Population Pharmacokinetics of Tislelizumab in Patients with Advanced Tumors

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Background

Tislelizumab, an investigational humanized IgG4 monoclonal antibody with high affinity and specificity for PD-1, was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy. It has shown robust antitumor activity and was generally well-tolerated in patients with advanced solid tumors and with classical Hodgkin lymphoma (cHL). The objectives of this analysis were to develop a population pharmacokinetics (popPK) model and quantify the impact of demographic and disease characteristics on tislelizumab PK.

Methods:

PopPK analysis was conducted using pooled data from three studies (001, 102, 203) in patients with advanced solid tumors and cHL. The dataset contained 5935 PK observations from 798 patients. A nonlinear mixed-effects modeling approach with first-order conditional estimation with interaction (FOCEI) method in NONMEM was used for the analysis. Covariates related to baseline demographics, tumor type, and tumor size on tislelizumab PK were investigated. Covariates were selected using a forward addition and backward elimination method.

Results:

Tislelizumab PK exhibited linearity over a dose range of 0.5 - 10 mg/kg without time-varying clearance. A three-compartment model with first-order elimination from the central compartment, and redistribution into the peripheral compartments best described the PK of tislelizumab. Clearance (CL), volume of distribution of central compartment (Vc), and terminal half-life were estimated to be 0.164 L/day, 2.92 L, and 25.9 days, respectively. Baseline tumor size, albumin and tumor type were significant covariates on CL, while body weight, sex and tumor type were significant covariates on Vc. However, sensitivity analysis showed that the impact of these covariates on tislelizumab exposures (area under the curve, maximum and trough concentrations) was not clinically significant.

Conclusions:

The final popPK model adequately described the observed tislelizumab PK. Results support the use of the current clinical dose of 200 mg Q3W and no dose adjustment is necessary based on patients' age, body weight, race, sex, tumor type and tumor size.