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Population Pharmacokinetics of Nivolumab in Japanese Patients with Nonsmall Cell Lung Cancer

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Background: Nivolumab is an antiprogrammed death-1 (PD-1) antibody used for immuno-oncological therapy of various cancers, including nonsmall cell lung cancer (NSCLC). This study aimed to characterize the real-world population pharmacokinetics (PK) of nivolumab in patients with NSCLC.

Methods: PK samples were collected by opportunistic sampling of Japanese patients with NSCLC treated with nivolumab monotherapy. Population PK analysis was performed using a two-compartment model in Nonlinear Mixed Effect Model. Patient-specific factors such as body weight, age, sex, serum albumin, estimated glomerular filtration rate, performance status, programmed cell death receptor ligand 1 expression in tumors, and treatment periods were evaluated as potential covariates for clearance.

Results: A total of 223 serum samples collected from 34 patients were available for analysis. The median (min–max) age and weight were 69 years (38–83 years) and 62.7 kg (36.8–80.5 kg), respectively. The mean (95% confidence interval) clearance estimate was 0.0064 L/h (0.0058–0.0070 L/h). The inclusion of the ALB level, estimated glomerular filtration rate, and treatment period significantly improved the model fit.

Conclusions: A real-world nivolumab population PK model was developed using an opportunistic sampling strategy in Japanese patients with NSCLC. Further studies are warranted to characterize the exposure–response relationship and determine the optimal dosing regimens for these patients.

Key Words: nivolumab, population pharmacokinetics, real-world data, nonsmall cell lung cancer

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BACKGROUND

Nivolumab is a fully human immunoglobulin G4 monoclonal antibody that inhibits the binding of programmed cell death protein 1 (PD-1) to programmed death ligand (PD-L1) and PD-L2. It is widely used to treat various cancers, including nonsmall cell lung cancer (NSCLC). It is the first-line treatment for patients with advanced NSCLC.[1,2] Recent clinical trials have demonstrated that nivolumab in combination with ipilimumab results in prolonged overall survival compared with conventional chemotherapy.[3] Notably, some patients treated with nivolumab responded well and showed long-term survival (termed "durable response"). A pooled analysis of clinical studies on advanced NSCLC reported that the estimated 4-year overall survival rate was 14% [95% confidence interval (CI): 11%–17%] in all patients receiving nivolumab (n = 664) compared with 5% (95% CI: 3%–7%) in patients treated with docetaxel.[4]

Nivolumab was initially approved with a weight-based dose of 3 mg/kg every 2 weeks (Q2W). In 2016, the US Food and Drug Administration revised the nivolumab dosage regimen to a fixed dose of 240 mg once Q2W for most approved indications such as renal cell carcinoma, metastatic melanoma, and NSCLC.[5] Another fixed-dose regimen of 480 mg every 4 weeks (Q4W) was later approved as an alternative to 240 mg Q2W. These fixed-dosing regimens were approved based on population pharmacokinetic (PK) modeling and simulation analyses, dose–exposure–response relationship data for efficacy and safety, and clinical safety profiles.[6,7] Fixed-dosing regimens can reduce dosing errors and simplify the drug preparation procedure, thereby contributing to consistent dosing.[8] Furthermore, the Q4W regimen can reduce the number of patient hospital visits for drug administration, which is likely to reduce the overall burden on both patients and clinical staff. This may be beneficial, especially for long-term treatment. However, the total dose amount of nivolumab with the fixed-dosing regimens is

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higher in patients with a body weight <80 kg compared with weight-based dosing. This indicates that more than 75% and 95% of Japanese adult men and women, respectively,[9] receive a higher dose with the fixed-dosing regimens than with the original weight-based dosing regimen. A personalized dosing strategy may benefit Japanese patients from a financial standpoint[10]; however, real-world evidence, such as clinical nivolumab pharmacology data, is still limited in the Japanese population.

The PK of nivolumab has been well characterized in global clinical trials during the drug development process.[11–13] In earlier population PK analyses, body weight, estimated glomerular filtration rate (eGFR), sex, and performance status were identified as significant covariates of nivolumab clearance (CL) and body weight and sex were associated with volume of distribution. Although these PK properties have been characterized in large populations, the PK properties of nivolumab in real-world clinical settings are not fully understood. In this study, we conducted a real-world population PK analysis using prospectively collected nivolumab serum concentration data obtained by opportunistic sampling of Japanese patients with NSCLC.

METHODS

Patients

Japanese patients with NSCLC treated with nivolumab monotherapy (flat dose: 240 mg/individual) at the Kobe City Medical Center General Hospital (Kobe, Japan) were enrolled in this study. Patients without remnant serum samples were excluded from this study. The following baseline patient information was collected from the electronic health records: age, sex, body weight, body surface area (BSA), serum albumin (ALB), eGFR (calculated using established formulas for the Japanese population[14]), histology, Eastern Cooperative Oncology Group performance status (ECOG PS), PD-L1 expression in tumors, and treatment period. This study was conducted in accordance with the principles of the Declaration of Helsinki. The studies involving human participants were reviewed and approved by the Ethics Committee of Kobe City Medical Center General Hospital (Approval Number: Zn190502).

Sample Collection and Pharmacokinetic Measurement

Remnant serum samples collected as part of routine laboratory tests in clinical practice were used for nivolumab concentration measurements, which were determined using a validated Liquid Chromatograph-tandem Mass Spectrometer assay.[15] In brief, nivolumab was captured using protein A resin (A Sepharose Fast Flow, BD Biosciences, San Jose, CA) and digested with trypsin. The ASGITFSNSGMHWVR peptide (multiple reaction monitoring [MRM] transition: m/z 550.6/661.4) was detected as a surrogate peptide of nivolumab using a QTRAP 4500 triple quadrupole mass spectrometer (AB Sciex, Framingham, MA). The lower limit of quantification for the assay was 5 mcg/mL. The samples were stored in serum at −30°C and measured within 6 months. The stability conditions for nivolumab were as follows: serum, −30°C for 33 months.

Pharmacokinetic Analysis

Nivolumab PK data were analyzed using the nonlinear mixed-effects modeling program Nonlinear Mixed Effect Model (version 7.41; ICON Development Solutions, Ellicott City, MD). A two-compartment model with first-order elimination was used as a structural model, according to previously reported nivolumab PK models.[11,12,16] We used the first-order conditional estimation method with interaction (FOCE-I) for parameter estimation.

The interindividual variability (IIV) in PK parameters was assessed using an exponential error model as follows:

$$\theta_i = \theta_{Tv} \times \exp(\eta i)$$

where θi is the PK parameter estimate of the individual (i), θtv is the typical value of the PK parameter in the study population, and ηi is an interindividual random effect for the individual (i) with a mean of 0 and variance of ω^2. The residual error model was tested using a proportional error model, additive error model, and combined residual error model.

Covariate Analysis on Nivolumab Clearance

Covariate analysis was conducted using a stepwise method based on the likelihood ratio test to evaluate factors influencing nivolumab CL. Potential covariates (age, sex, body weight, BSA, ALB levels, eGFR, histology, ECOG PS, and PD-L1 expression in tumors) were added to the base model. In forward inclusion, a drop in the objective function value (OFV) of more than 3.84 was considered statistically significant ($P < 0.05$). Body weight, BSA, ALB levels, and eGFR were measured approximately every 2 weeks and included as time-varying covariates. After developing a full covariate model, each factor was removed in the backward elimination step with more restrictive criteria (>6.63 drop in OFV, $P < 0.01$). The following equation was used for the categorical (0 or 1) and continuous covariate values:

$$\theta_i = \theta_{Tv} \times \theta cov^{covi} \text{ Categorical Covariates}$$

$$\theta_i = \theta_{Tv} \times \left(\frac{covi}{covmedian} \right)^{\theta cov} \text{ Continuous Covariates}$$

where θi is the PK parameter estimate of an individual (1) and θtv is the typical value of the PK parameter in the study population. θcov is the covariate coefficient, COVi is the individual (2) value of the covariates, and COVmedian is the median value of the continuous covariates in the study population.

The effect of treatment duration on nivolumab CL was evaluated according to previous studies.[11,12] The time-varying nivolumab CL was described using a sigmoidal E_{max} model, as follows:

$$CL_{t,\ i} = CL_i \cdot exp\left(\frac{E_{maxi} \cdot t^{\gamma}}{T50_i^{\gamma} + t^{\gamma}} \right)$$

where $CL_{t,i}$ represents the CL of patient i at a given time t and E_{max} represents the estimate of the maximal change in CL.

The T50 parameter represents the time at which the change in typical CL is 50% of $E_{max,}$ and γ represents the Hill coefficient. For the sigmoidal E_{max} model, both the estimated and fixed parameters were attempted. The fixed parameters for E_{maxi} (−0.285), T50 (1510 h), and γ (2.020) were adapted from a previous study by Osawa et al.[12]

Final Model Evaluation

Goodness-of-fit plots were used to identify potential biases due to model structure. The population prediction (PRED) versus observation plots, individual prediction (IPRED) versus observation plots, conditional weighted residuals (CWRES) versus PRED plots, and CWRES versus time after the last dose (TAD) plots were evaluated.

A nonparametric bootstrap resampling method[17] was used to evaluate the precision of the estimated PK parameters. Nonparametric bootstrapping was run with 1000 resamplings, and the estimated medians and 95% CI were compared with the model estimates.

A prediction-corrected visual predictive check (pcVPC[18]) was used to evaluate the final population PK model. Using the final PK parameters, 1000 replicates of the data set were simulated and the distribution of the simulated concentrations was graphically compared with the observations.

Monte Carlo Simulation Analysis

To evaluate the difference in steady-state concentration ($C_{ss.min}$) among patients with different dosing regimens and covariate values, a Monte Carlo simulation analysis was performed using the final model. The 1000 replicates of $C_{ss.min}$ were generated in virtual patients with 2 different dosing regimens (3 mg/kg or 240 mg fixed dose) and various eGFR values (30, 60, 90, and 120 mL/min/1.73 m^2) and ALB concentrations (2.5, 3.5, and 4.5*g*/dL). Using R software (version 3.6.0), 1000 replicates of body weight in the data set were randomly generated based on the normal distribution of the study population (mean: 59.7 kg and SD: 12.3 kg).

TABLE 1. Demographic Characteristics of Patients (n = 34)

Parameter	Median	Range
Age (yr)	69	38–83
Body weight (kg)	62.7	36.8–80.5
Height (cm)	163.8	146.6–180.1
BSA (m^2)	1.67	1.24–1.94
eGFR (mL min^{-1} 1.73 $m^{2(-1)}$)	70	29–144
ALB (g dL^{-1})	3.6	2.5–4.8
Sex (n)		
Male	25	
Female	9	
Histology (n)		
Adenocarcinoma	22	
Squamous cell carcinoma	11	
Not otherwise specified	1	
PD-L1 expression (n)		
<1%	8	
1%–49%	13	
≥50%	3	
Unknown	10	
Performance status (n)		
0	10	
1	22	
2	1	
Unknown	1	

RESULTS

Patients

Thirty-four patients were included in this study. Demographic characteristics are presented in Table 1. Thirty-three patients received nivolumab at 240 mg Q2W, and 1 patient received nivolumab every 3 weeks. The number of nivolumab doses and treatment periods varied among the patients. The median (range) number of doses and treatment period was 16.5 (1–75) and 296 days (14–1217), respectively.

Population Pharmacokinetic Modeling

Base Model

In total, 223 nivolumab serum concentrations (1–12 points per patient) were available for the population PK analysis. The number of samples collected in each time window was 14, 104, 43, and 62 at TAD: 0–1, 1–2, 2–3, and 4 weeks or later, respectively. As the base model significantly improved the model fit of the two-compartment model (Akaike's Information Criterion [AIC]: 1408.1) compared with the one-compartment model (AIC: 1426.2), the former was used to describe the PK data. The proportional error model provided an adequate fit, whereas the combined proportional and additive residual error model did not perform significantly better. Therefore, a proportional error model was used for the base model. IIV in PK parameters was estimated for CL and V1, while IIV for Q2 and V2 could not be estimated reasonably and was fixed to zero.

Final Model

Covariate analysis was conducted using a stepwise method based on the likelihood ratio test to evaluate the influencing factors of nivolumab CL. The results of the stepwise covariate analysis are shown in **Supplemental Digital Content 1** (see **Table S1**, http://links.lww.com/TDM/A584 and **Table S2**, http://links.lww.com/TDM/A585). The covariate analysis showed a significant improvement in model fit by including ALB levels, eGFR, and treatment periods (time-varying CL) as covariates in CL ($\Delta OFV = -54.301$, $P < 0.01$). The IIV of CL and V1 in the final model was reduced from the base model (CL: 26.9%–19.4%, V1: 101.0%–46.3%). ALB levels negatively correlated with nivolumab CL, whereas eGFR positively correlated with nivolumab CL. No systematic changes were observed in ALB levels and eGFR during the treatment period (see **Supplemental Digital Content 1**, **Table S3**, http://links.lww.com/TDM/A586). The inclusion of time-varying CL using the sigmoidal E_{max} model with fixed parameters adapted from Osawa et al resulted in a significantly better model fit. However, Emax and γ could not be estimated from our data set, and T50 was

estimated at 1170 hours (RSE 56%) using fixed E_{max} and γ. The effects of these covariates on the individual post hoc Bayesian estimated CL are shown in Figure 1. The final estimated model parameters are listed in Table 2. The mean CL in this study population was 0.0064 L hour^{-1} (coefficient of variation = 20%). In the final model, CL is represented by the following equation:

$$\text{Nivolumab CL (L/h)} = 0.0064 \times \left(\frac{ALB}{3.6}\right)^{-1.48} \times \left(\frac{eGFR}{70}\right)^{0.411} \times exp\left(\frac{-0.285 \cdot t^{2.02}}{1501^{2.02} + t^{2.02}}\right)$$

Model Evaluation

Figure 2 shows the goodness-of-fit plots of the final model. Observations versus PRED or IPRED plots were symmetrically distributed around the diagonal line, indicating good model predictability. No systematic bias was observed in the CWRES versus PRED or TAD plots. Thus, no misspecifications were found in the structural or residual models.

The mean and 95% CI of the final PK parameters by nonparametric bootstrap analysis are presented in Table 2. All mean values were close to the model estimates and demonstrated the robustness of the model PK parameters. pcVPC demonstrated that the model-simulated concentrations were in good agreement with the observations (Fig. 3).

Monte Carlo Simulation Analysis

The results of the Monte Carlo simulation analysis are shown in **Supplemental Digital Content 1** (see **Figure S1**, http://links.lww.com/TDM/A583). $C_{ss.min}$ values differed substantially depending on dosing regimen, ALB levels, and eGFR. The median $C_{ss.min}$ with the fixed 240 mg dose was 32.2%–38.3% higher than that with the 3 mg/kg dose in this study population. The median $C_{ss.min}$ of ALB with 2.5 g/dL was 45.7%–51.9% and 64.5%–71.4% lower than that of ALB with 3.5 and 4.5 g/dL, respectively. The median $C_{ss.min}$ of eGFR with 30 mL/min/1.73 m^2 was 36.6%–49.3%, 67.3%–93.0%, and 85.9%–129.8% higher than that of eGFR with 60 mL/min/1.73 m^2, 90 mL/min/1.73 m^2, and 120 mL/min/1.73 m^2, respectively. In addition to regimen type, ALB and eGFR values resulted in large PK variability in this simulation.

DISCUSSION

In this study, we evaluated the PK of nivolumab in Japanese patients with NSCLC who received a fixed dose (240 mg) of nivolumab. The serum concentration data collected using opportunistic sampling provided reasonable PK parameter estimates and identified significant covariates for nivolumab CL. This indicates the usability of opportunistic sampling for PK characterization of monoclonal antibodies in patients receiving cancer immunotherapy. ALB levels, eGFR, and time-varying CL were significant CL covariates. To the best of our knowledge, this is the first report describing the PK of nivolumab in a real-world population of Japanese patients that includes time-varying CL.

When evaluating the final model, goodness-of-fit plots and pcVPC analysis indicated no bias in the model predictions. Interestingly, the mean nivolumab CL in this study (0.0064 L hour^{-1}) was lower than that in previous studies (0.0094 L/h [CV = 35%],[11] 0.011 L/h [CV = 31%],[12] and 0.0088 L/h [CV = 31%][16]). Factors associated with the observed lower CL could not be determined in this study but may be partially explained by the lower body weight (62.7 kg) of this study's Japanese population than that of past reports (79.09 kg,[11] 80 kg,[12] and 78.5 kg[16]). These studies reported body weight or body surface area as covariates of CL and adjusted CL against these, resulting in values of 0.0082 L/h,[11] 0.0097 L/h,[12] and 0.0076 L/h,[16] respectively. However, the ALB and eGFR values observed in this study were comparable with those in previous reports. Another reason for these observations could be that our study population

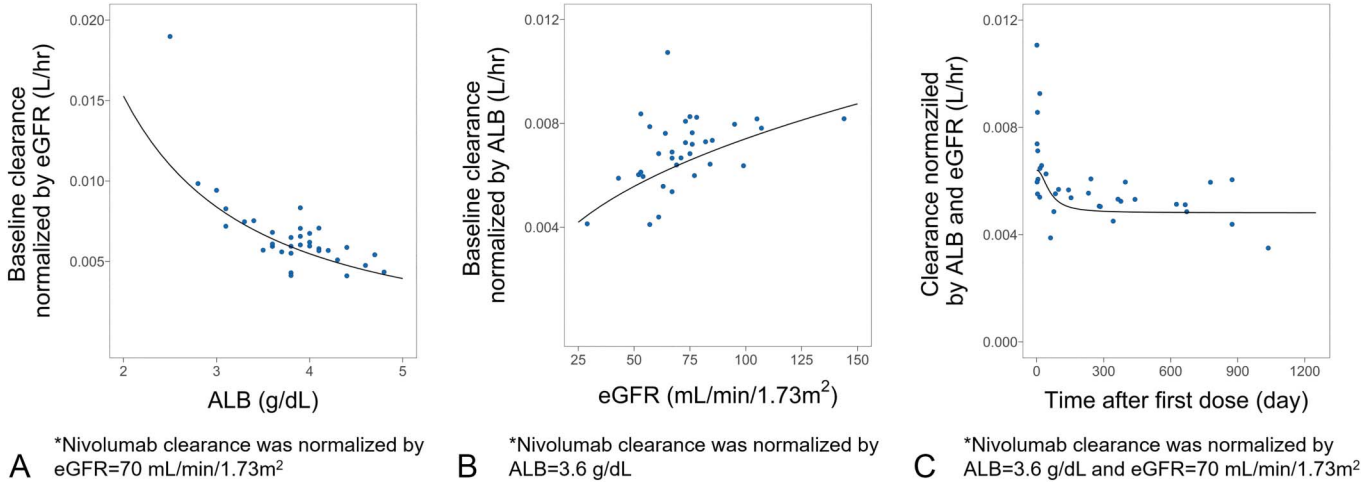

FIGURE 1. Correlations between nivolumab clearance and baseline ALB (A), eGFR (B), and time after first dose (C). The solid line indicates the effect of each covariate on the population mean clearance in the final model.

TABLE 2. Parameter Estimates for the Final Population Pharmacokinetic Model and Bootstrap Analysis

				Bootstrap Analysis (n = 1000)		
					95% CI	
Parameter	**Estimate**	**RSE (%)**	**Shr. (%)**	**Median**	**Lower**	**Upper**
CL (L h^{-1})	0.0064	5		0.0064	0.0058	0.0070
V1 (L)	2.28	17		2.18	0.97	3.17
V2 (L)	1.81	11		1.88	0.93	2.81
Q (L h^{-1})	0.018	26		0.016	0.003	0.057
θ for albumin	−1.48	33		−1.40	−2.21	−0.67
θ for eGFR	0.411	23		0.429	0.245	0.607
θ for EMAX	−0.285 (FIX)	—				
θ for TM50	1510 (FIX)	—				
θ for HILL	2.02 (FIX)-					
IIV for CL (CV%)	19.4	39	9	18.1	11.4	24.9
IIV for V1 (CV%)	46.3	45	35	46.8	14.1	91.9
Residual variability (CV%)						
Proportional error	16.0	16	9	15.7	13.6	17.9

Q, intercompartmental clearance; V1, volume of distribution of the central compartment; V2, volume of distribution of the peripheral compartment.

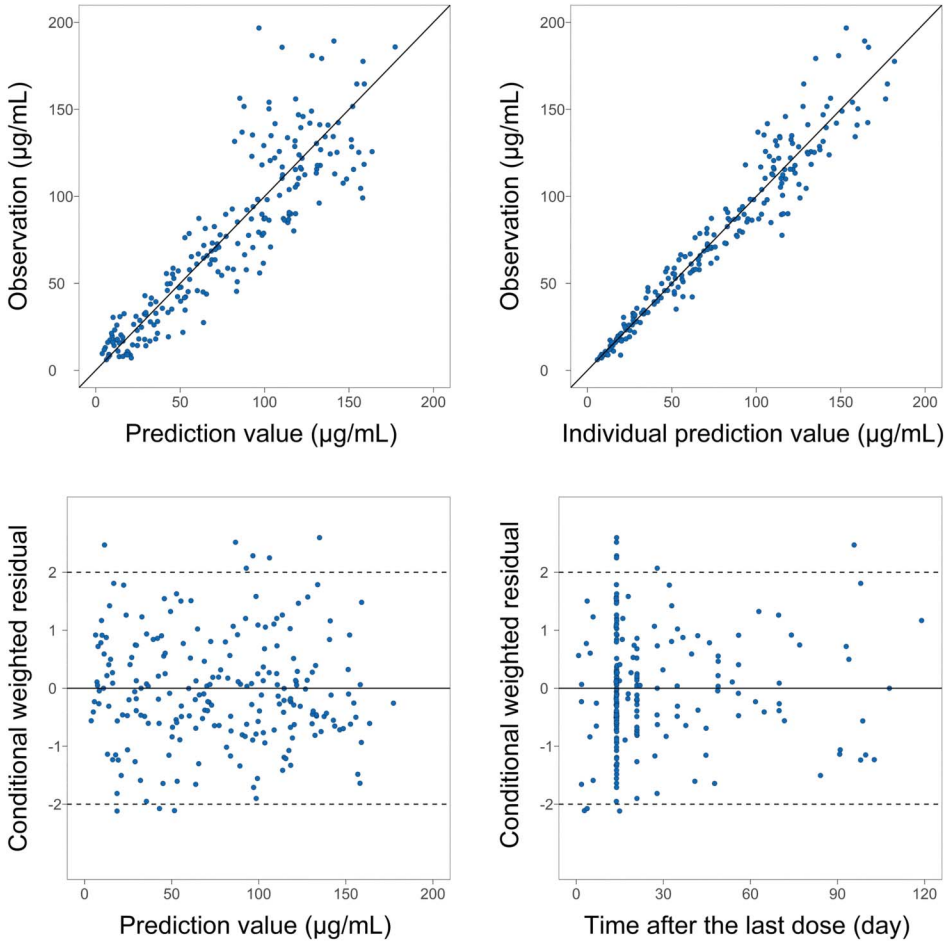

FIGURE 2. Goodness-of-fit plots for the final nivolumab pharmacokinetic model.

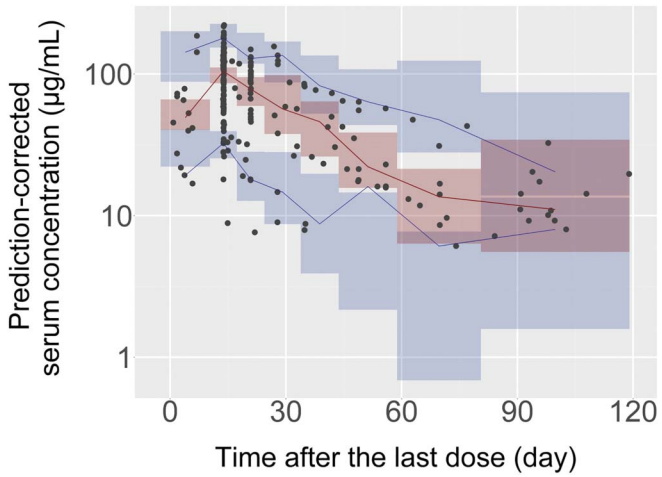

FIGURE 3. Prediction-corrected visual predictive check for the final nivolumab pharmacokinetic model. Closed circles represent observed serum concentrations. Lines represent the median and the 5th and 95th percentiles of the observed data. The shaded regions represent 95% CI for the fifth, 50th, and 95th percentiles of simulation.

included many long-term responders who showed a relatively low nivolumab CL. The median progression-free survival in patients treated with nivolumab was 3.5 months in patients with advanced squamous NSCLC[1] and 2.3 months in patients with advanced nonsquamous NSCLC.[2] In this study, 24 patients (70.6%) had continued nivolumab treatment for more than 3 months, which could have resulted in the relatively low mean CL values observed in the study population.

Previous population PK modeling studies have demonstrated that nivolumab CL decreases over the course of treatment. This time-varying change in nivolumab CL was described using a sigmoidal E_{max} model and has been reported to be a significant covariate in previous studies.[11–13] We observed a similar time-varying CL to nivolumab in real-world patients. Thus, patients with a long-term response to nivolumab had a lower CL and higher blood levels of the drug. However, E_{max}, T50, and γ could not be estimated from our data set owing to the limited number of sample points. When we only estimated T50, which was 1170 hours (RSE 56%), the T50 values of previous reports were within the 95% CI.[12] Therefore, we used the previously reported fixed E_{max} model. Further research is needed to determine the appropriate E_{max} model parameters for real-world patients.

Our covariate analysis also indicated that ALB and eGFR values were significant predictive factors for nivolumab CL. ALB has been shown to be associated with the CL of other monoclonal antibodies, such as vedolizumab,[19] durvalumab,[20] and infliximab.[21–23] Nevertheless, nivolumab is not eliminated from the kidney, and eGFR does not seem to directly affect nivolumab CL. For nivolumab, the mechanism underlying the association between serum ALB and eGFR and CL may be explained by cachexia. Hypoalbuminemia is a marker of cachexia and elevated protein turnover, induced by chronic systemic inflammatory conditions. The endogenous catabolism of ALB is highly correlated with catabolic turnover of IgG.[24] In addition, patients with cancer cachexia often experience muscle loss, which may lead to decreased serum creatinine levels. As a lower serum creatinine level is associated with higher eGFR, this could be a possible cause of the positive correlation between eGFR and nivolumab CL. Although both higher ALB and lower eGFR are potentially associated with cachexia, an independent effect of these parameters on nivolumab CL was observed in this study (Fig. 1). Other studies also suggest that eGFR is an influencing factor of nivolumab CL and other immune checkpoint inhibitors.[11,25]

In a previously published real-world PK study of nivolumab, sex, BSA, and baseline serum ALB were found to be significant covariates of CL in patients with NSCLC.[16] This study also demonstrated a correlation between drug CL and response in patients with NSCLC.[16] In our study, sex and body size metrics such as body weight and BSA were not significant covariates for nivolumab CL. This might be due to the limited sample size (n = 34) and the relatively narrow distribution of body weight and BSA in the study population (the ranges of weight and BSA were 36.8–80.5 kg and 1.24–1.94 m^2, respectively). Further studies are warranted to fully characterize the relationship between body size and nivolumab PK parameters in real-world Japanese populations.

This study has some limitations. To fully characterize the PK of nivolumab, the sample size (n = 34) was relatively small and the PK data that were gathered within a two-week period were insufficient. In addition, owing to limited data, we could not prepare a cohort for external model evaluation in this study. Therefore, a large-scale PK study, including external validation, is required to verify the results. However, by leveraging a previously published PK model, nivolumab CL was reasonably estimated with good precision (the relative standard error was 6%) and the effect of patient-specific factors on CL was successfully characterized in a real-world setting. Monte Carlo simulation analyses demonstrated that different dosing regimens (3 mg/kg vs. 240 mg fixed dose), eGFR, and ALB levels resulted in a 26.7–231.6 mcg/mL difference in median $C_{ss.min}$. This suggests that individualization of dosing regimens may be helpful in reducing the variability in nivolumab exposure. Further studies are warranted to characterize the exposure effect/toxicity relationship to identify target exposure in nivolumab therapy.

CONCLUSIONS

We conducted a real-world PK analysis of nivolumab in Japanese patients with NSCLC. The analysis indicated that serum ALB levels, eGFR, and time-varying CL were significant covariates predictive of nivolumab CL. These findings provide additional insights into ongoing efforts to develop optimal and personalized dosing regimens for nivolumab in patients with NSCLC.

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