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Q-TWIST Analysis of Quizartinib vs. Salvage Chemotherapy in Patients with R/R FLT3-ITD AML

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Hello and welcome to *Managing AML*. I am Jorge Cortes and I am live at the 61st ASH Conference in Orlando, Florida. Today I will be reviewing the results of an oral presentation where we reported on an analysis called the quality adjusted time without symptoms or toxicity, or Q-TWiST for short, in the quizartinib versus salvage chemotherapy in patients with refractory relapse FLT3 ITD AML, the Quantum-R study. As a reminder, the patients with FLT3 ITD-mutated disease and particularly those with refractory or relapsed disease in this setting have very poor prognosis and there has been a lot of interest in developing new strategies for these patients. That led to the development of quizartinib, an orally active, very potent and selective FLT3 inhibitor, that in a randomized study, as a single agent, comparing it to standard chemotherapy demonstrated a significant improvement in overall survival. That was the primary endpoint for these analyses. Now, when you have a survival benefit in a study like this, in a randomized analyses, one of the questions that we always ask is, are we just prolonging life? But it comes at the expense of increased toxicity where patients spend most of their time in the hospital being treated for side effects or being treated for salvage because they didn't respond and getting additional chemotherapy etc. Or is it really valuable time, so sort of a quality of life assessment? In this analysis what we did was precisely to investigate the quality of that survival benefit through these Q-TWiST analyses in the patients treated in the Quantum-R.

For the primary analysis of this study, we included the intention-to-treat cohort, that is everybody that was treated with either the quizartinib or the control arm, and that included 367 patients. The sign was a two to one randomization, so there's 245 with quizartinib and 122 with standard of care. The primary objective as I've said, was the overall survival. We did some sensitivity analysis looking at the per protocol analysis said that excluded patients that were randomized but not treated or were not exactly eligible. For example, if you did not have confirmation of the FLT3 mutation, etc., that includes 231 patients on quizartinib and 88 patients on the standard of care. The way these Q-TWiST analyses works is that you can envision that a patient in their survival state after you start treatment, you can divide that period of prolonged survival into three health states. One is the time with any grade 3 or 4 treatment emergent adverse event. That's called the toxicity time. The other is the time that is spent after relapse, which is time that the patient may have symptoms of the disease, possibly even getting additional chemotherapy or other treatments. And then in between those two, you have the time without relapse or toxicity, which is the twist time, which is the valuable time, the quality time for a patient. That's where you want your patient to spend the most time

after a given intervention. So the Q-TWiST was assessed after 24 months, which is sort of the median follow up that we have at the time of cut-off for this for these analyses. And then what you do is you measure the area under the curve for each one of these three states for all the patients, and you assign a utility value to each one of these states. The convention is that the utility value for the toxicity and for the relapse states is of 0.5. So the utility value goes from 0 to 1, 0 meaning the least valuable, the 1 is the most valuable. So the toxicity time and the relapse time are giving a value of 0.5 and the twist time, the time without symptoms or toxicity, is given a 1 because it's the ideal time, and you add all of these. Then you can calculate the absolute and the relative improvement in this quality adjusted survival with the intervention of interest versus the control arm.

This analysis, Q-TWiST, has been used for a long time. It started in the 1980s. It's been extensively used in the literature in cancer, but not in leukemia, it hasn't been used in leukemia, but throughout the literature, it's been a convention that relative improvement in these quality time of 15% or greater is considered to be of clear clinical importance. So that was our goal to see if we could get to that time. Throughout this analysis, we also used a variation of the different thresholds. I mentioned that we assigned specific utility values of 0.5 for toxicity and relapse and 1 for the valuable time, the twist time, but we also did variations assigning values of anywhere from 0 to 1 to each one of them to see what impact it could have if we were underestimating or overestimating the value of each one of these types. And we also did some sensitivity analyses looking at different scenarios. As I've mentioned, the base case was looking at the intention-to-treat population and any treatment emergent adverse events. In the sensitivity analyses we did one with intention-to-treat and considering only treatment-related grade 3 or 4 adverse events. Another one where we looked at a per patient population with any treatment emergent adverse events. And the other one was a per patient population looking only treatment-related grade 3 or 4 treatment emergent adverse events. So, different permutations to try to look at all the different possibilities to better assess the value of that survival benefit of quizartinib.

For the base analysis for the intention-to-treat analysis, first I will remind you that on the overall results, the mean survival benefit, the absolute survival benefit for quizartinib was of two months. And when you do that Q-TWiST analysis, what we see is that there is an absolute gain for quizartinib compared to the standard of care for these 1.5 months, which is a relative gain of 20.3%. I remind you, this is well above that 15% threshold that is defined as clearly clinically significant for the patients. When we varied the utility value assigned to these different states, the toxicity, the relapse, and the twist time, between 0 and 100, we did all the different permutations and all of them have a relative gain above the 15% threshold, from 15.2% all the way to well above 20%, even getting to 25%, and all of them had an absolute benefit for quizartinib of at least 1.2 months and some of them going to 2.0 months. So, all the different permutations, we confirmed that survival benefit for the patients in this valuable time, the twist time. Then we did the sensitivity analysis that I mentioned and when you look at all these three different scenarios that that I described earlier, all of them had, again, a benefit for

quizartinib, with an absolute benefit of anywhere between 6.9 weeks and 7.5 weeks in favor of quizartinib, and the relative gain was anywhere between 20.7% and 22.5% gain with the quizartinib-treated patients.

In conclusion, what these analyses show is that the survival benefit that we saw with quizartinib, which was the primary endpoint and is by itself very valuable, results mostly from quality time for the patients. It is not time spent in toxicity, it is not time spent in relapse, it's mostly valuable time, which essentially you can interpret as time the patient can be at home with their families having the ability to do the things that they enjoy. So, I think this is important, because it further demonstrates the benefit of this drug compared to the standard of care. And it's also important because it provides another element for the clinician when they're trying to decide what is more valuable for the patients and explain to a patient what is the real benefit of a given drug, if they're just going to live longer, or they're going to be longer and better compared to the standard of care. So, with all of these elements, again, this supports the value of quizartinib in this patient population. I thank you for your attention.

Reference: Cortes JE, Ganguly S, Khaled SK, et al. Quality-Adjusted Time without Symptoms or Toxicity (Q-TWiST) Analysis of Quizartinib Vs Salvage Chemotherapy in Patients with Relapsed/Refractory (R/R) FLT3-ITD Acute Myeloid Leukemia (AML). *Blood.* 2019;134 (Supplement_1):382.
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