The growing landscape of FLT3 inhibition in AML

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Midostaurin and gilteritinib are FLT3 inhibitors that have been recently approved for use in *FLT3*-mutant acute myeloid leukemia (AML). These approved drugs represent a new standard of care for patients with *FLT3* mutations in both the first-line and salvage settings. The success of midostaurin used in combination with induction chemotherapy has prompted exploration of newer, more potent and targeted inhibitors (including gilteritinib) in the first-line setting in combination with chemotherapy. At the same time, the success of gilteritinib and other newer FLT3 inhibitors as monotherapy in the salvage setting has been tempered by the development of resistance because of diverse mechanisms. Investigational strategies that incorporate FLT3 inhibitors in combination with hypomethylating agents and as maintenance therapy after allogeneic stem cell transplantation have shown promise. Other novel combination strategies are also undergoing clinical investigation. In this article, we review the current landscape of approved and investigational FLT3 inhibitors in AML, including the current standard of care and investigational strategies.

Learning Objectives

- Understand the landscape and use of currently approved FLT3 inhibitors in AML
- Recognize common FLT3 inhibitor resistance mechanisms
- Review key ongoing clinical trials, including therapeutic combinations and maintenance strategies

Clinical case

A 46-year-old female presented to her primary care physician with a 1- to 2-month history of gum bleeding, progressive weakness, and fatigue. A complete blood count was remarkable for a white blood cell count of 222 × 10^9/L with 90% blasts and a hemoglobin of 5.2 g/dL. A bone marrow aspirate and biopsy revealed 90% myeloid blasts consistent with acute myeloid leukemia (AML). Cytogenetics were normal. FMS-like tyrosine kinase 3 (*FLT3*) mutation testing revealed an *FLT3* internal tandem duplication (ITD) mutation with a mutant:wild-type (WT) allelic ratio (AR) of 0.80. A myeloid malignancy sequencing panel confirmed an insertion mutation in exon 14 of *FLT3* consistent with an ITD mutation as well as a 4-nucleotide insertion in exon 12 of NPM1 without other co-occurring mutations.

FLT3 biology

FLT3 is a member of the class III receptor tyrosine kinase family that includes c-KIT, PDFGR-α and PDGFR-β, and CSF-1R. Large genomic sequencing studies have identified *FLT3* as the most commonly mutated gene in both adult and pediatric patients with AML. Constitutively activating mutations of FLT3 are found in ~30% of adult patients with AML[1,2] and are also common in pediatric patients with AML.[3] Mutations in FLT3 most often occur as in-frame ITDs located within the autoinhibitory juxtamembrane domain of the receptor and less commonly as point mutations within the tyrosine kinase domain (TKD).[1,2] Clinically, *FLT3*-ITD mutations are associated with earlier time to relapse and poorer overall survival (OS).[4] More recently, it has become clear that patients with a high *FLT3*-ITD–mutant allelic burden (usually defined as a mutant:WT AR of >0.51) have the worst clinical outcomes,[5,6] which has led the European LeukemiaNet to reclassify *FLT3*-ITD$^+$ AML patients with low AR and concurrent *NPM1* mutations as low risk.[7]

Development of FLT3 inhibitors

Given the prevalence and adverse prognosis imparted by *FLT3* mutations in AML, targeting FLT3 signaling via small-molecule inhibitors has been a heavily studied therapeutic strategy over the last decade and half. First-generation, multitargeted FLT3 tyrosine kinase inhibitors (TKIs) such as midostaurin (PKC412), sorafenib, and lestaurtinib (CEP-701) were limited by poor drug selectivity, weak potency, and unfavorable protein-binding characteristics. Early monotherapy trials with these inhibitors showed little activity beyond transient decrease in circulating peripheral blasts,[8,9] unimpressive results that were attributed to limited effective in vivo FLT3 kinase inhibition.

Despite this initial lack of efficacy with single-agent therapy, hope remained that combining these early inhibitors with induction chemotherapy would yield higher dividends. However, results in this setting have been mixed. In the United Kingdom Medical Research Council AML15 and AML17 clinical trials, 500 patients with *FLT3* mutations, mostly younger than age 60 years, were randomly assigned to lestaurtinib or control in combination with induction and consolidation chemotherapy. No significant difference in either 5-year OS or relapse-free survival (RFS) was observed between the groups.[10] Patients who achieved >85% FLT3 inhibition, as measured by plasma inhibitory assay, seemed to demonstrate a survival benefit compared with those who had lower levels of FLT3 inhibition, which implies that improved outcomes may be tied to the depth of FLT3 inhibition. In contrast, in an unselected population of AML patients age 60 years or younger, addition of sorafenib to

Conflict-of-interest disclosure: C.C.S. has received research support from Astellas Pharma, Plexxikon Inc., and FujiFilm.

Off-label drug use: Investigational use of FF-10101, PLX3397 (pexidartinib), quizartinib, crenolanib, and sorafenib in AML.

induction and consolidation chemotherapy resulted in an improved median event-free survival (EFS) of 21 months (95% confidence interval [CI], 9-32 months) vs 9 months (95% CI, 4-15 months) for placebo.[11] The observed benefit regardless of *FLT3* mutation status suggested either that the benefit of sorafenib lies outside of its FLT3 inhibitory activity or alternatively that inhibition of unmutated FLT3 has a broader role in AML treatment.

In the largest study of this kind to date, the international, randomized, placebo-controlled, phase 3 trial of midostaurin in combination with chemotherapy (RATIFY) reported the most compelling evidence of clinical benefit. In that study, 717 patients age 18 to 60 years with previously untreated *FLT3*-mutant (ITD or TKD) AML were randomly assigned to receive either midostaurin 50 mg orally twice per day on days 8 to 21 or placebo in conjunction with standard daunorubicin and cytarabine (7+3) induction chemotherapy and high-dose cytarabine (HiDAC) consolidation therapy.[12] Patients who remained in complete remission (CR) after consolidation entered the maintenance period with midostaurin or placebo for a total of twelve 28-day cycles. CR rates and time to CR were not significantly different between groups. Results did show clinically significant benefit in EFS (hazard ratio [HR], 0.78; $P = .002$) and OS (HR, 0.78; $P = .009$) for those in the midostaurin group. This was a consistent finding across FLT3 mutation subtypes, including TKD mutations and ITD mutations with high (>0.7) or low (0.05 to 0.7) AR. Moreover, the difference in EFS and OS was observed even when censored for allogeneic hematopoietic stem cell transplantation (allo-HSCT), which was ultimately performed in 57% of patients. The fact that benefit was observed, even in the subgroup of patients with low *FLT3*-ITD AR, again suggested that the activity of midostaurin maybe at least in part attributable to one of its other kinase targets. Regardless, in light of these favorable results, induction chemotherapy with midostaurin has become the new standard of care for younger adult patients with newly diagnosed *FLT3*-mutant AML.

Clinical case continued

The patient underwent 7+3 induction chemotherapy with midostaurin. Unfortunately, a bone marrow biopsy performed on day 21 of induction showed 40% $CD34^+$ blasts by morphology, consistent with residual disease. A second cycle of induction therapy consisting of 5+2 with midostaurin was administered, but a subsequent bone marrow biopsy again shows 40% $CD34^+$ blasts by morphology, consistent with persistent AML.

FLT3 inhibitors in relapsed/refractory disease

The lack of efficacy of earlier, multitargeted FLT3 inhibitors used as monotherapy in relapsed/refractory (R/R) *FLT3*-mutant patients initially dampened enthusiasm for FLT3 inhibitor therapy and called into question the role of FLT3 overall as a therapeutic target in AML. However, reports of bone marrow responses achieved with sorafenib in some small case series of R/R *FLT3*-ITD^+ AML patients[13] hinted that in some patients, sorafenib monotherapy may achieve sufficient FLT3 kinase inhibition to effect clinical response. The activity of sorafenib in some patients suggested that FLT3 TKI monotherapy may yet have promise if sufficient kinase inhibition can reliably be achieved.

Quizartinib (AC220) is a second-generation FLT3 inhibitor with improved selectivity and potency for WT FLT3 and FLT3-ITD in in vitro biochemical and cellular assays.[14] The increased potency, selectivity, and favorable pharmacokinetic properties of quizartinib resulted in much higher clinical response rates compared with first-generation FLT3 inhibitors. An initial open-label international multicenter single-arm phase 2 trial evaluated 2 cohorts: the first cohort had patients older than age 60 years with refractory AML or relapse within 1 year; the second cohort had patients older than age 18 years with AML relapsed or refractory to second-line chemotherapy or after HSCT.[15] The first 17 patients received a dose of 200 mg/day but because of clinically significant QT prolongation, subsequent patients received reduced doses (135 mg/day for men and 90 mg/day for women). End points were CR and composite CR (CRc), which is defined as the combination of CR, CR with incomplete platelet recovery, and CR with incomplete hematologic recovery (CRi). In that study, 56% of *FLT3*-ITD^+ patients in cohort 1 and 46% of *FLT3*-ITD^+ patients in cohort 2 achieved CRc. The majority of responders did not achieve sufficient recovery of blood counts to meet the definition of CR, and response duration was limited (with a median treatment duration of 14.2 weeks in cohort 1 and 9.2 weeks in cohort 2). Significantly, *FLT3*-ITD^+ patients who relapsed after achieving CRc while receiving quizartinib, did so because of acquired secondary FLT3-ITD kinase domain (KD) mutations involving either the gatekeeper F691 or activation loop (AL) D835 residues.[16] This observation showed that the activity of quizartinib was mediated through inhibition of FLT3-ITD and not through off-target effects, which definitively established FLT3-ITD as a valid therapeutic target in this patient population.

A subsequent randomized phase 2b study explored 2 lower doses of quizartinib (30 or 60 mg/day, with escalations to 60 or 90 mg/day for lack of or loss of response)[17] in 76 *FLT3*-ITD^+ patients. CRc rates were 47% in both groups, similar to the CRc rate observed with higher quizartinib doses. However, despite the lower doses of quizartinib, the majority of patients in that study did not achieve CR (only 2 patients in the 30-mg and 1 patient in the 60-mg group achieved this response). Incidence of QT intervals corrected by Fridericia's formula (QTcF) were lower compared with rates observed with higher quizartinib doses. The median duration of CRc was short in both dose groups (4.2 and 9.1 weeks), and dose escalation for lack of or loss of response occurred in 61% and 14% of patients in the 30- and 60-mg groups, respectively. The short duration of response and need for dose escalation suggest that rapid development of resistance may be a problem for patients treated with lower doses of quizartinib.

QuANTUM-R, a pivotal global randomized controlled phase 3 trial of quizartinib 60 mg vs salvage chemotherapy demonstrated significantly prolonged OS for quizartinib compared with salvage chemotherapy (SC) in patients with R/R *FLT3*-ITD AML.[18] Patients age 18 years or older with *FLT3*-ITD AML in first relapse or refractory (duration of first remission ≤6 months) after standard AML therapy were randomly assigned 2:1 to receive quizartinib 60 mg or 1 of 3 preselected investigator's choice of SC regimens: low-dose cytarabine (LoDAC); mitoxantrone, etoposide, and intermediate-dose cytarabine (MEC); or fludarabine, cytarabine, and granulocyte colony-stimulating factor with idarubicin (FLAG-IDA). In all, 367 patients were randomly assigned: 245 to quizartinib and 122 to chemotherapy. At a median follow-up of 23.5 months, the median OS was 6.2 months (95% CI, 5.3-7.2 months) for quizartinib compared with 4.7 months (95% CI, 4.0-5.5 months) with SC (HR, 0.76; 95% CI, 0.58-0.98; stratified log-rank test, one-sided $P = .0177$). The transplantation rate was favorable for quizartinib (32% vs 12% for SC; nominal $P < .0001$), indicating that enhanced bridge to transplant may be one factor contributing to improved survival in the quizartinib arm. Consistent with previous studies, duration of CRc

remained short in the quizartinib arm at 12.1 weeks (95% CI, 10.4-27.1 weeks), and EFS HR was nonsignificant for differences between treatment groups.

Early on, the vulnerability of quizartinib to acquired resistance-causing FLT3 KD mutations at the AL residue D835,[16,19] which bias the active kinase conformation and are unfavorable to the binding of type II inhibitors such as quizartinib, drove the development of type I FLT3 inhibitors capable of binding the active kinase conformation. Gilteritinib is a potent type I FLT3 inhibitor with preclinical activity against FLT3 D835 mutations,[20] although it has relative vulnerability to the FLT3 gatekeeper F691L mutation. In a phase 1/2 trial in adult patients with R/R AML, 252 patients received oral gilteritinib once per day in 1 of 7 (20 to 450 mg) dose-escalation (n = 23) or dose-expansion (n = 229) cohorts.[21] Of the 191 *FLT3*-mutant patients in the full analysis set, 70 (37%) achieved CRc; most of these responses occurred in patients who received doses of 80 mg/day or higher (n = 69 [41%]). Notably, patients with D835 mutations did respond to gilteritinib, although at a lower rate than patients with *FLT3*-ITD mutations. At doses of 80 mg/day and higher, overall responses were achieved in 77 (55%) of 141 patients with ITD mutations in *FLT3*, 2 (17%) of 12 who had point mutations in codon D835, and 8 (62%) of 13 who had both ITD and TKD mutations at codon D835.[21]

In the phase 3 ADMIRAL study, adults with FLT3-mutant (including ITD and D835/I836 mutations) AML refractory to induction chemotherapy or in untreated first relapse were randomized (2:1) to receive 120 mg/day gilteritinib or prerandomization selected SC: LoDAC, azacitidine (AZA), MEC, or FLAG-IDA. A total of 371 patients were randomized: 247 to gilteritinib and 124 to SC. Patients randomized to gilteritinib had significantly longer OS (9.3 months) than those receiving SC (5.6 months; HR for death = 0.637; P = .0007); 1-year survival rates were 37.1% and 16.7%, respectively. The CR/CRh rates for gilteritinib and SC were 34.0% and 15.3%, respectively (P = .0001) with CRh defined as <5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets $>50 \times 10^9$/L and absolute neutrophil count $>0.5 \times 10^9$/L). CR rates in the study were 21.1% and 10.5% (two-sided P = .0106) for gilteritinib and SC, respectively. Median duration of response was 11 months in the gilteritinib arm and 1.8 months in the SC arm. Importantly, similar response rates were observed in both ITD- and TKD-mutant patients. On the basis of an interim analysis in the ADMIRAL trial, on November 28, 2018, the US Food and Drug Administration (FDA) approved gilteritinib for treatment of adult patients who have R/R AML with an *FLT3*-ITD or D835/I836 mutation.[22] In light of this approval, gilteritinib has become the new standard of care for patients with R/R *FLT3*-mutant AML.

In addition to gilteritinib, crenolanib is another type I FLT3 inhibitor that has demonstrated preclinical activity against FLT3 D835 mutations.[23] Clinically, crenolanib has also demonstrated single-agent activity in patients with R/R *FLT3*-mutant AML. In a trial evaluating crenolanib 100 mg 3 times per day or 200 mg/m^2 per day in 3 divided doses, crenolanib therapy resulted in a 39% CRi and 11% partial remission among the 18 FLT3 TKI–naïve patients (6 D835, 9 ITD, 3 ITD + D835) with R/R *FLT3*-mutant AML. In 36 patients who received crenolanib after progressing on prior FLT3 TKIs, the overall response rate was lower at 31% (6 CRi, 5 partial responses). Development of crenolanib is currently focused on exploration of its activity in combination with chemotherapy in both in the first-line and salvage settings (Table 1).

Resistance to FLT3 inhibitors

Despite the relative success of newer FLT3 inhibitors such as quizartinib, gilteritinib, and crenolanib, primary and acquired resistance remains a ubiquitous clinical problem for all these drugs. Similar to the experience with BCR-ABL TKIs in chronic myeloid leukemia, on-target secondary KD mutations in FLT3 are the most common mechanism of acquired resistance in patients responding to type II inhibitors such as quizartinib[24] and sorafenib.[13,25] The most common resistance-causing mutations occur at the FLT3 gatekeeper F691 and AL D835 residues but may also involve other residues in the FLT3 KD.[19] These mutations directly impair drug binding or result in an active kinase conformation unfavorable to interaction with type II inhibitors.

Although both gilteritinib and crenolanib have demonstrated preclinical and clinical activity against quizartinib resistance–causing FLT3 D835 mutations, both of these drugs have vulnerability to the FLT3 gatekeeper F691L mutation,[20,23] which has also been implicated in clinical resistance to quizartinib[16] and sorafenib.[25] Both the CSF1R/KIT/FLT3-ITD inhibitor pexidartinib (PLX3397) and the ABL/FLT3 inhibitor ponatinib have activity against the FLT3 F691L mutation in cell line models[19,26] and have been explored clinically in FLT3-mutant AML patients.[19,27] However, neither drug is currently approved for an AML indication, although ponatinib is FDA approved for chronic myeloid leukemia, and pexidartinib is in late-stage clinical development for tenosynovial giant cell tumor.[28] Additional clinical development of novel FLT3 inhibitors with the potential to suppress quizartinib-resistant FLT3 KD mutations is ongoing, including FF-10101, the first irreversible inhibitor in this class.[29]

Despite the fact that both crenolanib and gilteritinib have been predicted to be vulnerable to a small number of FLT3 KD mutations in vitro,[20,23] recent translational studies in patients reveal KD mutations, including F691L, to be less commonly associated with clinical resistance to both crenolanib[30] and gilteritinib.[31] In a study of crenolanib-treated patients that used whole-exome sequencing and targeted deep sequencing of serial samples, an F691L mutation developed or expanded in only 2 of 18 crenolanib-treated patients.[30] In 1 additional patient, a mutation in the FLT3 extracellular domain K429E was acquired and conferred crenolanib resistance when introduced into FLT3-dependent cell lines. Similarly, in a study of gilteritinib resistance, treatment-emergent FLT3-F691L gatekeeper mutations were identified in only 5 (12.2%) of 41 patients.[31]

Instead, diverse genetic mechanisms seem to be responsible for clinical resistance to both crenolanib and gilteritinib. The majority of crenolanib-treated patients exhibited a diverse spectrum of mutations associated with chromatin modifiers, cohesion, spliceosomes, and transcription factors. Higher frequencies of preexisting *NRAS*, *TET2*, *IDH1*, *IDH2*, *U2AF1*, *STAG2*, *KRAS*, *CSF3R*, *TET2* truncation, and *ASXL1* mutations were present in poor responders compared with crenolanib good responders. Variant allele frequencies of variants of *NRAS*, *BCOR*, *STAG2*, *CEBPA*, and *ASXL1* increased during crenolanib treatment, suggesting that these mutations contribute to drug resistance. In addition, the authors experimentally confirmed several mechanisms of crenolanib resistance.[30]

Activating mutations in the Ras/MAPK pathway seem to be a particularly common resistance mechanism for both crenolanib[30] and gilteritinib.[31] Mutations in Ras signaling pathway genes (*NRAS*, *PTPN11*, *KRAS*, and *CBL*) were enriched in crenolanib poor

Table 1. Selected ongoing and planned FLT3 inhibitor clinical trials

Clinical trial	Status	Agents	Location	Web site
First-line chemotherapy combinations				
QuANTUM-First: Quizartinib With Standard of Care Chemotherapy and as Continuation Therapy in Patients With Newly Diagnosed FLT3-ITD (+) Acute Myeloid Leukemia (AML)	Active	Cytarabine and daunorubicin/idarubicin; HiDAC/HSCT; quizartinib vs placebo	Multicenter, international	https://ClinicalTrials.gov/show/NCT02668653
HOVON 156 AML: Phase 3, multicenter, open-label, randomized, study of gilteritinib versus midostaurin in combination with induction and consolidation therapy followed by 1-year maintenance in patients with newly diagnosed acute myeloid leukemia (AML) or myelodysplastic syndromes with excess blasts-2 (MDS-EB2) with FLT3 mutations eligible for intensive chemotherapy	Planned	Cytarabine and daunorubicin; mitoxantrone + etoposide/HiDAC/HSCT; gilteritinib vs midostaurin	Multicenter, international	http://www.hovon.nl/studies/studies-per-ziektebeeld/aml.html?action=showstudie&studie_id=148&categorie_id=4
Study of Crenolanib vs Midostaurin Following Induction Chemotherapy and Consolidation Therapy in Newly Diagnosed FLT3 Mutated AML	Active	Cytarabine and daunorubicin; HiDAC/HSCT; crenolanib vs midostaurin	Multicenter	https://clinicaltrials.gov/ct2/show/NCT03258931
HMA combinations				
LACEWING: A Study of ASP2215 (Gilteritinib) by Itself, ASP2215 Combined With Azacitidine or Azacitidine by Itself to Treat Adult Patients Who Have Recently Been Diagnosed With Acute Myeloid Leukemia With a FLT3 Gene Mutation and Who Cannot Receive Standard Chemotherapy	Active	Gilteritinib vs gilteritinib + azacitidine vs azacitidine	Multicenter, international	https://ClinicalTrials.gov/show/NCT02752035
Quizartinib and Decitabine in Treating Participants With Untreated or Relapsed FLT3-ITD Mutated Acute Myeloid Leukemia or Myelodysplastic Syndrome	Active	Decitabine + quizartinib	Single center	https://ClinicalTrials.gov/show/NCT03661307
SC combinations				
Study Investigating the Efficacy of Crenolanib With Chemotherapy vs Chemotherapy Alone in R/R FLT3 Mutated AML	Active	HAM or FLAG-Ida; crenolanib vs placebo	Multicenter, international	https://clinicaltrials.gov/ct2/show/NCT03250338
Cladribine Plus Idarubicin Plus Cytarabine (ARAC) in Patients With Acute Myeloid Leukemia (AML), High Risk Myelodysplastic Syndrome (HR MDS) or Myeloid Blast Phase of Chronic Myeloid Leukemia (CML)	Active	Cladribine, cytarabine, idarubicin, midostaurin	Single center	https://ClinicalTrials.gov/show/NCT02115295

FLAG-Ida, fludarabine, cytarabine, and granulocyte colony-stimulating factor with idarubicin; HAM, high-dose cytarabine and mitoxantrone; PD-L1, programmed death-ligand 1.

Table 1. (continued)

Clinical trial	Status	Agents	Location	Web site
Novel combinations				
A Study of ASP2215 (Gilteritinib) Combined With Atezolizumab in Patients With Relapsed or Treatment Refractory FMS-like Tyrosine Kinase (FLT3) Mutated Acute Myeloid Leukemia (AML)	Planned	Gilteritinib + atezolizumab (anti-PD-L1 monoclonal antibody)	Multicenter	https://ClinicalTrials.gov/show/NCT03730012
A Study to Assess Safety and Efficacy of Venetoclax in Combination With Gilteritinib in Subjects With Relapsed/Refractory Acute Myeloid Leukemia	Active	Venetoclax (BCL2 inhibitor) + gilteritinib	Multicenter	https://ClinicalTrials.gov/show/NCT03625505
Venetoclax and Quizartinib in Treating Patients With FLT3-mutated Recurrent or Refractory Acute Myeloid Leukemia	Active	Quizartinib + venetoclax (BCL2 inhibitor)	Single center	https://ClinicalTrials.gov/show/NCT03735875
Milademetan Plus Quizartinib Combination Study in FLT3-ITD Mutant Acute Myeloid Leukemia (AML)	Active	Quizartinib + milademetan (MDM2 inhibitor)	Multicenter	https://ClinicalTrials.gov/show/NCT03552029
A Safety and Efficacy Study of LGH447 in Patients With Acute Myeloid Leukemia (AML) or High Risk Myelodysplastic Syndrome (MDS)	Active	LGH447 (Pim kinase inhibitor) + midostaurin	Multicenter, international	https://ClinicalTrials.gov/show/NCT02078609
Maintenance post-HSCT				
BMT CTN 1506: A Trial of the FMS-like Tyrosine Kinase 3 (FLT3) Inhibitor Gilteritinib Administered as Maintenance Therapy Following Allogeneic Transplant for Patients With FLT3/Internal Tandem Duplication (ITD) Acute Myeloid Leukemia (AML)	Active	Gilteritinib vs placebo	Multicenter, international	https://ClinicalTrials.gov/show/NCT02997202
Crenolanib Maintenance Following Allogeneic Stem Cell Transplantation in FLT3-positive Acute Myeloid Leukemia Patients	Active	Crenolanib	Single center	https://ClinicalTrials.gov/show/NCT02400255
Maintenance postchemotherapy				
A Study of ASP2215 (Gilteritinib), Administered as Maintenance Therapy Following Induction/ Consolidation Therapy for Subjects With FMS-like Tyrosine Kinase 3 (FLT3/ITD) Acute Myeloid Leukemia (AML) in First Complete Remission	Active	Gilteritinib vs placebo	Multicenter, international	https://ClinicalTrials.gov/show/NCT02927262

FLAG-Ida, fludarabine, cytarabine, and granulocyte colony-stimulating factor with idarubicin; HAM, high-dose cytarabine and mitoxantrone; PD-L1, programmed death-ligand 1.

Table 2. Comparison of FLT3 inhibitors in clinical development

Drug	Type I or II inhibitor	Active as monotherapy	Cellular potency	Selectivity	Half-life	Protein binding (%)	Clinical resistance mechanisms	FDA-approved	FDA approved for AML indication
Midostaurin	I	No	++	+	19 h	>99.8	One reported case of an acquired FLT KD mutation (N676K[41])	Yes, in combination with induction chemotherapy only	Yes
Sorafenib	II	Yes	++	++	25-48 h	99.5	FLT3 KD mutations (D835, F691L[13,25])	Yes	No
Quizartinib	II	Yes	+++	+++	~1.5 d	>99	FLT3 KD mutations (D835, F691L)[16]	No	Development ongoing
Crenolanib	I	Yes	++	++	6-8 h	95.9	F691L, Ras pathway mutations[30]	No	Development ongoing
Gilteritinib	I	Yes	++	++	113 h	~94	F691L, Ras pathway mutations[31]	Yes	Yes

responders and expanded or were acquired during crenolanib treatment. Mutation patterns differed between *PTPN11*- and *RAS*-mutant crenolanib-treated patients. Three of 4 *PTPN11* mutations seemed to co-occur with *FLT3* TKD or ITD mutations, as inferred by similar variant allele frequencies for both mutations. FLT3-dependent cell lines transduced with *PTPN11* mutations exhibited decreased sensitivity to crenolanib. *NRAS* and *KRAS* mutations were thought to be largely present in independent clones that did not harbor the *FLT3* mutations in crenolanib-treated patients. Mutations in the Ras pathway were also commonly implicated in gilteritinib resistance. Targeted next-generation sequencing at the time of progression in patients receiving gilteritinib identified treatment-emergent mutations that activate Ras/MAPK pathway signaling in 15 (36.6%) of 41 patients, mostly in *NRAS* or *KRAS*. An additional 2 patients acquired BCR-ABL1 fusions at progression. In contrast to the observation in crenolanib-treated patients, single-cell targeted DNA sequencing of gilteritinib-treated patients revealed diverse patterns of clonal selection and evolution of Ras pathway mutant subclones, including the emergence of activating mutations (both *RAS* and *PTPN11*) in *FLT3*-mutated subclones, the expansion of alternative independent *RAS*- or *PTPN11*-mutant *FLT3* WT subclones, or both patterns simultaneously. Nonetheless, these findings suggest that future strategies to combat resistance to type I FLT3 inhibitors such as gilteritinib and crenolanib should focus on suppression of Ras/MAPK signaling.

FLT3 inhibitor combinations

On the basis of the activity of first-generation, less targeted FLT3 inhibitors when used in combination with chemotherapy[11,12] or with hypomethylating agent (HMA) treatment,[32] current ongoing development efforts have focused on assessment of FLT3 TKI combination strategies (Table 1) with the hope that more potent FLT3 inhibition achieved with newer agents might result in even better clinical outcomes. Thus far, reported results of trials combining next-generation FLT3 TKIs with induction and consolidation chemotherapy in the first-line setting have been encouraging. In a trial of crenolanib in combination with induction and consolidation chemotherapy, patients received 7+3 induction with cytarabine 100 mg/m^2 for 7 days and either daunorubicin 90 mg/m^2 or idarubicin 12 mg/m^2 for 3 days along with crenolanib 100 mg 3 times per day continuously starting 24 hours after chemotherapy until 72 hours before the next chemotherapy cycle.[33] Consolidation consisted of up to 4 cycles of high-dose cytarabine (HiDAC: 3 g/m^2 for patients age <60 years and 1 g/m^2 for those age 60 years) once every 12 hours on days 1, 3, and 5 with crenolanib starting 24 hours after the final HiDAC dose in each cycle. Eligible patients proceeded to allo-HSCT. Maintenance crenolanib at 100 mg 3 times per day was started after HiDAC or HSCT for a maximum of 12 cycles. In an interim report, 22 (81%) of 27 patients were alive with a median follow-up of 20.8 months. Median OS, EFS, and cumulative incidence of relapse had not been reached.[33]

Another phase 1 study assessed gilteritinib in combination with 7+3 and HiDAC consolidation followed by single-agent maintenance.[34] In that study, successive cohorts of 3 to 6 patients received 40, 80, 120, or 200 mg/day gilteritinib. Patients received ≤2 cycles of a 7+3 induction regimen (cytarabine 100 mg/m^2 per day on days 1-7 plus idarubicin 12 mg/m^2 per day on days 1-3) and once-per-day gilteritinib on days 4 to 17 (schedule 1). After completion of the dose-expansion cohort using schedule 1, a second cohort received gilteritinib on days 8 to 21 (schedule 2) and daunorubicin 90 mg/m^2 per day in place of idarubicin. During consolidation, patients received cytarabine (1.5 g/m^2 once every 12 hours on days 1, 3, and 5) and once-per-day gilteritinib (days 1-14) for ≤3 cycles. Transplantation was allowed for patients who responded. After consolidation or transplantation with stable engraftment, patients received maintenance therapy with once-per-day gilteritinib (28-day cycles; ≤26 cycles). The end-of-treatment investigator-reported CRc rate for response-evaluable *FLT3*-mutant patients receiving gilteritinib 120 mg on schedule 1 (n = 17) was 100%. The CRc rate in *FLT3*-mutant patients receiving schedule 2 induction with daunorubicin was also 100%. Among patients who received ≥80 mg/day gilteritinib (n = 47), CRc rates for *FLT3*-mutant patients were 88.9% (24 of 27).[34] A similar phase 1 study of quizartinib combined with induction and consolidation chemotherapy demonstrated a 74% CRc rate in unselected newly diagnosed AML patients.[35] On the basis of these promising results, multiple trials of FLT3 TKIs in combination with induction and consolidation chemotherapy in the first-line setting are planned or are currently ongoing (Table 1). QuANTUM-First (NCT02668653) is a phase 3, double-blind, placebo-controlled study of quizartinib in combination with induction and consolidation chemotherapy. In other trials, crenolanib (NCT03258931) and gilteritinib (HOVON 156 AML) are being compared with midostaurin in this setting (Table 1).

Next-generation FLT3 inhibitor and HMA combinations have also shown encouraging early response rates, and clinical trials are ongoing in both the first-line and the R/R setting (Table 1). In a phase 1/2 trial that incorporated quizartinib at 2 planned dose levels (60 mg or 90 mg orally once per day in combination with AZA

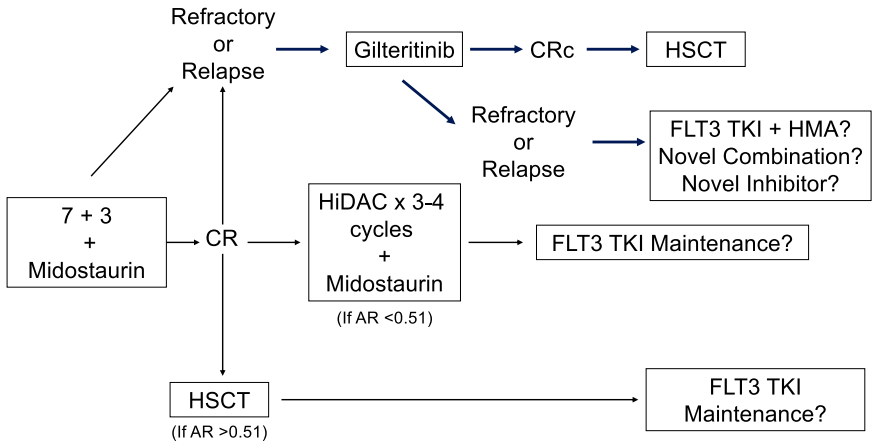

Figure 1. Treatment of newly diagnosed *FLT3*-mutant AML in patients eligible for induction chemotherapy.

75 mg/m^2 for 7 days per cycle or cytarabine 20 mg subcutaneously twice per day for 10 days per cycle (LoDAC), the overall response rate was 75% among patients with FLT3-ITD mutation (n = 55), and 5 (9%) had no detectable minimal residual disease (MRD).[36] A randomized trial of gilteritinib, gilteritinib combined with AZA, and AZA alone has been initiated in newly diagnosed patients with *FLT3*-mutant AML who are ineligible for chemotherapy (NCT02752035). In a safety cohort treated with escalating doses of oral gilteritinib (80 or 120 mg/day) in combination with subcutaneous or intravenous AZA (75 mg/m^2 per day), a CRc rate of 67% (10 of 15) was observed.[37] Several other novel combination strategies are also under investigation in the R/R setting, including combinations with SC, immunotherapy, or targeted therapy (Table 1).

Clinical case continued

On the basis of the superior outcomes observed with gilteritinib compared with chemotherapy, the patient began treatment with gilteritinib 120 mg once per day. On day 20 of gilteritinib therapy, the patient developed a diffuse macular rash and a fever of 104°F in the setting of neutropenia. She was hospitalized for treatment with antibiotics and a workup for infections. No source of infection was identified. During the course of her hospitalization, her absolute neutrophil count began to rise and reached 1.03×10^9/L by day 24. Prednisone was started for treatment of presumptive gilteritinib-induced differentiation syndrome, a reported complication of FLT3 inhibitor therapy.[24] The patient defervesced soon afterward, and a bone marrow biopsy performed after 2 months of receiving gilteritinib therapy showed blasts <5%, although the patient remained dependent on platelet transfusions. The patient subsequently underwent allo-HSCT from a matched unrelated donor. On posttransplant day +60, the patient's peripheral blood donor chimerism was noted to be 100%. However, the patient, fearful of future relapse, asked whether she would benefit from further treatment with gilteritinib.

FLT3 inhibitors as remission maintenance therapy

The benefit of FLT3 TKI maintenance in the posttransplant setting is currently a subject of some controversy. Two randomized studies presented at the 2018 American Society of Hematology Annual Meeting suggest a benefit for posttransplant maintenance.[38,39] In the SORMAIN trial, adult patients with FLT3-ITD$^+$ AML who had undergone allo-HSCT and were in confirmed CR were randomized 1:1 between day +30 and day +100 posttransplant to receive sorafenib or placebo for up to 24 months. The primary end point was RFS with OS as a secondary end point. Between October 2010 and May 2016, 83 patients were accrued at 15 sites in Austria and Germany. The study was ultimately terminated because of low accrual, but 2-year RFS showed a benefit for sorafenib compared with placebo with an EFS of 85.0% (95% CI, 69.5%-93.0%) in the sorafenib group compared with 53.3% (95% CI, 36.5%-67.5%) in the placebo group (HR, 0.39; 95% CI, 0.18-0.85; $P = .0135$).[39] The Radius trial randomized *FLT3*-ITD$^+$ adult patients in first CR after myeloablative HSCT to midostaurin 50 mg twice per day continuously for 12 cycles or standard of care (SOC). Study treatment started on days +28 to +60 posttransplant. With estimated relapse rates of 24% and 11% in the SOC and midostaurin arms, respectively, there was a 46% relative reduction in the risk of relapse with the addition of midostaurin. However, the study was not powered to detect a statistical difference between arms, and median RFS was not reached in either arm.[39] Although both of these studies suggest benefit to posttransplant FLT3 TKI maintenance, it is not clear that they establish a new SOC for all *FLT3*-ITD$^+$ patients undergoing HSCT in the current (post-midostaurin) era. The majority of the patients enrolled in the SORMAIN and Radius trials had not received previous FLT3 TKI therapy. Given that the current SOC for newly diagnosed *FLT3*-ITD$^+$ patients includes midostaurin with induction, patients may not derive the same benefit as those not previously exposed to FLT3 TKI treatment. In addition, no biomarker has been established for patients who might or might not benefit from post-HSCT maintenance. Given that these drugs are not without adverse effects, such a biomarker would be very useful for treatment decision making. The currently ongoing Blood and Marrow Transplant Clinical Trials Network 1506 trial is an international, multicenter, randomized, double-blind, placebo-controlled phase 3 trial of gilteritinib maintenance after allo-HSCT with a planned target accrual of 346 *FLT3*-ITD$^+$ AML patients. In contrast to patients in the SORMAIN and Radius trials, patients are consented and randomized before transplantation to better understand the proportion of patients who are able to proceed to maintenance post-HSCT. In addition, in an effort to identify a biomarker that can differentiate patients that may or may not benefit, the trial also incorporates measurement of MRD by next-generation sequencing of *FLT3*.[40] It is hoped that this study will definitively establish whether or not FLT3 TKI maintenance post-HSCT should be considered a true SOC for patients who go to HSCT in first remission. Studies exploring FLT3 TKIs in postchemotherapy remission maintenance are also ongoing (Table 1).

Which FLT3 inhibitor is best?

Currently, 3 FLT3 inhibitors have been approved by the FDA for use in the United States: sorafenib, midostaurin, and gilteritinib. Of these, 2 are approved for an AML indication: midostaurin in first-line treatment in combination with chemotherapy and gilteritinib in R/R disease. Two other inhibitors, quizartinib and crenolanib, are in late-stage clinical development in AML in the first-line and R/R settings. These drugs differ substantially with regard to potency, selectivity, half-life, and protein-binding capacity (Table 2), and these distinct properties have translated to differing degrees of clinical success as monotherapy. In general, inhibitors with increased potency, selectivity, longer half-life and decreased protein binding have demonstrated the greatest degree of activity as monotherapy, with quizartinib being the most potent and the most selective in this group. An additional critical differentiating point is susceptibility to secondary resistance–causing FLT3 KD mutations, with the potent, selective type I FLT3 inhibitors crenolanib and gilteritinib being least vulnerable to this mechanism of resistance[30,31] (Table 2). The activity of sorafenib and midostaurin when used in combination with chemotherapy, particularly in *FLT3* WT patients or those with low *FLT3* mutation, AR suggests that the benefit of these drugs may, at least in part, be a result of off-target mechanisms, although this remains to be proven. Alternatively, targeting of WT FLT3 may have some benefit in an unselected AML population. It is likely that the most potent, selective, bioavailable FLT3 TKI with the least vulnerability to resistance-causing FLT3 KD mutations will be most effective when used in an FLT3-mutant AML population. However, differences in tolerability as a result of adverse effects in individual patients will always make it preferable to have a wider selection of clinically active agents available for use.

Current SOC and future directions

The current SOC for a newly diagnosed eligible-for-treatment adult patient with *FLT3*-mutant AML with AR $\geq$0.05 is induction chemotherapy in combination with midostaurin (Figure 1). In patients who do not achieve remission or who relapse after initial chemotherapy, gilteritinib is superior to salvage chemotherapy. Patients with *FLT3*-ITD mutations with a high AR who are candidates for transplantation should be considered for allo-HSCT in first CR. The role of transplantation in patients with low AR and otherwise good risk disease (ie, *NPM1* mutant) is debated. In this case, monitoring of MRD during induction and consolidation may aid in treatment decision making.[42] The role of posttransplant FLT3 TKI maintenance is not clearly established, although some studies suggest increased RFS with maintenance therapy starting 28 to 100 days posttransplant and lasting for 12 to 24 months. The ongoing BMT CTN 1506 trial hopes to determine whether MRD can serve as a biomarker for patients who will benefit from posttransplant maintenance therapy. Patients who are not eligible for chemotherapy have high response rates to FLT3 TKI-HMA combinations, and this is the subject of ongoing clinical trials. In the R/R setting, multiple novel combination trials incorporating chemotherapy, immunotherapy, and targeted therapy are ongoing. Activating Ras/MAPK mutations seems to be a major cause of resistance to type I inhibitors such as crenolanib and gilteritinib and will need to be a focus of future trials targeted at resistant disease. High CR rates achieved with gilteritinib and crenolanib in the first-line setting have prompted randomized trials comparing these agents with midostaurin in induction, consolidation and maintenance postchemotherapy to test the idea that more potent and specific FLT3 inhibitors can improve upon outcomes observed with a less targeted agent. In the future, if high durable remission rates can be achieved with this strategy in the absence of transplantation, it may be possible to cure a larger group of *FLT3*-mutant patients without the need for allo-HSCT. Finally, on the basis of the broad expression of FLT3 in AML, other FLT3-targeted therapies, including chimeric antigen receptor T cells[43] and T-cell engagers,[44] are in clinical development and may extend the targeting of FLT3 beyond patients with *FLT3*-activating mutations.

This article was selected by the Blood and Hematology 2019 American Society of Hematology Education Program editors for concurrent submission to Blood and Hematology 2019. It is reprinted from Blood 2019, Volume 133.

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