Population pharmacokinetic analysis of avelumab in different cancer types

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Objectives: Avelumab is a human anti–PD-L1 IgG1 antibody that has shown promising efficacy and manageable safety in multiple tumors. Avelumab is approved in the US for treatment of metastatic Merkel cell carcinoma (mMCC) and platinum-treated advanced urothelial carcinoma, and in clinical development in other cancer types. This analysis presents a population pharmacokinetic (PopPK) analysis accounting for covariates after multiple dose infusions, considering models for time-varying clearance (CL) and covariate relationships.

Methods: Pharmacokinetic and covariate data from clinical studies EMR.100070-001 (phase 1, various cancers), -002 (phase 1, various cancers in Japan), and -003 (phase 2, mMCC), comprising 1827 patients with 14 different cancer types, were used to build the PopPK model using NONMEM software. Two-compartment models with covariates including time-constant and alternative time-varying CL (1), in addition to time-varying covariates (2), were tested.

Results: A two-compartmental model incorporating time-varying CL (1) was found to provide the best description of avelumab concentration, which was observed to increase over time. CL was found to decrease relative to baseline in patients with head and neck cancer and MCC by 24.7% and 32.1%, respectively, although this decrease was not considered clinically relevant (CL_{baseline}=0.0308 L/h; T_{50/reference}=68.4 days). Other significant covariates on CL at baseline included body weight, serum albumin, tumor burden, age, sex, race, eGFR, immunogenicity, platelet count, AST, concomitant opioid use and previous use of biologics, although only weight was clinically relevant. Incorporation of time-varying covariates (2) did not result in model improvement, as judged by plots of conditional-weighted residuals against time.

Conclusions: The PopPK model for avelumab incorporating time-varying CL described the observed data well. Identified covariates did not warrant dose adjustment.