Current and Emerging Targeted Strategies in *FLT3*-Mutated Acute Myeloid Leukemia

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Faculty
Amir T. Fathi, MD, MSc
Assistant Professor of Medicine
Harvard Medical School
Director, Leukemia Program
Massachusetts General Hospital
Boston, MA

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Overview
This activity is designed to inform physicians about the current and developing strategies in treating patients with acute myeloid leukemia (AML) with *FLT3* mutations.

Target Audience
This activity is directed towards medical oncologists, primary care physicians, nurses, and nurse practitioners who treat and/or manage patients with AML. Surgical oncologists, radiation oncologists, pathologists, internists, fellows, physician assistants, and other health care providers are also invited to participate.

Learning Objectives
After participating in this CME/CE activity, learners should be better prepared to:
- Describe the biologic function of *FLT3*, its mutational subtypes, and the rationale behind targeted inhibition in AML
- Explain the development history leading to the approval of targeted therapeutic inhibitors in *FLT3*-mutated AML
- Discuss emerging treatment options and ongoing trials of FLT3 inhibitors

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Contact information for questions about the activity:
Physicians' Education Resource®, LLC
2 Clarke Drive, Suite 110
Cranbury, NJ 08512
Phone: (888) 949-0045
E-mail: info@gotoper.com

Introduction

Acute myeloid leukemia (AML) is an aggressive cancer of the blood and bone marrow. In 2017, an estimated 21,380 new cases of AML will be diagnosed in the United States, accounting for 30% of all new leukemias and 1.3% of all new cancers.[1,2] AML is most common in older patients, with a median age at diagnosis of 68 years. However, 26% of patients are aged less than 55 years at diagnosis.[1] Over the past 40 years, the 5-year survival rate has more than quadrupled, but it remains at 28.1%, the lowest rate among major leukemias.[1,2] In 2017, an estimated 10,590 people will die of AML, accounting for 1.8% of all cancer deaths in the United States. The median age at death is 72 years.[1] Currently, an estimated 364,000 people are living with all types of leukemia in the United States.[3]

Standard treatment for patients with AML employs a "7+3" strategy during induction chemotherapy: administration of cytarabine for 7 days plus an anthracycline, typically daunorubicin or idarubicin, for 3 days. Induction chemotherapy, when resulting in remission, is followed with consolidation chemotherapy, typically cycles of high-dose cytarabine, to extend remission. Stem cell transplantations are also sought in patients who have reached remission. Strategies of treatment vary depending on patient characteristics and associated risk factors.[4]

The changing clinical understanding of *FLT3* mutations in patients with AML has impacted the landscape of treatment options for those patients.

FLT3 Mutations

The FMS-like tyrosine kinase 3 (*FLT3*) gene is a receptor tyrosine kinase that binds the FL cytokine ligand. When bound to FL, FLT3 dimerizes and autophosphorylates, signaling downstream pathways involved in the control of proliferation, differentiation, and survival of hematopoietic cells, including phospholipid metabolism, transcription, and apoptosis.[5,6] Wild-type *FLT3* consists of an extracellular domain made of 5 immunoglobulin-like loops, a transmembrane domain, and in the intracellular region: a juxtamembrane domain, 2 kinase domains with a kinase insert, and a C-terminal domain.[6,7] Wild-type and mutated *FLT3* are expressed in 93% and 30% of patients with AML, respectively.[6] Mutations of *FLT3* are associated with a worse prognosis, decreased overall survival (OS), and increased rate of relapse in patients with AML.

There are 2 classes of *FLT3* mutations. Internal tandem duplication (*FLT3*-ITD) mutations are in-frame duplications in the coding region of the juxtamembrane domain. Insertions range from 12 to more than 200 base pairs. Insertions in *FLT3*-ITD result in ligand-independent receptor dimerization and phosphorylation, constitutively activating hematopoiesis pathways.[6] Mutations of the tyrosine kinase domain (*FLT3*-TKD) are the result of missense mutations of the D835 residue or the mutation or deletion of the I836 residue; rarer de novo mutations have also been observed in some patients. *FLT3*-TKD mutations interrupt the activation loop that blocks ligand-independent ATP binding, resulting in a mimicked and then constitutive activation.[6] *FLT3*-ITD is found in approximately 23% of patients with AML, and is associated with a worse prognosis compared with *FLT3*-TKD. A higher ratio of *FLT3*-ITD to wild-type *FLT3* is further associated with a worsened prognosis. *FLT3*-TKD is found in approximately 7% of patients with AML, and is believed to have a more disparate level of constitutive activation than *FLT3*-ITD.[6,8]

Therapies that target FLT3 are an active area of investigation in the treatment of AML and have been revolutionized with the FDA approval of midostaurin in April 2017.[9]

Targeted Therapies

Midostaurin

Midostaurin is a multitargeted kinase inhibitor shown to target FLT3 as well as KIT, PDGF-Rβ, VEGFR-2, and protein kinase C.[10,11] These inhibitors block the autophosphorylation of mutated *FLT3*, halting proliferation and inducing apoptosis.[12] After synergy was established between midostaurin and chemotherapy, a phase Ib trial established that midostaurin could be safely administered at a dose of 50 mg twice daily for 2 weeks, starting on day 8 of standard 7+3 induction chemotherapy.[10] In this trial, midostaurin combination therapy was associated with high complete remission (CR) and OS rates, especially in adults less than 60 years who were diagnosed with AML.

As a result of this trial, the phase III RATIFY trial randomized 717 patients to receive midostaurin in combination with 7+3 chemotherapy (360 patients), or to receive placebo with standard chemotherapy (357 patients).[11] The *FLT3*-ITD (high) subtype found in 214 patients and defined by a ratio >0.7; *FLT3*-ITD (low) was in observed 341 patients and defined by a ratio of 0.05 to 0.7; and *FLT3*-TKD was seen in 162 patients. Of the 359 patients who survived, median duration of follow-up was 59 months. Median OS was 74.7 months (95% CI, 31.5-not reached) for patients receiving midostaurin and 25.6 months (95% CI, 18.6-42.9 months) for patients receiving placebo (P = .009). The hazard ratio (HR) for death was 0.78 (95% CI, 0.63-0.96; P = .009). Four-year OS was 51.4% in the midostaurin arm and 44.3% in the placebo arm.[11]

Secondary outcomes included event-free survival (EFS). Events observed in this trial included 298 failures to achieve CR, 181 relapses, and 57 deaths without relapse. Median EFS was 8.2 months (95% CI, 5.4-10.7) in patients receiving midostaurin and 3.0 months (95% CI, 1.9-5.9) in patients receiving placebo. Patients receiving midostaurin had an associated 21.6% reduction in risk of an event compared with patients receiving placebo (HR, 0.78; 95% CI, 0.66-0.93; P = .002). Four-year EFS rates were 28.2% and 20.6% for the midostaurin and placebo groups, respectively.[11]

Another secondary outcome measured the OS rate of patients who received a stem cell transplant following remission. A total of 101 patients who received midostaurin also underwent allogeneic stem cell transplantation, and 81 patients who received placebo underwent transplant, both during first CR. Median OS has not been reached in either group. In the 227 patients across both groups who underwent transplant after first CR, no treatment benefit was found.[11]

Adverse events (AEs) were similar and occurred at comparable rates between the 2 groups. The most common AEs included thrombocytopenia, neutropenia, and anemia. High-grade anemia and rash were observed more in patients receiving midostaurin; high-grade nausea was more commonly observed in patients receiving placebo.[11]

As a result of this trial, midostaurin has been approved in combination with induction or consolidation chemotherapy for newly diagnosed adult patients with *FLT3*-mutated AML.[9]

Sorafenib

Sorafenib, like midostaurin, is a multikinase inhibitor, and has been shown to inhibit VEGFR-2, FLT3, c-KIT, and RET signaling pathways.[13] In phase I trials, sorafenib was shown to achieve CR in 10% of patients, all of whom had *FLT3*-ITD mutations, prompting multiple phase II investigations into its benefits in these patients.[13]

In a randomized, double-blind, phase II trial (SORAML) investigating sorafenib versus placebo in patients aged less than 60 years with newly diagnosed AML, sorafenib was shown to have an added benefit in the treatment of AML.[14] Patients received sorafenib at a dose of 400 mg twice daily for 10 days starting on day 10 of induction chemotherapy cycles, as well as during consolidation chemotherapy starting on day 8, and as maintenance therapy through the duration of treatment. EFS was 21 months (95% CI, 9-32) for patients receiving sorafenib compared with 9 months (95% CI, 4-15) for patients receiving placebo. Three-year EFS rate was 40% (95% CI, 29%-51%) for patients in the sorafenib arm and 22% (95% CI, 13%-32%) for patients receiving placebo (HR, 0.64; 95% CI, 0.45-0.91; $P = .013$). AEs were more common in patients receiving sorafenib; they included fever, diarrhea, bleeding, cardiac events, hand-foot-skin reaction, and rash.[14]

Other trials have looked at sorafenib in combination with additional therapies. A phase II trial showed that combining sorafenib with the hypomethylating agent azacytidine in patients aged 60 years or older with relapsed or refractory AML with a *FLT3*-ITD mutation was an effective therapy.[12] Patients receiving the combination had an overall response rate (ORR) of 46%, and a CR rate of 16%. Common AEs for patients receiving sorafenib included thrombocytopenia, anemia, and neutropenia.[12]

Sorafenib was approved by the FDA for use in renal cell carcinoma in December 2005.[15] This approval was expanded for use in hepatocellular carcinoma in November 2007 and recurrent or metastatic differentiated thyroid carcinoma in November 2013.[15] Sorafenib is not FDA approved for use in patients with AML, but is available off-label.

Quizartinib

Quizartinib is a second-generation FLT3 inhibitor shown to be highly selective for FLT3, with at least a 10-fold reduction in affinity for other kinases, including KIT and RET. Quizartinib is more effective in treating *FLT3*-ITD–mutated AML than *FLT3*-TKD.[16]

In a phase I trial investigating quizartinib in patients with relapsed or refractory AML, not limited to *FLT3* mutations, patients receiving quizartinib had an ORR of 30%; in patients with *FLT3*-ITD mutations, ORR was 53%.[16] Median duration of response was 13.3 weeks. AEs included nausea, vomiting, prolonged QT interval, and dysgeusia. The maximum tolerated dose was determined to be 200 mg daily.[16]

Multiple phase II trials investigating quizartinib as a monotherapy in the relapsed or refractory setting demonstrated an ORR between 61% to 72%.[17] Median duration of response in these trials ranged from 11.3 to 12.7 weeks. While quizartinib is promising as a single agent, 50% of patients relapse in the first 3 months of treatment. Acquired resistance is suspected to be due to emergence of *FLT3*-TKD mutations in *FLT3*-ITD patients.[17]

The phase III QuANTUM-R trial (NCT02039726) is investigating quizartinib as a therapy versus salvage chemotherapy in patients with *FLT3*-ITD–mutated AML. This study is ongoing and currently recruiting participants.[18]

Crenolanib, Gilteritinib, and Ponatinib

Other second-generation FLT3 inhibitors include crenolanib and gilteritinib. Crenolanib, a selective FLT3 inhibitor, has particular activity against the D835 mutation in *FLT3*-TKD, allowing it to overcome quizartinib resistance. In a phase II study investigating crenolanib in patients with relapsed or refractory AML, with either a *FLT3*-ITD or *FLT3*-TKD mutation, a preliminary ORR of 47% was presented.[19] Crenolanib is currently being investigated in multiple phase II studies, including in combination with chemotherapy in newly diagnosed AML (NCT02283177), as maintenance therapy following stem cell transplantation (NCT02400255), and in combination with a hypomethylating agent, azacitidine (NCT02400281); all of these studies are currently active and recruiting.[20–22] A phase III trial investigating crenolanib in combination with chemotherapy in relapsed or refractory patients with *FLT3*-mutated AML is also currently recruiting patients (NCT02298166).[23]

Gilteritinib is also a selective inhibitor of FLT3. In a phase I/II trial investigating gilteritinib in patients with relapsed or refractory AML, an ORR of 57% was reported.[24] Gilteritinib is currently being investigated in multiple phase III studies, including as maintenance therapy following induction or consolidation

chemotherapy (NCT02927262), as maintenance therapy following stem cell transplantation (NCT02997202), and in combination with azacitidine (NCT02752035).[25-27]

Ponatinib is a novel third-generation tyrosine kinase inhibitor (TKI) that is an especially potent pan–BCR-ABL1 inhibitor.[28] Ponatinib was fully approved in November 2016 for use in adult patients with chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia.[29] In a phase I trial investigating ponatinib in patients with refractory AML, ORR was 25%.[28] Another phase I trial showed ponatinib had clinical efficacy in treating patients with acquired quizartinib resistance.[30] Ponatinib is currently being investigated in a phase I/II trial in combination with cytarabine consolidation chemotherapy for patients with *FLT3*-ITD–mutated AML (NCT02428543).[31]

For more information on the current and emerging use of FLT3 inhibitors in the treatment of AML, see our interview with Dr Fathi below.

Amir T. Fathi, MD, MSc, is an assistant professor of medicine at Harvard Medical School and the director of the Leukemia Program at Massachusetts General Hospital (MGH). Dr Fathi also directs the clinical research in leukemia program at MGH Cancer Center in Boston, Massachusetts.

The *FLT3* gene is mutated in about 30% of patients with AML. What are the differences between *FLT3*-TKD and *FLT3*-ITD mutations, and what are the clinical implications in patients harboring these mutations?

The *FLT3* gene, also known as FMS-like tyrosine kinase 3, was among the first alterations detected in patients with acute myeloid leukemia. As you mentioned, about a third of patients have a *FLT3* mutation that can be detected. These come in 2 major varieties. One is the ITD, the internal tandem duplication mutation. This is the most common variant, affecting about a quarter of all patients with AML. The other, less-common variant is the TKD, or tyrosine kinase domain mutation, which can impact various portions of the tyrosine kinase domain of the enzyme. The TKD mutations affect approximately 5% to 7% of patients with AML.

There have been a series of studies in the last decade-and-a-half that have looked at *FLT3* mutations both preclinically and clinically. A series of clinical studies have demonstrated that *FLT3*-ITD mutations seem to portend poorer outcomes for patients with AML. Patients generally present with disease that's more proliferative, more aggressive, and more monocytic. They also tend to have a much higher rate of relapse following achievement of remission and often following bone marrow transplant. The prognostic impact and clinical implications of *FLT3*-TKD mutations are a little bit more controversial. There's not yet consensus, but most folks believe that TKD mutations do not have the same degree of negative clinical impact as ITD mutations. Nevertheless, TKD alterations can also lead to proliferative and aggressive disease.

Given the aggressive and poor-risk features of the disease, for younger or more robust *FLT3*-mutant patients, who can tolerate more aggressive treatment, the recommendation has been intensive induction chemotherapy to achieve remission followed by a bone marrow transplant. Nevertheless, as I mentioned, the chance for relapse for these patients after transplant remains high. For those who are older and are not transplant candidates, it becomes even more challenging. Sometimes you can treat these patients with single-agent FLT3 inhibitor therapy, or other types of more gentle combination therapies. However, since transplant is not an option for these patients, the more aggressive approaches are not available. Historically, at least up until very recently, that has been the therapeutic approach with this patient population.

How are *FLT3*-ITD and *FLT3*-TKD mutations detected, and is there a specific biomarker that predicts susceptibility to FLT3-targeted therapy?

The majority of patients who present with newly diagnosed AML, and sometimes those with relapsed disease, undergo mutational testing. These days, the majority of hospitals have a variety of PCR-based platforms that can detect both ITD and TKD mutations. The window whereby these results are available has changed over time. Most academic centers can provide the results of a mutational assay in anywhere from 3 to 14 days, depending on the assay and the facility. Therefore, the turnaround time can vary somewhat.

Nevertheless, there has been a push to try to expedite results of *FLT3* mutational analysis. With the approval of midostaurin for the frontline setting, there is now an approved assay available, and most centers have their own assays that have turnaround times that are increasingly faster. When a patient comes in with acute leukemia, they may not have the luxury to wait for mutational analysis before starting treatment, simply because of the aggressiveness of the disease and the nature of its presentation.

Both classes of mutation can be detected relatively quickly if the appropriate platform is available. If they are, these patients can be candidates for induction chemotherapy with midostaurin, which is a fairly potent FLT3 inhibitor. The study and the FDA approval suggest that these patients can be started around day 8 following the initiation of induction chemotherapy. If results are obtained in that timeframe, you can start them on the appropriate targeted agent, in this case FLT3 inhibitor, in combination with chemotherapy.

As far as biomarkers go, there have been a series of studied assays specifically in relation to *FLT3* mutations. One is the allelic frequency, which is essentially the mutational burden of *FLT3*. The midostaurin study that was recently published did not seem to suggest that mutational burden impacted long-term outcomes.

It appears that both high and low mutational burden groups of patients benefit.

There is also a series of studies that have looked at the length of the internal tandem duplication segment, suggesting that those who have a longer ITD may have worse prognosis. I think both analyses need further evaluation and investigation before we can optimally incorporate their use in the clinical setting, when it comes to emerging *FLT3* inhibitors.

Midostaurin was approved for treatment of patients with AML with a *FLT3* mutation in April of this year based on results from the phase III RATIFY trial. What are the highlights and potential shortcomings from this trial?

Our options for patients with AML remain limited, and only recently are we seeing some progress. For younger or more robust patients, we generally offer induction chemotherapy, often a combination of cytarabine and anthracycline, in order to produce a remission. If and when a remission is achieved, we try and prolong that remission to achieve cure, either by proceeding with additional chemotherapy or a bone marrow transplant.

For older patients or those who are less robust, the options have been even more limited. In the last decade, hypomethylating agents have been increasingly used in AML. These treatments are generally more gentle and tolerable, and can be administered in the outpatient setting. They provide an alternative for patients who are not candidates for more intensive therapies. However, the rates of remission with hypomethylating agents are significantly lower and responses occur later in the course of treatment.

Really, the armamentarium for AML, which has not changed for decades, was limited in what we could offer these patients. Therefore it is exciting when a phase III clinical trial demonstrates an improvement in overall survival. This particular phase III study, the RATIFY study, looked at patients with AML and a *FLT3* mutation, both ITD and TKD. It is important to mention that this study looked at patients between the ages of 18 and 59. On day 8 of traditional, aggressive induction chemotherapy, participants were initiated on the oral FLT3 inhibitor, midostaurin, or placebo. Midostaurin is not the most selective FLT3 inhibitor; it is fairly nonspecific and also hits a variety of other targets, which, in addition to FLT3, may be relevant in the leukogenesis of AML.

Patients received midostaurin for approximately 2 weeks during induction chemotherapy. Those patients who achieved remission and went on to receive consolidation chemotherapy also received midostaurin during consolidation. In those completing consolidation therapy and who remained on study, they could continue on to receive maintenance therapy with midostaurin or placebo. This study demonstrated that there was a significant improvement in overall survival. The risk of death was 22% lower in patients who had received combination treatment with midostaurin as opposed to placebo. These results were first presented at the American Society of Hematology a few years ago, and have since led to FDA approval of the combination.

Patients, regardless of ITD or TKD mutations—and regardless of high or low mutant *FLT3* ratio—all appeared to have a longer overall survival if they received midostaurin versus placebo. However, the rate of remission between patients who received midostaurin versus placebo was not significantly different.

The exposure to midostaurin in this study was relatively brief. The median duration of treatment was 3 months. This means the major impact for the addition of midostaurin may have occurred in the early phases of the treatment, during induction chemotherapy, causing a reduction in disease burden then, rather than down the road during consolidation and maintenance. Although that's not completely possible to establish, that is how some are looking at the data.

Although this study looked at patients between the ages of 18 and 59, the FDA approval is not limited by age. Further, while this study looked at induction, consolidation, and maintenance, the approval for the addition of midostaurin is only applicable to induction and consolidation. With the approval, a variety of cancer centers across the country are now beginning to, and appropriately so, use midostaurin in combination with chemotherapy for patients who have *FLT3*-mutant disease and are eligible for induction chemotherapy.

Are the results of this trial practice changing? How have the results from this trial changed the way you treat your patients?

I believe the results are practice changing. I think that as with anything, the change in practice will be gradual, but I hope this will be expeditious. I think it is important to translate this to practice for patients who are receiving induction chemotherapy. It's not every day that you see an improvement in overall survival in a phase III clinical trial of AML, or in patients who have a *FLT3* mutation.

Patients who qualify should either be in a clinical trial studying FLT3 inhibitors specifically, or they should be placed on induction chemotherapy plus midostaurin followed by assessment for consolidation or a bone marrow transplant. I think the incorporation of midostaurin into chemotherapy is certainly something that is now supported by the available data. It should be incorporated into our practice and into the treatment of patients with *FLT3*-mutant AML.

***FLT3* mutations can often confer a high-risk status. How does this affect your decision to have a patient undergo hematopoietic stem cell transplant?**

It is true that patients with *FLT3* mutations have this higher propensity for proliferative disease, aggressive disease, monocytic disease, and an increased likelihood of relapse. As a result, for patients who can tolerate and are deemed appropriate candidates for a stem cell transplant, this should be considered after achieving remission following induction chemotherapy. It's probably relevant

to mention that there are a series of studies underway and planned that are looking at FLT3 inhibitors in the posttransplant setting as maintenance, to prevent relapse in that specific setting.

Another first-generation FLT3-targeting agent is sorafenib. Can you comment on its clinical development so far and results from key trials?

Sorafenib is a potent and effective FLT3 inhibitor. It's relatively nonspecific and it's currently approved for use in hepatocellular carcinoma and renal cell carcinoma. Since it is FDA approved, it's available, and leukemia physicians have been using it as a FLT3 inhibitor off-label. There have been a series of phase I studies that have looked at sorafenib in AML, and have demonstrated that the agent is well tolerated. There is an established toxicity profile that includes those impacting the gastrointestinal tract, liver, and skin. These toxicities have to be monitored, and doses may need to be adjusted in patients who are receiving the drug.

In those with relapsed or refractory *FLT3*-mutant AML, sorafenib often leads to reduction in peripheral blood and marrow leukemic cells, and it can help bridge certain individuals to stem cell transplant. Since patients with relapsed or refractory *FLT3*-mutant AML have very limited options, sorafenib can be used effectively as a single agent in this setting. A few studies have also looked at the combination of azacytidine, a hypomethylating agent, and sorafenib for relapsed or refractory patients. This combination was associated with a relatively high rate of remission in those patients with very high-risk disease. That finding was exciting and has changed our therapeutic approach to some of these patients.[12]

There have also been attempts to combine sorafenib with induction chemotherapy. A European randomized placebo-controlled phase II study of this combination was presented a few years ago, and was recently published. In this study of more than 250 younger patients, the combination was studied across all patients, not solely among those with *FLT3*-mutant AML. It revealed an improvement in event-free survival across all patients subgroups, again suggesting that sorafenib may be acting not just on FLT3-altered pathways, but also on other potentially leukemogenic targets in AML. In our practice, sorafenib is now usually reserved for patients who have relapsed or refractory disease.[14]

Same question for the second-generation FLT3-targeting agents: quizartinib, gilteritinib, and crenolanib. Can you comment on their clinical development so far, and results from key trials?

Quizartinib, gilteritinib, and crenolanib are very potent and very specific FLT3 inhibitors. As opposed to other FLT3 inhibitors in development, such as midostaurin, lestaurtinib, and sorafenib, the potential protein targets for these newer generation of FLT3 inhibitors are more limited, and these TKIs tend to be more potent in terms of their inhibitory activity.

Quizartinib was among the first of these second-generation FLT3 inhibitors to emerge. It is a very potent, selective, and effective drug. In phase I and phase II studies, it was very well tolerated. There were data presented a few years ago on quizartinib monotherapy in phase II trials among both younger and older patient populations. Quizartinib produced a composite remission rate north of 50% among studied patients. For relapsed or refractory *FLT3*-mutant AML, these data are quite promising. Many of these patients receiving quizartinib on trial were able to proceed to stem cell transplantation. This data led to a significant amount of hope and promise for those patients.

There are also studies looking at quizartinib in combination with conventional therapies, including induction chemotherapy and hypomethylating agents. There is also a phase III placebo-controlled trial, the QuANTUM-R study, that is seeking to enroll patients across multiple centers worldwide in order to fully assess the role of quizartinib when combined with conventional chemotherapy in patients with *FLT3*-ITD–mutant AML. Quizartinib is not a very potent *FLT3*-TKD inhibitor, in my view, but it's very potent as an ITD inhibitor specifically.

Crenolanib, on the other hand, inhibits both ITD- and TKD-altered proteins and also seems to have significant promise as a single agent in patients with relapsed or refractory AML. There are ongoing studies to look at crenolanib in combination with various standard treatments as well as in combination with upfront induction chemotherapy.

Finally, gilteritinib, which like crenolanib also has efficacy against certain TKD mutations and ITD-mutant *FLT3* AML, in my view, has much promise. It is well tolerated and has a high composite remission rate of around 46% in relapsed or refractory *FLT3*-mutant AML patients. There are also multiple ongoing studies, including a randomized phase III study that compares gilteritinib monotherapy with conventional therapies in the relapsed or refractory setting. Other studies are looking at gilteritinib in combination with conventional treatments in the frontline setting.

There's also the third-generation inhibitor, ponatinib. Do you think ponatinib has a future in the treatment of AML?

Ponatinib is also a FLT3 inhibitor. Ponatinib is a very potent inhibitor of BCR-ABL and it particularly inhibits the T315I-altered BCR-ABL tyrosine kinase. It has a significant role and activity in chronic myeloid leukemia, but is also a potent and selective FLT3 inhibitor, so I think it does deserve further study in AML as well.

Acquired resistance to FLT3 inhibitors has been a significant challenge to the treatment of AML. How will we be able to overcome it?

This is a very important question. Among the biggest challenges we have with treating patients with *FLT3*-mutant AML, specifically those who have ITD mutations, is the development of resistance TKD mutations and disease progression after initial achievement of remission. TKD mutations are commonly the D835 variant, but there are various other forms of TKD

mutations that can emerge. This can be quite frustrating because certain FLT3 inhibitors do not have efficacy against TKD-mutant AML, and in that scenario, without an approved drug being available, we are limited in what we can provide patients in terms of effective targeted therapy.

As I mentioned earlier, there are now various FLT3 inhibitors that are emerging that do inhibit certain TKD-mutant enzymes effectively. These include crenolanib and gilteritinib. Certainly, following development of secondary mutations and subsequent disease progression, the therapeutic goal is to re-establish a remission. This may be more easily achievable with the advent of newer FLT3 inhibitors that are emerging and are currently under study. These agents hold significant promise in possibly allowing patients to maintain a therapeutic benefit from targeted therapies.

Midostaurin is approved in combination with chemotherapy. In your opinion, is the future of *FLT3*-mutated AML in combination therapies or monotherapies?

One can speculate, of course, but as of now, the drugs that we have available for the treatment of patients include midostaurin in combination with induction chemotherapy in the frontline setting, and sorafenib, which can be used off-label for patients who have *FLT3*-mutated AML in the relapsed or refractory setting, potentially in combination with hypomethylating agents.

There are now a series of ongoing studies studying potent and selective FLT3 inhibitors, both as monotherapy in the relapsed or refractory setting and in combination with conventional therapies across various settings, including with frontline induction chemotherapy and with hypomethylating therapy. If these treatments ultimately reveal significant improvement in clinical outcomes, they may soon become part of our armamentarium in the treatment of *FLT3*-mutant AML. This may be in the frontline or in the relapsed or refractory setting; it may be monotherapy or in combination with other approaches that we've been using for years. I remain hopeful that the future will yield exciting new therapeutic options for these patients.

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