Model-Based Analysis of the Relationship between Pembrolizumab Exposure and Response in Melanoma

Manash S. Chatterjee1*, David C. Turner1, David Dong1, Malidi Ahamadi1, Julie Stone1, Dinesh P. De Alwis1, Anna Kondic1

1Merck Research Laboratory, Merck & Co., Inc., USA

Objectives: Pembrolizumab is a PD-1 antibody that has shown robust antitumor activity in multiple tumor types. Here we characterized the relationship between exposure to pembrolizumab in serum (i.e. AUC over 6 weeks at steady state) and melanoma antitumor response measured as the sum of the longest dimension of tumor lesions across protocols KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006.

Methods: Pooled data from 1366 subjects treated for melanoma was first graphically analyzed to evaluate changes in tumor size at 24 weeks versus exposure. Logistic regression analysis quantified the relationship between exposure and ORR. Longitudinal tumor size data were next analyzed using a nonlinear mixed effects model. The structural model was parameterized with both first-order tumor growth and shrinkage rates, assuming that only some fraction of lesions was accessible for antitumor effect. Patient- and study-specific factors were explored as covariates to explain variability on model parameters. The influence of pembrolizumab exposure was included as an additional estimated parameter on the modeled tumor shrinkage rate. Due to co-linearity of patient ipilimumab treatment history and dose, independent exposure-response parameters were estimated for the ipilimumab-naive and ipilimumab-experienced subpopulations. Simulations were conducted with final parameter estimates, and for graphical presentation, converted to response categories analogous to RECIST.

Results: Pembrolizumab exposures showed a small and statistically insignificant influence on the final model estimated tumor decay parameter. A covariate search on the base structural model revealed PD-L1 expression and baseline tumor size to have a significant association with estimated rate of tumor size decline, while ipilimumab treatment history and baseline tumor size were predictive of the fraction of tumor responding. In addition, BRAF mutation status was related to the tumor growth rate.

Conclusions: This exposure-response analysis indicates the currently approved 2 mg/kg Q3W dose is near the maximal response plateau of the exposure-response curve. Baseline tumor size, ipilimumab treatment history, BRAF mutation, and PD-L1 expression status are significant predictors of model parameters.