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Gilteritinib in the treatment of relapsed and refractory acute myeloid leukemia with a FLT3 mutation

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***Abstract*:** Acute myeloid leukemia (AML) is a malignancy of uncontrolled proliferation of immature myeloid blasts characterized by clonal evolution and genetic heterogeneity. FMS-like tyrosine kinase 3 (FLT3) mutations occur in up to a third of AML cases and are associated with highly proliferative disease, shorter duration of remission, and increased rates of disease relapse. The known impact of activating mutations in FLT3 in AML on disease pathogenesis, prognosis, and response to therapy has led to the development of tyrosine kinase inhibitors targeting FLT3. Gilteritinib is a potent, second generation inhibitor of both FLT3 and AXL, designed to address the limitations of other FLT3 inhibitors, particularly in targeting mechanisms of resistance to other drugs. In this review, we present comprehensive data on recent and ongoing studies evaluating the role of gilteritinib in the relapsed and refractory FLT3 mutated AML setting.

Keywords: acute myeloid leukemia, gilteritinib, FMS-like tyrosine kinase 3 inhibitors, FLT3

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Background

Acute myeloid leukemia (AML) is a malignancy of uncontrolled proliferation of immature myeloid blasts characterized by clonal evolution and genetic heterogeneity. The known impact of genetic alterations on disease pathogenesis, prognosis, and response to therapy has led to the development of specific targeted therapies. One of the most common genomic alterations in AML is the FMS-like tyrosine kinase 3 (FLT3), which can occur in about one-third of cases. FLT3 is a class III tyrosine kinase receptor that plays a role in both cell survival and proliferation, and is expressed primarily on hematopoietic stem cells and progenitor cells. When the FLT3 ligand binds to its receptor, it results in dimerization, auto-phosphorylation, and activation of downstream signaling of several pathways, including JAK/STAT, PI3K/AKT, and RAS/MEK/ERK, resulting in the cellular differentiation and proliferation that is the hallmark of acute leukemia. The two main types of FLT3 mutations are the internal tandem duplication (ITD), which occurs in the FLT3 juxtamembrane domain, and the tyrosine kinase domain (TKD) mutation, which is a missense/point mutation.[1–4]

The FLT3-ITD mutation is present in about 25–30% of patients and is associated with highly proliferative disease, shorter duration of remissions, and increased rates of disease relapse.[5–8] The impact of the FLT3-TKD mutation, which occurs in up to 10% of AML patients, is not as clear. Several recently published reports provide conflicting results as to the degree in which this is an adverse prognostic indicator.[9–11] Historically, the presence of a FLT3-ITD mutation, regardless of the presence of other cytogenetic and/or molecular abnormalities, confers an adverse prognosis. More recent data show that the burden of FLT3-ITD clone and the presence of co-occurring mutations play a significant role in survival and clinical outcomes. The presence of FLT3-ITD and nucleophosmin 1 (NPM1) mutations have been shown to improve response and survival outcomes. The burden of FLT3-ITD clone is determined using DNA fragment analysis, which looks at the ratio of the area under the curve

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(AUC) of the mutated to AUC of wild-type FLT3.[12] According to the National Comprehensive Cancer Network (NCCN) guidelines for AML, the cutoffs for high and low allelic ratios are ≥ 0.5 and <0.5, respectively. The NCCN guidelines stratify FLT3-ITD mutated patients into three different risk categories based on allelic ratio in conjunction with the presence of an NPM1 mutation.[13]

Overview of FLT3 inhibitors

The development of FLT3 inhibitors for the treatment of FLT3-mutated AML has improved clinical outcomes significantly. As shown in Table 1, the first generation FLT3 inhibitors (midostaurin, sunitinib, lestaurtinib, sorafenib) are multikinase inhibitors with lower affinity for FLT3 binding. These agents are relatively nonspecific to FLT3 and have off-target effects that may contribute to higher toxicity profile. As a result, second generation FLT3 inhibitors (ponatinib, crenolanib, quizartinib, gilteritinib) were developed. Second generation FLT3 inhibitors are more potent against FLT3 than the first generation inhibitors, with fewer off-target inhibition/toxicities. FLT3 inhibitors are also categorized as being type I or type II, which determines the type of anti-FLT3 activity the compounds possess. All of these drugs competitively inhibit the activity of FLT3 by binding to the adenosine triphosphate (ATP) binding site, with the difference lying in the conformation of the structure's activation loop. Type I inhibitors bind to the "in" structural conformation of the enzyme and are active against both the ITD and TKD mutations (D835 and Y842). Type I inhibitors also bind more strongly to the FLT3-ITD mutated kinase than type II inhibitors, suggesting these may show more promise for use in AML treatment. Type II inhibitors bind to both the "out" conformation of the enzyme, as well as an additional region on the enzyme termed the "back pocket" region, and, as a result, are active only against FLT3-ITD mutations, and not TKD mutations.[14–17] This lack of activity against TKD mutations may result in development of secondary mutations in the activating loop residues (e.g., D835, I836, D839, Y842). Midostaurin is the first FLT3 inhibitor approved in the United States by the Food and Drug Administration (FDA) for the treatment of FLT3 mutated AML. In early-phase studies, midostaurin monotherapy was found to transiently decrease both bone marrow and peripheral blast percentages in patients with myelodysplastic syndrome (MDS) and relapsed/refractory (R/R) AML in both FLT3-mutated and FLT3-wild-type disease.[18,19] In the multinational, randomized, phase III (RATIFY) study, a total of 717 newly diagnosed FLT3 mutated AML patients (aged 18–60 years) were randomized to receive midostaurin (50 mg twice daily on days 8–21) or placebo in combination with induction chemotherapy, followed by high-dose cytarabine consolidation or hematopoietic stem cell transplant (HSCT), followed by maintenance. Patients were stratified based on FLT3 subtype: 47.6% had low ITD allelic ratio, 29.8% had high ITD allelic ratio, and 22.6% had TKD mutation.[20] The median overall survival (OS) was significantly longer in the midostaurin group *versus* placebo (74.7 *versus* 25.6 months; $p = 0.007$), though it did not show a difference in complete remission (CR) rates. In addition, the survival benefit was seen even after censoring for HSCT in first CR, and also across all FLT3 mutation subtypes. More patients in the midostaurin group underwent HSCT after first CR compared with placebo (28% *versus* 23%; $p = 0.01$). The 4-year OS was longer in the midostaurin group compared with placebo (63.7 *versus* 55.7%). Maintenance therapy post-HSCT continues to be a topic of discussion in FLT3 mutated AML. An ongoing phase II Radius trial evaluated the use of midostaurin in combination with standard of care (SOC) *versus* SOC alone in this setting. Preliminary results at 18 months post-HSCT predict a relative risk reduction in the risk of relapse of 54% with midostaurin use. In addition, midostaurin has been shown to reduce the plasma phosphorylated FLT3 levels to $<70\%$ of baseline in 14 patients, resulting in improved relapse-free survival (RFS) and OS.[21,22]

Sorafenib is a first generation, type II FLT3 inhibitor that has limited activity as a single-agent in AML, with bone marrow remissions achieved in $<10\%$ of patients.[23–30] In the SORAML study, a total of 267 patients (aged 18–60 years) with newly diagnosed AML, irrespective of FLT3 status, were randomized to receive sorafenib (400 mg twice daily) or placebo in combination with induction chemotherapy, followed by high-dose cytarabine consolidation or HSCT, followed by maintenance for 12 months. Patients who received sorafenib had an improvement in both event-free survival (EFS) and RFS compared with placebo (EFS 40% *versus* 22%; $p = 0.01$, and RFS 56%

Table 1. Characteristics of FLT3 inhibitors.

Class	FLT3 inhibitor	Type	FLT3-TKD inhibition	Non-FLT3 targets	Major toxicities	Approval status
First generation	Lestaurtinib	Type I	Yes	JAK 2/3, TrKA	Infection	Investigated for FLT3 mutated AML, pancreatic cancer, and prostate cancer
	Midostaurin	Type I	Yes	c-KIT, PKC, PDGFR-α/β, VEGFR-2, SRC	GI toxicity, myelosuppression, pulmonary toxicity	US FDA and EMA approved for adults with newly diagnosed FLT3 mutated AML in combination with intensive chemotherapy and mast cell leukemia
	Sorafenib	Type II	No	c-KIT, PDGFR-β, RAF-1, BRAF, *m*BRAF, VEGFR (1,2,3), RET, RET/PTC	Rash, myelosuppression, QTcF prolongation, elevated liver transaminases	Available off-label (US FDA approved for RCC, differentiated thyroid cancer, and hepatocellular)
	Sunitinib	Type I	Yes	c-KIT, PDGFR-α/β, VEGFR (1,2,3), RET, CSF-1R	GI toxicity, rash, headache	Available off-label (US FDA approved for GIST, pancreatic neuroendocrine tumors, and RCC)
Second generation	Crenolanib	Type I	Yes	PDGFR-α/β, ULK2, SNARK, CDK7, MLK1, JAK3, TrKA, TYK2, ROCK2	GI toxicity, elevated liver transaminases	Investigated for FLT3 mutated AML and GIST
	Gilteritnib	Type I	Yes	AXL, LTK, ALK	GI toxicity, elevated liver transaminases	US FDA approved for adult with relapsed and refractory FLT3 mutated AML
	Ponatinib	Type II	No	c-KIT, PDGFR-α, VEGFR-2, FGFR-1, RET, BCR/ABL, SRC, TIE2, EPHR	Hypertension, pancreatitis, arterial thrombosis	US FDA approved for CML, GIST, Ph+ ALL
	Quizartinib	Type II	No	c-KIT, PDGFR-β, RET	QTcF prolongation, myelosuppression	Approved in Japan FDA did not grant approval for relapsed and refractory FLT3-ITD mutated AML

AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CSF-1R, colony stimulating factor receptor Type 1; EMA, European Medicines Agency; EPHR, ephrin receptor; FGFR, fibroblast growth factor receptor; FLT3, FMS-like tyrosine kinase 3; GI, gastrointestinal; GIST, gastrointestinal stromal tumor; ITD, internal tandem duplication; MLK1, mixed-lineage kinase 1; PDGFR, platelet-derived growth factor receptor; PKC, protein kinase C; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukemia; RCC, renal cell carcinoma; RET, rearranged during transfection; TKD, tyrosine kinase domain; TrKA, Trk system potassium uptake protein; ULK2, Unc-51–like kinase 2; US FDA, United States Food and Drug Administration; VEGFR, vascular endothelial growth factor receptor.

versus 38%; $p=0.017$).[28] The benefits with sorafenib continued to be seen at longer follow up (median 78 months); however, no OS benefit was observed, perhaps due to inclusion of FLT3-wild-type patients.[29] In a more recent study, patients with newly diagnosed FLT3 mutated AML receiving sorafenib plus intensive chemotherapy showed a median EFS of 35 months compared with 8 months in the chemotherapy alone arm ($p=0.031$). In this study, there was an OS benefit favoring sorafenib (42 *versus* 13 months; $p=0.026$), and these benefits were seen even when censoring for allogeneic HSCT.[31] The combination of low-intensity chemotherapy (azacitidine) with sorafenib has also been shown to be effective in the relapsed AML setting. In a

study of 43 AML patients who had received a median of two prior treatment regimens (9 of whom had had prior FLT3 inhibitor therapy), the median overall response rate (ORR) was 46%, including 10 (27%) with a complete response with incomplete count recovery (CRi) and additional six patients (16%) with a CR.[24] Though the median duration of CR/CRi was only 2.3 months, more than 85% of patients achieved adequate FLT3 inhibition within one cycle of therapy. Another small case series of six patients treated with decitabine and sorafenib demonstrated ORR in five (83%), and four of the five patients who had R/R AML achieved a CR.[25] Maintenance therapy with sorafenib post-HSCT has been evaluated in the SORMAIN trial, in which 83 patients were randomized to receive sorafenib or placebo for up to 24 months. The 2-year median RFS was 85% in the sorafenib arm, and 53.3% in the placebo arm ($p = 0.013$). At a median follow up of 55.4 months, OS was also significantly longer with sorafenib compared with placebo ($p = 0.03$).[32,33] Though sorafenib has not been FDA-approved for the treatment of FLT3 mutated AML, it is listed as an option in the NCCN guidelines to be used in combination with hypomethylating agents in patients who are not candidates for intensive chemotherapy.[13,24,25]

Quizartinib is a second-generation FLT3 inhibitor that has shown activity as monotherapy in the R/R setting, demonstrating overall composite CR (CRc) rates >40% with doses up to 450 mg/day.[34–36] This is an important distinction from first-generation FLT3 inhibitors, given their overall lack of CR achievement as monotherapy. In the multicenter, randomized phase III (QuANTUM-R) study, 367 FLT3 mutated AML were randomized 2:1 to receive either single-agent quizartinib at 30 mg lead-in dose, then increased to 60 mg daily after QTc assessment, compared with investigators' choice of salvage chemotherapy [mitoxantrone, etoposide, and cytarabine (MEC); fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-IDA) and low-dose cytarabine]. After a median follow up of 23.5 months, the OS was longer with quizartinib than chemotherapy (6.2 months *versus* 4.7 months; $p = 0.02$), with rates of grade 3 QTc prolongation in the quizartinib group reported as 3% by central reading and 4% by investigator report. The lower dose of 30–60 mg/day resulted in equivalent CRc rates seen with higher doses and acceptable cardiac toxicity.[36,37] Despite this OS benefit seen in QuANTUM-R study, the US FDA did not grant approval to quizartinib for treatment of patients with FLT3-ITD mutated R/R AML, though it was approved for use in Japan. In the ongoing phase I/II study evaluating the use of quizartinib in combination with low-intensity chemotherapy, 61 FLT3-ITD mutated AML patients received 60 or 80 mg of quizartinib plus azacitidine ($n = 24$) or low-dose cytarabine ($n = 37$). The median OS was 14.8 and 7.4 months in the azacitidine and low-dose cytarabine combination arms, respectively. These results demonstrated that quizartinib in combination with azacitidine or low-dose cytarabine is highly effective in patients with FLT3-ITD mutated AML.[38] Ongoing clinical trials are underway evaluating the use of quizartinib in newly diagnosed FLT3-ITD mutated AML patients in combination with standard chemotherapy [ClinicalTrials.gov identifier: NC002668653] and decitabine plus venetoclax [ClinicalTrials.govidentifier:NCT03661307], as well as in the FLT3 R/R setting with azacitidine or low-dose cytarabine [ClinicalTrials.gov identifier: NCT01892371] and venetoclax [ClinicalTrials.gov identifier: NCT03735875].

Gilteritinib is a potent, rationally designed, second generation inhibitor of both FLT3 and AXL. This drug was designed to address the limitations of other FLT3 inhibitors, particularly in targeting mechanisms of resistance to other drugs. *In vitro*, gilteritinib has been shown to be a potent inhibitor of both FLT3-ITD and TKD, notably in cell lines with mutations in the codon D835, which is the most commonly acquired point mutation that confers resistance to other FLT3 inhibitors, including midostaurin and quizartinib.[39,40] In addition, the fact that gilteritinib inhibits AXL is important, as it is an oncogenic tyrosine kinase frequently overexpressed in AML and facilitates FLT3 activation, which is known to be a mechanism of FLT3 TKI resistance.[40,41] A comprehensive evaluation of 78 different kinases demonstrated gilteritinib to also be a strong inhibitor of anaplastic lymphoma kinase (ALK) and leukocyte receptor tyrosine kinase (LTK), but notably, unlike other FLT3 inhibitors, this drug does not significantly inhibit c-KIT.[39,42]

Preclinical studies

Gilteritinib was shown to inhibit phosphorylation of FLT3-ITD receptor and activation of FLT3-D835Y mutations. Through *in vitro* kinase assays,

gilteritinib was also shown to have strong inhibition of AXL and a weaker inhibition of c-KIT compared with FLT3, by approximately 800-fold.[43] Inhibition of AXL has shown to prevent the proliferation of both FLT3 mutant and FLT3 wild-type AML cells.[40,42,44,45] In addition, AXL has been shown to play a significant role in suppressing immune response, and its inhibition could lead to autoimmunity and potentially promote development of inflammatory-associated malignancies, particularly when utilized as long-term maintenance therapy.[46] Weaker c-KIT inhibition with gilteritinib lends to a lower incidence of myelosuppression that is often seen with other FLT3 inhibitors. In the xenograft mouse model, gilteritinib also showed activity against FLT3 at the F691 position, a mutation seen in relapsed AML patients who received quizartinib treatment. However, the inhibition of FLT3-F691 was approximately 20-fold weaker than cells expressing FLT3-ITD. Although, gilteritinib has some activity against FLT3-F691, secondary FLT3-F691 have been reported in patients receiving gilteritinib doses of <200 mg/day, suggesting that this resistance could potentially be overcome with higher plasma levels. Plasma and intratumor concentration of gilteritinib peaks at 2 h and declines over a 24-h period.[47]

Given that gilteritinib as a single agent has demonstrated potent inhibition of FLT3 and durable anti-leukemic effects, the addition of chemotherapy (cytarabine plus daunorubicin/idarubicin, or combined with azacitidine) was evaluated in preclinical cellular and xenograft mouse models of FLT3-ITD positive AML. The addition of chemotherapy upregulated the expression of cleaved poly (ADP-ribose) polymerase (cPARP) resulting in enhanced apoptotic activity.[48] Gilteritinib also decreased the expression of induced myeloid leukemia cell differentiation protein (MCL-1), B-cell lymphoma 2-like protein 10 (BCL2L10), and survivin, all of which are anti-apoptotic proteins, and which play a significant role in chemotherapy sensitivity after 24 h of treatment.[49] Gilteritinib given prior to chemotherapy did not reduce the anti-leukemic effects of chemotherapy seen with other FLT3 inhibitors.[47,48,50] Gilteritinib in combination with azacitidine reduced leukemic burden significantly when compared with gilteritinib monotherapy.[47,49] No difference in pharmacokinetics was seen when gilteritinib was administered as monotherapy or in combination with chemotherapy, suggesting that drug interactions with combination therapy is unlikely. Preclinical studies have also shown that the combination of gilteritinib and venetoclax synergistically induces apoptosis in FLT3-ITD positive patients. Gilteritinib is thought to enhance the apoptotic activity of venetoclax through downregulation of MCL-1 expression by the FLT3 inhibitor.[51]

Phase I/II studies

In a non-randomized, single-arm, open-label phase I/II study, 252 patients with R/R AML were assigned to one of seven dose escalations of gilteritinib, ranging from 20 mg/day to 450 mg/day, or to dose-expansion cohorts. Of the 252 R/R AML patients, 162 had FLT3-ITD, 13 had FLT3-TKD (D835), 16 had both FLT3-ITD/TKD, and 58 had FLT3-wild-type mutation. Although presence of a FLT3 mutation was not an inclusion criterion, at least 10 patients with confirmed FLT3 mutation were required to be enrolled in the expansion cohorts of each dose level. Based on initial findings, the study was further expanded to include only FLT3 mutated patients in the 120 mg and 200 mg dose cohorts.[52] Gilteritinib was overall well-tolerated, with the most common treatment-related adverse events being diarrhea (16%), fatigue (15%), elevated aspartate aminotransferase (AST) (13%), and elevated alanine aminotransferase (ALT) (10%).[52] The maximum tolerated dose of gilteritinib was determined to be 300 mg/day. Grade 3 diarrhea and elevated AST were dose-limiting toxicities seen in two out of three patients receiving a gilteritinib dose of 450 mg/day. Other notable grade 3–4 adverse events included febrile neutropenia (39%), anemia (24%), thrombocytopenia (13%), sepsis (11%), and pneumonia (11%).[52] Furthermore, gilteritinib showed a long elimination half-life, supporting the use of once-daily dosing.

Potent FLT3 inhibition was noted at all dose levels studied, with increased inhibition of FLT3 phosphorylation noted with higher doses of gilteritinib. Although anti-leukemic activity of gilteritinib was seen in all dose levels, a dose of 120 mg/day was chosen for further study because of its potent FLT3 inhibition and tolerable side effects. This allowed for dose adjustment without compromising efficacy and safety. At gilteritinib doses of 80 mg/day or higher, anti-leukemic activity was seen in patients regardless of whether they had previously received another FLT3 inhibitor. At doses of 80 mg/day or higher,

overall responses were achieved in 55% of patients with FLT3-ITD, 17% of patients with FLT3-TKD, and 62% of patients with both FLT3-ITD/TKD.[52] ORR of 40% was seen in all patients across all dose levels, with 8% achieving CR, 22% achieving CRi, and 10% achieving partial remission. The median OS was 25 weeks in all patients and 20 weeks in FLT3 mutated patients. Responses were also seen with some FLT3-wild-type patients, which may be due to the AXL inhibition and other off-target effects of gilteritinib.[52] Of the 191 FLT3 mutated patients, 36 (18%) underwent HSCT. Of the 58 FLT3-wild-type patients, only 1 (2%) underwent HSCT, with 13 of the 37 (35%) HSCT patients continuing gilteritinib maintenance therapy after engraftment. The OS was similar between groups of FLT3 mutated patients who underwent HSCT *versus* those who did not (42 *versus* 47 weeks, respectively). Due to the small sample size of patients receiving maintenance therapy, further studies are warranted to confirm the efficacy and feasibility of gilteritinib maintenance therapy.

Preclinical data suggested that gilteritinib in combination with venetoclax is highly synergistic.[51,53] A multicenter, open-label phase Ib clinical trial [ClinicalTrials.gov identifier: NCT03625505] was conducted to evaluate the safety and efficacy of venetoclax 400 mg/day in combination with gilteritinib 80 mg/day or 120 mg/day in R/R AML patients. Of the 15 R/R AML patients who were included in the study, 5 had FLT3-wild-type, 8 had FLT3-ITD, 1 had FLT3-TKD, and 1 had both FLT3-ITD/TKD. These patients were heavily pre-treated, and had received a median of 2 (range 1–4) prior lines of therapy. Six (60%) of the FLT3 mutated patients had previously received a FLT3 inhibitor.[53] A total of 55% of FLT3 mutated patients achieved CR, and 40% achieved morphologic leukemia free state (MLFS), resulting in an ORR of 90% (9/10 patients). The ORR in patients with FLT3-wild-type was 20% (1/5 patients). The most common grade 3–4 adverse events were febrile neutropenia (47%), anemia (27%), thrombocytopenia (7%), and neutropenia (7%). No cases of tumor lysis syndrome were reported. Venetoclax in combination with gilteritinib was well tolerated, and demonstrated blast clearance in 90% of FLT3-mutated AML patients.[53] Because of the small sample size in this study, these results should be confirmed with further investigation.

Phase III study

In a randomized phase III (ADMIRAL) trial, 371 R/R FLT3-mutated AML patients were randomly assigned to receive gilteritinib 120 mg/day or salvage chemotherapy (MEC; FLAG-IDA; low-dose cytarabine; and azacitidine) in a 2:1 ratio. MEC and FLAG-IDA were classified as high-intensity regimens, and low-dose cytarabine and azacitidine were classified as low-intensity regimens. Overall, 73% of the patients had intermediate cytogenetics, 12.4% had prior FLT3 inhibitor therapy with either midostaurin or sorafenib, 88% had FLT3-ITD mutation, 8.4% had FLT3-TKD (D835 or I836) mutation, and 1.9% of patients had both FLT3-ITD/TKD mutations.

Gilteritinib was associated with significantly improved median OS compared with chemotherapy (9.3 months *versus* 5.6 months; $p < 0.001$). A trend toward significantly prolonged OS was seen with gilteritinib than with chemotherapy across all subgroups, including the high-intensity and low-intensity chemotherapy cohorts, and patients with high FLT3-ITD allelic ratio. Notably, OS in patients with primary refractory disease was improved with gilteritinib compared with chemotherapy (10.4 *versus* 6.9 months). More patients in the gilteritinib group achieved CR/CRi of 34% compared with 15.3% in the chemotherapy group. CR was achieved in 21.1% of patients in the gilteritinib group and 10.5% in the chemotherapy group. Among patients with FLT3-ITD mutations, 20.5% of patients in the gilteritinib group achieved CR compared with 9.7% in the chemotherapy group. Similar percentages of CR in patients with FLT3-TKD mutations alone (19.0%), FLT3-ITD mutations alone (20.5%), and in those with both FLT3-ITD/TKD (28.6%) were seen in the gilteritinib group.[54] Median OS was also similar in the gilteritinib group among those with FLT3-ITD mutations alone (9.3 months), FLT3-TKD mutations alone (8.0 months), and those with both FLT3-ITD/TKD mutations (10.2 months). More patients in the gilteritinib group underwent HSCT than in the chemotherapy group (25.5% *versus* 15.3%), and OS benefit for gilteritinib was also maintained when survival data was censored at the time of transplantation. The most commonly co-mutated genes were NPM1 (46.6%) and DNMT3A (31%).[54] Gilteritinib therapy resulted in longer survival when compared with chemotherapy across all cohorts of patients with co-mutations, especially in patients with both DNMT3A and

NPM1 mutation (median OS: 10.8 months). Furthermore, baseline levels of AXL expression did not impact survival with gilteritinib.[54]

Gilteritinib was well tolerated, and adverse events occurred less frequently than in the chemotherapy group. The most common gilteritinib-related adverse events were pyrexia (42.7%), increased ALT (41.9%), and increased AST (40.2%). Notable grade 3–4 adverse events included febrile neutropenia (45.9%), anemia (40.7%), and thrombocytopenia (22.8%).[54] These findings were consistent with the phase I/II trial. Some limitations of this study included small sample sizes in the subgroup analysis of FLT3-TKD, making it challenging to determine the benefit of gilteritinib in this patient population. In addition, patients who had prior therapy with FLT3 inhibitors were included in the study; therefore, survival benefits remain unclear in this subset of patients due to lack of data of ideal sequencing of FLT3 inhibitors.

Mechanism of resistance

Similar to other FLT3 inhibitors, patients may develop resistance to gilteritinib after the initial response. A paucity of literature has suggested that the activation of mutations in the Ras/MAPK pathway genes NRAS and KRAS mediates secondary resistance to gilteritinib in patients with FLT3 mutated R/R AML. In the ADMIRAL trial, 361 FLT3 mutated patients were analyzed for co-mutations at baseline, 25 (6.9%) had Ras/MAPK pathway gene mutations. Of the 25 patients with Ras/MAPK pathway gene mutations, 18 patients received gilteritinib.[55] A total of 61% of patients ($n = 11/18$) had >1 Ras/MAPK pathway gene mutation at relapse compared with 12% of patients ($n = 3/25$) at baseline. Multiple Ras/MAPK pathway gene mutations at relapse likely mediates continued Ras/MAPK signaling in patients with FLT3 mutated R/R AML receiving gilteritinib.[55] Therefore, the combination of gilteritinib with inhibitors of the JAK kinase pathway may help prevent acquired mutational resistance to gilteritinib. Less frequently, secondary FLT3-F691L and BCR-ABL1 fusions were also identified at relapse. Data suggest that higher doses of gilteritinib above 200 mg/day may potentially overcome resistance associated with FLT3-F691L mutations.[56] It is important to note that doses of 200–300 were tolerated in the phase I/II trial; however, a dose of 120 mg/day was assessed in the randomized phase III trial and is currently the FDA approved dose.

Conclusion

FLT3-ITD mutations are associated with highly proliferative disease, shorter duration of remissions, and increased rates of disease relapse. Due to the impact of FLT3 mutations on clinical outcomes, it is important to evaluate the presence of FLT3 mutation at diagnosis, throughout therapy, and at relapse. Unlike other FLT3 inhibitors, gilteritinib was rationally designed to inhibit both FLT3 and AXL to overcome resistance. Gilteritinib has demonstrated safety and efficacy as a single agent in the R/R AML setting. Importantly, it has been shown to have a survival benefit over chemotherapy, as well as efficacy in patients who received prior FLT3 inhibitors. The optimal selection and the ideal sequencing of FLT3 inhibitors to minimize the risk of resistance remains a future challenge. Clinical trials are underway evaluating the use of gilteritinib in first-line induction setting with intensive chemotherapy ([ClinicalTrials.gov identifier: NCT02310321], [ClinicalTrials.gov identifier: NCT02236013]) and azacitidine [ClinicalTrials.gov identifier: NCT02752035], maintenance setting ([ClinicalTrials.gov identifier: NCT02927262], [ClinicalTrials.gov identifier: NCT02997202]), and in the R/R setting with atezolizumab [ClinicalTrials.gov identifier: NCT03730012], venetoclax [ClinicalTrials.gov identifier: NCT03625505], and venetoclax plus azacitidine [ClinicalTrials.gov identifier: NCT01410487] in FLT3 mutated AML patients.

Conflict of interest statement

The author(s) declare that there is no conflict of interest.

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