Assessment of Pembrolizumab (MK-3475) Dosing Strategy Based on Population Pharmacokinetics and Exposure-Response Models

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Objectives: Most monoclonal antibodies (mAbs) have generally some contribution of body size to pharmacokinetic variability; therefore, dosing of mAbs is mostly based on body weight [1]; early pembrolizumab studies (pembrolizumab targets the programmed cell death 1 [PD-1] receptor) followed this approach. The dosing strategy of pembrolizumab was reassessed using population pharmacokinetics (PopPK) and exposure-response models to determine if weight-scaled dosing was necessary.

Methods: A PopPK model was fit to pooled data (KEYNOTE-001, 002 and 006). Model parameter estimation included power function exponents (α) describing the weight effect on CL and V. Predicted AUC distributions with fixed dosing were compared to the range of exposures from the pembrolizumab doses evaluated in early studies (2 mg/kg Q3W, 10 mg/kg Q3W/Q2W) to check whether fixed dosing would maintain exposures within the range of clinical experience. The safety profile has been similar and the efficacy near maximal across this entire dose range.

Results: CL and V were allometrically scaled by weight, with an estimated α of 0.578 [0.481, 0.666] and 0.492 [0.432, 0.553], respectively. The intermediate values of ~0.5 estimated for the α between extremes of 0.0 (no relation to weight) and 1.0 (perfect weight scaled) suggest that the 2 dosing approaches would perform similar. Simulations of exposures at 200 mg Q3W indicate these to lie within the range of clinical experience associated with near maximal efficacy and good tolerability and to be close to those obtained with the 2 mg/kg Q3W dose approved in several countries for melanoma, without substantive change in PK variability (Figure 1).

Conclusions: Both weight-based as well as fixed-dose regimens would be appropriate for pembrolizumab. Doses of 200 mg and 2 mg/kg provide similar exposure distributions, with no advantage to either dosing approach.