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Clinical considerations for the use of FLT3 inhibitors in acute myeloid leukemia

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ABSTRACT

Internal tandem duplications and tyrosine kinase mutations in the fms-like tyrosine kinase 3 (FLT3) receptor can occur in acute myeloid leukemia (AML) and portend a poor prognosis. Midostaurin, a multikinase inhibitor that targets FLT3, demonstrated a survival benefit in FLT3-mutated AML in combination with front-line chemotherapy. Despite this advancement, the use of FLT3 inhibitors in clinical practice is complicated by significant drug-drug interactions and uncertainty about optimal timing, duration, and sequencing of therapy. As monotherapy, the utility of FLT3 inhibitors was initially limited by incomplete and transient clinical responses and the development of acquired resistance. This led to the development of more potent and selective FLT3 inhibitors designed to overcome common resistance mechanisms. One of these second generation FLT3 inhibitors, gilteritinib, is now FDA-approved for the treatment of relapsed or refractory AML. Now that multiple FLT3 inhibitors are commercially available, it is important to further delineate the role of these agents in the AML population. This review aims to provide a comprehensive overview of the role of FLT3 inhibitors in AML and apply the current literature to clinical practice.

1. Introduction

The diverse molecular architecture of acute myeloid leukemia (AML) has become increasingly apparent over the past decade. Internal tandem duplications and tyrosine kinase mutations in the *fms-like tyrosine kinase 3* (FLT3) receptor, which is encoded by the *FLT3* gene located on chromosome 13q12, can occur and portend a poor prognosis (Patel et al., 2012). Despite this disparity, until recently standard first-line treatment for AML had not changed in more than 45 years (Döhner et al., 2010). Induction with 3 + 7 (3 days of anthracycline and 7 days of continuous-infusion cytarabine) remained the standard chemotherapy regimen for "fit" patients. With the advent of FLT3 inhibitors, the treatment armamentarium for FLT3-mutated (FLT3+) AML is beginning to expand. Midostaurin, a multikinase inhibitor that targets FLT3, became the first targeted therapy FDA approved for FLT3 + AML in 2017 (Stone et al., 2017). Although FLT3 inhibitors have promise to improve outcomes in a high-risk subset of AML patients, questions still remain around the use and management of these agents in such a complex population. In this review, we summarize the clinical evidence supporting the use of FLT3 inhibitors for the treatment of AML and discuss how to apply the data to clinical practice.

2. FLT3 receptor

FLT3 is a class III family trans-membrane tyrosine kinase receptor which serves an important role in normal hematopoietic cell survival and proliferation (Stirewalt and Radich, 2003). FLT3 acts as a cytokine receptor for the ubiquitously expressed FLT3 ligand (FL). Upon binding to FL, FLT3 dimerizes and undergoes a conformational change to allow auto-phosphorylation of the ATP-binding pocket. The resulting FLT3 receptor activation leads to increased cell proliferation, decreased apoptosis, and reduced differentiation of hematopoietic cells via PI3K/AKT, MAPK/ERK, and STAT signaling cascades (Fig. 1) (Scholl et al., 2008).

3. FLT3 mutations in AML

FLT3 mutations occur in approximately 30 percent of AML patients with normal cytogenetics, making it the most common molecular aberrancy in AML (Schlenk et al., 2008). These molecular mutations are broken down into two subtypes: internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations (Fig. 1). FLT3-ITD occurs in approximately 25 percent of patients with de novo AML and occurs in the juxtamembrane domain of the FLT3 receptor, which is responsible

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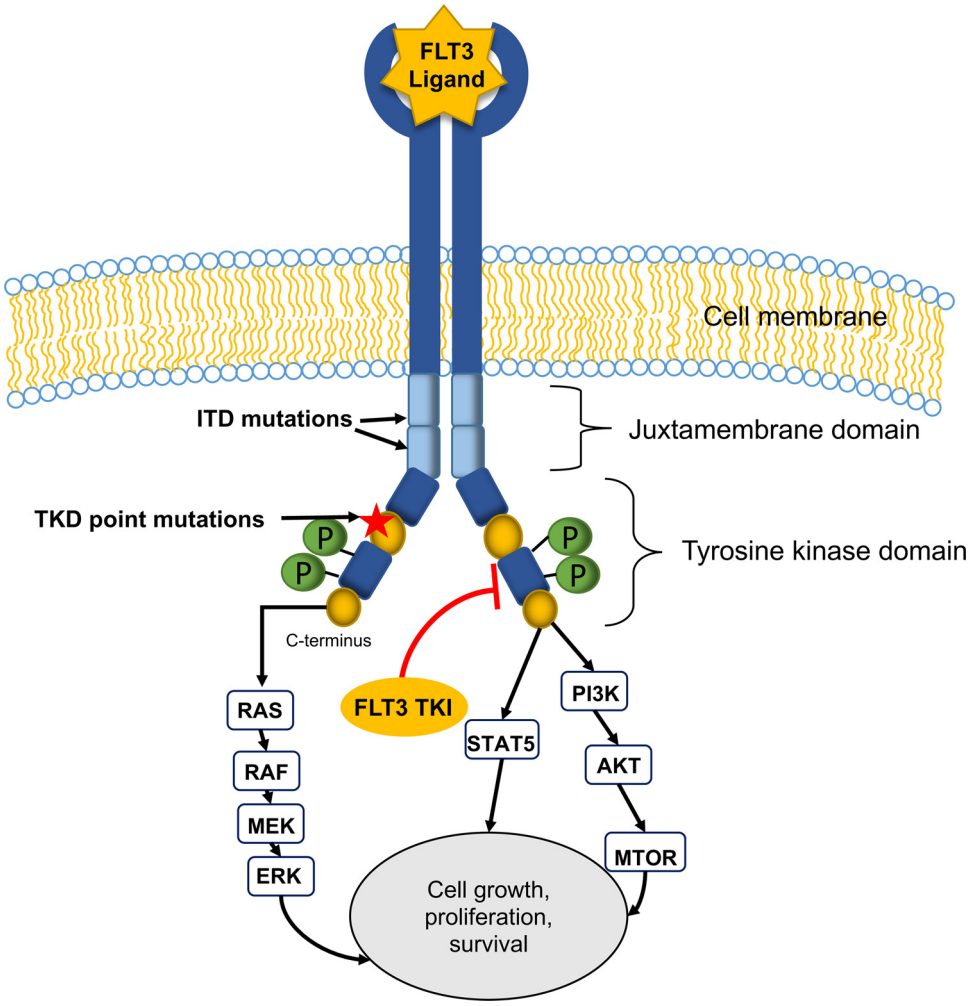

Fig. 1. FLT3 Receptor.

for the auto-inhibitory function (Horiike et al., 1997). The FLT3 receptor becomes more responsive to FL, leading to increased proliferation of leukemia cell lines. Point mutations in the activating loop of the tyrosine kinase domain (FLT3-TKD), most commonly at aspartic acid residue D835, occur in approximately 7 percent of de novo AML patients. Both ITD and TKD mutations lead to constitutive FLT3 receptor activation.

FLT3-ITD has been shown to impact prognosis and long term outcomes in AML (Fernandez et al., 2009; Fröhling et al., 2002; Kottaridis et al., 2001). To illustrate, a phase 3 randomized trial by Fernandez, et al. found that patients with FLT3-ITD mutations had inferior median survival compared to the FLT3-wild type (WT) population (15.2 versus 28.6 months, $p = 0.009$) (Fernandez et al., 2009). Although rates of complete remission (CR) appear to be similar to FLT3-WT patients, FLT3-ITD mutations have also been associated with a higher blast percentage and white blood cell count (WBC) at diagnosis, increased risk of relapse, and decreased event-free survival (EFS) (Ravandi et al., 2014). OS and EFS are also negatively correlated with increasing length of ITD mutations, bi-allelic disease (loss of FLT3-WT allele), and increasing allelic ratio ≥ 0.51 (Stirewalt et al., 2006; Whitman et al., 2001; Schlenk et al., 2014). Patients with concurrent FLT3 and NPM1 mutations demonstrate improved outcomes, compared with a FLT3 mutation alone, although the magnitude of benefit is diminished with higher FLT3 allelic ratios (Gale et al., 2008). In contrast, the impact of TKD mutations on clinical outcomes is not clearly established (Bacher et al., 2008).

Allogeneic hematopoietic cell transplantation (allo-HCT) is recommended in first complete remission (CR1) for patients with poor risk disease, including FLT3-ITD AML with high allelic ratio (FLT3-ITD^{high}). Patients with FLT3-ITD^{high} AML have demonstrated significantly improved relapse free survival (RFS) and OS after allo-HCT; however, this benefit has not been consistently demonstrated with low FLT3-ITD allelic ratios (Schlenk et al., 2014; Gale et al., 2008; Bacher et al., 2008; Schnittger et al., 2011). The role of allo-HCT is also controversial when FLT3-ITD mutations coincide with mutated NPM1. In fact, the 2017 European LeukemiaNet (ELN) Risk Stratification by Genetics, also adopted by the National Comprehensive Cancer Network (NCCN) for risk stratification, considers patients with mutated NPM1 with FLT3-ITD allelic ratio < 0.5 (FLT3-ITD^{low}) to have favorable risk disease (Döhner et al., 2017National Comprehensive Cancer Network (NCCN), 2019). Retrospective data suggests allo-HCT in CR1 does not reduce the risk of relapse or prolong OS in this population (Pratcorona et al., 2013). In contrast, another retrospective study by Sakaguchi, et al reported that patients with combined NPM1 and FLT3-ITD^{low} AML had improved RFS after allo-HCT (Sakaguchi et al., 2018). Similarly, the prognostic significance for patients with FLT3-TKD mutations in the absence of other genetic abnormalities is uncertain and allo-HCT is controversial (Bacher et al., 2008). Unfortunately, patients that do receive allo-HCT have high rates of treatment-related mortality, and many still end up relapsing and dying from their disease (Gaballa et al., 2017). The need for better-tolerated therapeutic agents and an enhanced understanding of AML pathogenesis have prompted the development of tyrosine kinase inhibitors (TKIs) directed at FLT3.

4. FLT3 inhibitors

First generation FLT3 inhibitors were not originally developed with FLT3 specifically in mind. Once the role of FLT3 in AML was elucidated, drug screening efforts began to identify small molecule inhibitors of FLT3 among TKIs developed for other oncogenic targets and indications (Weisberg et al., 2002). First generation FLT3 inhibitors are therefore relatively nonspecific inhibitors with additional activity against receptor targets such as c-Kit, platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR). In contrast, the second generation FLT3 inhibitors were developed to have potent and selective FLT3 inhibition, with the goal of improving activity and tolerability among patients with FLT3 + AML.

FLT3 inhibitors are further classified based on the mechanism of interaction with the receptor. All FLT3 inhibitors prevent ATP from binding to the tyrosine kinase domain, blocking phosphorylation and activation of the FLT3 receptor (Fig. 1) (Yamamoto et al., 2001Kiyoi et al., 1998). Type I inhibitors (e.g., lestaurtinib, midostaurin, crenolanib, gilteritinib) bind to FLT3 in the active or inactive conformation, whereas type II inhibitors (e.g., sorafenib, quizartinib, ponatinib) interact with a hydrophobic region of FLT3 only accessible in the inactive conformation. D835 mutations on the tyrosine kinase domain cause FLT3 to favor the active conformation, thus preventing the ability of type II inhibitors to interact and inhibit FLT3-TKD. Treatment with type II inhibitors over time may select for D835 mutations and result in acquired resistance, while type I inhibitors are able to retain activity at both FLT3-ITD and FLT3-TKD mutations (Smith et al., 2015).

5. First generation FLT3 inhibitors

5.1. Sorafenib

Sorafenib is one of the mostly widely used FLT3 TKIs, with FDA-approved indications for hepatocellular carcinoma, differentiated thyroid carcinoma, and renal cell carcinoma. The antiproliferative activity of sorafenib varies depending on the tumor type and mechanism of proliferation. Originally developed as an inhibitor targeting Raf kinase and MAPK signaling pathway, it was found to have additional potent inhibitory activity against FLT3, c-Kit, VEGFR, RET and PDGFR (Wilhelm et al., 2006Wilhelm et al., 2004). While not currently FDA-approved for treatment of FLT3-mutated AML, sorafenib is used off-label in this population as monotherapy or as an adjunct to chemotherapy.

Small phase II clinical trials initiated the use of sorafenib in AML. Ravandi, et al. evaluated sorafenib (400 mg BID continuously) in combination with the hypomethylating agent azacitidine (75 mg/m^2 IV daily for 7 days per 28-day cycle) in relapsed or refractory FLT3 + AML. The study reported a median OS of 6.2 months (Ravandi et al., 2013). These results are less impressive in the context of a recent large international cohort study of a similar population of AML patients irrespective of FLT3 status (n = 655), reporting a median OS of 6.7 months with use of hypomethylating agents alone (Stahl et al., 2018). Sorafenib was later studied sequentially after front-line 3 + 7 induction in an elderly population (60 years of age or older) irrespective of FLT3 mutational status. Unfortunately, the results showed higher treatment-related morbidity, lower CR rates, and similar EFS and OS when sorafenib was compared to placebo (Serve et al., 2013). There are several aspects of this trial that may have contributed to treatment failure. Although baseline characteristics were mostly well balanced between groups, sorafenib-treated patients had higher LDH at baseline, suggesting greater leukemia burden. The older patient population assessed in this study was less equipped to tolerate the increase in sorafenib-related adverse events (mainly driven by increased infections), and therefore received less consolidation chemotherapy overall. Interestingly, these outcomes were consistent in a subgroup analysis of FLT3-ITD patients, although FLT3-mutated AML comprised only 14% of the total study population. The authors speculated the lack of benefit was due in part to the upregulation of FLT3 ligand which occurs following chemotherapy and this may interfere with FLT3 inhibitor activity. Additionally, the authors suggested those with low allelic burden may have less addiction to FLT3 signaling, although outcomes based on allelic ratios were not reported in this study. Lastly, bone marrow stromal cells may have protected leukemic blasts from sorafenib.

The utility of sorafenib in the front-line setting was also examined in the SORAML trial, which included a younger AML patient population (18–60 years old) irrespective of FLT3 mutational status (Röllig et al., 2017). Patients were randomized to sorafenib or placebo in combination with 3 + 7, with sorafenib or placebo continued through consolidation and into a maintenance phase. Median EFS was improved in the sorafenib-treated arm compared to placebo (21 versus 9 months, p = 0.012), and benefit was seen regardless of FLT3 mutational status (FLT3-wild-type, FLT3-ITD, or FLT3-TKD). The HR of death for sorafenib compared to placebo was not significant (p = 0.322); however, an exploratory analysis of FLT3-ITD + patients found a numerical but non-significant increase in overall survival (not reached versus 19 months) in the sorafenib cohort. Interestingly, rates of CR were similar between sorafenib and placebo (60% versus 59%), suggesting sorafenib helps maintain remission but is unable to increase rates of remission.

After front-line chemotherapy, many fit patients with FLT3-ITD + AML will proceed to allo-HCT due to the aggressive nature of their disease and high risk of relapse. Despite allo-HCT, post-transplant relapse remains a significant concern in FLT3-ITD + AML due to high rates of early relapse and poor response to salvage chemotherapy (Gaballa et al., 2017; Deol et al., 2016Song et al., 2016). In addition to the inhibition of FLT3, sorafenib has been shown to increase transcription of IL-15 in FLT3-ITD + AML cells, leading to increased cytotoxic T-cell response and an immune-mediated graft-versus-leukemia effect (Mathew et al., 2018). Thus, post-transplant FLT3 inhibition with sorafenib to prevent relapse is a rational strategy for improving outcomes in this high-risk patient population. Battipaglia, et al. assessed the efficacy and tolerability of sorafenib in 27 patients undergoing allo-HCT for FLT3 + AML and observed a significantly improved 1-year OS of 92% compared to 60–70% in historical controls (Deol et al., 2016; Battipaglia et al., 2017). A retrospective study of 26 FLT3-ITD + patients comparing allo-HCT with or without sorafenib maintenance therapy suggests a therapeutic benefit with sorafenib, including improved 2-year OS (81% vs. 62%, p = 0.029), 2-year PFS (82% vs. 53%, p = 0.0081), and lower 2-year incidence of relapse (8.3%. 47.7%, p = 0.0077) (Brunner et al., 2016). Additional retrospective data have corroborated the positive results of sorafenib in FLT3-ITD + AML after allo-HCT(Xuan et al., 2018Metzelder et al., 2017). The randomized, multicenter SORMAIN trial compared sorafenib to placebo as maintenance therapy after allo-HCT in patients with FLT3-ITD + AML in confirmed CHR (Burchert et al., 2018). The study team reported improved 2-year RFS (85.0% vs. 53.3%, p = 0.0135) and significantly improved overall survival at 30 months in the sorafenib arm. There is a rational concern that sorafenib may exacerbate graft versus host disease (GVHD) as a result of increased IL-15 and donor cytotoxic T-cell activity, yet chronic GVHD rates in the aforementioned studies were consistent with rates observed in the general bone marrow transplant population (approximately 50%) (Passamonti et al., 2015Blaser et al., 2005). Based on available data, sorafenib is the only FLT3 inhibitor to demonstrate a survival benefit as maintenance after allo-HCT in randomized trials and is our preferred FDA-approved agent in this setting over midostaurin and gilteritinib for FLT3-ITD + AML. An important exception to this recommendation is patients with isolated FLT3-TKD + AML, as this group was excluded from the SORMAIN trial (Burchert et al., 2018). Additionally, as a type II inhibitor, sorafenib is unlikely to have anti-leukemic activity against FLT3-TKD mutations. In this population, type I inhibitors (e.g. midostaurin, gilteritinib) are preferred.

Although sorafenib may be a highly effective, tolerable option for

post-transplant maintenance therapy, there exist several caveats to keep in mind. Sorafenib was introduced at a median of 30 to 100 days post-transplant in these studies, eliminating patients from analysis with early transplant-related mortality and potentially biasing any non-randomized comparisons with historical cohorts or non-sorafenib-treated patients (Battipaglia et al., 2017). These studies generally initiated sorafenib at a dose between 200 mg BID to 400 mg BID and subsequently dose adjusted on the basis of suspected toxicity (dose range, 200–800 mg daily). In our practice, we often initiate sorafenib at a lower dose (200 mg BID) around day 56 post allo-HCT out of concern for count suppression early on, and will increase the dose to 400 mg BID as tolerated. This approach is supported by a study which simulated the exposure-response relationship between sorafenib and sorafenib N-oxide with FLT3-ITD and ERK inhibition in patients with FLT3 + AML. Simulations demonstrated that sorafenib 200 mg BID resulted in similar FLT3-ITD and ERK inhibition compared with 400 mg BID. Thus 200 mg BID is a rational starting dose. Given the wide interpatient variability in sorafenib exposure, patients tolerating sorafenib could be escalated to 400 mg BID while patients with significant toxicity can be decreased to 200 mg daily and even down to 200 mg every other day (Jain et al., 2011). Patients should still derive some benefit at lower doses based on the aforementioned exposure-response relationship (Liu et al., 2018).

To complicate matters, sorafenib is metabolized largely through CYP3A4 to its primary active metabolite, sorafenib N-oxide. Pharmacodynamic data suggests that sorafenib N-oxide has more affinity to the FLT3 receptor than its parent compound, with dissociation constants of 70 nM and 95 nM, respectively (Inaba et al., 2011). If patients are receiving concomitant CYP3A4-inhibiting drugs (e.g., azole antifungals), the FLT3-ITD active metabolite (sorafenib N-oxide) is reduced by approximately 68% and thus could lower efficacy (Liu et al., 2018). Accordingly, a sorafenib dose of 400 mg BID administered with strong CYP inhibitors is likely required to attain similar sorafenib N-oxide exposure as 200 mg BID without CYP inhibitors. Regardless, caution should be taken when administering sorafenib with potent CYP inhibitors as it is unknown if this inhibition increases other metabolites that change the toxicity profile of sorafenib. More data are needed to determine the optimal dose of sorafenib in the context of CYP3A4 inhibition. In the post-transplant setting, we aim for a maintenance dose of 400 mg BID (although rarely attained post-transplant) with concomitant azole antifungals and encourage discontinuation of unnecessary medications inhibiting CYP450. Regardless of the scenario, tolerability of the individual patient will guide further dose adjustments.

5.2. Midostaurin

Midostaurin is a semi-synthetic derivative of staurosporine, the original “pan-kinase” inhibitor, derived from the bacterium *Streptomyces staurosporeus*. Midostaurin has a broad spectrum of kinase activity, including protein kinase C (PKC), FLT3, VEGR, PDGFR, CDK1, c-Src, c-Syk, c-Fgr, and c-KIT (Tamaoki et al., 1986; Propper, 2001; Fabbro et al., 1999). Although originally developed for treatment of solid tumors, FLT3-inhibitory activity of midostaurin was discovered in a drug screen of apoptosis-inducing compounds in cells expressing FLT3-ITD (Weisberg et al., 2002). Midostaurin was subsequently studied for its potential anti-leukemic effect.

In early-phase trials, midostaurin demonstrated modest biologic activity. A phase II trial of 20 patients with FLT3+ relapsed/refractory AML or high-grade myelodysplastic syndrome utilized midostaurin at a dose of 75 mg three times daily until toxicity or disease progression (Stone et al., 2005). Significant reductions in blast counts occurred within days of midostaurin initiation. Seventy percent of patients had a decrease in peripheral blast count of at least 50%, and 35% of patients experienced a 2-log reduction or greater which lasted a median of 13 weeks. No patients achieved CR. The most common treatment-related adverse events were grade 1 or 2 nausea and vomiting, but midostaurin was otherwise well tolerated. A subsequent phase IIb trial of relapsed or refractory patients, including wild-type (n = 60) or mutated (n = 35) FLT3 AML, assigned patients to received midostaurin at 50 or 100 mg BID (Fischer et al., 2010). Patients achieved BR (defined as reduction in peripheral blood or bone marrow blasts by > 50%) in 71% and 42% of FLT3 mutant and FLT3-WT patients, respectively. Midostaurin demonstrated activity in both FLT3+ and FLT3-WT AML patients, but only one patient achieved a partial response (PR) and no patients obtained a CR. Of the blast responders, median time to treatment failure (disease progression or study discontinuation due to death or adverse event) was only 60 days in the FLT3+ group and 83 days in the FLT3-WT group. Although midostaurin demonstrated biologic activity, response durability as a single agent was limited.

A phase I/II single-arm study subsequently reported the anti-leukemic activity of midostaurin (25–50 mg BID) in combination with azacitidine (75 mg/m^2 on day 1–7 of each cycle) in patients with AML or high risk MDS, irrespective of FLT3 mutational status (Strati et al., 2015). Patients included in the study were either relapsed/refractory to front-line therapy or were unable to receive or refused standard induction chemotherapy. Among the 54 patients included in the study, the overall response rate (ORR) was 26% [2% CR, 11% CRi, 11% morphologic leukemia free state (MLFS) and 2% PR] after a median of 2 treatment cycles. In order to evaluate the safety and appropriate administration of midostaurin in addition to standard therapy, a phase Ib trial assessed midostaurin with 3 + 7 induction in newly diagnosed AML (Stone et al., 2012). The initial regimen of midostaurin 100 mg BID on either days 1–28 or 8–28 was deemed to be excessively toxic due to intolerable gastrointestinal side effects. The study protocol was amended to reduce the dose of midostaurin to 50 mg BID and limit the midostaurin treatment course to 14 days per 28-day cycle. CR rates with this combination were 80% for FLT3-WT and 92% for FLT3 + AML, with similar OS at 1 year (78% versus 85%, respectively). Ultimately, these studies determined midostaurin could be administered safely in combination with conventional chemotherapy and potentially improve response rates.

The highly-anticipated global, randomized, placebo-controlled phase III CALGB10603 (“RATIFY”) trial compared midostaurin 50 mg BID to placebo in combination with 3 + 7 induction, consolidation, and maintenance for previously-untreated FLT3 + AML (Stone et al., 2017). Patients were further stratified according to the FLT3 mutation subtype: TKD, ITD, with either high (0.7) or low (0.05-0.7) mutant to wild-type allelic ratio. Median OS (74.7 vs. 25.6 months, p = 0.009) and median EFS (8.2 vs. 3.0 months, p = 0.002) were both significantly improved with midostaurin compared to placebo, and was consistent throughout all FLT3 mutational subtypes. Of note, CR rates were similar between midostaurin and placebo cohorts (58.9% vs. 53.5%, p = 0.15). Midostaurin created excitement as one of the few recent interventions for AML shown to improve overall survival, and was the first drug to receive regulatory approval for AML in the United States since 2000. Significant questions still remain to be addressed regarding the role of midostaurin in AML and the management in combination treatment and prophylactic agents in this setting.

The RATIFY trial included patients 18 to 60 years old and administered midostaurin in combination with daunorubicin 60 mg/m^2 for three days as part of 3 + 7 induction. Several studies have evaluated higher daunorubicin doses with induction. Löwenberg, et al. and Fernandez, et al. collectively found a survival benefit in patients up to 65 years old with high-dose daunorubicin (90 mg/m^2) compared to a lower dose (45 mg/m^2) (Fernandez et al., 2009; Lowenberg et al., 2009). The AML17 study sought to compare daunorubicin 90 mg/m^2 to an intermediate 60 mg/m^2 dose. Although outcomes appeared to be similar between the two groups, results were difficult to interpret due to the study design. Patients in AML17 received two instead of one course of induction (420 mg/m2 versus 330 mg/m2) and therefore received a higher cumulative anthracycline dose during induction than the aforementioned studies (270 mg/m^2 vs. 135 mg/m^2) (Burnett et al.,

2015). Induction with daunorubicin 60 mg/m^2 or 90 mg/m^2 has not been directly compared and the difference in outcomes and toxicity is unknown. It is currently standard practice at many institutions to administer 90 mg/m^2 during induction for patients 65 years of age or younger, and 60 mg/m^2 for older patients who are still candidates for intensive therapy. Midostaurin and daunorubicin do have overlapping toxicities such as myelosuppression and GI upset, therefore the relative risk of adding midostaurin to a higher dose of daunorubicin is a concern. On the other hand, a lower 60 mg/m^2 dose may negatively impact the efficacy of induction chemotherapy. In fact, a subgroup analysis from the AML17 trial suggests a significant benefit with 90 mg/m^2 vs. 60 mg/m^2 on relapse, relapse-free survival, and OS in FLT3-ITD mutant patients specifically (Burnett et al., 2016). A subsequent analysis of the E1900 trial also supports FLT3-ITD as an independent predictor of benefit from high-dose daunorubicin (Luskin et al., 2016).

Another concern is a lack of clear guidance on the management of drug-drug interactions with CYP3A4 inhibitors/inducers and midostaurin. A pharmacokinetic study by Dutreix, et al. assessed midostaurin concentrations with and without ketoconazole, a strong CYP3A4 inhibitor, and reported a greater than ten-fold increase in midostaurin concentrations with the combination (Dutreix et al., 2013). The RATIFY study protocol reports that pulmonary toxicity, including fatal pulmonary events, was observed in patients receiving midostaurin with co-administration of azole antifungal drugs. Although the package insert does note that co-administration with strong CYP3A4 inhibitors may increase midostaurin drug concentrations and the risk of adverse events, the recommendation is to seek alternative therapies that do not strongly inhibit CYP3A4 activity. This may not be practical in many cases.

One of the more serious complications in patients with hematological malignancies is the development of invasive fungal infections (IFIs), commonly caused by Aspergillus *spp* and Candida *spp*. Incidence of IFIs is highest among patients with AML, especially during the periods of profound and prolonged neutropenia that occur with induction chemotherapy (Pagano et al., 2006). Cornely, et al. conducted a prospective, randomized trial comparing the use of posaconazole to fluconazole or itraconazole for antifungal prophylaxis in patients undergoing induction chemotherapy for AML or myelodysplastic syndrome (MDS) (Cornely et al., 2007). The study reported a reduction in the incidence of proven/probable IFIs and an improvement in overall survival. The number needed to treat with posaconazole to prevent one death was 14. Since the introduction of 3 + 7 induction, posaconazole and midostaurin are among the very few pharmacological agents to confer a survival benefit in AML. Due to the strong inhibition of CYP3A4 enzymes by posaconazole and significant drug-drug interaction with midostaurin, clinicians are left with a significant dilemma due to the unclear safety and lack of recommended dose adjustments with this combination. The question then arises, should clinicians prioritize optimal antifungal prophylaxis or midostaurin during initial 3 + 7 induction?

There are a few potential options to mitigate this interaction. The first option is to use optimal mold-active azole antifungals (posaconazole, voriconazole, or isavuconazole), dose-reduce midostaurin empirically, and monitor closely for pulmonary toxicity; however, there is no data to support this method or indicate an optimal dose adjustment. A second option is to substitute an azole antifungal with an echinocandin for IFI prophylaxis, although echinocandins have been associated with a potentially increased rate of IFIs in this setting (Gomes et al., 2014). The third option is to hold midostaurin during induction when the risk of IFIs is the highest, acknowledging the fact that midostaurin did not increase rates of CR during induction in RATIFY (Stone et al., 2017; Pagano et al., 2006). In our practice we favor the latter option and instead of administering midostaurin on days 8 through 21 of induction, we either wait until bone marrow recovery or hold completely until consolidation and maintenance phases. A theoretical downside of this strategy is that delaying midostaurin initiation may abate the survival benefit seen in RATIFY. The overall survival curve comparing midostaurin to placebo appears to run parallel after an initial separation in the first 3–6 months of treatment, suggesting the survival benefit due to midostaurin may be due to its upfront efficacy in preventing early relapse. Due to high rates of allo-HCT in the midostaurin group (59%) and discontinuation of midostaurin after allo-HCT per the study protocol, the median duration of trial treatment was only three months, and therefore the benefit of long-term midostaurin administration cannot be adequately assessed by this study. Some also believe that the benefit occurs early on during induction and consolidation by inducing deeper remissions, despite no difference in CR rates. This is merely speculation, as there are minimal data to suggest deeper remissions occur more frequently with midostaurin or that MRD negativity in FLT3-mutated AML has prognostic significance (Ivey et al., 2016Jongen-Lavrencic et al., 2018). Many patients that do attain MRD negativity following induction still relapse (Parkin et al., 2017). Since CR rates were similar between the midostaurin and placebo groups (58.9% versus 53.5%, p = 0.15), our opinion is that the survival benefit of midostaurin is driven by prevention of early relapses by consolidating or maintaining the CR until the many of the patients could receive allo-HCT. Among the 227 patients that underwent allo-HCT in first CR, median OS was not reached in either the midostaurin or placebo group. Ultimately, the phase of treatment at which midostaurin provides most benefit (induction, consolidation, maintenance, or a combination) and the optimal duration of treatment is poorly understood.

The management of patients post allo-HCT remains a topic of debate. The phase 2 RADIUS trial randomized 60 patients to standard of care (SOC) with or without midostaurin 50 mg BID continuously for up to one year (Maziarz et al., 2018). The study team presented preliminary results at the 2018 ASH Annual Meeting, and the primary outcome of median RFS was not reached in either group. RFS at 18 months was numerically increased but not statistically different between the midostaurin + SOC or SOC alone groups (89% vs. 75%, p = 0.2655), although the study was not adequately powered for this endpoint. It is challenging to compare outcomes between the RADIUS and SORMAIN trials with midostaurin and sorafenib, respectively, given the varying patient populations, treatment duration (12 vs. 24 months), and follow-up duration. Based on promising data with sorafenib post-transplant, FLT3 inhibitors likely have a role to keep patients in remission and prolong survival. Unfortunately, because midostaurin was discontinued post-HCT per the RATIFY study protocol and sorafenib is not FDA approved for AML, drug acquisition is often an issue in this setting. Even with adequate financial coverage, the adequate dose and duration of FLT3-inhibitors post-HCT is unknown. In our practice, we utilize sorafenib over midostaurin for post-transplant maintenance given the lack of positive data for midostaurin in this setting, the drug interactions with midostaurin for those receiving azole antifungal prophylaxis or treatment, and the survival benefit demonstrated with sorafenib as post allo-HCT maintenance. In those who do not tolerate sorafenib or have isolated FLT3-TKD mutations, we petition and appeal to insurance companies for midostaurin or gilteritinib.

5.3. Lestaurtinib

Lestaurtinib, another staurosporine analog, was originally developed as a tropomyosin receptor kinase (Trk) A neurotropin receptor inhibitor before being identified as a potent FLT3 inhibitor at nanomolar concentrations in vitro (Levis, 2002). In addition to targeting TrkA, TrkB, TrkC, and FLT3, lestaurtinib inhibits JAK2 and JAK3 (Hexner et al., 2008). In relapsed or refractory AML, lestaurtinib demonstrated transient reductions in peripheral blood or bone marrow blasts as a single agent (Smith et al., 2004). The Cephalon 204 trial was a randomized, phase III study comparing salvage chemotherapy alone or followed by lestaurtinib 80 mg BID for FLT3 + AML patients in first relapse (Levis et al., 2011a). Although rates of CR and duration of

Table 1
Comparison of FLT3 inhibitors.

Name	Generation	Type	Phase	Typical Starting Dose	FLT3-ITD IC_{50} (Gozgit et al., 2011; Pratz et al., 2010; Lee et al., 2017; Zhang et al., 2006; Weisberg et al., 2017)	Off-target receptors (Gozgit et al., 2011)	Metabolism (Levis et al., 2017; Weisberg et al., 2017; Levis et al., 2011b)	$T_{1/2}$ (hrs) (YE et al., 2017)	Adverse drug reactions
Sorafenib	First	2	Phase III, FDA approved	400 mg BID	12 nM	RAF, VEGF, PDGFR	Hepatic via CYP3A4 and UGT1A9; active metabolite	24	-Any grade: Diarrhea, hand foot skin reaction -Grade 3/4: infection, rash, nausea
Midostaurin	First	1	Phase III, FDA approved	50 mg BID	6.3 nM	VEGF, PDGFR, c-KIT, protein kinase C family receptors	Hepatic, primarily via CYP3A4	21	-Any grade: Nausea, vomiting, diarrhea, fatigue -Grade 3/4: febrile neutropenia, infection -Significant: pulmonary toxicity
Lestaurinib	First	1	Phase III	80 mg BID	5 nM	Tropomyosin receptor kinase A neurotropin receptor, JAK2	Hepatic, primarily via CYP3A4	3	-Any grade: diarrhea, rash, nausea, fatigue -Grade 3/4: rash, abdominal pain, weight loss
Ponatinib	First	2	Phase II	45 mg daily, Reduce to 30 mg daily with strong CYP3A4 inhibitors	4 nM	BCR/ABL, RET, c-KIT, TIE2, VEGFR, PDGFR, FGFR, EPH and SRC kinases	Hepatic, primarily through CYP3A4; CYP2C8, CYP2D6, and CYP3A5 also contribute. Phase II occurs via esterase and/or amidases	24-66	-Any grade: rash, abdominal pain, fatigue, arthralgia, hypertension, headache -Grade 3/4: myelosuppression, pancreatitis, hepatotoxicity, abdominal pain, rash, arterial ischemic events
Quizartinib	Second	2	Phase III	30 – 60 mg daily	0.3 nM	c-KIT, PDGFR	Hepatic, primarily via CYP3A4	36-48	-Any grade: nausea, vomiting, diarrhea, pyrexia, fatigue -Grade 3/4: febrile neutropenia, nausea -Significant: QT prolongation
Crenolanib	Second	1	Phase III	100 mg TID	2.4 nM	PDGFR	Unreported, likely hepatic via CYP450	8	-Any grade: nausea, vomiting, diarrhea, infections, rash -Grade 3/4 AEs: infections, rash, nausea
Gilteritinib	Second	1	Phase III, FDA approved	120 mg daily	1.6 nM	AXL, ALK, LTK	Hepatic, primarily via CYP3A4	49-159	-Any grade: diarrhea, fatigue, abnormal liver function -Grade 3/4: febrile neutropenia, infection, pneumonia

*IC50 models differ between cell lines, therefore it is difficult to make direct comparisons between agent.

Table 2
Ongoing clinical trials: FLT3 inhibitors for the treatment of AML.

FLT3 Inhibitor	Patient population	TKI Administration	Phase	Clinicaltrial.gov
Sorafenib				
	Untreated, elderly	Combination with azacitidine	II	NCT02196857
	Remission s/p induction	Maintenance monotherapy	II	NCT01578109
	Remission s/p induction and allo-HCT	Maintenance monotherapy	II/III	NCT02474290
Midostaurin				
	Untreated, elderly	Combination with decitabine	II	NCT01846624
	Remission s/p induction and allo-HCT	Post allo-HCT maintenance monotherapy	II	NCT01883362
	Remission s/p midostaurin and decitabine, elderly	Post allo-HCT maintenance monotherapy	II	NCT02723435
Ponatinib	First remission s/p induction	Combination with high or intermediate-dose cytarabine as consolidation therapy	I/II	NCT02428543
	Untreated	Personalized kinase inhibitor therapy (nilotinib, ponatinib, sorafenib, or sunitinib) in combination with standard chemotherapy	Ib	NCT02779283
Quizartinib	Untreated	Combination with standard induction, consolidation and maintenance	I	NCT01390337
	Untreated, elderly, AML or MDS	Combination with standard chemotherapy	I/II	NCT01236144
	R/R, AML or MDS	Combination with azacitidine or low-dose cytarabine	I/II	NCT01892371
	Untreated	Combination with standard induction and maintenance	III	NCT02668653
	R/R	Monotherapy compared to standard salvage chemotherapy	III	NCT02039726
	Remission s/p allo-HCT	Maintenance monotherapy	I	NCT01468467
Crenolanib				
	Untreated	Crenolanib versus midostaurin in combination with standard induction, consolidation, and maintenance	III	NCT03258931
	R/R	Combination with standard chemotherapy or azacitidine	I/II	NCT02400281
	Untreated	Combination with standard chemotherapy	II	NCT02283177
	R/R	Monotherapy	II	NCT01657682
	R/R	Combination with standard salvage chemotherapy	Ib	NCT02626338
	R/R	Combination with standard salvage chemotherapy	III	NCT02298166
	Remission s/p allo-HCT	Maintenance monotherapy	II	NCT02400255
	R/R	Combination with sorafenib	I	NCT02270788
Gilteritinib				
	Untreated, ineligible for standard induction	Combination with azacitidine versus azacitidine alone	II/III	NCT02752035
	Untreated	Combination with standard induction and consolidation	I	NCT02236013
	R/R	Monotherapy versus standard salvage chemotherapy	III	NCT02421939
	R/R in remission with MRD	Monotherapy versus standard salvage chemotherapy	III	NCT03070093
	Remission s/p allo-HCT	Maintenance monotherapy	III	NCT02997202
	Remission s/p induction and consolidation	Maintenance monotherapy	III	NCT02927262

survival were no different between groups, there was a correlation between clinical response and degree of in vivo FLT3 inhibition. Unfortunately, patients in this study failed to achieve optimal free drug levels in vivo and lestaurtinib was unable to find its place in therapy. Further attempts to assess lestaurtinib in front-line chemotherapy as part of the UK AML15 and AML17 trials found similarly disappointing results (Knapper et al., 2017). Patients with FLT3 + AML were randomized to lestaurtinib (80 mg BID) or placebo during induction chemotherapy, but no maintenance or post-transplant doses were given. Similar to midostaurin, lestaurtinib is metabolized by CYP3A4 (Table 1), therefore the investigators chose to empirically dose-reduce lestaurtinib to 40–60 mg BID if coadministered with an azole antifungal. No difference between lestaurtinib and placebo was seen with respect to 5-year OS (46% vs. 45.5%, p = 0.3) or 5-year RFS (40% vs. 36%, p = 0.3), but an exploratory analysis associated improved OS with concomitant azole antifungal use and sustained FLT3 inhibition > 85%. These findings associate clinical benefit with the degree of FLT3 inhibition, indicating a need for potent inhibitors targeted at the FLT3 receptor. Although impressive overall, remission rate [CR or CR with incomplete count recovery (CRi)] was not different between cohorts (92% vs. 94%, p = 0.4), and CRi rates were not reported separately. Due to a lack of positive studies, lestaurtinib is no longer in clinical development (Knapper et al., 2017). If lestaurtinib is studied again in the future, similar concerns about other first generation inhibitors (e.g. drug interactions, post-transplant use, daunorubicin dose if used with 3 + 7) still need to be addressed.

5.4. Ponatinib

Ponatinib is another potent FLT3 inhibitor with broad inhibitory activity against variety of kinases, including RET, c-KIT, PDGFR, FGFR, and BCR-ABL (Gozgit et al., 2012). It has additional activity against TKI resistant BCR-ABL kinase domain mutations, including the gatekeeper T315I mutation, leading to FDA approval in chronic myeloid leukemia (CML) and Philadelphia chromosome-positive (Ph+) acute lymphocytic leukemia (ALL). Although it is not currently FDA approved for AML, preclinical models demonstrated substantial inhibition of FLT3-ITD AML at greater potency than other available FLT3 inhibitors (Table 1) (Gozgit et al., 2011). Clinical activity was later demonstrated in small cohort of FLT3-ITD relapsed or refractory AML patients receiving ponatinib orally 45 mg daily (n = 12) (Talpaz et al., 2011). Two patients attained a CRi, one patient attained a PR, and no patients attained a CR, indicating an overall response rate of 25%. Three patients developed grade 2 pancreatitis leading to one patient to discontinue therapy at investigator discretion.

Just as ponatinib overcomes TKI resistance secondary to BCR-ABL point mutations, it demonstrates activity in murine myeloid cells injected with FLT3-ITD and common secondary point mutations in the TKD of FLT3. Activation loop mutations (D835, D839 and Y842) are implicated in treatment resistance to type II inhibitors by destabilizing the inactive conformation of FLT3 and preventing drug binding, while point mutations at the TKD (F691) often confer resistance to both type I and type II inhibitors. These mutations comprise a common barrier to drug durability (Zirm et al., 2012Smith et al., 2012). Although ponatinib is a type II FLT3 inhibitor, it was hypothesized to retain activity against the multi-drug resistant F691 gatekeeper mutation based on

activity against the analogous T315I BCR-ABL gatekeeper mutation. This was confirmed in in vitro models of FLT3-ITD/F691mutations, where ponatinib retained activity (albeit moderately reduced) with an IC_{50} of 52 nM. The F691 L mutation created only minor steric clashes with ponatinib that did not completely eliminate drug-receptor interactions, although activation loop mutations still conferred a high level of resistance (Smith et al., 2013). Additionally, due to high rates of serious adverse vascular events observed in phase I and II trials of ponatinib for Philadelphia chromosome-positive leukemias, ponatinib was withdrawn from the market in October 2013 by the FDA. Although reintroduced to the market in January of 2014, the increased risk of arterial occlusive events is still a concern, particularly in patients with cardiovascular risk factors (Cortes et al., 2012aCortes et al., 2013). Further studies in AML patients are needed to determine the minimum effective dose that can minimize toxicity. A dose adjustment is recommended for ponatinib when used in combination with strong CYP3A4 inhibitors for CML and ALL indications, suggesting dose-reduced ponatinib could be used in AML patients without compromising optimal azole antifungal prophylaxis (Narasimhan et al., 2013). Limited data in AML combined with potentially life-threatening adverse events may limit the utility of ponatinib in FLT3 + AML, although a study of ponatinib is currently underway in combination with consolidation chemotherapy (Table 2).

6. Second generation inhibitors

The first generation FLT3 inhibitors demonstrated that targeting FLT3 can reduce risk of relapse in AML, irrespective of FLT3 status. While their multi-targeted nature may contribute to efficacy, the clinical benefit is limited by off-target side effects and resistance. The development of agents with more selective and potent activity at FLT3 receptors was hypothesized to lead to improved patient tolerability and increase response rates.

6.1. Quizartinib

Quizartinib (AC220) was the next FLT3 inhibitor developed for AML. Although quizartinib has activity against c-KIT, PDGFR, and CSF1R, it is highly potent and selective for the FLT3 receptor at nanomolar concentrations. It has an extended half-life of approximately 1.5–3.5 days, theoretically allowing for a more sustained, potent inhibition of FLT3 (Li et al., 2015). Initial trials studying quizartinib as a single agent found impressive response rates in relapsed or refractory AML patients. Two phase II studies by Levis et al. and Cortes et al. characterized quizartinib response rates in AML patients in two cohorts: 60 years of age or older and refractory to 1st line of treatment (cohort 1, n = 132) and 18 years of age or older and relapsed or refractory to 2nd line of treatment or allo-HCT (cohort 2, n = 138) (Cortes et al., 2012bLevis, 2012). The primary outcome was composite CR rate (CRc), defined as CR, PR, CRi or CR with incomplete platelet recovery (CRp). Cohort 1 reported CRc rates of 74% and 46% in FLT3-ITD and FLT3-WT AML, respectively. Of these, 68% attained CRi and less than 5% attained CRp (Cortes et al., 2012b). Cohort 2, a more treatment-refractory population, demonstrated CRc rates of 46% and 32% in FLT3-ITD and FLT3-WT patients, respectively. Once again, the majority of these responses were CRis, with 6% of these attaining a CRp (Levis, 2012). By comparison, midostaurin as monotherapy in the relapsed or refractory setting demonstrated mostly reductions in blast counts, with only 5% of patients attaining PR and no patients attaining CR/CRi (Stone et al., 2005). Although responses observed in Levis et al. and Cortes et al. were transient (approximately 12 weeks), 35% of patients were able to proceed to allo-HCT. These results support the idea that more potent FLT3 inhibitors may yield higher response rates as single agents.

The moderate success of single agent quizartinib in these trials encouraged the initiation of the Phase III, randomized controlled QuANTUM-R trial in patients with FLT3-ITD mutated relapsed/refractory AML (Cortes et al., 2018a). A total of 367 patients were randomized 2:1 to quizartinib (n = 245) or investigators choice (n = 122) [low dose cytarabine (LoDAC), n = 29; mitoxantrone/etoposide/cytarabine (MEC), n = 40; fludarabine/cytarabine/granulocyte colony-stimulating factor/idarubicin (FLAG-IDA), n = 53]). The primary endpoint, median overall survival, was significantly improved with quizartinib compared with investigator choice (26.9 vs. 20.4 weeks, p = 0.0177), and rates of CRc (CR + CRp, + CRi) were also significantly increased (48% vs. 27%, p = 0.0001). Treatment related adverse events were comparable between the groups. Of the patients in the quizartinib arm, only two patients discontinued quizartinib due to QTc prolongation, only 3% demonstrated grade 3 QTc prolongation (QTc > 500 ms), and no patients experienced grade 4 QTc prolongation. This suggests the dose of quizartinib in this study (60 mg once daily with a 30 mg lead-in phase) is a reasonably safe and effective dose going forward. Although this is a modest improvement in survival, it offers patients a tolerable oral regimen that can be potentially administered outpatient and a less intensive bridge to transplant. An important difference in study design between QuANTUM-R compared with studies conducted with midostaurin, crenolanib, and gilteritinib, is the inclusion of only patients with the high risk FLT3-ITD mutations, excluding patients with isolated FLT3-TKD mutations. As a type II inhibitor, quizartinib has little activity against FLT3-TKD mutations, and may theoretically select for FLT3-TKD mutations when administered as monotherapy (Smith et al., 2015). Although the median duration of response was only 12.1 weeks (range: 10.4–27.1 weeks) with quizartinib, this was longer than the median duration of 5 weeks observed in the salvage chemotherapy arm (range: 3.3–12.6 weeks) (Cortes et al., 2018b). The percentage of patients with prior use of FLT3 inhibitors at randomization from the QuANTUM-R trial has not yet been reported, although patients that received FLT3 inhibitors other than midostaurin were excluded. Therefore, the efficacy of quizartinib after exposure to other FLT3 TKIs is currently unknown. In May 2019 the significance of the QuANTUM-R trial was called into question by FDA's Oncologic Drugs Advisory Committee (ODAC) (ZZZZZ, 2019a). The committee voted 8-3 against approving quizartinib for adult patients with relapsed/refractory FLT3-ITD + AML. Due to the risk of QT prolongation, modest survival results, and methodologic concerns (e.g. high rates of patients not treated or preselected for low-intensity chemotherapy), it was felt by the majority of the committee that the risks of quizartinib in this setting outweighed the benefit. As the QuANTUM-R results have only been presented in abstract form, greater detail from a final publication of the results is still eagerly anticipated.

Although the ultimate role of quizartinib in therapy remains to be fully elucidated, early data suggested use as a bridge to transplant. Quizartinib is currently in a variety of phase III trials, including in combination with front line 3 + 7 (QuANTUM-First), as maintenance treatment after allo-HCT, and as salvage therapy (QuANTUM-R) in relapsed or refractory AML (Table 2). Similar to the study design of RATIFY, the currently recruiting QuANTUM-First study will continue to dose daunorubcin at 60 mg/m^2 as part of 3 + 7. The concern remains that younger, FLT3 + AML patients are receiving suboptimal doses of induction chemotherapy due to the study design. Similar to other FLT3 inhibitors, quizartinib is metabolized by CYP3A4, and guidance is lacking with respect to managing drug-drug interactions faced in the AML population. Quizartinib carries a notable risk of dose-limiting toxicities such as QT prolongation and myelosuppression, which may be exacerbated by increased drug exposure caused by strong CYP3A4 inhibitors (Cortes et al., 2012bLevis, 2012). Finally, the ability of quizartinib to produce durable responses may be limited by development of FLT3-TKD mutations at D835, a common mechanism of resistance of type II FLT3 inhibitors (Smith et al., 2015; Smith et al., 2013). Ongoing clinical trials will hopefully aim to address these questions (Table 2).

6.2. Crenolanib

Crenolanib is another potent FLT3-ITD inhibitor, with an FLT3-ITD IC_{50} of 2.4 nM compared to an IC_{50} of 0.3 and 6.3 nM with quizartinib and midostaurin, respectively (Table 1**)** (Pratz et al., 2010Galanis et al., 2012). Crenolanib is more selective for FLT3 than previous inhibitors and primarily inhibits FLT3 and PDGFR, although it retains activity at c-KIT with 100-fold less potency (Heinrich et al., 2012Barry et al., 2007). The activity of quizartinib at c-KIT has been associated with dose-limiting side effects such as myelosuppression and QT prolongation, suggesting crenolanib may be better tolerated than previous FLT3 inhibitors (Kumar et al., 2009). Crenolanib is a type I inhibitor with cytotoxic activity toward both FLT3-ITD and several important FLT3-TKD mutations, including at codon D835. Cell models demonstrated that crenolanib retained activity against quizartinib-resistant D385Y, D835 F, and D835 V mutations, although F691 L gatekeeper mutations still conferred resistance. Preliminary data suggests crenolanib may overcome common resistance mechanisms seen with type II inhibitors (e.g. quizartinib, sorafenib), with increased potency towards FLT3 inhibition than other type I inhibitors (e.g. midostaurin) (Barry et al., 2007Kumar et al., 2009).

To confirm this hypothesis, Cortes et al. conducted a phase II study to assess the response rate of crenolanib 100 mg TID continuously in relapsed or refractory FLT3 + AML patients (n = 65) (Cortes et al., 2016). Patients were stratified into three categories: FLT3-TKI naïve (n = 18), prior FLT3-TKI exposure (n = 36), and secondary AML (n = 8). Crenolanib had promising overall response rates of 50% (7 CRi, 2 PRs) in the FLT3-TKI naïve group and 31% (6 CRi, 5 PRs) in the FLT3-TKI exposed group. Median OS was 234 days and 94 days in the TKI naïve and prior exposed groups, respectively. Although no patients achieved CR and OS is relatively short, the prior TKI cohort contained 28% of patients with two or more prior TKIs and 69% with acquired FLT3-ITD or FLT3-D385 mutations from prior therapy. Ultimately, the results demonstrated the ability of crenolanib to retain activity and prolong survival after resistance develops to other FLT3 inhibitors.

A phase II study by Wang et al. aimed to assess the role of crenolanib in combination with 3 + 7 induction for FLT3 + AML aged 60 years old or younger (n = 44) (Wang, 2017). Patients were treated with 3 + 7 induction with daunorubicin 90 mg/m^2 for 3 days, high dose ara-C (HiDAC) consolidation, and allo-HCT (if eligible). Patients received crenolanib 100 mg TID continuously through induction, consolidation, and as maintenance therapy before and after allo-HCT. Of the 29 patients included in the analysis, 83% attained a CR/CRi and 66% of patients went on to receive allo-HCT. The only phase III randomized controlled trial to demonstrate an overall survival benefit by adding a FLT3 inhibitor to induction chemotherapy was the RATIFY trial comparing midostaurin to placebo (n = 717) (Stone et al., 2017). Although a cross-trial comparison is inappropriate due to differences in study populations and overall management, it is interesting to note higher CR rates (89% vs 50%) and OS at 2 years (90% vs. 60%) with crenolanib compared to midostairin in the RATIFY trial.

Both studies included FLT3 + AML patients aged 60 years or younger. As discussed previously, the RATIFY trial utilized daunorubicin 60 mg/m^2 during induction, while Wang et al. used a more optimal 90 mg/m^2 dose. Unlike the RATIFY trial, the study by Wang et al. allowed patients to continue crenolanib post-HSCT, potentially delaying the time to relapse and improving survival rates. The promising rates of survival in this study emphasize the importance of post allo-HCT maintenance with FLT3 inhibition and optimization of care. It is uncertain whether the ability of crenolanib to overcome resistance mechanisms is partially responsible for the promising survival rates or whether it was due to patients staying on therapy longer. Regardless, these preliminary data suggest crenolanib may have a role in induction to improve response rates and OS in the front-line setting or as salvage therapy after failure or relapse with prior FLT3 inhibitors. To address these questions, a phase III randomized study of FLT3 + AML patients (age $\leq$ 60) comparing crenolanib versus midostaurin in combination with 3 + 7 (daunorubicin 90 mg/m^2) is currently recruiting (Table 2).

6.3. Gilteritinib

Gilteritinib is a pyrazinecarboxamide derivative that demonstrated potency, selectivity, and activity against both FLT3-ITD and FLT3-TKD mutations (Lee et al., 2017). Gilteritinib has additional inhibitory activity against EML4-ALK and Axl (a tyrosine kinase implicated in the maintenance of constitutive FLT3-ITD phosphorylation) (Park et al., 2013). Activation of Axl has been implicated as a mechanism of secondary resistance to FLT3 inhibitors. in vivo models demonstrate that Axl inhibition diminishes FLT3 phosphorylation and allows myeloid differentiation in FLT3-AML cell lines. The phase I/II CHRYSALIS trial studied gilteritinib in relapsed/refractory AML and reported potent FLT3 inhibition with doses $\geq$ 80 mg (Perl and Altman, 2016). Seventy percent of subjects received 2 or more prior lines of AML therapy, 29% had prior allo-HCT, and 25% had prior treatment with a TKI (most commonly with sorafenib). Overall response rates were 49% FLT3+ and 12% for FLT3-WT patients, with 9% and 2% of patients attaining CR, respectively. Antileukemic activity was observed irrespective of prior TKI treatment. Gilteritinib was generally well tolerated, with diarrhea, neutropenia, and fatigue reported as the most common treatment-related adverse events. Thus far in clinical trials, potential unique toxicities that have emerged have been a dose dependent prolongation of the QTc interval, elevation in creatine kinase, and elevations in liver transaminases. A few cases of posterior reversible encephalopathy syndrome have occurred in patients while receiving gilteritinib. Other adverse events reported have been events commonly observed in patients with AML receiving treatment. Even in a heavily pre-treated population, FLT3+ patients receiving gilteritinib had an OS of approximately 31 weeks. The single-agent antileukemic activity of gilteritinib is especially promising in patients with FLT3 mutations, including those acquired at the FLT3-D835 tyrosine kinase domain.

Based on an interim analysis of the phase III, randomized ADMIRAL study of gilteritinib 120 mg daily versus salvage chemotherapy in relapsed/refractory FLT3-mutated AML, gilteritinb was approved by the FDA in November of 2018 (Gilteritinib, 2019b, U.S. Food and Drug Administration, 2019). Preliminary results were reported at the 2019 AACR Annual Meeting. The ADMIRAL trial randomized 371 patients to gilteritinb (n = 247) or pre-randomization selected salvage chemotherapy [LoDAC (14.7%), azacitidine (22.9%), MEC (25.7%), FLAG-IDA (36.7%] (n = 124) (Perl et al., 2019). CR/CRh rates were 34.0% in the gilteritinib arm and 15.3% with salvage chemotherapy (p = 0.0001). Patients randomized to gilteritinib also demonstrated an OS benefit over salvage chemotherapy (9.3 months vs 5.6 months, p = 0.0007). Patients that were able to proceed to allo-HCT had the option to continue gilteritinb maintenance, and patients who received gilteritinb maintenance had a numerically higher survival compared to no maintenance (16.2 vs 8.4 months, p = 0.24). Gilteritinib was overall well tolerated, with less serious treatment-emergent adverse events per patient year compared to salvage chemotherapy (7.1% vs. 9.2%). The most common grade 3+ adverse events included anemia, febrile neutropenia, and thrombocytopenia. Although an improvement in response rates and survival is noted, similar concerns raised for the QuANTUM-R trial (quizartinib) are also noted for the ADMIRAL trial. Of the patients in the salvage chemotherapy arm, 37.6% received low-intensity therapy with single-agent LoDAC or azacitidine. These low-intensity therapies lead to modest response rates of approximately 10–15% in the relapsed/refractory setting, thus a comparison between gilteritinb and more intensive therapy (MEC or FLAG-IDA) may be more informative for clinical practice (Stahl et al., 2018; Döhner et al., 2014). Outcomes for the individual salvage regimens have not yet been reported. Overall, the ADMIRAL results demonstrate that gilteritinb is a well-tolerated and effective treatment option for patients with relapsed/refractory FLT3-mutated disease, although results from the final publication are needed

to address the aforementioned questions.

There are several important considerations to keep in mind when employing gilteritinb in clinical practice. Although gilteritinib has activity against both FLT3-ITD and FLT3-TKD mutations as a type I inhibitor, 0 of the 12 patients with isolated FLT3-TKD mutations (no FLT3-ITD mutations) attained a CR/CRh in the initial ADMIRAL report (PR Newswire, 2019). Additionally, only 13% (n = 32) of patients in the gilteritinib arm received a prior FLT3 TKI, and response rates in this subset are not yet reported. The proportion of patients with prior FLT3 TKI exposure is likely much higher in clinical practice since the FDA approval of midostaurin in 2017. Although early phase data suggested gilteritinib may retain activity after exposure to FLT3 TKIs, it is unknown if response rate would be attenuated in a more FLT3-TKI refractory population (Park et al., 2013). Gilteritinib is a CYP3A4 substrate, and therefore drug-drug interactions are an important consideration. A pharmacokinetic study demonstrated that concomitant administration with strong and moderate CYP3A4 inhibitors increases gilteritinib exposure by 120% and 40%, respectively (Levis et al., 2017). The gilteritinib package insert states if the concomitant use of strong CYP3A4 inhibitors cannot be avoided, monitoring patients more frequently for adverse reactions is a reasonable strategy (ZZZZZ, 2019b). Further studies are underway assessing gilterinitib in combination with induction chemotherapy, post allo-HCT, and as maintenance therapy after consolidation (Table 2).

7. Clinical dilemmas

In order for clinicians to optimize use of FLT3 inhibitors in the AML population, more evidence and experience is needed. Although there are known drug-drug interactions between sorafenib, midostaurin, and gilteritinib with CYP3A4 inhibitors/inducers, little information is currently available addressing management of these interactions in terms of dose adjustments or timing of administration. Metabolism and interaction information on the newer FLT3 inhibitors (e.g. quizartinib, crenolanib) is not readily available, although these agents are still being evaluated in clinical trials. Rapid molecular testing to determine FLT3 status is not available across all institutions, therefore FLT3 status may not be known until after induction chemotherapy for a significant fraction of patients. Empiric midostaurin during induction may increase toxicity without confirmed survival benefit for FLT3-WT patients, yet foregoing FLT3 inhibitor therapy could diminish the survival benefit demonstrated in RATIFY.

Patients who relapse or are refractory to standard induction with 3 + 7 plus a FLT3 inhibitor, pose a clinical dilemma. It is uncertain if the patient's disease is only resistant to 3 + 7, or both 3 + 7 and the FLT3 inhibitor. Of course, clinical trial would be in the best interest of the patient, however, this is not always possible. In the context of suspected FLT3 TKI resistance, it would be intuitive to switch to a different FLT3 inhibitor in order to retain activity via different binding mechanisms and kinase profiles, although this would be merely speculative. There are in vitro data to suggest that sorafenib and other type II FLT3 TKIs may retain activity against certain subtypes of TKD mutations, and that resistance to one type II inhibitor does not always confer resistance to another (Smith et al., 2015). Unfortunately, testing for specific FLT3-TKD mutations is not available for routine clinical practice. In order to characterize response rates to FLT3 inhibitor therapy after prior FLT3 TKI exposure, a single-center, retrospective study by Alfayetz, et al. was conducted and presented in abstract form at the 2018 ASH annual meeting. The study included patients with FLT3-ITD AML that received at least one FLT3 inhibitor-based therapy (as monotherapy or in combination with cytotoxic chemotherapy). As anticipated, ORR (CR + CRp + CRi + PR) declined with subsequent lines of FLT3 inhibitor therapy, reporting an ORR of 49%, 27%, 17%, and 25% with first, second, third, and fourth line FLT3 inhibitor therapy, respectively. Overall survival declined as well (8.7, 4.2, 3.5, and 3.9 months with first, second, third, and fourth line FLT3 inhibitors, respectively). Patients in the QuANTUM-R trial were eligible to receive quizartinib if they received midostaurin but no other FLT3 inhibitor. ADMIRAL (gilteritinib) allowed patients to receive either sorafenib or midostaurin in combination with initial induction, consolidation, and maintenance, but other FLT3 TKI use was excluded. Unfortunately, the proportion of patients in QuANTUM-R (quizartinib) and ADMIRAL (gilteritinib) with prior FLT3 inhibitor exposure was low. In the current state of FLT3 + AML treatment, the majority of patients presenting with relapsed/refractory disease will have already received 3 + 7 with midostaurin, and does not adequately reflected in the QuANTUM-R and ADMIRAL patient populations. Consequently, response rates to FLT3 inhibitor monotherapy in the relapsed/refractory setting are likely lower than currently reported, therefore consideration for combination therapy with FLT3-TKI and cytotoxic chemotherapy may be warranted. Ultimately, patients should be encouraged to enroll into a clinical trial.

Efficacy and safety data of FLT3 inhibitors with non-3 + 7 induction strategies such as a high dose cytarabine based regimen or agents recently approved for AML induction therapy (e.g. liposomal daunorubicin and cytarabine, gemtuzumab ozogamicin [GO], and venetoclax) are minimal. The CLTR0310-301 study randomized older patients with secondary AML to liposomal daunorubicin and cytarabine or 3 + 7 and included a small subset of patients with FLT3 + AML. Liposomal daunorubicin and cytarabine resulted in a dramatic improvement in CR/CRi rates in patients with FLT3 + AML compared with 3 + 7, 68.2% (n = 15) vs 23.8% (n = 5), respectively (Lancet et al., 2018). These results are in line with preclinical data which have shown increased sensitivity and increased drug uptake with liposomal daunorubicin and cytarabine in FLT3+ versus FLT3 negative AML. Importantly, the addition of the FLT3 inhibitor quizartinib to liposomal daunorubicin and cytarabine led to robust synergy when initiated simultaneously or 24 h following liposomal daunorubicin and cytarabine, while the administration of quizartinib prior liposomal daunorubicin and cytarabine was antagonistic (Edwards et al., 2016). While the evidence for the use of liposomal daunorubicin and cytarabine in FLT3 + AML is intriguing, an N of 22 in a subgroup analysis is inadequate to recommend its use in FLT3 + AML.

The observation that FLT3 mutated AML blasts highly express CD33 has stimulated interest in novel concepts to target CD33 with anti-body drug conjugates such as GO (Ehninger et al., 2014). The ALFA-0701 trial demonstrated an improvement in EFS and RFS with the addition of GO to 3 + 7 in patients with FLT3 + AML (Lambert et al., 2019). Similar to data with liposomal daunorubicin and cytarabine in FLT3 + AML, the ALFA-0701 trial included a small subgroup analysis of FLT3+ patients, lacked an overall survival benefit, and had a comparator arm with suboptimal dosing of daunorubicin. The Children's Oncology Group trial AAML0531 also randomized patients aged 0 to 29 years old to standard chemotherapy alone or in combination with two doses of GO (Gamis et al., 2014). In a subgroup analysis, patients with FLT3-ITD + AML with high allelic ratio (> 0.4) were the only high risk patient subset to benefit from the addition of GO in terms of reduced relapse risk (p = 0.02). Nonetheless, GO did not improve OS and was associated with increased treatment-related mortality in the overall cohort. Given the lack of compelling evidence, gemtuzumab should not be advocated for in patients with FLT3 + AML outside of a clinical trial. Additionally, with the increased risk for sinusoidal obstructive disorder in a population destined for allo-HCT, GO is an unattractive option for these patients.

The BCL2 inhibitor venetoclax was FDA approved in January 2019 in combination with azacitidine or decitabine or low-dose cytarabine in patients with newly diagnosed AML that are unable to receive intensive induction chemotherapy. This approval was based on a study by Dinardo et al. which reported outcomes in treatment-naïve, elderly patients with AML who received oral venetoclax in combination with decitabine (20 mg/m^2 days 1–5) or azacitidine (75 mg/m^2 days 1–7) (DiNardo et al., 2019). The study reported an overall response rate

Table 3
Summary of key trials: FLT3 Inhibitors for the treatment of AML.

FLT3 Inhibitor	Patient population	Phase	TKI Administration	Outcomes
Sorafenib	R/R FLT3 + AML N = 43 (Ravandi et al., 2013)	II	Sorafenib 400 mg BID continuously + azacitidine 75 mg/m^2 day 1 – 7 each cycle	ORR: 46% (16% CR, 27% CRi, 3% PR) Median OS: 6.2 months
	Previously untreated FLT3+ or FLT3-WT elderly AML patients N = 211 (Serve et al., 2013)	II	Sorafenib 400 mg BID or placebo with 3 + 7 induction and consolidation	ORR: 57% (Sorafenib) vs. 64% (Placebo), p = 0.34 Median OS: 13 (Sorafenib) vs. 15 months (Placebo), p = 0.88 Median EFS: 5 (Sorafenib) vs. 7 months (Placebo), p = 0.12
	Previously untreated FLT3+ or FLT3-WT AML N = 276 (Röllig et al., 2017)	II	Sorafenib 400 mg BID vs. placebo with 3 + 7 induction, consolidation, and maintenance	CR: 60% (Sorafenib) vs. 59% (Placebo) Median OS: Not reached in either group at 3 years (p = 0.382) Median EFS: 21 (Sorafenib) vs. 9 months (Placebo), p = 0.13
	FLT3-ITD AML s/p allo-HCT in CHR (Burchert et al., 2018)	II	Sorafenib 400 mg BID vs. placebo	RFS at 2 years: 85.0% (Sorafenib) vs. 53.3% (Placebo), p = 0.0135 Median OS significantly longer in Sorafenib arm vs. Placebo: HR = 0.447 (95% CI, 0.20 – 0.97), p = 0.03
Midostaurin	R/R FLT3 + AML N = 20 (Stone et al., 2005)	II	Midostaurin 75 mg TID (monotherapy)	Blast reduction > 50% (BR): 70% CR: 0%
	R/R FLT3+ or FLT3-WT AML or MDS N = 95 (Fischer et al., 2010)	IIb	Midostaurin 50 or 100 mg BID	BR: 71% (FLT3+), 42% (FLT3-WT)
	R/R or unable to receive/ refused standard induction chemotherapy, FLT3+ or FLT3-WT N = 54 (Strati et al., 2015)	I/II	Midostaurin 25-50 mg BID + azacitidine 75 mg/m^2 day 1 – 7 each cycle	ORR: 26% (2% CR, 11% CRi, 11% MLFS, 2% PR)
	Previously untreated FLT3+ or FLT3-WT AML N = 69 (Stone et al., 2012)	Ib	Midostaurin 100 mg BID days 1 – 28 or 8 – 28 (amended to 50 mg BID for 14 days) with 3 + 7 induction	CR: 92% (FLT3+), 80% (FLT3-WT)
	Previously untreated FLT3 + AML N = 717 (Stone et al., 2017)	III	Midostaurin 50 mg BID vs. placebo with 3 + 7 induction, consolidation, and maintenance	CR: 58.9% (Midostaurin) vs. 53.5% (Placebo), p = 0.15 Median OS: 74.7 (Midostaurin) vs. 25.6 months (Placebo), p = 0.009 Median EFS: 8.2 (Midostaurin) vs. 3.0 months (Placebo), p = 0.002
	FLT3-ITD + AML s/p allo-HCT in CR1 N = 60 (Maziarz et al., 2018)	II	Midostaurin 50 mg BID continuously + standard of care (SOC) vs. SOC alone	18-month RFS: 89% (Midostaurin) vs. 76% (SOC alone), p = 0.2655
Lestaurtinib	FLT3 + AML in first relapse N = 2 (Levis et al., 2011a)	III	Salvage chemotherapy alone vs. salvage chemotherapy followed by lestaurtinib 80 mg BID	CR/CRp: 26% (Lestaurtinib) vs. 21% (Control), p = 0.35 No difference in median OS between groups
	Previously untreated FLT3 + AML (meta-analysis) N = 500 (Knapper et al., 2017)	III	Lestaurtinib 80 mg BID (40-60 BID if concomitant azole antifungal) vs. placebo with anthracycline-based induction chemotherapy	CR/CRi: 92% (Lestaurtinib) vs. 94% (Placebo), p = 0.4 5-year OS: 46% (Lestaurtinib) vs. 45% (Placebo), p = 0.3 5-year RFS: 40% (Lestaurinib) vs. 36% (Placebo), p = 0.3
Ponatinib	R/R FLT3-ITD AML N = 12 (Talpaz et al., 2011)	I	Ponatinib 45 mg once daily	ORR = 25% (16% CRi, 8.3% PR)
Quizartinib	R/R after first line treatment N = 131 (Cortes et al., 2012b)	II		CRc: 74% (FLT3-ITD), 46% (FLT3-WT)
	R/R after second line treatment or allo-HCT N = 138 (Levis, 2012)	II		CRc: 45% (FLT3-ITD), 32% (FLT3-WT)
	R/R FLT3-ITD AML in CR1 N = 367 (Cortes et al., 2018a)	III	Quizartinib 60 mg once daily vs. investigator's choice (low dose cytarabine, MEC, or FLAG-IDA)	CRc: 48% (Quizartinib) vs 27% (Control), p = 0001 Median OS: 27 (Quizartinib) vs. 20.4 weeks, p = 0.0177
Crenolanib	R/R FLT3 + AML, irrespective of prior FLT3-TKI exposure N = 54 (Cortes et al., 2016)	II	Crenolanib 100 mg TID continuously	ORR: 50% (FLT3-TKI naïve), 31% (Prior FLT3-TKI exposure) Median OS: 234 days (FLT3-TKI naïve), 94 days (Prior FLT3-TKI exposure)
	Previously untreated FLT3 + AML N = 29 (Wang, 2017)	II	Crenolanib 100 mg TID with 3 + 7 induction, consolidation, and maintenance	CR/CRi: 83%
Gilteritinib	R/R FLT3+ or FLT3-WT AML N = 252 (Perl and Altman, 2016)	I/II	Gilteritinib 20 – 450 mg once daily (dose-escalation) or 120 – 200 mg once daily (dose-expansion)	ORR: 49% (FLT3+), 12% (FLT3-WT), 42% (FLT3+ with prior FLT3-TKI exposure), 56% (FLT3+ without prior TKI exposure) Median OS: 31 weeks Median duration of response: 20 weeks
	R/R FLT3 + AML N = 369 (Perl et al., 2019)	III	Gilteritinb 120 mg once daily vs. salvage chemotherapy	CR/CRh: 34% Median OS: 9.3 months vs 5.6 months, p = 0.0007

(CR + CRi) of 67% for the entire cohort. Of the 18 patients harboring a FLT3 mutation, 72% attained a CR or CRi and median OS was not reached (95% CI, 8.0 months – NR), although presence of a FLT3 mutation was not an independent predictor of outcome. These results compare favorably to a study which assessed midostaurin + HMA in a similar patient population (CR/CRi = 31%), albeit only 17 patients were included (Gallogly et al., 2017). Thus, venetoclax combined with a hypomethylating agent (HMA) may be a viable option for patients with FLT3-mutated AML unable to receive intensive chemotherapy. A potential real world challenge not reflected in clinical trials, however, is the proliferative nature of patients with FLT3+ disease. Some require several days of hydroxyurea or leukopheresis prior to initiating hypomethylating agent + venetoclax, while others cannot wait for low intensity regimen response, and thus intensive induction therapy is sometimes warranted. If venetoclax based therapy is selected, clinicians should proceed with caution and diligently monitor for complications of hyperleukocytosis. in vitro studies with FLT3-ITD + AML models have demonstrated synergistic antileukemic activity with combined BCL-2 and FLT3-ITD inhibition, although this combination should not be recommended until safety and efficacy is confirmed in clinical trials (Mali et al., 2017).

8. Summary and conclusions

Over the past 10 years, detecting the presence of FLT3 mutations in AML has evolved from simply indicating prognosis to guiding treatment decisions. The advent of FLT3 inhibitors filled a previously unmet need for AML patients, demonstrating a survival benefit in combination with front-line chemotherapy. As monotherapy, first generation inhibitors lacked the ability to induce durable remissions, leading to the development of more potent and selective second generation inhibitors (Heinrich et al., 2012). The clinical benefit of FLT3 inhibitors continues to be limited by rapid development of acquired resistance, therefore potent, novel FLT3 inhibitors designed to overcome common resistance mechanisms have recently been FDA-approved (gilteritinib) or are in phase III clinical trials (crenolanib) (Table 2) (Smith et al., 2012). Preliminary data in both the relapsed/refractory and post allo-HCT setting demonstrates FLT3 TKI monotherapy can produce a survival benefit in these settings, and may represent a less intensive treatment option to induce and maintain CR for patients with FLT3 + AML (Burchert et al., 2018; Cortes et al., 2018a). A summary of currently published FLT3-TKI clinical trials and relevant clinical outcomes is presented in Table 3.

Despite these advances, it is still uncertain how to optimize use of these agents in the real world clinical setting. Practical considerations of FLT3 TKIs, including use with concomitant azole antifungals, timing and dosing with chemotherapy, and duration of therapy are currently ill-defined. Additionally, due to the FDA approval of three FLT3 inhibitors (gilteritinib, midostaurin, and sorafenib), patients may be exposed to multiple FLT3 inhibitors along the course of their AML treatment. Development of resistance and attenuation of efficacy after multiple FLT3 TKI exposures is a rational concern and should be addressed in future randomized controlled trials. Ongoing studies of FLT3 inhibitors in the front-line, post-transplant, and relapsed/refractory settings will be necessary to elucidate optimal sequencing of these agents in the FLT3 + AML population (Table 2).

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