respectively).

The study was conducted per the Declarations of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Eligibility criteria. Patients were required to have been refractory to or relapsed after HSCT or one second-line salvage regimen and were required to have *FLT3*-ITD activating mutation in bone marrow or peripheral blood. Patients were deemed eligible based on local laboratory results, with all samples subsequently tested at a central laboratory to confirm *FLT3* mutation status using a previously published method.[20] The *FLT3*-ITD allelic burden was calculated as the percentage of *FLT3*-ITD–mutated (dominant allele) to total *FLT3* (wild type + *FLT3*-ITD–mutated) in samples sent to the

central laboratory. Patients with an allelic frequency ≥10% were considered to have *FLT3*-ITD–mutated disease. Allelic frequencies were not corrected for blast percentages. Patients with *FLT3*-ITD-mutated allelic ratio <10% identified in the confirmatory *FLT3* testing at the central laboratory were allowed to remain in the study and were included in the intent-to-treat (ITT) population. The decision was at the discretion of the investigator if felt that treatment could offer benefit. Patients who had received prior *FLT3* inhibitor therapy were allowed. Additional inclusion criteria were Eastern Cooperative Oncology Group performance status of 0 to 2 and adequate renal, hepatic, and coagulation parameters as indicated by the following laboratory values: aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x institutional upper limit of normal (ULN); total bilirubin ≤ 1.5 x institutional ULN; serum creatinine ≤ 1.5 x institutional ULN and glomerular filtration rate > 30 mL/min (calculated by Cockcroft and Gault formula). Patients with acute promyelocytic leukemia, clinically active central nervous system leukemia, or treatment-related myeloid neoplasm were excluded. Patients with QTcF ≥450 msec were excluded. Concomitant treatment with drugs that prolonged QT/QTc interval or strong inhibitors/inducers of cytochrome P450-isozyme 3A (CYP3A) were prohibited unless these agents were deemed essential to patient care by the investigator. These agents included but were not limited to: antibiotics, antifungals, and other antimicrobials that were used as standard of care for the prevention or treatment of infections. (Appendix 1: Supplemental Table 1). No study drug dose modifications were required but patients underwent additional ECG monitoring.

***Criteria for dose reductions and increases*.** Dose escalation from 30 to 60 mg or from 60 to 90 mg was permitted in patients who did not achieve complete remission (CR), or CR with incomplete platelet recovery (CRp), or CR with incomplete hematologic recovery (CRi) by the end of Cycle 1 (ie, Day 28); or in those who achieved a response (CR/CRp/CRi/partial response [PR]) and later relapsed. Dose reduction (from 60 to 30 mg and subsequently to 20 mg, or from 30 to 20 mg) with or without dose interruption was required for grade ≥2 QTcF prolongation, persistent grade ≥3 nonhematologic AEs, or myelosuppression in patients achieving CRp/CRi who had received ≥2 cycles of treatment. No dose modifications were required for patients receiving concomitant drugs that prolonged QTcF interval or strong inhibitors/inducers of cytochrome P450-isozyme3A (CYP3A).

***Primary and secondary endpoints*.** The co-primary objectives were to evaluate the composite CR rate (CRc; defined as the rate of CR+CRp+CRi) and the rate of grade ≥2 QTcF (>480 msec). Responses to quizartinib were based on the Cheson criteria with modifications for CRi and partial remission (PR) (Appendix 1).[21]

Secondary endpoints reported here include the CR rate, overall survival (OS), event-free survival, leukemia-free survival, time to CRc, duration of CRc, rate of patients bridged to HSCT, and overall safety. Other secondary endpoints included pharmacokinetic and pharmacodynamic analyses and will be reported separately. Definitions of efficacy endpoints are presented in Appendix 1: Supplemental Methods.

***Study assessments*.** Electrocardiograms obtained at screening, pre-dose, and 2, 4, and 6 hours post-dose on Days 1 and 15 of Cycle 1; pre-dose and 2 hours post-dose on Day 8 of Cycle 1; pre-dose on Day 22 of Cycle 1; and pre-dose on Day 1 of all

subsequent cycles and were centrally reviewed. Patients receiving a CYP3A inhibitor or a drug known to cause QT/QTc prolongation during the study were required to undergo additional ECG monitoring pre-dose and 2 hours post-dose on Days 1 and Days 8 of subsequent cycles. Bone marrow biopsies were obtained at screening and on Day 1 of each cycle starting with Cycle 2.

Statistical analysis. The sample size was based on precision consideration for the rate estimate of CRc and QTcF prolongation (grade ≥2). A sample size of 32 patients per arm was estimated to result in a ~25% width of the 2-sided 90% confidence interval (CI) for both QTcF prolongation (grade ≥2) and CRc rates.

Primary efficacy analyses were conducted in the ITT population, defined as all randomized patients, according to their randomized treatment arms. Safety analyses were conducted in the safety population, defined as all patients who received ≥1 dose of study drug, according to their randomized treatment arms. Efficacy measurements were summarized using descriptive statistics for the initial dose level. Survival curves and medians for the time-to-event analyses were estimated using the Kaplan-Meier method and reported along with the corresponding 95% CIs. In patients achieving a CRc who subsequently relapsed, the duration of CRc was measured from the start of the first observed response to the date of documented relapse; in those patients who did not relapse, the duration of CRc was censored at the last evaluation visit at which the patient was known to be relapse-free, or at the end of treatment for those patients bridging to HSCT. For OS analysis, OS was censored at the date of last contact. Date of last contact was defined as the death date or the latest of the following dates: treatment discontinuation date, last dosing administration date, last disease assessment date, or

the last follow-up date on which the patient was known to be alive. Long term survival was defined as an OS ≥ 1 year.

Results

Patient characteristics

Between May 2012 and March 2015, 76 patients were enrolled (ITT population) (Figure 1). Baseline characteristics were generally well balanced between the 2 treatment arms (Table 1). Median age was 55 years (range, 19 to 77 years). The majority of patients (67%) had intermediate cytogenetic risk at baseline. Cytogenetic risk classifications were comparable in the 30-mg arm (favorable, 0; intermediate, 68%; unfavorable, 10%; unknown 21%) and 60-mg arm (favorable, 5%; intermediate, 66%; unfavorable, 8%; unknown 18%). The frequency of *NPM1* and *CEBPA* mutations were also similar across arms (Table 1). The distribution of *FLT3*-ITD mutated allelic ratio in the 30mg and 60 mg arms, respectively were: ≥10% to ≤25% (21% and 11%), ≥25% to ≤50% (53% and 34%), and >50% (18% and 45%). There were 3 patients in each arm with *FLT3* allele burden <10% at central review confirmation; 2 of whom had undetectable levels (Table 1). Patient's received a median 3 prior chemotherapy regimens for AML (range, 1 to 9), 28% of patients had prior HSCT, 92% prior anthracycline, and 15% prior *FLT3* inhibitors. Overall, 70% of patients were refractory to their last AML therapy and 30% had documented response (CR or PR) with median duration of response being 6.5 months (range, 0.4 to 18.0 months).

Seventy-four patients received at least 1 dose of quizartinib (30 mg arm, n = 38; 60 mg arm, n = 36) (Table 2). Overall, 18 (47%) in the 30 mg arm and 23 (64%) patients in the 60 mg arm had dose reductions/interruptions for management of AEs. As allowed

per protocol, 23 of 38 (61%) patients in the 30 mg arm were escalated to 60 mg/day quizartinib and 5 of 36 (14%) patients in the 60 mg arm were escalated to 90 mg/day quizartinib (Table 2).

Overall, 24% of patients received concomitant medications with a potential for QTcF prolongation (9 patients in each arm) and 53% received a strong CYP3A inhibitor (18 and 21 patients in the 30 mg and 60 mg arm, respectively) (Appendix 1: Supplemental Table 1).

Efficacy results

Of the 76 patients in the ITT analysis set, 47.4% achieved a best response of CRc (18 patients in each arm (Table 3). Of the patients achieving CRc, 12 of 18 in the 30 mg arm and 11 of 18 in the 60 mg arm had CRc at the end of Cycle 1. In addition, 5 of 38 patients in the 30 mg arm and 9 of 38 patients in the 60 mg arm achieved PR. Thus, the overall response rate (ORR; defined as CRc+PR) was 61% in 30 mg arm and 71% in the 60 mg arm (Table 3). The median duration of CRc and OS were longer in the 60 mg arm (4.2 [95% CI, 2.1-9.7] and 9.1 [95% CI, 4.1-22.3] weeks, and 20.9 [95% CI, 17.7-25.3] and 27.3 [95% CI, 17.3-34.9] weeks in the 30 mg and 60 mg arms, respectively) (Table 3, Figure 2). Six patients had OS duration ≥ 1 year; 1 in the 30-mg arm and 5 in the 60-mg arm.

Twelve (32%) patients in the 30-mg arm and 16 (42%) in the 60-mg arm bridged to HSCT (Table 3). The last recorded response before discontinuing quizartinib for HSCT was CR in 3 patients, CRi in 12 patients, PR in 6 patients, and no response (NR) in 6 patients. One patient did not have a response evaluation prior to HSCT. Patients

who bridged to HSCT were not permitted to restart quizartinib following transplant. Four of the 6 long term survivors were patients who bridged to HSCT; 1 in the 30-mg arm and 3 in the 60-mg arm.

Exploratory ad hoc analyses

In an exploratory ad hoc analysis, the CRc rate without dose escalation was 37% (14/38 patients) in patients randomized to the 30-mg arm. Of 23 patients with dose escalations to 60 mg, five achieved CRc after dose escalation (4 escalated for lack of initial response and 1 for loss of initial response). In patients randomized to the 60-mg arm, the CRc rate without dose escalation was 47% (18/38 patients). Dose escalation to 90 mg occurred in 5 patients (14%) and no patient achieved CRc after dose escalation.

Six patients with *FLT3*-ITD-mutated allelic ratio who were found to be below the protocol-defined cutoff during central laboratory confirmation benefitted from quizartinib treatment. Among the 4 patients with *FLT3*-ITD-mutated allelic ratio <10% in central *FLT3* testing, 3 patients achieved a response (1 CR; 2 CRi). Both the patients in whom *FLT3*-ITD-mutated allele was not detectable achieved a response (1 CR; 1 CRp).

Safety and toxicity results

Assessment of QTcF prolongation showed that 11% of patients in the 30-mg arm and 17% of patients in the 60-mg arm had QTcF >480 msec (grade 2 or greater) (Table 4). Grade 3 QTcF prolongation (>500 msec) was reported in 5% and 3% of patients in the 30-mg arm and 60-mg arm, respectively; there were no instances of torsade de pointes or other grade 4 ventricular arrhythmias or sudden death. Nine patients had an increase in QTcF of >60 msec from baseline: 3 with QTcF values >500 msec and 6 with <500

msec. Of the three with QTcF > 500 msec, 1 patient experienced ventricular tachycardia 22 days after discontinuation of quizartinib and while receiving multiple other QT prolonging agents for treatment of pneumonia. Of the remaining 8 patients, 2 were receiving 30 mg, 5 were receiving 60 mg, and 1 was receiving 90 mg after having been dose escalated from 60 mg. In these 8 patients, median time to QTcF prolongation was 19 days (range, 8 to 113 days). Of these 8 patients, median age at onset was 59 years (range, 28 to 74 years), and 5 were female. QTcF prolongation resolved or improved within 7 days in all patients. Resolution/improvement in QTcF occurred in 5 patients with no adjustments in quizartinib dosing, and 3 patients recovered after dose interruption. Two of these 3 patients were successfully re-challenged with no QTcF elevation exceeding Common Terminology Criteria for Adverse Events [CTCAE] grade 1. All patients with QTcF >500 msec and/or >60-msec change from baseline had risk factors for QTcF prolongation including electrolyte abnormalities and concomitant use of medications associated with QTcF prolongation and/or strong CYP3A inhibitors.

Grade ≥3 treatment emergent adverse events (TEAEs) regardless of relationship to study treatment reported in ≥10% of patients by initial dose arm (Appendix 2: Supplemental Table 2) were most frequently hematologic; gastrointestinal TEAEs were typically grade ≤2. Adverse events were considered treatment-related in 59 of 74 (80%) patients in the Safety Population. Treatment-related TEAEs (TR-TEAEs; includes both “probably” and “possibly” related AEs) were reported at similar rates across both arms (Table 5). The most common TR-TEAEs were hematologic events (anemia [20%], febrile neutropenia [11%]), gastrointestinal events (nausea [16%], diarrhea [11%]), and fatigue (12%). Four (5.4%) patients discontinued treatment owing to TR-TEAEs (1

patient with pericardial effusion and pericarditis; 1 patient each with diarrhea, neutropenic sepsis, and pleural effusion), all of whom had been randomized to the 30-mg arm. However, in 2 patients, onset of the event leading to discontinuation occurred after dose escalation to 60 mg.

Serious adverse events (SAEs) were considered by the investigator treatment-related in 10 (26%) patients in the 30-mg arm and 8 (22%) patients in the 60-mg arm. The most common treatment-related SAEs in the 30-mg arm were febrile neutropenia (3 events) and thrombocytopenia, pericardial effusion, and gastrointestinal hemorrhage (2 events each). The most common treatment-related SAEs in the 60-mg arm included febrile neutropenia and QT prolongation (2 events each). Among deaths not attributed to AML, the leading causes regardless of relationship to treatment were infections and respiratory/thoracic disorders. Two events occurred in the same patient in the 30-mg arm who was dose escalated to 60 mg (fatal pericardial effusion and pleural effusion) that were considered possibly related to study drug.

The majority of patients with elevated liver enzymes had values within 3 to 5 times the upper limit of normal (ULN); no patient met Hy's criteria (bilirubin >2 × ULN concurrently with alanine aminotransferase and/or aspartate aminotransferase >3 × ULN with no increase in alkaline phosphatase) (Appendix 3: Supplemental Table 3).

Discussion

Relapsed/refractory *FLT3*-ITD-positive AML has a poor prognosis and a low response rate to salvage therapy.[22,23] Currently, there are no approved therapies specifically targeting *FLT3*-ITD mutations in the R/R setting, thereby representing a

major unmet need for patients who require more effective and tolerable therapies that offer the possibility to bridge to transplant. The results of this phase 2b study of single-agent quizartinib, an oral, highly potent, and selective next-generation *FLT3* inhibitor, evaluating two dosing regimens of 30 mg and 60 mg demonstrated promising anti-leukemic activity and an improved safety profile, particularly in terms of QTcF prolongation. Quizartinib was generally well tolerated with manageable safety profile and an observed incidence of grade 3 QTcF prolongation of 3-5%.

The overall CRc rate (47%) and ORR (66%) reported here were consistent with those observed in a previous study of higher doses of quizartinib in R/R *FLT3*-ITD-mutated AML.[19] The ORR, duration of CRc, and median OS were numerically higher in the 60 mg arm. Responses observed with quizartinib were rapid, and 37% and 47% of patients who achieved CRc did so by the end of Cycle 1 in the 30 mg and 60 mg arms, respectively. Dose escalations to 60 mg were more frequent in the 30 mg arm and more patients in the 60 mg arm achieved a CRc without a dose escalation compared to the 30 mg arm.

The patients in this study had very poor prognosis due to having *FLT3*-ITD mutated AML and having heavily pretreated R/R disease (median 3 prior chemotherapy regimens, prior anthracyclines in 92%, and history of HSCT in 27%). Eligible patients were enrolled regardless of the duration of response to prior therapy with most (70%) patients refractory to their last treatment. The median OS of 21-27 weeks observed in this study is clinically relevant as historically patients with *FLT3*-ITD mutated AML in first relapse were reported to have a median survival of ~13 weeks following standard chemotherapy.[22]

As HSCT is an important goal for patients with R/R AML, the ability to provide HSCT to more patients is of benefit to patients with an otherwise low probability of long-term survival. In our study, the bridge to HSCT rate in the 60-mg arm (42%) was higher than in the 30-mg arm (32%) and was substantially higher than historical data (8% in the UK NCRI database).[24] This analysis demonstrated that those who were transplanted had a longer OS and quizartinib may offer the opportunity of bridging patients to transplant.[24] Quizartinib was not restarted following transplant in this study; however, it may provide benefit in the post-transplant setting. Based on this, ongoing studies have been designed to allow for the re-initiation of quizartinib therapy after transplant.[25,26]

Consistent with prior Phase 1 and 2 studies,[18,19] responses were documented in two patients with undetectable *FLT3*-ITD mutation. The mechanism by which quizartinib induced remission in patients with undetectable *FLT3*-ITD mutations is unknown and requires further investigation.

Quizartinib was specifically developed to target *FLT3* and demonstrates a high specificity for this kinase in vitro.[17] Higher specificity could potentially result in improved therapeutic activity in patients with *FLT3*-ITD–mutated AML. The promising clinical activity (46%-56% CRc rate) of quizartinib monotherapy (90 or 135 mg) in an earlier phase 2 study[19] is reinforced by this study, in which quizartinib dosing regimens of 30 and 60 mg/day (with escalation to 60 and 90 mg/day as necessary) demonstrated comparable CRc rates (47%). The high CRc rate, ORR (71%), and bridge to HSCT rate (42%) in the 60-mg quizartinib arm, offer a promising treatment option with this highly potent and selective *FLT3* inhibitor, given the limited single-agent efficacy with less selective *FLT3* inhibitors.[27,28,29,30] The response rates observed with quizartinib in the

current study are comparable to those with gilteritinib in a study with a similar patient population and similar response criteria.[30] Taken together, these findings demonstrate clinically meaningful antitumor activity with quizartinib monotherapy in patients with R/R *FLT3*-ITD mutated AML.

Quizartinib was generally well tolerated with similar TR-TEAE profiles in both dose groups, possibly because a substantial proportion of patients in the 30 mg arm were dose escalated to 60 mg during the study. The grade 2 or greater incidence of QTcF prolongation of 11% in the 30 mg arm and 17% in the 60 mg arm are of relevance given the higher rates in previous reports with higher doses.[18,19] Moreover, the incidence of grade 3 QTcF prolongation (>500 msec) was also substantially lower in this study (5% and 3% in 30-mg and 60-mg arms, respectively, with no grade ≥4 events) than in the earlier phase 2 trial using higher quizartinib doses (15% and 17% in 135-mg and 90-mg arms, respectively, with 1 grade 4 event).[19] None of the patients in this study experienced arrhythmias associated with QTcF prolongation while on quizartinib treatment, supporting an acceptable benefit-risk profile for quizartinib in this difficult-to-treat patient population. Additional analysis of data from this study regarding pharmacokinetics/pharmacodynamics modeling aimed at examining the relationship between quizartinib dose and QTcF prolongation will be reported in a separate publication.

The phase 2 trial design and sample size may limit the generalizability of the results from this study. In addition, the study was not powered to allow for statistical comparative analyses between arms. The numeric difference in efficacy outcomes between the 30 mg/day and 60 mg/day dose groups may have been influenced by

differences in baseline prognostic factors, lack of standardization in making dose escalation decisions, the rate of dose escalation for lack/loss of response and / or the censoring in CRc duration calculations at the end of treatment for patients bridged to HSCT.

In summary, the totality of evidence from the two Phase 2 studies of quizartinib monotherapy in R/R *FLT3*-mutated AML suggests that quizartinib may be a valuable treatment option for patients with R/R *FLT3*-ITD-mutated AML. Further investigation of quizartinib 60 mg once daily dose is warranted and is currently under evaluation in an ongoing phase 3 clinical trial (QuANTUM-R) to assess the efficacy of quizartinib as monotherapy versus salvage chemotherapy in patients with R/R *FLT3*-ITD–mutated AML. The dosing regimen in QuANTUM-R incorporates the 60 mg/day dose with a 30-mg/day lead-in to assess QTcF prolongation before dose escalation. Outcomes from QuANTUM-R are awaited.

Acknowledgments

This work was supported in part by the NCI Leukemia SPORE P50 CA100632 (J.E.C., H.M.K. and M.J.L.) and Cancer Center Support Grant P30 CA16672 (J.E.C. and H.M.K.). This study was sponsored by Daiichi Sankyo, Inc., a member of the Daiichi Sankyo Group.

Financial support for medical editorial assistance was provided by Daiichi Sankyo. We thank Vinay Pasupuleti, MD, PhD, Accuverus Inc., for his medical editorial assistance with this manuscript.

Authorship

J.E.C., M.J.L. designed the study; J.E.C., S.L.G., M.J.L., M.S.T., D.T. collected and analyzed data, and wrote the paper; J.E.C, H.M.K., G.G., S.L.G., M.J.L., J.P.M., M.S.T., D.T., performed the statistical analysis and wrote the paper; J.E.C., S.L.G., M.J.L., G.M., A.E.P., G.J.S., M.S.T., D.T., collected data and wrote the paper; and all authors critically revised the manuscript for important intellectual content and approved the manuscript for publication.

Conflict-of-interest disclosure

The authors declare the following conflicts of interest (I = Immediate Family Member, Inst = My Institution): J.E.C. is in a consulting or advisory role for Ambit, Daiichi Sankyo, Astellas, and Novartis and receives research funding from (Inst) Ambit, Daiichi Sankyo, Astellas, AROG, Flexus, and Novartis. M.S.T. is in a consulting or advisory role for Daiichi Sankyo and receives research funding from AROG, Cellerant, ADC Therapeutics, Celgene. G.J.S. receives research funding from Ambit. D.T. was employed by Daiichi Sankyo (at the time of the conduct of this trial), Ambit Biosciences (currently). G.C. was employed by Daiichi Sankyo (at the time of the conduct of this trial), is currently in a consulting or advisory role for Daiichi Sankyo (as CEO of Guy Gammon Consulting), owns stock or other ownership in Daiichi Sankyo, and travel is provided with accommodations and reimbursement for expenses from Daiichi Sankyo. S.L.G. and A.E.P. current COI information may be found on the ASCO Web site. J.P.M. receives honoraria from ICON Clinical. G.M. is in a consulting or advisory role with Celgene, Pfizer, Amgen, Ariad; speakers' bureau for Incyte-Teva. H.M.K. receives honoraria from AbbVie, Actinium, Amgen, Ariad, BMS, Immunogen, Orsuex, Pfizer and research funding from (Inst) Amgen, Pfizer, Novartis, BMS, Astex, Ariad. M.J.L. receives honoraria from Daiichi Sankyo, Novartis, and Agios is in a consulting or Advisory Role for Daiichi Sankyo, Novartis, Agios and receives research funding from Astellas and Novartis.

Appendix

CONSORT Checklist – page numbers to be updated once manuscript is finalized

PAPER SECTION And topic	Item	Description	Reported on Page #
TITLE & ABSTRACT	1	How participants were allocated to interventions (*e.g.*, "random allocation", "randomized", or "randomly assigned").	1, 4
INTRODUCTION Background	2	Scientific background and explanation of rationale.	5, 6
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	7, 8
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	7
Objectives	5	Specific objectives and hypotheses.	8, 9
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors).	8, 9
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	8, 9
Randomization -- Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (*e.g.*, blocking, stratification)	7
Randomization -- Allocation concealment	9	Method used to implement the random allocation sequence (*e.g.*, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	7
Randomization --	10	Who generated the allocation sequence, who	N/A

Implementation		enrolled participants, and who assigned participants to their groups.	
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.	7
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.	9
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	10
Recruitment	14	Dates defining the periods of recruitment and follow-up.	10
Baseline data	15	Baseline demographic and clinical characteristics of each group.	10; Table 1
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (*e.g.*, 10/20, not 50%).	10
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (*e.g.*, 95% confidence interval).	10, 11
Ancillary analyses	18	Address multiplicity by reporting any other	N/A

		analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	
Adverse events	19	All important adverse events or side effects in each intervention group.	11-13
DISCUSSION Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	13-15
Generalizability	21	Generalizability (external validity) of the trial findings.	15
Overall evidence	22	General interpretation of the results in the context of current evidence.	15, 16

Appendix 1: Supplemental Methods

Classifications and criteria for responses to quizartinib

Responses to quizartinib were based on the Cheson criteria[21] and classified in a hierarchical fashion as complete remission (CR; <5% bone marrow blasts, ≤1% peripheral blood blasts [if available], no Auer rods, transfusion independence [defined as no red blood cell (RBC) transfusions within 4 weeks prior to disease assessment and no platelet transfusions within 1 week prior to disease assessment], absolute neutrophil count >1 × 10^9/L, and platelet count ≥100 × 10^9/L) and CR with incomplete platelet recovery (CRp; same as CR except platelet count <100 × 10^9/L; still requires RBC and platelet transfusion independence). The criteria were modified for CR with incomplete hematologic recovery (CRi) to be as follows: <5% bone marrow blasts, ≤1% peripheral blood blasts (if available), no Auer rods, and no requirement for transfusion independence (modification from Cheson). Patients satisfying the above-mentioned criteria with incomplete neutrophil recovery were still classified as CRi. Similarly, those with incomplete platelet recovery but who were transfusion dependent were also still classified as CRi, as were those with complete platelet and neutrophil recovery but who remained transfusion dependent. Partial remission (PR) was defined as a decrease in bone marrow blasts of ≥50% from baseline (to total bone marrow blasts of 5%–25%), and no requirement for transfusion independence.

~~Responses to quizartinib were based on the Cheson criteria and classified in a hierarchical fashion as complete remission (CR; <5% bone marrow blasts, ≤1% peripheral blood blasts [if available], no Auer rods, transfusion independence, absolute~~

~~neutrophil count >10^9/L, and platelet count ≥100×10^9/L) and CR with incomplete platelet recovery (CRp; same as CR except platelet count <100×10^9/L; independent of platelet transfusion [no RBC transfusion within 4 weeks before response date, and no platelet transfusion 1 week before response date]). The criteria for CR with incomplete hematologic recovery (CRi) were modified to be as follows: <5% bone marrow blasts, ≤1% peripheral blood blasts (if available), no Auer rods, but no requirement for transfusion independence (modification from Cheson). Patients satisfying the above criteria with incomplete platelet recovery who were transfusion dependent were still classified as CRi. Similarly, those with complete platelet and neutrophil recovery but who were transfusion dependent were also still classified as CRi. Partial remission (PR) was defined as a decrease in bone marrow blasts of ≥50% from baseline to total bone marrow blasts of 5% to 25%, and no requirement for transfusion independence, plus satisfying other conditions of CRi (≤1% peripheral blood blasts [if available]).~~

Appendix 1: Supplemental Table 1

Patients taking concomitant medications with a potential for QT/QTc interval prolongation or strong inhibitors/inducers of CYP3A (Safety population)

	Quizartinib 30-mg arm* (n = 38)	Quizartinib 60-mg arm† (n = 36)‡	Total (N = 74)
Potential QT/QTc-prolonging medications			
Overall	9 (23.7)	9 (25.0)	18 (24.3)
Azithromycin	4 (10.5)	5 (13.9)	9 (12.2)
Clarithromycin§	1 (2.6)	0	1 (1.4)
Erythromycin	0	1 (2.8)	1 (1.4)
Prochlorperazine	3 (7.9)	3 (8.3)	6 (8.1)
Amiodarone	2 (5.3)	0	2 (2.7)
Moxifloxacin	0	1 (2.8)	1 (1.4)
Strong CYP3A inhibitors			
Overall	18 (7.4)	21(58.3)	39 (52.7)
Voriconazole	11 (28.9)	12 (33.3)	23 (31.1)
Posaconazole	7 (18.4)	11 (30.6)	18 (24.3)
Itraconazole	0	1 (2.8)	1 (1.4)
Ketoconazole	1 (2.6)	0	1 (1.4)
Strong/Moderate CYP3A inducer			
Overall	1 (2.6)	0	1 (1.4)
Modafinil	1 (2.6)	0	1 (1.4)

Quizartinib 30 mg and 60 mg are equivalent to 26.5 mg and 53 mg free base, respectively.

CYP3A, cytochrome P450-isozyme3A.

*30-mg starting dose with permitted escalation to 60 mg for lack of or loss of initial response.

†60-mg starting dose with permitted escalation to 90 mg for lack of or loss of initial response.

‡Two patients were randomized but did not receive drug owing to ineligibility.

§Clarithromycin is a strong CYP3A inhibitor.

Appendix 2: Supplemental Table 2

Grade 3 or higher TEAEs (regardless of relationship to study treatment) reported in ≥10% of patients per dose group (safety population)

TEAE by preferred term‡	Quizartinib 30-mg arm* (n = 38)		Quizartinib 60-mg arm† (n = 36)	
	Grade ≥3	All grades	Grade ≥3	All grades
Overall, n (%)	31 (81.6)	37 (97.4)	32 (88.9)	36 (100)
Febrile neutropenia	12 (31.6)	12 (31.6)	13 (36.1)	13 (36.1)
Anemia	14 (36.8)	18 (47.4)	6 (16.7)	9 (25.0)
Thrombocytopenia	10 (26.3)	10 (26.3)	7 (19.4)	7 (19.4)
Neutropenia	1 (2.6)	1 (2.6)	5 (13.9)	5 (13.9)
Pyrexia	4 (10.5)	11 (28.9)	3 (8.3)	14 (38.9)
Pneumonia	3 (7.9)	3 (7.9)	6 (16.7)	8 (22.2)
Blood bilirubin increased	2 (5.3)	3 (7.9)	4 (11.1)	4 (11.1)
Alanine aminotransferase increased	0	3 (7.9)	4 (11.1)	5 (13.9)

Quizartinib 30 mg and 60 mg are equivalent to 26.5 mg and 53 mg free base, respectively.

TEAE, treatment-emergent adverse event.

*30-mg starting dose with permitted escalation to 60 mg for lack of or loss of initial response.

†60-mg starting dose with permitted escalation to 90 mg for lack of or loss of initial response.

‡Patients may have more than 1 TEAE per preferred term. Patients are counted once per preferred term.

Appendix 3: Supplemental Table 3

Summary of clinically significant values in liver function tests (safety population)

Parameter	Criteria	Quizartinib 30-mg arm* (n = 38)	Quizartinib 60-mg arm† (n = 36)	Total (N = 74)
ALT, n/N (%)	>3 × ULN	7/38 (18.4)	8/36 (22.2)	15/74 (20.3)
	>5 × ULN	1/38 (2.6)	3/36 (8.3)	4/74 (5.4)
	>10 × ULN	0	0	0
	>20 × ULN	0	0	0
AST, n/N (%)	>3 × ULN	2/38 (5.3)	2/35 (5.7)	4/73 (5.5)
	>5 × ULN	0	0	0
	>10 × ULN	0	0	0
	>20 × ULN	0	0	0
ALT or AST, n/N (%)	>3 × ULN	8/38 (21.1)	8/36 (22.2)	16/74 (21.6)
Total bilirubin, n/N (%)	>2 × ULN	5/38 (13.2)	5/36 (13.9)	10/74 (13.5)
Alkaline phosphatase, n/N (%)	>1.5 × ULN	15/38 (39.5)	12/36 (33.3)	27/74 (36.5)
ALT and/or AST and total bilirubin, n/N (%)	ALT and/or AST >3 × ULN and Total Bilirubin >2 × ULN	2/38 (5.3)	0	2/74 (2.7)
ALT and/or AST and total bilirubin without an increase in ALP, n/N (%)	ALT and/or AST >3 × ULN and Total Bilirubin >2 × ULN and ALP < ULN	0	0	0

Quizartinib 30 mg and 60 mg are equivalent to 26.5 mg and 53 mg free base, respectively.

Maximum value on treatment is presented for each liver function parameter.

The denominators for percentages are based on number of subjects who had at least 1 non-missing value during treatment in each treatment group.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; and ULN, upper limit of normal.

*30-mg starting dose with permitted escalation to 60 mg for lack of or loss of initial response.

†60-mg starting dose with permitted escalation to 90 mg for lack of or loss of initial response.

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Tables

Table 1. Patient characteristics and treatment history (ITT population)

	Quizartinib 30-mg arm* (n = 38)	Quizartinib 60-mg arm† (n = 38)	Total (N = 76)
Secondary AML, n (%)	3 (8)	7 (18)	10 (13)
Median age, years (range)	57 (19-77)	53 (20-74)	55 (19-77)
Male, n (%)	22 (58)	22 (58)	44 (58)
Race, n (%)			
White	29 (76)	30 (79)	59 (78)
Black or African American	1 (3)	2 (5)	3 (4)
Other or missing‡	8 (21)	6 (16)	14 (18)
Median weight, kg (range)	76.8 (40-116)	75.1 (47-101)	75.9 (40-116)
ECOG PS, n (%)§			
Grade 0	8 (21.1)	7 (18.4)	15 (19.7)
Grade 1	23 (60.5)	24 (63.2)	47 (61.8)
Grade 2	7 (18.4)	4 (10.5)	11 (14.5)
FLT3-ITD–mutated allelic ratio, n (%)‖	37 (97)	36 (95)	73 (96)
>0 to <10%	2 (5)	2 (5)	4 (5)
≥10% and ≤25%	8 (21)	4 (11)	12 (16)
≥25% and ≤50%	20 (53)	13 (34)	33 (43)
>50%	7 (18)	17 (45)	24 (32)
FLT3-ITD size, median (range) base pairs¶	51.0 (21-201)	54.2 (18-114)	54.0 (18-201)
Risk status with specific cytogenetic patterns, n (%)#			
Favorable	0	2 (5)	2 (3)
Intermediate	26 (68)	25 (66)	51 (67)
Unfavorable	4 (11)	3 (8)	7 (9)
Unknown	8 (21)	7 (18)	15 (20)
AML with recurrent genetic abnormalities			
AML with mutated *NPM1*	8 (21)	11 (29)	19 (25)
AML with mutated *CEBPA*	0	0	0
Previous HSCT, n (%)	9 (24)	12 (32)	21 (28)
Prior AML chemotherapy regimens, median (range) **	3 (1-6)	3 (1-9)	3 (1-9)
Prior anthracycline treatment, n (%)**	35 (92)	33 (92)	68 (92)
Refractory, n (%)**	26 (68)	26 (72)	52 (70)
Relapsed, n (%)**	12 (32)	10 (28)	22 (30)
Duration of best response (CR or PR)	5 (0.4-12)	8 (1-18)	6.5 (0.4-18)

to last AML therapy, months, median (range) **			
Prior *FLT3* therapy, n (%)**††	5 (13)	6 (17)	11 (15)

Quizartinib 30 mg and 60 mg are equivalent to 26.5 mg and 53 mg free base, respectively.

AML, acute myeloid leukemia; CR, complete remission; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplant; ITD, internal tandem duplication; and ITT, intent to treat; PR, partial remission.

*30-mg starting dose with permitted escalation to 60 mg for lack of or loss of initial response.

†60-mg starting dose with permitted escalation to 90 mg for lack of or loss of initial response.

‡Ethnicity was not collected from patients in France per local regulations.

§At screening, all patients had ECOG performance status <2. However, by the time patients started on the study, their performance status might have changed so the baseline characteristics do not match eligibility criteria.

||*FLT3*-ITD-mutated allele was not detectable (below the assay's limit of detection) in 1 patient each in the 30-mg arm and the 60-mg arm; 1 patient in the 60-mg arm had missing values.

¶Total number of patients, N (%) = 30-mg arm, 37 (97); 60-mg arm, 36 (95); Total, 73 (96).

#Cytogenetic information based on available data.

**Total number of patients (Safety analysis set), N = 30-mg arm, 38; 60-mg arm, 36; Total, 74.

††10 patients received sorafenib and 1 patient received both sorafenib and midostaurin.

Table 2. Quizartinib treatment exposure and dose modifications (safety population)

	Quizartinib 30-mg arm* (n = 38)	Quizartinib 60-mg arm† (n = 36)‡	Total (N = 74)
Median duration of treatment, weeks (range)	9.4 (2.1-32.7)	10.1 (1.7-109)	10.0 (1.7-109)
Dose interrupted, n (%)	8 (21)	13 (36)	21 (28)
Dose reduced, n (%)	10 (26)	10 (28)	20 (27)
Dose escalated, n (%)	23 (61)	5 (14)	28 (38)

Quizartinib 30 mg and 60 mg are equivalent to 26.5 mg and 53 mg free base, respectively.

*30-mg starting dose with permitted escalation to 60 mg for lack of or loss of initial response.

†60-mg starting dose with permitted escalation to 90 mg for lack of or loss of initial response.

‡Two patients were randomized but did not receive drug owing to ineligibility.

Table 3. Key efficacy outcomes (ITT population)

	Quizartinib 30-mg arm* (n = 38)	Quizartinib 60-mg arm† (n = 38)	Total (N = 76)
Overall response (CRc+PR), n (%)	23 (60.5)	27 (71.1)	50 (65.8)
CRc (CR+CRp+CRi), n (%)	18 (47.4)	18 (47.4)	36 (47.4)
CR, n (%; 95% CI)	2 (5.3; 0.6-17.7)	1 (2.6; 0.1-13.8)	3 (3.9; 0.8-11.1)
CRp, n (%; 95% CI)	0	2 (5.3; 0.6-17.7)	2 (2.6; 0.3-9.2)
CRi, n (%; 95% CI)	16 (42.1; 26.3-59.2)	15 (39.5; 24.0-56.6)	31 (40.8; 29.6-52.7)
PR, n (%; 95% CI)	5 (13.2; 4.4-28.1)	9 (23.7; 11.4-40.2)	14 (18.4; 10.5-29.0)
Median duration of CRc, weeks (95% CI)‡	4.2 (2.1-9.7)	9.1 (4.1-22.3)	5.4 (4.1-11.9)
Median time to CRc, weeks (95% CI)	4.4 (4.1-7.7)	4.6 (4.1-8.0)	4.5 (4.3-6.6)
Bridge to HSCT transplant rate, n (%)	12 (31.6)	16 (42.1)	28 (36.8)
Median OS, weeks (95% CI)‡§	20.9 (17.7-25.3)	27.3 (17.3-34.9)	22.6 (19.9-28.3)
Deaths, n (%)	36 (94.7)	30 (78.9)	66 (86.8)
Censored, n (%)	2 (5.3)	8 (21.1)	10 (13.2)
Median EFS, weeks (95% CI)	12.0 (8.3-16.1)	13.7 (9.7-26.1)	12.3 (9.7-16.1)
Median LFS, weeks (95% CI)	4.1 (2.1-9.7)	9.1 (4.0-22.3)	5.3 (4.1-11.9)

Quizartinib 30 mg and 60 mg are equivalent to 26.5 mg and 53 mg free base, respectively.

Responses were assessed using modified Cheson criteria as described in Appendix.

CI, confidence interval; CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; EFS, event-free survival; HSCT, hematopoietic stem cell transplant; ITT, intent to treat; LFS, leukemia-free survival; PR, partial remission, and OS, overall survival.

*30-mg starting dose with permitted escalation to 60 mg for lack of or loss of initial response.

†60-mg starting dose with permitted escalation to 90 mg for lack of or loss of initial response.

‡From Kaplan-Meier analysis.

§Reflects median OS until the time of database lock (study termination).

Table 4. QTc prolongations with quizartinib (safety population)

	Quizartinib 30-mg arm* (n = 38)	Quizartinib 60-mg arm† (n = 36)
Maximum value of QTcF msec, n (%)‡		
≥450 to ≤480	16 (42.1)	17 (47.2)
>480 to ≤500	2 (5.3)	5 (13.9)
>500	2 (5.3)	1 (2.8)
Maximum change from baseline in QTcF msec, n (%)‡		
>30 to ≤60	18 (47.4)	15 (41.7)
>60	2 (5.3)	7 (19.4)

Quizartinib 30 mg and 60 mg are equivalent to 26.5 mg and 53 mg free base, respectively.

QTc, corrected QT interval; and QTcF, QT interval corrected for heart rate by Fridericia's formula.

*30-mg starting dose with permitted escalation to 60 mg for lack of or loss of initial response.

†60-mg starting dose with permitted escalation to 90 mg for lack of or loss of initial response.

‡Criteria for maximum QTcF duration and maximum QTcF change from baseline are not mutually exclusive —ie, the same patient could have met either or both criteria.

Table 5. Treatment-related TEAEs (all grades) reported in ≥10% of patients per dose group (safety population)

Treatment-related TEAE by preferred term*	Quizartinib 30-mg arm† (n = 38)	Quizartinib 60-mg arm‡ (n = 36)	Total (n = 74)
Overall, n (%)	30 (78.9)	29 (80.6)	59 (79.7)
Anemia	8 (21.1)	7 (19.4)	15 (20.3)
Nausea	4 (10.5)	8 (22.2)	12 (16.2)
Fatigue	5 (13.2)	4 (11.1)	9 (12.2)
Febrile neutropenia	4 (10.5)	4 (11.1)	8 (10.8)
Diarrhea	4 (10.5)	4 (11.1)	8 (10.8)
Electrocardiogram QT prolonged	2 (5.3)	5 (13.9)	7 (9.5)
Thrombocytopenia	4 (10.5)	2 (5.6)	6 (8.1)
Abdominal pain	2 (5.3)	4 (11.1)	6 (8.1)
Neutropenia	1 (2.6)	4 (11.1)	5 (6.8)
Vomiting	1 (2.6)	4 (11.1)	5 (6.8)
Dysgeusia	4 (10.5)	1 (2.8)	5 (6.8)
Dyspepsia	4 (10.5)	0	4 (5.4)

Quizartinib 30 mg and 60 mg are equivalent to 26.5 mg and 53 mg free base, respectively.

TEAE, treatment-emergent adverse event.

*Patients may have more than 1 treatment-related TEAE per preferred term. Patients are counted once per preferred term.

†30-mg starting dose with permitted escalation to 60 mg for lack of or loss of initial response.

‡60-mg starting dose with permitted escalation to 90 mg for lack of or loss of initial response.

Figure Legends

Figure 1. CONSORT flowchart. AEs, adverse events; HSCT, hematopoietic stem cell transplant; ITD, internal tandem duplication.

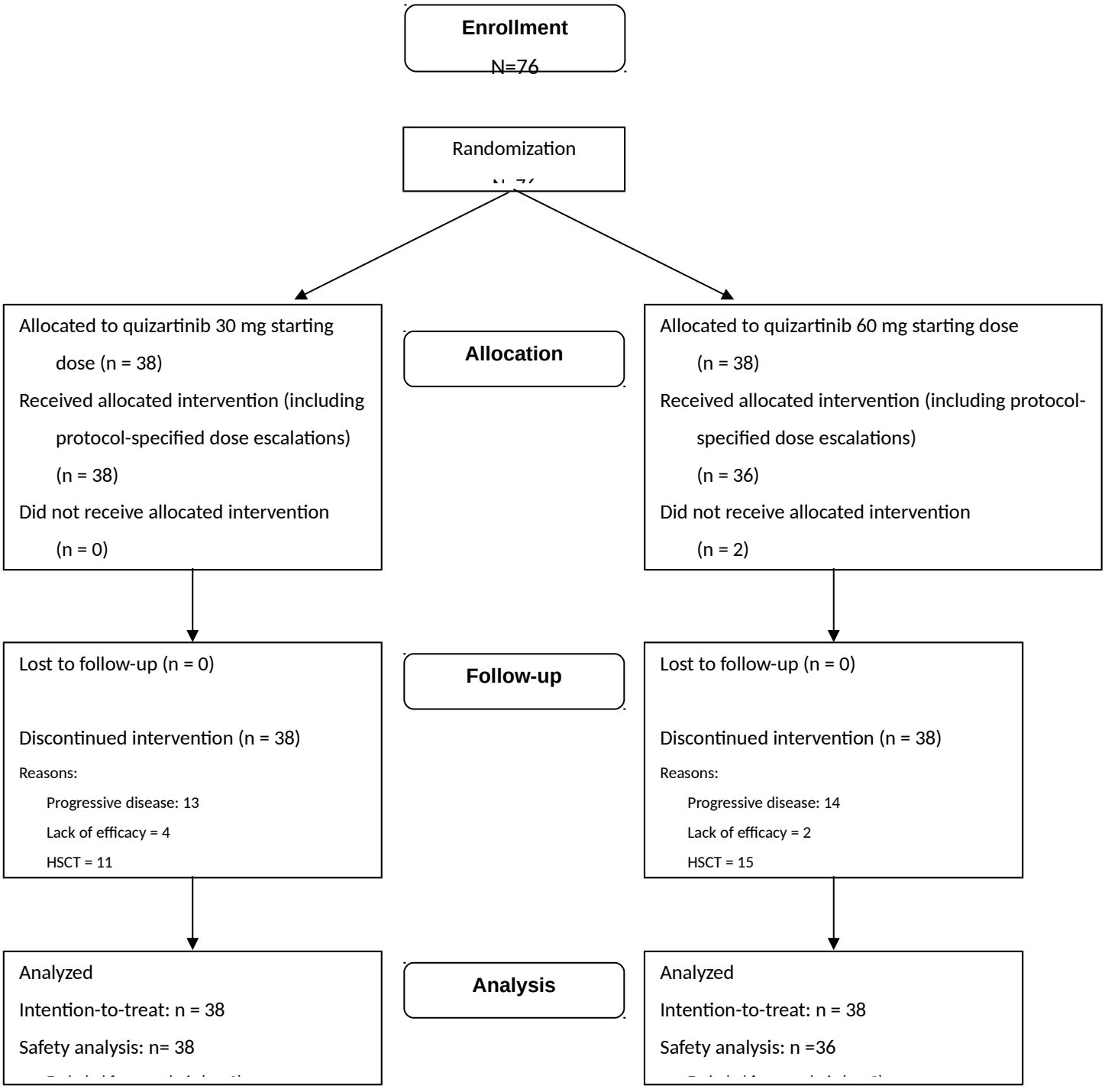
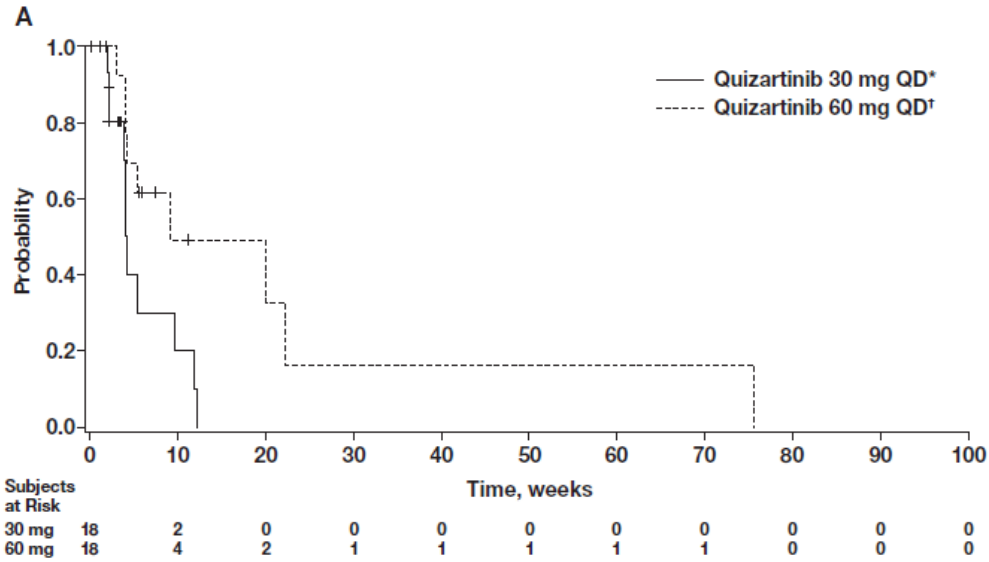
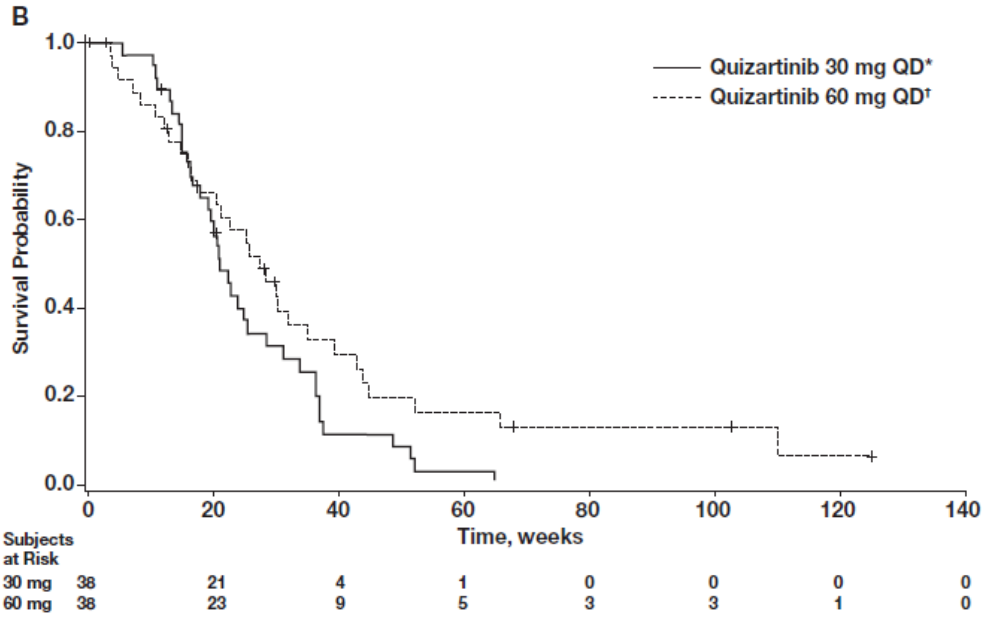


Figure 2. Kaplan-Meier plots of (A) duration of CRc and (B) overall survival (ITT analysis set). CRc, composite complete remission; ITT, intent to treat; and QD, once daily. *30-mg starting dose with permitted escalation to 60 mg for lack of or loss of initial response. †60-mg starting dose with permitted escalation to 90 mg for lack of or loss of initial response.


A
Quizartinib 30 mg QD*
Quizartinib 60 mg QD†
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
70
80
90
100
Time, weeks
Subjects at Risk
30 mg 18 2 0 0 0 0 0 0 0 0 0
60 mg 18 4 2 1 1 1 1 1 0 0 0


B
Quizartinib 30 mg QD*
Quizartinib 60 mg QD†
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
140
Time, weeks
Subjects at Risk
30 mg 38 21 4 1 0 0 0 0
60 mg 38 23 9 5 3 3 1 0