Population Pharmacokinetics for Atezolizumab in Cancer Patients
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Objectives: Atezolizumab, a humanized immunoglobulin G1 (IgG1) monoclonal antibody that targets human programmed death-ligand 1 (PD-L1) on tumor cells and immune cells, was recently approved in the US in bladder cancer and is being developed to treat patients with various solid tumors. The aim of the analysis was to characterize atezolizumab pharmacokinetics (PK) and evaluate impact of clinically relevant covariates on atezolizumab pharmacokinetics.

Methods: The PK of atezolizumab in serum was evaluated in 472 PK evaluable patients with 4563 samples from the two Phase I studies (PCD4989g and JO28944) who received 1 to 20 mg/kg of atezolizumab every 3 weeks (q3w) single agent, or the fixed 1200 mg dose q3w. NONMEM was used for pharmacokinetic analysis. The impact of about 20 covariates (i.e. body size, gender, disease characteristics, organ function markers) on the PK of atezolizumab was investigated. Covariates were selected using forward addition followed by backward elimination method.

Results: Atezolizumab exhibited linear pharmacokinetics over a dose range of 1 – 20 mg/kg, including the 1200 mg dose. The population clearance (CL), volume of distribution (V1), and terminal half-life estimates of 0.200 L/day, 6.91 L, and 27 days, respectively, were consistent with expectations for an IgG1. Body weight was identified as a statistically significant covariate on both CL and V1. In patients who were positive for anti-therapeutic antibodies (ATA), CL was estimated to be 16% higher than in patients with negative ATA. Albumin and tumor burden were also identified as statistically significant covariates on CL. In females, V1 and V2 would be 13% and 27% lower than in males, respectively. No covariate effect resulted in more than 32% change in exposure (i.e., AUCss) from the typical patient receiving 1200 mg q3w.

Conclusions: A population PK model was developed for atezolizumab in cancer patients. Covariates had minimal impact on steady-state exposure. The data support the recommended 1200 mg fixed dose q3w for all patients.