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## **A Phase 1/2 Trial of Low-Dose Continuous Azacitidine in Combination with Lenalidomide and Low-Dose Dexamethasone in Relapsed/Refractory Multiple Myeloma**

Welcome to *Managing Myeloma*. My name is Beth Faiman, I am a nurse practitioner at the Cleveland Clinic in Cleveland, Ohio, and today I'd like to review a phase 1/2 trial of low-dose continuous azacitidine in combination with lenalidomide and dexamethasone in patients with relapsed and refractory multiple myeloma. As you are well aware, epigenetic changes can contribute to the evolution of therapy resistant myeloma plasma cell clones. The DNA methyltransferase inhibitor azacitidine can overcome some of this resistance in combination with lenalidomide and dexamethasone primarily thought through reactivation of genes required for apoptosis and adaptive immune response. So here we reported the results of a phase 1/2 study which used azacitidine in combination with lenalidomide and dexamethasone orally in patients with relapsed/refractory myeloma. The patients received either 25 mg of lenalidomide if they had adequate renal function or 10 mg if the GFR of patients was between 30 and 59 ml/min. That was given in combination with five cohorts of escalating dosing of azacitidine subcutaneously. The first cohort was 30 mg/m<sup>2</sup> weekly and we escalated up to a dose of 50 mg/m<sup>2</sup> twice weekly. The dose-limiting toxicities were first and foremost evaluated in this phase 1/2 design, and the response was according to the International Myeloma Working Group 2011 response criteria. So the primary endpoint was safety in this phase 1 design and then efficacy included the secondary endpoint such as progression-free survival and overall survival. We also in the study had correlative analysis of the azacitidine activating enzyme in the plasma cell activity, cytidine deaminase or CDA was by Zymo Research Corporation in California and that was obtained weekly for four weeks and then every 28 days among the patients that were on study. Between 2010 and 2016, 51 patients with relapsed/refractory myeloma were evaluated for this study but 43% were actually enrolled and took drug, there were 26 in the phase 1 portion and then there were 17 in the phase 2 portion. The median age of patients on study was 62.5 years and females represented 56% of the cohort. Impressively, there were 77% of patients that were refractory to lenalidomide, which was important because the response that we were assessing. Two dose-limiting toxicities were observed at the 40 mg/m<sup>2</sup> cohort such as neutropenic fever and GGT elevation, however, patients did tolerate 50 mg/m<sup>2</sup> in six of six patients in a future cohort in those patients with a GFR greater than 60 ml/min. For the extension study, azacitidine 50 mg/m<sup>2</sup> subQ was selected as the appropriate dose and the lenalidomide was dosed 25 mg PO days 1-21 of a 28-day cycle with dexamethasone. The toxicities in this cohort in the extension study primarily were mostly hematologic such as neutropenia, anemia, and lymphopenia, and we did see about five patients had infections. At a median follow-up of 39 months, the overall response rate was 28% and the clinical benefit rate was 35%, so there was some activity among those patients that had the azacitidine, len-dex; six patients had achieved a partial response and a very good partial response was achieved as well in a number of patients. The plasma cell median CDA activity was also assessed and at screening was 1233 and some patients who had the lower levels actually saw an inverse correlation with clinical benefit rate, which was interesting. In conclusion, azacitidine at a dose of 50 mg subQ bi-weekly

and given in combination with lenalidomide and dexamethasone in patients with adequate renal function can have some activity. Interestingly enough, again those patients who had a lower plasma CDA of less than 1000 mU/ml actually had a better clinical benefit rate of 50% and perhaps that would be taken into consideration in future selection. Thank you so much for viewing this activity.

**Reference:** Khouri J, et al. A Phase 1/2 Trial of Low-Dose Continuous Azacitidine in Combination with Lenalidomide and Low-Dose Dexamethasone in Relapsed/Refractory Multiple Myeloma. IMW 2019. SP-108.