Iipilimumab Exposure-Response (E-R) Analysis of Overall Survival (OS) in Patients with Advanced Melanoma

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Objectives: The human monoclonal antibody ipilimumab selectively binds CTLA-4 on a subset of T-cells, thereby augmenting anti-tumor immune response. Based on an earlier analysis, steady-state trough concentration (Cminss) was a significant predictor of OS in previously treated advanced (stage III/IV metastatic) melanoma patients[1]. Our objective was to describe the relationship between Cminss and OS in both previously treated, and chemotherapy naive advanced melanoma patients using a pooled analysis.

Methods: An E-R of OS analysis was performed with data from four Phase 2 ipilimumab monotherapy studies in previously treated advanced melanoma patients and one Phase 3 study of ipilimumab administered with dacarbazine in chemotherapy naive advanced melanoma patients (N=1007, ipilimumab doses of 0.3, 3, and 10 mg/kg). The relationship between Cminss and OS was characterized using Cox proportional-hazards (CPH) models. A full CPH model was developed by incorporating all covariates of interest with appropriate functional forms into the base model.

Results: Figure 1 shows the estimated hazard ratios (95% CI) for predictors in the CPH model. Notably, prior chemotherapy is not a predictor of OS. Higher Cminss is associated with a decrease in the risk of death. A poor ECOG performance score (ECOG > 0), high baseline lactate dehydrogenase (LDH), and advanced M-stage at study entry (M1C) increase the risk of death. There was also a significant interaction between Cminss and dacarbazine (hazard ratio 95% CI does not include 1.0) suggesting a reduced ipilimumab effect in the presence of dacarbazine.

Conclusions: The risk of death for previously treated and chemotherapy naive advanced melanoma patients decreased with increasing ipilimumab Cminss over the range of exposures achieved with the doses evaluated; however, concomitant dacarbazine administration reduced this benefit. The risk of death increased with high baseline LDH, and in patients with ECOG > 0 and M1C metastatic disease.

References: