Clearance over time and effect of response in the pharmacokinetics of avelumab

Justin Wilkins¹, Shaonan Wang², Brigitte Brockhaus², Haiqing Dai³, Yulia Vugmeyster³, Berend Neuteboom³, Satjit Brar⁴, Carlo Bello⁴, Janet Wade¹, Akash Khandelwal² & Pascal Girard⁵

¹Occams, Amstelveen, Netherlands ²Merck KGaA, Darmstadt, Germany ³EMD Serono, Billerica, MA, USA ⁴Pfizer, La Jolla, USA ⁵Merck Institute for Pharmacometrics, Lausanne, Switzerland

Objectives: Time-dependent clearance (CL) has been reported recently for some immune checkpoint inhibitors (1). 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. We present comparisons between several population pharmacokinetic models of avelumab, investigating time-varying clearance (TVCL), covariate effects (2), and impact of response status.

Methods: Data from three clinical trials involving 1827 patients were used for modeling. Two approaches for describing TVCL were used (1,3). Seven model variants were compared: four two-compartment base models (one single-dose [SD] and three multiple-dose [MD] models, with and without TVCL), and three of these models after covariate inclusion. CL from the final SD and MD models was compared by objective response status (RECIST 1.1).

Results: Differences between SD model predictions were small; post-hoc CL estimates were slightly lower in the MD models if the TVCL term was not included. A model incorporating TVCL was found to be best in the MD context (1). Steady state mean ± standard deviation CL in responders and non-responders for patients with MCC (n=88) from the final MD model were 0.018 ± 0.005 and 0.023 ± 0.009 L/h, respectively. Corresponding CL values from the final SD model were 0.028 ± 0.007 and 0.033 ± 0.009 L/h, respectively.

Conclusions: TVCL was identified for mMCC, potentially as a result of disease response altering the CL distribution between baseline and steady state in mMCC. Accounting for time variation in CL was critical for adequately characterizing the avelumab dose-exposure relationship.