Quizartinib versus salvage chemotherapy in relapsed or refractory *FLT3*-ITD acute myeloid leukaemia (QuANTUM-R): a multicentre, randomised, controlled, open-label, phase 3 trial

Jorge E Cortes, Samer Khaled, Giovanni Martinelli, Alexander E Perl, Siddhartha Ganguly, Nigel Russell, Alwin Krämer, Hervé Dombret, Donna Hogge, Brian A Jonas, Anskar Yu-Hung Leung, Priyanka Mehta, Pau Montesinos, Markus Radsak, Simona Sica, Meena Arunachalam, Melissa Holmes, Ken Kobayashi, Ruth Namuyinga, Nanxiang Ge, Antoine Yver, Yufen Zhang, Mark J Levis

Lancet Oncol 2019; 20: 984–97

Published Online June 4, 2019 http://dx.doi.org/10.1016/S1470-2045(19)30150-0

This online publication has been corrected. The corrected version first appeared at thelancet.com/oncology on July 1, 2019

See Comment page 896

Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA (Prof J E Cortes MD); City of Hope National Medical Center, Duarte, CA, USA (S Khaled MD); Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori IRCCS, Meldola FC, Italy (Prof G Martinelli MD); Abramson Center of the University of Pennsylvania, Philadelphia, PA, USA (A E Perl MD); The University of Kansas Health System, Kansas City, KS, USA (Prof S Ganguly MD); Nottingham University Hospital, Nottingham, UK (Prof N Russell MD); Universität Heidelberg and German Cancer Research Center, Heidelberg, Germany (Prof A Krämer MD); University Paris Diderot, Paris, France (Prof H Dombret MD); Vancouver General Hospital, Vancouver, BC, Canada (Prof D Hogge MD); University of California Davis Comprehensive Cancer Center, Sacramento, CA, USA (B A Jonas MD); The University of Hong Kong, Pokfulam, Hong Kong (Prof A Y-H Leung MD); University Hospitals Bristol NHS Trust, Bristol, UK (P Mehta FRCPath); Hospital Universitari I Politècnic La Fe, València, Spain (P Montesinos MD); CIBERONC, Instituto de Salud Carlos III, Madrid, Spain (P Montesinos); University Medical Center of

Summary

Background Patients with relapsed or refractory *FLT3* internal tandem duplication (*FLT3*-ITD)-positive acute myeloid leukaemia have a poor prognosis, including high frequency of relapse, poorer response to salvage therapy, and shorter overall survival than those with FLT3 wild-type disease. We aimed to assess whether single-agent quizartinib, an oral, highly potent and selective type II FLT3 inhibitor, improves overall survival versus salvage chemotherapy.

Methods QuANTUM-R is a randomised, controlled, phase 3 trial done at 152 hospitals and cancer centres in 19 countries. Eligible patients aged 18 years or older with ECOG performance status 0–2 with relapsed or refractory (duration of first composite complete remission ≤6 months) *FLT3*-ITD acute myeloid leukaemia after standard therapy with or without allogeneic haemopoietic stem-cell transplantation were randomly assigned (2:1; permuted block size of 6; stratified by response to previous therapy and choice of chemotherapy via a phone-based and web-based interactive response system) to quizartinib (60 mg [30 mg lead-in] orally once daily) or investigator's choice of preselected chemotherapy: subcutaneous low-dose cytarabine (subcutaneous injection of cytarabine 20 mg twice daily on days 1–10 of 28-day cycles); intravenous infusions of mitoxantrone (8 mg/m² per day), etoposide (100 mg/m² per day), and cytarabine (1000 mg/m² per day on days 1–5 of up to two 28-day cycles); or intravenous granulocyte colony-stimulating factor (300 µg/m² per day or 5 µg/kg per day subcutaneously on days 1–5), fludarabine (intravenous infusion 30 mg/m² per day on days 2–6), cytarabine (intravenous infusion 2000 mg/m² per day on days 2–6), and idarubicin (intravenous infusion 10 mg/m² per day on days 2–4 in up to two 28-day cycles). Patients proceeding to haemopoietic stem-cell transplantation after quizartinib could resume quizartinib after haemopoietic stem-cell transplantation. The primary endpoint was overall survival in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT02039726, and follow-up is ongoing.

Findings Between May 7, 2014, and Sept 13, 2017, 367 patients were enrolled, of whom 245 were randomly allocated to quizartinib and 122 to chemotherapy. Four patients in the quizartinib group and 28 in the chemotherapy group were not treated. Median follow-up was 23·5 months (IQR 15·4–32·3). Overall survival was longer for quizartinib than for chemotherapy (hazard ratio 0·76 [95% CI 0·58–0·98; p=0·02]). Median overall survival was 6·2 months (5·3–7·2) in the quizartinib group and 4·7 months (4·0–5·5) in the chemotherapy group. The most common non-haematological grade 3–5 treatment-emergent adverse events (within ≤30 days of last dose or >30 days if suspected to be a treatment-related event) for quizartinib (241 patients) and chemotherapy (94 patients) were sepsis or septic shock (46 patients [19%] for quizartinib *vs* 18 [19%] for chemotherapy), pneumonia (29 [12%] *vs* eight [9%]), and hypokalaemia (28 [12%] *vs* eight [9%]). The most frequent treatment-related serious adverse events were febrile neutropenia (18 patients [7%]), sepsis or septic shock (11 [5%]), QT prolongation (five [2%]), and nausea (five [2%]) in the quizartinib group, and febrile neutropenia (five [5%]), sepsis or septic shock (four [4%]), pneumonia (two [2%]), and pyrexia (two [2%]) in the chemotherapy group. Grade 3 QT prolongation in the quizartinib group was uncommon (eight [3%] by central reading, ten [4%] by investigator report); no grade 4 events occurred. There were 80 (33%) treatment-emergent deaths in the quizartinib group (31 [13%] of which were due to adverse events) and 16 (17%) in the chemotherapy group (nine [10%] of which were due to adverse events).

Interpretation Treatment with quizartinib had a survival benefit versus salvage chemotherapy and had a manageable safety profile in patients with rapidly proliferative disease and very poor prognosis. Quizartinib could be considered a new standard of care. Given that there are only a few available treatment options, this study highlights the value of targeting the *FLT3*-ITD driver mutation with a highly potent and selective FLT3 inhibitor.

Funding Daiichi Sankyo.

Research in context

Evidence before this study

We searched PubMed and congress abstracts to identify studies of FLT3 inhibitors in relapsed or refractory acute myeloid leukaemia published between database inception and Dec 17, 2018, using the search terms "FLT3 inhibitor" AND "relapsed acute myeloid leukaemia" or "refractory acute myeloid leukaemia" AND "clinical trial", with no language restrictions. We selected articles that reported primary clinical trial data. Trials investigating the first-generation FLT3 inhibitors (lestaurtinib, midostaurin, and sorafenib) in relapsed or refractory acute myeloid leukaemia showed poor efficacy, with no improvement in response rate or poor duration of clinical benefit, particularly when each was investigated as single-agent therapy. In some cases, combinations with these first-generation inhibitors led to increased toxicity. By contrast, midostaurin in combination with chemotherapy in newly diagnosed disease resulted in a survival benefit, which led to recent US Food and Drug Administration and European Medicines Agency approvals. Next-generation inhibitors, including quizartinib, gilteritinib, and crenolanib, are under investigation in relapsed or refractory acute myeloid leukaemia and have shown promising results in phase 1 and 2 studies. However, results from large phase 3 trials of these agents have not been previously presented or published.

Added value of this study

Quizartinib is an oral, highly potent and selective type II FLT3 inhibitor. QuANTUM-R is a randomised phase 3 study comparing quizartinib with standard-of-care salvage chemotherapy in *FLT3*-ITD acute myeloid leukaemia and, to our knowledge, is the first to show a survival benefit with a FLT3 inhibitor in patients with relapsed or refractory (duration of first composite complete remission ≤6 months) *FLT3*-ITD acute myeloid leukaemia and the first to show a survival benefit for a FLT3 inhibitor given as a single agent in any setting of acute myeloid leukaemia.

Implications of all the available evidence

Single-agent quizartinib significantly improved overall survival versus salvage chemotherapy in patients with relapsed or refractory *FLT3*-ITD acute myeloid leukaemia and had a manageable safety profile. Results were similar to those of phase 2 trials of single-agent quizartinib in relapsed or refractory *FLT3*-ITD acute myeloid leukaemia and show a consistent effect across multiple trials. Taken together, these data highlight the benefit of targeting the *FLT3*-ITD mutation with quizartinib, a highly potent and selective type II FLT3 inhibitor, and show that quizartinib can be given as a single agent in the outpatient setting. Given the dismal prognosis and restricted options for treatment, these results could provide a new treatment option for patients with relapsed or refractory *FLT3*-ITD acute myeloid leukaemia.

Johannes Gutenberg University, Mainz, Germany (M Radsak MD); **Fondazione Policlinico Universitario A Gemelli-IRCCS, Istituto di Ematologia Università Cattolica Sacro Cuore, Rome, Italy** (S Sica MD); **Daiichi Sankyo, Basking Ridge, NJ, USA** (M Arunachalam PharmD, M Holmes BS, K Kobayashi MD, R Namuyinga MD, N Ge PhD, A Yver MD, Y Zhang PhD); **and The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA** (Prof M J Levis MD)

Correspondence to:
Prof Jorge Cortes, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
jcortes@mdanderson.org

Introduction

Patients with acute myeloid leukaemia harbouring *FLT3* internal tandem duplication (*FLT3*-ITD) have a poor prognosis,[1–3] characterised by high frequency of relapse, decreased response to salvage therapy, and shorter overall survival than patients with *FLT3* wild-type acute myeloid leukaemia.[3–5] *FLT3*-ITD occurs in about 25% of patients with newly diagnosed acute myeloid leukaemia,[1,6] inducing constitutive activation of the FLT3 receptor and triggering downstream pathways leading to leukaemic cell proliferation, impaired differentiation, and resistance to apoptosis.[7–9]

Quizartinib is a once-daily, oral, highly potent and selective, next-generation, type II FLT3 inhibitor that moderately inhibits KIT—another type III receptor tyrosine kinase—and has shown antitumour activity in *FLT3*-ITD acute myeloid leukaemia in animal models.[10] Quizartinib showed clinically significant single-agent antileukaemic activity in phase 2 trials,[11,12] including composite complete remission (CRc) in 46–56% of patients with relapsed or refractory *FLT3*-ITD acute myeloid leukaemia, and median overall survival of 20·9–27·3 weeks. Grade 3 QT interval prolongation, the dose-limiting toxicity in phase 1 studies,[13] was seen in 3–5% of patients treated with 30 mg and 60 mg daily quizartinib dihydrochloride.[12]

Here, we evaluated whether single-agent quizartinib improves overall survival versus standard-of-care salvage chemotherapy in patients with relapsed or refractory *FLT3*-ITD acute myeloid leukaemia.

Methods

Study design and participants

QuANTUM-R was a global, multicentre, randomised, controlled, open-label, phase 3 trial comparing quizartinib versus investigator's choice of salvage chemotherapy from three regimens. This trial was done at 152 hospitals and cancer centres in 19 countries. We enrolled patients aged 18 years or older with ECOG performance status 0–2 with *FLT3*-ITD primary acute myeloid leukaemia or acute myeloid leukaemia secondary to myelodysplastic syndromes who were refractory to or relapsed after at least one cycle of a standard anthracycline-containing or mitoxantrone-containing acute myeloid leukaemia therapy (duration of first CRc ≤6 months), with or without allogeneic haemopoietic stem cell transplant. First relapse was defined as achievement of CRc after initial therapy (with or without consolidation, maintenance, or haemopoietic stem-cell transplantation) followed by relapse; duration was measured from dates of confirmed response to identified relapse. Refractory acute myeloid leukaemia

was defined as no CRc and a reduction in bone marrow blasts of less than 50% after one cycle or no CRc after two cycles. Disease needed to be morphologically documented as defined by WHO criteria and was determined by pathology review at study sites. *FLT3*-ITD mutations were determined from peripheral blood or bone marrow aspirate by central laboratory assessment, using a polymerase chain reaction-based molecular assay (Navigate BioPharma Services, Carlsbad, CA, USA). *FLT3* status was confirmed with the commercially available LeukoStrat CDx *FLT3* Mutation Assay (Invivoscribe Technologies, San Diego, CA, USA).

Patients had to be eligible, by investigator's assessment, for preselected salvage chemotherapy, have discontinued previous acute myeloid leukaemia treatment before the start of study drug (except hydroxyurea or other treatments to control leukocytosis) for at least 2 weeks for cytotoxic agents or at least five half-lives for noncytotoxic agents, and have had total serum bilirubin of no more than 1·5 times the upper limit of normal and serum aspartate aminotransaminase or alanine aminotransaminase (or both) of no more than 2·5 times the upper limit of normal, serum creatinine of no more than 1·5 times the upper limit of normal or a glomerular filtration rate of more than 25 mL/min, and serum potassium, magnesium, and calcium within institutional normal limits. Exclusion criteria were acute promyelocytic leukaemia (acute myeloid leukaemia subtype M3); acute myeloid leukaemia secondary to prior chemotherapy for other neoplasms (except myelodysplastic syndromes); history of another malignancy (unless the patient had been disease free for ≥5 years); persistent clinically significant (grade >1) non-haematological toxicity from prior acute myeloid leukaemia therapy; clinically significant graft-versus-host disease or graft-versus-host disease requiring initiation of treatment or treatment escalation within 21 days, or persistent or clinically significant (grade >1) non-haematological toxicity related to haemopoietic stem-cell transplantation; or history of central nervous system involvement with acute myeloid leukaemia. We also excluded patients with clinically significant coagulation abnormalities or uncontrolled or clinically significant cardiovascular disease, defined as QT interval corrected using Fridericia's formula (QTcF) greater than 450 ms; bradycardia <50 beats per min; history of long QT syndrome, clinically relevant ventricular arrhythmias, or second-degree or third-degree heart block; myocardial infarction or uncontrolled angina pectoris within 6 months prior to screening; New York Heart Association class III or IV congestive heart failure; left ventricular ejection fraction of 45% or less or below the institutional lower limit of normal; uncontrolled hypertension; or complete left or right bundle branch block. Other exclusion criteria were receipt of major surgery or radiotherapy within 4 weeks of screening; active uncontrolled infection, hepatitis B or C, or clinically relevant liver disease; known infection with HIV; serious illness that could jeopardise safety or interfere with study objectives; unwillingness to receive infusion of blood products according to the protocol; pregnancy, breastfeeding, or unwillingness to use contraception (women of childbearing age or men with female partners of childbearing age); or refusal of permission to allow their general practitioner to be notified of study participation (UK only). Patients who received prior quizartinib or another FLT3-targeted therapy (excluding midostaurin and sorafenib) were ineligible. Sorafenib was initially allowed but was excluded after a protocol amendment on May 26, 2015.

The study protocol was approved by each site's institutional review board or ethics committee. All patients provided written informed consent, as per the Declaration of Helsinki and Good Clinical Practice.

Randomisation and masking

Patients were randomly assigned (2:1) to receive single-agent quizartinib or the investigator's choice of one of three preselected chemotherapy regimens: low-dose cytarabine (LoDAC); mitoxantrone, etoposide, and cytarabine (MEC); or fludarabine, cytarabine, and granulocyte colony-stimulating factor with idarubicin (FLAG-IDA). Randomisation was stratified by response to previous therapy (relapsed with no prior haemopoietic stem-cell transplantation, relapsed with prior haemopoietic stem-cell transplantation, or refractory) and preselected chemotherapy (high-intensity chemotherapy [ie, MEC or FLAG-IDA] or low-intensity chemotherapy [ie, LoDAC]) using a permuted block size of six, and was implemented using a phone-based and web-based interactive response system. The statistical vendor generated the randomisation codes, which were given to the interactive response system vendor to do the randomisation. Study site staff enrolled patients.

This trial was open label; neither investigators nor participants were masked to treatment allocation. The funder of the study did not have access to aggregate data until database lock. At database lock for the final analysis, randomisation codes were released to the funder's statistician.

Procedures

Patients randomly assigned to quizartinib received a starting dose of 30 mg quizartinib dihydrochloride orally once daily (equivalent to 26·5 mg quizartinib free base; Patheon France SAS, Bourgoin-Jallieu, France), which was increased to 60 mg quizartinib dihydrochloride once daily (equivalent to 53·0 mg quizartinib free base) on day 16 (±1 day) of cycle 1 if the patient's mean QTcF interval of triplicate ECG readings was 450 ms or shorter on or before day 15 of cycle 1 (±1 day). Triplicate ECGs were obtained at prespecified timepoints before and during therapy and were reviewed by investigators and central cardiologists. Full details of ECG procedures are given in the appendix (pp 5–6).

See Online for appendix

Patients receiving concurrent strong CYP3A inhibitors had a reduced starting dose of 20 mg quizartinib dihydrochloride once daily (equivalent to 17·7 mg quizartinib free base), which was increased to 30 mg (26·5 mg free base) once daily if the same QT interval criteria were met. Quizartinib was given in continuous 28-day cycles with or without food. Stepwise dose reductions were permitted: 53·0 mg to 26·5 mg to 17·7 mg free base daily for patients with CYP3A inhibitor initiation, QT prolongation, non-haematological toxicity, or myelosuppression. Additional quizartinib dose-modification details are given in the appendix (p 4).

The relative dose intensity for patients treated with quizartinib was defined as the actual daily dose divided by the planned daily dose (adjusted for patients receiving dose increases on day 16 [±1 day] per the dose-escalation criteria).

For patients randomly assigned to the quizartinib group who underwent haemopoietic stem-cell transplantation, quizartinib was discontinued 7 days before the start of a conditioning regimen. Decisions to transplant and to resume therapy after transplant were made at the discretion of the investigators. Treatment with quizartinib after haemopoietic stem-cell transplantation was allowed per protocol starting at 30–100 days after the transplant, provided that certain criteria were met (appendix p 4). After haemopoietic stem-cell transplantation, patients started quizartinib at 26·5 mg or 17·7 mg free base daily and escalated to 53·0 mg or 26·5 mg free base daily using the same criteria as for initial treatment.

Patients assigned to salvage chemotherapy received either LoDAC (subcutaneous injection of cytarabine 20 mg twice daily on days 1–10 of 28-day cycles), MEC (intravenous infusions of mitoxantrone 8 mg/m² per day, etoposide 100 mg/m² per day, and cytarabine 1000 mg/m² per day on days 1–5 of up to two 28-day cycles), or FLAG-IDA (granulocyte colony-stimulating factor intravenous infusion 300 µg/m² per day or 5 µg/kg per day subcutaneously on days 1–5, fludarabine intravenous infusion 30 mg/m² per day on days 2–6, cytarabine intravenous infusion 2000 mg/m² per day on days 2–6, and intravenous infusion idarubicin 10 mg/m² per day on days 2–4 in up to two 28-day cycles).

Quizartinib or LoDAC was given until lack of benefit, unacceptable toxicity, or discontinuation for haemopoietic stem-cell transplantation. Up to two cycles of MEC or FLAG-IDA were permitted; the second cycle was given at the discretion of the investigator if clinical benefit without remission was seen during the first cycle (appendix p 19).

Patients underwent bone marrow testing at screening (within 14 days of randomisation). Patients receiving quizartinib were assessed for response on day 1 of cycle 2 and subsequent cycles unless the patient had achieved a CRc. In patients who achieved CRc, bone marrow testing was done after every three cycles (unless evidence of relapse was seen) and at the end of treatment. Patients receiving MEC or FLAG-IDA received one 28-day cycle of therapy and were assessed at day 29 (±14 days).

Physical examinations, laboratory tests (including serum chemistry, urinalysis, and haematology assessments), and assessments of vital signs and adverse events were done throughout the study. We assessed adverse events and serious adverse events at the 30-day follow-up visit.

Safety analyses included all patients who received at least one dose of study treatment. Treatment-emergent adverse events included adverse events reported during study treatment or no more than 30 days after the last dose and adverse events reported greater than 30 days after if determined by an investigator to be treatment related. Per protocol, adverse events were graded in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4·03) and were coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology (version 16·1). Adverse events were grouped under clinically relevant terms using standard MedDRA methods (appendix p 7) for more sensitive and informative determination of the safety profile. We calculated patient-year exposure as the sum of the total exposure, in years, for all patients in each treatment group.

Treatment was withdrawn in the event of any intolerable adverse event related to study treatment, grade 4 QT prolongation, resting left ventricular ejection fraction of less than 45%, pregnancy, study termination, withdrawal of informed consent, or any clinical adverse event or laboratory test result indicating that study treatment was not in the patient's best interest. Patients could be withdrawn from the study at any time at the investigator's discretion.

Major protocol deviations were inclusion of patients who were neither refractory nor relapsed after no more than 6 months of a standard anthracycline-containing induction regimen; had a negative *FLT3*-ITD test result per the central laboratory; or were randomly assigned to a treatment group but not treated with any study medication. These patients were excluded from the per-protocol analysis set.

Outcomes

The primary endpoint was overall survival in the intention-to-treat population, defined as time from randomisation until death from any cause.

The secondary endpoint was event-free survival in the intention-to-treat population. Event-free survival was defined as the time from randomisation until documented failure to achieve CRc (both no response and partial remission were considered failure, with the event assigned on day 1 by prespecified protocol convention), relapse after CRc, or death from any cause, whichever occurred first. CRc comprised complete remission (CR), CR with incomplete platelet recovery, and CR with incomplete haematological recovery. CR with incomplete

haematological recovery and partial remission were assessed per sponsor-modified[11,12] International Working Group criteria (appendix p 5).[14] Prespecified exploratory endpoints assessed in this study were the proportions of patients achieving a CRc and CR, time to response, and transplantation rate. Other exploratory endpoints of leukaemia-free survival, QT-prolonging effects of quizartinib in relation to plasma drug concentrations, pharmacokinetics of quizartinib and its active metabolite (AC886), exposure–response relationship, resource use, identification of acute myeloid leukaemia-associated mutations, and pharmacogenomic and pharmacoproteomic determinations will be reported elsewhere. Responses were derived by the funder using an algorithm based on the collected laboratory data and were not centrally reviewed. Duration of CRc and time to CRc were added as exploratory endpoints after the study began, but before the database was locked. Outcome assessors were not masked to treatment allocation.

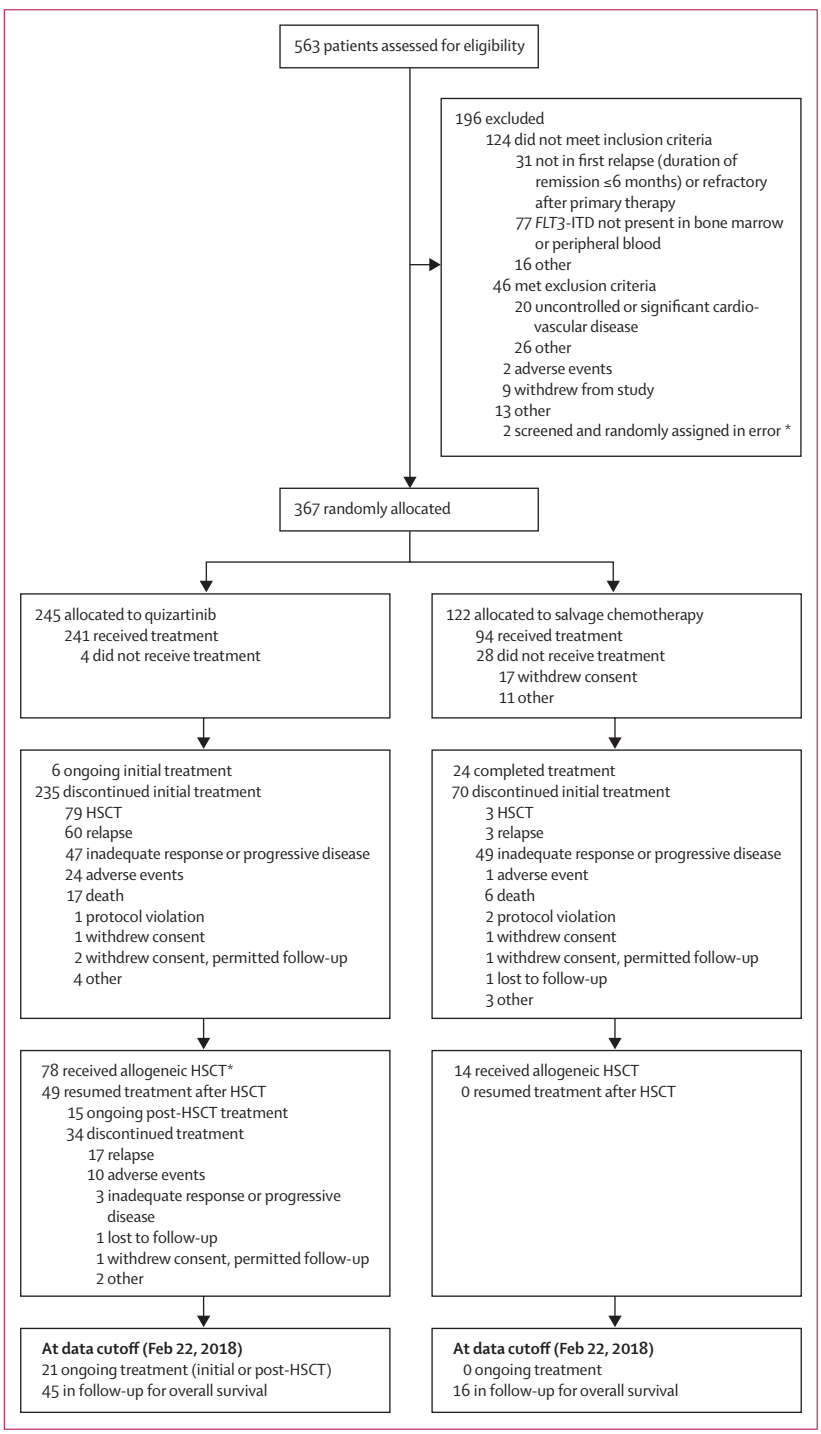


Figure 1: **Trial profile**
FLT3-ITD=FMS-related tyrosine kinase 3 internal tandem duplication. HSCT=haemopoietic stem cell transplantation. *Included twice in the assessed for eligibility box and included in both the excluded and randomly assigned boxes in error. †Received allogeneic HSCT without any intervening therapy for acute myeloid leukaemia not specified in the protocol.

Statistical analysis

Based on the assumption of a median overall survival of 6 months in the quizartinib group and 3·9 months in the chemotherapy group (hazard ratio [HR] 0·65), 280 deaths were required to ensure 90% power using a log-rank test and two-look (interim look at 140 events; final look at 280 events) group sequential Lan-DeMets design with an O'Brian-Fleming boundary for superior efficacy and a conditional power of 10% for futility at a 2·5% one-sided, cumulative significance level. The sample size calculation wording in the original protocol specified a 5%, two-sided calculation; however, this wording was inaccurate, and subsequently, a one-sided calculation at 2·5% was implemented to solely test for superiority of quizartinib, which is consistent with the primary aim of the study. With an assumed accrual of 19·2 patients per month, 10% dropout, and 2:1 randomisation, about 363 patients were required to reach the target event number within 17 months. The formal interim analysis was done by an independent statistical analysis centre and evaluated by an independent data monitoring committee.

Kaplan-Meier methods were used to summarise all time-to-event data (eg, overall survival, event-free survival, and duration of CRc). HRs were obtained from a stratified Cox proportional hazards model. For the primary and secondary outcomes, stratified log-rank test p values were provided for treatment comparison; tests were stratified with the same factors used in randomisation. No adjustments were made for multiple comparisons; therefore, p values for sensitivity analyses were calculated for descriptive purposes.

The intention-to-treat population included all patients who were allocated to treatment. The per-protocol analysis set included all patients in the intention-to-treat population who had no major protocol deviations that affected assessment of efficacy endpoints.

Three prespecified overall survival sensitivity es were done: in the per-protocol analysis set to exclude patients with major prespecified protocol deviations; by censoring overall survival at the haemopoietic stem-cell

transplantation date; and by censoring overall survival at receipt of other post-randomisation FLT3-inhibitor therapy. In addition, the primary endpoint was in predefined subgroups based on demographics analysed and baseline disease characteristics. Because more than 5% of patients in the chemotherapy group were allocated to treatment but were not treated, a prespecified analysis was done to compare overall survival in treated versus untreated patients. This analysis was added in an amendment to the statistical analysis plan to address any potential imbalance between study arms after the sponsor became aware that a notable number of patients in the overall pooled population were being randomly assigned and not treated. The SAP amendment occurred before database lock and before any final analyses were done. Event-free survival analyses were done in the intention-to-treat and per-protocol analysis sets. All analyses were done using SAS software (version 9.4). This trial is registered with ClinicalTrials.gov, number NCT02039726, and follow-up is ongoing.

Role of the funding source

The funder of the study had a role in study design, data analysis, data interpretation, and writing of the report, but not in data collection. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 7, 2014, and Sept 13, 2017, 367 patients were enrolled, of whom 245 were allocated to single-agent quizartinib and 122 to salvage chemotherapy (29 to LoDAC, 40 to MEC, and 53 to FLAG-IDA; figure 1, appendix p 19). 32 patients were allocated to treatment, but did not receive treatment (four [2%] in the quizartinib group and 28 [23%] in the chemotherapy group). 207 (86%) of 241 patients treated with quizartinib received an initial dose of 26·5 mg daily. 33 (14%) of 241 patients had an initial dose of 17·7 mg daily due to concomitant use of strong CYP3A inhibitors (n=31) or investigator choice (n=2). During initial therapy before haemopoietic stem-cell transplantation, 172 (71%) patients treated with quizartinib received protocol-planned dose increases owing to the absence of QT prolongation. By the cutoff date (Feb 22, 2018), which constituted the predefined final analysis, 239 patients in the quizartinib group and 122 in the chemotherapy group had completed or discontinued initial treatment; six patients were still receiving initial quizartinib and none were still receiving chemotherapy. The most common reasons for initial quizartinib discontinuation were haemopoietic stem-cell transplantation, relapse, and progressive disease or lack of response. The most common reasons for chemotherapy discontinuation were progressive disease or lack of response and completion of therapy per protocol (figure 1). Overall (including after haemopoietic stem-cell transplantation), 45 patients in the quizartinib group and 16 in the chemotherapy group were still being followed up at the data cutoff date. There was one overdose event, wherein a patient took 30 quizartinib tablets instead of one 30-mg tablet and vomited; this event was considered a major deviation.

	Quizartinib group (n=245)	Salvage chemotherapy group (n=122)
Age, years		
Median (IQR)	55·0 (46·0–65·0)	57·5 (44·0–66·0)
≥75	12 (5%)	3 (2%)
Sex		
Male	113 (46%)	64 (52%)
Female	132 (54%)	58 (48%)
Race*		
White	184 (75%)	93 (76%)
Black or African–American	9 (4%)	3 (2%)
Asian	24 (10%)	16 (13%)
Other	8 (3%)	2 (2%)
ECOG performance status		
0–1	218 (89%)	101 (83%)
2	27 (11%)	21 (17%)
Response to previous therapies		
Refractory	80 (33%)	41 (34%)
Relapsed ≤6 months with HSCT	56 (23%)	27 (22%)
Relapsed ≤6 months without HSCT	109 (44%)	54 (44%)
Median duration of first complete remission (IQR), weeks	15·0 (10·3–20·4)	16·0 (10·5–20·0)
Transplant history	61 (25%)	28 (23%)
Previous midostaurin or sorafenib	5 (2%)	7 (6%)
FLT3-ITD variant allele frequency†		
<3%	3 (1%)	0
≥3% to ≤25%	66 (27%)	37 (30%)
>25% to ≤50%	86 (35%)	42 (34%)
>50%	90 (37%)	43 (35%)
Other molecular abnormalities		
NPM1, mutated	115 (47%)	57 (47%)
CEBPA, mutated	5 (2%)	5 (4%)
Cytogenetic risk‡		
Favourable	12 (5%)	8 (7%)
Intermediate	191 (78%)	81 (66%)
Unfavourable	23 (9%)	14 (11%)
Unknown	19 (8%)	19 (16%)

Data are median (IQR) or n (%). CEBPA=CCAAT enhancer binding protein α. *FLT3*-ITD=FMS-related tyrosine kinase 3 internal tandem duplication. HSCT=haemopoietic stem cell transplantation. NPM1=nucleophosmin 1. *One patient in the quizartinib group identified as American Indian or Alaska Native; 19 patients in the quizartinib group and eight patients in the chemotherapy group had missing race data. †Defined as the ratio of *FLT3*-ITD to total *FLT3* and was reported by central laboratory testing. ‡Risk categories for acute myeloid leukaemia were based on cytogenetic classifications from the UK Medical Research Council AML11 trial.[35]

Table 1: **Baseline characteristics in the intention-to-treat population**

Baseline characteristics were similar between the two groups (table 1). Most patients had relapsed disease, and similar proportions of patients had previously had haemopoietic stem-cell transplantation between the two groups. At baseline, most patients had intermediate cytogenetic risk, and more than a third of patients in each group had at least 50% *FLT3*-ITD variant allele frequency.

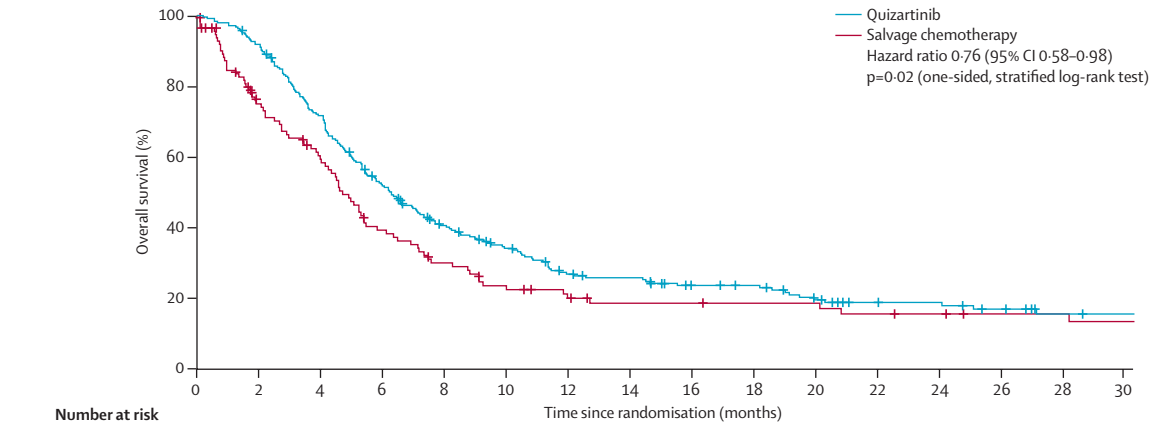


Figure 2: **Overall survival in the intention-to-treat population**

	Quizartinib group		Salvage chemotherapy group		Hazard ratio (95% CI)	Stratified p value
	Patients censored	Median (95% CI), months	Patients censored	Median (95% CI), months		
Primary analysis						
Intention-to-treat population	55/245	6·2 (5·3–7·2)	36/122	4·7 (4·0–5·5)	0·76 (0·58–0·98)	0·02
Sensitivity analyses						
Censored at HSCT	106/245	5·7 (4·8–6·3)	48/122	4·6 (3·8–5·2)	0·79 (0·59–1·05)	0·05
Censored at use of other FLT3 inhibitors	75/245	6·6 (5·5–7·7)	52/122	5·0 (3·9–6·1)	0·74 (0·55–0·99)	0·02
Per-protocol analysis set	52/231	6·2 (5·3–7·1)	18/88	4·6 (3·8–5·8)	0·75 (0·57–1·00)	0·02

Data are n/N unless otherwise stated. FLT3=FMS-related tyrosine kinase 3. HSCT=haemopoietic stem cell transplant. Hazard ratios were obtained from a stratified Cox proportional hazards model. p values are one-sided, from log-rank test.

Table 2: **Sensitivity analyses of overall survival**

Median follow-up was 23·5 months (IQR 15·4–32·3). Overall survival was longer in the quizartinib group than in the chemotherapy group (HR 0·76 [95% CI 0·58–0·98]; stratified log-rank test, one-sided p=0·02). At data cutoff, 190 patients in the quizartinib group and 86 patients in the salvage chemotherapy group had an overall survival event; median overall survival was 6·2 months (95% CI 5·3–7·2) for quizartinib and 4·7 months (4·0–5·5) for chemotherapy (figure 2; table 2). Estimated 12-month survival was 27% (95% CI 21–32%) for quizartinib and 20% (12–28%) for chemotherapy.

216 (88%) patients in the quizartinib group and 92 (75%) in the chemotherapy group had an event-free survival event during the study (figure 3). In 115 of those receiving quizartinib and 49 receiving chemotherapy, the treatment did not induce a response (partial remission as best response was deemed an event-free survival event at day 1 by prespecified protocol convention; 52 [quizartinib group] and four [chemotherapy group] patients achieved a partial remission), which contributed to the decrease in event-free survival in both groups at day 1 (figure 3). The prespecified event-free survival analysis in the per-protocol analysis set showed a greater treatment effect (figure 3B).

Patients could receive haemopoietic stem-cell transplantation based on investigator discretion. 78 (32%) of 245 patients in the quizartinib group proceeded to receive allogeneic haemopoietic stem-cell transplantation (plus one autologous haemopoietic stem-cell transplantation) without intervening acute myeloid leukaemia therapy, compared with 14 (11%) of 122 in the chemotherapy group. Of those who underwent haemopoietic stem-cell transplantation, 52 (67%) patients in the quizartinib group did so with a last recorded response of CRc or partial remission (n=42 [54%] for CRc and n=10 [13%] for partial remission) compared with nine patients (64%; n=9 [64%] for CRc; n=0 for partial remission) in the chemotherapy group. Of the 78 patients proceeding to haemopoietic stem-cell transplantation in the quizartinib group, 48 (62%) resumed quizartinib after transplant (median duration of 129 days [IQR 67–419]); 15 (31%) of

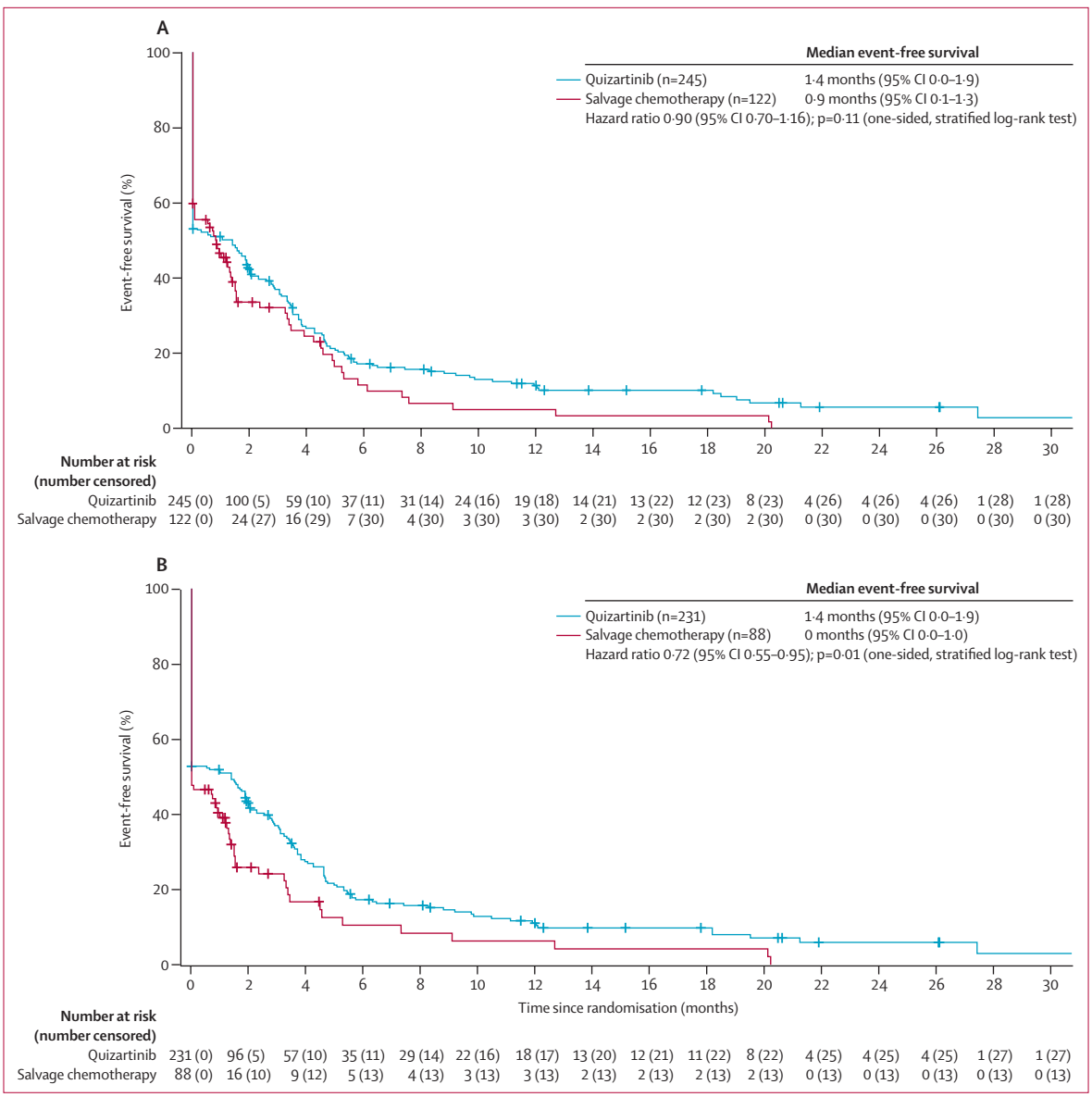


Figure 3: **Event-free survival**
Intention-to-treat population (A) and per-protocol analysis set (B).

these 48 patients were still receiving quizartinib at data cutoff.

Median drug exposure was 97 days for quizartinib (about four 28-day cycles; IQR 60·0–166·0) and was one cycle for chemotherapy (one to two cycles, given over 1–2 weeks), yielding a total drug exposure of 101·9 patient-years for quizartinib and 3·7 patient-years for chemotherapy. Overall, the median relative dose intensity of quizartinib was 0·89 (0·6–1·0). The median dose intensity for chemotherapy was neither defined nor calculated in this study.

76 (32%) of 241 patients in the quizartinib group required dose reduction; reasons included adverse event (n=29, 12%), QT prolongation (n=22, 9%), concomitant CYP3A4 inhibition (n=14, 6%), or other reasons (n=11, 5%). 13 (14%) patients in the chemotherapy group had dose interruptions for other reasons but did not have dose reductions.

238 (99%) of 241 patients receiving quizartinib and 93 (99%) of 94 receiving chemotherapy had a treatment-emergent adverse event, despite longer total drug exposure to quizartinib than to chemotherapy. The most common any-grade treatment-emergent adverse events in cycle 1 were thrombocytopenia, nausea, anaemia, neutropenia, and fatigue in the quizartinib group, and pyrexia, nausea, diarrhoea, thrombocytopenia, and anaemia in the chemotherapy group (appendix p 20).

	Quizartinib group (n=241)				Salvage chemotherapy group (n=94)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Nausea	110 (46%)	6 (2%)	0	0	38 (40%)	1 (1%)	0	0
Fatigue	76 (32%)	19 (8%)	0	0	26 (28%)	1 (1%)	0	0
Thrombocytopenia	9 (4%)	12 (5%)	72 (30%)	1 (<1%)	0	6 (6%)	26 (28%)	0
Pyrexia	86 (36%)	6 (2%)	0	0	38 (40%)	4 (4%)	0	0
Musculoskeletal pain	81 (34%)	10 (4%)	0	0	23 (24%)	4 (4%)	0	0
Anaemia	16 (7%)	70 (29%)	2 (1%)	0	3 (3%)	26 (28%)	1 (1%)	0
Febrile neutropenia	7 (3%)	68 (28%)	6 (2%)	0	6 (6%)	18 (19%)	2 (2%)	0
Neutropenia	5 (2%)	12 (5%)	64 (27%)	0	1 (1%)	1 (1%)	22 (23%)	0
Vomiting	72 (30%)	8 (3%)	0	0	19 (20%)	1 (1%)	0	0
Hypokalaemia	50 (21%)	26 (11%)	2 (1%)	0	18 (19%)	8 (9%)	0	0
Diarrhoea	66 (27%)	4 (2%)	0	0	31 (33%)	3 (3%)	0	0
Electrocardiogram QT prolonged	54 (22%)	10 (4%)	0	0	..	..	..	..
Cough	55 (23%)	1 (<1%)	0	0	13 (14%)	0	0	0
Rash	49 (20%)	6 (2%)	0	0	17 (18%)	0	0	0
Abdominal pain	49 (20%)	5 (2%)	0	0	15 (16%)	1 (1%)	0	0
Headache	51 (21%)	1 (<1%)	0	0	16 (17%)	0	0	0
Sepsis or septic shock	6 (2%)	26 (11%)	14 (6%)	6 (2%)	7 (7%)	10 (11%)	6 (6%)	2 (2%)
Oedema, peripheral	48 (20%)	3 (1%)	0	0	22 (23%)	0	0	0
Decreased appetite	43 (18%)	6 (2%)	0	0	..	..	..	..
Dyspnoea	37 (15%)	11 (5%)	1 (<1%)	0	3 (3%)	5 (5%)	0	0
Constipation	47 (20%)	0	0	0	22 (23%)	0	0	0
White blood cell count decreased	5 (2%)	12 (5%)	30 (12%)	0	1 (1%)	0	15 (16%)	0
Stomatitis	35 (15%)	4 (2%)	1 (<1%)	0	14 (15%)	4 (4%)	0	0
Pneumonia	9 (4%)	18 (7%)	2 (1%)	9 (4%)	2 (2%)	5 (5%)	1 (1%)	2 (2%)
Hypomagnesemia	37 (15%)	0	0	0	..	..	..	..
Dizziness	36 (15%)	0	0	0	10 (11%)	0	0	0
Alanine aminotransferase increased	23 (10%)	9 (4%)	0	0	2 (2%)	1 (1%)	1 (1%)	0
Hypotension	23 (10%)	8 (3%)	1 (<1%)	0	8 (9%)	2 (2%)	0	0
Graft-versus-host disease	18 (7%)	7 (3%)	2 (1%)	2 (1%)	..	..	..	..
Hypocalcaemia	28 (12%)	1 (<1%)	0	0	8 (9%)	2 (2%)	0	0
Petechiae	25 (10%)	2 (1%)	0	0	..	..	..	..
Weight decreased	26 (11%)	1 (<1%)	0	0	..	..	..	..
Blood bilirubin increased	..	..	..	..	0	3 (3%)	0	0
Oropharyngeal pain	25 (10%)	0	0	0	..	..	..	..
Hypophosphataemia	13 (5%)	10 (4%)	1 (<1%)	0	5 (5%)	4 (4%)	1 (1%)	0
Hyponatremia	14 (6%)	7 (3%)	1 (<1%)	0	..	..	..	..
Urinary tract infection	12 (5%)	9 (4%)	1 (<1%)	0	..	..	..	..
Upper respiratory tract infection	16 (7%)	5 (2%)	0	0	..	..	..	..
Cellulitis	8 (3%)	8 (3%)	0	0	..	..	..	..
Hyperglycaemia	10 (4%)	3 (1%)	2 (1%)	0	4 (4%)	3 (3%)	0	0
Leukocytosis	8 (3%)	4 (2%)	2 (1%)	1 (<1%)	0	2 (2%)	1 (1%)	0
Renal failure, acute	9 (4%)	3 (1%)	1 (<1%)	1 (<1%)	..	..	..	..
Pancytopenia	2 (1%)	11 (5%)	0	0	..	..	..	..
Syncope	2 (1%)	9 (4%)	0	0	..	..	..	..
Clostridioides difficile infection	6 (2%)	4 (2%)	1 (<1%)	0	..	..	..	..
Device-related infection	3 (1%)	8 (3%)	0	0	2 (2%)	5 (5%)	0	0

(Table 3 continues on next page)

	Quizartinib group (n=241)				Salvage chemotherapy group (n=94)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Haematoma	..	..	..	..	2 (2%)	2 (2%)	0	0
Decreased lymphocyte count	4 (2%)	4 (2%)	2 (1%)	0	0	1 (1%)	3 (3%)	0
Hypertension	..	..	..	..	5 (5%)	3 (3%)	0	0
Intracranial haemorrhage	0	0	2 (1%)	6 (2%)	0	1 (1%)	0	2 (2%)
Pneumonia, fungal	2 (1%)	5 (2%)	0	0	3 (3%)	1 (1%)	0	1 (1%)
Respiratory distress	0	3 (1%)	1 (<1%)	2 (1%)	..	..	..	..
Insomnia	..	..	..	..	13 (14%)	0	0	0
Lung disorder	..	..	..	..	0	1 (1%)	0	1 (1%)
Malnutrition	..	..	..	..	0	2 (2%)	0	0
Mucosal inflammation	..	..	..	..	2 (2%)	2 (2%)	0	0
Positive for *Staphylococcus* test	..	..	..	..	1 (1%)	2 (2%)	0	0

All events that occurred in at least 10% (grade 1–2) or 2% (grade ≥3) of patients are shown, regardless of relation to study drug. Double midline decimals (··) indicate values that were below both thresholds (<10% grade 1–2 and <2% grade 3). All treatment-emergent adverse events, regardless of relation to treatment, are listed in the appendix (p 11).

Table 3: **Treatment-emergent adverse events**

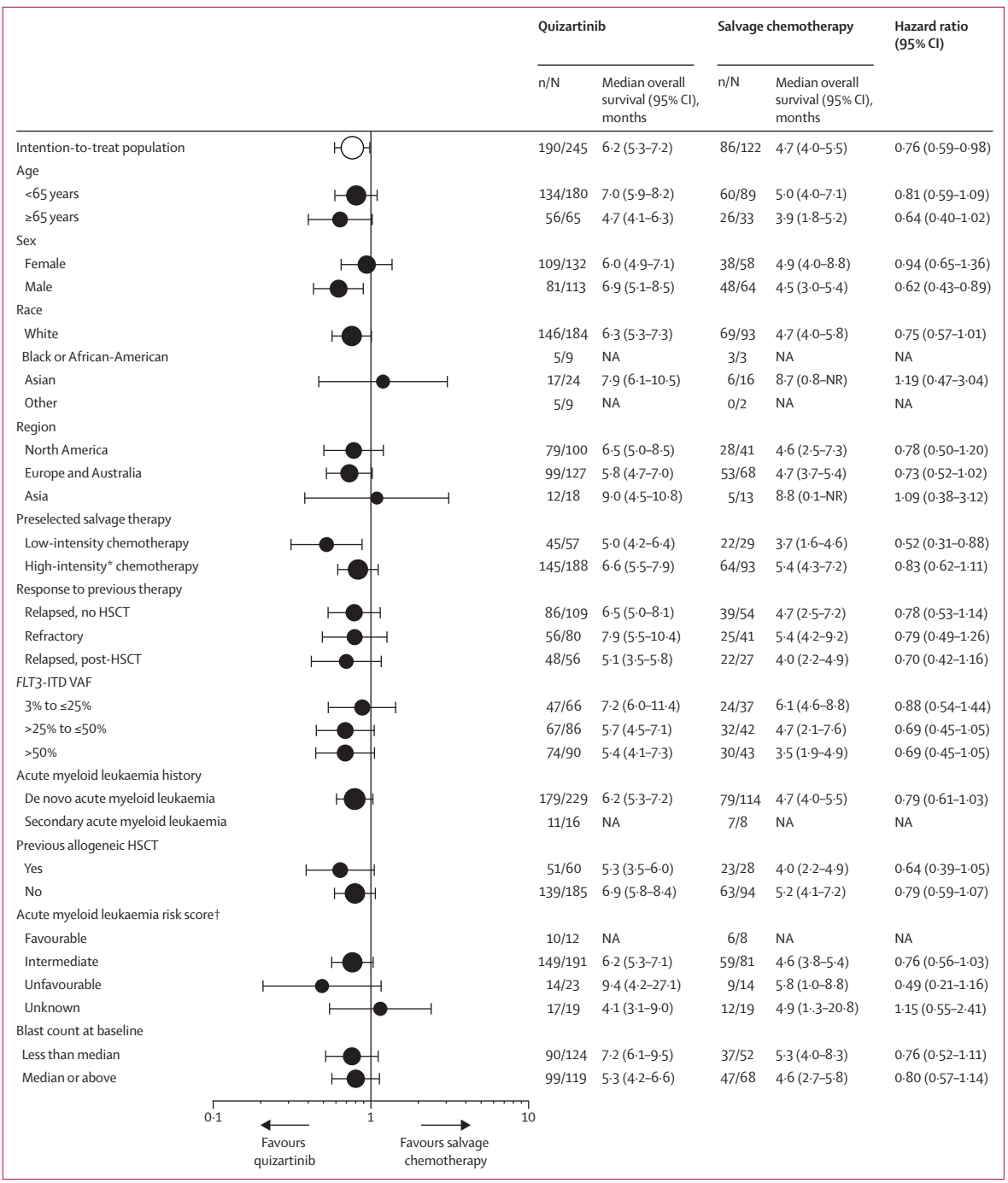
Grade 3 or worse treatment-emergent adverse events occurring in at least 5% of patients in the quizartinib group were haematological events, electrolyte abnormalities, infections, dyspnoea, and fatigue (table 3), whereas in the chemotherapy group these were haematological events, electrolyte abnormalities, infections, and dyspnoea. The most common non-haematological grade 3–5 treatment-emergent adverse events (within ≤30 days of last dose or >30 days for treatment-related events) for quizartinib (241 patients) and chemotherapy (94 patients) were sepsis or septic shock (46 patients [19%] for quizartinib *vs* 18 [19%] for chemotherapy), pneumonia (29 [12%] *vs* eight [9%]), and hypokalaemia (28 [12%] *vs* eight [9%]). 44 (18%) patients had treatment-emergent adverse events leading to quizartinib discontinuation; the most common reasons were pneumonia (six patients [2%]), intracranial haemorrhage (five [2%]), graft-versus-host disease (four [2%]), and sepsis or septic shock (four [2%]).

Grade 3 QT prolongation was uncommon with quizartinib (eight [3%] by central reading, ten [4%] by investigator report; appendix pp 8–9), despite concomitant use of QT- or QTc-prolonging drugs, including strong CYP3A inhibitors in 177 (73%) patients in the quizartinib group. No patients had torsade de pointes or other grade 4 QT prolongation events; however, one event of cardiac arrest was seen in the chemotherapy group (appendix p 9). Treatment-emergent adverse events of QT prolongation led to quizartinib interruption in 11 (5%) patients. Two (1%) patients discontinued quizartinib because of QT prolongation; both events were grade 2 without arrhythmias or other cardiac abnormalities.

The most frequent treatment-related serious adverse events were febrile neutropenia (18 patients [7%]), sepsis or septic shock (11 [5%]), QT prolongation (five [2%]), and nausea (five [2%]) in the quizartinib group, and febrile neutropenia (five [5%]), sepsis or septic shock (four [4%]), pneumonia (two [2%]), and pyrexia (two [2%]) in the chemotherapy group (appendix p 10). There were 80 (33%) treatment-emergent deaths in the quizartinib group (31 [13%] of which were due to adverse events) and 16 (17%) in the chemotherapy group (nine [10%] of which were due to adverse events; appendix p 15). All study deaths are listed in the appendix (p 16).

Results from all three prespecified sensitivity analyses for overall survival were consistent and generally supported the results of the primary endpoint: those censored for haemopoietic stem-cell transplantation, those censored for other post-study drug FLT3 inhibitor use, and those in the per-protocol analysis set (table 2). None of the protocol deviations affect the interpretation of the efficacy and safety outcomes of the study, because analyses using the per-protocol analysis set were supportive of the intention-to-treat analyses. Overall survival analyses by protocol-predefined subgroups, including variant allele frequency, previous haemopoietic stem-cell transplantation, acute myeloid leukaemia risk score, and response to previous therapy are shown in figure 4.

Given that 28 patients in the chemotherapy group were allocated to treatment but not treated, a prespecified analysis to assess potential bias favouring quizartinib in the overall population compared differences for the untreated versus treated patients in the chemotherapy group. Baseline characteristics were similar between the two groups (appendix p 17), except for a higher percentage of relapsed patients in the treated group than in the untreated group. Median overall survival was 21·3 weeks (3·6–32·9) for the untreated patients and 20·0 weeks (16·7–26·6) for the treated patients, suggesting no evidence of bias.



	Quizartinib		Salvage chemotherapy		Hazard ratio (95% CI)
	n/N	Median overall survival (95% CI), months	n/N	Median overall survival (95% CI), months	
Intention-to-treat population	190/245	6·2 (5·3–7·2)	86/122	4·7 (4·0–5·5)	0·76 (0·59–0·98)
Age					
<65 years	134/180	7·0 (5·9–8·2)	60/89	5·0 (4·0–7·1)	0·81 (0·59–1·09)
≥65 years	56/65	4·7 (4·1–6·3)	26/33	3·9 (1·8–5·2)	0·64 (0·40–1·02)
Sex					
Female	109/132	6·0 (4·9–7·1)	38/58	4·9 (4·0–8·8)	0·94 (0·65–1·36)
Male	81/113	6·9 (5·1–8·5)	48/64	4·5 (3·0–5·4)	0·62 (0·43–0·89)
Race					
White	146/184	6·3 (5·3–7·3)	69/93	4·7 (4·0–5·8)	0·75 (0·57–1·01)
Black or African-American	5/9	NA	3/3	NA	NA
Asian	17/24	7·9 (6·1–10·5)	6/16	8·7 (0·8–NR)	1·19 (0·47–3·04)
Other	5/9	NA	0/2	NA	NA
Region					
North America	79/100	6·5 (5·0–8·5)	28/41	4·6 (2·5–7·3)	0·78 (0·50–1·20)
Europe and Australia	99/127	5·8 (4·7–7·0)	53/68	4·7 (3·7–5·4)	0·73 (0·52–1·02)
Asia	12/18	9·0 (4·5–10·8)	5/13	8·8 (0·1–NR)	1·09 (0·38–3·12)
Preselected salvage therapy					
Low-intensity chemotherapy	45/57	5·0 (4·2–6·4)	22/29	3·7 (1·6–4·6)	0·52 (0·31–0·88)
High-intensity* chemotherapy	145/188	6·6 (5·5–7·9)	64/93	5·4 (4·3–7·2)	0·83 (0·62–1·11)
Response to previous therapy					
Relapsed, no HSCT	86/109	6·5 (5·0–8·1)	39/54	4·7 (2·5–7·2)	0·78 (0·53–1·14)
Refractory	56/80	7·9 (5·5–10·4)	25/41	5·4 (4·2–9·2)	0·79 (0·49–1·26)
Relapsed, post-HSCT	48/56	5·1 (3·5–5·8)	22/27	4·0 (2·2–4·9)	0·70 (0·42–1·16)
FLT3-ITD VAF					
3% to ≤25%	47/66	7·2 (6·0–11·4)	24/37	6·1 (4·6–8·8)	0·88 (0·54–1·44)
>25% to ≤50%	67/86	5·7 (4·5–7·1)	32/42	4·7 (2·1–7·6)	0·69 (0·45–1·05)
>50%	74/90	5·4 (4·1–7·3)	30/43	3·5 (1·9–4·9)	0·69 (0·45–1·05)
Acute myeloid leukaemia history					
De novo acute myeloid leukaemia	179/229	6·2 (5·3–7·2)	79/114	4·7 (4·0–5·5)	0·79 (0·61–1·03)
Secondary acute myeloid leukaemia	11/16	NA	7/8	NA	NA
Previous allogeneic HSCT					
Yes	51/60	5·3 (3·5–6·0)	23/28	4·0 (2·2–4·9)	0·64 (0·39–1·05)
No	139/185	6·9 (5·8–8·4)	63/94	5·2 (4·1–7·2)	0·79 (0·59–1·07)
Acute myeloid leukaemia risk score†					
Favourable	10/12	NA	6/8	NA	NA
Intermediate	149/191	6·2 (5·3–7·1)	59/81	4·6 (3·8–5·4)	0·76 (0·56–1·03)
Unfavourable	14/23	9·4 (4·2–27·1)	9/14	5·8 (1·0–8·8)	0·49 (0·21–1·16)
Unknown	17/19	4·1 (3·1–9·0)	12/19	4·9 (1··3–20·8)	1·15 (0·55–2·41)
Blast count at baseline					
Less than median	90/124	7·2 (6·1–9·5)	37/52	5·3 (4·0–8·3)	0·76 (0·52–1·11)
Median or above	99/119	5·3 (4·2–6·6)	47/68	4·6 (2·7–5·8)	0·80 (0·57–1·14)

Figure 4: **Prespecified subgroup analyses of overall survival in the intention-to-treat population**
The size of the circle corresponds to the subgroup size. *FLT3* ITD=FMS-related tyrosine kinase 3 internal tandem duplication. HSCT=haemopoietic stem cell transplant. NA=not applicable. NR=not reached. VAF=variant allele frequency. All predefined subgroups were only analysed if the total number of enrolled patients per subgroup was 30 or greater. Hazard ratios were from an unstratified Cox proportional hazards model. *High-intensity chemotherapy includes mitoxantrone, etoposide, and cytarabine, and fludarabine, cytarabine, and granulocyte colony-stimulating factor with idarubicin. †Acute myeloid leukaemia risk scores were based on the cytogenetic classifications determined in the United Kingdom Medical Research Council AML11 trial.[15]

A prespecified exploratory analysis showed that 118 (48%) of 245 patients in the quizartinib group and 33 (27%) of 122 in the chemotherapy group achieved CRc (appendix p 18); CR with incomplete haematological recovery was the most frequent response in both groups. Median time to first CRc was 4·9 weeks (IQR 4·3–8·4) for quizartinib and 4·0 weeks (2·4–5·3) for chemotherapy. Median duration of CRc was 12·1 weeks (IQR 5·0–67·1)

for quizartinib and 5·0 weeks (3·9–12·6) for chemotherapy (appendix pp 18, 21).

Discussion

To our knowledge, QuANTUM-R is the first trial to report a FLT3 inhibitor that significantly improves overall survival compared with salvage chemotherapy in patients with relapsed or refractory *FLT3*-ITD acute myeloid leukaemia. Patients with relapsed or refractory acute myeloid leukaemia have a poor prognosis; median overall survival with current salvage therapy is about 3·3–6·3 months.[3,16–18] Prognostic risk factors associated with worse overall survival include refractory disease, relapse at less than 6 months, previous haemopoietic stem-cell transplantation, older age, unfavourable cytogenetics, and *FLT3* mutation.[4,19] In one study,[20] patients with *FLT3*-ITD acute myeloid leukaemia who relapsed less than 6 months after initial treatment had a median overall survival of less than 4 months. Patients in QuANTUM-R had several characteristics suggestive of poor prognosis; all had either a short first remission or were refractory after previous therapy. About a fifth had previously received haemopoietic stem-cell transplantation.

Single-agent quizartinib reduced relative risk of death during the observation period (HR 0·76 [95% CI 0·58–0·98], p=0·02), with an estimated 12-month survival of 27% for quizartinib and 20% for chemotherapy. Prespecified overall survival sensitivity analyses (per-protocol analysis set, censoring for haemopoietic stem-cell transplantation and FLT3 inhibitors) showed an independent treatment effect consistent with that of the primary analysis, supporting the clinical and biological effect of quizartinib. The observed median overall survival of 4·7 months in the chemotherapy group exceeded historically reported median overall survival and trial-design assumptions. Because 28 (23%) of 122 patients allocated to chemotherapy were not treated, the prespecified per-protocol analysis set addressed this unanticipated imbalance between the two groups and the analysis validated observed results. A survival analysis comparing treated and untreated patients within the chemotherapy group showed no difference in overall survival, suggesting no bias favouring quizartinib. The outcomes in the chemotherapy group were more similar to results of a retrospective analysis[21] of the UK National Cancer Research Institute database. Patients with similar eligibility criteria as in QuANTUM-R (n=261) had a reported median overall survival of 131 days (about 4·3 months), excluding early deaths.[21]

Event-free survival outcomes supported the observed improvement in overall survival. Event-free survival was calculated from randomisation to documented failure to achieve a response, relapse after CRc, or death from any cause, whichever occurred first. Refractory disease and partial remission were both considered as no response (ie, failure), with the event assigned on day 1, although evaluation of response typically occurred around day 28. Considering that more patients in the quizartinib group than in the chemotherapy group achieved partial remission, more day 1 events were recorded for quizartinib, contributing to the decrease in the quizartinib curve. Additionally, the imbalance in the number of patients who were allocated but not treated, led to more patients in the chemotherapy group being censored at day 1. Censoring prevents patients from ever being counted as events, favouring the chemotherapy group in this instance. A prespecified event-free survival sensitivity analysis using the per-protocol analysis set, which excluded these patients, aligned more closely with the overall survival results.

The proportion of patients achieving a CRc or CR, a key exploratory endpoint, was consistent with the findings of the primary outcome. The higher proportion of patients achieving complete remission with incomplete haematological recovery than achieving complete remission with quizartinib might reflect a delay in haematological recovery attributed to quizartinib's moderate inhibition of KIT.[10,22] The clinical benefit of complete remission with incomplete haematological recovery seems to contribute to the improvement in overall survival seen with quizartinib versus chemotherapy. As such, the median time to first response with quizartinib was short, with an improved median duration of response versus chemotherapy.

Allogeneic haemopoietic stem-cell transplantation is an important treatment modality for relapsed or refractory acute myeloid leukaemia in select patients.[23,24] The current practice for salvage therapy is to reduce leukaemic burden, achieving as deep a remission as possible, and follow with haemopoietic stem-cell transplantation.[25] However, a poor response to salvage therapy in patients with relapsed or refractory *FLT3*-ITD acute myeloid leukaemia often prevents them from bridging to haemopoietic stem-cell transplantation.[26] In QuANTUM-R, we tested the hypothesis that quizartinib could improve survival over salvage chemotherapy as an important element of the overall treatment strategy (induction, followed by haemopoietic stem-cell transplantation [if eligible], followed by continuation of therapy [if eligible]). Although the decision to transplant was at the investigator's discretion, the three-times higher proportion of patients who had transplants in the quizartinib group versus the salvage chemotherapy group (ie, 32% *vs* 11%) might reflect enhanced tumour control resulting from a high response rate, rapid time to response, duration of CRc, and tolerable safety profile. In this rapidly proliferative disease, the quick and durable response seen with quizartinib stabilised patients and potentially enabled them to receive haemopoietic stem-cell transplantation. However, because the decisions to transplant and resume therapy after transplant were left to the investigators, QuANTUM-R could not show the value of haemopoietic stem-cell transplantation or detect any difference between the treatment groups as related

to haemopoietic stem-cell transplantation; thus, no conclusions can be made in this regard at this stage.

The favourable safety profile of quizartinib was consistent with that observed at similar doses in the clinical development programme[11–13] (at data cutoff, >1400 patients had received quizartinib across several trials[27]), suggesting that quizartinib has a well-characterised and manageable safety profile. QT prolongation has emerged as a class effect with FLT3 inhibitors (>60 ms increase from baseline 7% with gilteritinib,[28] 18% with midostaurin[29]). The risk-mitigation dosing strategy used in QuANTUM-R permitted successful administration of quizartinib, with a high median relative dose intensity and mostly grade 1 or 2 and transient QT prolongation. Grade 3 QT prolongation was infrequent, and no grade 4 events were seen, even with frequent concomitant administration of other QT- or QTc-prolonging agents commonly used in the treatment of acute myeloid leukaemia.

Our study has a few limitations. First, the open-label design, which was necessary given the different dosing and administration of the study treatments, might have resulted in some patients assigned to chemotherapy withdrawing consent before treatment. However, pre-specified sensitivity analyses correcting for this issue reaffirmed the overall survival and event-free survival benefit of quizartinib. Second, transplant procedures and continuation of post-transplant therapy were allowed per investigator assessment and medical practice and were not controlled. Finally, the randomisation protocol resulted in a small number of patients allocated to chemotherapy and limits interpretation of subgroup analyses.

Whereas quizartinib was, to our knowledge, the first FLT3 inhibitor to show an overall survival benefit for patients with relapsed or refractory *FLT3*-ITD acute myeloid leukaemia, during the time in which QuANTUM-R was done, two first-generation, multikinase FLT3 inhibitors became the standard of care in newly diagnosed acute myeloid leukaemia. In a phase 3 trial[30] of patients with newly diagnosed *FLT3*-mutated acute myeloid leukaemia, midostaurin improved overall survival (HR 0·77; 95% CI 0.63–0.95; p=0·016) when combined with standard induction and consolidation chemotherapy versus placebo plus chemotherapy.[29,30] In a randomised, phase 2 trial[31] in patients aged 18–60 years with newly diagnosed acute myeloid leukaemia, sorafenib plus standard induction and consolidation chemotherapy showed a significant event-free survival improvement versus placebo plus chemotherapy (HR 0·61, p=0·01 by multivariate analysis) at long-term follow-up. Median overall survival from randomisation was not reached for sorafenib and was 83 months for placebo (HR 0·81, p=0·26).

In addition to quizartinib, other next-generation FLT3 inhibitors with various pharmacological properties (including crenolanib and gilteritinib) are being evaluated in relapsed or refractory *FLT3*-ITD acute myeloid leukaemia (eg, NCT02421939 and NCT03250338). It is impossible to compare the relative benefits of these agents with quizartinib because the trial designs differ and results for most are not fully available at this time. Presumably, several of these agents will find a role in managing this complex patient population.

In summary, the findings from QuANTUM-R highlight the value of targeting the *FLT3*-ITD mutation with a highly potent and selective FLT3 inhibitor. QuANTUM-First, an ongoing, phase 3, double-blind, randomised, placebo-controlled trial (NCT02668653), is investigating whether quizartinib plus standard chemotherapy followed by single-agent quizartinib continuation therapy provides clinical benefit to patients with newly diagnosed *FLT3*-ITD acute myeloid leukaemia.

Contributors

JEC, GM, AEP, HD, MR, NG, and MJL contributed to the study design. SK, GM, AEP, SG, NR, AK, BAJ, AY-HL, PMe, MR, SS, KK, MH, and AY collected the data and helped with patient accrual and enrolment. JEC, SK, GM, AEP, SG, NR, AK, HD, BAJ, PMe, PMo, MR, KK, RN, NG, AY, YZ, MA, and MJL analysed and interpreted the data. NG provided statistical support. JEC, GM, AEP, SG, NR, AK, DH, BAJ, PMe, PMo, MR, MA, KK, RN, AY, YZ, and MJL wrote or reviewed the manuscript. All authors approved the final version of the manuscript for submission.

Declaration of interests

JEC reports grants and personal fees from Daiichi Sankyo, during this study; grants and personal fees from Pfizer, Astellas, and Novartis; and grants from Celgene, ImmunoGen, Merus, and Arog, outside the submitted work. SK reports travel support and honoraria from Daiichi Sankyo, during this study. GM reports grants from AbbVie and Pfizer; personal fees from AbbVie, Amgen, Ariad, Celgene, Incyte, Janssen, Jazz Pharmaceuticals, Novartis, Pfizer, and Roche; trial support from Pfizer; and nonfinancial support from Celgene and Pfizer, outside the submitted work. AEP reports personal fees and non-financial support from Daiichi Sankyo during this study; personal fees and non-financial support from AbbVie, Agios, Arog, Asana Biosciences, Astellas, Daiichi Sankyo, Jazz Pharmaceuticals, NewLink Genetics, Novartis, Seattle Genetics, and Takeda Oncology; and personal fees from Actinium and Pfizer, outside the submitted work. SG reports research support from Daiichi Sankyo, during this study, and personal fees from Amgen, Janssen, Kite Pharma, and Seattle Genetics, outside the submitted work. NR reports personal fees from Daiichi Sankyo, Jazz Pharmaceuticals, and Pfizer, during this study. AK reports personal fees from Daiichi Sankyo, during this study. HD reports personal fees from Daiichi Sankyo; grants and personal fees from Novartis and Pfizer; and personal fees from Astellas, outside the submitted work. BAJ reports grants from Daiichi Sankyo, during this study; grants and personal fees from AbbVie and Celgene; personal fees from Amgen, Jazz Pharmaceuticals, Rigel, and Tolero; and grants from Accelerated Medical Diagnostics, Arog, Esanex, Forma, Genentech/Roche, GlycoMimetics, Incyte, KaloBios, LP Therapeutics, and Pharmacyclics, outside the submitted work. AY-HL reports grants from Daiichi Sankyo during this study and grants from Daiichi Sankyo, outside the submitted work. PMe reports personal and other fees from Daiichi Sankyo and Jazz Pharmaceuticals and personal fees from Pfizer, outside the submitted work. PMo reports a consultancy agreement with Daiichi Sankyo, outside the submitted work. MR reports personal fees from Celgene, Incyte, Novartis, and Takeda, and non-financial support from Celgene, Daiichi Sankyo, and Jazz Pharmaceuticals, outside the submitted work. SS reports personal fees from Jazz Pharmaceuticals, Incyte, Alexion, and Daiichi Sankyo, during this study. MA, MH, KK, RN, NG, AY, and YZ are employed by Daiichi Sankyo. MJL reports advisory board membership with Daiichi Sankyo and grants from Astellas, FujiFilm, and Novartis, outside the submitted work. DH declares no competing interests.

Data sharing

De-identified individual participant data and applicable supporting clinical trial documents may be available upon request at Vivli-Center for Global Clinical Research Data. In cases where clinical trial data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo will continue to protect the privacy of our clinical trial participants. Details on data sharing criteria and the procedure for requesting access can be found online.

Acknowledgments

This study was sponsored, funded, and supported by Daiichi Sankyo. The study was designed by the funder in collaboration with the study investigators. Data were collected by investigators and analysed by the funder's biostatisticians. We thank the patients and their families, the QuANTUM-R investigators and their staff, the Daiichi Sankyo team who contributed to the execution of this study, and Mark Rocco PhD and Melanie Vishnu PhD (SciMentum, a Nucleus Global company) for providing medical writing support, which was funded by Daiichi Sankyo in accordance with Good Publication Practice guidelines. The results of this trial were presented at the 23rd Congress of the European Hematology Association on June 16, 2018, and at the 60th Annual Meeting and Exposition of the American Society of Hematology on Dec 3, 2018.

References

1 Levis M. FLT3 mutations in acute myeloid leukemia: what is the best approach in 2013? *Hematology Am Soc Hematol Educ Program* 2013; **2013:** 220–26.

2 Boissel N, Cayuela JM, Preudhomme C, et al. Prognostic significance of FLT3 internal tandem repeat in patients with de novo acute myeloid leukemia treated with reinforced courses of chemotherapy. *Leukemia* 2002; **16:** 1699–704.

3 Ravandi F, Ritchie EK, Sayar H, et al. Vosaroxin plus cytarabine versus placebo plus cytarabine in patients with first relapsed or refractory acute myeloid leukaemia (VALOR): a randomised, controlled, double-blind, multinational, phase 3 study. *Lancet Oncol* 2015; **16:** 1025–36.

4 Chevallier P, Labopin M, Turlure P, et al. A new Leukemia Prognostic Scoring System for refractory/relapsed adult acute myelogeneous leukaemia patients: a GOELAMS study. *Leukemia* 2011; **25:** 939–44.

5 Wattad M, Weber D, Dohner K, et al. Impact of salvage regimens on response and overall survival in acute myeloid leukemia with induction failure. *Leukemia* 2017; **31:** 1306–13.

6 Kottaridis PD, Gale RE, Linch DC. Flt3 mutations and leukaemia. *Br J Haematol* 2003; **122:** 523–38.

7 Mizuki M, Fenski R, Halfter H, et al. Flt3 mutations from patients with acute myeloid leukemia induce transformation of 32D cells mediated by the Ras and STAT5 pathways. *Blood* 2000; **96:** 3907–14.

8 Hayakawa F, Towatari M, Kiyoi H, et al. Tandem-duplicated Flt3 constitutively activates STAT5 and MAP kinase and introduces autonomous cell growth in IL-3-dependent cell lines. *Oncogene* 2000; **19:** 624–31.

9 Kiyoi H, Towatari M, Yokota S, et al. Internal tandem duplication of the FLT3 gene is a novel modality of elongation mutation which causes constitutive activation of the product. *Leukemia* 1998; **12:** 1333–37.

10 Zarrinkar PP, Gunawardane RN, Cramer MD, et al. AC220 is a uniquely potent and selective inhibitor of FLT3 for the treatment of acute myeloid leukemia (AML). *Blood* 2009; **114**: 2984–92.

11 Cortes J, Perl AE, Dohner 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; **19:** 889–903.

12 Cortes JE, Tallman MS, Schiller GJ, et al. Phase 2b study of 2 dosing regimens of quizartinib monotherapy in FLT3-ITD mutated, relapsed or refractory AML. *Blood* 2018; **132:** 598–607.

13 Cortes JE, Kantarjian H, Foran JM, et al. Phase I study of quizartinib administered daily to patients with relapsed or refractory acute myeloid leukemia irrespective of FMS-like tyrosine kinase 3-internal tandem duplication status. *J Clin Oncol* 2013; **31:** 3681–87.

14 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:** 4642–49.

15 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 AML11 trial. *Blood* 2001; **98:** 1312–20.

16 Roboz GJ, Rosenblat T, Arellano M, et al. International randomized phase III study of elacytarabine versus investigator choice in patients with relapsed/refractory acute myeloid leukemia. *J Clin Oncol* 2014; **32:** 1919–26.

17 Faderl S, Wetzler M, Rizzieri D, et al. Clofarabine plus cytarabine compared with cytarabine alone in older patients with relapsed or refractory acute myelogenous leukemia: results from the CLASSIC I trial. *J Clin Oncol* 2012; **30:** 2492–99.

18 Greenberg PL, Lee SJ, Advani R, et al. Mitoxantrone, etoposide, and cytarabine with or without valspodar in patients with relapsed or refractory acute myeloid leukemia and high-risk myelodysplastic syndrome: a phase III trial (E2995). *J Clin Oncol* 2004; **22:** 1078–86.

19 Schlenk RF, Frech P, Weber D, et al. Impact of pretreatment characteristics and salvage strategy on outcome in patients with relapsed acute myeloid leukemia. *Leukemia* 2017; **31:** 1217–20.

20 Levis M, Ravandi F, Wang ES, et al. Results from a randomized trial of salvage chemotherapy followed by lestaurtinib for patients with FLT3 mutant AML in first relapse. *Blood* 2011; **117:** 3294–301.

21 Hills RK, Burnett AK, Gale R, Linch DC, Gilkes A, Russell NH. Outcomes in relapsed/refractory patients with FLT3-ITD mutated AML are poor when treated with non-targeted therapy with a potential role for stem cell transplantation: results from the NCRI AML trials. *Blood* 2018; **132:** 1392 (abstr).

22 Lee LY, Hernandez D, Rajkhowa T, et al. Preclinical studies of gilteritinib, a next-generation FLT3 inhibitor. *Blood* 2017; **129:** 257–60.

23 Frazer J, Couban S, Doucette S, Shivakumar S. Characteristics predicting outcomes of allogeneic stem-cell transplantation in relapsed acute myelogenous leukemia. *Curr Oncol* 2017; **24:** e123–30.

24 Tsirigotis P, Byrne M, Schmid C, et al. Relapse of AML after hematopoietic stem cell transplantation: methods of monitoring and preventive strategies. A review from the ALWP of the EBMT. *Bone Marrow Transplant* 2016; **51:** 1431–38.

25 Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* 2017; **129:** 424–47.

26 Forman SJ, Rowe JM. The myth of the second remission of acute leukemia in the adult. *Blood* 2013; **121:** 1077–82.

27 Daiichi Sankyo. Oncologic Drugs Advisory Committee briefing document for the May 14, 2019, FDA Oncologic Drugs Advisory Committee: quizartinib. https://www.fda.gov/media/124897/download (accessed May 20, 2019).

28 Astellas Pharma. Xospata (gilteritinib). Northbrook, IL: Astellas Pharma US; 2018.

29 Novartis Pharmaceuticals. Rydapt (midostaurin). East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2018.

30 Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med* 2017; **377:** 454–64.

31 Rollig C, Serve H, Hüttmann A, et al. The addition of sorafenib to standard AML treatment results in a substantial reduction in relapse risk and improved survival. updated results from long-term follow-up of the randomized-controlled Soraml trial. *Blood* 2017; **130:** 721 (abstr).

For more on the **Vivli-Center** see https://vivli.org/

For **data sharing criteria and procedures** see https://vivli.org/ourmember/daiichi-sankyo/