Clinical Cancer Research

Nivolumab Exposure–Response Analyses of Efficacy and Safety in Previously Treated Squamous or Nonsquamous Non–Small Cell Lung Cancer

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Abstract

Purpose: Nivolumab is a fully human IgG4 monoclonal antiprogrammed death-1 antibody with demonstrated efficacy, including durable responses and prolonged survival, in patients with previously treated, advanced non–small cell lung cancer (NSCLC). Exposure–response (E–R) analyses for efficacy and safety were conducted to inform the benefit–risk assessment of nivolumab in this patient population.

Experimental Design: The analyses used clinical trial data from patients with squamous ($n = 293$) or nonsquamous ($n = 354$) NSCLC from four clinical trials who received nivolumab doses of 1 to 10 mg/kg every 2 weeks. E–R efficacy analyses were performed by investigating the relationship between time-averaged nivolumab concentration after the first dose (C_{avg1}) and the probability of overall survival by histology. E–R safety analyses examined relationships between nivolumab C_{avg1} and hazards of adverse events leading to discontinuation or death (AEs-DC/D).

Results: Nivolumab exposure was not associated with overall survival [the 95% confidence interval (CI) of effect included 1] in patients with squamous (HR, 0.802; 95% CI, 0.555–1.16) or nonsquamous NSCLC (HR, 0.94; 95% CI, 0.683–1.29). Similarly, nivolumab exposure was not associated with AEs-DC/D in the overall population (HR, 0.917; 95% CI, 0.644–1.31). The risk of AEs-DC/D was similar among patients with squamous or nonsquamous histology.

Conclusions: Nivolumab monotherapy demonstrated a wide therapeutic margin, as evidenced by relatively flat E–R relationships over the range of exposures produced by doses of 1 to 10 mg/kg every 2 weeks (Q2W), supporting the use of the initially approved dose of 3 mg/kg Q2W in patients with NSCLC. *Clin Cancer Res; 23(18); 5394–405. ©2017 AACR.*

Introduction

The programmed death-1 (PD-1) receptor is an important immune inhibitory molecule ("checkpoint") expressed on activated T cells that modulates peripheral immune responses (1, 2). The binding of the PD-1 molecule to its ligands, programmed death ligand 1 (PD-L1) and 2 (PD-L2), inhibits T-cell signaling, downregulates expression of apoptotic molecules, and regulates the balance between immune tolerance and immunopathology (1). The expression of PD-L1 by tumor cells is one of several means by which cancer cells may evade immune surveillance and has been associated with poor clinical outcomes in patients with cancer (3–6). The blockade of tumor-mediated PD-L1 signaling restores antitumor immune responses and has emerged as a validated treatment strategy in cancer therapy. Nivolumab, a fully human IgG4 monoclonal antibody, selectively binds PD-1 receptors and antagonizes PD-L1 and PD-L2 (2). In principle, the efficacy of PD-1 blockade by nivolumab and other drugs is not limited to any single tumor type, but may augment the immune response to a number of histologically distinct tumors.

A regimen of nivolumab 3 mg/kg every 2 weeks (Q2W) is approved for use in melanoma, squamous and nonsquamous non–small cell lung cancer (NSCLC), renal cell carcinoma (RCC), classical Hodgkin lymphoma, and recurrent or metastatic squamous cell carcinoma of the head and neck (7). This dose was selected for clinical development based on the totality of *in vitro*, preclinical, pharmacodynamic, biomarker, and clinical efficacy and safety data (8). In phase III studies, nivolumab has demonstrated an overall survival (OS) benefit in squamous NSCLC (9), nonsquamous NSCLC (10), melanoma (11), RCC (12), and squamous cell carcinoma of the head and neck (13), and is being developed for several other tumor types. In addition, nivolumab has been well tolerated, with consistently lower adverse event (AE) rates than conventional chemotherapies. The percentage of treatment-related grade 3–4 AEs observed with nivolumab was similar between advanced NSCLC (9%; refs. 9, 10, 14) and melanoma (13%; refs. 11, 15, 16).

Exposure–response (E–R) analyses of efficacy and safety can be used to optimize dosing regimens and establish a benefit–risk profile. Earlier E–R evaluations led to the selection of the 3-mg/kg

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Translational Relevance

This study describes exposure–response analyses of the efficacy and safety of nivolumab in patients with previously treated non–small cell lung cancer (NSCLC). These analyses include data from 648 patients with squamous or nonsquamous NSCLC who received nivolumab 1 to 10 mg/kg every 2 weeks (Q2W) across four clinical trials. In a multivariate analysis, nivolumab exposure [defined as C_{avg1} (time-averaged nivolumab concentration after the first dose)] was not associated with overall survival or adverse events leading to discontinuation or death. Nivolumab monotherapy demonstrated a wide therapeutic margin, as evidenced by relatively flat exposure–response relationships with doses of 1 to 10 mg/kg Q2W. These results support the use of nivolumab 3 mg/kg Q2W, the initial approved dose, in patients with NSCLC. These analyses also supported the eventual approval of a 240-mg Q2W flat dose and further research exploring feasibility of a 480-mg dose given every 4 weeks in NSCLC.

dose for phase III evaluation (8, 17). The benefit–risk profile of nivolumab has previously been examined in E–R analyses in patients with advanced melanoma, which showed that nivolumab exposure, measured by the time-averaged concentration after the first dose (C_{avg1}), was not significantly associated with objective response rate (ORR) or AEs leading to discontinuation or death (AEs-DC/D; ref. 18). The availability of data from patients with squamous and nonsquamous NSCLC from two phase III studies (9, 10) and from earlier phase I (19) and phase II (14) studies allows comprehensive E–R analyses of nivolumab in NSCLC. Using data from these four studies (9, 10, 14, 19), we performed E–R analyses that provide insights into the relationships between nivolumab exposure and efficacy and safety endpoints among patients with NSCLC and that inform benefit–risk assessments for long-term use of nivolumab in this patient population. Results from these analyses supported subsequent approval of a 240-mg Q2W flat dose by the FDA in September 2016 (20, 21).

Materials and Methods

Analysis data

E–R analyses of efficacy and safety were performed with data from patients with squamous and nonsquamous NSCLC enrolled in four clinical studies: a phase I study in patients with advanced solid tumors (CA209003; ClinicalTrials.gov identifier: NCT00730639; ref. 19), a phase II study in treatment-refractory squamous NSCLC (CA209063, CheckMate 063; NCT01721759; ref. 14), a phase III study in previously treated squamous NSCLC (CA209017, CheckMate 017; NCT01642004; ref. 9), and a phase III study in previously treated nonsquamous NSCLC (CA209057, CheckMate 057; NCT01673867; ref. 10). Data from patients in the phase I study (CA209003) whose primary cancer was not NSCLC were excluded from analysis.

Nivolumab C_{avg1} obtained from a previously published population pharmacokinetic (PPK) model (22) was selected as the exposure metric in both the E–R efficacy (OS) and safety (AEs-DC/D) analyses. This early exposure metric was selected because it reflected the average exposure prior to the occurrence of the majority of clinical safety and efficacy events, and was available in all patients who received nivolumab treatment. In addition, the earlier PPK analysis showed that nivolumab clearance changes with time. These time-varying pharmacokinetics may be associated with improvement in disease status and the corresponding decrease in the rate of cancer-related cachexia. Therefore, using the early exposure metric C_{avg1} could avoid this confounding effect in the characterization of causal E–R relationships. It was expected that the E–R relationship of C_{avg1} would be similar to other early exposure metrics, such as C_{min1} (defined as the trough serum concentration after the first dose), as these summary measures were highly correlated ($r > 0.9$).

All studies were approved by Institutional Review Boards and independent ethics committees at participating institutions and were carried out in accordance with the ethical principles of the Declaration of Helsinki.

E–R efficacy: OS. Separate E–R analyses of OS were performed for squamous and nonsquamous NSCLC cohort to enable independent estimation of the E–R and covariate effects for each histology. OS was the primary endpoint in CA209017 and CA209057, whereas it was a secondary endpoint in CA209003 and CA209063.

E–R OS in squamous NSCLC. The E–R of OS included data from 293 patients with previously treated squamous NSCLC from a phase I study [CA209003 ($n = 53$); ref. 19], a phase II study [CA209063, CheckMate 063; NCT01721759 ($N = 115$); ref. 14], and a phase III study [CA209017 ($N = 125$); ref. 9; Table 1; Supplementary Table S1].

E–R OS in nonsquamous NSCLC. The E–R of OS included data from 354 patients with previously treated nonsquamous NSCLC in a phase I study [CA209003 ($n = 74$); ref. 19] and a phase III study [CA209057 ($n = 280$); ref. 10; Table 1; Supplementary Table S1].

E–R safety: AEs-DC/D and grade ≥3 AEs. A model-based assessment of the relationship between nivolumab exposure and safety was performed with data from patients with squamous or nonsquamous NSCLC with respect to AEs-DC/D. This was selected as a clinically meaningful endpoint, as it represents AEs that prevent a patient from continuing nivolumab therapy. AEs leading to discontinuation and AEs leading to death were therefore counted together as the safety endpoint. Events were included without regard to their association with nivolumab treatment, and AE terms that were clearly related to underlying disease progression (e.g., metastasis) were excluded from analysis.

The E–R of AEs-DC/D included data from 648 patients with squamous or nonsquamous NSCLC from one phase I study [CA209003 ($n = 128$); ref. 19], one phase II study [CA209063 ($n = 115$); ref. 14], and two phase III studies [CA209017 ($n = 125$); ref. 9 and CA209057 ($n = 280$); ref. 10; Table 1; Supplementary Table S1]. Graphic assessments were also conducted to evaluate the relationships between nivolumab dose and grade ≥3 AEs (any-cause and treatment-related).

Analysis methods

E–R efficacy: OS. The relationships between nivolumab exposure and OS in patients with squamous and nonsquamous NSCLC were described by separate semiparametric Cox proportional hazards (CPHs) models for each histology and included

Table 1. Baseline characteristics of patients included in the E–R analyses

Characteristic	E–R safety (AEs-DC/D) ($n = 648$)	E–R efficacy (squamous OS) ($n = 293$)	E–R efficacy (nonsquamous OS) ($n = 354$)
Dose, mg/kg, *n (%)*			
1	33 (5.1)	15 (5.1)	18 (5.1)
3	557 (85.9)	258 (88.1)	299 (84.5)
10	58 (9.0)	20 (6.8)	37 (10.4)
Sex, *n* (%)			
Male	408 (63.0)	220 (75.1)	187 (52.8)
Female	240 (37.0)	73 (24.9)	167 (47.2)
Cell type, *n* (%)			
Squamous	293 (45.2)	293 (100.0)	0
Nonsquamous	354 (54.6)	0	354 (100.0)
Unknown	1 (0.2)	0	0
Age, years, mean (SD)	62.5 (9.2)	63.5 (8.6)	61.6 (9.7)
Body weight, kg, mean (SD)	72.4 (16.5)	76.9 (17.0)	72.4 (15.9)
Disease stage at baseline, *n* (SD)			
Stage II or IIIA/IIIB	72 (11.1)	49 (16.7)	23 (6.5)
Stage IV	575 (88.7)	244 (83.3)	331 (93.5)
Not reported	1 (0.2)	—	0
ECOG PS, *n* (%)			
0	161 (24.8)	62 (21.2)	98 (27.7)
≥1	487 (75.2)	231 (78.8)	256 (72.3)
PD-L1 expression status, *n* (%)			
Positive (≥1%)	—	120 (41.0)	133 (37.6)
Negative (<1%)	—	93 (31.7)	122 (34.5)
Unknown	—	80 (27.3)	99 (28.0)
Nivolumab C_{avg1}, μg/mL, mean (SD)	32.1 (19.7)	30.0 (16.9)	33.7 (21.4)

Abbreviations: AEs-DC/D, adverse events leading to discontinuation or death; C_{avg1}, model-predicted time-averaged steady-state concentration; ECOG PS, Eastern Cooperative Oncology Group performance status; E-R, exposure-response; OS, overall survival; PD-L1, programmed death ligand 1; SD, standard deviation.

assessments of the modulatory effects of covariates on these E–R relationships. Separate efficacy analyses were performed for the squamous and nonsquamous NSCLC subtypes to allow determination of potential histology-specific E–R relationships.

Model development was conducted in several stages for each histology. First, the relationship between nivolumab exposure measures and OS was characterized using a base CPH model. Two functional forms of C_{avg1} were assessed as a predictor of the hazard of death: linear and log-linear. The model with the lowest value of the Bayesian information criterion (BIC) was selected. Second, a full covariate model was developed by incorporating all covariates of interest in the base CPH model for each histology. The full CPH model for squamous NSCLC was developed by incorporating the following baseline covariates into the base model: PD-L1 status (expression level ≥1%), smoking status, body weight, age, nivolumab baseline clearance, albumin, Eastern Cooperative Oncology Group performance status (ECOG PS), lactate dehydrogenase (LDH), baseline tumor size (the sum of the longest diameters of target lesions), disease stage, sex, and line of therapy. The full CPH model for nonsquamous NSCLC was developed by incorporating the same covariates as squamous NSCLC, except for disease stage, and also included prior maintenance therapy and *EGFR* mutation status. The majority of patients (93%) with nonsquamous NSCLC had stage IV disease; therefore, the effect of disease stage (stages II/III/IIIB vs. IV) on OS was not assessed in the E–R analysis for nonsquamous NSCLC. Nivolumab baseline clearance was obtained from a previously reported PPK model (22). Nivolumab baseline clearance was included in both squamous and nonsquamous OS full models, as drug clearance has been previously shown to be associated with OS in patients with advanced melanoma, in which lower baseline clearance was associated with better OS (18, 23). To evaluate the confounding effects of nivolumab baseline clearance and exposure (C_{avg1}) on OS, a sensitivity analysis was performed by excluding nivolumab baseline clearance from the full model.

Inference of covariate effects was based on the full model. The CPH model was evaluated by comparing the model-predicted cumulative probability of OS versus time with that obtained by Kaplan–Meier (K–M) analyses.

E–R safety: AEs-DC/D and grade ≥3 AEs. Although the efficacy analysis was histology-specific, the E–R safety analysis included combined data from patients with squamous and nonsquamous NSCLC. The risk of AEs-DC/D was expected to be similar regardless of tumor histology based on an earlier analysis showing the nature, frequency, and severity of treatment-related AEs to be similar across multiple dose levels and tumor types (8). AEs-DC/D were selected as safety endpoints for the model-based analysis, because they reflect a broad range of event types that may prevent patients from receiving treatment. The relationship between nivolumab exposure and AEs-DC/D was described by a semiparametric CPH model and included assessments of the modulatory effect of covariates on this E–R relationship (see methods in E–R OS).

Model development was conducted in a manner similar to the E–R models of efficacy. First, the relationship between nivolumab exposure measures and AEs-DC/D was characterized using a base CPH model. Second, a full covariate model was developed by incorporating all covariates of interest in the base CPH model. These covariates were body weight, age, ECOG PS, LDH, sex, albumin, line of therapy, disease stage, and histology.

The CPH model was evaluated by comparing model-predicted cumulative probability of AEs-DC/D versus time to that obtained by K–M analyses. In addition to the model-based assessment, the relationships between nivolumab dose and grade ≥3 AEs (any-cause and treatment-related) were visualized by the K–M analysis.

The E–R analysis, diagnostic graphics, and model evaluations were performed using S-Plus software (version 7.0 or higher; TIBCO Software Inc.).

Results

E–R efficacy: OS

Squamous NSCLC. Nivolumab exposure (C_{avg1}) was not associated with OS [the 95% confidence interval (CI) of the effect included 1] in patients with squamous NSCLC (HR, 0.802; 95% CI, 0.555–1.16). Because the base model with log(C_{avg1}) had a lower BIC relative to linear C_{avg1}, log-transformed C_{avg1} was selected for subsequent model development. The estimated effects of all covariates on the HR of OS were evaluated in the full model (Fig. 1A). Although nivolumab C_{avg1} was not significantly associated with OS, there was a slight trend toward improved OS with increasing exposure. Risk of death increased with increasing baseline clearance. Evaluation of the full E–R model for squamous NSCLC showed that the model-predicted means (90% CI) of OS for different doses (Fig. 2A) were consistent with the observed K–M curves of OS, indicating that the model provided a reasonable description of the observed data. Model evaluation was also performed for the sensitivity analysis (the model without baseline clearance) to further evaluate the impact of baseline clearance on the prediction of OS. This evaluation showed that both the full model and the full model without baseline clearance (Fig. 2B) provided reasonable descriptions of the observed OS data.

The associations between exposure, baseline clearance, and OS in the observed data were also explored. The marked differences between the K–M curves of OS for patients grouped by tertiles of C_{avg1} were not consistent with the relatively modest differences in the K–M curves of OS by dose level, even though the exposure in patients receiving 10 mg/kg was more than threefold higher than the exposure in patients receiving 3 mg/kg (Supplementary Fig. S1). These findings indicate that the within-dose differences in OS between patients grouped by tertiles of C_{avg1} were due to factors other than exposure, and demonstrate the drawbacks of comparing K–M curves of OS from nonrandomized patients, as well as the importance of employing a multivariable model to adjust for confounding

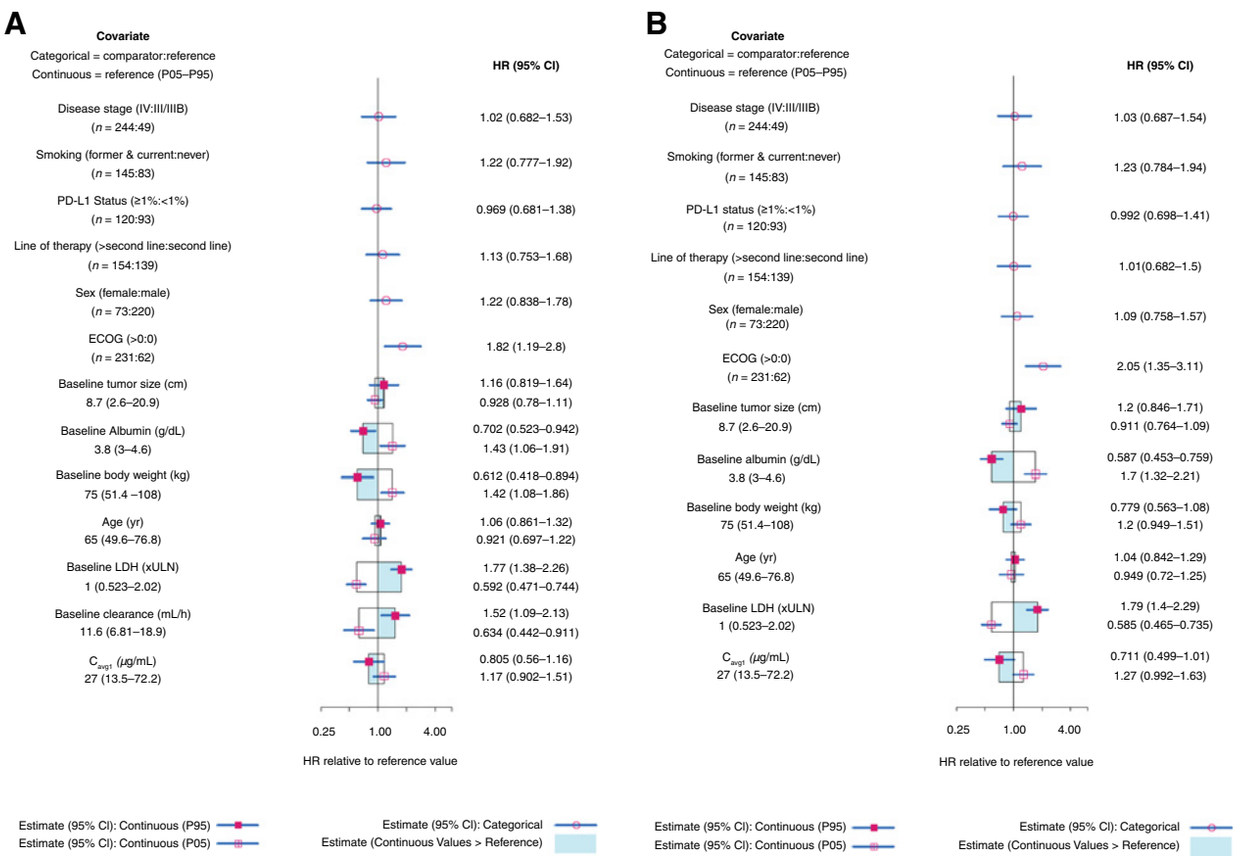

Figure 1.

Effect of nivolumab C_{avg1} and selected covariates on the HRs of squamous NSCLC OS in (**A**) the full model and (**B**) the sensitivity analysis. For continuous variables in the covariate analysis, median reference values with their 5th and 95th percentiles (P05–P95) are shown. Abbreviations: C_{avg1}, model-predicted time-averaged steady-state concentration; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death ligand 1; ULN, upper limit of normal.

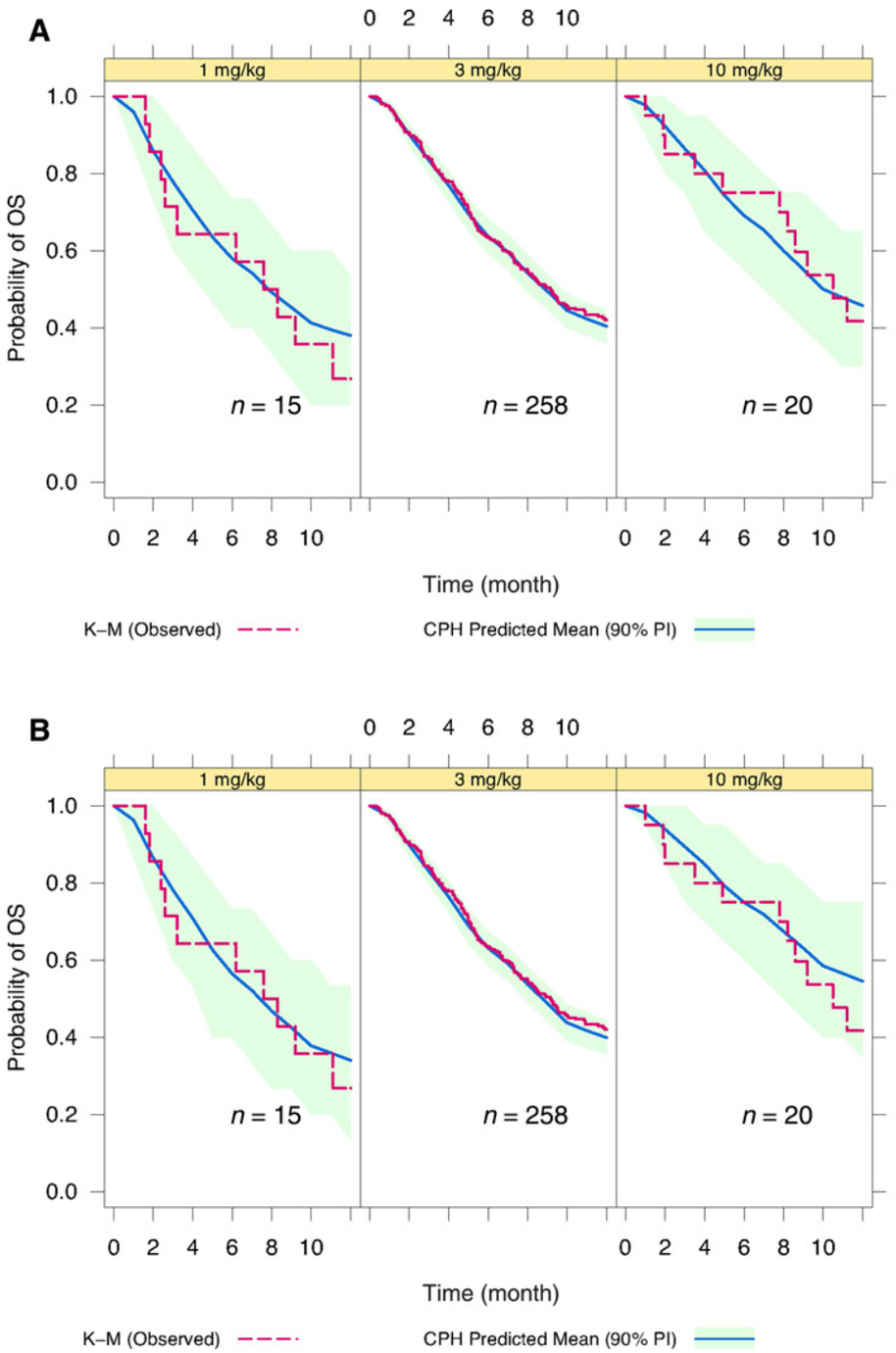

Figure 2.
Evaluation of squamous NSCLC E–R (OS) analysis using (**A**) the full model and (**B**) the model for sensitivity analysis by dose. The full model provided a reasonable description of the OS data, as the VPCs of the model-predicted mean (90% CI) OS by dose level were consistent with the observed OS based on the K–M analysis for doses ranging from 1 to 10 mg/kg. OS was slightly underpredicted at the 10-mg/kg dose in the sensitivity analysis when the clearance effect was not taken into account. Abbreviations: CI, confidence interval; CPH, Cox proportional hazards; E-R, exposure-response; K-M, Kaplan-Meier; NSCLC, non-small cell lung cancer; OS, overall survival; PI, prediction interval; VPC, visual predictive check.

factors. After taking into account the effect of baseline clearance, further evaluation of the E–R relationship was performed, and patients were then categorized into three groups based on baseline clearance value (Supplementary Fig. S2). After accounting for the effect of baseline clearance, there was no association found between exposure and response, except in the third tertile of baseline clearance (the group having the poorest OS).

In addition, the risk of death was greater among patients with lower baseline albumin, ECOG PS >0, lower baseline body weight, and higher baseline LDH (the 95% CI of the effect did not include 1). The 95% CI of all other covariates evaluated (PD-L1 status, smoking status, baseline tumor size, line of therapy, disease stage, sex, and age) included unity, indicating a lack of evidence for the effect of these variables on OS.

Nivolumab C_{avg1} is a function of nivolumab clearance and dose; therefore, the potential for confounding the estimated effects of these predictors was assessed by examining the correlation between the estimated coefficients for these predictors. The correlation between the estimated effects was low ($r = 0.3$),

indicating that the full model containing these effects was not overparameterized and that both of these effects could be estimated simultaneously in the same model.

Furthermore, the consequence of not including baseline clearance as a predictor in the model was assessed by a sensitivity analysis (excluding the effect of baseline clearance). The estimated effects of all variables (C_{avg1} and covariates) on the HR of OS were assessed in the full model without baseline clearance effect (Fig. 1B). The model that included baseline clearance had a slightly numerically lower BIC than the model that did not include baseline clearance, supporting the model that incorporated baseline clearance. After removing baseline clearance from the analysis, ECOG PS, baseline albumin, and baseline LDH remained significantly associated with OS (the 95% CI of the effect did not include 1), which was consistent with the full model that included clearance. Although the effect of nivolumab C_{avg1} on OS remained nonsignificant (the 95% CI of the effect included 1) after removing the effect of baseline clearance, there was a trend toward improved OS in patients with higher nivolumab exposure. Baseline body weight was not associated with OS in this sensitivity analysis, which was not surprising, considering the correlation between baseline clearance and body weight observed in the PPK analysis (20).

The E–R model was applied to assess the sensitivity of the HR of OS over the range of C_{avg1} values for the 3-mg/kg Q2W dose, using the median C_{avg1} at the 3-mg/kg dose as the reference exposure (Supplementary Table S2). The HR was slightly lower at the C_{avg1} median of the 10-mg/kg dose (HR, 0.772; 95% CI, 0.502–1.19) and the 95th percentile of the 3-mg/kg dose (HR, 0.926; 95% CI, 0.814–1.05) relative to C_{avg1} at the median of the 3-mg/kg dose. However, the 95% CI of the HR included 1, suggesting a relatively flat E–R relationship over this exposure range.

Nonsquamous NSCLC. Similar to the results with squamous NSCLC, nivolumab exposure (C_{avg1}) was not associated with OS (the 95% CI of effect included 1) in patients with nonsquamous NSCLC (HR, 0.94; 95% CI, 0.683–1.29). Two functional forms of C_{avg1} (linear and log-transformed) were assessed as covariates of the hazard of death in nonsquamous NSCLC. C_{avg1} was not associated with OS based on BIC. In addition, the base model with $\log(C_{avg1})$ had a lower BIC relative to untransformed C_{avg1}. Therefore, log-transformed C_{avg1} was selected in the base model for subsequent model development. The estimated effects of all covariates (C_{avg1}, baseline clearance, and others) on the HR of OS were evaluated in the full model (Fig. 3A). Nivolumab C_{avg1} was not significantly associated with OS, and the effect of C_{avg1} on OS in nonsquamous NSCLC was markedly less than that in the squamous NSCLC E–R analysis (Fig. 2A). The risk of death increased with increasing baseline clearance, and the magnitude of the effect of baseline clearance on OS was much greater relative to that in the squamous E–R analysis (Figs. 1A and 3A).

Aside from baseline clearance, the covariates with a significant effect on OS were ECOG PS, PD-L1 status, line of treatment, body weight, and baseline LDH (the 95% CI of the effect did not include 1). The 95% CIs of all other covariates evaluated (prior maintenance therapy, *EGFR* mutation status, smoking status, sex, baseline albumin, baseline tumor size, and age) included unity, indicating a lack of evidence for the effect of these variables on OS.

The potential confounding of the effects of baseline clearance and C_{avg1} was assessed by examining the correlation between these estimated effects. The correlation between the estimated effects was low ($r = 0.31$), indicating that the full model containing these effects was not overparameterized and both effects could be estimated simultaneously in the same model.

A sensitivity analysis (excluding the effect of baseline clearance) was performed to assess the potential confounding effect of nivolumab baseline clearance on the estimated effects of C_{avg1}. The model that included baseline clearance had a much lower BIC than the model that did not include baseline clearance (2423.2 vs. 2450.6), indicating that the model including baseline clearance provided a better description of the data. After removing the effect of baseline clearance, nivolumab C_{avg1} and baseline albumin were significantly associated with OS (the 95% CI of the effect did not include 1), and patients with higher exposure or higher baseline albumin had better OS. Baseline body weight was not associated with OS in this model (Fig. 3B).

To understand the impact of nivolumab treatment on the risk of death, the HR of OS was predicted from the full model in nonsquamous NSCLC at various values of C_{avg1}. The median C_{avg1} at the 3-mg/kg dose was used as the reference (Supplementary Table S2). The HRs were comparable at the C_{avg1} median of the 10-mg/kg dose (HR, 0.93; 95% CI, 0.64–1.35) and the 95th percentile of the 3-mg/kg dose (HR, 0.979; 95% CI, 0.875–1.09) relative to C_{avg1} at a median of the 3-mg/kg dose. The similar HRs at the 10- and 1-mg/kg doses, relative to the 3-mg/kg dose, further supported a flat E–R relationship in nonsquamous NSCLC.

Similar to the results in the E–R analysis in patients with squamous NSCLC, evaluation of the full nonsquamous NSCLC E–R model showed that model-predicted means (90% CI) of OS for different doses (Fig. 4A) were consistent with the observed K–M analyses of OS, indicating that the full model provided a reasonable description of the observed data. Model evaluation was also performed for the sensitivity analysis (the model without baseline clearance) to further evaluate the impact of baseline clearance on prediction of OS in the nonsquamous E–R analysis. Unlike results for the model evaluation from the squamous E–R analysis, the model without baseline clearance overpredicted OS at the high end of the dose range (10 mg/kg) and underpredicted OS at the low end of the dose range (1 mg/kg; Fig. 4B). The evaluation results for the sensitivity analysis further supported the use of the full model that included baseline clearance, as it provided a better description of the observed OS data.

Further exploration of observed data was performed to evaluate the association between exposure, baseline clearance, and OS. Observed OS data in NSCLC from the K–M analysis with the 3- and 10-mg/kg doses, with pooled data from squamous and nonsquamous NSCLC, were presented graphically (Supplementary Fig. S3). Although there was an E–R relationship within each dose level, the E–R relationship was not consistent across dose levels. Specifically, although the exposure of patients in the highest tertile of the 3-mg/kg dose (29–75 μg/mL) was lower than the exposure in the second tertile of the 10-mg/kg dose (79–96 μg/mL), OS was better (median OS of 17.4 vs. 9.2 months, respectively). This suggested that unknown factors (other than exposure) were associated with OS. To evaluate the E–R relationship after taking into account the baseline clearance effect, patients were categorized into three groups based on baseline clearance value (Supplementary Fig. S2A). After accounting for baseline clearance effect, there was no association between

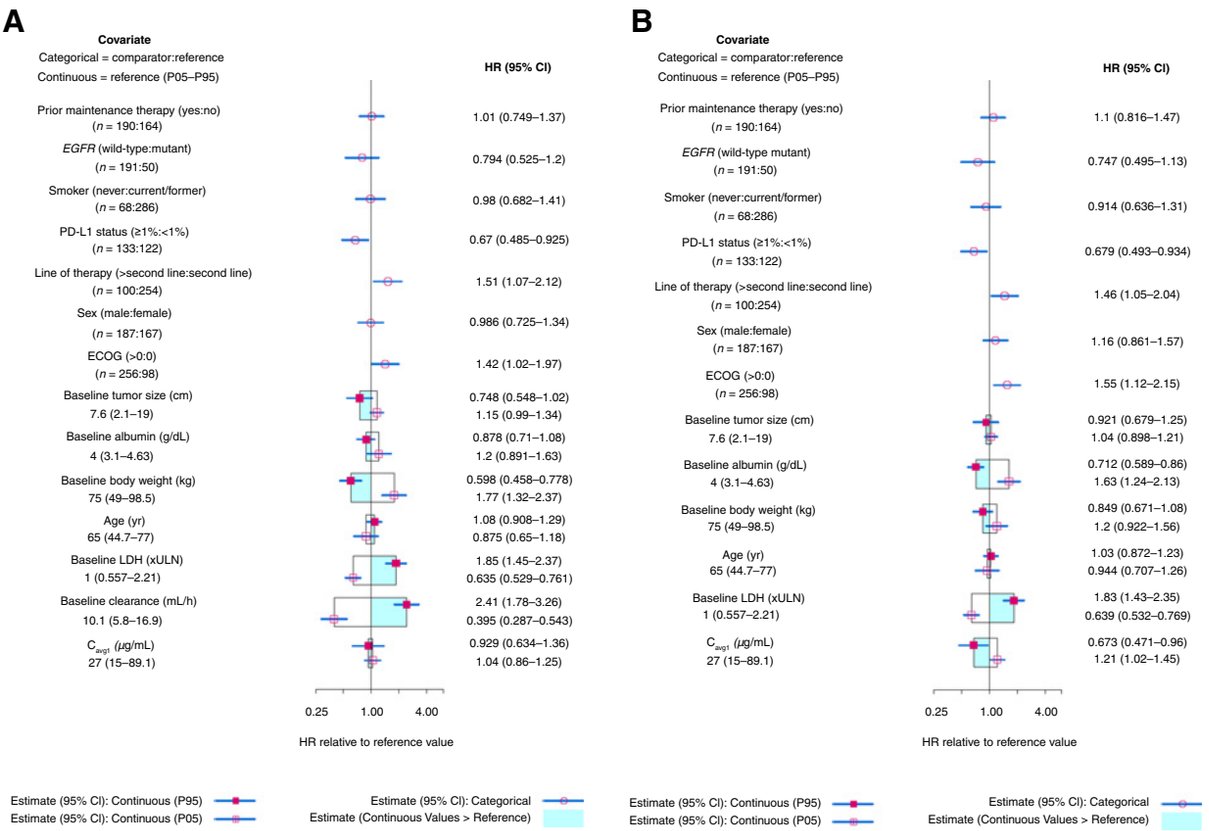

Figure 3.

Effect of nivolumab C_{avg1} and selected covariates on HRs of nonsquamous NSCLC OS in (**A**) the full model and (**B**) the sensitivity analysis. For continuous variables in the covariate analysis, median reference values with their 5th and 95th percentiles (P05–P95) are shown. Abbreviations: C_{avg1}, model-predicted time-averaged steady-state concentration; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death ligand 1; ULN, upper limit of normal.

exposure and response, except in the third tertile of baseline clearance (the group with the poorest OS).

E–R safety: AEs-DC/D and grade ≥3 AEs. Similar to the efficacy results, nivolumab exposure (C_{avg1}) was not associated with toxicity. Two functional forms of C_{avg1} (linear and log-linear) were assessed as potential predictors of the hazards of AEs-DC/D. Although C_{avg1} was not significantly associated with the hazard of AEs-DC/D in either of these models, the log-linear model was selected based on the BIC. All estimated effects in the full model were presented graphically (Fig. 5A), with HRs across the predictor ranges and associated 95% CIs. There was no significant effect of C_{avg1} on the risk of AEs-DC/D. Covariates with a significant effect on the hazard of AEs-DC/D (the 95% CI did not include 1) were line of therapy, ECOG PS, baseline serum albumin, and baseline LDH. Specifically, the risk of AEs-DC/D was greater for patients who had received more than two previous therapies and had an ECOG PS >0. Furthermore, the risk of AEs-DC/D increased with decreasing albumin and increasing baseline LDH. The interactions between these effects and C_{avg1} were not significant, indicating that these effects were independent of nivolumab exposure. The 95% CI of the effect of all other variables (disease stage, histology, sex, body weight, and age) in the full model included unity, indicating a lack of effect of these variables on AEs-DC/D. Notably, the risk of AEs-DC/D was similar for patients with squamous or nonsquamous histology. Correlations between the parameter estimates were all small, indicating that the model was not overparameterized. The highest correlation was between the parameter estimates for histology and line of therapy ($r = -0.286$). Model evaluation results were determined by dose (Fig. 5B); the K–M curves were generally in good agreement with the CPH model predictions, indicating adequate model performance. Similar to the AEs-DC/D results, K–M curves showed that there was no apparent relationship between nivolumab dose and any-cause or treatment-related grade ≥3 AEs (Supplementary Fig. S4A and S4B, respectively).

Discussion

In this analysis of clinical data from four studies of nivolumab in patients with NSCLC (9, 10, 14, 19), nivolumab monotherapy demonstrated a wide therapeutic margin, as evidenced by relatively flat E–R relationships over the range of nivolumab exposures (measured by C_{avg1}) produced by doses of 1 to 10 mg/kg Q2W. Results were consistent among patients with squamous and nonsquamous NSCLC. Exposure was not significantly associated with OS after accounting for the

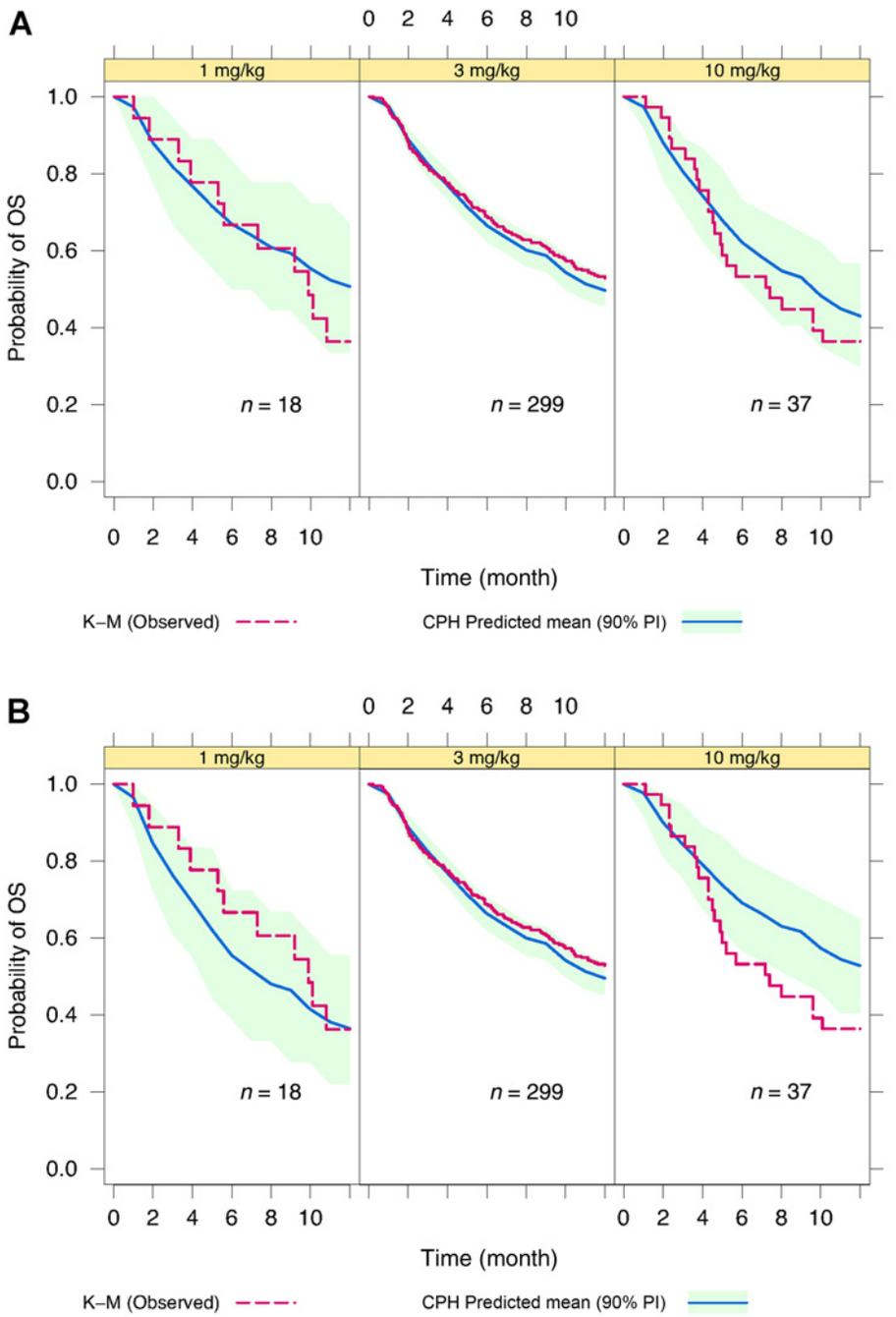

Figure 4.

Evaluation of nonsquamous NSCLC E–R (OS) analysis using the (**A**) full model and (**B**) model for sensitivity analysis by dose. The full model provided a reasonable description of OS data, as the VPCs of the model-predicted mean (90% CI) OS by dose level were consistent with the observed OS based on K–M analysis for doses ranging from 1 to 10 mg/kg. The model without including clearance effect provided a poor description of the OS data (sensitivity analysis). OS data were under- and overpredicted at the 1-mg/kg and 10-mg/kg doses, respectively. Abbreviations: CI, confidence interval; CPH, Cox proportional hazards; E-R, exposure-response; K-M, Kaplan-Meier; NSCLC, non-small cell lung cancer; OS, overall survival; PI, prediction interval; VPC, visual predictive check.

effect of baseline clearance. However, baseline clearance was significantly associated with OS in both the squamous and nonsquamous NSCLC E–R analyses. Similarly, in a previous E–R analysis of nivolumab using ORR as an efficacy measure, baseline CL, but not exposure, was a significant covariate in both squamous and nonsquamous NSCLC (24). Our results

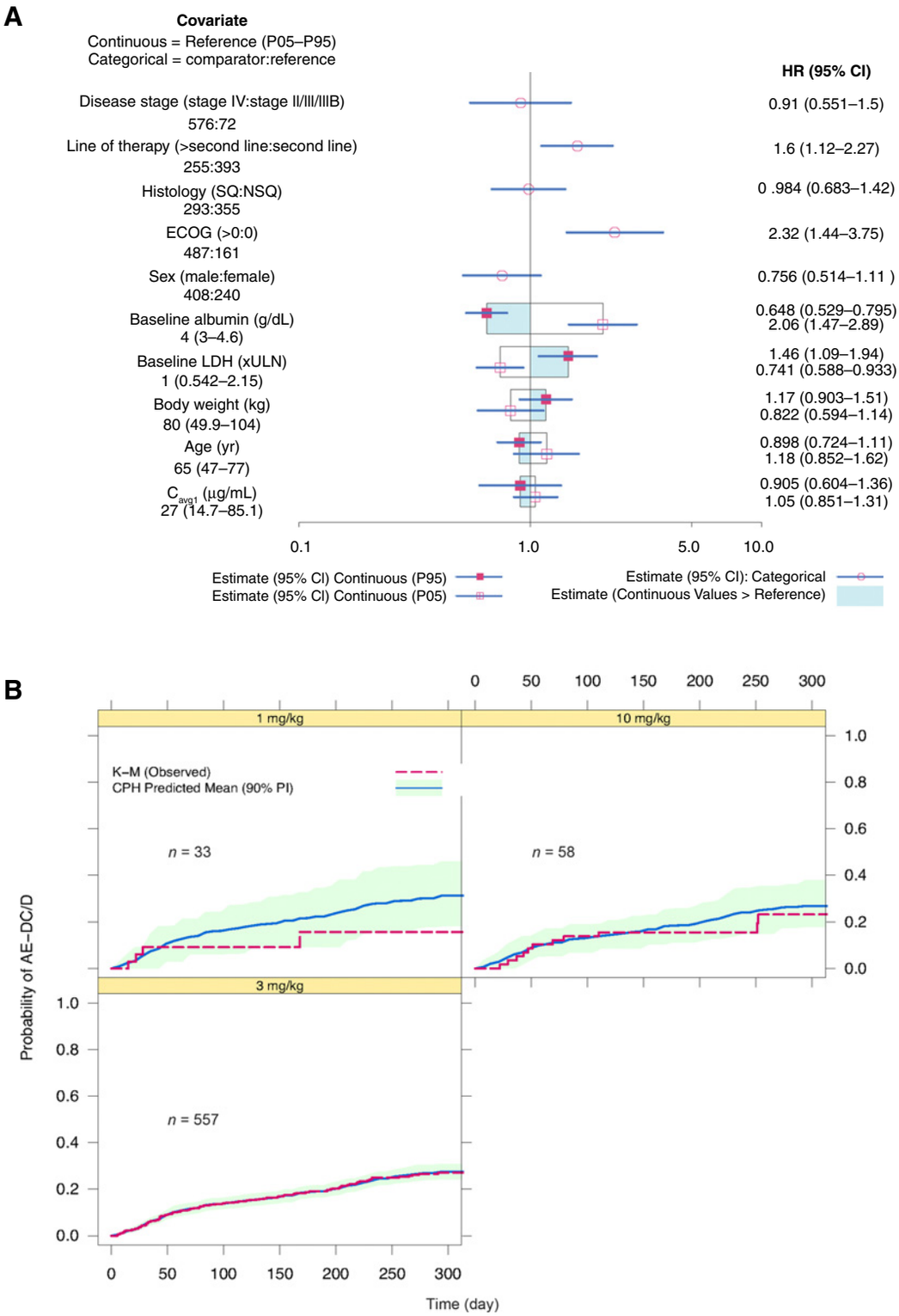

Figure 5.

Evaluation of E–R (AEs-DC/D) in NSCLC in the full model using (**A**) estimated covariate effects and (**B**) VPCs. For continuous variables in the covariate analysis, median reference values with their 5th and 95th percentiles (P05–P95) are shown. Abbreviations: AEs-DC/D, adverse events leading to discontinuation or death; C_{avg1}, model-predicted time-averaged steady-state concentration; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; E-R, exposure-response; HR, hazard ratio; LDH, lactate dehydrogenase; NSCLC, non-small cell lung cancer; NSQ, non-squamous; PI, prediction interval; SQ, squamous; ULN, upper limit of normal; VPC, visual predictive check.

were also similar to those reported in advanced melanoma, in which patients with lower baseline clearance had improved OS (18, 22). The effect of exposure (C_{avg1}) was not expected to be completely confounded by the effect of clearance in these analyses, because the nivolumab C_{avg1} values were obtained from a range of doses, and the correlation of these parameter estimates was not high ($r < 0.9$). Exposure was not significantly associated with OS in both full model analyses, and HRs at the lower (1-mg/kg) and higher (10-mg/kg) doses were similar to the HR at the 3-mg/kg dose, suggesting that increasing nivolumab exposure by administering doses higher than the currently approved nivolumab dose (3-mg/kg Q2W) is unlikely to improve OS in patients with squamous or nonsquamous NSCLC.

In a sensitivity analysis that excluded nivolumab baseline clearance, the risk of death was greater among patients with baseline ECOG PS >0 and lower baseline albumin. This might be due to the fact that baseline clearance was reflective of the overall baseline disease state of patients and, therefore, that the effect was redistributed among other covariates that were indicative of disease state. This finding is supported by results from a PPK analysis showing that higher ECOG PS was associated with higher nivolumab baseline clearance (22) and was also consistent with previous reports indicating that clearance could be a surrogate for the disease state (23, 25). The magnitude of the effect of baseline clearance on OS was greater in nonsquamous than in squamous NSCLC; this result may be associated with differences in baseline disease status between the squamous and nonsquamous NSCLC populations. In addition, nonsquamous histology has historically been associated with better OS than squamous histology (26). Furthermore, in previous analyses, poor ECOG PS (27) and lower baseline albumin were independent prognostic factors for reduced OS in patients with NSCLC (27, 28).

An OS benefit with nivolumab has been demonstrated regardless of tumor PD-L1 expression level in previously treated squamous NSCLC (9), whereas the magnitude of the OS benefit appeared to be greater with increasing PD-L1 expression in previously treated nonsquamous NSCLC (10, 29). In our analyses, PD-L1 expression was significantly associated with OS in patients with nonsquamous but not squamous NSCLC, which is consistent with observations in the clinical trials (9, 10). Although only patients with PD-L1–positive tumors had objective responses after treatment with nivolumab in the phase I study (19), patients with either PD-L1–positive or PD-L1–negative melanoma and NSCLC in a series of larger subsequent studies responded to nivolumab, with a similar duration of response (9–11). For this reason, PD-L1 status alone did not appear to be sufficient for the selection of previously treated patients with NSCLC for nivolumab therapy.

Body weight was significantly associated with efficacy in both E–R efficacy models, with lower OS in patients with lower body weight. Cachexia due to loss of appetite is a common symptom associated with cancer severity. Although it must be acknowledged that lower baseline body weight in patients with cancer was not always associated with weight loss, the association between body weight and lower OS was consistent with previous reports of lower progression-free survival in patients with NSCLC who lost weight during chemotherapy (30).

In our study, nivolumab exposure was not associated with toxicity, measured using AEs-DC/D, in the overall population. The risk of AEs-DC/D was similar among patients with squamous or nonsquamous histology. Similar to the AEs-DC/D results, there was no apparent relationship between nivolumab exposure and any-cause or treatment-related grade $\geq$3 AEs. These results were consistent with a previous E–R analysis of the safety of nivolumab 0.1 to 10 mg/kg Q2W in patients with melanoma (18, 31). In our analysis, baseline ECOG PS and line of therapy were significantly associated with the risk of AEs-DC/D in patients with NSCLC, which was not unexpected, given that ECOG PS and extensive prior treatment have been recognized as indicators of poor prognosis in patients with diverse cancer types, and may also reflect comorbidities and residual AEs associated with prior treatment regimens.

Results of the comprehensive E–R analysis we present here among patients with NSCLC were consistent with results of a previous E–R analysis of data from the phase II study alone (CA209063, CheckMate 063; NCT01721759; ref. 32). In that analysis, which included only patients with squamous NSCLC treated with nivolumab 3-mg/kg Q2W and examined ORR rather than OS, the relationships between nivolumab exposure measured by C_{min1} (defined as the trough serum concentration after the first dose) and the ORR and between nivolumab C_{avg1} and safety events (first occurrence of a grade $\geq$3 treatment-related AE and AEs-DC/D) were flat. The relatively flat E–R relationships for both efficacy (OS) and safety (AEs-DC/D) provided evidence for the recent FDA approval of a flat dosing regimen for nivolumab in melanoma, NSCLC, and RCC (20), namely, that the safety and efficacy profile of a flat-dose regimen of 240 mg Q2W (equivalent to 3-mg/kg Q2W for patients weighing 80 kg) is expected to be similar to the FDA-approved weight-based (3-mg/kg Q2W) dose regimen. In addition, the flat E–R relationship served as a basis for exploring the feasibility of further dose optimization, by decreasing the dosing frequency to once every 4 weeks with a 480-mg flat dose, which would be more convenient for patients, caregivers, and clinicians (24).

The exposure metric in our analysis was C_{avg1}, in contrast to a previous study with pembrolizumab, an anti–PD-1 antibody, that used steady-state area under the curve (AUC_{ss}; ref. 33). Since nivolumab clearance was found to change with time in a PPK analysis (22), and this change could be associated with improved disease status and the corresponding decrease in the rate of cancer-related cachexia (34, 35), early exposure metrics such as C_{avg1} may be more appropriate than steady-state exposure metrics such as AUC_{ss} to characterize E–R relationships with nivolumab treatment. Using C_{avg1} may therefore avoid the confounding effect of time-varying pharmacokinetics on nivolumab E–R relationships.

The present analysis had certain limitations. Only a small number of patients included in the analysis received nivolumab doses that were higher or lower than the FDA-approved dose of 3-mg/kg Q2W. Furthermore, PD-L1 status in squamous and nonsquamous NSCLC was not determined in all patients included in the analysis (~27% unknown). In addition, no data were available on the mutational burden or combinations of immune markers, which have recently been reported to influence the response to PD-1 blockade (36, 37).

The current analyses of data from patients with squamous or nonsquamous NSCLC are, to our knowledge, the most extensive E–R analyses of the safety and efficacy of nivolumab in any cancer to date. Nivolumab exposure (measured by C_{avg1}) was not significantly associated with efficacy (measured by OS) in previously treated patients with squamous or nonsquamous NSCLC, and the risk of toxicity (measured by AEs-DC/D and

any-cause and treatment-related grade ≥3 AEs) did not increase with nivolumab exposure over the dosage range of 1 to 10 mg/kg Q2W. These results substantiate previous research on nivolumab dose selection (8) and support the use of the 3-mg/kg Q2W dose of nivolumab in patients with squamous and nonsquamous NSCLC.

Disclosure of Potential Conflicts of Interest

F.G. Finckenstein is an employee of F Hoffmann La Roche Ltd and holds ownership interest (including patents) in Bristol-Myers Squibb and F. Hoffmann La Roche Ltd. A. Roy holds ownership interest (including patents) in Bristol-Myers Squibb. No other potential conflicts of interest were disclosed by the other authors.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Agrawal, B. Lestini, F.G. Finckenstein
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Feng, X. Wang, G. Bajaj, S. Agrawal, A. Bello, B. Lestini, A. Roy
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