Phase 3, Multi-Center, International, Randomized, Double-Blind, Placebo Controlled Study of Oral Rigosertib + Injectable Azacitidine Versus Injectable Azacitidine in Treatment-Naive Patients with Higher-Risk Myelodysplastic Syndrome

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I'm Dr. Shyamala Navada, and I'm live at the 61st ASH conference in Orlando, Florida. Today, I will be reviewing Abstract 4268 which is the data recently reported on the Phase 2/3 Multi-Center, International, Randomized, Double-Blind, Placebo-Controlled Study of Oral Rigosertib and Injectable Azacitidine Versus Injectable Azacitidine in Treatment-Naïve Patients with Higher-Risk MDS.

The only approved medications for treatment of first-line higher-risk MDS are hypomethylating agents, azacitidine and decitabine in the U.S. and azacitidine only in Europe. It is estimated that progression to acute myeloid leukemia as well as median overall survival for these patients is less than one to three years. Although azacitidine monotherapy demonstrated improvement in overall survival in higher-risk MDS, clinically meaningful and durable responses continued to be limited to a subset of patients. One obvious strategy is to identify a novel drug that can be administered effectively in combination with azacitidine and has minimal overlapping toxicity with azacitidine. Based on this current approach and favorable results of the phase 2 study, the first pivotal phase 2/3 adaptive design randomized study of oral rigosertib in combination with azacitidine has been developed as part of an effort to increase overall responses as well as reduce risk of transformation to AML for patients with treatment-naive higher-risk MDS. Studies have demonstrated that rigosertib binds directly to the RAS-binding domains found in RAS-effector proteins such as the RAF kinases and PI3K and inhibits the RAS/RAF/MEK and the PI3 kinase pathways. In vitro, the combination of rigosertib with azacitidine synergistically inhibits growth and induces apoptosis of leukemic cells in a sequence-dependent fashion. Sequential exposure with rigosertib followed by azacitidine achieved maximum synergy with clinically achievable concentrations. In a phase 2 study, oral rigosertib at doses greater than or equal to 840 mg/day administered in combination with azacitidine demonstrated efficacy in HMA-naive MDS patients with an overall response rate of 90% and a CR rate of 34%. The combination administered in repetitive cycles for more than two years was well tolerated, and the observed genitourinary toxicity was mitigated using specific management guidelines. Based on the efficacy data and favorable safety profile, the pivotal phase 2/3 adaptive design study presented here in treatment-naive higher-risk MDS population has been developed.

Patients who will be eligible for this study will have to have higher-risk MDS with an IPSS-R score greater than 3 and 5% to 19% blasts. They must be MDS treatment-naive, eligible for treatment with azacitidine, or greater than or equal to 18 years of age. Patients will further be stratified but intermediate versus high versus very high risk per IPSS-R less than 75 years versus greater than 75 years and geographical location. There will be a 1:1:1 randomization with one cohort being azacitidine plus placebo; one cohort being azacitidine plus rigosertib dose at 560 mg in the morning and 280 mg in the afternoon; and one cohort of azacitidine plus rigosertib at 560 mg in the morning and 560 mg in the afternoon. Primary endpoint will be CR plus PR and key secondary endpoint will be overall survival. After the best cohort is determined for the rigosertib dose, that is either 560 mg/280 mg or 560 mg/560 mg, the study will then proceed to a phase 3 study where the cohort that had the best responses will be then compared to the azacitidine plus placebo cohort with the same endpoints. Treatment will continue until progression of disease as defined by IWG 2006 or unacceptable toxicity, after which patients will be followed for survival every two months until death or three years, whichever comes first. The primary analysis of all efficacy endpoints will be in the intention-to-treat population. This safety population will include all patients classified according to the protocol treatment they received regardless of random assignment. Randomized patients who receive no treatment will be excluded. Management guidelines for treatment-emergent adverse events requiring dose adjustments, either dose delay or dose modification at time of adverse event, will be defined as well.

This pivotal phase 2/3 randomized adaptive trial in treatment-naive higher-risk MDS patients has been developed based on efficacy data and a favorable safety profile from prior studies combining rigosertib and azacitidine. The Intergroup randomized phase 2 combination study in patients with higher-risk MDS treated with azacitidine plus lenalidomide or azacitidine plus vorinostat had a similar overall response rate to patients treated with azacitidine monotherapy. In contrast, the phase 2 study of oral rigosertib in combination with azacitidine had an overall response rate of 90% and a CR rate of 34%. This proposed study is the first phase 2/3 adaptive randomized study of oral rigosertib with azacitidine and may provide a potential new treatment for first line in a patient population with a poor prognosis and limited therapeutic options. Thank you.

Reference: Garcia-Manero G, et al. Phase 3, Multi-Center, International, Randomized, Double-Blind, Placebo Controlled Study of Oral Rigosertib + Injectable Azacitidine (AZA) Versus Injectable Azacitidine in Treatment-Naive Patients with Higher-Risk Myelodysplastic Syndrome (HR-MDS). Abstract 4268. ASH 2019.
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