
A Phase 3 Randomized Study (PRIMULA) of the Epigenetic Combination of Pracinostat, a Pan-Histone Deacetylase (HDAC) Inhibitor, with Azacitidine (AZA) in Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) Unfit for Standard Intensive Chemotherapy (IC)

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Welcome to *Managing AML*. I am Dr. Guillermo Garcia-Manero I'm live at the 61st ASH Conference in Orlando, Florida. Today I will be reviewing Abstract 2652, which reported on a phase III randomized study known as PRIMULA of the epigenetic combination of pracinostat a pan-histone deacetylase inhibitor (HDAC) with azacitidine in patients with newly diagnosed acute myeloid leukemia unfit for a standard intensive chemotherapy. This is a very important study. The study actually was based on an initial phase II trial that we conducted at MD Anderson in patients with AML with azacitidine and pracinostat that resulted in a high response rate and durability of these responses. Therefore, this phase III study is trying to prove that addition of pracinostat to azacitidine will improve outcomes, both response and survival, in patients with AML. Pracinostat is a second third-generation HDAC inhibitor with an excellent toxicity profile that has demonstrated significant activity in patients with acute myelogenous leukemia. The study is a very ambitious multi-country study, combining azacitidine with pracinostat in the randomized fashion. Patients are with acute myelogenous leukemia, they are non-eligible for intensive chemotherapy and this is based basically on being older than 75 years of age, or protocol, or patients that are younger with a protocol defined comorbidities. As I mentioned, this is a very large study, we plan to enroll close to 500 patients, then randomization is one to one, meaning one arm pracinostat and azacitidine and the other placebo with azacitidine. So this is important to emphasize that this arm contains a placebo. So therefore, the data will be quite significant and the study will open at around 140 study centers worldwide in basically every continent. The randomization criteria is based on cytogenetic classification and ECOG performance. The standard therapy is given with azacitidine with 28-day cycles, seven days administration of azacitidine, whereas the pracinostat is given orally as a 60 milligram capsule every day, three times a week for three weeks with a week of rest to allow to recover from some of the HDAC-related toxicities. The primary end point of this study is survival with secondary endpoints that are classic in terms of efficacy, morphological cytogenetic complete remissions, and of course, rate of transmission dependency and toxicity profile of these combinations.

Enrollment is open to the PRIMULA study as of July 2019, and of note, 257 patients have been randomized to this trial.

Reference: Garcia-Manero G, et al. A Phase 3 Randomized Study (PRIMULA) of the Epigenetic Combination of Pracinostat, a Pan-Histone Deacetylase (HDAC) Inhibitor, with Azacitidine (AZA) in Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) Unfit for Standard Intensive Chemotherapy (IC). Abstract 2652. ASH 2019.

<https://ash.confex.com/ash/2019/webprogram/Paper125924.html>

Pharmacokinetic Exposure Equivalence and Preliminary Efficacy and Safety from a Randomized Cross over Phase 3 Study (ASCERTAIN study) of an Oral Hypomethylating Agent ASTX727 (cedazuridine/decitabine) Compared to IV Decitabine

I will be reviewing Abstract 846, which reported on the pharmacokinetic exposure equivalence and preliminary efficacy and safety from a randomized crossover phase 3 study known as ASCERTAIN of an oral hypomethylating agent ASTX727 compared to IV decitabine in patients with MDS and CMML. ASTX727 is a combination of cedazuridine with decitabine and it's a total oral formulation. As the audience knows, the hypomethylating agents are the standard of care for patients with myelodysplastic syndrome and CMML. We have two of those agents, decitabine and azacitidine, and they need to be given either IV or subcutaneous respectively for multiple days every month on a chronic type of basis. An oral compound with the same clinical activity on safety profile would be a major benefit for our patients with MDS and AML and potentially other myeloid alterations. So the study on ASCERTAIN is a very important phase 3 trial that can result actually in the regulatory approval of this particular compound for patients with MDS and CMML. As I mentioned earlier, this is a combination of an oral azacitidine deaminase inhibitor with oral decitabine and the data presented will clearly confirm that the PK exposure mainly the pharmacokinetic profile of this compound is virtually identical to that of IV decitabine.

In this study, mainly done in North America, we treated 138 patients with MDS and/or CMML. The patients were randomized to two schedules in one, the patient received first the IV form, followed by the oral form on the second cycle, in the other arm was basically the reverse. And then on the third cycle of therapy, patients went on to receive all oral decitabine or the ASTX727. This is very important because basically it allows for intra-patient calculation of PK and PV exposure in terms of just doing whole cohort analysis. So the data from this study is quite robust. The patient characteristics were similar to what you will expect in the label of IV decitabine. The arms were very well randomized in terms of high risk, low risk, CMML, and MDS, and basically reflects the fact that the absorption of oral ASTX727 is 99% similar to that of IV decitabine,

confirming prior data that we presented on prior phase 2 and phase 1 studies in multiple presentations on papers. So this is a very important development. This compound actually a safe with a very low rate of GI toxicity and adverse event profile identical to IV decitabine and an effect on global DNA methylation that is again, similar if not identical to that of IV decitabine. The follow up of this phase 3 studies very short around five months, but we're seeing clinical activity similar to what you will expect with IV decitabine. So in summary, this very important study has met its primary endpoint and that was basically the comparison of the PK profile of IV versus oral decitabine and we believe this is going to be a very important part of our clinical armamentarium for patients within the MDS, CMML and in the future, potentially other leukemias, thank you very much for your attention.

Reference: Garcia-Manero G, et al. Pharmacokinetic Exposure Equivalence and Preliminary Efficacy and Safety from a Randomized Cross over Phase 3 Study (ASCERTAIN study) of an Oral Hypomethylating Agent ASTX727 (cedazuridine/decitabine) Compared to IV Decitabine. Abstract 846. AHS 2019. <https://ash.confex.com/ash/2019/webprogram/Paper122980.html>