A PKPD analysis of circulating biomarkers and their relationship to the tumor size time-course in atezolizumab treated non-small cell lung cancer patients

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Objectives: To explore the utility of a pharmacometric framework in assessing circulating biomarkers as predictors of tumor response following treatment with atezolizumab (anti-PD-L1).

Methods: Serum atezolizumab PK and 94 plasma biomarkers data were analyzed in 88 relapsed/refractory non-small cell lung cancer (NSCLC) patients who received IV q3w doses of atezolizumab from 10-20 mg/kg and 1200 mg in the PCD4989g study [1]. Biomarkers were screened for biological relevance, on-treatment changes from baseline, and trends in relation to atezolizumab exposure and tumor size. Indirect response PKPD models and tumor growth inhibition (TGI) models [2] were developed to describe the longitudinal PKPD data and tumor size (the sum of the longest diameter, SLD). The atezolizumab AUC and various metrics of the biomarkers were assessed as predictors of the tumor shrinkage rates, along with selected baseline factors. A drop-out model was developed to assess TGI model performance. Software: NONMEM-7.3.

Results: Data were adequately described by the models. Atezolizumab exposure (AUC) and model predicted levels of Interleukin 18 (IL-18) relative change from baseline at day 21 (RCFBIL-18,d21) significantly correlated with tumor size shrinkage. While AUC was a major predictor of tumor shrinkage (ΔOFV=-27), the effect was estimated to dissipate with an average half-life of 80 days, and RCFBIL-18,d21 appeared important for the duration of the response (Figure 1). Baseline metastatic sites, liver metastases at baseline, and smoking status were significant covariates for baseline tumor size, tumor growth rate, and tumor shrinkage rate, respectively.

Conclusions: 1) Circulating IL-18 may be a useful predictive marker for long-term tumor response in NSCLC patients, 2) A pharmacometric framework was useful in guiding the search of predictive biomarkers


![Fig 1. Predictions of the SLD time-course for the typical patient in the final TGI model (solid blue and green lines). The predicted typical patient is a former/current smoker, has two or less metastases at baseline and no liver metastases at baseline. The different shades of blue and green indicate different simulations where different values of RCFBIL-18,d21 were applied. For all predictions, the AUC corresponded to the typical value given a fixed dose of 1200 mg.](image-url)