
Quizartinib: An Emerging Treatment Option for Relapsed/Refractory FLT3 ITD AML

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Welcome to *Managing AML*, I am Dr. Mark Levis. Today, I am going to review an abstract presented at the European Hematology Association's Annual Congress last month in Stockholm. The abstract (paraphrased) is, "Quizartinib significantly prolongs the overall survival of relapsed/refractory FLT3 mutant patients in the Phase 3 randomized QuANTUM-R trial." By way of background, the patients enrolled on this study had a FLT3-ITD mutation. Remember there are two different kinds of FLT3 mutations, a FLT3-TKD and a FLT3-ITD mutation. The ITD mutation is the more common one, is more obviously associated with a poor outcome, and – importantly – quizartinib does not have activity against the TKD mutations; therefore, this trial specifically selected FLT3-ITD patients. There are currently no agents approved for the treatment of relapsed or refractory FLT3-ITD AML. By way of context, midostaurin, which is a more pan-kinase inhibitor that has activity against FLT3 is approved for newly-diagnosed FLT3 mutant patients (that would include both TKD and ITD) when the drug is given in combination with chemotherapy. Quizartinib is a very different drug than midostaurin. Quizartinib actually was developed specifically for FLT3-mutant AML, whereas midostaurin originally was developed for a variety of cancers and it kind of settled on working in FLT3. Quizartinib specifically came out as trying to target the FLT3-ITD mutation. It is far more selective and potent as a result. It does have activity in the relapse setting, unlike midostaurin. Following on the basis of several earlier phase studies, predominantly a couple of large phase 2 studies that showed a significant level of activity in FLT3-ITD AML that was relapsed or refractory,^{1,2} this QuANTUM-R trial was launched. To finish up the background, quizartinib has quite a remarkable level of activity as a single agent in patients with FLT3-ITD AML that are relapsed. You get about a 50% composite complete remission rate, and most of those are what we call CRi, complete remission with incomplete count recovery. There are very few actual Cheson criteria CRs with the drug. Again, most of these are so-called CRi but the question is, do those have significant clinical benefit? In addition, there are a lot of partial responses as well. The overall response rate in the phase 2 settings was in the 60% to 75% range, really quite high.

The design of the QuANTUM-R is to take that single-agent drug quizartinib and compare it in the relapsed setting to conventional chemotherapy. The patients were very carefully selected; they had to have an ITD mutation, they had to have been relapsed within six months of their remission, or they had to be refractory to a conventional induction regimen (defined as a standard-dose cytarabine anthracycline regimen). Ultimately, the patient could have relapsed

after an allogeneic transplant and be eligible for this trial. The total number of patients accrued to this trial were 367, randomized 2:1 to receive quizartinib versus salvage chemotherapy. There was a total of 245 patients that got quizartinib and the remainder (122) who got the salvage chemotherapy. The salvage chemotherapy consisted of either MEC or FLAG-IDA (typical salvage regimens), or there was an option to get low-dose AraC; not a lot of patients got that, I think it was 29 in total out of the 122 randomized to salvage chemotherapy. If they got a remission and/or proceeded to an allogeneic transplant afterwards, if they were on the quizartinib arm, they could continue on quizartinib of course, and that was another important component of this. The trial began accrual in 2014 and finished up middle of last year, and so the early results were presented just last month at the EHA meeting.

The patients accrued were kind of typical for this patient population; they tend to be younger. We did have an age range going all the way up to nearly 80, but for the most part the median age of this disease is around 58 to 60. About a quarter of them had relapsed after a transplant. Most of them had intermediate cytogenetics, which is typical for this population. The outcome slide at first look does not show a dramatic difference in overall survival between the quizartinib arm and the salvage arm, but it shows a pretty clear one: 7% difference, which is interestingly the same degree of margin that midostaurin was approved on in the upfront setting. At 27% overall survival at 12 months (it was landmark analysis) versus 20% in the salvage chemo arm, and there was a hazard ratio of 0.76, the *P*-value was 0.0177. The primary endpoint of this study was overall survival and that did meet the predefined endpoint. Secondary endpoints were response rates and event-free survival. The composite response rate (CRi, which is the predominant response, plus CR plus CRP) was 48% versus 27% in the salvage arm. The overall response in the quizartinib arm was 69%, which is really quite high, but exactly what we saw in the phase 2 studies. The overall response rate in the salvage chemo arm was 30%, so the response rates were very consistent with exactly what we saw in the phase 2 studies. In comparison with salvage chemotherapy, it was an essentially positive trial with clear survival benefit; again, nothing dramatic.

I think the important point to realize is this. You can look at that survival curve and say, well so what it's 7%, everybody is doing horribly. Relapsed/refractory FLT3-ITD AML is a disastrous clinical condition and that is not where you want to be using this drug. Just like midostaurin in contrast had almost minimal activity in the relapsed setting, but when you combined it with chemotherapy it led to an overall survival benefit. While I am very excited about this QuANTUM-R result, I am more excited about the trial that is accruing where we are taking quizartinib and doing essentially what midostaurin did: adding it to induction chemotherapy in the newly-diagnosed setting. That trial is called QuANTUM-First. I should note, no one has ever really shown a drug to work better than anything else in the relapsed/refractory setting for AML, period, in a randomized study like this. That alone is a fairly stunning finding, which is why this was presented at the plenary session. The magnitude of benefit should not be discounted. There is a clear benefit to a patient receiving quizartinib at home as an oral drug as opposed to inpatient getting MEC or FLAG-IDA. I think there are intangible benefits here as well.

To summarize the important findings here, we do have a drug that works better than chemotherapy for relapsed/refractory FLT3-ITD AML. We have the first clinical trial showing in a randomized setting a benefit of one agent over another in the relapsed setting for AML. Finally, we can look forward to the results of the QuANTUM-First trial because we clearly have an active agent here, and we really want to be able to use it in the circumstances where it is going to benefit the most patients, and that is going to be the upfront setting.

Thank you for viewing this activity.

Abstract

Cortes J, Khaled S, Martinelli G, et al. Quizartinib Significantly Prolongs Overall Survival in Patients with FLT3-Internal Tandem Duplication–Mutated (Mut) Relapsed/Refractory AML in the Phase 3, Randomized, Controlled QUANTUM-R Trial. EHA23: 2018. Abstract LB2600.
https://learningcenter.ehaweb.org/eha/2018/stockholm/218882/jorge.cortes.quizartinib.significantly.prolongs.overall survival.in.patients.html?f=ce_id=1346*ot_id=19045*media=3

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