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What FLT3 inhibitors are being evaluated in AML and what is the development status of these agents?

Welcome to *Managing AML*. I am Dr. Naval Daver. I am frequently asked, "What FLT3 inhibitors are being evaluated in AML and what is the status of the development of these agents?" The FLT3 inhibitors have been evaluated in acute myeloid leukemia now for almost the last 10 years. The initial FLT3 inhibitors that went into clinical trials were drugs such as lestaurtinib, sorafenib, and midostaurin. Now more recently, there are more targeted, more specific FLT3 inhibitors that have emerged and are being evaluated, including drugs such as quizartinib (also called AC220), gilteritinib (also called ASP2215), and crenolanib. The FLT3 inhibitors target patients who have the FLT3 mutation, and the FLT3 mutation is seen in about 30% to 35% of patients with acute myeloid leukemia. There are two types of FLT3 mutations. There is the FLT3 ITD* and the FLT3 D835, with the FLT3 ITD being the more common of the two. Patients who have the FLT3 ITD especially have a more proliferative disease, higher risk of relapse, and poor survival. With the advent of FLT3 inhibitors, we have actually been able to target patients with FLT3 ITD, and their survival has significantly improved over the last decade since the use of the FLT3 inhibitors.

At this time, the FLT3 inhibitor that has already shown activity and positive impact in a phase 3 randomized study was the drug midostaurin. Midostaurin, or PKC412, is one of the older FLT3 inhibitors and it targets both the ITD and the D835. In a recently concluded phase 3 study, patients with newly diagnosed AML who were below age 60 were randomized to receive either 7+3** alone or 7+3 in combination with midostaurin. It was shown that the 7+3 in combination with midostaurin arm had a superior overall survival, which is the primary endpoint of the study.

Another FLT3 inhibitor which is currently in two phase 3 studies is quizartinib. This is a newer generation, more specific FLT3 inhibitor. As a single agent it was able to produce remission in about 50% of patients, which is quite impressive when you consider the fact that even with high-dose chemotherapy in relapsed AML, the response rates are about 30%, and this was able to do that as a single oral agent. So, these phase 3 studies are ongoing and we are awaiting the results.

The third one is gilteritinib, which, like quizartinib, is a specific, focused FLT3, also produced a response rate in salvage AML of about 50% to 55% and is also very well-tolerated. So, we expect that in the next few years, there will be multiple options with multiple different FLT3 inhibitors.

They do have some different toxicity profiles, so it will be ideal to have more than one of these available so that we can select the appropriate one for the patient based on their current condition, toxicities, and other needs. Thank you for viewing this activity.

*ITD=internal tandem duplication

**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.*