Emerging Mutations at Relapse in Patients with FLT3-Mutated Relapsed/ Refractory Acute Myeloid Leukemia Who Received Gilteritinib Therapy in the Phase 3 ADMIRAL Trial

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Welcome to *Managing AML*. I'm Dr. Alexander Perl from the University of Pennsylvania. I'm live at the 61st ASH Conference in Orlando, Florida. And today I'll be reviewing the results of an oral presentation that reported on emerging mutations that relapse in patients with FLT3 mutated relapsed and refractory AML who received gilteritinib therapy in the phase 3 ADMIRAL trial. This was presented by my colleague, Dr. Catherine Smith from the University of California, San Francisco. The major conclusions from the ADMIRAL trial was that gilteritinib, an oral, selective and potent FLT3 inhibitor, led to superior response and survival when compared to standard chemotherapy in a phase 3 trial that was recently published in the *New England Journal of Medicine*. This led to the approval of gilteritinib as the first FLT3 inhibitor for the therapy of relapsed and refractory FLT3-mutated AML and the drug is approved as monotherapy. The current objective of this study was to look at patients who are enrolled on the pivotal trial of gilteritinib and look at the presence of mutations that emerged at resistance to this therapy to gain insight into potential mechanisms of resistance to the drug. We were able to collect a large number of baseline mutations on patients on this study, and a subset of patients who responded to the drug with at least a composite complete remission, and then progress for study for the presence of new mutations in comparison to their baseline study. What we found was that approximately two-thirds of patients had new mutations at the time of disease progression that were not present using a next-generation sequencing panel when we looked at their baseline samples. So the most common mutations that we saw grouped into two mechanistic groups that points some insight into why these patients' leukemias might be growing on the drug. And the two groups that we saw were mutations in the RAS and MAP kinase pathway, most commonly NRAS or KRAS or PTPN11, which are all mutations that will activate a signaling cascade that's downstream of FLT3, and it is thought for this reason that this is why patients may be resistant to the drug. It had been predicted by preclinical models. The second mutation that was seen commonly were mutations and FLT3 itself and suggests that there may be ways that the gene can be mutated that are less sensitive to the drug. This also was predicted by preclinical models. And the most common mutation seen was analogous in structure to a gatekeeper residue. In FLT3, this occurs in F691L, and it's analogous to the T315I mutation that seen at BCR ABL and causes resistance to inhibitors of that target in CML. So the conclusions that we draw is that activation of signal transduction appears to be the mechanism of resistance to FLT3 inhibitors, such as gilteritinib, which is similar in mechanism to what we see with BCR ABL inhibitors in terms of activation of the downstream targets from new mutations. This points to

the opportunity perhaps to develop either combination studies, or perhaps new inhibitors that have better protection against emergence of these resistance mutations. At present, those are investigational questions and focus with gilteritinib therapy is both on combinations and moving the drug earlier in therapy so that hopefully we see less clonal diversity at relapse.

Reference: Smith CC, et al. Emerging Mutations at Relapse in Patients with FLT3-Mutated Relapsed/Refractory Acute Myeloid Leukemia Who Received Gilteritinib Therapy in the Phase 3 Admiral Trial. Abstract 14, ASH 2019.
https://ash.confex.com/ash/2019/webprogram/Paper122620.html

Effect of Co-Mutations and FLT3-ITD Variant Allele Frequency (VAF) on Response to Quizartinib or Salvage Chemotherapy (SC) in Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML)

Today, I'll be reviewing the results of an oral presentation, which reported on effects of co-mutations and FLT3 ITD variant allele frequency or VAF on response to quizartinib or salvage chemotherapy in relapsed or refractory AML. These results come from the QuANTUM-R, which was a phase 3 evaluation of the investigational FLT3 inhibitor quizartinib, which is a highly potent and selective inhibitor of FLT3, which is commonly mutated in AML, and FLT3 ITD mutations identify a high-risk population with a high rate of either refractoriness to frontline chemotherapy or relapsed after frontline chemotherapy. This study showed a survival improvement from the use of quizartinib, although the drug at present remains investigational in the United States. And this presentation is an analysis of mutations other than FLT3 that we're seeing in patients treated on the trial in both arms of the study, as well we looked at whether the allele frequency of FLT3, which has been known as a predictor of response and survival to frontline chemotherapy, retains that predictive ability in relapsed and refractory patients treated on this trial.

What we found in this study was that the activity of quizartinib was maintained in terms of response rates across a broad number of mutations, including the most commonly seen mutations, which were again in the genes DNMT3A, NPM1, ASXL1, TET2, IDH, and CEBP Alpha. We did see some patterns of both response and changes in overall survival based on certain mutations that were noted at study entry. For example, patients with DNMT3A mutations seem to have a greater magnitude of survival benefit than patients with nucleophosmin who had similar survival on the quizartinib and the chemotherapy arms. However, when we looked at patients who were wild-type for nucleophosmin, they had a superior response and survival with was quizartinib therapy, and many of these patients actually had co-mutations in DNMT3A. One of the populations that actually had the greatest clinical benefit from quizartinib in terms of

survival benefit was actually the group who was mutated for DNMT3A and was wild-type for NPM1. We secondarily looked at the role of FLT3 allele frequency or allele burden on the outcome of the study. And from this we noted that similar to newly diagnosed patients, patients who had a high allele burden for FLT3 ITD had inferior survival on the study, regardless of which arm they were assigned to from the randomization. However, the survival benefit of quizartinib was primarily seen in patients with the high allele frequency, who again were really the highest risk patients on the study. So what we conclude is that looking at this study, even within the population of patients with FLT3 ITD positive AML, there are relatively higher- or lower-risk patients in terms of their survival when we look at outcome from relapse or refractoriness to frontline chemotherapy. Within this context, there may be predictors of outcome to quizartinib; however, an independent validation cohort needs to be studied for us to draw any firm conclusions. Thank you for viewing this activity.

Reference: Perl AE, et al. Effect of Co-Mutations and FLT3-ITD Variant Allele Frequency (VAF) on Response to Quizartinib or Salvage Chemotherapy (SC) in Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML). Abstract 737. ASH 2019. https://ash.confex.com/ash/2019/webprogram/Paper121880.html