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DEVELOPMENTAL THERAPEUTICS—IMMUNOTHERAPY

A six-weekly (Q6W) dosing schedule for pembrolizumab based on an exposure-response (E-R) evaluation using modeling and simulation.

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Abstract

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Background: Pembrolizumab is currently approved for use in multiple cancer indications at a dose of either 200 mg or 2 mg/kg Q3W. An alternative extended dosing regimen would provide convenience and flexibility to patients and prescribers. Robust characterization of

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pembrolizumab pharmacokinetics (PK) and E-R relationships for efficacy and safety allow the use of model-based approaches to support alternative dosing regimens. **Methods:** The dose for a Q6W schedule was selected by matching exposures with the approved Q3W (200 mg and 2 mg/kg) regimens; efficacy and safety are bridged based on E-R assessments. Exposures were simulated using the established population PK model of pembrolizumab that adequately described PK across multiple tumor types. Regimens are compared on - A) Exposure metrics at steady state: AUCss or time-averaged concentration (Cavg,ss) and trough concentrations (Cmin,ss); B) Predicted clinical endpoints (e.g., objective response rate) in patients with multiple approved tumor types. Safety at the Q6W schedule is bridged by ensuring predicted peak concentrations at steady state (Cmax,ss) are below those at the maximum clinically administered and well-tolerated dose of 10 mg/kg Q2W. **Results:** The 400 mg Q6W dosing regimen had similar predicted exposures (Cavg,ss or AUCss, geometric mean (GM) ~1% higher) compared to those achieved at 200 mg Q3W. Less than 1% subjects had Cmin,ss lower than that for 200 mg Q3W. The GM of predicted Cmax,ss for 400 mg Q6W was ~65% lower than for 10 mg/kg Q2W. Given the similar exposures and established E-R relationships for pembrolizumab over a 5-fold range of clinically tested doses, the clinical outcomes achieved with 400 mg Q6W are predicted to be similar as with 200 mg Q3W across tumor types. **Conclusions:** A 400 mg Q6W dosing regimen of

pembrolizumab leads to exposures that are similar to the approved 200 mg Q3W dosing regimen. Based on the robust understanding of pembrolizumab clinical pharmacology, including well-established E-R profiles, such a less frequent dosing regimen is expected to produce similar efficacy, safety, and benefit-risk profile in all clinical treatment settings where 200 mg Q3W pembrolizumab is currently approved.

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