Flat Dose Selection of Urelumab in Cancer Patients

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Objective/Purpose: Population PK analysis to support flat dose selection of Urelumab

Methods: Population PK (PPK) analysis was employed to support dose selection of urelumab using serum concentrations (N=3103) -time data from 346 pts in monotherapy trials (CA186001, 006 and 011). The evaluable urelumab dose range was 0.1 to 15 mg/kg administered every 3 or 6 weeks. A base model was developed to describe PK of urelumab, along with inter-individual variability (IIV) on PK parameters, residual variability (RUV) (i.e. combined proportional and additive error) and effect of baseline body weight (BBWT) on PK parameters. A full model was developed including all prespecified covariates parameter relationships. Urelumab exposure are related to severity of transaminitis and exposure resulting from 0.1 mg/kg are shown to be in safe range.1 Simulations were performed using full model to achieve target exposures in cancer patients across body weights observed in the clinical trials.

Results: Urelumab PK was best described by a 2 compartment model with parallel linear and non-linear CL. The linear portion represents the FcRn mediated CL and non-linear component represents target mediated CL. The linear CL was 0.173 L/day, volume of distribution in the central compartment (VC) was 3.99 L. The maximum rate of non-linear elimination (Vmax) was 2.04 mg/day, and the concentration that achieved 50% of Vmax (Km) was 3.57 ug/mL. The IIV with full model on linear CL, VC and Vmax were 60.3%, 19.7% and 5.6% respectively. The effect of BBWT, baseline LDH, age on CL and, BWT on VC, Q and V2 were found to be statistically significant (effect size of +/-20%). The simulated exposure from an 8 mg flat dose was similar to the observed exposures from 0.1 mg/kg that had been shown to safe and well tolerated.1

Conclusion: An 8 mg flat dose urelumab is predicted to maintain target exposures, and was shown to be safe in cancer patients who had previously received weight based dosing.