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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Cortes J, Perl A E, Döhner H, et al. Quizartinib, an FLT3 inhibitor, as monotherapy in patients with relapsed or refractory acute myeloid leukaemia: an open-label, multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2018; published online May 30. http://dx.doi.org/10.1016/S1470-2045(18)30240-7.

Quizartinib, an FLT3 inhibitor, as monotherapy in patients with relapsed or refractory acute myeloid leukemia: an open-label, multicenter, phase 2 trial

Supplementary Appendix

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Additional inclusion and exclusion criteria

Baseline cytogenetic information was categorized according to the UK Medical Research Council classification.[1]

Monitoring and management of QTcF prolongation

Triplicate electrocardiogram (ECG) readings were made at screening, during cycle 1 prior to dosing, and 2 hours after dosing on days 1, 2, 8, and 15 and additionally 4 hours after dosing on days 1 and 15. Thereafter, ECGs were recorded predose and 2 hours postdose on day 1 of all subsequent cycles. QT intervals were corrected using Fridericia's formula: $QTcF=QT/RR^{0.33}$. Confirmation of grade 3 QTcF prolongation was required by repeat ECG within 2 hours. ECGs were analyzed by the investigators and subsequently by a central ECG laboratory (eRT, Philadelphia, PA, USA); the results were summarized by changes from baseline values using descriptive statistics. Per the study protocol, dosing was interrupted for up to 14 days in patients with QTcF interval increases >500 ms and restarted at a lower dose if QTcF returned to within 30 ms of baseline. Stepwise dose reductions (without interruption) were permitted at the discretion of the investigator in patients with QTcF prolongation >60 ms from baseline and a resultant QTcF >480 ms (grade 2). These patients were followed per the cycle 1 ECG monitoring schedule at the initiation of the reduced dose. Maintenance of normal serum electrolytes was required.

Classifications and criteria for responses to quizartinib

Responses to quizartinib were based on the Cheson criteria[2] and classified in a hierarchical fashion as complete remission (CR; <5% bone marrow blasts, ≤1% peripheral blood blasts [if available], no Auer rods, no evidence of extramedullary disease, 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 $>1 \times 10^9$/L, and platelet count $\geq 100 \times 10^9$/L) and CR with incomplete platelet recovery (CRp; same as CR except platelet count $<100 \times 10^9$/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, no evidence of extramedullary disease, 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%), no evidence of extramedullary disease, and no requirement for transfusion independence.

Definition of relapsed disease

Relapse after CRc was defined as an increase in bone marrow blasts to ≥5% or the appearance of leukemic blasts (>1%) in peripheral blood. Relapse after PR was similarly defined as an increase in the percentage of blasts in the bone marrow aspirate to >25%. Presence of extramedullary leukemia after achieving CRc or PR was also considered relapse.

Liver chemistry abnormalities

Seven patients had liver chemistry abnormalities that fit the numerical criteria for Hy's Law (alanine aminotransferase or aspartate aminotransferase >3 × upper limit of normal and total bilirubin >2 × upper limit of normal[3]). However, to be considered an actual Hy's Law case, no other reason to explain these abnormalities should be identified. In this study, all seven patients had at least one alternative concomitant factor associated with liver injury (eg, sepsis, massive transfusion following a major bleed, biliary sludge/cholecystitis/choledocholithiasis). Thus, none of these cases were considered to be quizartinib related (appendix p 20) and therefore do not represent Hy's Law cases. Furthermore, none of these patients died of liver failure.

References

1. Grimwade D, Walker H, Harrison G, et al. The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML 11 Trial. *Blood* 2001; **98:** 1312–20.
2. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol* 2003; **21**: 4642–9.
3. US Food and Drug Administration. Guidance for industry. Drug-induced liver injury: premarketing clinical evaluation. 2009. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm174090.pdf (accessed April 3, 2017).

Supplemental Table S1: **Patient enrollment sites, principal investigators, and patients enrolled per site**

Principal investigator(s)	Clinical trial site	Patients enrolled (N=333)
Jorge Cortes	University of Texas, MD Anderson Cancer Center	30
Alexander Perl	University of Pennsylvania Health System	21
Mark Levis	Johns Hopkins University	16
Michele Baccarani/Giovanni Martinelli	Azienda Ospedaliero–Universitaria di Bologna - Policlinico S. Orsola-Malpighi	14
Tibor Kovacsovics	Oregon Health and Science University	13
Hartmut Döhner	Universitätsklinikum Ulm	13
Philippe Rousselot	Centre Hospitalier de Versailles	9
Björn Steffen	Klinikum der Johann Wolfgang-Goethe-Universität	8
Elihu Estey	Seattle Cancer Care Alliance	7
Hamid Sayar	Indiana University Simon Cancer Center	7
Stephen Strickland	Vanderbilt-Ingram Cancer Center	7
Hervé Dombret	Hôpital Saint Louis	7
Jessica Altman	Northwestern Medical Faculty Foundation	6
Alwin Krämer	Uniklinik Heidelberg, Medizinische Klinik und Poliklinik V	6
Claudia Baldus	Charité Universitätsmedizin Berlin	6
Micheal Heuser/Jürgen Krauter	Medizinische Hochschule Hannover	6
Edo Vellenga	Universitair Medisch Centrum Groningen	6
Nigel Russell	Nottingham City Hospital NHS Trust	6
Ivana Gojo	University of Maryland	5
Neil Shah	University of California San Francisco Medical Center	5
Eunice Wang	Roswell Park Cancer Institute	5
David Claxton	Penn State Health Milton S. Hershey Medical Center	5
Norbert Vey	Institut Paoli Calmettes Centre Régional de Lutte Contre le Cancer	5
Arnaud Pigneux	Hôpital Haut Leveque, Service des Maladies du Sang, Centre Francois Magendie	5
Bruno Quesnel	Hôpital Claude Huriez, Service des Maladies du Sang	5
Daniel Lipka	Klinik der Otto-Von-Guericke-Universität Magdeburg	5
Richard Larson	University of Chicago	4
Rod Ramchandren	Karmanos Cancer Institute	4
Mark Minden	Princess Margaret Hospital	4
Christian Recher	Centre Hospitalier Universitaire Purpan	4
Jean-Yves Cahn	Centre Hospitalier Universitaire Grenoble Hôpital Michalon	4
Katharina Götze	Klinikum Rechts der Isar der Technischen Universität München	4
Monica Bocchia	Azienda Ospedaliero Universitaria Senese, Policlinico S. Maria alle Scotte	4
Jürgen Kuball	Universitair Medisch Centrum Utrecht	4
Gary Schiller	University of California Los Angeles Medical Center	3
Jean-Pierre Marie	Hôpital Hotel Dieu	3
Stéphane Lepetre	Centre Henri-Becquerel (C.R.L.C.C.), Department of Hematology	3
Pascal Turlure	Centre Hospitalier Universitaire Limoges	3
Markus Schaich	Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden	3
Marco Gobbi	Azienda Ospedaliera Universitaria San Martino	3
Maria Belén Vidriales	Hospital Universitario de Salamanca, Hospital Clinico, Servicio de Hematología	3
David Bowen	Saint James's University Hospital	3
Mark Litzow	Mayo Clinic–Rochester	2
Katarzyna Jamieson	University of Iowa Hospitals and Clinics	2
Norbert Ifrah	Centre Hospitalier Universitaire d'Angers	2
Sebastian Scholl	Universitätsklinikum Jena	2
Andreas Neubauer	Klinikum der Philipps–Universtät Marburg	2
Carsten Müller-Tidow	Universitätsklinikum Münster	2
Jörg Westermann	Charité Campus Virchow Klinikum	2
Daniela Cilloni	University of Turin, San Luigi Gonzaga Hospital	2
Frances Di Raimondo	Ospedale Ferrarotto	2
Andrzej Lange	Dolnoslaskie Centrum Transplantacji Komórkowych z Krajowym Bankiem Dawców Szpiku	2
David Gallardo	Instituto Catalán de Oncología-Hospital Universitari de Girona “Dr. Josep Trueta"	2
Jordi Esteve Reyner	Hospital Clinic I Provincial - Servicio de Hematología y Hemoterapia	2
Albert Oriol Rocafiguera	Institut Catalá de Oncología, Hospital Universitari Germans Trias i Pujol, Servicio de Hematología	2
Jenny Craig	Addenbrooke's Hospital	2
Sahra Ali	Castle Hill Hospital	2
Harry Erba	University of Michigan Health System	1
Ryan Mattison	University of Wisconsin Hospital and Clinics	1
Sanford Kempin	Saint Vincent's Comprehensive Cancer Center	1
Xavier Thomas	Hôpital Edouard Herriot, Service Hématologie	1
Bruno Lioure	Centre Hospitalier Régional Universitaire, Hôpital de Hautepierre	1
Francis Witz	Centre Hospitalier Universitaire Nancy, Hôpital Brabois Adultes	1
Richard Noppeney	Universitätsklinikum Essen	1

Eva Lengfelder	Universitätsmedizin Mannheim	1
Volker Kunzmann	Universitätsklinikum Würzburg	1
Dietger Niederwieser	Universitätsklinikum Leipzig	1
Norbert Schmitz	Asklepios Klinik Saint Georg	1
Emanuele Angelucci	Presidio Ospedaliero "A. Businco" - Centro di Riferimento Oncologico Regionale	1
Domenico Russo	Azienda Ospedaliera Spedali Civili di Brescia	1
Anna Candoni	Azienda Ospedaliero Universitaria S. Maria della Misericordia di Udine	1
José Rifón Roca	Clínica Universitaria de Navarra, Servicio de Hematología	1
Angela Figurea	Hospital de la Princesa, Servicio de Hematologia	1
Miguel Sanz Alonso	Hospital La Fe, Servicio de Hematología	1
Gabriela Rodriguez Macías	Hospital General Universitario Gregorio Marañon	1
Katy Rezvani	Hammersmith Hospital, Department of Hematology	1

Supplemental Table S2a: **Response to quizartinib compared with response to prior therapy in FLT3-ITD–positive and FLT3-ITD–negative patients from cohort 1**

	Best response to quizartinib				
Best response to prior AML therapy	**CRc n (%)**	**PR n (%)**	**NR n (%)**	**Unknown n (%)**	**Total N**
FLT3-ITD–positive patients					
Patients with relapsed disease					
CRc	41 (60)	12 (18)	13 (19)	2 (3)	68
*Patients with refractory disease**					
PR	2 (29)	4 (57)	1 (14)	0	7
NR	18 (51)	7 (20)	6 (17)	4 (11)	35
Unknown prior response	2 (100)	0	0	0	2
FLT3-ITD–negative patients					
Patients with relapsed disease					
CRc	6 (26)	3 (13)	10 (43)	4 (17)	23
*Patients with refractory disease**					
PR	2 (67)	0	1 (33)	0	3
NR	8 (44)	1 (6)	6 (33)	3 (17)	18
Unknown prior response	0	0	0	0	0

AML=acute myeloid leukemia. CRc=composite complete remission. FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication. NR=no response. PR=partial remission.

*Refractoriness was defined as a failure to achieve a CRc after one or two cycles of induction chemotherapy, ie, those with a PR or NR as the best response to prior AML therapy.

Supplemental Table S2b: **Response to quizartinib compared with response to prior therapy in FLT3-ITD–positive and FLT3-ITD–negative patients from cohort 2**

	Best response to quizartinib				
Best response to prior AML therapy	**CRc n (%)**	**PR n (%)**	**NR n (%)**	**Unknown n (%)**	**Total N**
FLT3-ITD–positive patients					
Patients with relapsed disease					
CRc	21 (43)	15 (31)	6 (12)	7 (14)	49
*Patients with refractory disease**					
PR	2 (29)	1 (14)	4 (57)	0	7
NR	39 (49)	23 (29)	14 (18)	4 (5)	80
Unknown prior response	0	0	0	0	0
FLT3-ITD–negative patients					
Patients with relapsed disease					
CRc	3 (30)	1 (10)	6 (60)	0	10
*Patients with refractory disease**					
PR	0	0	0	0	0
NR	9 (30)	5 (17)	10 (33)	6 (20)	30
Unknown prior response	0	0	0	0	0

AML=acute myeloid leukemia. CRc=composite complete remission. FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication. NR=no response. PR=partial remission.

*Relapsed/refractory refers to response to last line of therapy, or the latter of first- or second-line therapy, including salvage chemotherapy or transplant. For patients who received other lines of therapy subsequent to second-line therapy, relapsed/refractory refers to response to second-line therapy.

†Refractoriness was defined as a failure to achieve a CRc, ie, those with a PR or NR as the best response to last prior AML therapy.

Supplemental Table S3a: **Response to quizartinib based on *FLT3* allele frequency in FLT3-ITD–positive patients from cohort 1**

	***FLT3* allele frequency**		
Response	**>10% to <25% (n=26)**	**≥25% to ≤50% (n=54)**	**>50% (n=32)**
CRc, n (%)	10 (38)	30 (56)	23 (72)
CR	0	3 (6)	0
CRp	2 (8)	1 (2)	1 (3)
CRi	8 (31)	26 (48)	22 (69)
PR, n (%)	8 (31)	11 (20)	4 (13)
ORR (CRc + PR), n (%)	18 (69)	41 (76)	27 (84)
Median duration of CRc, weeks	16·6	12·1	12·1
95% CI, weeks	4·1–32·1	6·1–14·3	4·1–18·4
n	10	30	23

CR=complete remission. CRc=composite complete remission. CRi=complete remission with incomplete hematologic recovery. CRp=complete remission with incomplete platelet recovery. FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication. ORR=overall response rate. PR=partial remission.

Supplemental Table S3b: **Response to quizartinib based on *FLT3* allelic frequency in FLT3-ITD–positive patients from cohort 2**

	***FLT3* allelic frequency**		
Response	**>10% to <25% (n=28)**	**≥25% to ≤50% (n=62)**	**>50% (n=46)**
CRc, n (%)	12 (43)	25 (40)	25 (54)
CR	1 (4)	3 (5)	1 (2)
CRp	1 (4)	1 (2)	0
CRi	10 (36)	21 (34)	24 (52)
PR, n (%)	10 (36)	18 (29)	11 (24)
ORR (CRc + PR), n (%)	22 (79)	43 (69)	36 (78)
Median duration of CRc, weeks	27·0	12·1	10·6
95% CI, weeks	4·0–64·0	8·1–19·1	6·6–11·3
n	12	25	25

CR=complete remission. CRc=composite complete remission. CRi=complete remission with incomplete hematologic recovery. CRp=complete remission with incomplete platelet recovery. FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication. ORR=overall response rate. PR=partial remission.

Supplemental Table S4: **Cumulative response assessment* by age in cohort 1**

Response	60–69 years (n=80)	≥70 years (n=75)	Total† (N=157)
Best response, n (%)			
CRc	41 (51)	39 (52)	80 (51)
CR	3 (4)	2 (3)	5 (3)
CRp	1 (1)	4 (5)	5 (3)
CRi	37 (46)	33 (44)	70 (45)
PR, n (%)	17 (21)	10 (13)	27 (17)
NR, n (%)	17 (21)	18 (24)	37 (24)
Unknown, n (%)	5 (6)	8 (11)	13 (8)
ORR (CRc + PR), n (%)	58 (73)	49 (65)	107 (68)
CRc after a single cycle, n/N (%)	23/41 (56)	17/39 (44)	40/80 (50)

CR=complete remission. CRc=composite complete remission. CRi=complete remission with incomplete hematologic recovery. CRp=complete remission with incomplete platelet recovery. FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication. NR=no response. ORR=overall response rate. PR=partial remission.

*****Best response was determined using response data from all quizartinib cycles.

†Two patients aged <60 years are not included in the age-specific counts, but are reflected in the total counts; these patients had a best response of NR (2/2=100%).

Supplemental Table S5: **Characteristics of FLT3-ITD–positive patients from cohort 2 who were bridged to HSCT following quizartinib treatment**

Characteristic	Bridged to HSCT after quizartinib treatment (n=47)	Not bridged to HSCT after quizartinib treatment (n=89)
Age		
Median, years (IQR)	46 (36–54)	52 (41–60)
≥60 years, n (%)	7 (15)	25 (28)
Achieved CR1 pre-quizartinib, n (%)	31 (66)	65 (73)
Duration of CR1*		
n	29	63
Median, weeks (IQR)	22 (16–44)	22 (12–44)
Any prior HSCT, n (%)†	8 (17)	33 (37)
No prior HSCT, n (%)†	39 (83)	56 (63)
Median baseline bone marrow blast count, % (IQR)	68 (45–90)	84 (61–91)
Best response to quizartinib, n (%)		
CRc	26 (55)	36 (40)
PR	19 (40)	20 (22)
NR	2 (4)	22 (25)
Unknown	0	11 (12)

CR1=first complete remission. CRc=composite complete remission. FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication. HSCT=hematopoietic stem cell transplant. IQR=interquartile range. NR=no response. PR=partial remission.

*Data are unavailable for two patients each in the "Bridged to HSCT after quizartinib treatment" and "Not bridged to HSCT after quizartinib treatment" groups.

†Prior HSCT includes allogeneic or other transplant.

Supplemental Table S6a: **Summary of adverse events in cohort 1**

Adverse event, n (%)	FLT3-ITD–positive (n=112)	FLT3-ITD–negative (n=44)	Total (N=157)*†	60–69 years (n=80)	≥70 years (n=75)
Any adverse event	112 (100)	44 (100)	157 (100)	80 (100)	75 (100)
Any treatment-related TEAE	106 (95)	39 (89)	146 (93)	74 (93)	70 (93)
Leading to discontinuation	20 (18)	3 (7)	23 (15)	11 (14)	12 (16)
Leading to death‡	8 (7)	2 (5)	10 (6)	2 (3)	8 (11)
30-day mortality (all causes)§	6 (5)	3 (7)	9 (6)	2 (3)	7 (9)

FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication. TEAE=treatment-emergent adverse event.
*One patient with unknown *FLT3*-ITD status is not included in the mutation level–specific counts, but is reflected in the total counts.
†Two patients aged <60 years are not included in the age-specific counts, but are reflected in the total counts.
‡Cause of death: FLT3-ITD–positive patients (acute hepatic failure, cellulitis, cerebral hemorrhage, encephalitis, febrile infection, pneumonia, sepsis syndrome, and septic shock) and FLT3-ITD–negative patients (pneumonia and sepsis).
§30-day mortality: 60 to 69 years (bacterial sepsis and subdural hematoma), ≥70 years (acute myeloid leukemia, cardiac failure, pneumonia [n=2], sepsis, systemic inflammatory response syndrome, and coma).

Supplemental Table S6b: **Summary of adverse events in cohort 2**

Adverse event, n (%)	FLT3-ITD–positive (n=136)	FLT3-ITD–negative (n=40)	Total (N=176)
Any adverse event	136 (100)	40 (100)	176 (100)
Any treatment-related TEAE	124 (91)	35 (88)	159 (90)
Leading to discontinuation	18 (13)	2 (5)	20 (11)
Leading to death*	7 (5)	1 (3)	8 (5)
30-day mortality (all causes)	7 (5)	1 (3)	8 (5)

FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication. TEAE=treatment-emergent adverse event.
*Cause of death: FLT3-ITD–positive patients (multiorgan failure, fungal pneumonia, hemorrhage, sepsis, febrile pancytopenia, lung infection, and neutropenia) and the FLT3-ITD–negative patient (cardiac arrest).

Supplemental Table S7: **TEAEs by grade in all patients (N=333)*†**

Adverse event, n (%)	Grade 1-2	Grade 3	Grade 4	Grade 5
Abdominal distension	-	1 (<1)	0	0
Abdominal pain	36 (11)	9 (3)	0	0
Abdominal pain upper	-	1 (<1)	0	0
Abscess neck	-	1 (<1)	0	0
Abscess rupture	-	1 (<1)	0	0
Accidental overdose	-	0	1 (<1)	0
Acinetobacter bacteremia	-	1 (<1)	0	0
Acute febrile neutrophilic dermatosis	-	5 (2)	0	0
Acute hepatic failure	-	0	0	1 (<1)
Acute myeloid leukemia	-	4 (1)	5 (2)	67 (20)
Acute respiratory failure	-	0	1 (<1)	0
Acute sinusitis	-	1 (<1)	0	0
Akathisia	-	1 (<1)	0	0
Alanine aminotransferase increased	-	11 (3)	1 (<1)	0
Anal abscess	-	1 (<1)	0	0
Anemia	-	76 (23)	11 (3)	0
Anorectal infection	-	1 (<1)	0	0
Anxiety	-	1 (<1)	0	0
Aplastic anemia	-	1 (<1)	0	0
Arthralgia	-	2 (1)	0	0
Arthritis	-	1 (<1)	0	0
Arthritis bacterial	-	0	1 (<1)	0
Aspartate aminotransferase increased	-	3 (1)	0	0
Aspergillosis	-	2 (1)	0	0
Asthenia	42 (13)	24 (7)	0	0
Atrial fibrillation	-	8 (2)	0	0
Autoimmune thrombocytopenia	-	1 (<1)	0	0
Azotemia	-	0	1 (<1)	0
Back pain	-	8 (2)	0	0
Bacteremia	-	8 (2)	1 (<1)	1 (<1)
Bacterial sepsis	-	1 (<1)	1 (<1)	2 (1)
Bladder pain	-	1 (<1)	0	0
Blood alkaline phosphatase increased	-	3 (1)	0	0
Blood bilirubin increased	-	6 (2)	1 (<1)	0
Blood calcium decreased	-	1 (<1)	0	0
Blood creatinine increased	-	2 (1)	0	0
Blood phosphorus decreased	-	2 (1)	0	0
Blood potassium decreased	-	1 (<1)	0	0
Blood uric acid increased	-	1 (<1)	0	0
Bone marrow failure	-	4 (1)	1 (<1)	0
Bone pain	-	2 (1)	0	0
Breast cellulitis	-	1 (<1)	0	0
Bronchitis	-	3 (1)	0	0
Bronchopulmonary aspergillosis	-	1 (<1)	0	1 (<1)
Bursitis	-	1 (<1)	0	0
Cachexia	-	1 (<1)	0	0
Candida sepsis	-	0	1 (<1)	0
Cardiac arrest	-	0	1 (<1)	2 (1)
Cardiac failure	-	1 (<1)	0	2 (1)
Cardiac failure congestive	-	0	1 (<1)	0
Cardiomegaly	-	1 (<1)	0	0
Cardiomyopathy	-	2 (1)	0	0
Cellulitis	-	8 (2)	0	1 (<1)
Cellulitis orbital	-	2 (1)	0	0
Central nervous system lesion	-	1 (<1)	0	0
Cerebral hemorrhage	-	0	1 (<1)	2 (1)
Cerebrovascular accident	-	3 (1)	0	0
Clostridial infection	-	3 (1)	0	0
Clostridium difficile colitis	-	6 (2)	1 (<1)	0
Coagulopathy	-	1 (<1)	0	0
Cognitive disorder	-	1 (<1)	0	0
Colitis	-	2 (1)	0	0
Coma	-	0	0	1 (<1)
Confusional state	-	3 (1)	0	0
Conjunctival hemorrhage	-	1 (<1)	0	0
Constipation	68 (20)	2 (1)	0	0
Convulsion	-	1 (<1)	0	0

Cough	63 (19)	0	0	0
C-reactive protein increased	-	4 (1)	0	0
Cytomegalovirus infection	-	1 (<1)	0	0
Death	-	0	0	1 (<1)
Decreased appetite	81 (24)	9 (3)	0	0
Deep vein thrombosis	-	1 (<1)	0	0
Dehydration	-	6 (2)	1 (<1)	0
Delirium	-	1 (<1)	0	0
Dental caries	-	2 (1)	0	0
Depression	-	1 (<1)	0	0
Device-related infection	-	12 (4)	0	0
Diabetes mellitus	-	1 (<1)	0	0
Diarrhea	122 (37)	14 (4)	0	0
Disseminated intravascular coagulation	-	0	1 (<1)	1 (<1)
Dizziness	45 (14)	0	0	0
Dysgeusia	78 (23)	0	0	0
Dyspepsia	53 (16)	2 (1)	0	0
Dysphagia	-	2 (1)	0	0
Dyspnea	44 (13)	7 (2)	3 (1)	0
Dysuria	-	1 (<1)	0	0
Eating disorder	-	1 (<1)	0	0
Edema	-	1 (<1)	0	0
Edema peripheral	88 (26)	3 (1)	0	0
Ejection fraction decreased	-	1 (<1)	0	0
Electrocardiogram QT prolonged	63 (19)	34 (10)	1 (<1)	0
Encephalitis	-	0	0	1 (<1)
Endotracheal intubation complication	-	1 (<1)	0	0
Enterobacter bacteremia	-	1 (<1)	0	0
Enterobacter infection	-	1 (<1)	0	0
Enterococcal infection	-	4 (1)	0	0
Enterocolitis	-	1 (<1)	0	0
Enterocolitis infectious	-	1 (<1)	0	0
Epistaxis	51 (15)	7 (2)	0	0
Erythema nodosum	-	1 (<1)	0	0
Escherichia bacteremia	-	2 (1)	0	0
Escherichia infection	-	1 (<1)	0	0
Escherichia sepsis	-	0	1 (<1)	0
Escherichia urinary tract infection	-	1 (<1)	0	0
Esophagitis	-	2 (1)	0	0
Eye hemorrhage	-	2 (1)	0	0
Eyelid bleeding	-	1 (<1)	0	0
Failure to thrive	-	1 (<1)	0	0
Fatigue	95 (29)	17 (5)	1 (<1)	0
Febrile bone marrow aplasia	-	3 (1)	1 (<1)	1 (<1)
Febrile infection	-	0	0	1 (<1)
Febrile neutropenia	-	124 (37)	13 (4)	0
Flank pain	-	1 (<1)	0	0
Fluid overload	-	1 (<1)	0	0
Fungal infection	-	2 (1)	0	0
Gastric hemorrhage	-	1 (<1)	0	0
Gastritis	-	2 (1)	0	0
Gastroenteritis	-	2 (1)	0	0
Gastroenteritis viral	-	1 (<1)	0	0
Gastroesophageal reflux disease	-	3 (1)	0	0
Gastrointestinal hemorrhage	-	7 (2)	3 (1)	0
Gastrointestinal infection	-	1 (<1)	0	0
General physical health deterioration	-	7 (2)	1 (<1)	2 (1)
Gingival bleeding	-	1 (<1)	0	0
Gingival hyperplasia	-	1 (<1)	0	0
Gingival infection	-	1 (<1)	0	0
Graft versus host disease in intestine	-	1 (<1)	0	0
Headache	41 (12)	5 (2)	0	0
Hematoma	-	4 (1)	1 (<1)	0
Hematoma infection	-	1 (<1)	0	0
Hematuria	-	2 (1)	0	0
Hemoglobin decreased	-	3 (1)	0	0
Hemoptysis	-	2 (1)	0	0
Hemorrhage	-	0	0	1 (<1)
Hemorrhage intracranial	-	0	1 (<1)	4 (1)
Hemorrhagic stroke	-	0	0	1 (<1)

Hemorrhoids	-	2 (1)	0	0
Hepatic enzyme increased	-	1 (<1)	0	0
Hepatic failure	-	0	0	1 (<1)
Hepatic infection	-	1 (<1)	0	0
Hepatocellular injury	-	1 (<1)	0	0
Herpes simplex	-	1 (<1)	0	0
Herpes virus infection	-	1 (<1)	0	0
Herpes zoster	-	3 (1)	0	0
Hyperbilirubinemia	-	3 (1)	1 (<1)	0
Hyperglycemia	-	8 (2)	0	0
Hypermagnesemia	-	2 (1)	0	0
Hypernatremia	-	1 (<1)	1 (<1)	0
Hypersensitivity	-	1 (<1)	0	0
Hypertension	-	5 (2)	0	0
Hyperthermia	-	1 (<1)	0	0
Hypertrophy	-	1 (<1)	0	0
Hyperuricemia	-	1 (<1)	0	0
Hypoalbuminemia	-	2 (1)	0	0
Hypocalcemia	-	3 (1)	3 (1)	0
Hypoglycemia	-	1 (<1)	1 (<1)	0
Hypokalemia	45 (14)	13 (4)	3 (1)	0
Hypomagnesemia	35 (11)	0	1 (<1)	0
Hyponatremia	-	9 (3)	0	0
Hypophosphatemia	-	6 (2)	0	0
Hypotension	-	10 (3)	0	0
Hypoxia	-	3 (1)	0	0
Ileitis	-	0	0	1 (<1)
Incontinence	-	1 (<1)	0	0
Infection	-	1 (<1)	1 (<1)	1 (<1)
Inguinal hernia	-	1 (<1)	0	0
Intraventricular hemorrhage	-	0	0	1 (<1)
Joint effusion	-	1 (<1)	0	0
Klebsiella bacteremia	-	1 (<1)	0	0
Klebsiella infection	-	1 (<1)	0	0
Laceration	-	2 (1)	0	0
Large intestine perforation	-	0	1 (<1)	0
Laryngitis	-	1 (<1)	0	0
Leukemic infiltration brain	-	2 (1)	0	0
Leukocytosis	-	3 (1)	1 (<1)	0
Leukopenia	-	7 (2)	18 (5)	0
Liver function test abnormal	-	2 (1)	0	0
Lobar pneumonia	-	3 (1)	1 (<1)	0
Lower gastrointestinal hemorrhage	-	0	1 (<1)	0
Lower respiratory tract infection	-	0	1 (<1)	0
Lower respiratory tract infection fungal	-	1 (<1)	0	0
Lung disorder	-	1 (<1)	0	0
Lung infection	-	9 (3)	1 (<1)	1 (<1)
Lung infection pseudomonal	-	1 (<1)	0	0
Lymph node pain	-	1 (<1)	0	0
Lymphocyte count decreased	-	2 (1)	1 (<1)	0
Lymphohistiocytosis	-	1 (<1)	0	0
Lymphopenia	-	1 (<1)	0	0
Malaise	-	1 (<1)	0	0
Melena	-	1 (<1)	0	0
Memory impairment	-	1 (<1)	0	0
Meningitis bacterial	-	0	0	1 (<1)
Mental status changes	-	1 (<1)	0	0
Micrococcus infection	-	1 (<1)	0	0
Mouth hemorrhage	-	1 (<1)	0	0
Mouth ulceration	-	1 (<1)	0	0
Mucosal hemorrhage	-	1 (<1)	0	0
Mucosal infection	-	1 (<1)	0	0
Mucosal inflammation	-	5 (2)	0	0
Multiorgan failure	-	0	0	2 (1)
Muscle hemorrhage	-	1 (<1)	0	0
Muscle spasms	-	1 (<1)	0	0
Musculoskeletal chest pain	-	1 (<1)	0	0
Musculoskeletal pain	-	3 (1)	0	0
Myalgia	-	2 (1)	0	0
Myocardial infarction	-	0	1 (<1)	1 (<1)

Myocardial ischemia	-	1 (<1)	0	0
Myositis	-	1 (<1)	0	0
Nausea	169 (51)	9 (3)	0	0
Necrotizing fasciitis	-	0	1 (<1)	0
Nephrolithiasis	-	1 (<1)	0	0
Neutropenia	-	9 (3)	25 (8)	1 (<1)
Neutropenic colitis	-	1 (<1)	0	0
Neutropenic sepsis	-	1 (<1)	1 (<1)	0
Neutrophil count decreased	-	2 (1)	12 (4)	0
Non-Hodgkin's lymphoma	-	0	1 (<1)	0
Oral candidiasis	-	3 (1)	0	0
Oral herpes	-	2 (1)	0	0
Oral infection	-	1 (<1)	0	0
Osteomyelitis	-	1 (<1)	0	0
Oxygen saturation decreased	-	1 (<1)	0	0
Pain	-	7 (2)	0	0
Pain in extremity	38 (11)	2 (1)	0	0
Pallor	-	1 (<1)	0	0
Pancreatitis acute	-	1 (<1)	0	0
Pancytopenia	-	6 (2)	4 (1)	1 (<1)
Parainfluenza virus infection	-	1 (<1)	0	0
Performance status decreased	-	1 (<1)	0	0
Pericoronitis	-	1 (<1)	0	0
Periorbital cellulitis	-	1 (<1)	0	0
Peritonitis	-	1 (<1)	0	0
Peritonsillar abscess	-	1 (<1)	0	0
Petechiae	57 (17)	4 (1)	0	0
Pharyngeal inflammation	-	1 (<1)	0	0
Pharyngitis	-	2 (1)	0	0
Platelet count decreased	-	3 (1)	24 (7)	0
Pleural effusion	-	1 (<1)	1 (<1)	0
Pleuritic pain	-	1 (<1)	0	0
Pneumonia	-	31 (9)	6 (2)	7 (2)
Pneumonia aspiration	-	1 (<1)	0	0
Pneumonia fungal	-	5 (2)	1 (<1)	3 (1)
Pneumonia pneumococcal	-	1 (<1)	0	0
Pneumonia streptococcal	-	1 (<1)	0	0
Post procedural hemorrhage	-	1 (<1)	0	0
Postictal state	-	0	1 (<1)	0
Presyncope	-	1 (<1)	0	0
Procedural pain	-	1 (<1)	0	0
Proctalgia	-	1 (<1)	0	0
Pruritus	-	2 (1)	0	0
Pseudomonal bacteremia	-	1 (<1)	0	0
Pseudomonal sepsis	-	0	1 (<1)	0
Pseudomonas infection	-	2 (1)	0	0
Pulmonary alveolar hemorrhage	-	0	0	1 (<1)
Pulmonary congestion	-	1 (<1)	0	0
Pulmonary embolism	-	1 (<1)	0	0
Pulmonary edema	-	0	1 (<1)	0
Pyrexia	89 (27)	12 (4)	0	1 (<1)
Rash	47 (14)	1 (<1)	0	0
Rectal abscess	-	1 (<1)	0	0
Rectal hemorrhage	-	3 (1)	0	0
Renal failure	-	1 (<1)	0	0
Renal failure acute	-	1 (<1)	0	1 (<1)
Renal tubular disorder	-	1 (<1)	0	0
Respiratory arrest	-	0	1 (<1)	0
Respiratory distress	-	0	0	1 (<1)
Respiratory failure	-	0	2 (1)	2 (1)
Respiratory tract infection	-	1 (<1)	0	0
Respiratory tract infection fungal	-	0	0	1 (<1)
Rhinovirus infection	-	2 (1)	0	0
Scrotal infection	-	1 (<1)	0	0
Secretion discharge	-	1 (<1)	0	0
Sepsis	-	6 (2)	10 (3)	9 (3)
Sepsis syndrome	-	0	0	1 (<1)
Septic shock	-	2 (1)	2 (1)	3 (1)
Serratia bacteremia	-	1 (<1)	0	0
Sinus tachycardia	-	1 (<1)	0	0

Sinusitis	-	2 (1)	0	0
Sinusitis fungal	-	1 (<1)	0	0
Skin disorder	-	1 (<1)	0	0
Skin infection	-	3 (1)	0	0
Soft tissue infection	-	1 (<1)	0	0
Soft tissue necrosis	-	1 (<1)	0	0
Somnolence	-	2 (1)	0	0
Staphylococcal bacteremia	-	2 (1)	0	0
Staphylococcal infection	-	2 (1)	0	0
Staphylococcal sepsis	-	3 (1)	1 (<1)	0
Stomatitis	-	4 (1)	0	0
Subcutaneous abscess	-	1 (<1)	0	0
Subdural hematoma	-	1 (<1)	0	2 (1)
Swelling face	-	1 (<1)	0	0
Syncope	-	6 (2)	0	0
Systemic inflammatory response syndrome	-	0	0	1 (<1)
Thrombocytopenia	-	10 (3)	39 (12)	0
Thrombosis	-	1 (<1)	0	0
Tinnitus	-	1 (<1)	0	0
Tongue ulceration	-	1 (<1)	0	0
Tonsillar hemorrhage	-	1 (<1)	0	0
Torsades de pointes	-	0	1 (<1)	0
Toxic skin eruption	-	1 (<1)	0	0
Transaminases increased	-	1 (<1)	0	0
Troponin T increased	-	1 (<1)	0	0
Tumor lysis syndrome	-	2 (1)	0	0
Tumor pain	-	1 (<1)	0	0
Upper gastrointestinal hemorrhage	-	2 (1)	2 (1)	0
Upper respiratory tract infection	-	2 (1)	0	0
Urinary retention	-	2 (1)	0	0
Urinary tract infection	-	8 (2)	0	0
Urinary tract infection bacterial	-	2 (1)	0	0
Urinary tract infection enterococcal	-	1 (<1)	0	0
Urogenital disorder	-	1 (<1)	0	0
Urosepsis	-	1 (<1)	0	0
Vaginal hemorrhage	-	1 (<1)	0	0
Ventricular extrasystoles	-	1 (<1)	0	0
Ventricular tachycardia	-	1 (<1)	0	0
Viral skin infection	-	1 (<1)	0	0
Viral upper respiratory tract infection	-	1 (<1)	0	0
Vitamin D deficiency	-	1 (<1)	0	0
Vocal cord paralysis	-	1 (<1)	0	0
Vomiting	120 (36)	10 (3)	1 (<1)	0
Vulval abscess	-	1 (<1)	0	0
Vulval cellulitis	-	2 (1)	0	0
Vulvitis	-	1 (<1)	0	0
Vulvovaginal pain	-	1 (<1)	0	0
Weight decreased	-	1 (<1)	0	0
White blood cell count decreased	-	4 (1)	7 (2)	0
Wound	-	1 (<1)	0	0
Wound infection	-	1 (<1)	0	0

TEAE=treatment-emergent adverse event.

*The table displays TEAEs across both cohorts (N=333), regardless of relation to treatment. Grade 1-2 TEAEs that occurred in ≥10% of patients and all grade ≥3 TEAEs are presented.

†For patients experiencing multiple events of the same type, only the maximum grade is reported.

Supplemental Table S8: **Treatment-related TEAEs of any grade occurring in ≥20% of patients***

Adverse event, n (%)	Cohort 1 (n=157)	Cohort 2 (n=176)	Total (N=333)
Any treatment-related TEAE	146 (93)	159 (90)	305 (92)
Nausea	66 (42)	64 (36)	130 (39)
Electrocardiogram QT prolonged	40 (26)	56 (32)	96 (29)
Fatigue	49 (31)	39 (22)	88 (26)
Vomiting	37 (24)	50 (28)	87 (26)
Anemia	39 (25)	45 (26)	84 (25)
Febrile neutropenia	34 (22)	44 (25)	78 (23)
Diarrhea	39 (25)	37 (21)	76 (23)
Dysgeusia	38 (24)	31 (18)	69 (21)

TEAE=treatment-emergent adverse event.

*For each type of event, patients were included only once, even if they experienced multiple events of that type. Treatment-related TEAEs were those considered to be definitely, probably, or possibly related to treatment.

Supplemental Table S9: **All on-study causes of death***

Cause of death, n (%)	**Total (N=333)**
Acute myeloid leukemia disease progression	71 (21)
Sepsis	12 (4)
Intracranial hemorrhage	7 (2)
Pneumonia	7 (2)
Fungal infection	4 (1)
Cardiac failure	3 (1)
Dyspnea	3 (1)
Hepatic injury	2 (1)
Unknown	2 (1)
Cellulitis	1 (<1)
Coma	1 (<1)
General physical health deterioration	1 (<1)
Hemorrhage	1 (<1)
Ileitis	1 (<1)
Meningitis (bacterial)	1 (<1)
Multiorgan failure	1 (<1)
Myocardial ischemia	1 (<1)
Neutropenia	1 (<1)
Pancytopenia	1 (<1)
Pleural effusion	1 (<1)
Pneumonitis	1 (<1)
Renal insufficiency	1 (<1)
Systemic inflammatory response syndrome	1 (<1)

*The on-study time frame includes the 30-day follow-up period.

Supplemental Table S10: **Clinically significant liver chemistry laboratory values**

Parameter	Criteria	Cohort 1 (n=157)	Cohort 2 (n=176)	Total (N=333)
ALT	>3 × ULN	19/155 (12·3)	35/173 (20·2)	54/328 (16·5)
	>5 × ULN	5/155 (3·2)	17/173 (9·8)	22/328 (6·7)
	>10 × ULN	2/155 (1·3)	2/173 (1·2)	4/328 (1·2)
	>20 × ULN	1/155 (0·6)	0	1/328 (0·3)
AST	>3 × ULN	8/154 (5·2)	18/175 (10·3)	26/329 (7·9)
	>5 × ULN	2/154 (1·3)	4/175 (2·3)	6/329 (1·8)
	>10 × ULN	0	0	0
	>20 × ULN	0	0	0
ALT or AST	>3 × ULN	21/156 (13·5)	41/175 (23·4)	62/331 (18·7)
Total bilirubin	>2 × ULN	9/156 (5·8)	13/175 (7·4)	22/331 (6·6)
Alkaline phosphatase	>1.5 × ULN	38/155 (24·5)	59/175 (33·7)	97/330 (29·4)
ALT or AST and total bilirubin	ALT or AST >3 × ULN and total bilirubin >2 × ULN	1/156 (0·6)	4/175 (2·3)	5/331 (1·5)*

ALT=alanine aminotransferase. AST=aspartate aminotransferase. ULN=upper limit of normal.
*A total of seven patients had liver chemistry abnormalities within Hy's range. Of these, two patients were identified after database lock, through a review and comparison of data from the trial and serious adverse event reporting systems.

Supplemental Table S11a: **Central analysis of ECG data from cohort 1***

Parameter, n (%)	Quizartinib dose		
	90 mg/day (n=77)	**135 mg/day (n=75)**	**200 mg/day (n=5)**
Maximum value of QTcF			
≤450 ms	8 (10)	19 (25)	1 (20)
>450 to ≤480 ms	30 (39)	23 (31)	1 (20)
>480 to ≤500 ms	24 (31)	19 (25)	2 (40)
>500 ms	14 (18)	11 (15)	1 (20)
Maximum change in QTcF from baseline			
≤30 ms	8 (10)	7 (9)	0
>30 to ≤60 ms	38 (49)	37 (49)	2 (40)
>60 ms[†]	30 (39)	28 (37)	3 (60)

ECG=electrocardiogram. QTcF=QT interval corrected using Fridericia's correction formula.

*Data unavailable as follows: one patient in each of the 90-mg/day and 135-mg/day dose groups did not have a change from baseline value and neither patient had a maximum postbaseline QTcF >450 ms; one additional patient in the 135-mg/day dose group had no postbaseline value, and another patient in this dose group had neither a baseline nor postbaseline value by central ECG.

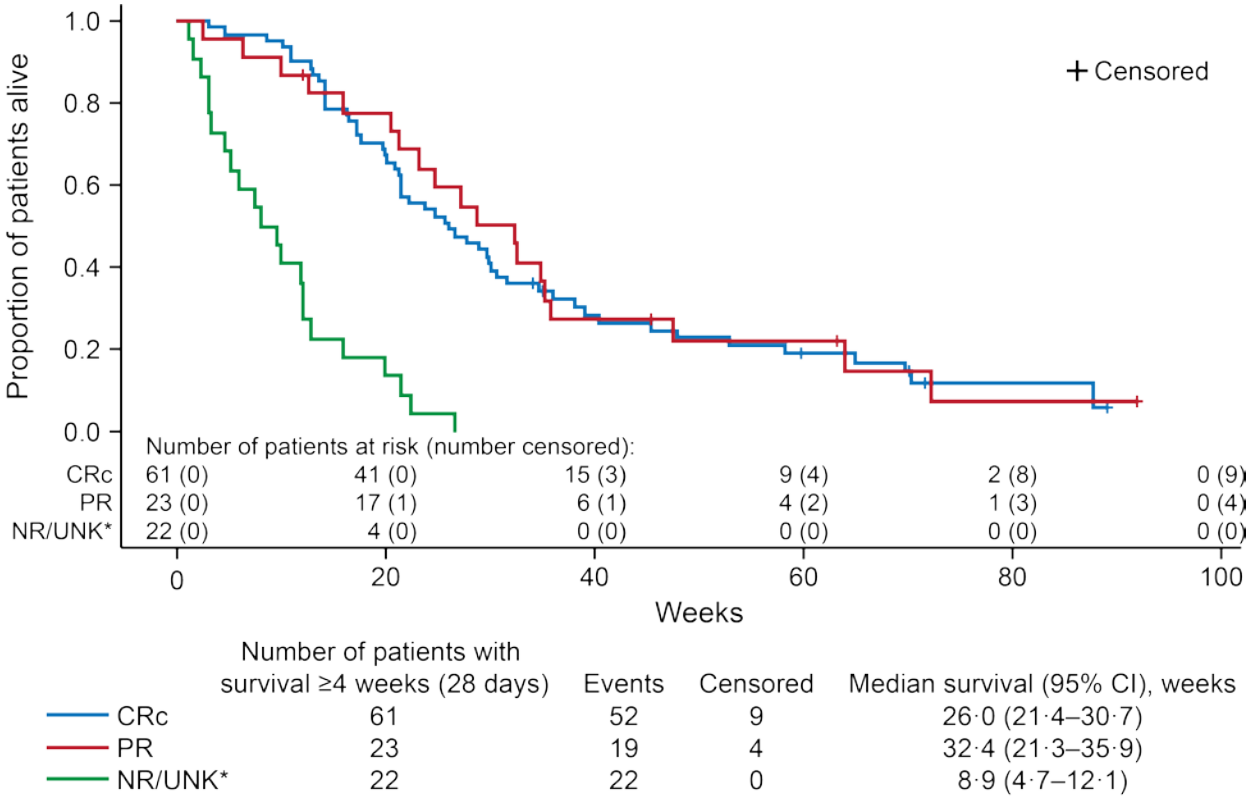
[†]There was only one reported case of grade 4 QTcF prolongation (change from baseline) in a female patient (receiving 90 mg/day of quizartinib) with multiple confounding factors, including electrolyte abnormalities, sepsis with episodes of respiratory arrest, and atrial fibrillation.

Supplemental Table S11b: **Central analysis of ECG data from cohort 2***

Parameter, n (%)	Quizartinib dose		
	90 mg/day (n=73)	**135 mg/day (n=91)**	**200 mg/day (n=12)**
Maximum value of QTcF			
≤450 ms	16 (22)	21 (23)	0
>450 to ≤480 ms	31 (42)	40 (44)	3 (25)
>480 to ≤500 ms	13 (18)	15 (16)	4 (33)
>500 ms	12 (16)	14 (15)	5 (42)
Maximum change in QTcF from baseline			
≤30 ms	5 (7)	11 (12)	0
>30 to ≤60 ms	36 (49)	45 (49)	1 (8)
>60 ms	31 (42)	34 (37)	11 (92)

ECG=electrocardiogram. QTcF=QT interval corrected using Fridericia's correction formula.
*Data unavailable as follows: one patient in each of the 90-mg/day and 135-mg/day dose groups did not have a change from baseline value and are not included in this analysis.

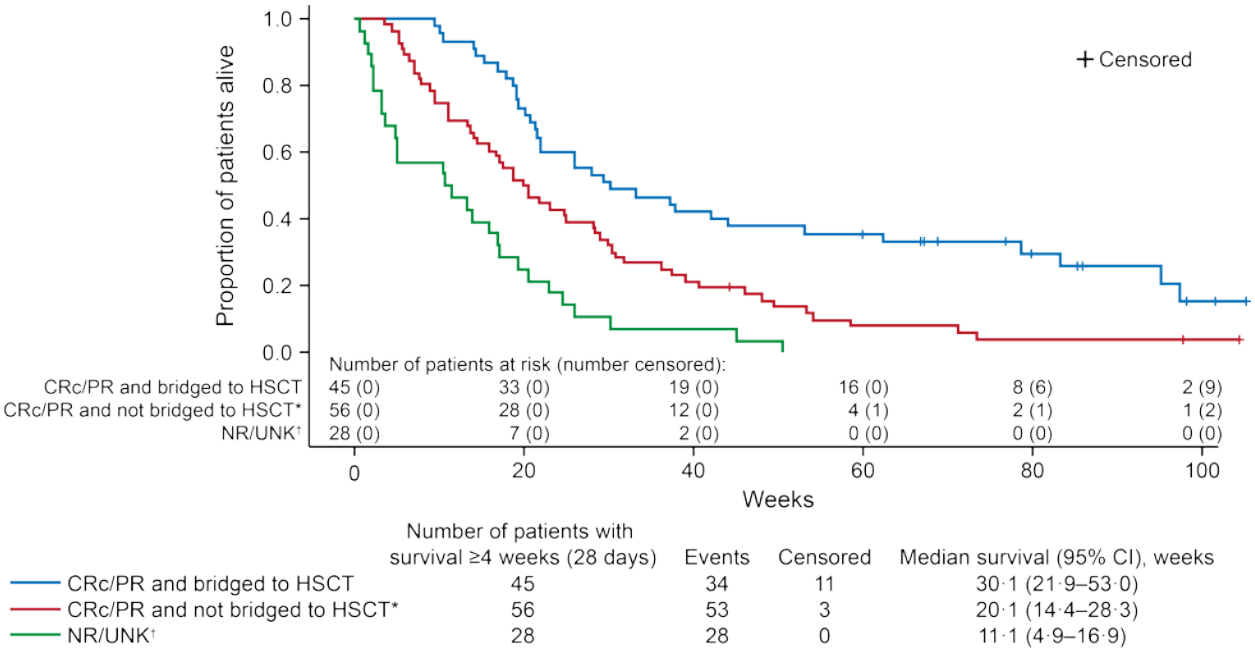
Supplemental Figure S1a: **Twenty-eight–day landmark analysis of OS in FLT3-ITD–positive patients in cohort 1 by response to quizartinib treatment.** Median OS was determined by Kaplan-Meier approximation. Patients who died prior to 28 days were excluded from this analysis.



	Number of patients with survival ≥4 weeks (28 days)	Events	Censored	Median survival (95% CI), weeks
CRc	61	52	9	26·0 (21·4–30·7)
PR	23	19	4	32·4 (21·3–35·9)
NR/UNK*	22	22	0	8·9 (4·7–12·1)

CRc=composite complete remission. FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication. NR=no response. OS=overall survival. UNK=unknown. PR=partial remission.
*In addition to patients with a nonresponse, the NR/UNK category includes patients whose response was unknown. Patients classified as unknown did not have a measurable posttreatment bone marrow aspirate or biopsy.

Supplemental Figure S1b: **Twenty-eight–day landmark analysis of OS in FLT3-ITD–positive patients in cohort 2 by response to quizartinib treatment and HSCT status.** Median OS was determined by Kaplan-Meier approximation. Patients who died prior to 28 days were excluded from this analysis.



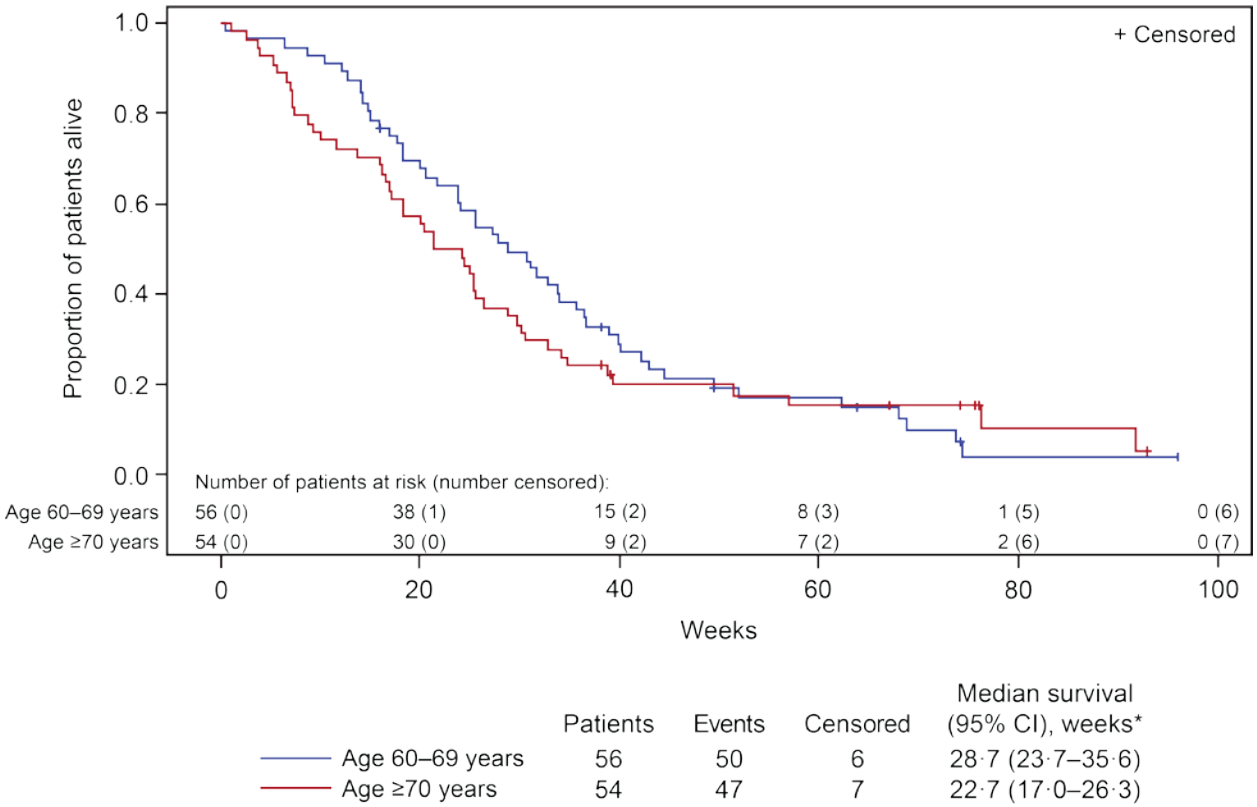
	Number of patients with survival ≥4 weeks (28 days)	Events	Censored	Median survival (95% CI), weeks
CRc/PR and bridged to HSCT	45	34	11	30·1 (21·9–53·0)
CRc/PR and not bridged to HSCT*	56	53	3	20·1 (14·4–28·3)
NR/UNK†	28	28	0	11·1 (4·9–16·9)

CRc=composite complete remission. FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication. HSCT=hematopoietic stem cell transplant. NR=no response. OS=overall survival. UNK=unknown. PR=partial remission.

*At the time of database cutoff, two patients from this cohort were still receiving quizartinib and are included in the "CRc/PR and not bridged to HSCT" group.

†In addition to patients with a nonresponse, the NR/UNK category includes patients whose response was unknown. Patients classified as unknown did not have a measurable posttreatment bone marrow aspirate or biopsy.

Supplemental Figure S2: **Kaplan-Meier plot of OS in FLT3-ITD–positive patients from cohort 1 who were aged 60 to 69 years and those aged ≥70 years.** FLT3-ITD–positive patients were stratified according to their age, and median OS was determined by Kaplan-Meier approximation.



	Patients	Events	Censored	Median survival (95% CI), weeks*
Age 60–69 years	56	50	6	28·7 (23·7–35·6)
Age ≥70 years	54	47	7	22·7 (17·0–26·3)

FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication. OS=overall survival.
*Two patients aged <60 years are not included in this analysis; however, they had a median OS equal to 25·9 weeks.