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Is there data to support routine use of FLT3 inhibitors in patients with AML outside of a clinical trial?

Welcome to *Managing AML*. I am Dr. Naval Daver. I am frequently asked, "Is there data to support routine use of FLT3 inhibitors in patients with AML outside of a clinical trial?" The FLT3 inhibitors have now been in development for about 10 years, starting with older FLT3 inhibitors such as lestaurtinib, sorafenib, and midostaurin, and now with newer, more targeted, specific FLT3 inhibitors such as quizartinib, gilteritinib, and crenolanib. The FLT3 inhibitors have actually shown a very significant single-agent activity in relapsed AML with response rates between 45% to 50% with quizartinib and gilteritinib. To put this into context, even with high-dose combination chemotherapy in relapsed FLT3 mutated AML, the best response rates we usually achieve are 25% to 30%, and this is usually with a cocktail of three to four chemotherapeutic drugs. To be able to get a 50% response rate in a similar salvage high-risk group of AML with a single oral agent, and with significantly lower toxicity, is indeed one of the major breakthroughs in AML therapy.

Most of these data come from phase 2 studies, so what are the phase 3 data now available that would support routine clinical use of these FLT3 inhibitors? There was a recent phase 3 study that was completed and presented at ASH at the end of 2016. This study looked at the use of FLT3 inhibitor midostaurin in young, newly diagnosed AML patients. The study had a total of 750 patients, and patients were randomized in a blinded fashion to receive either standard induction with 7+3,* which was the standard of care practice, or receive 7+3 with a FLT3 inhibitor midostaurin. The midostaurin was given with induction on day 8 through 22, then continued through the consolidation cycles, and then as a maintenance for 1 year. The primary endpoint of the study was survival, and secondary endpoints were remission rates and early mortality. It was shown that the survival was significantly improved, with about 20% more patients alive at 5-year follow-up who had received the midostaurin in combination with 7+3, as opposed to those who received 7+3 alone. In addition to this, the secondary endpoints were also met with the improvement in response rate and an improvement in bridging to transplant. The main concern was, was there any added toxicity? It did not seem that there was any significant added toxicity or increase in the early mortality with the addition of midostaurin. So, this study, which is a phase 3 study, I think confirmed what lot of us have been seeing in phase 2 studies with FLT3 inhibitors, which is that they do have a significant benefit when added to standard chemotherapy, they improve response rates, and

more importantly, they improve the durability of responses and survival of patients. I think this established the use of FLT3 inhibitors in younger patients.

Now, there are additional phase 3 studies that are ongoing with a number of other FLT3 inhibitors. Two of these are quizartinib and gilteritinib. Quizartinib has been one of the most potent FLT3 inhibitors in the phase 2 study; the single agent is now being evaluated in two phase 3 studies. One study is in the younger frontline population where patients are getting 7+3 with quizartinib versus 7+3 alone and the endpoint is survival, and the other is in salvage 1 patients who are getting either quizartinib alone or are randomized to the investigator choice of high-dose chemotherapy. Gilteritinib also is being evaluated in a similar fashion in frontline as well as salvage FLT3 approaches.

One of the major mechanisms of resistance to the FLT3 inhibitors is acquisition of a second FLT3 mutation that is different from the initial one, and it becomes resistant to the FLT3 inhibitors. So, there are a couple of new drugs, such as crenolanib, that have broader activity and may cover multiple different types of FLT3 mutations including ITD and D835, and these are also now going into phase 3. All in all, I think there is clear data to support use of FLT3 inhibitors in younger patients, in addition to standard chemotherapy. Of course, to do that one must check the FLT3 mutation at baseline, and I think this should now be established standard of care across the United States and Europe, Additionally, data is now awaited to see if these drugs also have the benefit in the salvage setting, and in the older population, and with multiple different FLT3 inhibitors. These are very exciting times, we definitely need to check for FLT3 mutation in our patients, and if they have them, try to get them on a FLT3 inhibitor, either commercially when these become available in the near future or on a clinical trial. Thank you for viewing this activity.

**7+3, referred to in the video as 3+7, is most often used today as first-line induction therapy in AML, and consists of 7 days of standard dose cytarabine and 3 days of an anthracycline, most often daunorubicin.*