Pooled Safety Analysis of Quizartinib Monotherapy in Patients with Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML)

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Hello. Welcome to *Managing AML.* I'm Jorge Cortes. I am live at the 61st ASH Conference in Orlando, Florida. And today, I will be reviewing the results of our presentation on the pooled safety analysis of quizartinib monotherapy in patients with refractory/relapsed AML. Quizartinib is an oral, very potent, very selective FLT3 inhibitor that in a randomized study in salvage FLT3 positive AML, called the QuANTUM-R study, demonstrated a survival benefit compared to standard chemotherapy in patients with this disease. What we are presenting in these analyses is pooled safety information because quizartinib development strategy has treated now more than 600 patients with these agents. So it provides a wealth of information in terms of what we can expect for adverse events in patients in the refractory/relapsed setting and we're focusing only on patients that have received the quizartinib as a single agent. There have been some studies that have looked at combinations, those are not included in these analyses. So the pooled analysis includes 673 patients, about half and half are male and female with the median age of 59 years, 38 were assigned a dose of 30 milligrams daily, 277 patients were treated at the dose of 60 milligrams daily, which is the one that's being taken forward for development of the of the drug, the one that was using that QuANTUM-R study, and 358 patients were treated at doses higher than 60 milligrams daily up to 300 milligrams daily. The initial Phase I had suggested that the MTD could be higher. Later on, we learned that 60 milligrams was good enough efficacy wise and it eliminated some of the safety concerns. So we're going to be talking about the different cohorts according to the dose. The median treatment duration for all of these patients was 79 days and it was longest in the 60 milligram dose cohort, about 95 days compared to the other strategies, which had 70 days in the more than 60 milligrams and 66 days in the 30 milligrams.

So when you look at the overall treatment of emergent adverse events, these are adverse events regardless of causality. The results of the overall population are very consistent to what we saw in the phase 3 randomized QuANTUM-R study. The overwhelming majority of the on-treatment deaths were related to disease progression, and were more frequently seen in the lower doses. So 130 of the 599 patients had disease progression, 22%, and then another 83 were because of our treatment emergent adverse events as the as the reason for discontinuation. In the 60 milligram dose group, which again is the most relevant because it is one that's been taking forward. The only treatment emergent adverse event associated with discontinuation in

more than 2% of the patients was pneumonia, which was exactly 2%. And of course, this is probably more likely related to the infectious complications from the disease etc. but they emerged during treatment. The most frequently reported grade 3 or greater treatment emergent adverse events at this dose 60 milligram was febrile neutropenia 36%, anemia 28%, thrombocytopenia 27%, and then pneumonia 18%, and sepsis or septic shock in another 18%. So, essentially, most of these of these events are complications related to the leukemia itself and the related complications of the immunosuppression of acute myeloid leukemia. The most important adverse event dose limiting toxicity with quizartinib was QTc prolongation. It is important to then define the frequency of QTc prolongation, again focusing on the patients with 60 milligrams daily, the prolongation to greater than 500 milliseconds which defines grade 3 prolongation occurred in nine patients of the 277 patients, that is 3%. That is exactly the same that we saw in the QuANTUM-R study, 3% of patients had this grade 3 prolongation of QTc. The median time to the onset of the QTc prolongation was shorter in the greater than 60 milligram dose group than in the 60 milligram dose group, and also the incidence was greater in the higher doses, that's why we abandoned those doses. So the onset was nine days with a higher doses and 46 days median in the 60 milligram dose, but more importantly, QTc prolongation is relevant because we don't want to see those serious arrhythmias that can be seen when you have QTc prolongation. And in the whole program, in the more than 600 patients that we are reviewing through this presentation, only two patients had serious arrhythmias. One patient developed torsade's de Pointes and one patient had a fatal cardiac arrest. And importantly, both of these patients were treated at doses greater than 60 milligrams. So what this tells you is that the frequency of QTc prolongation grade 3 is low and the consequences, the clinical consequences are really minimal, particularly on the patients treated at the 60 milligram daily dose.

So with all of these, I think what we can conclude is that the overall safety profile of quizartinib in these refractory/relapsed population of patients with AML, most of them with FLT3 mutations is very consistent to what we saw in the recently published QuANTUM-R study. There has been a clear reduction in the incidence of QTc prolongation, to very acceptable levels, as we have gone down on the doses to the 30 and 60 milligram daily dose compared to the higher doses that were used in the initial stages of the development of these drugs. There's also been a significant reduction in other adverse events, minimal gastrointestinal toxicity. There's been some infections and bleeding, but at the lower doses, these have been much lower and I think that with these pooled analyses, it demonstrated that quizartinib not only prolonged survival, but that it is a very well-tolerated medication at the proposed dose of 60 milligrams once daily, and I'll remind you that in QuANTUM-R we started with 30 milligrams and if there was no QTc prolongation we escalated to 60, so it has that ramping up element. Obviously, quizartinib is currently being evaluated in the frontline setting in combination with chemotherapy. This is a study that that's called the QuANTUM-First. We should be hearing the results in the near future, it's coming close to completing enrollment and that'll hopefully be a positive study that will give us another valuable option for patients with FLT3 mutated AML. So what these analyses tells us for our colleagues who treat

patients with acute myeloid leukemia, one important lesson is that sometimes the phase I studies can be misleading. We thought that the MTD was 200 milligrams daily, and as we had more patients, we understood that that was higher. But I think that these analyses further emphasize the safety of quizartinib specifically, which allows us that opportunity to combine it with other agents. And that is important because we know that with a single agent, as potent as quizartinib may be, it'll be very difficult to cure a significant number of patients, we're going to have to combine it with other agents The good safety profile of quizartinib allows us that opportunity. And again, I think that the QuANTUM-First will show us whether there will be a benefit which is what we hope and will establish a new treatment option for these patients with FLT3 mutations. Thank you for viewing this activity.

Reference: Cortes JE, et al. Pooled Safety Analysis of Quizartinib Monotherapy in Patients with Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML). Abstract 1372. ASH 2019. https://ash.confex.com/ash/2019/webprogram/Paper121762.html