Maximizing Efficacy Across the Spectrum of AML: Early Clinical Trial Results of the FLT3 Inhibitor Quizartinib in Newly Diagnosed and R/R AML

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563. Efficacy and Safety of Single-Agent Quizartinib (Q), a Potent and Selective FLT3 Inhibitor (FLT3i), in Patients (pts) with FLT3-Internal Tandem Duplication (FLT3-ITD)-Mutated Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML) Enrolled in the Global, Phase 3, Randomized Controlled Quantum-R Trial

I am Dr. Mark Levis, and I am live at the 60th ASH Conference in San Diego, California. Today, I am going to be reviewing the results of the efficacy and safety of single-agent quizartinib, which is a potent selective FLT3 inhibitor in patients with FLT3 internal tandem duplication, mutated, relapsed/refractory AML, enrolled in the global phase 3 randomized controlled QuANTUM-R trial.

FLT3 is perhaps the most common mutation in AML and the most common FLT3 mutation is the ITD mutation. It is associated with higher relapse rate and poorer overall survival. Worse though in the relapse setting, these patients have just a dismal outcome. Quizartinib is perhaps the most potent in selective FLT3 inhibitors. We have actually had two approved already in the last year or so, midostaurin and gilteritinib, but quizartinib is a type 2 inhibitor, different from the type 1's that have already been approved. This particular trial focused on this very poor risk group of patients. They were either refractory to initial chemotherapy or they had relapsed within 6 months of getting standard induction and consolidation chemotherapy. They almost never respond to conventional chemotherapy and so, this was a randomized trial, 2:1 randomization, comparing such patients single-agent therapy with quizartinib, with a doctor's choice regimen of chemotherapy consisting of MEC, FLAG-IDA, or low-dose Ara-C, and there was 367 patients enrolled. The primary endpoint was overall survival, and I think it is important to remember that you are comparing an agent that is a pill where patients pretty much get to go home, come back to clinic twice a week, and that is being compared with treatment where they are receiving MEC chemotherapy, for example, where they are inpatient for 30 days, experiencing mucositis and all of the fun of chemotherapy. With that in mind, in fact, with the primary endpoint of overall survival, it was a positive trial, the hazard ratio is around 0.76. There was a clear benefit for quizartinib, but again, just to think about this, this is a pill that you go home with, come back to clinic as opposed to salvage chemotherapy, and it still had an overall survival benefit. The main

toxicity of this compound that everybody is worried about is QT prolongation. There was something like 3% of cases that had grade 3 QT prolongation. There were no actually arrythmia events or any deaths as a result of this. All in all, this was a far better way to spend a couple of months for a patient with relapse/refractory AML taking a pill versus the salvage chemotherapy. This is, I think, an exciting trial on the basis of this they are filing for approval.

Reference: Cortes J, Khaled S, Martinelli G, et al. Efficacy and Safety of Single-Agent Quizartinib (Q), a Potent and Selective FLT3 Inhibitor (FLT3i), in Patients (pts) with FLT3-Internal Tandem Duplication (FLT3-ITD)–Mutated Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML) Enrolled in the Global, Phase 3, Randomized Controlled Quantum-R Trial. ASH 2018. Abstract 563.

564. Updated Results from a Phase 1 Study of Gilteritinib in Combination with Induction and Consolidation Chemotherapy in Subjects with Newly Diagnosed Acute Myeloid Leukemia (AML)

Today, I will be reviewing the updated results from a phase 1 study of gilteritinib in combination with induction and consolidation chemotherapy in subjects with acute myeloid leukemia, newly diagnosed. The agent in question here is gilteritinib. This is a novel FLT3 inhibitor that actually just received regulatory approval in the US and in Japan quite recently. It is specific for the population relapsed/refractory, that is what this has been approved for, but what we are looking at here is how to move this drug upfront. Really the best bang for our buck with this type of drug, I think, is going to be used in the newly diagnosed population, but in order to do that, you have got to incorporate it into induction and consolidation chemotherapy. That is the purpose of this study.

This was a phase 1B study in which newly diagnosed AML patients were treated with a conventional induction regimen of 7+3. The initial escalation cohort used the platform of 100 mg/m^2 cytarabine plus 12 of idarubicin. We then explored additional 7+3 recipes including 90 mg of daunorubicin and we also played around with the sequence. The initial sequence starts the study drug on day 4 of induction. So, of a 7-day infusion of cytarabine, we start gilteritinib on day 4; however, in subsequent cohorts, we looked at starting it on day 8, which imitates the schedule seen with midostaurin. So, 68 patients were enrolled but only 61 patients were actually evaluable for results because we enrolled the patients before knowing their molecular profile and some of these patients had favorable risk AML. They were excluded as they would not be expected the benefit from gilteritinib. The results population is 61 patients, 34 of whom actually had FLT3 mutations. Now, the response rate in those 34 patients actually was over 90%, which was gratifying. We did identify a dose-limiting toxicity, which is essentially prolonged neutropenia. There was a patient who had neutropenic enterocolitis, and that was actually at 200 mg. The approved dose of gilteritinib in the relapsed refractory setting is 120 mg/day in the US and that turns out to be our dose for this phase 1B study as well. So, 120 mg of gilteritinib combined

with 7+3 is safe, well-tolerated, and appears to have a high level of activity in FLT3 mutant patients. This is going to serve as the jumping-off point for a number of large randomized studies around the world comparing chemotherapy plus gilteritinib with chemotherapy plus other FLT3 inhibitors, and those trials are just getting underway.

Reference: Pratz K, Cherry M, Altman J, et al. Updated Results from a Phase 1 Study of Gilteritinib in Combination with Induction and Consolidation Chemotherapy in Subjects with Newly Diagnosed Acute Myeloid Leukemia (AML). ASH 2018. Abstract 564.