Model-Based Pooled Analysis of Exposure and Safety of Pembrolizumab with Advanced Melanoma and Non-Small Cell Lung Carcinoma (NSCLC)

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Objectives: Pembrolizumab, a humanized monoclonal IgG4 antibody against PD-1 that elicits T-cell–mediated antitumor activity, is approved in several countries for the treatment of advanced melanoma. The objective of this model-based analysis was to characterize exposure-response relationships for pembrolizumab with respect to safety in patients with melanoma and non-small cell lung carcinoma (NSCLC) treated in KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006. We also sought to estimate the impact of potential predictors on the frequency of adverse events (AEs).

Methods: Data from 1720 patients who received pembrolizumab 2 or 10 mg/kg every 3 weeks (Q3W) or 10 mg/kg Q2W were pooled. Exposure was defined as the area under the serum concentration curve over 6 weeks (AUCss-6wk) to account for the different dosing frequencies. Safety was assessed based on the incidence of AEs of special interest (AEOSIs) related to pembrolizumab’s immune-mediated mechanism of action. Exposure-response relationship of pembrolizumab for safety was investigated using a non-linear mixed effects modeling approach.

Results: A two-compartment population PK model with linear clearance from the central compartment described pembrolizumab concentration. The PK profile of pembrolizumab indicated a low clearance (~0.2 L/day), limited volume of distribution (~7 L) and low variability (15 -30%), consistent with other monoclonal antibodies. A flat relationship for the occurrence of adverse event of special interest (AEOSIs) in this population was also suggested by logistic regression. Among the investigated covariates, duration of treatment was found to be a significant predictor for the occurrence of AEOSIs.

Conclusions: Pembrolizumab exhibits no exposure-response relationships for safety over the clinically tested dose range in melanoma and NSCLC patients, suggesting that no significant clinical benefit would be observed at higher dose levels. These results support the use of the approved pembrolizumab dose of 2 mg/kg Q3W.