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REVIEW

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Quizartinib: a potent and selective *FLT3* inhibitor for the treatment of patients with *FLT3*-ITD–positive AML

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Abstract

Mutations in *FMS*-related receptor tyrosine kinase 3 (*FLT3*) are among the most common alterations in acute myeloid leukemia (AML), present in ≈30% of newly diagnosed AML cases. Internal tandem duplications (ITD) in *FLT3* (*FLT3*-ITD) occur in ≈25% of newly diagnosed AML cases and are associated with unfavorable outcomes. Quizartinib (formerly AC220) is a novel, second-generation, highly potent, and selective type II FLT3 inhibitor. Quizartinib is approved in Japan as monotherapy for the treatment of adult patients with *FLT3*-ITD–positive relapsed/refractory (R/R) AML. Quizartinib is also approved in the United States, Japan, Europe, and United Kingdom in combination with chemotherapy during induction and consolidation, and as maintenance monotherapy (but, in the United States, not after allogeneic hematopoietic cell transplantation [allo-HCT]), for the treatment of adult patients with newly diagnosed *FLT3*-ITD–positive AML. In this review, we summarize preclinical studies that established quizartinib as a potent and selective type II FLT3 inhibitor as well as early and pivotal phase 3 clinical studies (QuANTUM-R and QuANTUM-First) that led to the approvals of quizartinib. We also summarize mechanisms of resistance to quizartinib along with its safety profile. Furthermore, we review the ongoing post hoc analyses of the QuANTUM-First data elucidating the impact of allo-HCT, the presence of measurable residual disease, and number and length of ITD on the clinical outcomes of quizartinib. We also describe the impact of quizartinib on patient-reported outcomes. Finally, we highlight some of the ongoing studies that test quizartinib in patients with *FLT3*-ITD–positive AML, patients with *FLT3*-ITD–negative AML, in both the first-line and R/R settings, in patients fit or unfit for intensive chemotherapy, including studies for quizartinib-based combination with other compounds such as decitabine and venetoclax. Future research should aim to further optimize the clinical value of quizartinib and explore its use in additional clinical settings, which could be achieved by testing quizartinib with other drugs, better characterization of the mechanisms of resistance, identification of the role of quizartinib as a maintenance therapy after allo-HCT, and investigating quizartinib in patients with *FLT3*-ITD–negative AML.

Keywords *FLT3*-ITD, AML, Quizartinib, QuANTUM-First, QuANTUM-R

Background

Acute myeloid leukemia (AML) is the most common form of leukemia in adults with an incidence of 3–4 cases per 100,000 globally [1], 4.1 cases per 100,000 in the United States [2], 3.7 cases per 100,000 in Europe [3], and 1.9 cases per 100,000 in Japan [4]; the median age of onset is approximately 68 years [5]. AML is a heterogeneous malignancy, with changing genetic profiles over time

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[6–9]. Mutations in *FMS*-related receptor tyrosine kinase 3 (*FLT3*) are among the most common alterations in AML (≈30% of newly diagnosed AML cases) [7, 10–14]. Mutations in the tyrosine kinase domain (TKD) of *FLT3* (*FLT3*-TKD) occur in ≈7% of newly diagnosed AML cases [7, 13]. The prognosis for patients with *FLT3*-TKD mutations is uncertain, with studies demonstrating weak or no association of the presence of *FLT3*-TKD mutations with clinical outcomes [7, 13]. Mutations involving internal tandem duplication (ITD) in *FLT3* (*FLT3*-ITD) occur in ≈25% of newly diagnosed AML cases and are considered driver mutations for disease progression [7, 13]. *FLT3*-ITD leads to overexpression, or constitutive activation of the FLT3 kinase, increasing signaling through MAPK/ERK, PI3K/AKT, and STAT5 pathways and ultimately contributing to leukemic cell proliferation, impaired differentiation of hematopoietic cells, and resistance to apoptosis [13, 15, 16]. Patients with *FLT3*-ITD–positive AML typically present with a high disease burden than those without *FLT3*-ITD [13, 15]. *FLT3*-ITD is associated with an unfavorable prognosis, including shorter survival and increased risk of relapse [7, 12, 13]. Patients with *FLT3*-ITD AML have worse survival than those with *FLT3*-TKD AML [17].

Standard chemotherapy with FLT3 inhibitors and allogeneic hematopoietic cell transplantation (allo-HCT) are the mainstay treatments for patients with newly diagnosed *FLT3*-ITD–positive AML (according to National Comprehensive Cancer Network [NCCN], European LeukemiaNet [ELN], and Japanese Society of Hematology [JSH]) [18–20]. For patients with *FLT3*-ITD AML treated with conventional induction chemotherapy, followed by allo-HCT, the risk of relapse ranges between 30% and 59% [21]. Midostaurin showed clinical benefit in the RATIFY phase 3 study conducted in patients with newly diagnosed *FLT3*-mutated (ITD or TKD) AML in combination with standard induction and consolidation chemotherapy, including allo-HCT, followed by up to 1 year of midostaurin or placebo single-agent maintenance [18, 19, 22–24]. In RATIFY, midostaurin was investigated in combination with chemotherapy in induction and consolidation, including allo-HCT, followed by up to 1 year of midostaurin or placebo single-agent maintenance (but not after allo-HCT), in patients with newly diagnosed *FLT3*-mutated (ITD or TKD) AML aged 18–59 years [24]. Of the 713 patients who enrolled in RATIFY, 23% had *FLT3*-TKD mutations and 77% had *FLT3*-ITD mutations. At the median follow-up of 59 months, the median overall survival (OS) favored midostaurin with 74.7 months (vs. 25.6 months with placebo; HR = 0.78, 95% CI = 0.63–0.96, $p = 0.009$), and the 4-year OS rate was 51.4% (vs. 44.3% with placebo). The median EFS also favored midostaurin with 8.2 months (vs. 3.0 months in the placebo group; HR = 0.78, 95% CI = 0.66–0.93, $p = 0.002$). In RATIFY, EFS was defined as the time from randomization to relapse, death, or failure to obtain a CR on or before 60 days of initiation of protocol therapy. In the United States and European Union, midostaurin in combination with standard induction and consolidation chemotherapy gained approval for the treatment of patients with *FLT3*-mutated AML [22, 23]. Midostaurin is approved as single-agent maintenance therapy for patients in complete remission (CR) after induction and consolidation in patients with *FLT3*-mutated AML in the European Union but not in the United States [22, 23]; its benefit as maintenance therapy after remission remains debatable [25–27]. The phase 2 midostaurin RADIUS study conducted in patients with *FLT3*-ITD AML in the post-transplant maintenance setting resulted in reduced risk of relapse with up to 1 year of midostaurin maintenance therapy [26]. Crenolanib is an investigational FLT3 inhibitor currently being studied in an ongoing randomized phase 3 study, ARO-021 (NCT03258931), versus midostaurin, in combination with standard induction and consolidation chemotherapy, including a maintenance phase with up to 1 year, in patients with newly diagnosed *FLT3*-mutated AML [28].

For patients not responding to initial induction or with relapsed disease, a comprehensive genomic profiling is crucial to identify actionable mutations and select patients who may be suitable for targeted salvage regimens [18, 19]. Gilteritinib single-agent is the current standard of care salvage therapy in patients with *FLT3*-mutated relapsed/refractory (R/R) AML, based on the results of the ADMIRAL phase 3 study [18, 19, 29–31]. In ADMIRAL, at the median follow-up of 17.8 months, the median OS was 9.3 months (vs. 5.6 months with salvage chemotherapy), and the 1-year OS rate was 37.1% (vs. 16.7% with salvage chemotherapy) [31]. Based on the phase 3 BMT-CTN 1506/MORPHO gilteritinib study, conducted in patients with *FLT3*-ITD AML who underwent allo-HCT in first remission and were then randomly assigned to 2-year gilteritinib or placebo maintenance therapy, post-HCT maintenance with gilteritinib conferred a RFS benefit only for patients with pre- or post-HCT *FLT3*-ITD MRD-positive disease [32]. Sorafenib, which is not approved for AML by health agencies, is included in the NCCN guidelines as an off-label treatment option in combination with azacitidine or decitabine for patients with newly diagnosed, R/R *FLT3*-ITD–positive AML, and in both the NCCN and ELN guidelines as single-agent therapy in the maintenance setting [18, 19]. The phase 2 SORAML study showed a significant prolongation of the median event-free survival (EFS), at a median follow-up of 3 years, when sorafenib was added to standard induction and consolidation

chemotherapy (21 months), compared with placebo plus chemotherapy (9 months) in patients with newly diagnosed AML, regardless of *FLT3*-ITD status [33]. The randomized phase 2 SORMAIN conducted in patients with *FLT3*-ITD AML in the post-transplant maintenance setting showed that a 2-year sorafenib maintenance therapy reduces the risk of relapse in patients in complete remission after allo-HCT, especially among those with MRD-positive disease after allo-HCT [34]. The phase 3 Sorafenib-Flt3 AML-2015 study confirmed the reduced risk of relapse with up to 6 months of sorafenib maintenance therapy, regardless of MRD status post-allo-HCT [35, 36]. Quizartinib clinical development was initially focused on the R/R setting of *FLT3*-ITD–positive AML, which led to quizartinib approval in Japan for this group of patients, but not in the United States nor Europe. Given that further clinical investigation of quizartinib in the first-line setting led to positive clinical results in patients with newly diagnosed *FLT3*-ITD–positive AML, this comprehensive review on quizartinib will bring together the overall clinical development of quizartinib to fully understand the current role and future potential of quizartinib in the treatment of *FLT3*-ITD–positive AML.

Quizartinib and its mechanism of action

Quizartinib (formerly AC220) is a second-generation, potent, and selective type II FLT3 inhibitor [37–48]. Quizartinib binds to and stabilizes the inactive conformation of the FLT3 receptor with ITD-activating mutations, preventing autophosphorylation of *FLT3*-ITD and activation of downstream signaling proteins; thereby, blocking *FLT3*-ITD–dependent cell proliferation and inducing apoptosis [38, 39, 42, 45, 49]. Both quizartinib and its active metabolite AC886 bind to FLT3 with high affinity, with K_d values of 3.3 and 1.1 nM, respectively [37]. In contrast, type I FLT3 tyrosine kinase inhibitors are essentially ATP mimetics, which bind to the ATP-binding site when the FLT3 receptor is in the active conformation, and can inhibit FLT3 signaling with either ITD or TKD mutations [48]. Compared with midostaurin, quizartinib is more potent (K_d values of 3.3 vs. 7.9 nM) and selective for *FLT3*-ITD mutations (quizartinib bound 8 kinases with $K_d < 100$ nM; midostaurin bound 54 kinases with $K_d < 100$ nM) [37]. Quizartinib displays a partial, selective inhibition of c-KIT ($K_d = 4.8$ nM) [49], another receptor tyrosine kinase that regulates myeloblast development [50]. Quizartinib has been shown to be an inhibitor of potassium channels (I_{Ks}), the slowly activating component of delayed rectifier potassium current, and is associated with prolongation of the corrected QT interval (QTc) in a dose-dependent manner [51–53].

Quizartinib preclinical data in cell lines and mouse models

In vitro treatment with quizartinib or its active metabolite AC886 of MV4-11 human leukemia cells, which harbor the *FLT3*-ITD mutations, induced potent inhibition of FLT3-dependent cell proliferation, with a concentration producing 50% inhibition (IC_{50}) of 0.4 nM for quizartinib and 0.2 for AC886 [37]. Both quizartinib and AC886 potently inhibited the growth of two other *FLT3*-ITD–positive human leukemia cell lines (MOLM-13 and MOLM-14) [37]. Quizartinib and AC886 produced marked and dose-dependent inhibition of tumor growth, with similar inhibitory effects, when administered orally once daily (QD) at doses ranging from 1 to 10 mg/kg in a mouse model of *FLT3*-ITD–dependent leukemia, intravenously xenografted with human *FLT3*-ITD–positive MV4-11 cells [37]. When antitumor activity of quizartinib was tested in combination with chemotherapy (cytarabine and daunorubicin) in an MV4-11 mouse xenograft model, the combination regimen demonstrated superior antitumor activity compared with chemotherapy alone [54]. Importantly, there were no meaningful changes in the general condition or body weight of the mice, suggesting that administration of quizartinib with cytarabine and daunorubicin was tolerated [54].

Quizartinib toxicology studies

In cardiovascular safety pharmacology studies conducted in vitro, quizartinib and AC886 at 3 μM showed statistically significant, but minor inhibition of human Ether-a-go-go related gene (hERG) currents by 16.4% and 12.0%, respectively, both of which were not considered relevant at therapeutic concentrations [54]. Quizartinib inhibited I_{Ks} with the maximum inhibition of 67.5% at 2.9 μM, while the maximum inhibition of I_{Ks} by AC886 was 26.9% at 2.9 μM, which was not considered relevant at therapeutic concentrations [54]. Neither quizartinib nor AC886 inhibited sodium and calcium channels (I_{Na}, $I_{Na\text{-}L}$, and $I_{Ca\text{-}L}$) at any concentration tested [54]. In cynomolgus monkeys, orally administered quizartinib prolonged QTc at ≥ 10 mg/kg and increased systemic blood pressure at ≥ 100 mg/kg [54]. Additional toxicology studies of quizartinib were conducted in rats, dogs, and monkeys. In all animal species studied, the principal target organs of toxicity were the bone marrow and lymphoid organs. Toxicity appeared to be dose and time dependent, and most toxicities were reversible after a 28-day or 30-day recovery period [54].

In repeated-dose toxicology studies for up to 13 weeks of quizartinib, toxic findings were identified in rats at 10 mg/kg/day, in dogs at 15 mg/kg/day, and in monkeys at 10 mg/kg/day and 6 mg/kg/day. Toxic findings included decreases in hematology parameters, increased

liver enzymes, and microscopic changes in bone marrow and lymphoid organs. No observed adverse effect levels (NOAEL) in the 13-week repeated-dose toxicity studies were 3 mg/kg/day in rats, 5 mg/kg/day in dogs, and 3 mg/kg/day in monkeys [54].

In genotoxicity studies, quizartinib demonstrated the potential for mutagenicity in a bacterial reverse mutation assay (Ames test), but not in a mammalian cell mutation assay (mouse lymphoma thymidine kinase) or transgenic rodent gene mutation assay with Big Blue rats [54]. Within the embryo-fetal toxicity studies of quizartinib in rats, there was no maternal toxicity and no evidence of quizartinib-related embryo lethality at up to 6 mg/kg/day. The NOAEL for embryo-fetal development was 2 mg/kg/day [54].

Quizartinib pharmacokinetics/pharmacodynamics and dosing

The half-life is 3 days (73 h) for quizartinib and 5 days (119 h) for AC886, which allow for oral QD administration of quizartinib as a single agent [6, 55–59]. Plasma concentration–time profiles after a single 30-mg dose of quizartinib were generally similar in healthy individuals under fasted and fed conditions, indicating that quizartinib can be administered with or without food [55]. The absolute oral bioavailability of quizartinib from the tablet formulation was approximately 71% [59]. Quizartinib can be co-administered with gastric acid–reducing agents [55, 56], as well as with P-glycoprotein substrates [60] and UGT1A1 substrates [61], as these had no clinically meaningful impact on the pharmacokinetics of quizartinib or AC886. In addition, mild and moderate hepatic impairment had no clinically meaningful impact on the pharmacokinetics of quizartinib and AC886 in patients receiving a single oral 30-mg dose of quizartinib when compared with healthy participants [62].

Treatment of cultured *FLT3*-ITD–positive MV4-11 human leukemia cells in vitro with quizartinib or AC886 induced a potent inhibition of FLT3 phosphorylation, with an IC_{50} of 0.5 nM for quizartinib and 0.18 nM for AC886 [37]. Single-agent quizartinib provided complete suppression of FLT3 phosphorylation, indicating target inhibition, in a rapid and sustained manner, at doses ranging from 18 to 60 mg/day, in ex vivo plasma inhibitory assays [6]. Similarly, quizartinib plus intensive chemotherapy resulted in complete inhibition of FLT3 phosphorylation when administered at 60 mg/day [63]. Dose reduction is recommended in patients receiving strong inhibitors of cytochrome P450 3A (CYP3A), including certain antibiotics and antifungals, as quizartinib is a substrate of CYP3A and exposure is increased significantly in the presence of such agents [56]. At the therapeutic dose of 60-mg quizartinib, the maximum plasma concentration was 376 ng/mL for quizartinib and 210 ng/mL for AC886, based on the geometric mean from a phase 2 study (NCT01565668/2689-CL-2004) [64].

Mechanisms of resistance to quizartinib

Genomic studies conducted on samples from 8 patients with *FLT3*-ITD–positive AML who relapsed on quizartinib revealed secondary mutations at the activation loop residue D835 or the gatekeeper residue F691 in the TKD of *FLT3*-ITD in all patients [65]. Four patients (50%) evolved more than one *FLT3*-TKD mutation at disease relapse, indicating a polyclonal mechanism of resistance [65]. In addition, targeted sequencing of single cells derived from 7 patients who relapsed on quizartinib identified D835 mutations on the native *FLT3* (ITD negative) allele in all patients [66]. In concordance with these findings, a retrospective chart review found that 25% (15/60) of patients with an *FLT3*-ITD mutation treated with FLT3 inhibitors (including quizartinib) progressed from a single *FLT3*-ITD mutation to develop combined *FLT3*-ITD and *FLT3*-TKD D835/I836 mutations, supporting the notion of a polyclonal mechanism of resistance to quizartinib [67].

Furthermore, the increased plasma levels of FLT3 ligand induced by standard induction chemotherapy is another mechanism of resistance for quizartinib, since the binding of the FLT3 ligand to the FLT3 receptor changes the conformation of the FLT3 receptor from inactive to active [68]. Other resistance mechanisms to FLT3 inhibition include upregulation of additional signaling pathways. For example, patients with *FLT3*-ITD–positive AML treated with quizartinib had increased FGF2 expression in marrow stromal cells, which can promote resistance through activation of FGFR1 and the downstream MAPK pathway [69].

Even in the context of loss of *FLT3*-ITD at R/R disease, a mechanism of resistance to FLT3 inhibition is the emergence of clones with different mutations than *FLT3* mutations, such as mutations in the RAS/MAPK signaling pathways found in patients with R/R disease after treatment with midostaurin in RATIFY [70]. A retrospective chart review conducted on 67 patients with *FLT3*-mutated AML treated with FLT3 inhibitors (as monotherapy or in combination regimens) in the first-line or R/R setting found that emergent mutations in the RAS/MAPK pathway detected at relapse were more common in patients treated with type I FLT3 inhibitors than those treated with type II FLT3 inhibitors (29% vs. 6%, $p = 0.014$) [71]. However, the mechanisms of resistance associated with the use of combination treatment of FLT3 inhibitors with chemotherapy in patients with *FLT3*-mutated AML have yet to be fully explored.

Clinical trials of quizartinib in AML

Efficacy for quizartinib monotherapy

Phase 1 studies

The first-in-human phase 1 study (NCT00462761/CP0001) enrolled 76 patients with AML regardless of *FLT3* mutation status, including patients with R/R disease and newly diagnosed AML not eligible for standard induction chemotherapy (Table 1) [6]. Quizartinib monotherapy was initially tested in an intermittent schedule (2 weeks on and 2 weeks off; at escalating doses of 12–450 mg/day) and a continuous schedule (200 or 300 mg/day for 4 consecutive weeks) was later added [6]. The overall response rate (ORR) in 76 patients was 30.3%, with 13.2% of the patients achieving composite complete remission (CRc) [6]. Among the 17 patients with *FLT3*-ITD–positive AML, the ORR was 52.9% and the CRc rate was 23.5%, with a median duration of complete remission (DoCR) of 10 weeks, indicating preliminary antitumor activity in patients with *FLT3*-ITD–positive AML [6]. This study showed that the maximum tolerated dose (MTD) was 200 mg/day of continuous quizartinib dosing [6]. The dose-limiting toxicity of grade 3 QTcF prolongation occurred in 23.5% (4/17) of patients treated with 200 mg/day of continuous quizartinib dosing, and in 37.5% (3/8) of patients treated with 300 mg/day of continuous quizartinib dosing [6].

Two additional phase 1 studies later evaluated lower doses of quizartinib after the findings in phase 2 studies (NCT00989261/AC220-002 and NCT01565668/2689-CL-2004) [64, 72], described later in this manuscript. A phase 1 study (NCT02675478/AC220-A-J101) in 16 Japanese patients with R/R AML tested three doses of quizartinib monotherapy (20, 30, and 60 mg/day) (Table 1) [73]. The ORR was 56.3% and the CRc rate was 37.5% [73]. Among the 7 patients with *FLT3*-ITD–positive AML, the CRc rate was 71.4% [73]. This study established 60 mg/day as the recommended dose for Japanese patients in subsequent trials [73].

Another phase 1 study (NCT01468467/2689-CL-0011) assessed two doses of quizartinib maintenance monotherapy (40 and 60 mg/day) for almost 2 years in 13 patients with *FLT3*-ITD–positive AML with CR after allo-HCT (Table 1) [74]. Relapse occurred in only 1 patient (7.6%) after allo-HCT [74]. Although there was no identified MTD, 60 mg/day was selected as the highest dose for continuous daily administration of quizartinib [74] in concordance with the optimal dose identified earlier in phase 2 studies (NCT00989261/AC220-002 and NCT01565668/2689-CL-2004) for treatment of patients with R/R AML [64, 72].

Phase 2 studies

A phase 2 study (NCT00989261/AC220-002) was later conducted [72]; this study initially used quizartinib at a dose of 200 mg QD, based on the MTD established in the phase 1 study (NCT00462761/CP0001) [6]. However, there was an unexpectedly high incidence of QTc prolongation in 82.4% of the 17 patients initially enrolled [72]. The study was thus amended to use lower doses as 90 mg QD for women and 135 mg QD for men [72]. These doses were based on observations from the dose reductions conducted in the initial cohort, suggesting greater susceptibility for QTc prolongation in women than in men [72]. Patients were enrolled in two cohorts, both with R/R AML regardless of *FLT3* mutation status as follows: patients aged ≥ 60 years with R/R disease within 1 year after first-line therapy (cohort 1; n = 157), and patients aged ≥ 18 years with R/R disease after salvage chemotherapy or after allo-HCT (cohort 2; n = 176) (Table 1) [72]. At the lower doses explored, there were lower rates of QTcF prolongation (grade ≥ 3 QTcF prolongation was 15.1% in men and 17.3% in women), which were reversible and successfully managed by treatment interruption and/or dose reductions [72]. Rates of CRc (primary endpoint) were higher among patients with *FLT3*-ITD–positive AML compared with those with *FLT3*-ITD–negative AML, in both cohorts [72]. Among a total of 248 patients with *FLT3*-ITD–positive AML, 50.4% achieved a CRc (56.3% in cohort 1 and 45.6% in cohort 2) [72].

In order to find the minimum effective dose of quizartinib and to further decrease the risk of QTcF prolongation reported in study NCT00989261/AC220-002 [72], a phase 2b study (NCT01565668/2689-CL-2004) was conducted (Table 1) [64]. In this study, two doses of quizartinib monotherapy (30 and 60 mg/day) were randomly assigned to 76 patients with R/R *FLT3*-ITD–positive AML [64]. In case of lack/loss of response, quizartinib doses could be increased to 60 or 90 mg/day, respectively [64]. Rates of CRc (primary endpoint) were 47.4% in both groups [64]. Median OS (20.9 vs. 27.3 weeks), median duration of CRc (4.2 vs. 9.1 weeks), and rate of patients bridged to transplant (31.6% vs. 42.1%) were higher in the 60-mg group than in the 30-mg group [64]. Dose escalation occurred in 61% and 14% of patients in the 30- and 60-mg groups, respectively [64]. The incidence of grade ≥ 3 QTcF prolongation was substantially lower in both the 30-mg group (5%) and the 60-mg group (3%) [64], compared with the incidence reported in the earlier NCT00989261/AC220-002 phase 2 study (15% in the 135-mg group and 17% in 90-mg group) [72]. This study further confirmed the clinical efficacy of quizartinib in patients with R/R *FLT3*-ITD–positive AML and supported the use of 60 mg/day in subsequent studies [64].

Table 1 Key clinical trials of quizartinib

Identifier(s)	Phase	Treatment arm(s) Number of patients	Disease	Median age, years	Efficacy			Status
					ORR (CRc + PR)	CRc and median DoCRc	Median OS	
Daiichi Sankyo–sponsored studies								
Quizartinib monotherapy studies								
NCT00462761 CP0001 [6]	1	Quizartinib monotherapy (escalation dose from 12 to 450 mg/day) N = 76	AML regardless of *FLT3* mutation status, including R/R AML and newly diagnosed AML not eligible for standard induction therapy	59.5 (range = 23–86)	All: 30.3% (23/76) ITD+: 52.9% (9/17) ITD −: 13.5% (5/37) ITD (ind): 40.9% (9/22)	CRc overall (CR + CRp + CRi): 13.2% (10/76) CR overall: 2.6% (2/76) CRi overall: 6.7% (5/76) CRp overall: 3.9% (3/76) CRc in ITD+: 23.5% (4/17) CRc in ITD−: 5.4% (2/37) CRc in ITD (ind): 18.2% (4/22)	All: 14 weeks (95% CI=11–19) ITD+: 18 weeks (95% CI = 11–27) ITD−: 10 weeks (95% CI = 6–14) ITD (ind): 19 weeks (95% CI = 14–21)	Completed
NCT02675478 AC220-A-J101 [73]	1	Quizartinib monotherapy (20, 30, and 60 mg/day) N = 16	R/R AML regardless of *FLT3* mutation status (Japanese patients)	68.0 (range = 33–91)	All: 56.3% (9/16)	CRc overall (CR + CRp + CRi): 37.5% (6/16) CRi overall: 31.5% (5/16) CRc in ITD+: 71.4% (5/7)	–	Completed
NCT01468467 2689-CL-0011 [74]	1	Quizartinib maintenance monotherapy (40 or 60 mg/day) N = 13	*FLT3*-ITD–positive AML after allo-HCT	43.0 (range = 23–61)	– Relapse rate: 7.6% (1/13)	–	Range = 13–142 weeks 9 patients (69.2%) survived ≥ 50 weeks 4 patients (30.8%) survived > 2 years (104 weeks)	Completed

Table 1 (continued)

Identifier(s)	Phase	Treatment arm(s) Number of patients	Disease	Median age, years	Efficacy			Status
					ORR (CRc + PR)	CRc and median DoCRc	Median OS	
NCT00989261 AC220-002 [72]	2	Quizartinib monotherapy (90, 135, and 200 mg/day) N = 333	R/R AML regardless of *FLT3* mutation status	Cohort 1[a] (n = 157): 69 (IQR = 66–73) Cohort 2[b] (n = 176): 51 (IQR = 40–60)	Cohort 1: ITD + : 76.8% (86/112) ITD − : 45.5% (20/44) Cohort 2: ITD + : 74.3% (101/136) ITD − : 45.0% (18/40)	Cohort 1: CRc (CR + CRp + CRi; primary endpoint) in ITD + : 56.3% (63/112) Median DoCRc: 12.1 weeks (95% CI = 6.3–15.7) CRc in ITD − : 36.4% (16/44) Median DoCRc: 16.4 weeks (95% CI = 8.1–30.4) Cohort 2: CRc in ITD + : 45.6% (62/136) Median DoCRc: 10.6 weeks (95% CI = 8.1–16.1) CRc in ITD − : 30.0% (12/40) Median DoCRc: 7.0 weeks (95% CI = 4.1–8.1)	Cohort 1: ITD + : 25.4 weeks (95% CI = 21.3–29.7) ITD − : 19.1 weeks (95% CI = 12.0–29.4) Cohort 2: ITD + : 24.0 weeks (95% CI = 21.1–27.1) ITD − : 25.1 weeks (95% CI = 18.1–37.0) Rate of patients bridged to transplant in cohort 2: 34.7% (61/176) ITD + : 34.6% (47/136) ITD − : 35.0% (14/40)	Completed
NCT01565668 2689-CL-2004 [64]	2b	Quizartinib monotherapy (30 vs 60 mg/day)[c] N = 76	R/R *FLT3*-ITD–positive AML	30 mg (n = 38): 57 (range = 19–77) 60 mg (n = 38): 53 (range = 20–74) Total (N = 76): 55 (range = 19–77)	Overall: 65.8% (50/76) 30 mg: 60.5% (23/38) 60 mg: 71.1% (27/38)	CRc (CR + CRp + CRi; primary endpoint) overall: 47.4% (36/76) CRc in 30 mg: 47.4% (18/38) CRc in 60 mg: 47.4% (18/38) Median DoCRc Overall: 5.4 weeks (95% CI = 4.1–11.9) 30 mg: 4.2 weeks (95% CI = 2.1–9.7) 60 mg: 9.1 weeks (95% CI = 4.1–22.3)	30 mg: 20.9 weeks 60 mg: 27.3 weeks Rate of patients bridged to transplant Overall: 36.8% (28/76) 30 mg: 31.6% (12/38) 60 mg: 42.1% (16/38)	Completed

Table 1 (continued)

Identifier(s)	Phase	Treatment arm(s) Number of patients	Disease	Median age, years	Efficacy			Status
					ORR (CRc + PR)	CRc and median DoCRc	Median OS	
NCT02984995 AC220-A-J201 [75]	2	Quizartinib monotherapy (30 or 20 mg/day for patients receiving strong CYP3A inhibitors)[d] N = 37	R/R *FLT3*-ITD–positive AML (Japanese patients)	65.0 (range = 31–81)	–	CRc (CR + CRp + CRi; primary endpoint): 53.8% (14/26) Median DoCRc: 16.1 weeks CRi: 50.0% (13/26) CRp: 3.8% (1/26)	34.1 weeks	Completed
NCT02039726 AC220-007 QuANTUM-R [46]	3	Quizartinib, 60 mg/day, with one starting dose of 30 mg/day (n = 245)[e] vs Standard salvage chemotherapy (n = 122)[f]	R/R *FLT3*-ITD–positive AML	Quizartinib: 55 (IQR = 46–65) Chemotherapy: 57.5 (IQR = 44–66)	–	Quizartinib CRc (CR + CRp + CRi): 48.2% (118/245) Median DoCRc: 12.1 weeks (IQR = 5.0–67.1) Chemotherapy CRc: 27.0% (33/122) Median DoCRc: 5.0 weeks (IQR = 3.9–12.6)	Median follow-up: 23.5 months (IQR = 15.4–32.3) Median OS (primary endpoint) Quizartinib: 6.2 months (95% CI = 5.3–7.2) Chemotherapy: 4.7 months (95% CI = 4.0–5.5) HR for death = 0.76; 95% CI = 0.58–0.98, $p = 0.02$ Rate of patients bridged to transplant Quizartinib: 31.8% (78/245) Chemotherapy: 11.5% (14/122)	Completed
Quizartinib combination studies								
NCT01390337 2689-CL-0005 [79]	1	Quizartinib (40 or 60 mg/day) + induction and consolidation chemotherapy N = 19	Newly diagnosed AML regardless of *FLT3* mutation status	43.0 (range = 22–60)	All: 84.2% (16/19)	CRc overall (CR + CRp + CRi): 73.7% (14/19) CRc in ITD + : 66.7% (6/9) CRc in ITD − : 80.0% (8/10)	– Rate of patients undergoing transplant: 47.4% (9/19)	Completed
NCT02834390 AC220-A-J102 [80, 81]	1b	Quizartinib (20 or 40 mg/day) + induction and consolidation chemotherapy N = 7	Newly diagnosed AML regardless of *FLT3* mutation status (Japanese patients)	62.0 (range = 34–68)	All: 85.7% (6/7)	CRi: 71.4% (5/7)	–	Completed

Table 1 (continued)

Identifier(s)	Phase	Treatment arm(s) Number of patients	Disease	Median age, years	Efficacy			Status
					ORR (CRc + PR)	CRc and median DoCRc	Median OS	
NCT02668653 AC220-A-U302 QuANTUM-First [47]	3	Quizartinib 40 mg/day in induction and consolidation; 30 then 60 mg/day in continuation (n = 268)[g] vs Placebo (n = 271)[h] (Both quizartinib and placebo were combined with standard induction and consolidation chemotherapy, followed by quizartinib or placebo single-agent continuation therapy for ≤ 3 years)	Newly diagnosed *FLT3*-ITD–positive AML aged 18–75 years	Quizartinib: 56 (IQR = 44.5–65; range = 20–75) Placebo: 56 (IQR = 47–64; range = 20–75)	–	Quizartinib CRc (CR + CRi): 71.6% (192/268) Median DoCRc: 27.2 months (95% CI = 17.7–NE) CR: 54.9% (147/268) Median DoCR: 38.6 months (95% CI = 21.9–NE) Placebo CRc: 64.9% (176/271) Median DoCRc: 12.4 months (95% CI = 8.7–22.7) CR: 55.4% (150/271) Median DoCR: 12.4 months (95% CI = 8.8–22.7)	Median follow-up: 39.2 months (IQR = 32.2–45.4 for quizartinib and 31.4–46.0 for placebo) Median OS (primary endpoint) Quizartinib: 31.9 months (95% CI = 21.0–NE) Placebo: 15.1 months (95% CI = 13.2–26.2) HR for death = 0.776; 95% CI = 0.615–0.979, $p = 0.0324$ Rate of patients undergoing transplant Quizartinib: 38.5% (102/268) Chemotherapy: 34.0% (91/271)	Completed

Selected investigator-initiated studies

Table 1 (continued)

Identifier(s)	Phase	Treatment arm(s) Number of patients	Disease	Median age, years	Efficacy			Status
					ORR (CRc + PR)	CRc and median DoCRc	Median OS	
NCT04687761 VEN-A-QUI [105–107]	1/2	Azacitidine + venetoclax + quizartinib (phase 1, n = 6; phase 2, n = 31) vs Low-dose cytarabine + venetoclax + quizartinib (phase 1, n = 9; phase 2, n = 30)	Newly diagnosed AML unfit for intensive induction chemotherapy (regardless of *FLT3*-ITD mutation status)	Phase 2 Azacitidine: 74.0 (range = 69–84) Low-dose cytarabine: 75.5 (range = 69–79)	All: 65.6% (40/61) Azacitidine: 64.5% (20/31) Low-dose cytarabine: 66.7% (20/30)	All CRc (CR + CRi + CRh; primary endpoint of phase 2) = 52.5% (32/61) Azacitidine CRc = 54.8% (17/31) Low-dose cytarabine CRc = 50.0% (15/30)	Median OS All: 9.77 months (95% CI = 5.6–NR) Azacitidine: 14.47 months Low-dose cytarabine: 9.07 months HR for death = 1.1, $p = 0.61$ ITD + : NR (95% CI = 9.77–NR) ITD − : 9.03 months (95% CI = 4–NR) $p = 0.042$ Median EFS All: 9.03 months (95% CI = 4.17–14.6) Azacitidine: 9.27 months Low-dose cytarabine: 6.27 months HR = 1.1, $p = 0.67$ ITD + : NR (95% CI = 9.67–NR) ITD − : 4.33 months (95% CI = 3.4–NR) $p = 0.0098$	Recruiting
NCT03661307 2018–0394 NCI-2018–01789 [102–104]	1/2	Decitabine + venetoclax + quizartinib (N = 57 patients with AML)	Newly diagnosed unfit for intensive induction chemotherapy (n = 14) or R/R *FLT3*-ITD–positive AML (n = 43), or high-risk MDS	1L setting: 70 (range = 62–85) R/R setting: 59 (range = 19–86)	–	CRc (CR + CRi + MLFS; secondary endpoint) 1L setting: 100.0% (14/14) R/R setting: 65.1% (28/43)	Median follow-up: 1L setting: 11 months R/R setting: 21 months Median OS (secondary endpoint) 1L setting: NR R/R setting: 7.5 months	Active, not recruiting

Table 1 (continued)

Identifier(s)	Phase	Treatment arm(s) Number of patients	Disease	Median age, years	Efficacy			Status
					ORR (CRc + PR)	CRc and median DoCRc	Median OS	
NCT04107727 QUIWI [111–113]	2	Quizartinib (or placebo) + induction and consolidation chemotherapy followed by single-agent quizartinib (or placebo) maintenance therapy (N = 273)	Newly diagnosed *FLT3* wild-type AML fit for intensive chemotherapy	Quizartinib (n = 180): 57.1 (range = 19–70) Placebo (n = 93): 58.5 (range = 21–70)	Quizartinib: 83.8% (140/167) Placebo: 80.0% (72/90)	Quizartinib CRc (CR + CRi): 78.4% (131/167) Placebo CRc: 77.8% (70/90)	Median follow-up Quizartinib: 21.5 months Placebo: 20.3 months Median EFS (primary endpoint) Quizartinib: 16.5 months Placebo: 10.6 months HR = 0.741, 95% CI = 0.535–1.026, $p = 0.059$ Median OS Quizartinib: NR Placebo: 20.2 months HR for death = 0.569, 95% CI = 0.385–0.841, $p = 0.004$ Median RFS in CRc patients Quizartinib: NR Placebo: 18.6 months HR = 0.631, 95% CI = 0.414–0.962, $p = 0.031$	Active, not recruiting

Table 1 (continued)

Identifier(s)	Phase	Treatment arm(s) Number of patients	Disease	Median age, years	Efficacy			Status
					ORR (CRc + PR)	CRc and median DoCRc	Median OS	
NCT02272478 NCRI AML-18 [108, 109]	2/3	After cycle 1 of intensive chemotherapy induction, patients receive, in cycles 2 and 3, either further chemotherapy + quizartinib (n = 233) or chemotherapy alone (n = 231). Patients on quizartinib (n = 233), receive maintenance therapy consisting of either 1 (n = 117) or 12 cycles (n = 116) of single-agent quizartinib (N = 464)	Newly diagnosed AML or high-risk MDS fit for intensive chemotherapy (regardless of *FLT3*-ITD mutation status)	All: 68 (range = 51–79) Quizartinib: 68 (range = 51–78) Chemotherapy alone: 68 (range = 58–79)	–	Remission status at the time of quizartinib randomization: CRc (CR + CRi): 78.4% (364/464) CR: 72.8% (338/464) CRi: 5.6% (26/464) CRc rates after quizartinib treatment Quizartinib: 96.6% (225/233) Chemotherapy alone: 93.9% (217/231)	Median follow-up: 54 months OS (primary endpoint) Quizartinib: 29 months Chemotherapy alone: 29 months HR for death = 1.035, 95% CI = 0.823–1.303, $p = 0.769$ RFS in CRc patients Quizartinib: 18 months Chemotherapy alone: 19 months HR = 1.070, 95% CI = 0.855–1.341, $p = 0.550$ Among 117 *FLT3*-mutated patients: OS with quizartinib: 33 months OS with chemotherapy alone: 26 months HR for death = 0.688, 95% CI = 0.428–1.106, $p = 0.121$ Among 112 *FLT3*-mutated patients who achieved CRc: RFS with quizartinib: 21 months RFS with chemotherapy alone: 13 months HR = 0.771, 95% CI = 0.493–1.206, $p = 0.255$)	Active, not recruiting

[a] Patients who were aged ≥ 60 years with R/R AML within 1 year after 1L therapy. [b]Patients who were aged ≥ 18 years with R/R AML after salvage chemotherapy or after allo-HCT. [c]In case of lack/loss of response, quizartinib doses (30 and 60 mg/day) could be increased to 60 or 90 mg/day, respectively. [d]Quizartinib dose could be increased from 30 mg/day to 60 mg/day or from 20 mg/day to 30 mg/day. [e]Four patients in the quizartinib arm were not treated. [f]Twenty-eight patients in the chemotherapy arm were not treated. [g]Three patients in the quizartinib arm were not treated. [h]Three patients in the chemotherapy arm were not treated

1L, first line; allo-HCT, allogeneic hematopoietic cell transplant; AML, acute myeloid leukemia; CI, confidence interval; CR, complete remission; CRc, composite complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete neutrophil or platelet recovery; CRp, complete remission with incomplete platelet recovery; CYP3A, cytochrome P450 3A; DoCRc, duration of composite complete remission; EFS, event-free survival; *FLT3*-ITD, *FMS*-related receptor tyrosine kinase 3–internal tandem duplication; HR, hazard ratio; ind, indeterminate/not tested; IQR, interquartile range; MDS, myelodysplastic syndrome; MLFS, morphological leukemia-free state; NE, not estimable; NR, not reached; ORR, overall response rate; OS, overall survival; PR, partial remission; RFS, relapse-free survival; R/R, relapsed/refractory

An additional phase 2 study in 37 Japanese patients with R/R *FLT3*-ITD–positive AML (NCT02984995/AC220-A-J201) tested 30 mg/day of quizartinib monotherapy (20 mg/day for patients receiving strong CYP3A inhibitors) (Table 1) [75]. In this study, the quizartinib dose could be increased from 30 mg/day to 60 mg/day or from 20 mg/day to 30 mg/day [75]. Among 26 patients evaluable for efficacy, the CRc rate (primary endpoint) was 53.8%, with 50.0% of the patients achieving CR with incomplete neutrophil or platelet recovery (CRi) and 3.8% CR with incomplete platelet recovery [75]. A summary of results of these studies leading to the identification of the optimal dose of quizartinib is presented in Table 2.

Phase 3 studies

The efficacy observed in all of these phase 1 and phase 2 studies led to the design of a phase 3 study, QuANTUM-R (NCT02039726/AC220-007), where quizartinib monotherapy was assessed versus salvage chemotherapy in 367 patients with *FLT3*-ITD–positive R/R AML (Table 1) [46]. Salvage chemotherapy included three physicians' choice chemotherapy regimens: low-dose cytarabine; mitoxantrone, etoposide, and cytarabine (MEC); or fludarabine, cytarabine, and granulocyte colony-stimulating factor with idarubicin (FLAG-IDA) [46]. Quizartinib was administered in all patients assigned to this cohort at a starting dose of 30 mg/day; the dose was increased to 60 mg/day on day 16 if the QTc had remained at 450 ms or less during the preceding 15 days [46]. Eligible patients had previously received standard anthracycline-containing induction chemotherapy and had R/R disease within 6 months of achieving CRc [46]. The primary endpoint of the study was OS, and the defined superiority was met [46]. At a median follow-up of 23.5 months, quizartinib monotherapy demonstrated a statistically significant improvement in OS versus chemotherapy (hazard ratio [HR] = 0.76, 95% confidence interval [CI] = 0.58–0.98, $p = 0.02$), reducing the relative risk of death during the observation period by 24% [46]. Median OS was 6.2 months in patients treated with quizartinib versus 4.7 months in patients treated with chemotherapy [46]. There was also a nonstatistically significant improvement in median EFS (secondary endpoint) in patients treated with quizartinib (1.4 months) compared with those who received chemotherapy (0.9 months) (HR = 0.90, 95% CI = 0.70–1.16, $p = 0.11$) [46]. These data illustrated the value of using quizartinib monotherapy to treat patients with *FLT3*-ITD–positive R/R AML [46]. Data from QuANTUM-R led to quizartinib approval for use as monotherapy in Japan for the treatment of adult patients with *FLT3*-ITD–positive R/R AML, as detected by an approved test [76]. The LeukoStrat® CDx *FLT3* Mutation Assay (Invivoscribe, Inc., San Diego, CA) is approved for the *FLT3*-ITD–positive R/R AML setting [77].

In the United States and European Union, gilteritinib gained approval for the treatment of patients with *FLT3*-mutated R/R AML, based on the results of the ADMIRAL phase 3 study [18, 19, 29–31]. In ADMIRAL, gilteritinib monotherapy (120 mg/day) was assessed versus salvage chemotherapy in 371 patients with *FLT3*-mutated R/R AML (with ITD or TKD mutations) [31]. Patients had received prior therapy with an anthracycline-containing regimen or a nonintensive chemotherapy, and had R/R disease after achieving CR, regardless of duration of remission [31]. At the median follow-up of 17.8 months, the median OS favored gilteritinib with 9.3 months (vs. 5.6 months with salvage chemotherapy; HR = 0.64, 95%

Table 2 Summary of the efficacy and QTcF findings across all 5 daily quizartinib doses studied in the phase 2 program

Parameter	NCT01565668/2689-CL-2004 [54, 64]		NCT00989261/AC220-002 [54, 72]		
	30 mg/day[a]	60 mg/day[b]	90 mg/day	135 mg/day	200 mg/day
Best response, n (%)					
n	38	38	57	67	12
CRc	18 (47.4)	18 (47.4)	27 (47.4)	30 (44.8)	5 (41.7)
PR	5 (13.2)	9 (23.7)	14 (24.6)	19 (28.4)	6 (50.0)
Maximum change in QTcF from baseline (ms), n (%)					
n	38	36[c]	150	166	17
≤ 30	18 (47.4)	14 (38.9)	13 (8.7)	18 (10.8)	0
> 30 to ≤ 60	18 (47.4)	15 (41.7)	74 (49.3)	82 (49.4)	3 (17.6)
> 60	2 (5.3)	7 (19.4)	61 (40.7)	62 (37.3)	14 (82.4)

[a] A 30-mg starting dose with permitted escalation to 60 mg for lack of or loss of initial response. [b]A 60-mg starting dose with permitted escalation to 90 mg for lack of or loss of initial response. [c]Two patients in the 60-mg/day group were randomized but never treated with quizartinib

CRc, composite complete remission (CR + CRp + CRi); CRi, complete remission with incomplete neutrophil or platelet recovery; CRp, complete remission with incomplete platelet recovery; PR, partial remission; QTcF, QT interval corrected with Fridericia's formula

CI = 0.49–0.83, $p < 0.001$) [31]. The median EFS was 2.8 months in the gilteritinib group and 0.7 months in the chemotherapy group, with an HR of 0.79, and was not significantly different between the treatment arms [31]. The median OS remained unchanged at a longer follow-up of 37.1 months [78]. A summary of QuANTUM-R and ADMIRAL is presented in Table 3. The design of the two studies were slightly different making comparisons challenging, but the overall benefit is similar. Importantly, quizartinib was not investigated and is not predicted to have meaningful clinical benefits for patients with *FLT3*-TKD mutation. Regardless, since quizartinib is only approved in Japan for patients with *FLT3*-mutated R/R AML, clinical decisions in most countries for this setting are limited to the use of gilteritinib, which is a very valuable option for these patients.

Efficacy for combination regimens including quizartinib

Phase 1 studies

The phase 1 study (NCT01390337/2689-CL-0005) evaluated two doses of quizartinib (40 and 60 mg/day) in combination with standard chemotherapy in 19 patients with newly diagnosed AML unselected for *FLT3* mutation status (Table 1) [79]. The ORR was 84.2%, with 73.7% of patients achieving CRc [79]. Of the 9 patients with *FLT3*-ITD mutations, 66.7% achieved CRc, and among all 19 patients, 47.4% proceeded to allo-HCT [79]. This study provided early evidence of antileukemic activity of quizartinib plus standard chemotherapy, supporting further studies to confirm these results in patients with newly diagnosed AML [79].

The phase 1b study (NCT02834390/AC220-A-J102) evaluated two doses of quizartinib (20 and 40 mg/day) in combination with standard chemotherapy in 7 Japanese patients with newly diagnosed AML unselected for *FLT3* mutation status (Table 1) [80, 81]. In this small study, the ORR was 85.7% and the CRi rate was 71.4% [80, 81].

Phase 3 studies

The phase 3 study QuANTUM-First (NCT02668653/AC220-A-U302) compared quizartinib versus placebo in combination with chemotherapy in induction and consolidation, including allo-HCT, followed by up to 3 years of quizartinib or placebo single-agent continuation, in 539 patients (quizartinib, n = 268; placebo, n = 271) with newly diagnosed *FLT3*-ITD–positive AML aged 18–75 years (Table 1) [47]. Patients received quizartinib or placebo at a starting dose of 40 mg/day on day 8 of the start of chemotherapy and continued treatment with quizartinib or placebo until day 21 [47]. Patients who did not achieve CR or CRi could receive a second cycle of induction (7 + 3 or 5 + 2 regimens plus quizartinib or placebo, at the discretion of the investigator) [47]. Patients who achieved CR or CRi could receive consolidation with high-dose cytarabine plus quizartinib (40 mg/day) or placebo for 14 days of each cycle, starting on day 6 [47]. Patients who concomitantly received a strong CYP3A inhibitor had their quizartinib dose reduced to 20 mg/day [47]. Patients could receive an allo-HCT at any time during the consolidation phase [47]. Continuation with quizartinib or placebo monotherapy was allowed after consolidation (with cytarabine and/or allo-HCT), with

Table 3 Summary of efficacy in QuANTUM-R and ADMIRAL studies

Parameter	QuANTUM-R [46]		ADMIRAL [31]	
	Quizartinib (n = 245)	Salvage chemotherapy (n = 122)	Gilteritinib (n = 247)	Salvage chemotherapy (n = 124)
Best response, n (%)				
CRc	118 (48.2)	33 (27.0)	134 (54.3)	27 (21.8)
CR	10 (4.1)	1 (0.8)	52 (21.1)	13 (10.5)
CRi	99 (40.4)	32 (26.2)	63 (25.5)	14 (11.3)
CRh	NA	NA	32 (13.0)	6 (4.8)
Median OS, months (95% CI)	6.2 (5.3–7.2)	4.7 (4.0–5.5)	9.3 (7.7–10.7)	5.6 (4.7–7.3)
OS, HR (95% CI)	0.76 (0.58–0.98); one-sided $p = 0.02$		0.64 (0.49–0.83); two-sided $p < 0.001$	
1-year OS rate, %	27	20	37	17
Eligibility	Refractory or relapsed (duration of first CRc of ≤ 6 months) to anthracycline-containing or mitoxantrone-containing chemotherapy *FLT3*-ITD		Refractory or relapsed to anthracycline-containing chemotherapy or an alternative therapy appropriate to induce remission *FLT3*-ITD or *FLT3*-TKD	

CI, confidence interval; CR, complete remission; CRc, composite complete remission (CR + CRp + CRi); CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; HR, hazard ratio; NA, not assessed; OS, overall survival. *FLT3*-ITD, *FMS*-related receptor tyrosine kinase 3–internal tandem duplication; *FLT3*-TKD, *FMS*-related receptor tyrosine kinase 3–tyrosine kinase domain

a quizartinib starting dose of 30 mg/day, escalated to 60 mg/day after 15 days if QTc remained at or less than 450 ms [47]. At the median follow-up of 39.2 months, the addition of quizartinib provided a statistically significant improvement in OS (primary endpoint) versus standard induction and consolidation chemotherapy (HR = 0.776, 95% CI = 0.615–0.979, $p = 0.0324$), reducing the relative risk of death during the observation period by 22.4% [47]. The median OS was 31.9 months for quizartinib versus 15.1 months for placebo [47]. The primary analysis of EFS (secondary endpoint) based on an induction treatment failure (ITF) according to the United States Food and Drug Administration (FDA) definition [82] (no CR by day 42 of the last induction cycle), showed no statistically significant difference between arms [47]. The EFS was favorable for quizartinib over placebo based on additional prespecified EFS sensitivity analyses with ITF defined as no CRc (HR = 0.729, 95% CI = 0.592–0.897, nominal $p = 0.0031$) or CR (HR = 0.818, 95% CI = 0.669–0.999, nominal $p = 0.0323$) by the end of induction up to day 56 [47]. Between day 42 and the end of the induction, there were 51 patients who achieved CR, with more patients in the quizartinib arm (n = 33) than the placebo arm (n = 18) [47, 83]. These 51 patients were considered as ITF with EFS event on day 1 in the primary analysis of EFS [47, 83]. Among these 51 patients, 9 patients (quizartinib, n = 5; placebo, n = 4) had CRi at day 42 and achieved CR after day 42 in the induction phase [83]. Therefore, the favorable EFS observed with quizartinib over placebo in the sensitivity analyses may be driven by late and durable responders in the quizartinib arm, indicating the relevance of a 56-day window for EFS assessment [83]. Furthermore, a prespecified sensitivity OS analysis that censored patients who received allo-HCT at any time during the study at the start of conditioning regimen for transplant, revealed that the HR for OS favored quizartinib over placebo (HR = 0.752, 95% CI = 0.562–1.008) [47]. Additionally, the median DoCR was longer with quizartinib, at 38.6 months (95% CI = 21.9–not evaluable), versus placebo, at 12.4 months (95% CI = 8.8–22.7) [47].

Quizartinib has recently been approved by the FDA [84, 85], the Japanese health agency [86], the European Medicines Agency [87, 88], and the United Kingdom health agency [89, 90]. The approved indication is in combination with chemotherapy across induction, consolidation, and as maintenance monotherapy (but not after allo-HCT in the United States), for the treatment of adult patients with newly diagnosed *FLT3*-ITD–positive AML, based on data of the QuANTUM-First study [47] as detected by the LeukoStrat CDx *FLT3* Mutation Assay as the companion diagnostic (CDx) [77, 85, 86, 88, 91–93]. Data from a bridging study demonstrated agreement between the clinical trial assay and the LeukoStrat CDx *FLT3* Mutation Assay in identifying patients with newly diagnosed *FLT3*-ITD–positive AML [93]. A comparable OS benefit in the intent-to-treat CDx–positive population of the bridging study and the intent-to-treat population of QuANTUM-First was also demonstrated [93]. Based on data from this bridging study [93], the LeukoStrat CDx *FLT3* Mutation Assay is approved for selecting patients with *FLT3*-ITD–positive AML for treatment with quizartinib in the first-line setting [77, 91, 92].

A post hoc multivariable extended Cox regression analysis stratified by region, age, and white blood cell count, with CR duration status as a time-dependent covariate, showed that CR duration was strongly predictive for OS (HR = 0.156, 95% CI = 0.113–0.216; nominal $p < 0.0001$), with similar results for CRc duration [83]. In addition, a post hoc multistate model showed that quizartinib was associated with lower risk of relapse after achievement of CR versus placebo (HR = 0.517, 95% CI = 0.331–0.807) [83]. According to another post hoc multivariable extended Cox regression analysis of OS in all randomized patients, stratified by region, age, and white blood cell count, including allo-HCT in first complete remission (CR1) as a time-dependent variable and adjusted for *FLT3*-ITD variant allele frequency, as well as for sex, quizartinib treatment (HR = 0.770, 95% CI = 0.609–0.973, $p = 0.0284$), and allo-HCT in CR1 (HR = 0.424, 95% CI = 0.301–0.597, $p < 0.0001$) were found to be favorable predictive factors for OS [94]. These analyses demonstrated that patients achieving CR on quizartinib had longer OS compared with placebo, regardless of whether they received an allo-HCT in CR1 or not [94].

Other important post hoc analyses from QuANTUM-First explored the value of *FLT3*-ITD–specific measurable residual disease (MRD) [47, 95, 96]. Quizartinib was associated with a reduction in *FLT3*-ITD leukemic burden by the end of induction, with a median *FLT3*-ITD variant allele frequency (VAF) three-fold lower in the quizartinib arm vs the placebo arm among patients who achieved CR (0.008% vs 0.025%; nominal $p = 0.016$), as well as among patients who achieved CRc (0.01% vs 0.03%; nominal $p = 0.0251$) [47, 95, 96]. Patients in CR and those in CRc with negative MRD based on a cutoff of 0 or 10^{-4} leukemia cells by the end of induction had a longer OS versus patients in CR or CRc with positive MRD, regardless of treatment arm [95, 96]. Using the 10^{-4} MRD cutoff, HR values for OS were 0.627 (95% CI, 0.427–0.922) for CR patients and 0.562 (95% CI, 0.398–0.794) for CRc patients [95, 96]. Further analysis by treatment arm showed that quizartinib provided a survival benefit vs placebo in patients achieving CR or CRc, irrespective of MRD status, using either MRD cutoffs. Therefore, the addition of quizartinib to induction chemotherapy resulted in a deeper remission with respect to

the level of *FLT3*-ITD MRD, and that deeper remission was associated with prolonged survival. Among patients undergoing allo-HCT in CR1 from the time of allo-HCT by latest pre–allo-HCT MRD status, longer OS was observed in those treated with quizartinib versus placebo, irrespective of pre–allo-HCT MRD status [95]. Patients with long ITD (longer than the median) have a worse OS compared with patients with short ITD, regardless of treatment arm. However, quizartinib provides OS benefit over placebo in both patients with long ITD (HR = 0.741, 95% CI = 0.545–1.007) and short ITD [96]. Patients with multiple ITDs have a worse OS compared with patients with just 1 ITD insert, and quizartinib provides OS benefit over placebo regardless of the number of ITD inserts, but especially among patients with multiple ITDs (HR = 0.567, 95% CI = 0.354–0.908) [96].

A post-hoc efficacy subgroup analysis by age [97] was consistent with the primary analysis [47], showing that the overall benefit provided by quizartinib versus placebo was evident irrespective of age group (< 60 years of age group and ≥ 60 years of age group), in terms of longer duration of CR, lower cumulative incidence of relapse (CIR), longer relapse-free survival (RFS), and EFS (56-day window) [97]. CIR at 24 months was lower with quizartinib vs placebo in patients < 60 years of age (22.6% vs 37.8%) as well as in patients ≥ 60 years of age (43.9% vs 51.0%) [97]. An exploratory efficacy analysis revealed a clinical benefit for continuation therapy with quizartinib over placebo as part of a continuum treatment regimen in newly diagnosed *FLT3*-ITD–positive AML patients that includes induction, consolidation, and continuation [98]. For the entire study population, in patients who received continuation, a numerical longer OS, higher RFS rates, and lower CIR rates were observed among those treated with quizartinib [98]. Quizartinib provided a numerical OS benefit over placebo in patients who received continuation therapy, with an HR of 0.683 (95% CI, 0.395–1.183) [98], in favor of quizartinib, which is better than the HR of the primary OS analysis (0.78) [47]. Among the patients who did not undergo transplantation before continuation, quizartinib provided an OS advantage over placebo [98]. Interestingly, more transplanted patients in the quizartinib arm could proceed to continuation compared with the placebo arm, but the number of events was limited among the transplanted patients who proceeded to continuation, precluding a meaningful assessment of the magnitude of efficacy in this patient subgroup [98].

Analysis of the impact of quizartinib on patient-reported outcomes (PRO), an exploratory endpoint in QuANTUM-First, showed an improvement in the quality of life (QOL) and symptoms, assessed using the European Organisation for Research and Treatment of Cancer Quality of life Questionnaire-Core 30 items, for all patients during induction and consolidation, which was maintained during continuation, irrespective of the treatment arm [99, 100]. Importantly, quizartinib showed no consistent short- or long-term deterioration of QOL and symptoms while providing a significant OS benefit in comparison with placebo [99, 100]. The survival analyses on time until definitive deterioration (defined as the time from baseline PRO score to first deterioration of the score beyond a minimal clinically important difference) showed that for most PRO scales, there was no consistent longitudinal difference between the two treatment arms [99, 100]. A subgroup analysis by age (≤ 60 years vs. > 60 years) showed no meaningful differences in QOL scores between treatment arms in either the age group [100]. These PRO analyses indicate that quizartinib was not associated with consistent short- or long-term deterioration of QOL nor symptoms, while providing a significant OS benefit relative to placebo [99, 100].

As previously mentioned, quizartinib and midostaurin, in combination with chemotherapy, have been approved in the United States and European Union as a first-line treatment for patients with newly diagnosed *FLT3*-mutated AML fit for chemotherapy [22, 23, 85, 88], based on QuANTUM-First [47] and RATIFY [24] trials, respectively. Undoubtedly both drugs are good options for patients with newly diagnosed *FLT3*-ITD AML, since both trials showed that quizartinib and midostaurin provided clinical benefits to these patients compared with chemotherapy alone [24, 47]. However, there remains a challenge facing physicians on deciding between quizartinib and midostaurin to treat patients, since no randomized controlled trial directly compared the efficacy and safety of these two drugs. Comparisons between data of the QuANTUM-First and the RATIFY trials are difficult due to differing trial designs and eligibility criteria [24, 47]. For instance, QuANTUM-First enrolled patients 18–75 years of age, while RATIFY enrolled patients 18–59 years of age. QuANTUM-First allowed idarubicin in induction, while RATIFY did not. In RATIFY, patients were randomized before cycle 1 induction therapy, while in QuANTUM-First, patients were randomized on day 7 after the start of induction therapy, which may reduce the incidence of early discontinuations and potentially enrich for a higher-risk population in QuANTUM-First. RATIFY enrolled 22.6% of the patients with the less aggressive *FLT3*-TKD mutations, while QuANTUM-First only enrolled patients with *FLT3*-ITD–positive AML. QuANTUM-First allowed post-transplant maintenance therapy with quizartinib for up to 36 cycles, while in RATIFY, midostaurin maintenance therapy was allowed for up to 1 year, and midostaurin was discontinued among patients who received allo-HCT; therefore, a patient receiving

early transplantation could have limited exposure to midostaurin and its potential effects. Taken together, physicians can use their judgment based on the status of each case and on available information on both drugs. Quizartinib is a more potent and selective FLT3 inhibitor [37–48] than midostaurin, which is considered to be of value for more profound responses in newly diagnosed *FLT3*-ITD–positive AML. Another value of quizartinib is that it is also approved as maintenance monotherapy (but not after allo-HCT in the United States), which can delay relapse and prolong survival. These considerations may render quizartinib the preferred option by physicians for many patients with newly diagnosed *FLT3*-ITD–positive AML who are fit for chemotherapy. In contrast, patients with *FLT3*-TKD mutations are not predicted to respond to quizartinib and are better served with midostaurin, which can be used in patients with either the ITD or TKD mutation. Patients with baseline QTc prolongation that cannot be corrected may also be preferred candidates for midostaurin.

Selected investigator-initiated studies

Several investigator-initiated studies involving quizartinib have begun and for some of them, preliminary data are available (selected studies presented in Table 1). These studies have shown generally encouraging, albeit preliminary results. The combination of venetoclax plus quizartinib at clinically relevant doses resulted in greater antitumor activity in primary blood samples from patients with *FLT3*-ITD–positive AML (ex vivo), as well as a significantly longer survival in a mouse model of MV4-11 cells and in a xenograft model with patient-derived *FLT3*-ITD–positive cells, compared with treatment with either agents alone [101]. Data from this preclinical study led to clinical trials using venetoclax in combination with quizartinib [102–104]. The ongoing phase 1/2 VEN-A-QUI (NCT04687761) study is assessing the triple combinations of azacitidine or low-dose cytarabine plus venetoclax plus quizartinib in patients with newly diagnosed AML aged ≥ 60 years, unfit for intensive induction chemotherapy (Table 1) [105–107]. Among 61 patients enrolled in the phase 2 portion of the study (31 with azacitidine; 30 with low-dose cytarabine), CRc was observed in 52% of patients, with no differences between the two treatment arms (azacitidine, 55%; low-dose cytarabine, 50%) [106]. Patients with *FLT3*-ITD–positive AML had better OS and EFS than those with *FLT3*-ITD–negative AML, as they did not reach median OS/EFS at the latest readout [106]. A biomarker analysis focused on natural killer (NK) cell populations, conducted on this study, found that DNAM-1 (CD226)–positive and TACTILE (CD96)-negative NK cells are associated with better OS [107]. Patients with DNAM-1–positive NK cells had significantly longer median OS (18.4 months) versus those with DNAM-1–negative NK cells (4.7 months, $p = 0.0001$) and patients with TACTILE-negative NK cells had significantly longer median OS (17.36 months) versus TACTILE–positive NK cells (4.6 months, $p = 0.005$) [107].

Another ongoing phase 1/2 study (NCT03661307/2018–0394) is evaluating the triple combination of quizartinib plus decitabine plus venetoclax in patients with newly diagnosed *FLT3*-ITD–positive AML unfit for intensive induction chemotherapy or patients with R/R *FLT3*-ITD–positive AML (Table 1) [102–104]. This study showed preliminary encouraging results, with 100% of the 14 newly diagnosed patients and 65% of the 43 patients with R/R *FLT3*-ITD–positive AML achieving CRc [102–104].

The ongoing phase 2/3 National Cancer Research Institute AML18 study (NCT02272478) is comparing the sequential addition of quizartinib in cycles 2 and 3 (followed by single-agent quizartinib maintenance), after cycle 1 with intensive chemotherapy versus continuing cycles 2 and 3 with chemotherapy alone, in 464 patients with newly diagnosed AML or high-risk myelodysplastic syndrome (MDS) aged ≥ 60 years (Table 1) [108, 109]. There was no difference in median OS between quizartinib-treated patients and those who did not receive quizartinib (29 months in both groups; HR = 1.035, 95% CI = 0.823–1.303, $p = 0.769$) [108]. Among the 443 patients who achieved CRc, there was no difference in median RFS between quizartinib-treated patients (18 months) and those who did not receive quizartinib (19 months; HR = 1.070, 95% CI = 0.855–1.341, $p = 0.550$) [108]. Among 117 *FLT3*-mutated patients, there was a nonsignificant trend towards improved median OS in quizartinib-treated patients (33 months) versus those who did not receive quizartinib (26 months; HR = 0.688, 95% CI = 0.428–1.106, $p = 0.121$) [108].

Safety

Safety data from the pivotal phase 3 QuANTUM-First study [47] were pooled with nine other completed clinical studies in AML (N = 1081; All AML Pool), including patients with newly diagnosed and those with R/R AML treated with quizartinib monotherapy (n = 791) or combined with chemotherapy (n = 290) [54]. In the pooled data, patients receiving various starting doses were included (< 30, 30–60, and > 60 mg, including those who received 90, 135, 200, 300, and 450 mg), regardless of whether quizartinib was given as a single agent or combined with chemotherapy [54].

Summary of safety

The incidence of severe (grade ≥ 3) treatment-emergent adverse events (TEAE) in the QuANTUM-First study was comparable between the quizartinib (92.1%) and placebo arms (89.6%), suggesting that most of the adverse events were chemotherapy driven. Still, the rates of occurrence of protocol-defined treatment-emergent serious adverse events, TEAEs associated with discontinuation and interruption, and drug-related TEAEs were higher with quizartinib than with placebo (Table 4) [47]. Collectively, the incidences of TEAEs in the total pool of patients treated with 30–60 mg of quizartinib were consistent with those treated with quizartinib of the QuANTUM-First study (Table 4) [47, 54].

Treatment-emergent adverse events

QTC prolongation, torsades de pointes, and cardiac arrest

A black box warning on the label of quizartinib mentions QTc prolongation, torsades de pointes, and cardiac arrest; therefore, quizartinib is available only through the Risk Evaluation and Mitigation Strategy (REMS) program [85]. Of the 265 patients with newly diagnosed *FLT3*-ITD–positive AML treated with quizartinib in QuANTUM-First, an increase from baseline QTcF > 500 ms was reported in 2.3% of patients and 10.2% of patients had a QTcF increase > 60 ms [47, 85]. In QuANTUM-First, there were no cases of torsades de pointes, and 0.8% (2/265) of the patients in the quizartinib group had cardiac arrest with recorded ventricular fibrillation on electrocardiogram [47]. Of the 1081 patients with AML treated with quizartinib in various clinical trials, cardiac arrest was reported in 0.6% of patients (including fatal outcome in 0.4% of patients), torsades de pointes in 0.2%, and ventricular fibrillation in 0.1% [54, 85]. Risk minimization measures for QTc prolongation include QTcF-based dose initiation and modification criteria, regular electrocardiogram monitoring, monitoring for and correction of relevant risk factors (including serum electrolyte abnormalities prior to and during administration of quizartinib), and minimizing and avoiding (when possible) the use of concomitant QT-prolonging medications,

Table 4 Summary of overall safety (safety analysis set)

TEAEs, n (%)	QuANTUM-First [47, 54]		All AML Pool [54][a]			
	Quizartinib (n = 265)	Placebo (n = 268)	Quizartinib < 30 mg (n = 30)	Quizartinib 30–60 mg (n = 669)	Quizartinib > 60 mg (n = 382)	Total quizartinib (N = 1081)
Any TEAE	264 (99.6)	265 (98.9)	29 (96.7)	664 (99.3)	380 (99.5)	1073 (99.3)
Grade 3/4	214 (80.8)	214 (79.9)	17 (56.7)	495 (74.0)	198 (51.8)	710 (65.7)
Grade ≥ 3 (including grade 5)	244 (92.1)	240 (89.6)	22 (73.3)	598 (89.4)	345 (90.3)	965 (89.3)
TEAEs associated with study drug discontinuation	54 (20.4)	23 (8.6)	3 (10.0)	135 (20.2)	119 (31.2)	257 (23.8)
TEAEs associated with study drug interruption	90 (34.0)	54 (20.1)	2 (6.7)	213 (31.8)	111 (29.1)	326 (30.2)
TEAEs associated with death as outcome	30 (11.3)	26 (9.7)	5 (16.7)	104 (15.5)	148 (38.7)	257 (23.8)
Study drug-related TEAEs[b]	160 (60.4)	97 (36.2)	19 (63.3)	501 (74.9)	332 (86.9)	852 (78.8)
Any TESAEs	143 (54.0)	123 (45.9)	9 (30.0)	412 (61.6)	304 (79.6)	725 (67.1)
TESAEs occurring in ≥ 5% of patients in quizartinib arm of QuANTUM-First or in All AML Pool						
Febrile neutropenia	29 (10.9)	22 (8.2)	0	106 (15.8)	131 (34.3)	237 (21.9)
Pneumonia	17 (6.4)	15 (5.6)	2 (6.7)	62 (9.3)	52 (13.6)	116 (10.7)
AML[c]	0	0	0	11 (1.6)	72 (18.8)	83 (7.7)
Sepsis	10 (3.8)	14 (5.2)	0	32 (4.8)	26 (6.8)	58 (5.4)
Pyrexia	8 (3.0)	5 (1.9)	0	26 (3.9)	20 (5.2)	46 (4.3)
ECG QT prolonged	1 (0.4)	1 (0.4)	0	8 (1.2)	36 (9.4)	44 (4.1)
Disease progression[b]	0	0	3 (10.0)	11 (1.6)	17 (4.5)	31 (2.9)
Study drug related TESAEs[b]	41 (15.5)	29 (10.8)	2 (6.7)	150 (22.4)	183 (47.9)	335 (31.0)

[a] Data were pooled from NCT00462761, NCT01390337, NCT01468467, NCT02675478, NCT02834390, NCT00989261, NCT01565668, NCT02984995, NCT02039726, and NCT026686539 studies. [b]Causality assessments were based on investigator-reported causality. [c]In studies NCT01565668 and NCT00989261, death due to disease progression or worsening of AML was recorded as a TEAE

AML, acute myeloid leukemia; ECG, electrocardiogram; QT, interval between the start of the Q wave and the end of the T wave; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

as per label instructions [46, 47]. It is recommended to reduce the dose of quizartinib when concomitant strong CYP3A4 inhibitors are administered [46, 47, 85].

Other TEAEs

The most frequently reported all-grade TEAEs (≥20% incidence) in the quizartinib arm of the QuANTUM-First study were febrile neutropenia, pyrexia, diarrhea, hypokalemia, nausea, headache, rash, vomiting, stomatitis, constipation, and neutropenia (Table 5) [47]. Among these, neutropenia and headache occurred more frequently (≥5 percentage points higher incidence) in the quizartinib arm than in the placebo arm (Table 5) [47]. The most frequently reported grade 3/4 TEAEs (≥10% incidence) in the quizartinib arm of the QuANTUM-First study were febrile neutropenia, hypokalemia, neutropenia, pneumonia, and thrombocytopenia (Table 6) [47]. Among these, neutropenia occurred more frequently (≥5 percentage points higher incidence) in the quizartinib arm than in the placebo arm (Table 6) [47]. For the All AML Pool, the pattern and incidence of TEAEs (≥20% incidence) and grade 3/4 TEAEs (≥10% incidence) in the 30- to 60-mg group were consistent with those in the quizartinib arm of QuANTUM-First (Tables 5 and 6) [47, 54]. Cytopenias (neutropenia, anemia, and thrombocytopenia) and febrile neutropenia were the most frequently reported grade 3/4 TEAEs in the All AML Pool with no consistent trend according to dose (Table 6) [54]. Infections (pneumonia) were the second most frequently reported type of severe TEAE (Table 6) [54]. Myelosuppression, which can trigger infections, should be managed by transfusions, growth factor support, and quizartinib dose modifications [47]. Importantly, patients should receive antimicrobial prophylaxis during periods of myelosuppression to decrease the risk of serious infections.

Subgroup analyses of safety

A subanalysis of the QuANTUM-First safety by treatment phase found that fatal infections were more common with quizartinib in induction and consolidation, but not in continuation [110]. In addition, rates of prolonged QTcF > 500 ms were low overall (2.3% for quizartinib in

Table 5 Summary of most frequent all-grade TEAEs that occurred in ≥20% of patients in quizartinib arm of QuANTUM-First or in All AML Pool (safety analysis set)

TEAEs of all grades, n (%)	QuANTUM-First [47, 54]		All AML Pool [54][a]			
	Quizartinib (n = 265)	Placebo (n = 268)	Quizartinib < 30 mg (n = 30)	Quizartinib 30–60 mg (n = 669)	Quizartinib > 60 mg (n = 382)	Total quizartinib (N = 1081)
Any TEAE	264 (99.6)	265 (98.9)	29 (96.7)	664 (99.3)	380 (99.5)	1073 (99.3)
Nausea	90 (34.0)	84 (31.3)	13 (43.3)	272 (40.7)	199 (52.1)	484 (44.8)
Febrile neutropenia	117 (44.2)	113 (42.2)	7 (23.3)	260 (38.9)	151 (39.5)	418 (38.7)
Pyrexia	112 (42.3)	109 (40.7)	8 (26.7)	258 (38.6)	120 (31.4)	386 (35.7)
Diarrhea	98 (37.0)	94 (35.1)	11 (36.7)	220 (32.9)	152 (39.8)	383 (35.4)
Vomiting	65 (24.5)	53 (19.8)	8 (26.7)	195 (29.1)	148 (38.7)	351 (32.5)
Hypokalemia	93 (35.1)	96 (35.8)	8 (26.7)	205 (30.6)	71 (18.6)	284 (26.3)
Anemia	29 (10.9)	19 (7.1)	6 (20.0)	165 (24.7)	113 (29.6)	284 (26.3)
Fatigue	29 (10.9)	23 (8.6)	2 (6.7)	136 (20.3)	133 (34.8)	271 (25.1)
ECG QT prolonged	36 (13.6)	11 (4.1)	3 (10.0)	133 (19.9)	106 (27.7)	242 (22.4)
Decreased appetite	46 (17.4)	36 (13.4)	7 (23.3)	122 (18.2)	98 (25.7)	227 (21.0)
Headache	73 (27.5)	53 (19.8)	5 (16.7)	157 (23.5)	56 (14.7)	218 (20.2)
Edema peripheral	30 (11.3)	37 (13.8)	6 (20.0)	105 (15.7)	104 (27.2)	215 (19.9)
Constipation	56 (21.1)	69 (25.7)	4 (13.3)	131 (19.6)	74 (19.4)	209 (19.3)
Cough	50 (18.9)	44 (16.4)	5 (16.7)	132 (19.7)	70 (18.3)	207 (19.1)
Rash	69 (26.0)	66 (24.6)	4 (13.3)	129 (19.3)	51 (13.4)	184 (17.0)
Pneumonia	39 (14.7)	41 (15.3)	4 (13.3)	101 (15.1)	78 (20.4)	183 (16.9)
Neutropenia	54 (20.4)	27 (10.1)	2 (6.7)	128 (19.1)	43 (11.3)	173 (16.0)
Stomatitis	57 (21.5)	56 (20.9)	7 (23.3)	111 (16.6)	23 (6.0)	141 (13.0)
Dysgeusia	9 (3.4)	5 (1.9)	4 (13.3)	40 (6.0)	81 (21.2)	125 (11.6)

[a] Data were pooled from NCT00462761, NCT01390337, NCT01468467, NCT02675478, NCT02834390, NCT00989261, NCT01565668, NCT02984995, NCT02039726, and NCT026686539 studies

AML, acute myeloid leukemia; ECG, electrocardiogram; QT, interval between the start of the Q wave and the end of the T wave; TEAE, treatment-emergent adverse event

Table 6 Summary of most frequent grade 3/4 TEAEs that occurred in ≥ 10% of patients in quizartinib arm of QuANTUM-First or in All AML Pool (safety analysis set)

Grade 3/4 TEAEs, n (%)	QuANTUM-First [47, 54]		All AML Pool [54][a]			
	Quizartinib (n = 265)	Placebo (n = 268)	Quizartinib < 30 mg (n = 30)	Quizartinib 30–60 mg (n = 669)	Quizartinib > 60 mg (n = 382)	Total quizartinib (N = 1081)
Any grade 3/4 TEAE	214 (80.8)	214 (79.9)	17 (56.7)	495 (74.0)	198 (51.8)	710 (65.7)
Febrile neutropenia	115 (43.4)	110 (41.0)	6 (20.0)	249 (37.2)	148 (38.7)	403 (37.3)
Anemia	15 (5.7)	14 (5.2)	5 (16.7)	128 (19.1)	101 (26.4)	234 (21.6)
Thrombocytopenia	21 (7.9)	26 (9.7)	3 (10.0)	108 (16.1)	55 (14.4)	166 (15.4)
Neutropenia	48 (18.1)	23 (8.6)	2 (6.7)	118 (17.6)	40 (10.5)	160 (14.8)
Pneumonia	30 (11.3)	30 (11.2)	2 (6.7)	65 (9.7)	56 (14.7)	123 (11.4)
Hypokalemia	50 (18.9)	44 (16.4)	4 (13.3)	84 (12.6)	23 (6.0)	111 (10.3)
WBC count decreased	5 (1.9)	7 (2.6)	3 (10.0)	46 (6.9)	11 (2.9)	60 (5.6)
ECG QT prolonged	8 (3.0)	3 (1.1)	0	21 (3.1)	40 (10.5)	61 (5.6)
Hypophosphatemia	18 (6.8)	16 (6.0)	3 (10.0)	34 (5.1)	7 (1.8)	44 (4.1)

[a] Data were pooled from NCT00462761, NCT01390337, NCT01468467, NCT02675478, NCT02834390, NCT00989261, NCT01565668, NCT02984995, NCT02039726, and NCT026686539 studies

AML, acute myeloid leukemia; ECG, electrocardiogram; QT, interval between the start of the Q wave and the end of the T wave; TEAE, treatment-emergent adverse event; WBC, white blood cell

consolidation phase) and only seen in induction and consolidation, not in continuation [110]. Another subanalysis of the QuANTUM-First safety by age (< 60 years vs. ≥ 60 years) showed that the rates of TEAEs leading to death (including early death) were higher in patients aged ≥ 60 years in each treatment arm, and were numerically higher in the quizartinib group (15.1%, older patients) versus placebo (13.0%, older patients), mainly due to infections [110]. Furthermore, rates of prolonged QTcF > 500 ms were more commonly seen with quizartinib versus placebo in the older patients (4.7%) [110].

Quizartinib in *FLT3*-ITD–negative AML

During the early clinical development of quizartinib, some studies enrolled patients with AML regardless of *FLT3*-ITD status; these studies provided early evidence of the potential role of quizartinib in patients with *FLT3*-ITD–negative AML. Among 37 patients with *FLT3*-ITD–negative R/R AML enrolled in a phase 1 study (NCT00462761/CP0001) of quizartinib monotherapy, the ORR was 13.5% and the CRc rate was 5.4%, with median DoCR of 24 weeks, indicating some efficacy in these patients (Table 1) [6]. More encouraging data emerged from the 84 patients with *FLT3*-ITD–negative R/R AML enrolled in a phase 2 study (NCT00989261/AC220-002) of quizartinib monotherapy, where 33.3% achieved a CRc (36.4% in cohort 1 [older, second-line setting] and 30.0% in cohort 2 [younger, third-line setting]; Table 1) [72]. Among 10 patients with newly diagnosed *FLT3*-ITD–negative AML enrolled in a phase 1 study (NCT01390337/2689-CL-0005) of quizartinib combined with standard chemotherapy, 80.0% achieved CRc (Table 1) [79].

The ongoing randomized, placebo-controlled phase 2 QUIWI (NCT04107727) study is comparing standard chemotherapy plus quizartinib versus standard chemotherapy plus placebo in patients, aged up to 70 years, with newly diagnosed *FLT3*-ITD–negative AML and fit for intensive chemotherapy (Table 1) [111–113]. Preliminary results on 257 patients evaluable for response indicate similar CRc rates (78% in each treatment arm) [112]. However, among all the 273 patients enrolled, quizartinib provided longer EFS (HR = 0.741, 95% CI = 0.535–1.026, $p = 0.059$) and significantly longer OS (HR = 0.569, 95% CI = 0.385–0.841, $p = 0.004$), compared with placebo [112]. In addition, among 201 patients who achieved CRc, quizartinib provided significantly longer RFS (HR = 0.631, 95% CI = 0.414–0.962, $p = 0.031$), compared with placebo [112]. A correlative analysis conducted on the QUIWI study identified a subset of patients with *FLT3*-ITD–negative AML with a *FLT3*-like gene expression signature (a gene signature similar to *FLT3*-ITD–positive AML) who derived significant clinical benefit from quizartinib versus placebo (HR for OS = 0.41, $p = 0.012$) [113]. Instead, in patients without *FLT3*-like signature, there was no difference in clinical outcome between quizartinib and placebo (HR for OS = 1.22, $p = 0.62$) [113]. Further analysis showed that among patients with *FLT3*-like signature, those with *NMP1* or *DNMT3A* mutations derived significant clinical benefit from quizartinib versus placebo (HR for OS = 0.20, $p = 0.02$) [113].

Table 7 Ongoing studies of quizartinib

Identifier(s)	Phase	Treatment arm(s)	Disease	Age	Status
NCT04687761 VEN-A-QUI [105]	1/2	Azacitidine + venetoclax + quizartinib vs. Low-dose cytarabine + venetoclax + quizartinib	Newly diagnosed AML unfit for intensive induction chemotherapy (regardless of *FLT3*-ITD mutation status)	≥ 60 years	Recruiting[a]
NCT03661307 2018–0394 NCI-2018–01789 [102]	1/2	Decitabine + venetoclax + quizartinib	Newly diagnosed unfit for intensive induction chemotherapy or R/R *FLT3*-ITD–positive AML, or high-risk MDS	≥ 18 years	Recruiting[a]
NCT04128748 2019–0351 NCI-2019–06051 [114]	1/2	Liposomal cytarabine and daunorubicin (CPX-351) + quizartinib	AML or high-risk MDS	18–60 years (1L cohort) ≥ 18 years (R/R cohort)	Recruiting
NCT04047641 2017 -0153 NCI-2019–04730 [115]	1/2	Cladribine, idarubicin, cytarabine (CLIA) + quizartinib	AML or high-risk MDS	18–65 years (1L cohort) ≥ 18 years (R/R cohort)	Recruiting
NCT04493138 2019–1178 NCI-2020–05261 [116]	1/2	Azacitidine + quizartinib	MDS or myelodysplastic/myeloproliferative neoplasm with *FLT3* or *CBL* mutations	≥ 18 years	Recruiting
NCT03793478 AC220-A-U202 [117]	1/2	Reinduction with fludarabine and cytarabine + quizartinib, followed by optional consolidation (cytarabine + etoposide + quizartinib) and by optional single-agent quizartinib maintenance therapy	R/R *FLT3*-ITD–positive AML	1 month–21 years (children and young adults)	Recruiting
NCT04107727 QUIWI [111]	2	Quizartinib (or placebo) + induction and consolidation chemotherapy followed by single-agent quizartinib (or placebo) maintenance therapy	Newly diagnosed *FLT3* wild-type AML fit for intensive chemotherapy	18–70 years	Active, not recruiting[a]
NCT05994690 2022–002885-34 2023–504999-25 2023–505000-27 CHIP-AML22/Master [118, 119]	2/3	Quizartinib + induction and consolidation chemotherapy followed by single-agent quizartinib maintenance therapy	Newly diagnosed *FLT3*-ITD–positive and *NPM1* wild-type AML	0–18 years (children and adolescents)	Recruiting
NCT02272478 NCRI AML18 [109]	2/3	After cycle 1 of intensive chemotherapy induction, patients receive (in cycles 2 and 3) either further chemotherapy + quizartinib or chemotherapy alone. Patients on quizartinib receive maintenance therapy consisting of either 1 or 12 cycles of single-agent quizartinib	Newly diagnosed AML or high-risk MDS fit for intensive chemotherapy (regardless of *FLT3*-ITD mutation status)	≥ 60 years	Active, not recruiting[a]
NCT06578247 QuANTUM-WILD	3	Quizartinib (or placebo) + induction and consolidation chemotherapy followed by single-agent quizartinib (or placebo) maintenance therapy	Newly diagnosed *FLT3* wild-type AML fit for intensive chemotherapy	≥ 18 years	Not yet recruiting

[a] Preliminary data for these ongoing trials are available, see Table 1

1L, first line; AML, acute myeloid leukemia; *FLT3*-ITD, *FMS*-related receptor tyrosine kinase 3–internal tandem duplication; MDS, myelodysplastic syndrome; R/R, relapsed/refractory

Ongoing clinical trials of quizartinib in AML

Many clinical trials that assess quizartinib combination with other agents with antineoplastic activity are currently ongoing (representative sample of these studies are presented in Table 7). Quizartinib is being tested not only in patients with *FLT3*-ITD–positive AML, but also in patients with *FLT3*-ITD–negative AML, in both the first-line (EudraCT: 2023-507936-20-00; NCT06578247; QuANTUM-WILD) and R/R settings, and in patients fit or unfit for intensive chemotherapy. Quizartinib is being assessed mainly in adult populations, but also in a few pediatric studies; some studies also include patients with MDS.

Results of these ongoing studies may open new avenues for quizartinib approvals in *FLT3*-ITD–negative AML, as well as for patients unfit for intensive chemotherapy.

Conclusions

In past decades, tremendous progress has been made in the development of FLT3 inhibitors to overcome the deleterious impact of *FLT3* mutations. The QuANTUM-First study established the benefits of adding quizartinib to induction and consolidation chemotherapy in patients with newly diagnosed *FLT3*-ITD–positive AML fit for intensive chemotherapy and led to the approval of quizartinib in the United States, Japan, and Europe in this setting. QuANTUM-R demonstrated the benefits of quizartinib monotherapy in *FLT3*-ITD–positive R/R AML and led to the approval of quizartinib in Japan in this setting. Quizartinib is a potent FLT3 inhibitor that has an overall manageable safety profile, although it has a black box warning mentioning QTc prolongation, torsades de pointes, and cardiac arrest in patients with newly diagnosed *FLT3*-ITD AML. It would be beneficial to further optimize the clinical value of quizartinib and find additional clinical settings for quizartinib use both in the frontline and salvage settings. This could be achieved by (1) testing quizartinib-based combination with various anticancer compounds, particularly for patients unfit for intensive chemotherapy, (2) better characterization of the mechanisms of resistance, (3) clarifying the role of quizartinib as a maintenance therapy after allo-HCT, and (4) investigating quizartinib in patients with *FLT3*-ITD–negative AML given the encouraging early phase 2 data.

Abbreviations

allo-HCT	Allogeneic hematopoietic cell transplantation
AML	Acute myeloid leukemia
CDx	Companion diagnostic
CI	Confidence interval
CIR	Cumulative incidence of relapse
CR	Complete remission
CR1	First complete remission
CRc	Composite complete remission
CRi	CR with incomplete neutrophil or platelet recovery
CYP3A	Cytochrome P450 3A
DoCR	Duration of complete remission
EFS	Event-free survival
ELN	European LeukemiaNet
FDA	Food and Drug Administration
FLAG-IDA	Fludarabine, cytarabine, and granulocyte colony-stimulating factor with idarubicin
FLT3	FMS-related receptor tyrosine kinase 3
hERG	Human Ether-a-go-go related gene
HR	Hazard ratio
IC_{50}	Concentration producing 50% inhibition
I_{Ca-L}	Calcium channels
I_{Ks}	Potassium channels
I_{Na}, I_{Na-L}	Sodium channels
ITF	Induction treatment failure
ITD	Internal tandem duplications
MDS	Myelodysplastic syndrome
MEC	Mitoxantrone, etoposide, and cytarabine
MRD	Measurable residual disease
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NOAEL	No observed adverse effect levels
ORR	Overall response rate
OS	Overall survival
PRO	Patient-reported outcomes
QD	Once daily
QOL	Quality of life
QTc	Corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
REMS	Risk Evaluation and Mitigation Strategy
RFS	Relapse-free survival
R/R	Relapsed/refractory (R/R)
TEAE	Treatment-emergent adverse events
TKD	Tyrosine kinase domain
VAF	Variant allele frequency

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JC conceived the organization and scope of the review, drafted, and reviewed the manuscript, and read, and approved the final manuscript.

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