# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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## FLT3 Inhibitors for Acute Myeloid Leukemia

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**H&O** What is the mechanism of action for the FLT3 inhibitors?

**JEL** FLT3 inhibitors are tyrosine kinase inhibitors. Like other tyrosine kinase inhibitors, they compete for the adenosine triphosphate (ATP) binding site in the active domain of the kinase, which inhibits the ability of the protein to be phosphorylated, and subsequently decreases in the activity of that protein. Mutations of *FLT3*, in particular of the internal tandem duplication, are among the most common in acute myeloid leukemia (AML), resulting in constitutive activation of the mutated FLT3 receptor and activation of multiple downstream signaling pathways that promote dysregulated growth and proliferation.

**H&O** Can you describe the first-generation FLT3 inhibitors?

**JEL** The first-generation FLT3 inhibitors were developed several years ago, and include midostaurin, lestaurtinib, sunitinib (Sutent, Pfizer), and sorafenib (Nexavar, Bayer/Onyx). They have been studied extensively through the years both as single agents and in combination therapy for AML. The first-generation inhibitors are relatively nonspecific for FLT3, with other potential targets that include KIT, platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), and Janus kinase 2 (JAK2). The off-target effects may contribute to a generally higher toxicity profile and clinical efficacy in non–*FLT3*-mutated AML, but diminished efficacy in mutated *FLT3* with high allelic burden.

**H&O** Could you describe any relevant clinical trials for the first-generation inhibitors?

**JEL** The drugs just discussed were tested in the context of single-agent and combination therapy. In general, as single agents, they had limited, modest activity in patients with *FLT3*-mutated AML, with the exception of sorafenib, which had significant single-agent activity across several different trials. A large North American Cooperative Group study is testing standard induction chemotherapy with or without midostaurin, with a primary endpoint of overall survival, and the results are pending, but are expected soon. Lestaurtinib was tested in some single-agent studies with very modest response rates. A larger randomized study comparing chemotherapy with or without lestaurtinib in first relapsed AML revealed no clinical benefit in terms of response rates or overall survival.

As mentioned, sorafenib has been tested in a number of single-agent studies, which have shown modest activity. Some full remissions also have been documented in patients with relapsed and refractory AML who are *FLT3*-mutation positive. What is likely the most important study with sorafenib was presented at the 2014 American Society of Hematology (ASH) annual meeting by Rollig and colleagues. In this phase 3 randomized study, patients with newly diagnosed AML were randomly assigned to receive conventional induction chemotherapy with or without the addition of sorafenib. This study demonstrated a superior event-free survival in patients who received sorafenib; however, no significant overall survival advantage was detected. Interestingly, the event-free

survival benefit with sorafenib was evident in the entire patient population, but not specifically within the *FLT3*-mutated group.

Another combination study was done by the MD Anderson group utilizing sorafenib with 5-azacitidine in relapsed or refractory *FLT3-ITD*–mutated AML. In this nonrandomized trial, the overall response rate was 46%, including 10 patients (27%) with complete responses. Given the promising efficacy shown in this trial, the same combination is now being studied as frontline therapy in *FLT3-ITD* AML.

**H&O** Why do you think these first-generation FLT3 inhibitors showed only modest effects?

**JEL** There are likely a number of reasons for the lack of success in the first-generation inhibitors. First, relapsed and refractory AML is a very difficult disease status and is likely driven by multiple abnormal signaling pathways that give the leukemic cell an advantage in overcoming any single pathway that is being inhibited. Second, the first-generation inhibitors are not as potent as the newer inhibitors, so their actual ability to inhibit FLT3 as the primary target is not as profound, which may be particularly important in higher allelic burden disease. Some studies suggest that the lack of target inhibition could explain the lack of efficacy, and with more potent and more selective inhibitors, this aspect of treatment failure could be overcome.

**H&O** How do the second-generation FLT3 inhibitors differ from the first-generation inhibitors?

**JEL** The second-generation inhibitors, including quizartinib, crenolanib, PLX3397, and ASP2215, are more potent and selective than the first-generation inhibitors, with lower $IC_{50}$ and less off-target inhibition. The greater potency and selectivity promises higher efficacy in *FLT3*-mutated AML (particularly in patients with a higher allele burden) and less toxicity.

**H&O** Could you describe any promising clinical trials for the second-generation inhibitors?

**JEL** A number of trials have been performed or are in progress. A large phase 2 study testing quizartinib in patients with relapsed or refractory AML, both *FLT3*-mutated and unmutated, was presented at the 2012 annual ASH meeting by Levis and colleagues. The composite complete response rate was almost 50% among patients with relapsed and refractory *FLT3*-positive AML, with a slightly lower percentage of responders (32%) in the non–*FLT3*-mutated population. Approximately one-third of patients were able to subsequently undergo allogeneic stem cell transplant. A follow-up study of lower-dose quizartinib (30 or 60 mg/day) in relapsed or refractory *FLT3*-mutated AML showed very similar efficacy. The high response rate in these monotherapy trials helped distinguish quizartinib from first-generation inhibitors.

Another second-generation FLT3 inhibitor, crenolanib, appears promising in *FLT3*-mutated AML. A small phase 2 study of a more heavily pretreated *FLT3*-mutated AML population (including patients who were previously treated with FLT3 inhibitors), presented at the ASH 2014 annual meeting by Randhawa and colleagues, found an 11% complete remission rate (23% in the FLT3 inhibitor–naive group). It is worth mentioning that crenolanib also is highly active against mutant models of drug-resistant *FLT3-ITD*–positive AML, suggesting a role in patients who have become resistant to other FLT3 inhibitors. Finally, and perhaps most promisingly, Levis and colleagues presented results of a phase 1/2 trial of ASP2215, a novel inhibitor of FLT3 and AXL, at the 2015 annual American Society of Clinical Oncology (ASCO) meeting. This particular trial focused on *FLT3*-mutated AML and found a high overall response rate, in the range of 50% to 60%. In a smaller subset of patients with wild-type *FLT3*, the response rate was much lower. All 3 of these agents appear promising as monotherapy in *FLT3*-mutated AML.

There are many ongoing studies using FLT3 inhibitors as monotherapy. Quizartinib is being tested across several settings, including a randomized trial against conventional salvage therapy, in combination with standard- or lower-intensity chemotherapy, and as a maintenance treatment for patients in remission or after allogeneic transplantation. Crenolanib is being studied in a similar fashion across many settings, and ASP2215 soon will be studied in a large randomized trial vs salvage chemotherapy in AML.

**H&O** At what stages are the FLT3 inhibitors being tested?

**JEL** They are being studied across virtually all disease settings, including frontline, relapsed and refractory, and maintenance, mainly in patients with *FLT3*-mutated AML.

**H&O** Are these drugs only effective in patients with *FLT3* mutations?

**JEL** In general, the inhibitors have been more effective in patients with *FLT3* mutations; however, most of the studies have been skewed toward that patient population, so it is less clear how well these drugs work in patients without *FLT3* mutations. As stated earlier, event-free survival

advantage in the sorafenib arm of the large randomized trial in treatment-naive patients was independent of *FLT3* mutation status, which suggests important off-target effects. The quizartinib and ASP2215 monotherapy trials discussed earlier demonstrated efficacy in non–*FLT3*-mutated AML patients, albeit to a lower degree. It stands to reason that the more potent and selective inhibitors will have a more robust effect in patients with *FLT3* mutations, especially in patients with higher allelic burden, whereas the earlier-generation drugs will have less selectivity for activity in *FLT3*-mutated AML.

**H&O** What do you think is the future of FLT3 inhibitors in AML?

**JEL** The future for FLT3 inhibitors appears bright. There are intriguing data with these drugs, especially in their ability to inhibit the target and produce responses as single agents and in combination. We have a randomized study now, with sorafenib, that demonstrates an event-free survival advantage, which I think is an important step in the right direction, even if the ultimate approval is not based upon that trial. The second-generation inhibitors have unexpectedly high activity that would predict for a better outcome for patients, especially if they have an appropriate *FLT3* mutation. In the end, it will be a matter of confirmatory testing in a randomized setting to ultimately prove the benefit of FLT3 inhibitors. The emergence of secondary *FLT3* mutations during the course of therapy with FLT3 inhibitors will raise new challenges toward effective therapy in this subset of AML.

**H&O** Is there anything else that you would like to emphasize?

**JEL** At the current time, the most intriguing data on these drugs are not yet fully published and have been presented only in abstract form. Therefore, we must be cautious in interpreting these results and applying them clinically before we have more definitive data, longer-term outcome analyses, and all the nuances that go along with a fully published data set compared with something that is presented in abstract form. In addition, in AML, we have seen many examples in which a treatment looks promising in smaller, selected clinical trials, but does not prove beneficial when tested in a randomized larger-group setting. We still must be cautious about how we interpret these data in such an early phase of drug development. Finally, the "bridge to transplant" concept is also an interesting one, albeit undefined. If indeed these agents serve as a conduit to a curative transplant in a significant percentage of patients, then the value of this class of agents could be magnified.

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