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 (<1 x 10^9/L) 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% to 25%), and no requirement for transfusion independence.

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 medication			
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 (47.4)	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.

CONSORT Checklist

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, 5
INTRODUCTION Background	2	Scientific background and explanation of rationale.	6, 7
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	8, 9
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	8
Objectives	5	Specific objectives and hypotheses.	10
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).	10,11
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	11
Randomization -- Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (*e.g.*, blocking, stratification)	8
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	8

		were assigned.	
Randomization -- Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	N/A
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.	8
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.	11,12
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.	12; Figure 1
Recruitment	14	Dates defining the periods of recruitment and follow-up.	12
Baseline data	15	Baseline demographic and clinical characteristics of each group.	12, 13; 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%).	13
Outcomes and	17	For each primary and secondary outcome, a	13, 14

estimation		summary of results for each group, and the estimated effect size and its precision (*e.g.*, 95% confidence interval).	
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	14
Adverse events	19	All important adverse events or side effects in each intervention group.	14-16
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.	16-20
Generalizability	21	Generalizability (external validity) of the trial findings.	17
Overall evidence	22	General interpretation of the results in the context of current evidence.	16, 17