

Population pharmacokinetics and clinical outcome of nivolumab in Japanese patients with non-small cell lung cancer

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BACKGROUND: Nivolumab is an anti-programmed death-1 (PD-1) antibody used for the treatment of various cancers including non-small cell lung cancer (NSCLC). Nivolumab is currently indicated to use at a fixed dose for all NSCLC patients; however, various hurdles in the nivolumab therapy such as severe immune-related adverse events, loss of response and the high cost of medication suggest the necessity of more rational personalized dosing. Nevertheless, nivolumab pharmacokinetics (PK) and the exposure-response relationship have not been studied well in a real-world setting. The aims of this study were to characterize the nivolumab PK and examine the PK-clinical outcome relationship in patients with NSCLC using the data obtained during routine clinical care. **METHOD:** Clinical data were obtained from Japanese NSCLC patients treated with nivolumab monotherapy. All patients received 240 mg of nivolumab once every 2 weeks. Discarded blood samples collected for laboratory tests were obtained for the PK assessment. Nivolumab plasma concentration was determined by a validated LC-MS/MS assay (Irie et al. TDM, 2018). Population PK analysis was performed with a 2-compartment model using NONMEM. Since PK data were mostly pre-dose concentrations, only clearance was estimated with the other parameters adapted from the literature (Osawa et al. CCP, 2019). The effect of patient-specific factors on clearance including body weight, age, sex, serum albumin, eGFR, performance status, PD-L1 expression in tumor and neutrophil to lymphocyte ratio were evaluated as part of the covariate analysis. **RESULTS:** A total of 223 plasma concentrations collected from 34 patients were available. The median (min-max) age and weight were 69 years (38-83) and 62.7 kg (36.8-80.5), respectively. The mean clearance estimate was 5.8 mL/h (95%CI: 5.2-6.4). Inclusion of serum albumin and eGFR significantly improved the model fit. Length of nivolumab treatment was negatively correlated with the nivolumab clearance. **CONCLUSION:** The nivolumab PK was characterized in Japanese patients with NSCLC. Serum albumin and eGFR found to be significant covariates on clearance. Our results indicate that the higher nivolumab clearance may be associated with the shorter length of nivolumab treatment. Further study is warranted to explore the optimal dosing regimens for those patients to improve treatment durability and sustainability.

Keywords: Population pharmacokinetics, antibodies, cancers, real-world setting