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ARTICLE

Population Pharmacokinetics of Nivolumab in Combination With Ipilimumab in Patients With Advanced Malignancies

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Nivolumab is a fully human monoclonal antibody that inhibits programmed cell death-1 activation. To assess covariate effects on nivolumab clearance (CL), a population pharmacokinetics model was developed using data from 6,468 patients with colorectal cancer, hepatocellular carcinoma, melanoma, non-small cell lung cancer, renal cell carcinoma, or small cell lung cancer who received nivolumab as monotherapy or in combination with ipilimumab or chemotherapy across 25 clinical studies. Nivolumab CL was similar across the tumor types examined; CL was higher for ipilimumab 1 mg/kg every 6 weeks (by 17%) and 3 mg/kg every 3 weeks (by 29%) vs. nivolumab monotherapy. Nivolumab CL over time was partially explained by time-varying covariates. A greater decrease in nivolumab time-varying CL was associated with increased albumin and body weight and a responder status. Our findings support the observed association between nivolumab CL and disease severity.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ A population pharmacokinetics (PPK) model of nivolumab was used to characterize the fixed and time-varying covariates that affect nivolumab clearance (CL) when nivolumab was coadministered with ipilimumab in patients with solid tumors. The decrease of nivolumab CL during the course of treatment was examined.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ The effect of combination therapy with nivolumab and ipilimumab on nivolumab CL and the relationship of decreased nivolumab CL with various factors.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Coadministration of nivolumab with ipilimumab is associated with higher nivolumab CL than during nivolumab monotherapy. Nivolumab CL decreases over time, and the decrease in CL is associated with improvements in time-varying covariates related to disease severity and cancer-related cachexia. Nivolumab PK was similar across tumor types.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
☑ This PPK model may be used for exposure–response efficacy and safety analyses. It could also assist in improving individualization of treatment in clinical practice.

Nivolumab (OPDIVO, Bristol-Myers Squibb, Princeton, NJ) is a fully human immunoglobulin G4 monoclonal antibody that selectively binds to the programmed death-1 (PD-1) membrane receptor on activated T and B lymphocytes.[1,2] Because the binding of PD-1 to its ligands results in the downregulation of lymphocyte activation,[3] nivolumab inhibits the interaction between PD-1 and its ligand, which augments antitumor immune responses. At the time of manuscript preparation, nivolumab was approved as monotherapy in the United States, European Union, and several other markets for the treatment of several malignancies, including microsatellite instability-high colorectal cancer (CRC), hepatocellular carcinoma (HCC), unresectable or metastatic melanoma, non-small cell lung cancer (NSCLC; second line), renal cell carcinoma (RCC), and small cell lung cancer (SCLC).[4–6] Nivolumab is also approved in the United States for use in combination with ipilimumab for the treatment of unresectable or metastatic melanoma, RCC, and CRC,[5] and in the European Union for the treatment of unresectable or metastatic melanoma and RCC.[4]

The pharmacokinetics (PK) of nivolumab monotherapy in patients with solid tumors has been previously characterized by population PK (PPK) analysis.[7] In this analysis, the nivolumab clearance (CL) maximally decreased by approximately 25% from baseline during the course of treatment.[7] In addition, the PK of nivolumab was previously described by a two-compartment model incorporating a time-varying CL, which reported that nivolumab exposure was dose proportional.[8]

The current analysis characterizes the PK of nivolumab CL when coadministered with ipilimumab or chemotherapy across multiple tumor types, including CRC, HCC,

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melanoma, NSCLC, RCC, and SCLC. The effect of ipilimumab coadministration vs. nivolumab monotherapy on nivolumab PK was evaluated as well as the comparison of nivolumab PK across tumor types. Moreover, in-depth analyses investigated the features of time-varying nivolumab CL, including time-dependent covariates.

METHODS

Data

PK data were obtained from 25 clinical studies that recruited patients with solid tumors who received nivolumab monotherapy or nivolumab in combination with ipilimumab or chemotherapy, which included gemcitabine plus cisplatin, pemetrexed plus cisplatin, paclitaxel plus carboplatin, and platinum-doublet chemotherapy. The data are from seven phase I, two phase I/II, six phase II, nine phase III, and one phase IIIb/IV clinical studies. The monotherapy studies included patients with melanoma, NSCLC, and RCC. The combination therapy studies enrolled patients with CRC, HCC, melanoma, NSCLC, SCLC, and RCC. A total of 32,835 PK samples (including 11,896 for nivolumab with ipilimumab coadministration) from 6,468 patients were included. The baseline covariates and studies analyzed in this analysis are summarized in **Table 1** and **Table S1**, respectively.

Table 1 Summary of baseline demographic, laboratory, treatment, and disease severity covariates

Covariate	PPK analysis index data set, *N* = 6,468
Continuous, mean (standard deviation) [95% range] {missing count}	
Baseline body weight, kg	77.6 (18.8) [47.7–122.0] {0}
Baseline lactate dehydrogenase, U/L	320 (326) [125–1090] {696}
Baseline serum albumin, g/dL	3.93 (0.493) [2.8–4.8] {2,087}
Baseline tumor size, cm	8.46 (6.01) [1.3–23.9] {1,158}
Categorical, *n* (%)	
Baseline performance status	
0	3,041 (47.02)
1	3,316 (51.27)
2	105 (1.62)
3	1 (0.02)
Missing	5 (0.08)
Tumor type	
Colorectal cancer	236 (3.65)
Hepatocellular carcinoma	381 (5.89)
Melanoma	1,742 (26.93)
Non-small cell lung cancer	2,474 (38.25)
Renal cell carcinoma	1,245 (19.25)
Small cell lung cancer	390 (6.03)
Coadministration regimen with nivolumab	
No coadministration	3,565 (55.12)
Ipilimumab 1 mg/kg q12w	36 (0.56)
Ipilimumab 1 mg/kg q6w	760 (11.75)
Ipilimumab 1 mg/kg q3w for 4 doses	974 (15.06)
Ipilimumab 3 mg/kg q3w for 4 doses	895 (13.84)
Chemotherapy	238 (3.68)
Best overall response	
Complete response	257 (3.97)
Partial response	1,391 (21.51)
Stable disease	1,512 (23.38)
Progressive disease	1,740 (26.90)
Noncomplete response/nonprogressive disease	22 (0.34)
No disease	4 (0.06)
Not evaluable	305 (4.72)
Not reported	34 (0.53)
Missing	1,203 (18.60)

PPK, population pharmacokinetics; q3w, every 3 weeks; q6w, every 6 weeks; q12w, every 12 weeks.

PPK model development

The PPK model was developed in three stages, consisting of the initial, full, and final models.

Initial model. Initial model development consisted of reestimating parameters of the previously developed final model for nivolumab monotherapy[7] with the current analysis data set. The previously developed final model was a two-compartment, zero-order intravenous infusion PK model and time-varying CL model (sigmoidal-Emax function) with a proportional residual error model that included the following: random effect on CL; volume of central compartment (VC), volume of peripheral compartment (VP), the maximal change in CL over time (Emax), and correlation of random effects between CL and VC.[7] We assumed that the interindividual variability (IIV) random effect of intercompartmental CL (Q) follows the same distribution as that of CL and that the IIV random effect of VP follows the same distribution as that of VC. This model included the effects of baseline body weight (BBWT), estimated glomerular filtration rate (eGFR), performance status (PS), sex, and race on CL as well as the effects of BBWT and sex on VC. The half-life value (T_{50}) was defined as the time when the change in nivolumab CL was 50% of the maximal change in CL over time (Emax).

Full model. The full model was developed from the initial model by incorporating additional covariates representing the effect of tumor type, line of therapy (first line vs. second line or greater), and ipilimumab coadministration (IPICO) or chemotherapy on nivolumab CL. The full model also incorporated the impact of PS and IPICO on Emax. These covariates reflect new information in the data or potential associations with treatment effects that can influence the time-varying CL of nivolumab. The functional relationships between continuous or categorical covariates and structural model parameters were modeled as described previously.[7] The covariate effect was considered statistically significant if the 95% confidence interval (CI) of the estimated effect did not include the null (no effect) value. Covariates that had an effect of less than ± 20% on model parameters compared with the reference were considered to be not clinically important.

Final model. A parsimonious final model was developed from the full model by stepwise backward elimination of the covariates added in the full model. The model with the

lowest Bayesian information criterion (BIC) was selected as the final model.

PPK model parameters were estimated using the first-order conditional estimation with interaction method implemented in NONMEM (v7.3, ICON Development Solutions, Hanover, MD). The precision of the final model parameter estimates was assessed by a nonparametric bootstrap approach involving 1,000 runs. The final model developed using the original data set was fitted to each of the bootstrap data sets to obtain bootstrap parameter estimates and standard errors. The 95% CIs of the final model parameter values were derived from the bootstrap parameter estimates.

Model evaluation

Model evaluation was performed using standard goodness-of-fit plots and prediction-corrected visual predictive check (pcVPC) to assess model assumptions and population parameter estimates. The pcVPC was performed using 500 simulated data sets that were obtained using parameter values from the final model. The pcVPC provides a graphical assessment of the agreement between the time course of model predictions and observations at the recommended dose for different tumor types. The pcVPC plotted the 5th, 50th, and 95th percentiles of observed plasma concentration–time data with their corresponding model-based 90% prediction intervals by dose level. The pcVPC and bootstrap approaches previously described were conducted using Perl-speaks-NONMEM (v4.4.8), and diagnostic plots were prepared using R (v3.0.2).

Sensitivity analyses

Sensitivity analyses were conducted to assess the effect on nivolumab CL of covariates for which data were not available in all patients. The covariates of baseline albumin (BALB), baseline lactate dehydrogenase (BLDH), and baseline tumor burden (BTSIZE) were tested.

The effect of antidrug antibodies (ADA) on CL was assessed in separate sensitivity analysis. ADA was added as a time-varying covariate to the final model, where the effect of ADAs was estimated at each time of nivolumab CL. A patient could have different ADA categorical values (i.e., positive, negative, or missing) at different times; hence, the impact of ADA on nivolumab CL is time dependent. ADA was included in the sensitivity analysis because ADA data were unavailable in some studies.

Another sensitivity analysis assessed the extent to which time-varying covariates may explain the temporal change in CL. The longitudinal effects of covariates for which baseline values had significant effects on nivolumab CL were assessed; the variables included body weight BBWT, PS, lactate dehydrogenase (LDH), and albumin (ALB). The longitudinal effects for these covariates were compared with their baseline values, and the time-varying effects were estimated in addition to baseline covariate effects because their magnitude and directionality were not hypothesized to be necessarily the same.

The functional relationships between effects of a covariate at baseline and over time and structural model parameters were modeled using the following equation[9]:

$$P_{TV,ij} = P_{TV,REF} \cdot \left(\frac{R_i}{R_{REF}}\right)^{P_i} \cdot \left(\frac{R_{i,j}}{R_i}\right)^{P_{i,j}}$$

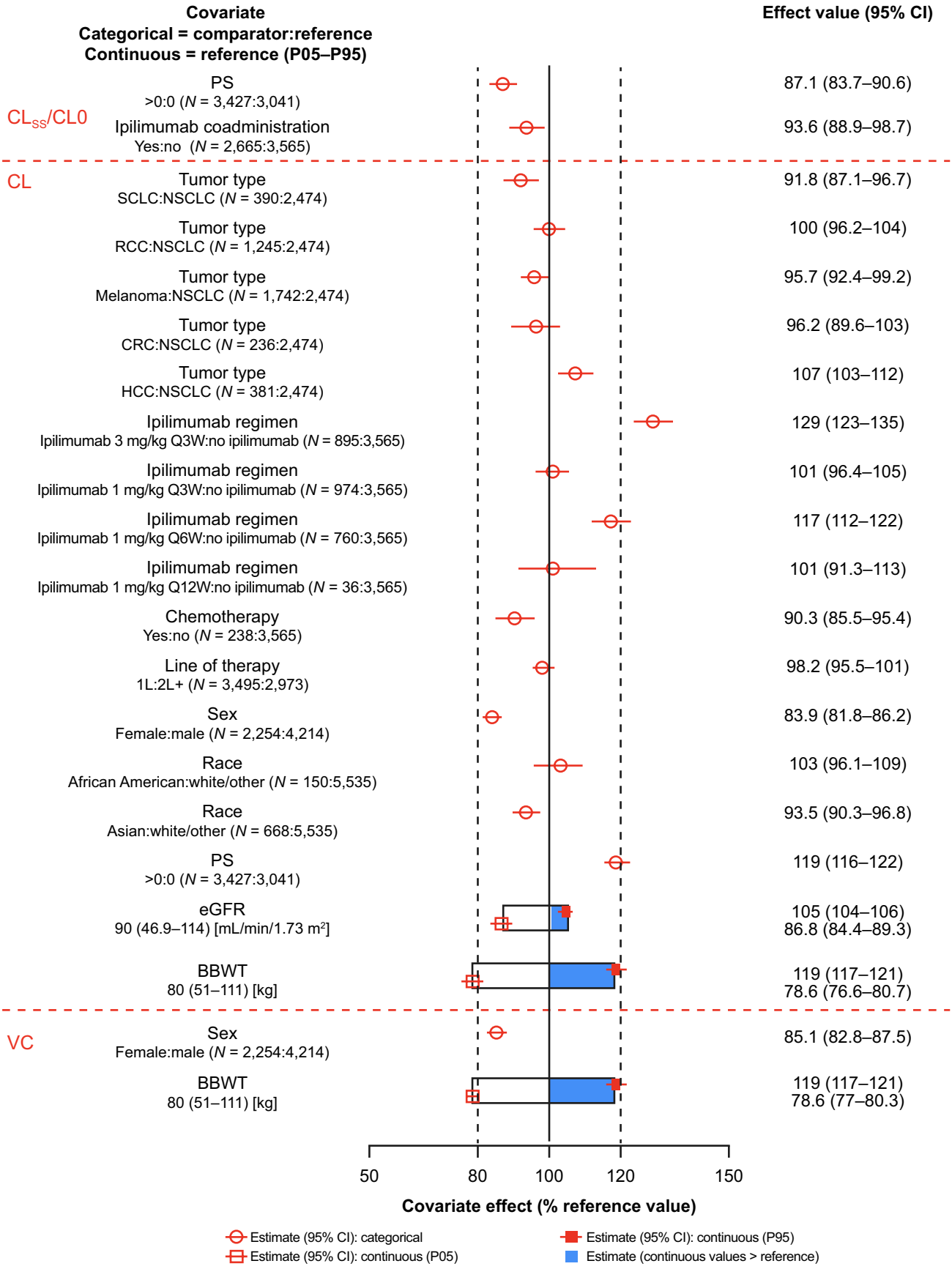
where $P_{TV,\,REF}$ is a fixed-effects parameter; P_i and $P_{i,j}$ are the parameter effects of a covariate at baseline and over time, respectively; R_i is the individual baseline covariate value; $R_{i,j}$ is the individual covariate value at each time point; and R_{REF} is the reference value of the covariate. For time-varying covariates, the reference value was defined as the baseline value.[7]

In another sensitivity analysis, the effect of best overall response (BOR) on Emax was added to test the hypothesis that reduction in disease severity is associated with a decrease in nivolumab CL.[8] BOR status in each patient is not a baseline predictor, but a result of treatment, therefore its effect was not included in the main analysis for baseline CL. The sensitivity analyses were conducted for studies with available BOR information.

Model application

Nivolumab maximum a posteriori Bayesian estimates of CL were obtained from the final model for each patient. Nivolumab CL0 was CL at time 0, and steady-state CL (CL_{SS}) was calculated as $CL0 \times e^{E\,max}$. The relationship between CL0 and the ratio of CL_{SS}/CL0 was evaluated across different ipilimumab dosing regimens and tumor types. Nivolumab trough concentration after the first dose, peak concentration after the first dose, time-averaged concentration during the first dosing interval, steady-state trough concentration, peak steady-state concentration, and average steady-state concentration were summarized for each patient for whom maximum a posteriori Bayesian estimates of PK parameters were available.

Figure 1 Covariate effects on nivolumab population pharmacokinetic full model parameters. Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines). Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded areas of boxes represent the range of covariate effects from the median to the 5th/95th percentile of the covariate. The reference patient is male, white/other race, has a BWT of 80 kg, PS of 0, eGFR of 90 mL/min/1.73 m^2, and received nivolumab monotherapy, with NSCLC as tumor type. Parameter estimate in the reference patient is considered as 100% (vertical solid line), with dashed vertical lines at 80% and 120% of this value. The effect of BBWT was added on Q and VP, and their estimates were fixed to be similar to those of CL and VC, respectively. Baseline CL of nivolumab in patients with PS > 0 was higher than in patients with PS 0 by 19%, whereas the reduction of nivolumab CL over time was greater in patients with PS > 0 than in patients with PS 0 by 13%. CL_{SS} was calculated as $CL0 \times e^{E\,max}$. 1L, first-line therapy; 2L+, second-line therapy or greater; BWT, body weight; BBWT, baseline body weight; CI, confidence interval; CL, clearance; CL0, clearance at time 0; CL_{SS}, clearance at steady state; CRC, colorectal carcinoma; eGFR, estimated glomerular filtration rate; Emax, the maximal change in clearance; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; P05, 5th percentile; P95, 95th percentile; PS, performance status; Q, intercompartmental CL; Q3W, every 3 weeks; Q6W, every 6 weeks; Q12W, every 12 weeks; RCC, renal cell carcinoma; SCLC, small cell lung cancer; VC, volume of the central compartment; VP, volume of the peripheral compartment.


Covariate
Categorical = comparator:reference
Continuous = reference (P05–P95)
Effect value (95% CI)
CLss/CL0
PS
>0:0 (N = 3,427:3,041)
87.1 (83.7–90.6)
Ipilimumab coadministration
Yes:no (N = 2,665:3,565)
93.6 (88.9–98.7)
CL
Tumor type
SCLC:NSCLC (N = 390:2,474)
91.8 (87.1–96.7)
Tumor type
RCC:NSCLC (N = 1,245:2,474)
100 (96.2–104)
Tumor type
Melanoma:NSCLC (N = 1,742:2,474)
95.7 (92.4–99.2)
Tumor type
CRC:NSCLC (N = 236:2,474)
96.2 (89.6–103)
Tumor type
HCC:NSCLC (N = 381:2,474)
107 (103–112)
Ipilimumab regimen
Ipilimumab 3 mg/kg Q3W:no ipilimumab (N = 895:3,565)
129 (123–135)
Ipilimumab regimen
Ipilimumab 1 mg/kg Q3W:no ipilimumab (N = 974:3,565)
101 (96.4–105)
Ipilimumab regimen
Ipilimumab 1 mg/kg Q6W:no ipilimumab (N = 760:3,565)
117 (112–122)
Ipilimumab regimen
Ipilimumab 1 mg/kg Q12W:no ipilimumab (N = 36:3,565)
101 (91.3–113)
Chemotherapy
Yes:no (N = 238:3,565)
90.3 (85.5–95.4)
Line of therapy
1L:2L+ (N = 3,495:2,973)
98.2 (95.5–101)
Sex
Female:male (N = 2,254:4,214)
83.9 (81.8–86.2)
Race
African American:white/other (N = 150:5,535)
103 (96.1–109)
Race
Asian:white/other (N = 668:5,535)
93.5 (90.3–96.8)
PS
>0:0 (N = 3,427:3,041)
119 (116–122)
eGFR
90 (46.9–114) [mL/min/1.73 m²]
105 (104–106)
86.8 (84.4–89.3)
BBWT
80 (51–111) [kg]
119 (117–121)
78.6 (76.6–80.7)
VC
Sex
Female:male (N = 2,254:4,214)
85.1 (82.8–87.5)
BBWT
80 (51–111) [kg]
119 (117–121)
78.6 (77–80.3)
50
80
100
120
150
Covariate effect (% reference value)
Estimate (95% CI): categorical
Estimate (95% CI): continuous (P05)
Estimate (95% CI): continuous (P95)
Estimate (continuous values > reference)

RESULTS

PPK model development

Initial model. The initial model was adequate with reasonable parameter precision, as indicated by a condition number 44. The goodness-of-fit plots demonstrated reasonable agreement between observed and predicted as well as individual predicted nivolumab concentrations.

Full model. The full model added IPICO regimens as covariates. Covariate effects in the full model are shown in **Figure 1**. Nivolumab CL was similar across tumor types. When administered with nivolumab, regimens of ipilimumab 1 mg/kg every 3 weeks (q3w) or every 12 weeks (q12w) had no statistically significant effect on nivolumab CL, whereas coadministration of ipilimumab 1 mg/kg every 6 weeks (q6w) resulted in a 17% (95% CI, 12–22%) increase in nivolumab CL, and ipilimumab 3 mg/kg q3w resulted in a 29% (95% CI, 23–35%) increase in nivolumab CL. The CL of nivolumab in combination with chemotherapy was 9.7% (95% CI, 4.6–15.5%) lower relative to nivolumab monotherapy.

Final model. The final model (NONMEM code in **Supplementary File S1**) was obtained by eliminating the covariate effects from the full model that were not in the base model, one at a time, guided by BIC. Backward elimination steps and their respective BIC values are presented in **Table S3**. The final model included the effects of (i) IPICO, chemotherapy coadministration, BBWT, eGFR, PS, sex, and race on CL; (ii) IPICO and PS on Emax; (iii) BBWT and sex on VC; and (iv) BBWT on *Q* and VP.

The final model is represented using the following equations:

$$\mathrm{CL0}_i = \mathrm{CL0}_{\mathrm{REF}} \cdot \left(\frac{\mathrm{BBWT}_i}{\mathrm{BBWT}_{\mathrm{REF}}}\right)^{\mathrm{CL}_{\mathrm{BBWT}}} \cdot \left(\frac{\mathrm{eGFR}_i}{\mathrm{eGFR}_{\mathrm{REF}}}\right)^{\mathrm{CL}_{\mathrm{eGFR}}} \cdot e^{\mathrm{CL}_{\mathrm{IPI3Q3W}}} \cdot e^{\mathrm{CL}_{\mathrm{IPI1Q6W}}} \cdot e^{\mathrm{CHEMO}} \cdot e^{\mathrm{CL}_{\mathrm{SEX}}} \cdot e^{\mathrm{CL}_{\mathrm{PS}}} \cdot e^{\mathrm{CL}_{\mathrm{RAAA}}} \cdot e^{\mathrm{CL}_{\mathrm{RAAS}}} \cdot e^{\eta \mathrm{CL}i}$$

$$E\max_i = E\max_{\mathrm{REF}_i} + E\max_{\mathrm{PS}} + E\max_{\mathrm{IPICO}} + \eta E\max_i$$

$$\mathrm{CL}_{i,t} = \mathrm{CL0}_i \cdot \exp\left(\frac{(E\max_i) \cdot t^{\mathrm{CL}_{\mathrm{HILL}}}}{T50_i^{\mathrm{CL}_{\mathrm{HILL}}} + t^{\mathrm{CL}_{\mathrm{HILL}}}}\right),$$

$$\mathrm{CL}_{\mathrm{SS},i} = \mathrm{CL0}_i \cdot \exp(E\max_i).$$

$$\mathrm{VC}_i = \mathrm{VC}_{\mathrm{REF}} \cdot \left(\frac{\mathrm{BBWT}_i}{\mathrm{BBWT}_{\mathrm{REF}}}\right)^{\mathrm{VC}_{\mathrm{BBWT}}} \cdot e^{\mathrm{VC}_{\mathrm{SEX}}} \cdot e^{\eta \mathrm{VC}i}$$

$$Q_i = Q_{\mathrm{REF}} \cdot \left(\frac{\mathrm{BBWT}_i}{\mathrm{BBWT}_{\mathrm{REF}}}\right)^{\mathrm{CL}_{\mathrm{BBWT}}} \cdot e^{\eta_{Q_i}}$$

$$\mathrm{VP}_i = \mathrm{VP}_{\mathrm{REF}} \cdot \left(\frac{\mathrm{BBWT}_i}{\mathrm{BBWT}_{\mathrm{REF}}}\right)^{\mathrm{VC}_{\mathrm{BBWT}}} \cdot e^{\eta_{\mathrm{VP}_i}}$$

Parameter estimates from the final PPK model are provided in **Table 2**, where symbols in the previous equations are explained in the footnote. Diagnostic plots of the PPK final model showed that a two-compartment model with zero-order infusion characterizes nivolumab PK.

Model evaluation

The predictive performance of the final PPK model was determined using goodness-of-fit plots and pcVPC with stratification by the selected nivolumab dosing regimen in different malignancies. The goodness-of-fit plots and pcVPC are shown in **Figure S1**. The combination regimens chosen for pcVPC were nivolumab 3 mg/kg or 240 mg every 2 weeks (q2w) monotherapy, nivolumab 3 mg/kg q2w plus ipilimumab 1 mg/kg q6w, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg q3w for 4 doses followed by nivolumab 3 mg/kg Q2W, and nivolumab 1 mg/kg plus ipilimumab 3 mg/kg q3w for four doses followed by nivolumab 3 mg/kg q2w. A small proportion of data points were out of the plotted range. The pcVPC plots showed that the model adequately characterized the data from the 5th to the 95th percentiles. Most lines representing the 5th, 50th, and 95th percentiles of the observed data passed through respective 90% prediction intervals of the predicted PK data from the final model up to the first 100 days after the previous dose and first 200 days after the first dose. Thus, the data were well characterized, enabling the predictions of the model to be used for the exposure response of efficacy and safety analyses.

Sensitivity analyses

For the sensitivity analyses assessing the effects of BALB, BLDH, and BTSIZE on nivolumab CL, these effects were incorporated into the final model as follows:

$$\mathrm{CL0}_i = \mathrm{CL0}_{\mathrm{REF}} \cdot \left(\frac{\mathrm{BW}_i}{\mathrm{BW}_{\mathrm{REF}}}\right)^{\mathrm{CL}_{\mathrm{BW}}} \cdot \left(\frac{\mathrm{eGFR}_i}{\mathrm{eGFR}_{\mathrm{REF}}}\right)^{\mathrm{CL}_{\mathrm{eGFR}}} \cdot \left(\frac{\log \mathrm{BLDH}_i}{\log \mathrm{BLDH}_{\mathrm{REF}}}\right)^{\mathrm{CL}_{\mathrm{BLDH}}} \cdot \left(\frac{\mathrm{BALB}_i}{\mathrm{BALB}_{\mathrm{REF}}}\right)^{\mathrm{CL}_{\mathrm{BALB}}} \cdot \left(\frac{\mathrm{BTSIZE}_i}{\mathrm{BTSIZE}_{\mathrm{REF}}}\right)^{\mathrm{CL}_{\mathrm{BTSIZE}}} \cdot e^{\mathrm{CL}_{\mathrm{IPI3Q3W}}} \cdot e^{\mathrm{CL}_{\mathrm{IPI1Q6W}}} \cdot e^{\mathrm{CL}_{\mathrm{SEX}}} \cdot e^{\mathrm{CL}_{\mathrm{PS}}} \cdot e^{\mathrm{CL}_{\mathrm{RAAA}}} \cdot e^{\mathrm{CL}_{\mathrm{RAAS}}} \cdot e^{\eta \mathrm{CL}i}$$

The definitions of the variables are defined in the **Table 2** footnote. The BALB, BLDH, and BTSIZE reference values were approximately the median of the values in the data set (3.8 g/dL, 200 IU/mL, and 7.1 cm, respectively). The effect of BALB on nivolumab CL was not clinically relevant (< 20%). Nivolumab CL was greater in patients with higher BLDH, and the effect (89% (95% CI, 83–95%) to 144% (95% CI, 116–179%) for the 90% range of BLDH values) was more marked than what has been previously reported,[7] mainly because of greater variability of BLDH values in the analyzed data set. Nivolumab CL was higher in patients with larger BTSIZE, but the effect was not clinically relevant (<20%).

When ADA data were present, nivolumab CL was estimated to be approximately 20% (95% CI, 16–24%) higher for ADA positive than ADA negative or missing. This finding is consistent with the previous PPK analysis using a time-dependent model.[7]

Table 2 Parameter estimates for the final nivolumab PPK model

Parameter[a] (units)	Estimate[b]	Standard error (RSE%)[c]	95% confidence interval[d]
Fixed effects			
$CL0_{REF}$ (mL/hour)	10.8	0.162 (1.50)	10.5–11.2
VC_{REF} (L)	4.27	0.0311 (0.728)	4.21–4.34
Q_{REF} (mL/hour)	34.9	2.41 (6.91)	30.4–40.7
VP_{REF} (L)	2.70	0.0668 (2.47)	2.58–2.83
CL_{BBWT}	0.530	0.0286 (5.40)	0.470–0.589
CL_{eGFR}	0.202	0.0199 (9.85)	0.162–0.243
CL_{SEX}	−0.181	0.0133 (7.35)	−0.206 to −0.155
CL_{PS}	0.181	0.0130 (7.18)	0.156–0.208
CL_{RAAA}	0.0374	0.0322 (86.1)	−0.0308–0.111
CL_{RAAS}	−0.0354	0.0169 (47.7)	−0.0670 to −0.00215
VC_{BBWT}	0.534	0.0240 (4.49)	0.489–0.579
VC_{SEX}	−0.161	0.0141 (8.76)	−0.189 to −0.132
$Emax_{REF}$	−0.240	0.0210 (8.75)	−0.283 to −0.199
T_{50} (hour)	2,200	131 (5.95)	1,970–2,500
HILL	2.77	0.263 (9.49)	2.30–3.34
$CL_{IPI1Q6W}$	0.159	0.0179 (11.3)	0.124–0.191
$CL_{IPI3Q3W}$	0.227	0.0213 (9.38)	0.185–0.269
CL_{CHEMO}	−0.104	0.0255 (24.5)	−0.155 to −0.0525
$Emax_{IPICO}$	−0.0668	0.0234 (35.0)	−0.118 to −0.0249
$Emax_{PS}$	−0.138	0.0200 (14.5)	−0.179 to −0.0987
Random effects			
ω^2_{CL} (-)	0.157 (0.396)	0.00856 (5.45)	0.141–0.175
ω^2_{VC} (-)	0.152 (0.390)	0.0149 (9.80)	0.123–0.185
$\omega^2_{E\,max}$	0.0874 (0.296)	0.0113 (12.9)	0.0662–0.114
ω^2_{CL}: ω^2_{VC}	0.0596 (0.386)	0.00894 (15.0)	0.0439–0.0792
Residual error			
Proportional (-)	0.245	0.00405 (1.65)	0.237–0.253

BBWT, baseline bodyweight; CHEMO, chemotherapy; CL, clearance; CL0, clearance at time 0; eGFR, estimated glomerular filtration rate; Emax, the maximal change in clearance; HILL, sigmoidicity of the relationship of clearance with time; IPI1Q6W, nivolumab combined with ipilimumab 1 mg/kg every 6 weeks; IPI3Q3W, nivolumab combined with ipilimumab 3 mg/kg every 3 weeks; IPICO, ipilimumab coadministration; PS, performance status; Q, intercompartmental clearance; RAAA, African American race; RAAS, Asian race; REF, reference; T_{50}, time at which the change in $CL_{t,i}$ is 50% of Emax; VC, central volume of distribution; VP, peripheral volume of distribution; ω^2_{CL}, interindividual variability of clearance; $\omega^2_{E\,max}$, interindividual variability of Emax; ω^2_{VC}, interindividual variability of VC.

[a]η shrinkage (%): ηCL: 11.9; ηVC: 28.0; ηEmax: 50.3; and ε shrinkage (%): 16.4. $CL0_{REF}$ is the typical value of CL at time 0 (CL0) in a reference patient of white/other race with typical BBWT, PS, and eGFR. VC_{REF}, Q_{REF}, and VP_{REF} are typical values of VC, Q, and VP, respectively. The reference patient is a white male with non-small cell lung cancer receiving nivolumab monotherapy as a second-line therapy, with a normal PS status and weighing 80 kg.[b]Random effects and residual error parameter estimates are shown as variance (standard deviation) for diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$) and covariance (correlation) for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$), and names containing a colon (:) denote correlated parameters.[c]RSE% is the relative standard error (standard error as a percentage of estimate).[d]Confidence interval values are taken from bootstrap calculations (494 of 1,000 successful runs).

BBWT and baseline PS had significant effects on nivolumab CL in the final model and were chosen for evaluation of their respective longitudinal effects. Furthermore, the effects of time-varying LDH and ALB were also tested as a marker of disease severity. The effects of time-varying covariates BWT, PS, LDH, and ALB were assessed relative to the final model. Model comparisons by BIC and estimates of Emax are shown in **Table 3**. The BIC value

Table 3 Comparison of time-invariant and time-varying clearance model with empirical and time-varying covariates

Model number	Includes empirical sigmoid function	Includes baseline covariates ALB and LDH	Includes time-varying covariates	BIC	Delta BIC (compared with model 1)	Emax estimate
1	No	No	No	67418.7	0	0 FIX
2	Yes	No	No	67300.6	–118.1	–0.197
3	No	Yes	Yes	66968.4	–450.3	0 FIX
4	Yes	Yes	No	67199.4	–219.3	–0.197
5	Yes	Yes	Yes	66886.2	–532.5	–0.160

ALB, albumin; BIC, Bayesian information criterion; Emax, the maximal change in clearance; FIX, the parameter value was fixed and not allowed to change when fitting to data; LDH, lactate dehydrogenase.

for the model with (vs. without) time-varying covariate effects was lower, demonstrating an improvement in model fit. However, the estimated geometric mean of Emax with time-varying covariates was –0.160, 18.8% lower than the Emax value of –0.197 estimated using the sigmoidal-Emax function without time-varying covariate effects, indicating that the incorporation of time-varying covariates accounted for a sizable proportion, but not all, of the time-varying CL.

At baseline, higher BBWT and PS > 0 were associated with greater CL within a given population. However, the effect of time-varying BWT showed an opposite effect to baseline, where an increase in BWT over time was associated with a decrease in CL of the patient. Increase in ALB was associated with a decrease in CL, and increases in LDH and PS were associated with increased CL.

Distributions of nivolumab CL0 by BOR and of the ratio of CL_{SS}/CL0 across BOR groups are shown in **Figure 2**. Nivolumab CL decreased more in patients with a complete response (CR) or partial response (PR) than in those with stable disease (SD), and CL decreased less in patients with progressive disease (PD) than in those with SD. When patient data were ordered by BOR as CR, PR, SD, and PD, the reductions in CL (changes in ratio of CL_{SS} to CL0) aligned from greatest to least magnitude (**Figure 2b**), in agreement with the expected trend.[8]

Model application

Distributions of nivolumab CL0 and the ratio of CL_{SS}/CL0 by nivolumab plus ipilimumab combination dosing regimens are presented in **Figure 3**. Baseline nivolumab CL was higher in the regimen of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg q3w for four doses compared with other dosing regimens, whereas CL_{SS}/CL0 during treatment was similar across regimens.

DISCUSSION

The nivolumab PK, when coadministered with ipilimumab or chemotherapy across multiple solid tumor types, was well described by a two-compartment, zero-order, intravenous infusion PK model and a time-varying nivolumab CL model. The primary PK parameter values were consistent with those of a previous analysis of time-varying nivolumab CL.[7] The nivolumab CL was similar across the six tumor types included in this analysis (CRC, HCC, melanoma, NSCLC, RCC, and SCLC). For our modeling, we used ipilimumab regimen rather than concentration as a covariate of nivolumab PK. Indeed, the PK of nivolumab and ipilimumab are both dose proportional, indicating that the elimination route is not likely to be easily saturated, which is in agreement with the general observation that the amount of therapeutically administered monoclonal antibodies comprises only a small fraction of endogenous antibodies.[10] The drug–drug interaction is more likely driven by pharmacodynamics, and the immunologic memory activated by ipilimumab could continue for a long period of time after the ipilimumab concentration becomes low.[11]

The CL of nivolumab was 29% (95% CI, 23–35%) higher in patients receiving the combination of nivolumab with ipilimumab 3 mg/kg q3w for four doses compared with nivolumab monotherapy. However, this increased CL may not be clinically relevant because this dosage was still associated with an improvement in progression-free survival and overall survival for a study of patients with advanced melanoma.[6] The CL of nivolumab was also 17% (95% CI, 12–22%) higher when the agent was administered in combination with ipilimumab 1 mg/kg q6w until disease progression. No statistically significant difference was found when nivolumab was coadministered with ipilimumab 1 mg/kg q3w for four doses or

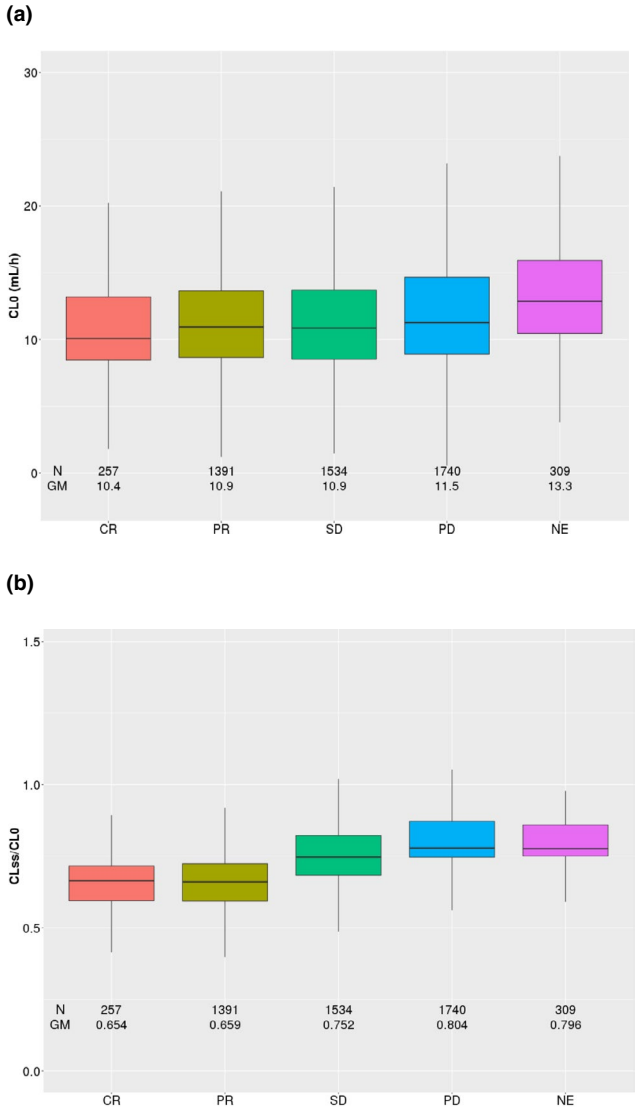


Figure 2 Model estimated change in nivolumab CL across BOR status. (**a**) Distribution of nivolumab baseline clearance. (**b**) Ratio of steady-state clearance to baseline clearance by BOR. The boxplots represent median (bold line) and 25th and 75th percentiles of the distribution. The whiskers represent 5th and 95th percentiles of the distribution. Outliers have been trimmed. NN were included with SD, and ND was included with NE in analysis. BOR, best overall response; CL, clearance; CL0, clearance at time 0; CL_{SS}, clearance at steady state; CR, complete response; GM, geometric mean; ND, no disease; NE, not evaluable; NN, noncomplete response or nonprogressive disease; PD, progressive disease; PR, partial response; SD, stable disease.

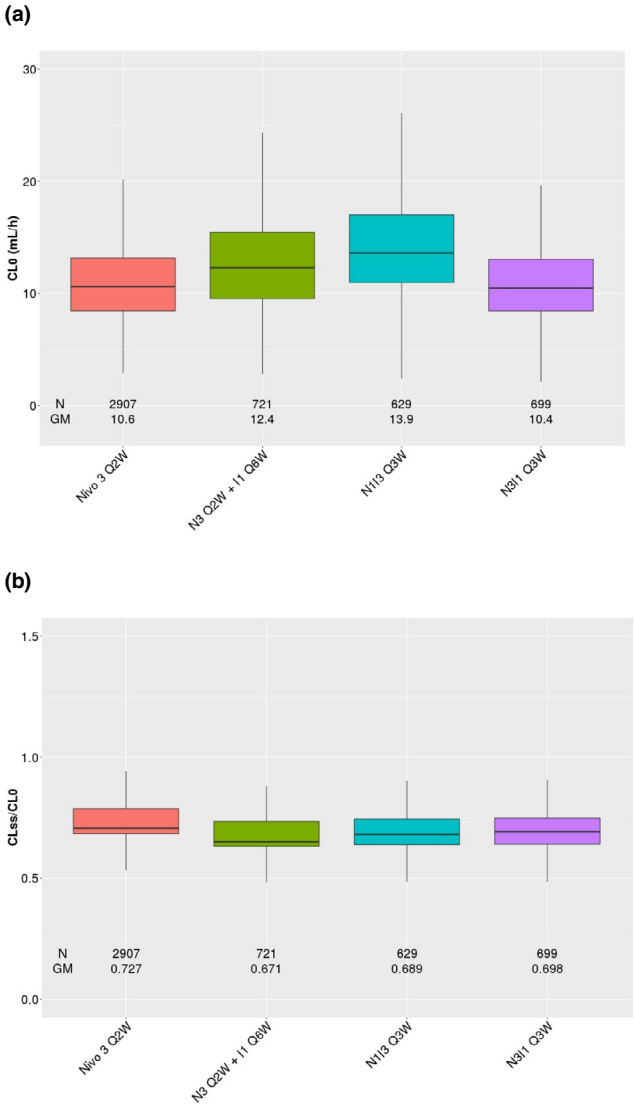


Figure 3 Model estimated change in nivolumab CL across treatment regimen. (**a**) Distribution of nivolumab baseline clearance. (**b**) Ratio of steady-state clearance to baseline clearance by select dosing regimens of nivolumab monotherapy and in combination with ipilimumab. The nivolumab 3 mg/kg q2w group included patients who received nivolumab 3 mg/kg or 240 mg q2w as monotherapy. The boxplots represent median (bold line) and 25th and 75th percentiles of the distribution. The whiskers represent 5th and 95th percentiles of the distribution. Outliers have been trimmed. CL, clearance; CL0, clearance at time 0; CL_{SS}, clearance at steady state; GM, geometric mean; q2w, every 2 weeks; q3w, every 3 weeks; q6w, every 6 weeks.

ipilimumab 1 mg/kg q12w until disease progression compared with nivolumab monotherapy. Although ipilimumab 1 mg/kg q3w was given more frequently than the ipilimumab 1 mg/kg q6w regimen, the latter regimen resulted in a greater nivolumab CL. This finding may partly be a result of the ipilimumab 1 mg/kg q6w regimen being given until disease progression, whereas the ipilimumab 1 mg/kg q3w regimen was given for only four doses.

The time-varying CL of nivolumab was assessed from various perspectives, and the decreases in CL over time were partially explained by the time-varying covariates. Specifically, a decrease in CL over time corresponded to increases in time-varying BWT and ALB as well as decreases in LDH and PS. Larger decreases of CL over time were also found in responders than in nonresponders. These results are supportive to the previously observed association between a decrease in CL over time and a reduction in disease severity.[8]

Surprisingly, although a higher BBWT corresponded to greater nivolumab CL, increases in time-dependent BWT during treatment corresponded with lower CL, in contradiction to the widely used positive allometric correlation between body weight and CL. This result actually supports the hypothesis that time-varying CL may result from the improvement of cancer-related cachexia.[7] Indeed, increases in BWT during treatment are consistent with reduction in disease severity and decreases in cachexia, leading to a reduction of CL during treatment. Patients with a more favorable BOR (i.e., CR/PR vs. SD; SD vs. PD) had a greater decrease in nivolumab CL. This finding also supports the view that a decrease in time-varying nivolumab CL is associated with a reduction in patient disease severity, which mechanistically may be the result of decreased cancer-related cachexia.

The decrease of nivolumab CL over time was greater with IPICO. The decrease of 21% (95% CI, 18–25%) for patients with baseline PS = 0 with nivolumab monotherapy at steady state relative to baseline (or first dose) is comparable to decreases (or mean maximal reductions) with pembrolizumab (23%),[12] durvalumab (23%),[13] and atezolizumab (17%),[14] but slightly lower than that seen with avelumab (32%).[15]

The characteristic time for nivolumab CL decrease for the combination, T_{50} = 92 days (95% CI, 82–104 days), was longer than reported with nivolumab monotherapy (59 days (95% CI, 50–77 days)).[7] In a further test run of our model with two T_{50} values for patients with and without IPICO, we found that the T_{50} for nivolumab monotherapy was 70 days, well within the 95% CI of the previous reported value for nivolumab monotherapy,[7] and that the T_{50} for nivolumab with IPICO was 109 days. Therefore, the T_{50} for nivolumab monotherapy was consistent with the previous report, whereas the T_{50} was longer for nivolumab with IPICO than for nivolumab monotherapy. The reason behind the longer T_{50} for IPICO is not yet clear. From the longer T_{50} and more significant CL decrease for patients with IPICO, we hypothesize that patients with better response may experience a longer period of continuous improvement of disease status, reflected by T_{50} and Emax. More evidence is needed to validate the hypothesis. In comparison, the T_{50} in a similar model for pembrolizumab CL change was 58 days for patients with PD, 87 days for those with PRs, and 178 days for other patients.[16] In addition, an empirical PK model of durvalumab, using a time-varying CL model, reported a T_{50} value of 173 days (95% CI, 74–395).[17]

Parameter values across different models are compared in **Table S2**. As expected, although the parameter values vary with data and choice of covariates, the parameters are similar between models, as the values are either similar (differ by < 20%) or within 95% CI of each other. The only two parameter values where the difference was beyond this range were T_{50} and Emax. T_{50} was addressed in the preceding paragraph. The magnitude of Emax was larger in the initial

model than in other models. This was expected, as the Emax in the initial model included all subjects regardless of IPICO and PS, whereas the Emax of the full and final models were for nivolumab monotherapy patients with PS = 0. Overall, the model parameters were consistent with each other.

The diagnostic plots demonstrated that the final model appropriately characterized nivolumab PK. The IIV of data for nivolumab and ipilimumab were found to be significantly correlated for the exposure metrics of CL (r = 0.40; $P < 2.2 \times 10^{-16}$) and Emax (r = 0.22; $P < 2.2 \times 10^{-16}$; **Figure S2**). These correlations support the association of both nivolumab and ipilimumab CL with patient disease severity. Part of disease severity was captured in the covariates such as PS, whereas the correlated IIV may be associated with the uncaptured part of disease severity. Together, considering our findings, we postulate that cancer-related cachexia is the common factor behind CL and decrease of CL during treatment for both nivolumab and ipilimumab.

In conclusion, this report is the first PPK study to characterize the fixed and time-varying effects of covariates on nivolumab CL with nivolumab coadministered with ipilimumab across six tumor types. This study demonstrated the effect of combination therapy and other factors on nivolumab CL. Nivolumab CL was similar across these six evaluated tumor types. The final model's significant covariates included the effects of ipilimumab coadministration regimen, chemotherapy coadministration, BBWT, eGFR, PS, sex, and race on CL; IPICO and PS on Emax; and BBWT and sex on VC. Among the ipilimumab coadministration regimens, it was notable that ipilimumab 3 mg/kg q3w for four doses followed by nivolumab monotherapy was predicted to have the greatest percentage decrease in nivolumab CL (approximately 29%) compared with nivolumab monotherapy. In-depth assessments from various perspectives supported the observed association between CL and disease severity.

Supporting Information. Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (www.psp-journal.com).

Figure S1. Goodness of fit plots and prediction-corrected visual predictive check plots.
Figure S2. Correlation between nivolumab and ipilimumab in terms of interindividual variability for (**a**) clearance ($r = 0.40$; $P < 2.2 \times 10^{-16}$) and (**b**) Emax ($r = 0.22$; $P < 2.2 \times 10^{-16}$), which characterizes the magnitude of change of clearance during treatment.
Table S1. Summary of clinical studies included in pharmacometric analyses.
Table S2. Comparison of parameters across multiple models.
Table S3. Backward elimination steps.
Supplementary Material S1. NONMEM code of final model.

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Conflict of Interest. J.Z., K.S., J.S., X.Z., Y.F., P.S., J.S., A.R., and L.Z. are employees of Bristol-Myers Squibb. J.Z., J.S., A.R., and L.Z. own shares in Bristol-Myers Squibb. X.Z. has received personal fees from Bristol-Myers Squibb.

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Data Sharing. Bristol-Myers Squibb's policy on data sharing can be found at https://www.bms.com/researchers-andpartners/independent-research/data-sharing-request-process.html.

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