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Pooled Population Pharmacokinetic and Immunogenicity Analysis of Pembrolizumab Using Data from KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006

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Objectives: Pembrolizumab is a potent antibody against the cellular immune 'switch' programmed death receptor 1 (PD-1) that has shown robust antitumor activity in patients with advanced solid tumors. We characterized the pharmacokinetic (PK) properties of pembrolizumab and quantified the effect of intrinsic and extrinsic factors on exposure. To investigate the immunogenicity potential of pembrolizumab, the development of antidrug antibodies (ADA) response on efficacy or safety was established.

Methods: Pooled data from KEYNOTE-001 (NCT01295827), KEYNOTE-002 (NCT01704287) and KEENOTE-006 were used to characterize the pembrolizumab serum concentrations over time in patients with advanced or metastatic melanoma and non-small cell lung carcinoma. The relationships between PK parameters and various baseline covariates were examined. Simulations were performed to evaluate the magnitude of the exposure effects of any covariates included in the model in order to assess their clinical relevance.

Results: The pharmacokinetics of pembrolizumab in the 1 to 10 mg/kg dose range was described by a two-compartment pop-PK model with linear clearance from the central compartment. 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. The effect of age, sex, geographic location, baseline ECOG PS, eGFR, AST, bilirubin, albumin, glucocorticoid coadministration, tumor type and burden, and prior ipilimumab on pembrolizumab exposure is limited, as alterations of 20% or less are predicted by the PopPK model. Thus, these marginal effects on exposure were clinically insignificant on PK properties of pembrolizumab. Of 392 patients evaluable for ADA, 1 (<1%) developed confirmed treatment-emergent ADA with no impact on efficacy or safety.

Conclusions: There was no clinically meaningful effect of baseline clinical factors on pembrolizumab exposure. Pembrolizumab has limited potential to elicit the formation of ADA. These results support the use of the approved pembrolizumab dose of 2 mg/kg Q3W.