**Phase II Study of Oral Rigosertib Combined with Azacitidine As First Line Therapy in Patients with Higher-Risk Myelodysplastic Syndromes**

**Shyamala C. Navada, MD, MSCR**
Assistant Professor
Mount Sinai School of Medicine
Department of Medicine
Division of Hematology/Oncology
New York, New York

I'm Dr. Shyamala Navada, and I'm live at the 61st ASH conference in Orlando, Florida. Today, I will be reviewing Abstract 566 which is the data recently reported on the Phase 2 Study of Oral Rigosertib Combined with Azacitidine as First Line Therapy in Patients with Higher-Risk MDS. Azacitidine monotherapy has demonstrated improvement in overall survival in higher-risk MDS. Clinically meaningful and durable responses continue to be limited to a subset of patients. One obvious strategy is to develop doublet therapy with drugs that are effective monotherapy in higher-risk MDS, and can be administered effectively and safely in combination with azacitidine. Several agents have been combined with azacitidine in first-line therapy for patients with higher-risk MDS achieving overall response rates and CRPR rates that are comparable to azacitidine monotherapy. RAS and other signaling molecules in the RAS pathway are frequently mutated in higher-risk MDS and are proposed to drive leukemic transformation. Given that rigosertib interferes with the RAS-binding domain of RAF kinases and inhibits the RAS/RAF/MEK and the PI3 kinase pathways, it is an attractive candidate for combination with azacitidine. Furthermore, in vitro combination rigosertib with azacitidine synergistically inhibits growth and induces apoptosis of leukemic cells in a sequence-dependent fashion. In the phase 2 study 0908, a total of 39 treatment-naive higher-risk MDS and RAEB-t patients received oral rigosertib in combination with standard dose azacitidine. Rigosertib was given at 840 mg/day, that was 560 mg in the morning and 280 mg in the afternoon, or 1120 mg/day in two cohorts either 560 mg in the morning and afternoon or 840 mg in the morning and 280 mg in the afternoon. Responses were determined by 2006 IWG criteria including transfusion independence, defined as 56 days without PRBC or platelet transfusion. Oral rigosertib was administered on days 1-21 of a 28-day cycle. Parenteral azacitidine was administered at standard dose for 75 $mg/m^2$/day for seven days from days 8-15. Patients were evaluable for response if they received three cycles of therapy or had progression of disease. Median age of the patients was 64 years with a range of 42 to 90. IPSS-R score at study entry was 9 were intermediate, 8 were high, and 17 were very high risk. In total, 20 patients were transfusion dependent at study entry. CR and PR responses were observed across all evaluable patients and IPSS-R cytogenetic prognostic subgroups including very poor 80%, poor 100%, intermediate 88%, and good 92%. CRPR responses were also observed across all IPSS-R prognostic risk categories, very high 42%, high 17%, and low intermediate 36%.

Median duration of response was 12.2 months with a range of 0.1 to 24.2 plus months and median duration of treatment was 8 months with a range of 1.3 to 27.3 months. Time to first and best responses was one and four months, respectively. The majority of adverse events were grade 1 and 2 other than hematologic toxicity, which could be from disease or treatment. Patients also did experience genitourinary toxicities including hematuria and dysuria, but there were genitourinary management strategies that mitigated the side effects. The majority of patients who experienced GU AEs is greater than or equal to grade 2 were successfully managed and continued to receive the doublet on study.

In conclusion, the efficacy and safety of oral rigosertib and azacitidine in combination is favorable as first line therapy in patients with higher-risk HMA-naive MDS, with an overall response rate of 90% and a CR rate of 34%. The transfusion independence of 30% in higher-risk MDS patients is clinically meaningful and needs to be confirmed in a large randomized phase 3 study. Oral rigosertib in combination with azacitidine was well tolerated and has now been administered in repetitive cycles for more than two years. Rigosertib is an attractive combination partner for azacitidine because of the oral formulation, non-overlapping toxicity, mechanism of action, and synergy. Based on the efficacy results and favorable safety profile, a pivotal phase 2/3 adaptive design study in higher-risk HMA-naive MDS population is planned.

**Reference:** Navada SC, et al. Phase II Study of Oral Rigosertib Combined with Azacitidine (AZA) As First Line Therapy in Patients (Pts) with Higher-Risk Myelodysplastic Syndromes (HR-MDS). Abstract 566. ASH 2019.
https://ash.confex.com/ash/2019/webprogram/Paper131676.html