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Targeting FLT3 Mutations in Acute Myeloid Leukemia: The Role of Quizartinib in Precision Medicine

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Abstract Acute Myeloid leukemia (AML) is a genetically heterogeneous hematologic malignancy that disproportionately affects older individuals. Among the various genetic alterations, FLT3 internal tendem duplication (FLT3-ITD) mutations are present in approximately 20-30% of patients and are linked to rapid disease progression and frequent relapses. This review evaluates the role of quizartinib, a second-generation, highly selective FLT3 inhibitor, as a targeted therapeutic option for relapsed or refractory AML. Preclinical studies have demonstrated that quizartinib offers potent inhibition of FLT3 signaling, favorable pharmacokinetic properties, and high bioavailability. Early-phase clinical trials reported promising remission rates in patients harboring FLT3-ITD mutations, while phase III studies further substantiated its efficacy by showing improved overall survival when used alone or alongside standard chemotherapy. Despite these advances, quizartinib's clinical use is limited by challenges such as acquired resistance, off-target effects—including QT interval prolongation—and complex drug-drug interactions. Ongoing research is focused on elucidating resistance mechanisms and developing effective combination regimens to optimize its therapeutic potential. Overall, quizartinib represents a significant breakthrough in precision medicine for AML, offering a promising avenue to improve patient outcomes in this challenging disease.

Keywords FLT3 Mutations, Acute Myeloid Leukemia (AML), Quizartinib, FLT3 Inhibitor, Relapsed/Refractory AML, FLT3-ITD Mutations

Introduction

Acute myeloid leukemia in cancer (CAML) is a disease complicated by major barriers to treatment (1,2). The pathophysiology and molecular heterogeneity of the disease have been understood through immense efforts (3), yet the standard cure for AML has not changed over the years. The most common genetic change is the FLT3 mutation, which accounts for 30% of AML cases (4).

Moreover, the bone marrow myeloid progeny cells grow malignantly, leading to acute myeloid leukemia (AML) (5,6). The indistinguishable precursor cells lead

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to abnormal hematopoiesis, causing organ dysfunction, bleeding, and infection (7,8). The average age of recognition is 67 years, and more than 50% of all AML cases are observed in people over the age of 65 (9). While the

The incidence of AML is 3.7 per 100,000. Another way to refer to Acute Myeloid Leukemia (AML) is as a heterogeneous cancer that leads to various clinical outcomes and treatment options.

Cytogenetics is currently the best predictor of the disease (13). Over the last several years,

A large number of molecular markers have been identified that are crucial for the prognosis of AML(14). Similar to FMS, internal tandem duplication of the tyrosine kinase (15) is one of the most common genetic irregularities and is present in 20 to 30% of cases (16). The treatment of AML caused by Flt3-Itd can be effectively achieved by blocking FLT3 and killing the neoplasm cells. In clinical trials, treatment of recurrent or refractory AML with Flt3-ITD mutation has shown promise. The main themes of this paper are Flt3/Itd mutations, quizartinib pharmacokinetics, and mechanisms of resistance (17,18).

The clinical experience and side effects of quizartinib were discussed, and its use for treating newly diagnosed and refractory AML was suggested (19), especially in patients with FLT3-ITD mutations (20). Quizartinib is an excellent drug for treating AML patients, especially those with FLT3-ITD mutations (21).

Chemistry

As a member of the urea group (22), quizartinib was differentiated by replacing the 5-tert-butyl-1, 2-oxazol-3-yl group, but in position 7(23), the other group was replaced by the 2-(morpholine-4-yl) ethoxy group(24), which was replaced by imidazole in the proposition[2,1-b] [1,3] Benzthiazol-2-yl group. It is a member of the Benz imidazothiazole group. This compound is contained in phenyl urea, isoxazole, and morpholine (25,26).

Pharmacodynamic

Quizartinib revealed antitumor activity in the FLT3-ITD-dependent mouse leukemia model. It has been shown to be a very effective inhibitor of slow potassium currents IKs in vitro, leading to an acceleration of the delay(27). The mean levels of FLT3 (tFLT3) and phosphorus-FLT3 (pFLT3) were reduced from 3312 RLU to 5639 RLU for 1 day, and for 8 days(28), they varied between 1235 RLU and 142 RLU after a dose of 90 mg/female and 135 mg/male in a 28-day regimen, as reported by Cipriani;(29)Click or tap here to enter text. In IDT mutation patients, with or without pFLT3, levels were reduced to a comparable level, which remains unspecified (30).

Acute Myeloid Leukemia (AML)

Acute Myeloid Leukemia (AML) is an aggressive blood cancer characterized by the rapid proliferation of immature myeloid blasts in the bone marrow, leading to its dysfunction. This bone marrow impairment causes a decrease in red blood cells and thrombocytopenia, and increases the individual's susceptibility to infections(31). When determining the appropriate treatment, the 2022 guidelines in accordance with the European LeukemiaNet (ELN) heavily depend on molecular risk stratification(32).

Etiology and Risk Factors

Acute myeloid leukemia (AML) can arise either spontaneously or as a consequence of conditions

Table 1: Quizartinib Antitumor Activity Summary

Aspect	Findings	References
Model	Quizartinib showed antitumor activity in the FLT3-ITD-dependent mouse leukemia model	(27)
Potassium Current Inhibition	Quizartinib is a potent inhibitor of slow potassium currents (IKs) in vitro, which lead to an acceleration of the delay.	(27)
FLT3 & pFLT3 Reduction	Mean FLT3 (tFLT3) and phosphorus-FLT3 (pFLT3) levels decreased from 3312 RLU to 5639 RLU within 1 day and from 1235 RLU to 142 RLU after 8 days.	(28)
Dose-Dependent Effects	In a 28-day Cipriani regimen, a dose of 90 mg (female) / 135 mg (male) results in a reduction of FLT3/pFLT3.	(29)
IDT Mutation Impact	In patients with the FLT3-ITD mutation, pFLT3 levels were reduced to a comparable level, regardless of mutation status.	(30)

such as myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPNs)(33). It may also emerge as a therapy-related disorder after exposure to alkylating agents, topoisomerase inhibitors, or radiation. Additionally, environmental factors, including exposure to benzene and tobacco smoke, contribute to the development of this disease(32).

Epidemiology

AML occurs at an annual rate of about 4.3 cases per 100,000 people in the U.S., resulting in more than 20,000 new cases each year. It tends to be more prevalent among older adults, with a median age of diagnosis of 68 years, and it is more frequently diagnosed in males (32).

Pathophysiology and Molecular Classification

Acute myeloid leukemia (AML) is influenced by genetic and molecular abnormalities that classify patients into low, medium, or high-risk groups. Low-risk AML is associated with genetic alterations such as t(8;21)(q22;q22.1) and inv(16)(p13.1q22). Medium-risk AML includes FLT3-ITD mutations and rearrangements like t(9;11)(p21.3;q23.3). High-risk AML is characterized by the presence of monosomy 5/del(5q), monosomy 7/del(7q), along with mutations in TP53, ASXL1, or EZH2. Mutations in IDH1/2, found in 15–30% of AML cases, are more frequent among older patients(32).

Clinical Presentation and Diagnosis

Acute Myeloid Leukemia (AML) often presents with general symptoms related to bone marrow failure, including fatigue, pallor, easy bruising, bleeding tendencies, and frequent infections, along with physical signs like hepatosplenomegaly and pallor; however, lymphadenopathy is rare(34). The diagnosis can be confirmed through a peripheral blood smear showing blasts, flow cytometry, and a bone marrow biopsy indicating at least 20% blasts. A specific subtype of AML, known as acute promyelocytic leukemia (APL), is identified by the presence of Auer rods and requires prompt treatment with all-trans retinoic acid (ATRA)(32).

Treatment and Management

Induction therapy is chosen based on the patient's overall fitness and their molecular risk classification. Typically, younger and fitter patients are treated

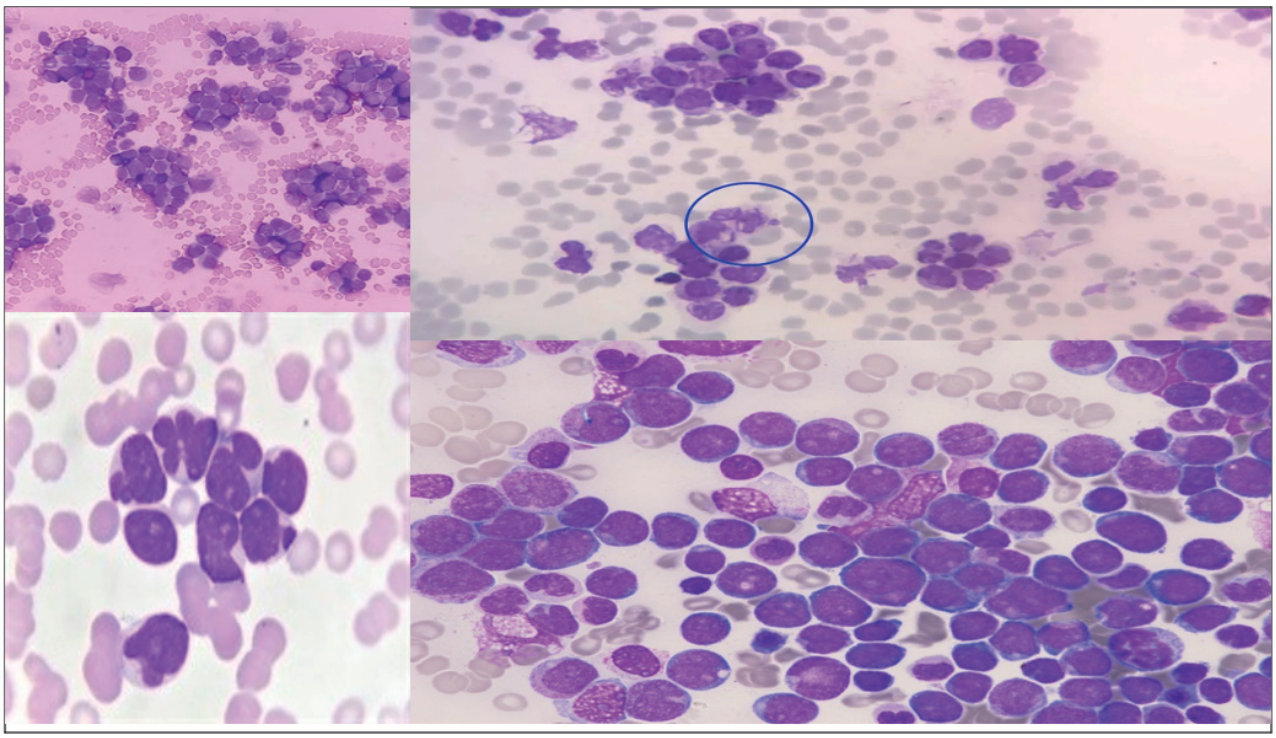


Figure 1: Microscopical observation of mutated cells in AML

with the "7+3" regimen, which includes 7 days of cytarabine followed by 3 days of an anthracycline, while those with high-risk profiles may require FLAG (fludarabine, cytarabine, G-CSF). Older or less fit patients are frequently managed with hypomethylating agents like azacitidine or decitabine in combination with venetoclax. Patients with FLT3 mutations gain advantages from quizartinib(35).

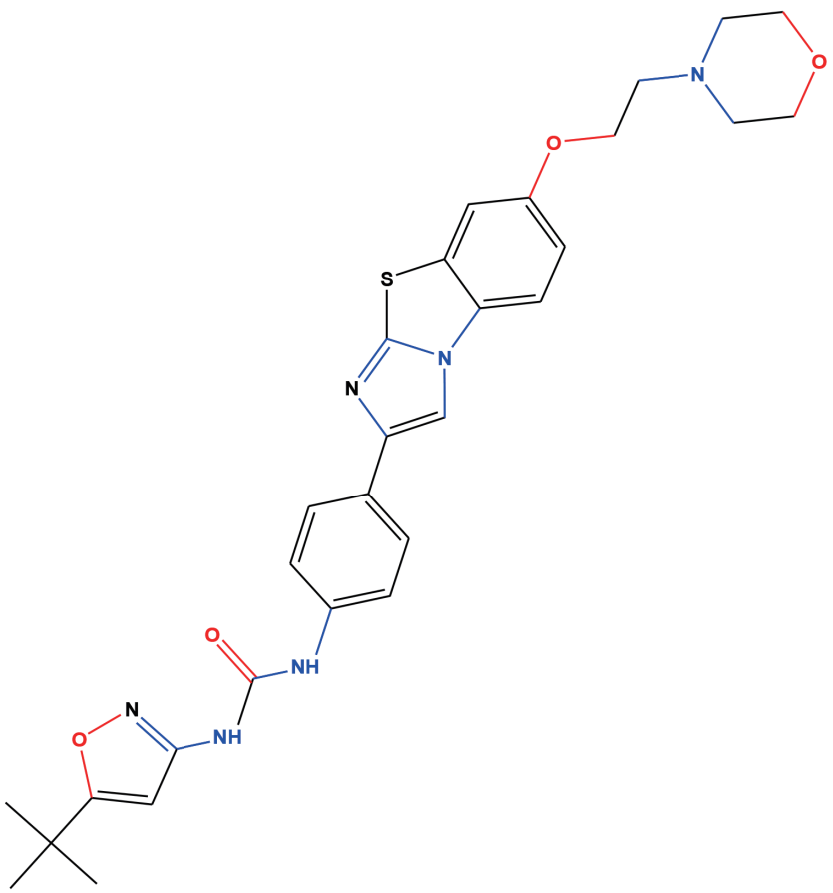
Assessing response entails a bone marrow biopsy following induction therapy, which is best done once the peripheral blood counts have recovered. Complete remission is characterized by having fewer than 5% blasts in the bone marrow(36).

Consolidation therapy focuses on eliminating minimal residual disease and preventing relapse. The standard treatment involves high-dose cytarabine (HiDAC), while allogeneic hematopoietic stem cell transplantation (HSCT) is advised for patients with intermediate- and high-risk profiles(37).

For relapsed AML, targeted therapies are utilized,

DRUG SUMMARY

Drug Name	**Quizartinib**
Phase	**III**
Pharmacological description	**Cancer, leukaemia, acute myelogenous** **Flt-3 kinase inhibitor**
Route of administration	**Oral**
Brand Names	***Vanflyta***
Synonyms	**Quizartinibum**



N-(5-tert-Butyl-1,2-oxazol-3-yl)-N'-(4-{7-[2-(morpholin-4-yl)ethoxy]imidazo[2,1-b][1,3]benzothiazol-2-yl}phenyl)urea

Table 2: All property of quizartinib

Property	Description
Chemical Formula	C29H32N6O4S
Category	FLT3 Inhibitor, Antineoplastic Agent
Brand Name	Vanflyta
Nature	Small molecule kinase inhibitor
Dose	17.7 mg, 26.5 mg, 50 mg (oral tablet)
Absorption	Well absorbed, high oral bioavailability
Distribution	Plasma, bone marrow, leukemic cells
Metabolism	Hepatic (CYP3A4-mediated metabolism)
Protein Binding	>99%
Half-life	~90 hours
Peak Blood Concentrations	400-600 ng/mL (dose-dependent)
Spectrum Of Activity	Selective for FLT3, including FLT3-ITD mutation
Mechanism Of Action	Inhibits FLT3 autophosphorylation and signaling
Acts Against	Acute Myeloid Leukemia (AML) with FLT3-ITD mutation(44)

including gilteritinib (FLT3 inhibitors), ivosidenib (IDH1 inhibitors), and enasidenib (IDH2 inhibitors). Maintenance therapy, such as sorafenib, proves particularly advantageous for patients with FLT3 mutations after HSCT.w(32).

FLT-3 Receptor

The co-structure of Quizartinib with Flt-3 develops the classical Type 2 Kinase Inhibitor binding mechanism in which the imidazobenzothiazole "head" occupies the Adenine binding pocket and the T-butyl-isoxazole tail is located in the kinase's allosteric back pocket(45).

L802 indicates the distal extremity of the rear pocket from αE helix, one of the hydrophobic sidechains that surround the terminal butyl group(46).

Every backbone - NH -of D829 of the DFG design and E661 of the αC helix are hydrogen bonded to the Urea binder connecting the Phenyl and Isoxazole structure. This a common feature across all type II kinase inhibitors containing urea and amides, as well as Imatinib, Sorafenib, Ponatinib (47). Central Phenyl structure in the conserved DFG motif is interacting margin-to-margin gatekeepers F691 & F830(48). inside proteins(46), edge-to-face Relation is the most common interface connecting aromatic residues that are not consecutive. Any perturbation of either F691 or F830, which are the components of the compact unit, is expected to result in a significant decrease in binding affinity. This is the reason why modification in Flt-3, leading to clinical demur to quizartinib, have affected only two residues thus far: The D835 remainder and the gatekeeper F691 residue of the Starting loop control the conformation condition of the DFG motif and the adjustment of F830. As a result of this binding mechanism and the hydrogen-bonding conditions at the hingeQuizartinib's imidazobenzothiazole is positioned inside the small cleft (46).

Although crystallographic examinations have failed to confirm these predictions of the binding mode by forcing quizartinib to make adenine-like hinge contacts, interestingly, the co-crystal structure reveals a workaround: instead of making direct contact with the hinge, the Imidazobenzothiazole group created+ Bidentate Hydrogen(H) bonds with 2 polar backbone Atoms by enlisting help of a water molecule. This modification of the Imadazobenzothiazole provides site selectivity to the accompanying morpholino ethoxy as solubilizing group(26). as mentioned above(46). In some solid and liquid cancers, Tyrosine kinase Inhibitors (TKIs) is employed to inhibit oncogenic RTK signaling(49).

" Many of these inhibitors competitively block ATP in the active area of RTKs, stopping automatic phosphorylation and downstream substrate activation.(50). “Lestaurtinib (CEP-701), Midostaurin (PKC412), Sorafenib (BAY 43-9006);, and Sunitinib (SU11248)(51)” are examples of early FLT3 inhibitors(49). These inhibitors were developed to target several distinct RTKs in a variety of malignancies rather than just FLT3 (52). Numerous investigations are still in progress, but in phase I/II trials, these medications did not, on average, demonstrate substantial and sustained responses

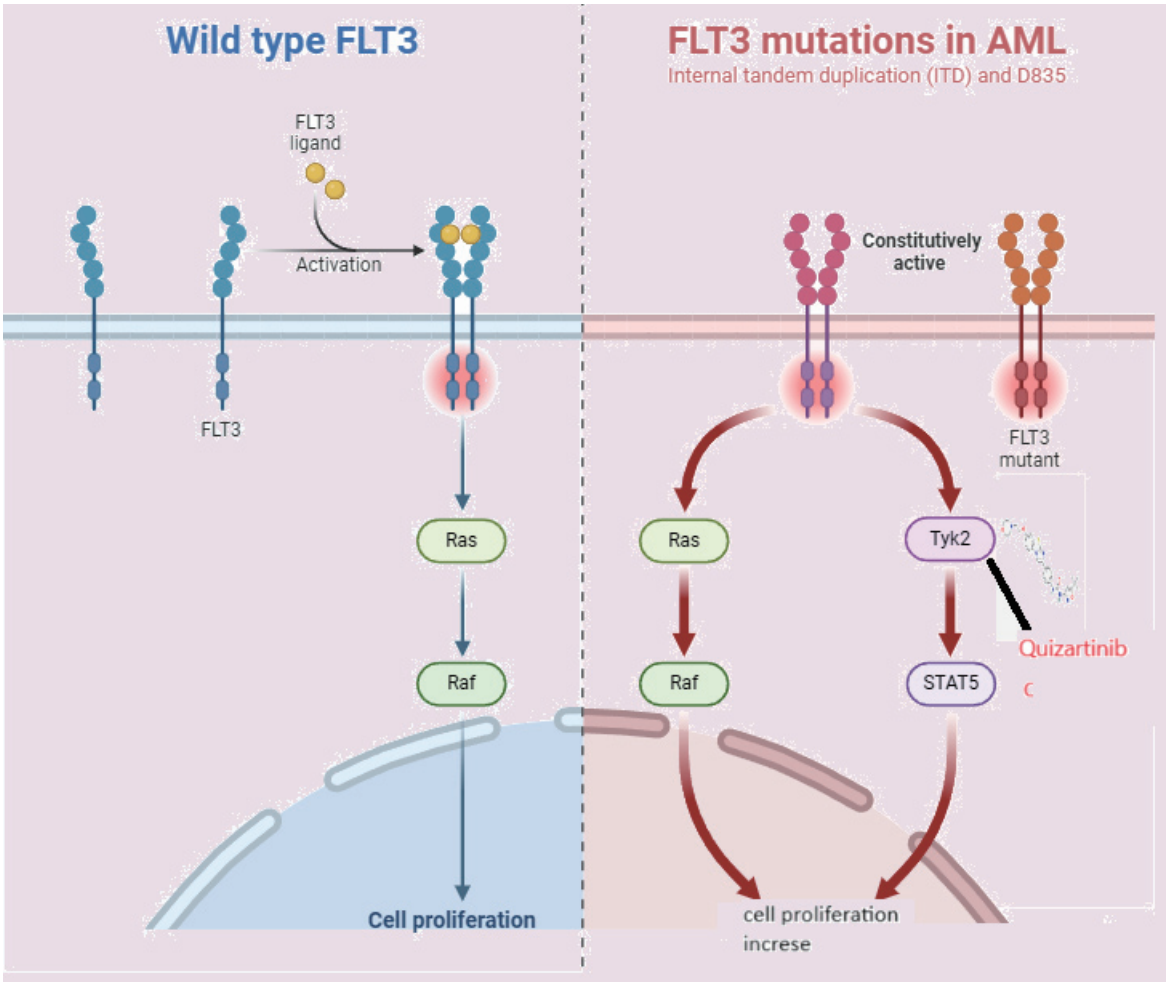


Figure 2: Normal FLT-3 receptor and mutated flt-3 receptor are shown in above figure

as single therapies in various categories of relapsed or refractory AML(53). Molecular discoveries about the processes underlying these poor reactions have influenced our comprehension(49).

Consequently, second-generation FLT3 inhibitors have also been developed(54).

The creation of better second-generation FLT3 inhibitors and our understanding of FLT3 pathobiology have both benefited from molecular insights into the processes driving these subpar(55). Responses". (56)

FLT-3 Inhibitor

Recently, efforts have been made to develop targeted Flt3 tyrosine kinase inhibitors (TKI). Notwithstanding early issues with initial generation of Tyrosine kinase inhibitors (TKIs), such noteworthy toxicity, inefficient Pharmacokinetics, off-target effects, inadequate(57). pick out completely stopped5,(57). many newly released Clinical trials have attracted interest. This paper will detail how FLT3 inhibitors are utilized to cure FLT3-Mutant AML(7)(58).

. Use of FLT3 inhibitors as a treatment after allogenic hematopoietic Stem cell transplantation (HSCT(59)) will be discussed after we discuss their usage as Exclusive therapy or in conjunction with traditional chemotherapy (60).

In years, clinical trials have shown significant promise for several increasingly selective and strong FLT3 inhibitors. Among these(61), quizartinib was first observed using a little-molecule Inhibitor screen.(57,62) Good pharmacokinetic properties, including optimal half-life in vivo and consistently high target inhibition, were also demonstrated by quizartinib(63). 55. 76 R/R AML Patients participated in a phase I test that showed potential efficacy and, notwithstanding the FLT3 irregulate status(62,64).

Of the thirty-three patients (30%) who experienced clinical responses, ten were categorized as either CR or CRi (complete remission with partial hematologic

recoveryCRC (65)(66).

Four cases of Cri or CR were observed in 17 FLT3/ITD patients.55. Despite the drug's tolerability, a small proportion of sufferers experience Gastrointestinal issues, Myelosuppression, and QT Prolongation(57,67). One of some additional targets for this highly selective medication, quizartinib, inhibits KIT, which may have contributed to some of the off-target effects . Phase II quizartinib evaluation data for the two groups of R/R patients are now available. Among 154 older patients (> 60 years), a 51% rate of `Composite fulfilled remission (CRC, which encompasses CR and CRI) was noted (14). The CRC rate for FLT3/ITD patients was 57%,(57) Whereas it was 36% for the 44 FLT3-WT sufferers. The 2nd circle was composed youngest individuals (n=137). Once more, it demonstrates an astounding 44% CRc rate among FLT/ITD participants."(57)- After a clinical response(60), more than one-third of the patients could safely continue receiving HSCT. When used in conjunction with conventional chemotherapy(68), Quizartinib has also been studied for newly diagnosed AML(69); a British study found that 42 evaluable patients had a 79% CR rate(57)(70,71).

Mechanism of Action

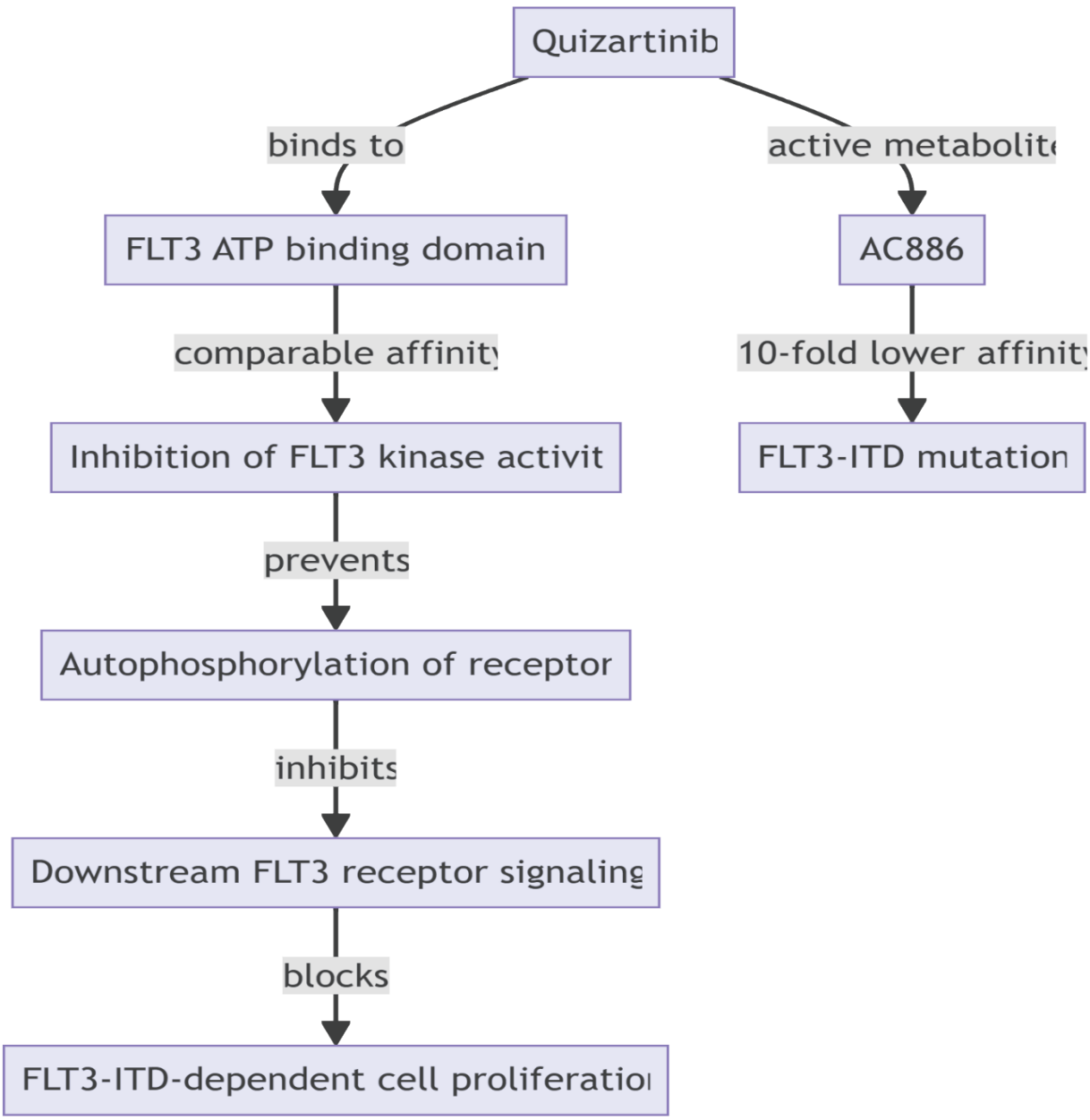


Figure 3: Flowchart explaining the mechanism of action of quizartinib

Quizartinib is a highly selective, orally bioavailable type II tyrosine kinase inhibitor (TKI) that has preferential activity against FMS-like tyrosine kinase 3 (FLT3), a receptor tyrosine kinase involved in hematopoiesis and in the pathogenesis of acute myeloid leukemia (AML). Its action mechanism focuses on blocking constitutively active FLT3 mutants, especially internal tandem duplication (FLT3-ITD) mutations, found in about 30% of AML patients and responsible for sustained proliferation and survival of leukemic blasts(72). FLT3-ITD mutations induce ligand-independent dimerization and autophosphorylation of the receptor, resulting in hyperactivation of downstream signaling cascades like STAT5, MAPK/ERK, and PI3K/AKT/mTOR, which drive cell cycle progression, suppress apoptosis, and increase genomic instability. Quizartinib competitively binds to the ATP-binding pocket of the FLT3 kinase domain, locking the enzyme in its inactive conformation and inhibiting autophosphorylation and subsequent activation of these pro-survival cascades(73). In contrast to type I TKIs (e.g., midostaurin), which bind the active conformation of FLT3, quizartinib's type II binding provides increased selectivity for FLT3-ITD versus wild-type FLT3 and other kinases, minimizing off-target effects while retaining activity against resistance-conferring mutations like FLT3-D835. Yet resistance may still arise through secondary FLT3 mutations (such as FLT3-ITD-D835Y) or engagement of collateral signaling pathways (such as RAS/MAPK, BCL-2)(74).

Clinically, quizartinib has shown substantial activity in relapsed/refractory FLT3-ITD-positive AML, with evidence through phase 3 trials (such as QuANTUM-R), in which it enhanced overall survival versus salvage chemotherapy. Its pharmacokinetic profile is characterized by fast absorption (peak plasma level at 2–4 hours), hepatic metabolism through CYP3A4, and a half-life of 36–72 hours, allowing for once-daily dosing. Its use is, however, restricted by prolongation of QT interval (need for ECG monitoring) and myelosuppression from on-target inhibition of wild-type FLT3 in hematopoietic progenitors(75). Current research investigates combination regimens with hypomethylating agents (e.g., azacitidine) or BCL-2 inhibitors (e.g., venetoclax) to improve efficacy and bypass resistance. Moreover, quizartinib's activity against c-KIT, another receptor tyrosine kinase, has generated interest in its possible use in malignancies caused by c-KIT mutations (e.g., systemic mastocytosis), although this is investigational. There has been ongoing work to define response and resistance biomarkers, further develop dosing schedules, and incorporate quizartinib into frontline AML therapy in order to enhance long-term survival in higher-risk groups(76).

Quizartinib causes natural leukemia cells to undergo apoptosis in vivo

The pro-apoptotic activity of Quizartinib in vitro leukemia & isogenic Mutant (TK models) was confirmed by testing isolated native blasts from patients with freshly diagnosed all.(77). Additional information on these individuals can be found in the extra files. Quizaratinib treatment caused these cells to undergo apoptosis. In a second patient sample taken from an elderly patient's bone marrow aspirate with MLL-associated AML, the IC50 was approximately 3000 nM. This included trisomy 13, which led to an over-representation of the Flt3 gene. Ex vivo IC50s in the lower micromolar ranges may correlate to antileukemic action in vivo due to Quizartinib's good bioavailability.(77). Nevertheless, clinical validation is necessary for this outcome(71,77)."Building on the pharmacodynamic potential of Quizartinib, clinical trials were initiated to evaluate its efficacy and safety in humans."

Clinical trials

Preclinical investigation of quizartinib

Quizartinib was initially discovered by Ambit Biosciences and obtained by Daiichi Sankyo in 2014. Quizartinib is an effective 2nd-generation type 2 Flt3 Inhibitor that inhibits the expression of KIT and PDGFR. The 2009 discovery of quizartinib, one of several medications, showed good tolerance and efficacy in Xenograft models. It is a very powerful Flt3 inhibitor, demonstrating sub-nanomolar effectiveness in tissue culture studies on animal models at concentrations as low as 1 mg/kg (78). Based on these promising preclinical discoveries, quizartinib was included in a clinical trial(79)(57).

Phase1

At the United States and Georgia, a Phase 1 welfare study examined Quizartinib with relapsed/refractory patients,(80) Regardless of the presence of Flt3 Mutations. (79). Seventy-six patients received quizartinib Exclusive therapy at an escalating dose.(81). With grade 3–4 QTc prolongation at 16% and the most used Dose-limiting hazard at 200 to

300 Mg, the Maximum tolerable dose was 200 mg daily(13,82).Thirteen percent of those surveyed had composite complete remission22 (CRc)(21), and thirty percent replied(83,84). According to the International Working Group, total remission (CR) is defined as having less than 5% bone marrow blasts, more than 1000 neutrophils/mm3, and more than 100,000 platelets/mm3.

Transfusion independence23, extramedullary illness/circulating blasts, and Cr with insufficient count recovery (CRi if neutrophils <1000/mm3 or CRp if only platelets < 100 K/mm3).(85) Five] patients who received a CRc experienced incomplete neutrophil recovery(87). and three experienced incomplete platelet recovery. Notably, 53% of patients with FLT3-ITD responded.(88), 5 of whom received CRcs. A phase 1 observation was conducted to determine the ideal dosage to potentially prevent relapse following transplantation because sufferers with FLT3-ITD had a high risk of relapse following allogenic transplantation. In a 3+3 design,(5) 13 were Sufferer included.(5), and a daily dosage of 60 mg was discovered.24. 77% of the patients continued to take Quizartinib for at least a year (5,89).

Phase 2

A single-arm center trial employing Quizartinib monotherapy was conducted to build on starting Phase 1 results. A cohort of individuals aged 18 to 85 who had relapsed or refractory 'AML(85) 'subsequent at least 1 salvage regimen or allogeneic transplant (more than 100 Days post-transplant) and a cohort of individuals 60 years and above it who had relapsed or refractory AML within 12 months of the initial induction cure without an Allogenic transplant were included.(90). While inclusion in the experiment did not require Flt3-Itd mutations, patients were classified as flt3-Itd+ if their allelic frequency was > 10% (91). Sufferer were started on 200 Mg per day, but due to QTc prolongation in the 1st Sufferer(85). the dosage was lowered to 135 Mg for man and 90 Mg for females because it was shown that women were more susceptible to QT 333 patients in all were enrolled(85,92).

There was 36% FLT3-ITD− and 56% (63/112) Flt3-itd+ sufferers in the first group. Of these, less than 10% of patients reached CRc, and one-third of the sufferer were weakly positive for the FLT3-itd variant allele frequency. However, CRi/CRp (60/63 FLT3-ITD+, ITD− 14/16) accounted for most of these cases. Only {3} FLT3-itd+ and {2} FLT3-ITD− patients were able to reach CR.25(93). Of the 136 sufferers in cohort 2 with FLT3-ITD+, 62 out of 136 (46%) and 12 out of 40 (30%) had CRc. Of the 2 groups, five sufferers with FLT3-itd + and 1 with FLT3-itd(5) − achieved CR. QTc Prolongation, Cytopenia (neutropenia, anemia, and thrombocytopenia)(5), and infections (Pneumonia and Febrile Neutropenia) were the all noted adverse events (94).

An adverse event believed to be connected to the medication caused the deaths of 5% of the Patients (18/332), & 1 patient experienced Torsade de points throughout the thesis. To calculate quizartinib dose reductions, a 2end Randomized Phase 2B test was carried out because of issues with cytopenia and QTc prolongation(95). Patients aged ≥18 years who had relapsed following Allogeneic Transplantation or patients with relapsed/refractory AML after at least 1 salvage therapy were qualified for a cure. Only patients who satisfied the FLT3-ITD+ criterion (specified as >10% allelic frequency) were included in phase 2, in contrast to the previous study. If required, there is an option to increase the dose by an additional 30 mg.

Patients were randomly assigned to either 30 Mg (n = 38) or 60 Mg (n = 36) daily. QTcB >480 (QT adjusted using Fridericia's technique) and CRc rate were the main goals(96).

The CRC rate for individuals who began taking 30 or 60 mg/day was 47%. In 17% of those starting at 60 mg and 11% of those starting at 30 mg, QTcB >480 was established.26. 60 MG group had high transplant rates (42.0% vs. 32.01%) (35), a high median subsistence (27.30 weeks vs. 20.90 weeks), Survivors exceeding one Year (5 vs. 1), and a longest duration of CRc (9.10 Weeks vs. 4.20 weeks) than the 30 Mg everyday group. That was just higher Numerically thus the study did not have the power to match these groups Statistically(85,97).

Interestingly, 61.0% (23/38) of the patients needed an increase in their dose to 60 mg per day, whereas four patients at 30 mg attained CRc after the dose increase(98).: In the group using 30 mg daily, the most frequent toxicities were Cytopenia (Anemia 21.10%, Thrombocytopenia 10.50%), nausea 10.5%, exhaustion 13.20%, Febrile neutropenia 10.50%, and Dysgeusia 10.5Extreme neutropenia (11.1%), Nausea (22.2%), Vomiting (11.1%) was more frequent in the 60 mg daily group.26"(81). There were comparable toxicities that persisted (52).

Phase 3

"Cytarabine dosage more intense regimens (FLAG-IDA (Fludarabine, Cytarabine, Granulocyte

colony-stimulating factor, 38) Idarubicin) or MEC (Mitoxantrone, Etoposide, Cytarabine)"(99). After the transplant(100), patients were permitted to resume taking Quizartinib for maintenance and transition to an allogeneic transplant if needed. The basic objective was to survive overall. There were 367 patients in all, 245 of whom were getting chemotherapy and Quizartinib, throughout just under 42 months. (101). Quizartinib is linked to a 24.0% lower chance of death than Chemotherapy (danger ratio 0.76, 95% CI 0.58–0.98; p=0.02). Additionally, the therapy group's Overall survival Increased from 4.7 months to 6.2 months, while the placebo groups did the same (54).

Most of them were Cri or CRp (108/118), and the CRc rate was 48.20%, consistent with past trials. Regarding allogeneic transplantation, only 14 (11.0%) of the 122 Patients received transplantation in the Immunotherapy. Arm, while 78 (32%) had it under quizartinib.27. The most frequent side event among the quizartinib circle was infection (19.0% sepsis or septic shock, 12% Pneumonia). About 3-4% of people on Quizartinib Experience Grade 3 QTc Prolongation. No grade 4 activities were taking place (54,55).

These findings supported the FDA's decision to approve Quizartinib as a stand-alone treatment for relapsed or Refractory illness. Despite encouraging results, the FDA denied quizartinib's application; we go into greater detail about this below (56).

Table 3: Summary of Quizartinib Clinical Trials (Phases 1-3) with References

Phase	Study Design	Population	Dosage	Efficacy	Adverse Events	References
Phase 1	A welfare study in the U.S. and Georgia examining Quizartinib in relapsed/refractory AML patients	76 patients, regardless of FLT3 mutation status	The doses are escalating, with the maximum tolerated dose (MTD) being 200 mg/day.	CRc in 13%, response rate of 30%, FLT3-ITD+ response rate of 53%	QTc prolongation (16% grade 3-4), dose-limiting toxicity at 200-300 mg	(13,21, 22,85,89)
Phase 2	Single-arm study using Quizartinib monotherapy	333 patients aged 18-85, with relapsed/ refractory AML, with or without prior transplant	Initially 200 mg/day, it was reduced to 135 mg for males and 90 mg for females due to QTc prolongation.	CRc: 10% in FLT3-ITD-negative patients, 46% in FLT3-ITD-positive patients	QTc prolongation, cytopenia, pneumonia, febrile neutropenia	(85,94,102)
Phase 2B	Randomized dose comparison study	74 patients, relapsed AML post-transplant or after at least 1 salvage therapy	30 mg/day (n=38) or 60 mg/day (n=36), with the option to increase by 30 mg	CRc rate: 47%, with a higher transplant rate in the 60 mg group.	Cytopenia, QTc prolongation, nausea, vomiting, neutropenia	(5,95,98)
Phase 3	Comparison of Quizartinib with chemotherapy	367 patients with relapsed AML, and 245 received Quizartinib.	Quizartinib maintenance therapy post-transplant allowed	OS improved from 4.7 to 6.2 months, 24% lower death risk (HR 0.76, p=0.02)	Infection (sepsis 19%, pneumonia 12%), QTc prolongation (3-4%)	(54, 55, 80-82)

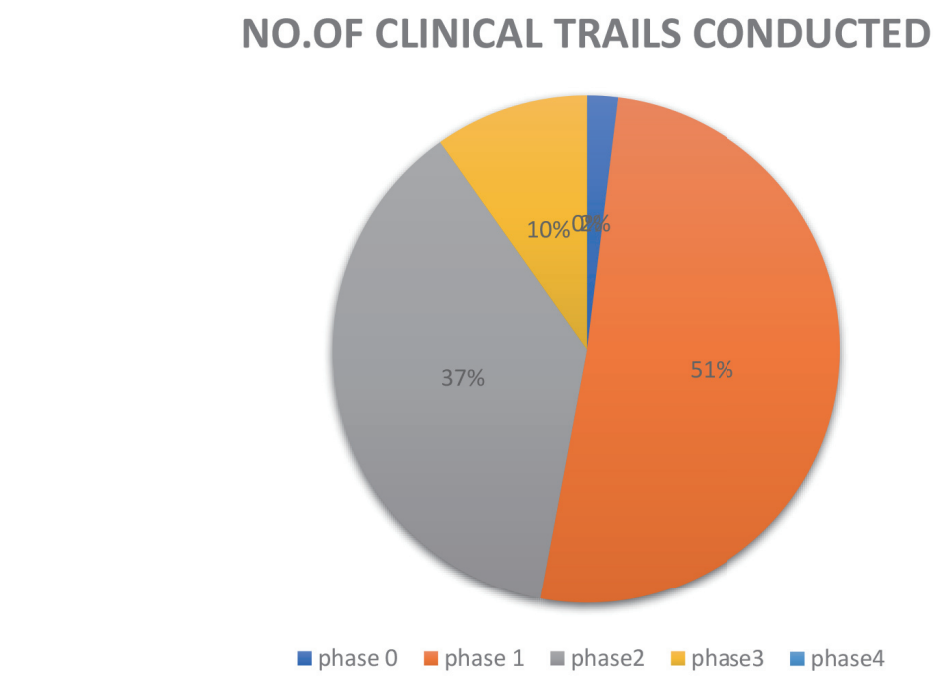
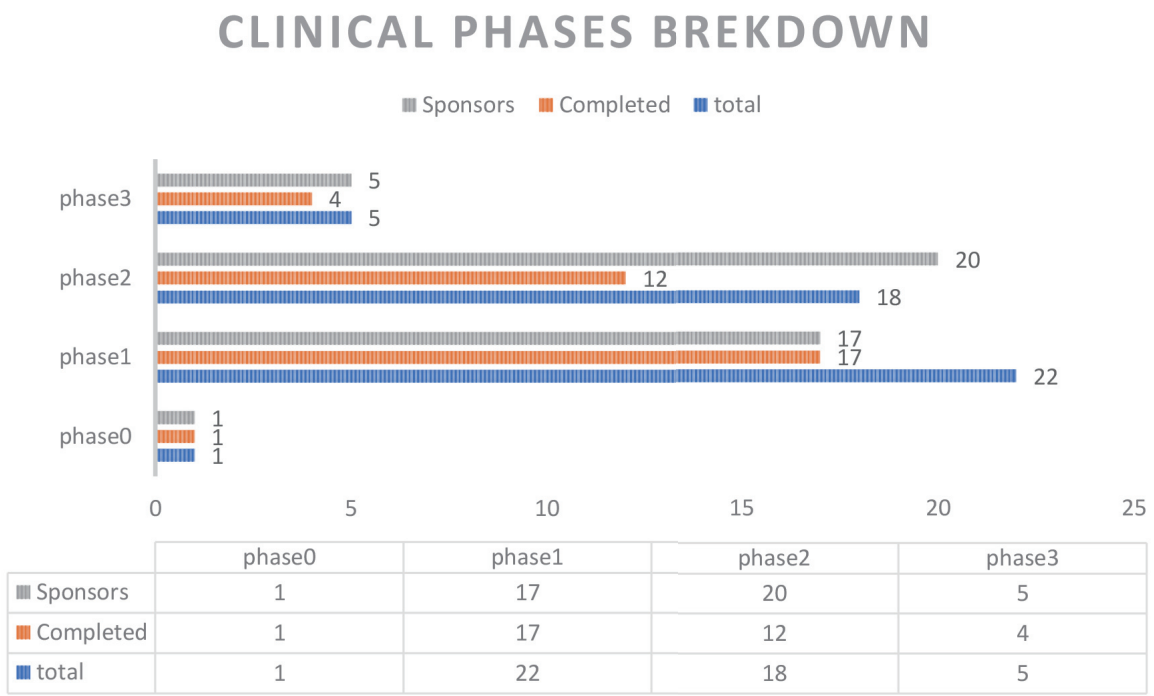


Figure 4: Pie chart showing no. of Clinical trials conducted



	phase0	phase1	phase2	phase3
Sponsors	1	17	20	5
Completed	1	17	12	4
total	1	22	18	5

Figure 5: Graph representing Clinical Phases Breakdown

With various clinical trials carried out on quizartinib, there are other tyrosine kinase inhibitors that quizartinib is compared with in the table 4.

Table 4: Comparison of Quizartinib with Other Tyrosine Kinase Inhibitors (TKIs) for FLT3-ITD AML

Feature	Quizartinib	Other TKIs (e.g., Midostaurin, Gilteritinib, Sorafenib)
FLT3 Selectivity	The compound is highly selective for FLT3-ITD, exhibiting minimal off-target effects.	Broad kinase inhibition can lead to off-target effects.
Potency	Stronger inhibition of FLT3-ITD is achieved with a lower IC50.	The potency varies depending on the TKI.
Efficacy in Relapsed/ Refractory AML	Improved overall survival (OS) was observed, with 6.2 months compared to 4.7 months with chemotherapy in the QuANTUM-R trial.	The efficacy varies; some TKIs show lower efficacy in relapsed cases.
Dosing Convenience	Once-daily oral dosing	Twice-daily dosing is required for some TKIs (e.g., Midostaurin).
Safety Profile	The safety profile is favorable with lower gastrointestinal toxicity, but there is a risk of QT prolongation.	There are more off-target toxicities, including GI toxicity and rash.
Resistance Profile	Retains activity in patients who are resistant to midostaurin.	Some TKIs are less effective in cases of resistance
Combination Potential	Shows synergy with chemotherapy and hypomethylating agents.	Some TKIs are also explored in combination therapies.

(103)

With the advantages of quizartinib, drug reactions also occur when other drugs are administered with quizartinib, as explained in the next table.

Table 5: Quizartinib's drug interaction with other drugs

Drug	Interaction
Abacavir	Combining Quizartinib with Abacavir can reduce their metabolism.
Abam tapir	When coupled with abametapir, quizartinib's serum levels can increase.
Abatacept	When coupled with Abatacept, Quizartinib's metabolism rate can increase.
Abemaciclib	Quizartinib, when coupled with Abemaciclib, can increase their serum levels(104).
Abrocitinib	Quizartinib's serum levels can rise when coupled with abrocitinib(104).
Acalabrutinib	Acalabrutinib and Quizartinib together may reduce the metabolism of Quizartinib.
Acebutolol	Acebutolol and Quizartinib together may enhance the chances or intensity of QTc prolongation.
Acetaminophen	Acetaminophen with Quizartinib together can raise the serum levels of Acetaminophen.
Acrivastine	Combining acrivastine with quizartinib may enhance the likelihood or severity of QTc prolongation(105).
Adagrasib	Adagrasib with Quizartinib together may increase the risk or intensity of QTc prolongation.
Adalimumab	Combining Adagrasib with Quizartinib may increase the likelihood or severity of QTc prolongation.
Adenosine	Combining adenosine with quizartinib may enhance the likelihood or severity of QTc prolongation.
Afatinib	When coupled with Quizartinib, Afatinib's serum levels can rise.
Ajmaline	Combining Ajmaline with Quizartinib may enhance the chance or severity of QTc prolongation.
Albuterol	Combining Ajmaline with Quizartinib may enhance the chance or severity of QTc prolongation(106).

(107,108)

Quizartinib interacts with many drugs, affecting metabolism and serum concentration, and increasing or lowering the likelihood of QTc prolongation. Its metabolism may be decreased with drugs like Abacavir or Acalabrutinib and increased with drugs like Abatacept or Adalimumab. Abametapir, Abrocitinib, or Afatinib may raise the serum concentration of Quizartinib. Quizartinib increases the drugs, such as Acetaminophen or Abemaciclib. The risk of QTc prolongation increases when used with Acebutolol, Acrivastine, Adenosine, Adagrasib, or Ajmaline. These

interactions necessitate careful monitoring, especially for cardiovascular effects or changes in drug efficacy. "In addition to navigating drug interactions, addressing Quizartinib's resistance mechanisms is crucial for optimizing its clinical utility.

Aversion to Quizartinib

Starting clinical effectiveness of Flt3 Inhibitors ex Quizartinib,(85) their use in the clinic is restricted since drug resistance develops after several months of treatment. (109) Though the rate at which resistance mutations occur and off-target consequences differ from drug to drug, all FLT3 inhibitors eventually cause clinical resistance. Quizartinib resistance could be broadly categorized as either Intrinsic or extrinsic(110). Activation of alternative signaling pathways, proliferation of all reddy exciting subclones with novel Gene modifications, and another point Mutations in the Flt3 Receptor are among the intrinsic tumor processes in the context of quizartinib (111). One of the extrinsic mechanisms is the reaction between leukemia cells and bone marrow Microenvironment cells that control the response to quizartinib(14,112).

Toxicity of Quizartinib

Main side effects of Quizartinib are Prolonged Cytopenias. Few patients in phase' second' and phase third studies got CRS 10/118 in phase third (QUANTUM-R], while most patients in phase' second 'and phase third studies achieved CRI or CRP.27. In contrast, the FLT3 inhibitor gilteritinib was used in the phase 3 ADMIRAL investigation, and 52/134 individuals obtained CR. One possible Explanation for this disparity is that Quizartinib also Inhibits KIT, a protein essential to the operation of both myeloid and erythroid progenitor cells. FLT3 and KIT inhibition's role in explaining more widespread Cytopenias is confirmed in vitro bone marrow progenitor cells studies(113).

Probation of the QT due to potassium channel blockage is another important side effect of quizartinib.31.1 The initial phase 1 and 2 tests showed this, and as was already indicated, the dosages were later changed to 90 Mg for female and 135 Mg for man. Because of concerns about QT prolongation, a phase 2b study was carried out using dosages of 30 and 60 Mg prior to the beginning of the phase three (QUANTUM) trial.

The FDA's examination of the (QUANTUM-R) study indicated concerns over four deaths that might have been caused by QTc prolongation. These fatalities might have been brought on by direct cardiac toxicity, such as myocardial infarction, heart failure, or a deadly subdural hemorrhage following a cardiac event-induced fall Furthermore, 5 cardiac deaths have occurred in the quitaramib arm of the Quantum-First study so far, compared to none in the placebo arm (two Cardiac arrests, one quick death, one Ventricular fibrillation, and one ventricular dysfunction), according to the Oncologic Drugs Advisory Committee meeting(ODACM).

Since midostaurin did not prolong t, the current phase 3 RATIFY clinical trial A involved dose modifications for prolonged QTc as well as close ECG monitoring the phase 3 ADMIRAL trial similarly showed a minimum rate of QTc prolongation (4.90%) for gilteritinib.28. Although QTc monitoring and dose low are advised in the package inserts, this concern had no bearing on the FDA's clearance of either of these medications(114).

The dilemma of whether or not to add FLT3 inhibitors to upfront induction chemotherapy has been replaced by the question of which one to employ and under what conditions, as two prospective studies of two different FLT3 inhibitors, quartino and midostaurin, in conjunction with induction chemotherapy have shown considerable gains in survival.

This study looked at how quizartinib affected ABC transporter-mediated multidrug resistance (MDR). Cytotoxic studies show that 0.75, 1.5, and 3 μM are the three some toxic concentrations for both healthy and malignant cells. In some cases, quizartinib at 3 μM dramatically reversed MDR mediated by ABCG2 and ABCB1 when compared to the Positive controls, Verapamil at 3 μM, and fumetrimorgin C at 3 μM, respectively.

MDR cell models(115).

Quizartinib dose

After taking 26.5 mg once day on Days 1 through 14, take 50 Mg once daily for a maximum of 36 28-day cycles. (116)

Conclusion

According to this review, quizartinib is a promising treatment for acute myeloid leukemia (AML), particularly in individuals with FLT3-ITD mutations. It continues with a thorough discussion of the resistance routes, modes of action, and pharmacological profile. The study highlights its effectiveness in several stages of clinical trials, including a statistically significant

remission rate when using it alone or in combination with chemotherapy. The issues of medication resistance, adverse effects (such as cytopenias and QTc prolongation), and drug interactions are addressed, nevertheless. With continued research targeted at maximizing its therapeutic usage and resolving its drawbacks, quizartinib is generally regarded as a strong second-generation FLT3 inhibitor.

With the advantages of quizartinib, drug reactions also occur when other drugs are administered with quizartinib, as explained in the next table.

Competing Interest

All the authors declare that they have no competing interests.

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