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ARTICLE

Population Pharmacokinetics of Ipilimumab in Combination With Nivolumab in Patients With Advanced Solid Tumors

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Ipilimumab is a fully human monoclonal antibody approved for the treatment of melanoma as monotherapy and for the treatment of melanoma, renal cell carcinoma, and colorectal cancer in combination with nivolumab. Ipilimumab time-varying clearance (CL) was assessed by a population pharmacokinetics (PPK) model developed using statistically significant covariates identified in a previous PPK analysis plus additional covariates. Data from 3,411 patients who received ipilimumab 0.3–10 mg/kg alone or in combination with nivolumab in 16 clinical trials were analyzed. Ipilimumab CL decreased over time; the change in CL was greater in patients treated with nivolumab combination than ipilimumab alone and in responders vs. nonresponders. Time-varying covariates including body weight, lactate dehydrogenase, albumin, and performance status were evaluated on change in ipilimumab CL. In addition, ipilimumab CL was similar across different tumor types, nivolumab dosing regimens, and lines of therapy. These data suggest an association of ipilimumab CL with disease severity.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Ipilimumab is a first-in-class anticancer monoclonal antibody (mAb) approved as monotherapy for the treatment of melanoma and adjuvant melanoma and in combination with nivolumab for melanoma, renal cell carcinoma, and colorectal cancer. Anti-programmed cell death receptor-1/programmed cell death ligand-1 (PD-1/PD-L1) mAbs have demonstrated time-varying clearance, which may be associated with disease severity.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This analysis characterized time-varying clearance for ipilimumab, an anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) mAb, and assessed the effects of nivolumab coadministration and tumor type on ipilimumab clearance.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ This is the first report of ipilimumab time-varying clearance across multiple tumor types and showed that ipilimumab pharmacokinetics is similar across nivolumab dosing regimens and different tumor types.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
☑ This expands our knowledge about time-varying clearance of anticancer mAbs beyond anti-PD-1/PD-L1-targeting agents. Change in mAb clearance over time may be a surrogate marker of cancer-related cachexia and disease severity. Consistent with this hypothesis is the finding that increases in body weight and albumin over time were associated with decreases in ipilimumab clearance.

Ipilimumab (Yervoy, Bristol-Myers Squibb, Princeton, NJ), a fully human monoclonal immunoglobulin G1 antibody, highly selectively binds to the immune checkpoint inhibitor cytotoxic T-lymphocyte antigen-4 (CTLA-4; CD152) expressed on T-cell subsets, thereby blocking the interaction between CTLA-4 and B7 on antigen-presenting cells and preventing the inhibitory modulation of T-cell activation.[1–4] Nivolumab (Opdivo, Bristol-Myers Squibb, Princeton, NJ, and Ono Pharmaceutical, Trenton, NJ) is a fully human monoclonal Immunoglobulin G4 programmed cell death receptor-1 (PD-1) antibody that enhances T-cell activation by inhibiting the interaction of PD-1 on T cells with programmed cell death ligand-1 (PD-L1) on antigen-presenting cells.[1,5] Ipilimumab in combination with nivolumab has shown to provide greater benefit to patients with advanced melanoma than monotherapy with either agent.[6] Ipilimumab is approved as monotherapy in advanced melanoma[1,7] and adjuvant melanoma[5] and in combination with nivolumab in advanced melanoma,[1] renal cell carcinoma (RCC),[1,7] and microsatellite instability-high or mismatch repair deficient colorectal carcinoma (CRC)[7]; these approvals span the United States [8] and European Union markets.[9] Time-varying clearance (CL) for monoclonal antibodies (mAbs) used in immuno-oncology was first demonstrated for nivolumab and was shown to be associated with tumor response.[10,11] Since then, other immunotherapeutic anti–PD-1/PD-L1 mAbs have also demonstrated time-varying CL using

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an empirical sigmoid function.[12–15] To better understand the mechanism of time-varying CL, models using longitudinal covariates are being explored for several anti–PD-1 agents.[14,16] Generally, factors related to disease severity such as tumor size and neutrophil-to-lymphocyte ratio, serum albumin (ALB), and lactate dehydrogenase were evaluated to explain time-varying CL.[14,16] This study describes a refinement of the previous ipilimumab population pharmacokinetics (PPK) model to assess time-varying CL and the effect of combination therapy with nivolumab.[17] Previous analyses included data only from patients with melanoma receiving ipilimumab monotherapy for up to four doses every 3 weeks (Q3W), largely precluding characterization of time-varying CL.[17] We present model development and evaluation of time-varying CL of ipilimumab using both baseline-only and time-varying covariates and present new assessments of the potential effects of tumor type and nivolumab dosing regimen on ipilimumab CL. Finally, we present simulations conducted to support switching the nivolumab dosing regimen from 240 mg every 2 weeks (Q2W) to 480 mg every 4 weeks (Q4W) following the last dose of combination therapy with ipilimumab in the treatment of advanced melanoma.

METHODS

Data

The ipilimumab PPK model was developed using data from 16 studies in 3,411 patients with solid tumors, i.e., melanoma, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), CRC, hepatocellular carcinoma (HCC), and RCC, who received ipilimumab as monotherapy (N = 893) or in combination with nivolumab (N = 2,518). **Table 1** describes the baseline demographic characteristics, laboratory measurements, and disease severity variables that comprised the covariates included in the model development. The ipilimumab dosing regimens included were 1 mg/kg Q3W, 3 mg/kg Q3W, 1 mg/kg every 6 weeks, and 1 mg/kg every 12 weeks. The integrated analysis included a data set of 12,545 ipilimumab serum concentrations from two phase I, two phase I/II, eight phase II, three phase III, and one phase IIIb/IV clinical trials (**Table S1**).

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

Covariate	PPK analysis index data set (N = 3,411)
Continuous, median (range)	
Baseline body weight, kg	76.8 (36.8,181)
Baseline lactate dehydrogenase, U/L	217 (74–6245)
Baseline albumin, g/dL	4.1 (1.8–5.3)
Baseline tumor size, cm	6.29 (0.9–67.2)
Categorical, *n* (%)	
Baseline performance status	
0	1,953 (57.26)
1	1,407 (41.25)
>2	47 (46.03)
Missing	4 (0.12)
Tumor type	
Colorectal cancer	121 (3.55)
Hepatocellular carcinoma	129 (3.78)
Melanoma	1,720 (50.43)
Nonsquamous non-small cell lung cancer	586 (17.18)
Renal cell carcinoma	448 (13.13)
Small cell lung cancer	177 (5.19)
Nivolumab dosing regimen	
No nivolumab	893 (26.18)
0.3 mg/kg Q3W	14 (0.41)
1 mg/kg Q2W	38 (1.11)
1 mg/kg Q3W	851 (24.95)
3 mg/kg Q2W	739 (21.67)
3 mg/kg Q3W	876 (25.68)
Best overall response	
Complete response	160 (4.69)
Partial response	680 (19.94)
Stable disease	619 (18.15)
Progressive disease	751 (22.02)
Noncomplete response/nonprogressive disease	17 (0.50)
No disease	4 (0.12)
Not evaluable	171 (5.01)
Not reported	18 (0.53)
Data not available	991 (29.05)

PPK, population pharmacokinetics; Q2W, every 2 weeks; Q3W, every 3 weeks.

PPK model development

The PPK model was developed in three stages, consisting of the base, full, and final models. All PPK model parameters were estimated using the first-order conditional estimation with interaction method implemented in NONMEM (v7.3, ICON Development Solutions, Hanover, MD).

Base model. The starting point of base model development was a previously developed time-invariant final model that included the effects of baseline body weight (BBWT) and baseline lactate dehydrogenase (BLDH) on CL and the effect of BBWT on the volume of distribution of the central compartment (VC), which were found to have significant effects on ipilimumab pharmacokinetics (PK).[17] The base model is a two-compartment model with zero-order intravenous infusion and first-order elimination, parameterized in terms of CL, VC, intercompartmental CL (Q), and the volume of distribution of the peripheral compartment (VP) and included the effects of BBWT and BLDH on CL and BBWT on VC, Q, and VP. Values of BLDH were rightward skewed and hence log transformed.

Structural model development assessed temporal changes in ipilimumab CL. Hyperbolic and sigmoid estimate of the maximal change in CL (Emax) models described the time-varying CL of ipilimumab and were compared with the model with time-invariant CL using Bayesian information criterion (BIC).

$$\text{Hyperbolic} - \text{Emax} = \exp\left(\frac{\text{Emax} \times T}{T_{50} + T}\right)$$

$$\text{Sigmoid} - \text{Emax} = \exp\left(\frac{\text{Emax} \times T^{\text{HILL}}}{T_{50}^{\text{HILL}} + T^{\text{HILL}}}\right)$$

The Emax parameter of a patient *i* is given by the following expression:

$$\text{Emax}_i = \text{Emax}_{\text{TV}} + \eta_{\text{Emax}_i}$$

where Emax_{TV} represents the population (typical value) estimate of the maximal change in CL over time (*T*); and $\eta_{\text{Emax}_i} \sim N\left(0,\omega^2\text{Emax}\right)$ is a normally distributed random variable, with mean 0, and variance ω^2Emax representing the interindividual variability (IIV) in Emax. T_{50} represents the time when the change in CL is 50% of Emax, and HILL, the sigmoidicity of the relationship with time.

Full model. The full model was developed from the base model by incorporating the following covariates on ipilimumab CL: tumor type (RCC, NSCLC, SCLC, CRC, or HCC vs. melanoma), line of therapy (first-line [1L] vs. second-line or greater [2L+]), and nivolumab dosing regimen (0.3 mg/kg Q3W, 1 mg/kg every 2 weeks [Q2W], 1 mg/kg Q3W, 3 mg/kg Q2W, and 3 mg/kg Q3W). The impact of performance status (PS) and coadministration with nivolumab on the magnitude of Emax was also assessed in the full model. The value of PS was derived from either the Eastern Cooperative Oncology Group PS or the Karnofsky PS scales. Functional relationships between continuous and categorical covariates and structural model parameters were modeled as described previously.[11,17] Estimated effects were considered statistically significant if their 95% confidence intervals (CIs) did not include 0. Covariates that had an effect of less than ± 20% on model parameters compared with the reference were considered to be similar and not clinically important. Covariates with an effect greater than ± 20% may be potentially clinically meaningful.

Final model. The final model was developed from the full model by stepwise backward elimination and utilized BIC to select the most parsimonious model. Covariates were retained if the BIC increased upon removing the effect of the covariate compared with the reference model at each step. A nonparametric bootstrap (*N* = 1,000) that evaluated the precision of the final estimated parameters was performed using the final model to determine parameter uncertainty and estimate 95% CIs. The bootstrap 95% CIs were compared with parameter values obtained from the original data set, and the analyses were conducted using Perl-speaks NONMEM (v4.4.8).

Model evaluation

Model evaluation was performed using standard goodness-of-fit plots and prediction-corrected visual predictive check (pcVPC) plots to provide an evaluation of model assumptions and population parameter estimates. The pcVPC was conducted using the final model (*N* = 500) and provided a graphical assessment of the agreement between the time course of model predictions and observations at the recommended dosing regimens for different tumor types. The check involved plotting the 5th, 50th, and 95th percentiles of observed serum concentration–time data with their corresponding 90% prediction intervals by dosing regimen. Diagnostic plots were prepared using R (v3.0.2) and pcVPC using Perl-speaks NONMEM.

Sensitivity analyses

Sensitivity analyses using the final model were conducted to estimate the effect of additional covariates on ipilimumab CL, which were not available in all patients. First, the effect of baseline ALB (BALB) on ipilimumab CL was tested because it was found to be associated with CL for anti–PD-1 agents.[11,16] Next, the effect of time-varying covariates such as ALB, lactate dehydrogenase (LDH), body weight (BWT) and PS (PST) were assessed on temporal change in CL. Covariates for which baseline values were significant toward ipilimumab CL were chosen for further assessment as time-varying covariates.

The functional relationships between baseline and time-varying covariate effects and structural model parameters were modeled using the following equation[18]:

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

where $\text{CL}_{\text{TV,REF}}$ is a fixed-effects parameter; P_i and $P_{i,j}$ are the parameter effects for baseline and time-varying covariates, 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. Missing covariate values over time within individuals were imputed using a next-observation-carried-backward approach.

The effect of best overall response (BOR) on magnitude of change in ipilimumab CL was assessed to test the hypothesis that improvement in disease condition is associated with a decrease in CL. BOR was assessed either by the bidimensional modified World Health Organization tumor response criteria or the unidimensional Response Evaluation Criteria in Solid Tumors (RECIST, v1.1).[19]

Model application

Simulations using the final model were conducted to support the safety of nivolumab 480 mg every 4 weeks (Q4W) following the last dose of combination therapy with nivolumab and ipilimumab in melanoma. The safety and efficacy of the combination of ipilimumab 3 mg/kg Q3W and nivolumab 1 mg/kg Q3W was approved for four doses followed by nivolumab monotherapy of 240 mg Q2W in patients with melanoma.[20] Nivolumab 3 mg/kg Q3W with ipilimumab 3 mg/kg Q3W exceeded the maximum tolerated dose.[21] Both monoclonal antibodies have distinct mechanisms of T-cell activation; therefore, starting high-dose nivolumab when ipilimumab concentrations are still present in the circulation after 3 weeks could exacerbate immune-mediated adverse events.

To ensure adequate safety, it was determined that the maintenance phase for nivolumab 480 mg Q4W be started 6 weeks after the last dose of induction therapy (as opposed to 3 weeks) to allow for adequate ipilimumab elimination. Ipilimumab exposures on days 1 (peak after the first dose), 21 (trough after

the first dose), 84 (trough after the fourth dose), and 105 (concentration 6 weeks after the fourth dose) were simulated in patients with melanoma who received induction treatment of ipilimumab 3 mg/kg Q3W and nivolumab 1 mg/kg Q3W for four doses to evaluate the extent of ipilimumab elimination.

RESULTS

PPK model development

Base model. Base model development included reassessment of the structural PK model and interindividual and residual error models developed previously.[17] Time-varying CL with a sigmoid Emax was selected as the BIC was lower than that of the models with time-invariant CL (by 84 points) and hyperbolic Emax (by 45 points). The interindividual variability on CL, VC, and Emax parameters were specified by a log-normal model and nonzero covariance as described previously.[11,17] The residual error was best described by a combined proportional and additive residual error model.

Full model. The full model was developed by simultaneously estimating the effects of all prespecified covariates. **Figure 1** shows the estimated effects of covariates on ipilimumab PPK parameters. The magnitude of the effect of BBWT on CL and VC was outside the ± 20% boundaries, which is consistent with results from the previous analysis.[17] Although the magnitude of the effect of BLDH on CL was statistically significant, it was < 20% and unlikely to be clinically meaningful, which is consistent with the previous analysis.[17]

The effect of nivolumab combination therapy on ipilimumab CL was tested as a categorical covariate with 5 levels (0.3 mg/kg Q3W, 1 mg/kg Q2W, 1 mg/kg Q3W, 3 mg/kg Q2W, and 3 mg/kg Q3W). Nivolumab 3 mg/kg Q2W, 1 mg/kg Q2W, and 1 mg/kg Q3W had statistically significant effects on ipilimumab CL, increasing it by approximately 18% (95% CI, 8–28%), 14% (95% CI, 1–28%), and 9% (95% CI, 5–13%), respectively, compared with monotherapy; however, the magnitudes of these effects were < 20% and were not considered to be clinically relevant. The effect of the nivolumab 0.3 mg/kg Q3W and 3 mg/kg Q3W regimens on CL were not statistically significant. Ipilimumab CL in patients with SCLC was significantly lower (–11.4%; 95% CI, –17.5% to –5%) than in patients with melanoma. However, there was no statistically significant difference in CL for NSCLC, CRC, HCC, or RCC compared with melanoma. Ipilimumab CL was significantly lower (–9.3%; 95 CI, –13.2% to –5.3%) in patients who received 1L treatment compared with patients who received 2L+ treatment; however, because the effect was < 20% it is not considered to be clinically important.

The magnitude of change in CL was represented as the ratio of CL at steady state (CL_{ss}) to CL at time 0 (CL0). The magnitude of the decrease in ipilimumab CL was significantly greater in patients receiving combination therapy with nivolumab than in patients receiving ipilimumab monotherapy. The effect of PS > 0 vs. PS = 0 on CL_{ss}/CL0 was not statistically significant.

Final model. Ipilimumab CL decreased over time and T_{50} was approximately 106 days (2,540 hours). The covariates retained in the final model were SCLC tumor type, line of therapy, the effect of the nivolumab dosing regimens of 1 mg/kg Q3W and 3 mg/kg Q2W on CL, and the effect of combination therapy with nivolumab on Emax. The final model is represented using the following equations and parameter estimates are shown in **Table 2**:

$$\mathrm{CL0}_i = \mathrm{CL0}_{\mathrm{REF}} \cdot \left(\frac{\mathrm{BBWT}_i}{\mathrm{BBWT}_{\mathrm{REF}}}\right)^{\mathrm{CL}_{\mathrm{BBWT}}} \cdot \left(\frac{\log(\mathrm{BLDH})_i}{\log(\mathrm{BLDH})_{\mathrm{REF}}}\right)^{\mathrm{CL}_{\mathrm{BLDH}}} \cdot e^{\mathrm{CL}_{\mathrm{SCLC}}} \cdot e^{\mathrm{CL}_{\mathrm{LINE}}} \cdot e^{\mathrm{CL}_{\mathrm{N1Q3W}}} \cdot e^{\mathrm{CL}_{\mathrm{N3Q2W}}} \cdot e^{\eta_{\mathrm{CLi}}}$$

$$\mathrm{Emax}_i = \mathrm{Emax}_{\mathrm{REF},i} + \mathrm{Emax}_{\mathrm{COMBO}} + \boldsymbol{\eta}\mathrm{Emax}_i$$

$$\mathrm{CL}_{i,j} = \mathrm{CL0}_i \cdot \exp\left(\frac{\mathrm{Emax}_i \cdot T^{\mathrm{HILL}}}{T_{50}^{\mathrm{HILL}} + T^{\mathrm{HILL}}}\right).$$

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

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

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

where $\mathrm{CL0}_{\mathrm{REF}}$ is the typical value of CL0 at the reference values of BBWT, BLDH, and the LINE value of 2L+; tumor type is referenced to melanoma, and nivolumab combined with ipilimumab is referenced to ipilimumab monotherapy. $\mathrm{VC}_{\mathrm{REF}}$, Q_{REF}, and $\mathrm{VP}_{\mathrm{REF}}$ are typical values of VC, *Q*, and VP, respectively, at the reference values of BBWT. $\mathrm{Emax}_{\mathrm{REF}}$ is the typical value of Emax at the reference value of ipilimumab monotherapy. $\mathrm{CL}_{\mathrm{BBWT}}$, $\mathrm{CL}_{\mathrm{BLDH}}$, $\mathrm{CL}_{\mathrm{SCLC}}$,$\mathrm{CL}_{\mathrm{LINE}}$, $\mathrm{CL}_{\mathrm{N1Q3W}}$, $\mathrm{CL}_{\mathrm{N3Q2W}}$ are the model parameters describing the effects of BBWT, BLDH, SCLC tumor type, line of therapy, nivolumab 1 mg/kg Q2W, and nivolumab 3 mg/kg Q2W on CL; $\mathrm{Emax}_{\mathrm{COMBO}}$ is the model parameter describing the effect of nivolumab coadministration on change in ipilimumab CL; and $\mathrm{VC}_{\mathrm{BBWT}}$ is the model parameter describing the effect of BBWT on VC. $\mathrm{CL}_{i,j}$ is the individual CL at each time point (*T*). VC_i, Q_i, VP_i, and Emax_i are the individual values of VC, *Q*, VP, and Emax, respectively, and ηCL_i, ηVC_i, and $\boldsymbol{\eta}\mathrm{Emax}_i$ are realizations from random distributions specific to individual *i* with means of 0 and variances of ω^2CL, ω^2VC, and ω^2Emax, respectively.

Model evaluation

The diagnostic plots of the final PPK model demonstrate that the model appropriately characterized ipilimumab PK. The pcVPC was conducted only in a subset of patients who received a dose and regimen that is approved or being evaluated in registrational studies for different tumor types (i.e., ipilimumab 3 mg/kg, ipilimumab 3 mg/kg Q3W plus nivolumab 1 mg/kg Q3W, ipilimumab 1 mg/kg Q3W plus nivolumab 3 mg/kg Q3W, and ipilimumab 1 mg/kg every 6 weeks plus nivolumab 3 mg/kg Q2W). **Figure 2** shows the pcVPC plots of all ipilimumab concentrations vs. time after the previous dose and ipilimumab trough concentrations after the first dose stratified by dosing regimen. The plots show that the model adequately

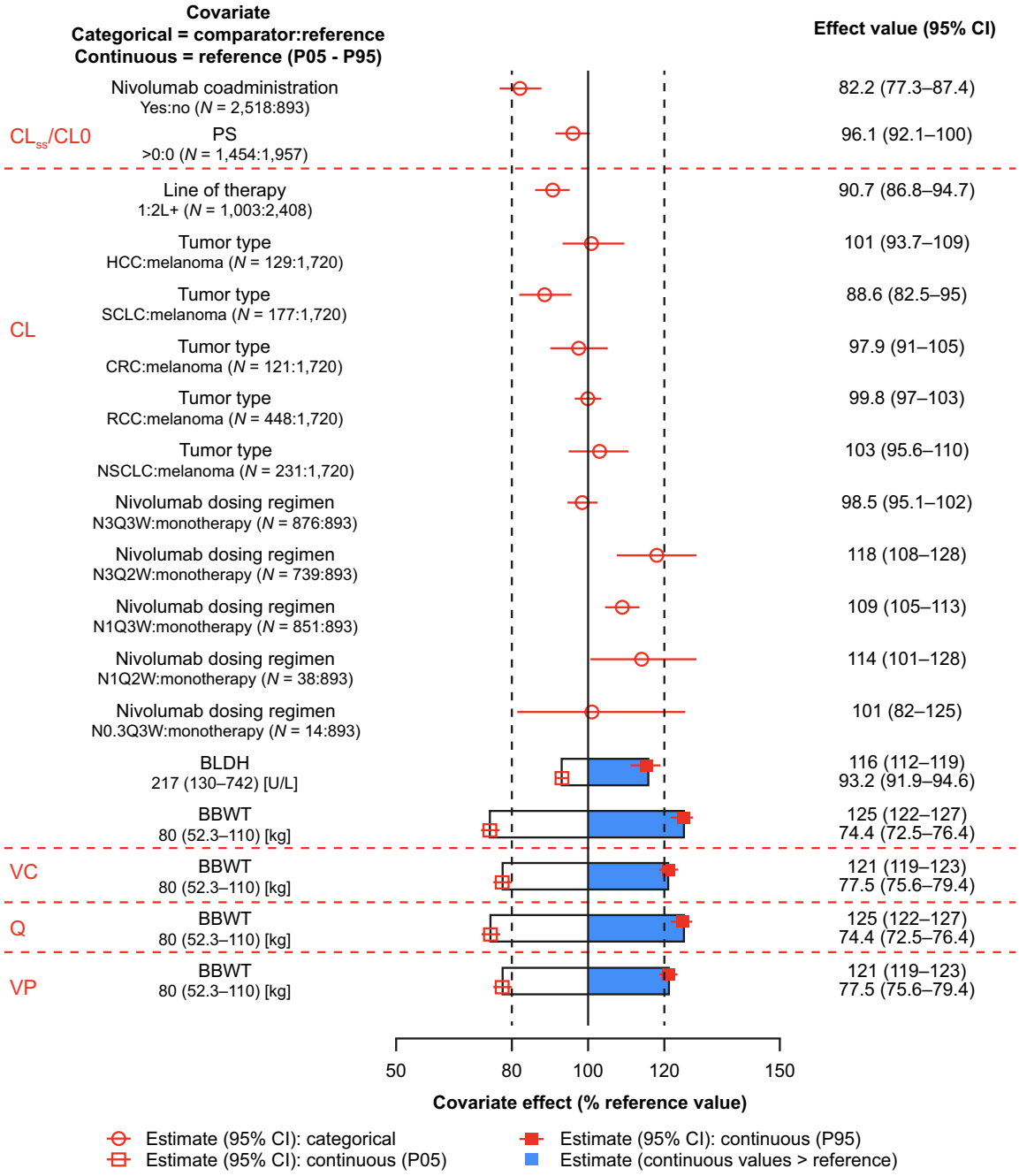

Figure 1 Covariate effects on ipilimumab pharmacokinetic full model parameters. Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines). Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the ends of horizontal boxes (horizontal lines). The open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate. The reference patient is defined as a patient with melanoma receiving ipilimumab monotherapy as 2L+, weighing 80 kg, and having a BLDH of 217 U/L. The parameter estimate in a reference patient is considered as 100% (vertical solid line); dashed vertical lines are at 80% and 120% of this value. Covariate effects on CL apply to both CL0 and CLss. CLss was calculated as CL0×exp(E_{max}). Estimated effects were considered statistically significant if their 95% CI did not cross the reference value (100%). 1L, first-line therapy; 2L+, second-line therapy or greater; BBWT, baseline body weight; BLDH, baseline lactate dehydrogenase; CI, confidence interval; CL, clearance; CL0, clearance at time 0; CLss, clearance at steady state; CRC, colorectal carcinoma; HCC, hepatocellular carcinoma; N0.3Q3W, nivolumab 0.3 mg/kg every 3 weeks; N1Q3W, nivolumab 1 mg/kg every 3 weeks; N3Q2W, nivolumab 3 mg/kg every 2 weeks; N3Q3W, nivolumab 3 mg/kg every 3 weeks; NSCLC, non-small cell lung cancer; P05, 5th percentile; P95, 95th percentile; PS, performance status; Q, intercompartmental clearance; Q2W, every 2 weeks; Q3W, every 3 weeks; RCC, renal cell carcinoma; SCLC, small cell lung cancer; VC, volume of distribution of the central compartment; VP, volume of distribution of the peripheral compartment.

Table 2 Parameter estimates for final model

Name[a] (units)	Estimate[b]	Standard error (RSE %)[c]	95% CI[d]
Fixed effects			
$CL0_{REF}$ (mL/hour)	14.1	0.231 (1.66)	13.6–14.5
VC_{REF} (L)	3.95	0.0255 (0.646)	3.90–4.00
Q_{REF} (mL/hour)	27.9	2.22 (7.97)	23.9–32.2
VP_{REF} (L)	3.18	0.0802 (2.52)	3.04–3.35
CL_{BBWT}	0.694	0.0315 (4.55)	0.63–0.75
V_{BBWT}	0.600	0.0293 (4.88)	0.54–0.66
$CL_{log-BLDH}$	0.703	0.0716 (10.2)	0.57–0.84
$Emax_{REF}$	−0.0644	0.0306 (47.4)	−0.12 to 0.002
T_{50} (hour)	2,540	86.5 (3.41)	2,365–2,727
HILL	7.43	1.58 (21.3)	4.93–19.3
CL_{SCLC}	−0.124	0.0317 (25.6)	−0.19 to −0.06
CL_{N1Q3W}	0.0950	0.0149 (15.6)	0.067–0.12
CL_{N3Q2W}	0.191	0.0185 (9.71)	0.15–0.23
CL_{LINE}	−0.0949	0.0162 (17.1)	−0.12 to −0.06
$Emax_{COMBO}$	−0.202	0.0305 (15.1)	−0.27 to −0.14
Random effects			
ω^2CL (-)	0.112 (0.334)	0.00514 (4.60)	0.102–0.123
ω^2VC (-)	0.0884 (0.297)	0.00939 (10.6)	0.070–0.110
ω^2*E*max	0.0158 (0.126)	0.00797 (50.5)	0.002–0.046
ω^2CL:ω^2VC	0.0404 (0.406)	0.00332 (8.22)	0.034–0.123
Residual error			
Proportional (-)	0.223	0.00568 (2.55)	0.21–0.23
Additive (μg/mL)	0.607	0.109 (17.9)	0.28–0.77

CLBBWT, CLlog - BLDH CL_{SCLC},CL_{LINE}, CL_{N1Q3W}, CL_{N3Q2W}, are the model parameters to describe the effect of BBWT, BLDH, SCLC tumor type, lines of therapy, N1Q3W and N3Q2W on CL, $Emax_{COMBO}$, is the model parameter to describe effect of nivolumab coadministration on change in ipilimumab CL and VC_{BBWT} is the model parameter to descibe effect of BBWT on VC.

2L+, second-line therapy or greater; BLDH, baseline lactate dehydrogenase; BBWT, baseline body weight; CI, confidence interval; CL, clearance; CL0, clearance at time 0; COMBO, combination therapy of ipilimumab with nivolumab; Emax, estimate of the maximal change in CL; *HILL*, representation of the sigmoidicity of relationship with time; *LINE*, line of therapy; N1Q3W, nivolumab 1 mg/kg every 3 weeks; N3Q2W, nivolumab 3 mg/kg every 2 weeks; PPK, population pharmacokinetics; *Q*, intercompartmental clearance; Q2W, every 2 weeks; Q3W, every 3 weeks; REF, reference value; RSE, relative standard error; SCLC, small cell lung cancer; T_{50}, time at which the change in $CL_{i,j}$ is 50% of Emax; VC, volume of distribution of the central compartment; VP, volume of distribution of the peripheral compartment.

[a]η shrinkage (%): η_CL: 12.9; η_VC: 29.1; η_Emax: 78.6, and ε shrinkage (%): 17.2. $CL0_{REF}$ is the typical value in a reference patient with melanoma, non-small cell lung cancer, renal cell carcinoma, hepatocellular carcinoma, or colorectal carcinoma tumor type, receiving ipilimumab monotherapy or combination therapy with nivolumab (0.3 mg/kg Q3W, 3 mg/kg Q3W, or 1 mg/kg Q2W) as 2L+, weighing 80 kg and BLDH of 217 U/L. VC_{REF}, Q_{REF}, and VP_{REF} are typical values in a reference patient weighing 80 kg. $Emax_{REF}$ is a typical value of change in magnitude of CL in a reference patient receiving ipilimumab monotherapy. These reference values represent the approximate median values in the PPK analysis data set. Random effects and residual error parameter names containing a colon (:) denote correlated parameters.

[b]Random effects and residual error parameter estimates are shown as variance (standard deviation) for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) 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]CI values are taken from bootstrap calculations (982 of 1,000 successful runs).

characterized the data from the 5th to the 95th percentiles. The plots show that the solid lines representing the 50th percentiles of the observed data pass through the respective 90% prediction interval (the shaded band) of the PK data up to the first 25 days after the previous dose and the first 100 days after the first dose. Thus, the data were well characterized, enabling the predictions of the model to be used for the subsequent exposure response of efficacy and safety analyses.

Sensitivity analyses

Ipilimumab CL was significantly lower in patients with higher BALB, but the magnitude of the change was < 20% and therefore not likely to be clinically important (data not shown).

The effects of BBWT, BLDH, and BALB on CL were statistically significant in the final model and hence were chosen to evaluate their respective longitudinal effects. In addition, the effect of time-varying PS was tested as a measure of disease severity. The effect of time-varying covariates was assessed relative to the model with time-invariant CL and time-invariant covariates. Model comparisons by BIC and estimates of the Emax are shown in **Table 3**. The BIC value for the model with time-varying covariates in addition to sigmoid Emax function was lower, demonstrating an improvement in the model fit. The estimate of Emax in the model with and without time-varying covariates was – 0.182 and – 0.213, respectively, showing that time-varying covariates only explained approximately 15% (calculated as (–0.182 to –0.213)/–0.213) of the change in CL.

Parameter estimates for the model with the sigmoid Emax function, including the effects of both baseline and time-varying

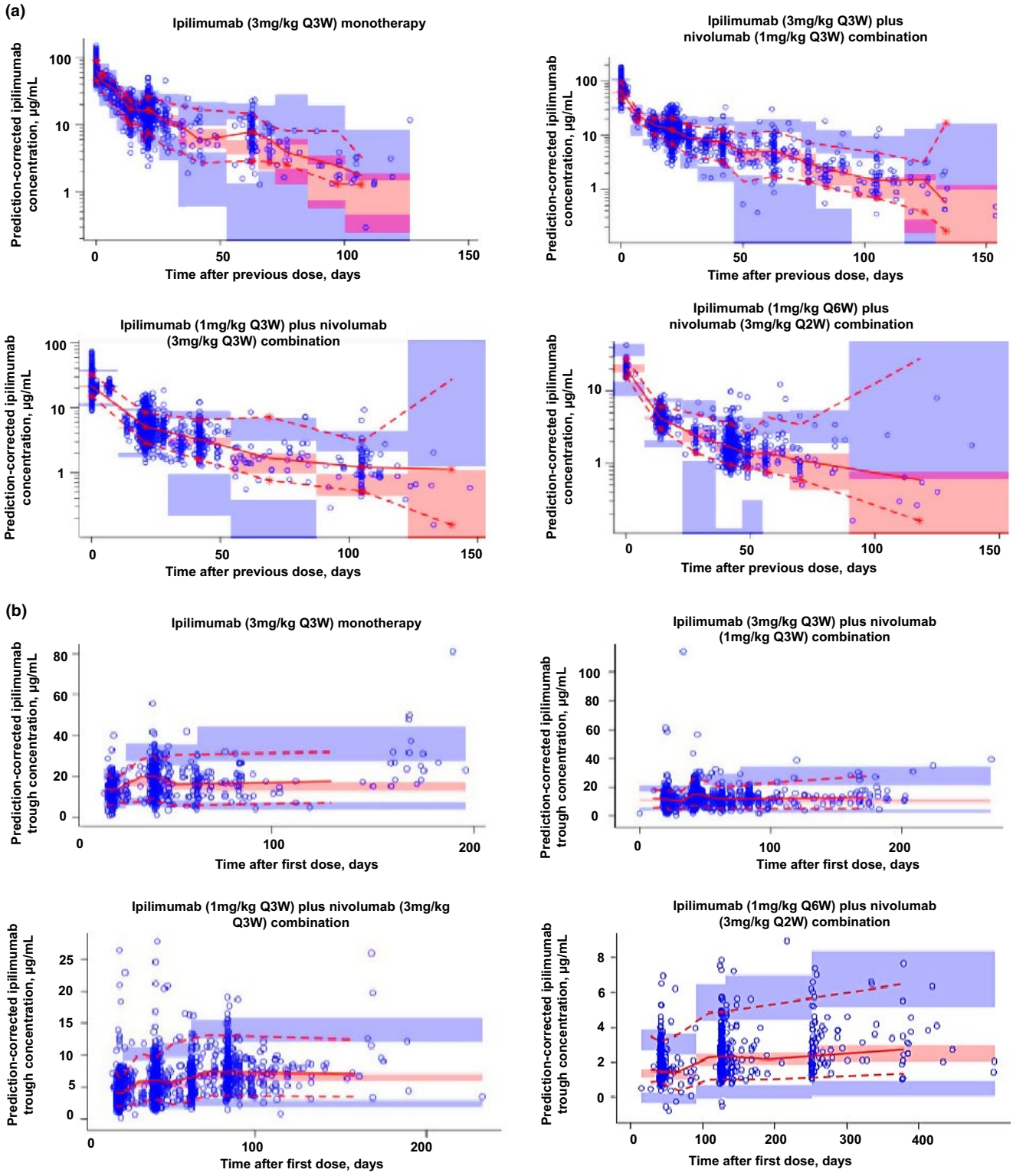

Figure 2 Prediction-corrected visual predictive check of concentrations vs. actual time (**a**) after previous dose and (**b**) after first dose, both stratified by selected ipilimumab dosing regimens. Plot points are observed data. Red solid and dashed lines represent the 5th and the 50th/95th percentiles of observed data, respectively. Blue-shaded areas represent the simulation-based 90% CIs for the 5th, 50th, and 95th percentiles of the predicted data. CI, confidence interval; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks.

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 timevarying 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

Empirical means the model that described time-varying clearance using the sigmoid Emax function with or without covariates.
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.

covariates, are presented in **Table S2**. The estimate of baseline covariates ($CL_{BBWT,}$ $CL_{log\text{-}BLDH,}$ $CL_{PS,}$ and CL_{BALB}) represents the between-patient effect of the covariate on CL, whereas the estimate of change in the time-varying covariates ($CL_{BWT,}$ $CL_{log\text{-}LDH,}$ $CL_{PST,}$ and CL_{ALB}) represents within-patient effects of the covariate on individual CL over time.

Higher baseline CL was associated with higher BBWT and BLDH, normal PS (PS > 0), and lower BALB. Estimated coefficients of time-varying PST and LDH were similar to baseline effects with respect to both magnitude and direction. However, CL decreased with increasing time-varying BWT. Thus, the effect of time-varying BWT is opposite in trend to that of the effect of BBWT. The effect of time-varying ALB on ipilimumab CL was greater in magnitude than the effect of BALB.

Changes in ipilimumab CL over time by BOR for monotherapy and combination therapy with nivolumab are presented in **Figure 3**. The typical CL_{ss} was 1.6% lower compared with baseline CL in patients with progressive disease (PD). The magnitude of change in CL (CL_{ss}/CL0) was significantly different (~ 15%) in patients with partial response vs. PD. In general, patients with response (responders; complete response and partial response) showed a greater decrease in CL over time compared with nonresponders (stable disease [SD] and PD). The magnitude of change in CL was greater in patients receiving combination therapy with nivolumab when compared with patients with the same BOR status who received ipilimumab monotherapy.

Model application

Simulated ipilimumab exposures following 3 mg/kg Q3W in combination with nivolumab 1 mg/kg Q3W are summarized in **Table 4**. The geometric mean ipilimumab exposure on day 84 was approximately one third of the peak exposure on day 1 and deemed to be safe. However, at the time of this analysis, no PK or safety data were available for the switch to monotherapy with nivolumab 480 mg Q4W. The predicted ipilimumab exposure of 9.3 μg/mL 6 weeks (day 105) after the last dose was sufficiently lower and supported the posology change to nivolumab 480 mg Q4W 6 weeks after the last combination dose of combination therapy.

DISCUSSION

This is the first report of time-varying CL for ipilimumab across multiple solid tumor types that includes data from both monotherapy and combination therapy with nivolumab, adding to the list of anticancer mAbs that demonstrate time-varying CL.[10–15,22] Serum ipilimumab concentrations were well described by a linear, two-compartment model with zero-order intravenous infusion and first-order elimination. The typical values of CL and VC (14.1 mL/hour and 3.95 L, respectively) referenced to patients with melanoma were similar (~10%) to those found in the previous analysis (15 mL/hour and 4.5 L, respectively), and the estimated half-life of 18 days in patients with melanoma was similar to that reported previously.[17]

The temporal change in ipilimumab CL was investigated in a previous analysis by addition of interoccasion variability; however, only four doses of ipilimumab monotherapy were administered over 12 weeks, and no clear change in CL over time was observed.[17] In this study, the availability of ipilimumab concentrations beyond the monotherapy dosing period of 12 weeks in patients with NSCLC and HCC, and the inclusion of PK data for ipilimumab plus nivolumab, enabled a more robust assessment of time-varying CL. Ipilimumab time-varying CL was described using a sigmoid Emax function similar to that used for other anti–PD-1 mAbs.[11,13–15,17] The magnitude of decline in CL was approximately 6% with ipilimumab monotherapy and was ~ 18% when combined with nivolumab. The extent of the decrease in CL with combination therapy was similar to that observed for nivolumab. A reversal of cachexia over time and thereby signaling a reduction in disease severity may be associated with a decrease in the CL of anticancer mAbs .[13,14] A phase III study showed that patients with melanoma who received ipilimumab and nivolumab combination therapy had significantly longer progression-free survival than ipilimumab alone,[20] which aligns with our findings that patients receiving the combination had a greater reduction in CL supporting the hypothesis that a decrease in CL over time may be a marker of treatment response. The T_{50} of approximately 106 days (2,540 hours) was similar to nivolumab when given in combination with ipilimumab. Typically cancer patients have their first scan at 8 weeks (56 days) and then a second confirmatory scan at around 16 weeks (112 days) after beginning therapy. Generally, patients who respond to immuno-oncology therapy show a decrease in tumor burden around the first and second scans. Thus, the 106 days for T_{50} may correspond to the timescale of tumor response. A high shrinkage on Emax interindividual variability was observed because of the limited data beyond 12 weeks and sparse sampling.

Implementation of a sigmoid Emax model empirically explains temporal changes in CL without assuming any mechanism. In our sensitivity analyses, the longitudinal effect of covariates whose baseline values were significant

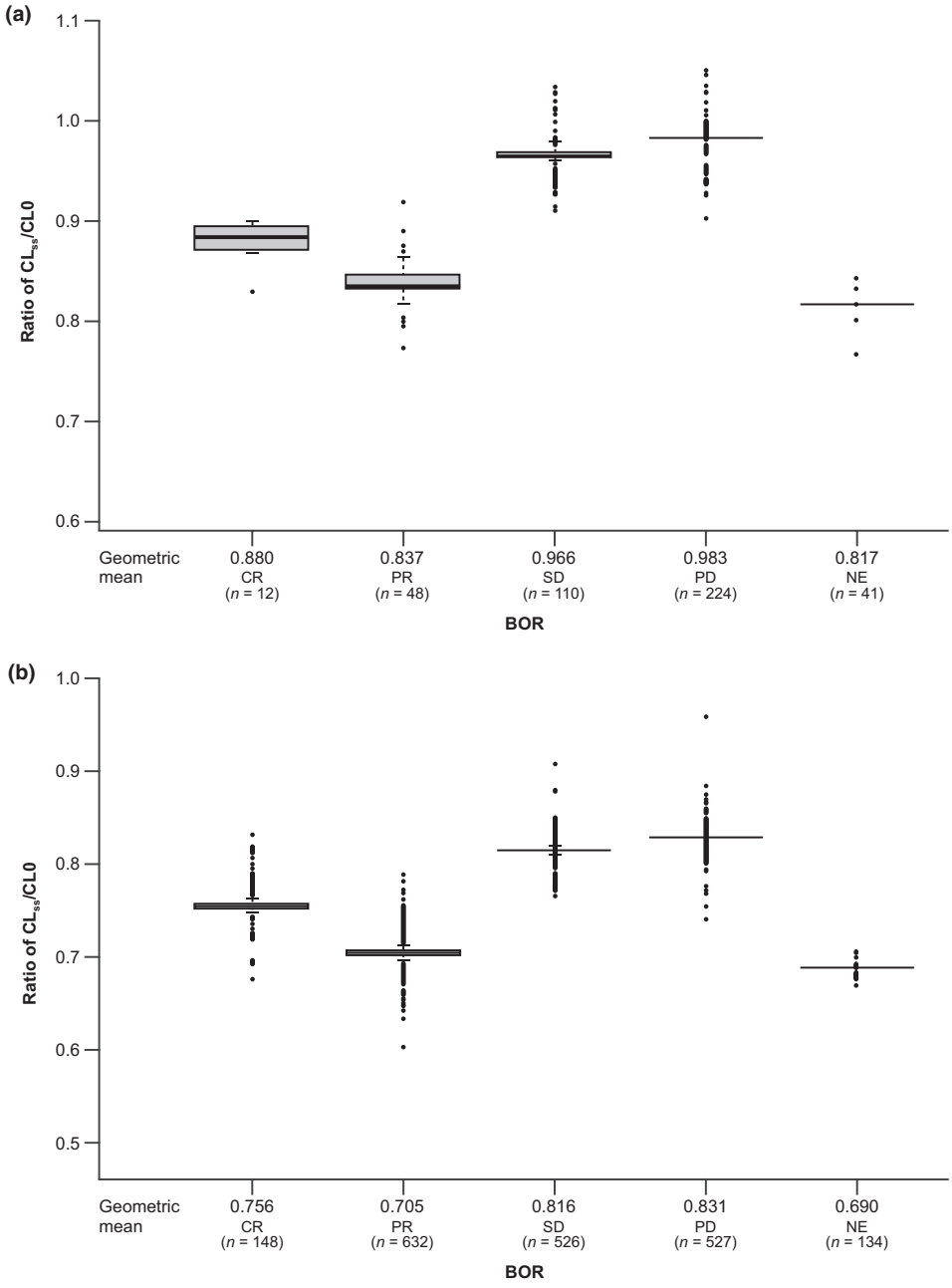

Figure 3 Model estimated change in ipilimumab CL across BOR status and treatment regimen. (**a**) Data plotted for ipilimumab monotherapy. (**b**) Data plotted for ipilimumab in combination with nivolumab in patients who received the dose and regimens that are approved or being evaluated in registrational studies for different tumor types. The boxplots represent median (bold line) and 25th and 75th percentiles of CL distribution. The whiskers represent 5th and 95th percentiles of the distribution. NN were included with SD and ND was included with NE in analysis. SD included patients reported with non-CR/non-PR and NE also included patients reported with no disease. BOR, best overall response; CL, clearance; CL0, clearance at time 0; CL_{ss}, clearance at steady state; CR, complete response; ND, no disease; NE, not evaluable; NN, non-complete response or non-progressive disease; PD, progressive disease; PR, partial response; SD, stable disease.

toward CL were evaluated on time-varying ipilimumab CL. These covariates are also indicators of disease severity.[23–25] Patients with higher BBWT had higher baseline CL. Fc receptor-mediated CL of immunoglobulin molecules occurs throughout the body in all cell types; therefore, patients with higher body weight (i.e., cellular mass) could be expected to have higher CL. However, an increase in body weight over time, which is often associated with reduced disease severity,[23] was associated with a decrease in ipilimumab time-varying CL. Intrapatient increases in ALB over time, which is another potential indicator of improvement in disease-related cachexia,[25] were associated with a decrease in ipilimumab time-varying CL. This result is consistent with those reported for association of ALB

Table 4 Ipilimumab exposure summary in patients with melanoma (induction: 1 mg/kg nivolumab and 3 mg/kg ipilimumab Q3W; maintenance: nivolumab 3 mg/kg Q2W)

Time after the first combination dose	*N*	Mean, μg/mL	Geometric mean, μg/mL	Median (minimum, maximum), μg/mL	Standard deviation	% CV
Day 1	618	65.3	62.6	61.4 (24.5, 376.0)	27.0	41.3
Day 21	618	11.0	10.4	10.9 (2.5, 28.3)	3.3	30.0
Day 84	618	21.7	20.0	20.7 (3.8, 87.2)	8.9	41.0
Day 105	618	10.9	9.3	9.8 (0.8, 67.5)	6.5	59.7

Day 1 represents peak concentration after the first combination dose. Day 21 represents trough concentration after the first combination dose; day 84 represents trough concentration after the fourth combination dose. Day 105 represents concentration at 6 weeks after the fourth combination dose.
CV, coefficient of variation; Q2W, every 2 weeks; Q3W, every 3 weeks.

with pembrolizumab and durvalumab CL.[14,16] Increase in LDH over time increased CL marginally, which is consistent with data reported for the nonsignificant effect of this covariate on pembrolizumab CL.[16] The improvement in PS was associated with a decrease in CL, although the results were not statistically significant. Directions of effects of these time-varying covariates were similar to those observed for nivolumab.

In our study, tumor size was assessed every 8 or 12 weeks, depending on the individual study protocol. Given that this is a treatment–response variable, simple backward imputation of missing tumor size collected infrequently does not seem appropriate. Also, the tumor size was measured using the methods of modified World Health Organization or RECIST. Therefore, the exclusion of tumor size from our model permits a more appropriate model to describe the time-varying CL of ipilimumab.

Inclusion of all time-varying covariates in the model explained only approximately 15% of the temporal effect estimated by the empirical model, suggesting that additional factors are associated with a change in ipilimumab CL. Although the time-varying covariates improved the goodness of fit of the model, their inclusion in the final model would limit future patient predictions. Therefore, time varying CL in the final model was described using a sigmoid Emax function and baseline covariates.

The CL of mAbs may serve as an early marker of treatment response.[13,14] In addition, we tested the association of treatment response and change in CL by evaluating the magnitude of the change in CL across different BOR categories through a sensitivity analysis. A greater decrease in ipilimumab CL was observed in responders vs. nonresponders and in patients receiving nivolumab combination therapy compared with ipilimumab monotherapy (**Figure 3**). Consistent with previous studies, these results indicate better treatment response in patients receiving combination therapy vs. monotherapy.[6,20] Although BOR was associated with a change in CL over time, its use to predict change in CL for future populations would not be possible.

This is the first report to describe ipilimumab PK when given in combination with nivolumab. The effect of nivolumab dosing regimens at 1 mg/kg Q2W and Q3W and 3 mg/kg Q2W had statistically significant effects on ipilimumab CL; however, the magnitudes of these effects were small (~14%, 9%, and 18% increase, respectively) and not expected to be clinically meaningful. There was no observed effect on ipilimumab CL with 0.1 or 3 mg/kg Q3W. In addition, the direction of change in ipilimumab CL was not consistent across nivolumab dosing regimens. The underlying mechanism for this interaction is unknown and the differences could be due to covariates not tested in the model. There are very few published examples of coadministered mAbs and PK interactions. Coadministration of rituximab or trastuzumab with bevacizumab did not alter the PK parameters for either drug.[26–28]

Ipilimumab CL was significantly different in patients with SCLC compared with advanced melanoma; however, the magnitude of the effect (11.4% decrease) was small and not expected to be clinically relevant. Ipilimumab CL values in NSCLC, RCC, HCC, and CRC tumor types were similar to data in melanoma. These findings are consistent with nivolumab PPK in that differences across advanced solid tumors are not considered to be clinically relevant.[11] In a phase IIIb/IV study, which started the maintenance phase with nivolumab 480 mg Q4W 6 weeks after the last combination dose, the results were found to be acceptable without any additional safety concerns.[29] These results showed that PK simulations from the model provided adequate support for the posology change in absence of clinical data at the time.

In conclusion, this is the first report of the PPK of an anti–CTLA-4-targeting anticancer agent demonstrating time-varying CL in patients receiving ipilimumab either as monotherapy or in combination with nivolumab. Our analyses demonstrate that similar temporal changes in CL are observed for other non–PD-1/PD-L1 anticancer mAbs, such as CTLA-4. We demonstrated that time-varying covariates could partially explain the phenomenon of change in CL over time, but an empirical function is required to account for unknown covariate effects. Increases in BWT and ALB over time were associated with decreases in CL, suggesting an association of CL reduction in disease severity. Ipilimumab CL was similar across both different tumor types and nivolumab dosing regimens.

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

Table S1. Summary of studies (in which ipilimumab was given for four doses or continuously) included in population pharmacokinetics analyses.

Table S2. Parameter estimates of model with time-varying covariate and empirical models.

Final Model Code

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Data Availability Statement. 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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