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ARTICLE

Nivolumab exposure–response analysis for adjuvant treatment of melanoma supporting a change in posology

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Abstract

Nivolumab monotherapy is approved as adjuvant treatment for melanoma based on results from the pivotal CheckMate 238 trial. We present a model-based, benefit–risk assessment of nivolumab in adjuvant melanoma supporting a posology change from a weight-based to a less frequent, flat-dosing regimen. The exposure–response (E–R) relationship for efficacy was evaluated using recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) end points from the CheckMate 238 trial. The E–R for safety was evaluated using data from 14 studies across a broad range of doses in several tumor types using grade 3+ adverse event (AE) and grade 2+ immune-mediated AE (IMAE) end points. Nivolumab trough exposures were not significant predictors of RFS or DMFS. Covariates significantly associated with increased risk of disease recurrence or death were programmed death ligand 1 (PD-L1; less than 5% cutoff), lower baseline lactate dehydrogenase, and higher age. Covariates associated with increased risk of distant metastasis or death were PD-L1 (less than 5% cutoff) and higher age. Higher nivolumab maximum concentration after first dose (Cmax1) was significantly associated with grade 2+ IMAEs, but not grade 3+ AEs. The risk of grade 3+ AEs was significantly lower in adjuvant versus advanced melanoma. Eastern Cooperative Oncology Group Performance Status higher than zero was associated with higher incidences of grade 2+ IMAEs and grade 3+ AEs. Female patients had significantly higher incidences of grade 2+ IMAEs than male patients. Nivolumab monotherapy in adjuvant melanoma demonstrated a relatively flat E–R relationship over the range of exposures produced by 3 mg/kg every 2 weeks and predicted a comparable benefit–risk profile to flat-dosing regimens.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Nivolumab exposure–response (E–R) relationships for efficacy and safety of nivolumab are well characterized in metastatic advanced tumors. However, there is no report on the E–R characterization for both efficacy and safety of nivolumab in patients receiving adjuvant treatment of melanoma. From a regulatory perspective,

an E–R with recurrence-free survival was conducted for the nivolumab 480 mg every 4 weeks approval.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study aimed to characterize E–R for efficacy and safety and to establish the benefit–risk profile of nivolumab in patients receiving adjuvant treatment in melanoma.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Nivolumab monotherapy in adjuvant melanoma shows a relatively flat E–R relationship for efficacy and safety over the range of exposures produced by 3 mg/kg every 2 weeks dosing and is predicted to have a comparable benefit–risk profile to nivolumab flat-dosing regimens.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

These E–R analyses advance our knowledge of covariates influencing nivolumab treatment in the adjuvant setting compared with advanced melanoma and provide a framework for understanding the contribution of nivolumab in combination with other drugs in the adjuvant treatment of melanoma.

INTRODUCTION

Nivolumab is a human immunoglobulin G4 monoclonal antibody that binds to programmed death-1 (PD-1), a negative regulatory molecule expressed by activated T and B lymphocytes that is involved in suppressing immune cell activation. Nivolumab monotherapy has shown wide clinical benefit across several advanced tumor types at a dose of 3 mg/kg every 2 weeks (q2w).[1–7] The positive benefit–risk profile of nivolumab 3 mg/kg q2w was demonstrated by longer recurrence-free survival (RFS) and lower grade toxicities compared with ipilimumab observed in the pivotal CheckMate 238 trial of adjuvant therapy for melanoma.[8] Nivolumab posology was later updated to flat dosing of 240 mg q2w or 480 mg every 4 weeks (q4w) across different tumor types, including advanced and adjuvant treatment of melanoma, based primarily on model-based analyses of population pharmacokinetic (PPK) and exposure–response (E–R) relationships.[1,2,9–12]

Nivolumab monotherapy pharmacokinetics (PKs) have been characterized in several tumor types and treatment settings.[9,13,14] Nivolumab clearance (CL) is time-varying in advanced tumors and decreases with time.[9,14] In contrast, nivolumab CL is time-invariant in adjuvant melanoma. Furthermore, nivolumab CL in adjuvant melanoma is 40% lower than baseline CL in metastatic melanoma, with the difference narrowing to 20% at steady state due to reduced time-varying CL in advanced melanoma.[13] Both lower baseline CL and a decrease in CL over time were shown to be associated with a greater extent of clinical benefit.[14–16]

Nivolumab E–R efficacy and safety relationships are established in advanced metastatic tumor types where dose-ranging clinical efficacy data were available.[15–17] In advanced tumors, time-varying CL could potentially have positive, biased effects on E–R efficacy relationships, suggesting an apparent E–R relationship where one may not exist, which is most evident when single-dose data are used.[14] Nivolumab exposures, when obtained from dose-ranging data, are not highly correlated with CL, because the relationship between disease status and CL are observed at low and high doses. Therefore, both baseline CL (as a measure of disease status) and early measures of exposure are typically used to minimize bias in E–R efficacy relationships when dose-ranging data are available.[12,15,16]

In this analysis, we present a robust characterization of nivolumab E–R relationships for efficacy and safety in adjuvant melanoma. Stationary CL in the adjuvant setting is not expected to have confounding effects on disease status over time, allowing for E–R efficacy analysis with data from a single-dose level. E–R efficacy analysis in adjuvant melanoma at a single dose, using the primary end point of RFS, was reported by the US Food and Drug Administration.[12] The previous report provides an application of E–R efficacy models for nivolumab posology change; however, extensive discussion on model development, effect of covariates on efficacy end points, and model evaluation methods have not been presented. In the current analysis, we present a detailed analysis of E–R efficacy with the RFS end point and further extend E–R efficacy evaluation to include an additional end point of distant metastasis-free survival (DMFS), a subset of RFS, as a surrogate end point for overall survival. Exposures in adjuvant melanoma are predicted to be higher than in advanced melanoma,[13] warranting robust characterization of E–R safety, which also has not been reported previously. We present an aggregate E–R safety analysis of two end

points using a pooled data set across a range of 1–10 mg/kg q2w or every 3 weeks (q3w) in several tumor types.

Overall, this work presents a framework of E–R model development in the adjuvant setting. Both the E–R efficacy and safety models are extensively characterized for covariates influencing each end point and rigorously validated using cross-validation and external validation methods. We also applied the E–R efficacy and safety models to the assessment of the benefit–risk of alternative dosing regimens (240 mg q2w and 480 mg q4w).

METHODS

The E–R relationship for nivolumab efficacy was evaluated using RFS and DMFS data from the randomized phase III CheckMate 238 trial. The E–R relationship for nivolumab safety across a broad dosing range in several advanced tumor types was evaluated using grade 3+ AEs and grade 2+ immune-mediated AEs (IMAEs), defined by the Medical Dictionary for Regulatory Activities as specific events (or groups of preferred terms describing specific events) such as diarrhea/colitis, hepatitis, pneumonitis, nephritis and renal dysfunction, rash, and endocrine-related events.[18] To be classified as an IMAE using the preferred terms, the event also required treatment with immune-modulating medication, with the exception of endocrine events.

Data

E–R relationships for nivolumab efficacy were evaluated using data from patients receiving postsurgical adjuvant treatment of melanoma with a dosing regimen of 3 mg/kg q2w in CheckMate 238.[8] Nivolumab exposure data were available for 448/452 patients treated with nivolumab.

E–R relationships for nivolumab safety were evaluated using pooled data from 3008 patients from 14 studies, of whom 448 were patients from CheckMate 238 with melanoma treated in the adjuvant setting. The remaining 2560 patients had advanced solid tumors, including melanoma, renal cell carcinoma, squamous/nonsquamous non-small cell lung cancer, squamous cell carcinoma of the head and neck, classical Hodgkin lymphoma, urothelial carcinoma, and others. Patients received nivolumab doses of 1–10 mg/kg q2w or q3w, as previously described in E–R safety analyses.[11]

Further details of the trials used in the analyses of E–R relationships for efficacy and safety have been published elsewhere.[8,11,13]

All studies were approved by local institutional review boards and independent ethics committees and carried out in accordance with the ethical principles of the Declaration of Helsinki. Patients provided informed written consent before undergoing any study-specific procedures. A summary of the baseline characteristics of patients treated for adjuvant melanoma in CheckMate 238 is presented in Table 1.

TABLE 1 Summary of baseline characteristics in patients treated with nivolumab for adjuvant melanoma enrolled in CheckMate 238

Baseline characteristic	Patients, $N = 448$
Sex, *n* (%)	
Male	254 (56.70)
Female	194 (43.30)
ECOG PS, *n* (%)	
0	408 (91.07)
1	40 (8.93)
Race, *n* (%)	
White	421 (93.97)
Asian	24 (5.36)
Other	3 (0.67)
Baseline body weight, kg	
Mean (SD)	81.15 (19.36)
Median (range)	80.00 (39.00–183.40)
Baseline eGFR, ml/min/1.73 m^2	
Mean (SD)	91.69 (17.00)
Median (range)	92.21 (30.67–138.79)
Missing, *n* (%)	1 (0.22)
PD-L1 status, *n* (%)[a]	
Negative	298 (66.52)
Positive	150 (33.48)
M-stage, *n* (%)	
M0	366 (81.70)
M1A/M1B	62 (13.84)
M1C	20 (4.46)
Line of therapy, *n* (%)	
First line	434 (96.88)
Second line and greater	14 (3.13)
Age, years	
Mean (SD)	54.3 (13.4)
Median (range)	55 (19–83)
Baseline LDH (×ULN)	
Mean (SD)	0.756 (0.175)
Median (range)	0.732 (0.308–1.53)
Missing, *n* (%)	7 (1.56)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; M-stage, melanoma disease stage; PD-L1, programmed death ligand 1; SD, standard deviation; ULN, upper limit of normal.

[a]Negative PD-L1 status is defined as less than 5%; positive PD-L1 status is defined as greater than or equal to 5%.

Predicted exposures used in E–R efficacy and safety analyses were determined using nivolumab PPK models[9,13] as described in the Supplemental Methods.

E–R efficacy analyses: model development and evaluation

Relationships between nivolumab exposure and RFS or DMFS were described by a semiparametric Cox proportional hazards (CPH) model. The hazard function CPH model in patient i was expressed as

$$h_i(t) = h_o(t)\exp(\beta^T X_i), \quad (1)$$

where $h_o(t)$ is the baseline hazard function, and $\boldsymbol{X_i}$ represents the vector of individual predictor variables (exposure and covariates). The vector of coefficients $\boldsymbol{\beta}$ was estimated by maximum partial-likelihood methods. Minimum concentrations during the first 14 days (Cmind14) and first 28 days of treatment (Cmind28) were used as conservative measures of nivolumab exposure that assess the effects of trough concentration achieved with 240 mg q2w and 480 mg q4w, respectively, on efficacy relative to 3 mg/kg q2w.[11]

E–R relationships for RFS or DMFS were assessed using the full model by estimating the modulatory effects of prespecified covariates, including sex, age, baseline body weight, Eastern Cooperative Oncology Group Performance Status (ECOG PS), melanoma disease stage, line of therapy, programmed death ligand 1 (PD-L1) greater than or equal to 5%, and baseline lactate dehydrogenase (LDH) (normalized to the upper limit of normal). Inclusion of unity within the 95% confidence interval (CI) of a covariate effect indicated a lack of statistical significance.

Model performance was assessed by visual predictive check (VPC) and fivefold cross-validation (details in the Supplement).

E–R safety analyses: model development and evaluation

For the model development of E–R safety analysis, random data samples from approximately two-thirds of the cohort of patients with melanoma treated with nivolumab as adjuvant therapy ($n = 298$) and from all other tumor types ($n = 2560$; development cohort) were used. Data from the remaining one-third of the cohort of patients with melanoma treated with nivolumab as adjuvant therapy ($n = 150$) were reserved for external model validation (validation cohort).

The relationships between nivolumab exposure (Cmax1) and time to first occurrence of AEs were described by a CPH model and included assessment of the effect of covariates on these E–R relationships. Cmax1 was used as a conservative measure of nivolumab exposure to assess the effects of peak concentrations achieved with 240 mg q2w or 480 mg q4w on safety, relative to 3 mg/kg q2w.[11]

The hazard function used in the CPH time-to-AE model was expressed in a similar manner to the efficacy model described in Equation (1). Covariates in the full model were baseline body weight, age, sex, line of therapy, ECOG PS, and tumor types found to be significant in a previous model.[16] Two functional forms of exposure, linear (untransformed) and log-transformed exposure, were evaluated to assess relationships with risk of AEs. The choice of functional form was based on the model with the lowest Bayesian information criterion (BIC). Inclusion of unity in the 95% CI of a covariate effect indicated lack of statistical significance.

Model performance was assessed by VPC using development and validation cohorts (details in the Supplement).

Model application: predicting nivolumab efficacy and safety at 240 mg q2w and 480 mg q4w to support posology change

The E–R efficacy and safety models were used to compare the cumulative probability of efficacy end points (RFS and DMFS) and safety end points (grade 3+ AEs or grade 2+ IMAEs) over time with nivolumab 240 mg q2w and 480 mg q4w relative to 3 mg/kg q2w in patients with melanoma receiving adjuvant nivolumab.

Predicted cumulative probability of RFS and DMFS versus time for nivolumab 240 mg q2w and 480 mg q4w were compared with predicted curves for nivolumab 3 mg/kg q2w and with the observed Kaplan–Meier curves for the ipilimumab arm in CheckMate 238. The model was used to predict individual RFS and DMFS probabilities for each nivolumab regimen (3 mg/kg q2w, 240 mg q2w, and 480 mg q4w) and was simulated 200 times to obtain 200 sets of RFS and DMFS events.

Predicted risk of grade 3+ AEs and grade 2+ IMAEs for nivolumab 240 mg q2w and 480 mg q4w was compared with predicted curves for 3 mg/kg q2w. The model predicted individual grade 3+ AE and grade 2+ IMAE probabilities for each nivolumab regimen and was simulated 1000 times to obtain 1000 sets of grade 3+ AEs and grade 2+ IMAEs.

All E–R analyses and presentations of data were performed using R (version 3.0.2).[19] PPK simulations were performed using NONMEM (version 7.3, ICON Development Solutions, Hanover, MD [version 7, level 3.0]).[20]

RESULTS

Exposure measures

Predicted geometric mean nivolumab concentration–time profiles for the first 28 days and at steady state in patients with melanoma treated in the adjuvant setting are presented

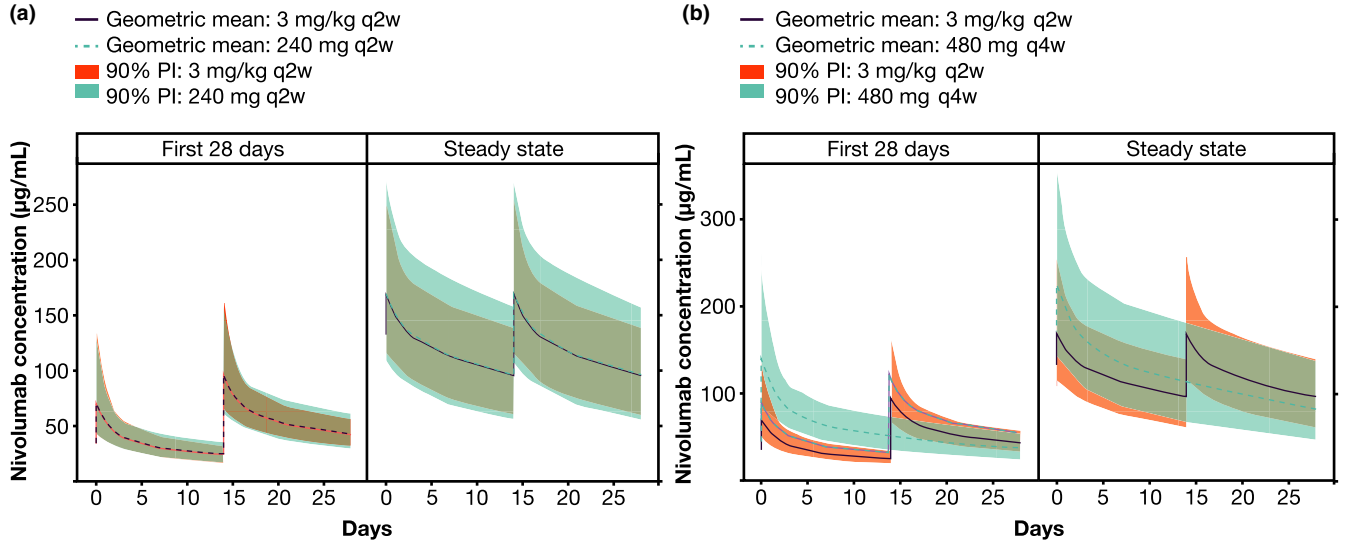

FIGURE 1 Predicted geometric mean nivolumab concentration–time profiles (first 28 days and steady state) by dosing regimen in adjuvant melanoma for (a) 3 mg/kg q2w versus 240 mg q2w and (b) 3 mg/kg q2w versus 480 mg q4w. PI, prediction interval; q2w, every 2 weeks; q4w, every 4 weeks

in Figure 1, with summary statistics presented in Table S1. Detailed results are shown in the Supplement.

E–R efficacy analyses

Of 448 nivolumab-treated patients in CheckMate 238 included in the E–R analyses of efficacy, 169 (37.7%) experienced an RFS event (recurrence or death) and 151 (33.7%) experienced a DMFS event (distant metastasis or death).

Two separate E–R models were developed using Cmind14 and Cmind28, which represent the first trough after a single dose for q2w and q4w dosing, respectively. Furthermore, nivolumab Cmind28 was the most sensitive exposure metric to use in the E–R efficacy analysis because this metric had the largest decrease with 480 mg q4w flat dosing relative to 3 mg/kg q2w (Figure 1 and Table S1). E–R efficacy results using Cmind14 or Cmind28 were consistent across RFS and DMFS end points. Neither Cmind14 nor Cmind28 were significant predictors of the risk of an event (disease recurrence, distant metastasis, or death) in adjuvant melanoma treatment, as shown in Figures 2 and S1 and Tables S2 and S3.

Covariates significantly associated with an increased risk of disease recurrence or death were PD-L1 less than 5% versus greater than or equal to 5% (51%), lower baseline LDH (approximately 28% lower from a median of 0.73 to the 5th percentile of 0.53 (× the upper limit of normal [ULN]), and higher age (approximately 33% from a median of 55 years to the 95th percentile of 74 years). Covariates associated with an increased risk of distant metastasis or death were PD-L1 less than 5% versus greater than or equal to 5% (approximately 47%) and higher age (approximately 33% from a median of 55 years to the 95th percentile of 74 years). The 95% CI of all other predictor variables included 1, indicating a lack of evidence for the effect of these variables on RFS or DMFS.

The performance of E–R models of RFS and DMFS was evaluated by comparing observed and predicted cumulative probabilities of RFS or DMFS for nivolumab 3 mg/kg q2w.

Model-predicted probabilities of RFS and DMFS were consistent with the observed probabilities of events. (Figure S2). Additional fivefold cross-validation of the E–R models is presented in Table S4. Overall, the average bias in prediction of the cross-validation models was similar in magnitude to the bias in the original models, confirming the robustness of the original E–R model predictions.

E–R safety analyses

Of the 448 nivolumab-treated patients in CheckMate 238 included in E–R safety analyses, 137 (30.5%) experienced at least one grade 3+ AE, and 146 (32.5%) experienced a grade 2+ IMAE. The incidence of grade 3+ AEs in adjuvant melanoma was lower than that observed in the combined incidence of other tumor types included in the analysis (59.6%). However, the incidence of grade 2+ IMAEs was similar to those observed in other tumor types (29.6%).

E–R safety analyses were developed using Cmax1 as the end point, as it represents the worst-case scenario of nivolumab associated with the risk of any AE. A log-transformed Cmax1 was chosen as BIC and was lower than the linear (untransformed) Cmax1. Covariate effects and parameter estimates from the full model in the pooled data set of 14 CheckMate trials, expressed

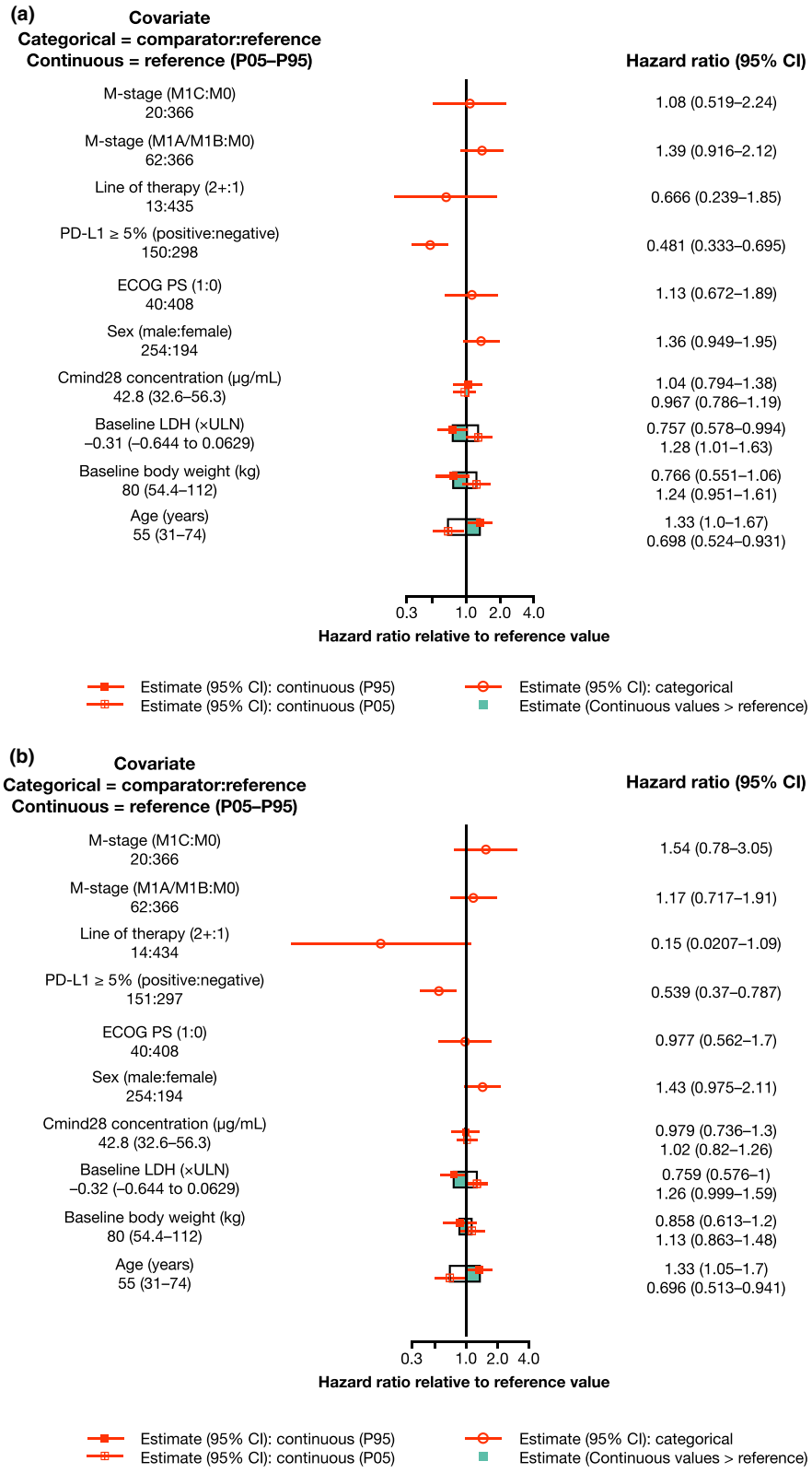

FIGURE 2 Covariate effects on hazard ratio for full Cox proportional hazards models of efficacy for (a) RFS and (b) DMFS using the nivolumab Cmind28 exposure measurement. Continuous covariate effects at the 5th (95% CI) and 95th (95% CI) percentiles are represented by open squares (horizontal lines) and solid squares (horizontal lines), respectively. The open/blue shaded boxes represent the range of covariate effects from the median to the 5th and 95th percentiles of the covariate. Hazard ratios shown are relative to a patient with reference value of covariates. Note: LDH (×ULN) values are presented in log-transformed scale in the figure. The untransformed median (5th–95th percentile) values of LDH (×ULN) are 0.73 (0.53–1.06). CI, confidence interval; Cmind28, minimum concentration at day 28; DMFS, distant metastasis-free survival; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; M-stage, melanoma disease stage; PD-L1, programmed death ligand 1; PS, performance status; RFS, recurrence-free survival; ULN, upper limit of normal

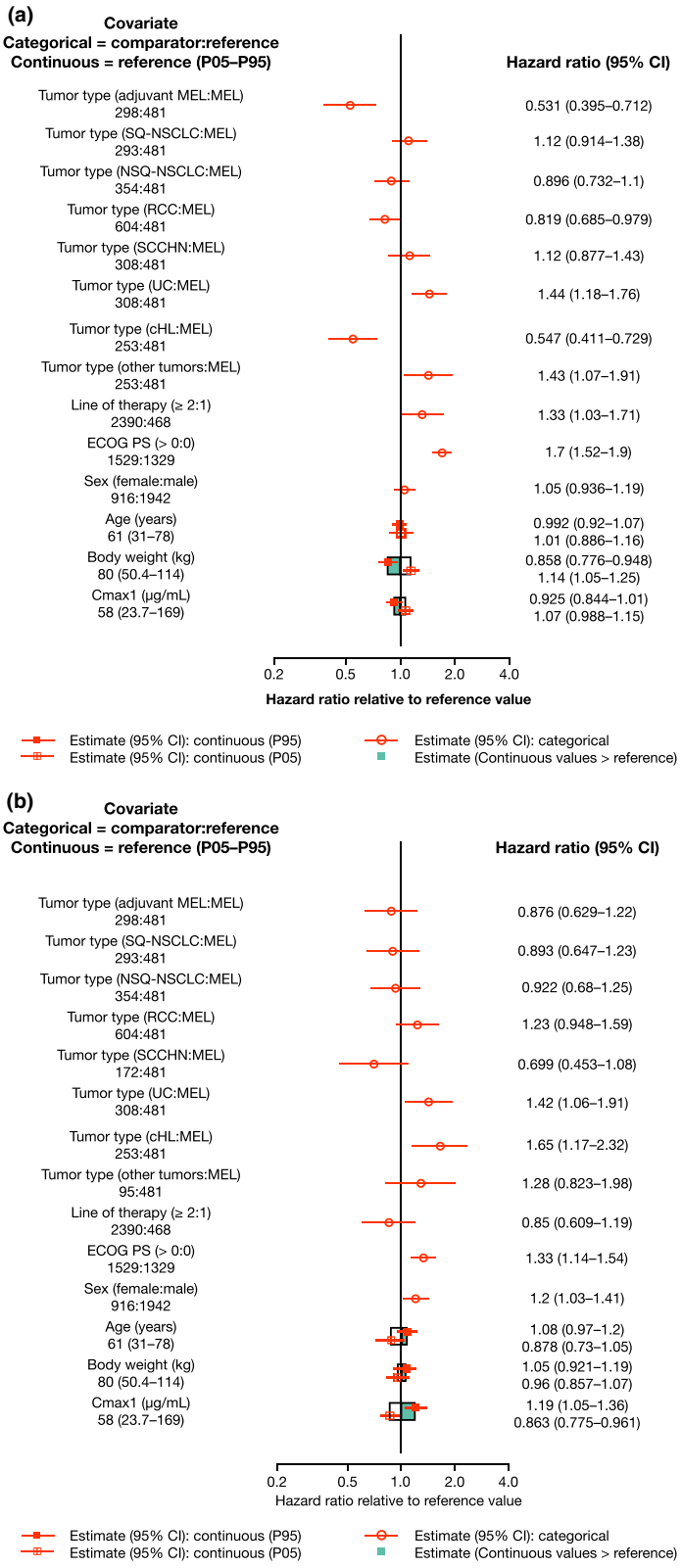

FIGURE 3 Covariate effects on hazard ratio for (a) grade 3+ AEs and (b) grade 2+ IMAEs with nivolumab in adjuvant melanoma using nivolumab Cmax1. Continuous covariate effects at the 5th (95% CI) and 95th (95% CI) percentiles are represented by open squares (horizontal lines) and solid squares (horizontal lines), respectively. The open/blue shaded boxes represent the range of covariate effects from the median to the 5th and 95th percentiles of the covariate. Hazard ratios shown are relative to a patient with reference value of covariates. Adj, adjuvant; AE, adverse event; cHL, classical Hodgkin lymphoma; CI, confidence interval; Cmax1, maximum concentration after the first dose; IMAE, immune-mediated adverse event; MEL, melanoma; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; PS, performance status; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; SQ, squamous; UC, urothelial carcinoma

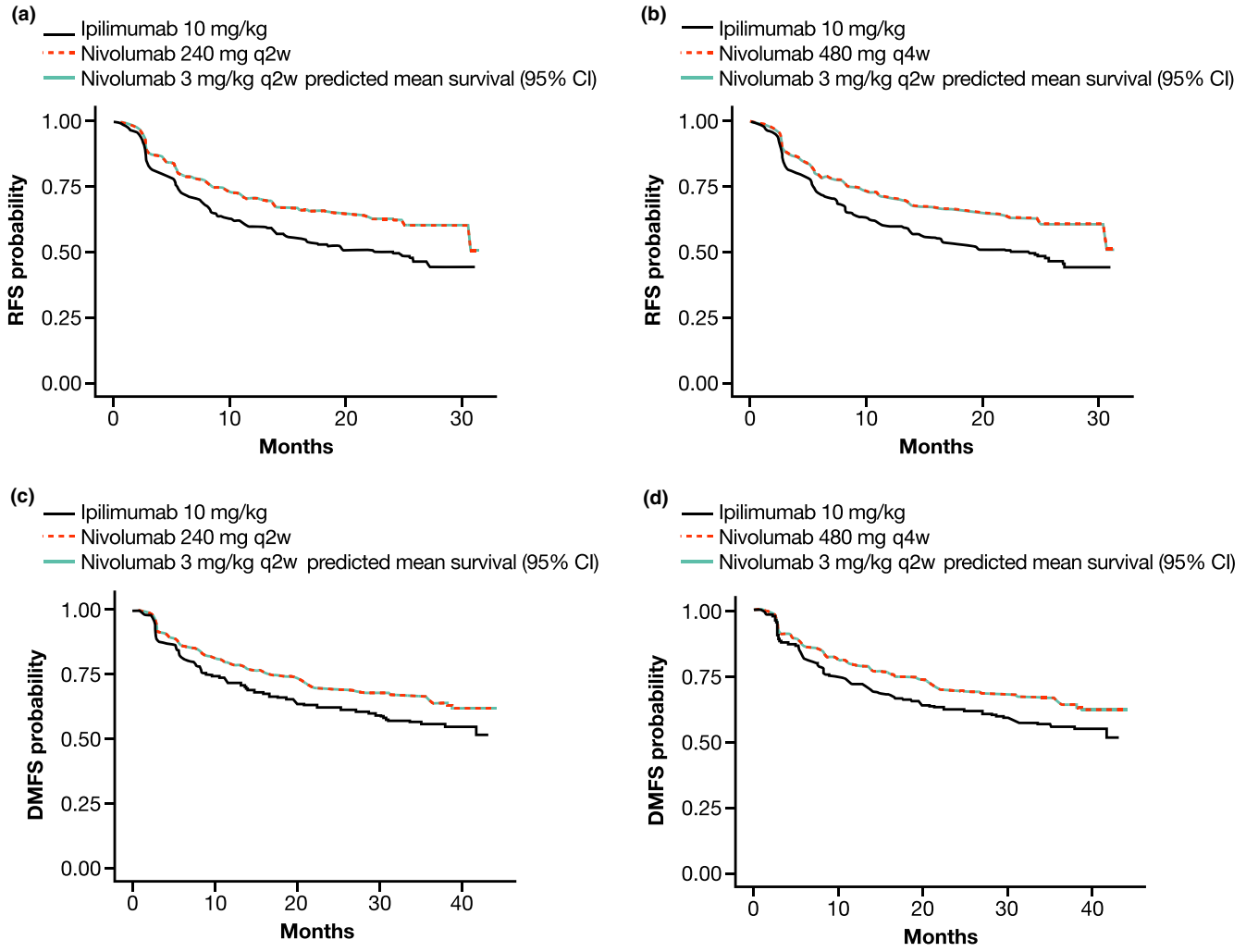

FIGURE 4 Kaplan–Meier curves for model-predicted mean RFS and DMFS relative to the observed mean RFS and DMFS from the ipilimumab comparator arm in CheckMate 238. (a) RFS for nivolumab 3 mg/kg q2w and 240 mg q2w using Cmind14. (b) RFS for nivolumab 3 mg/kg q2w and 480 mg q4w using Cmind28. (c) DMFS for nivolumab 3 mg/kg q2w and 240 mg q2w using Cmind14. (d) DMFS for nivolumab 3 mg/kg q2w and 480 mg q4w using Cmind28. CI, confidence interval; Cmind14, minimum concentration during the first 14 days of treatment; Cmind28, minimum concentration during the first 28 days of treatment; DMFS, distant metastasis-free survival; q2w, every 2 weeks; q4w, every 4 weeks; RFS, recurrence-free survival

as a hazard ratio and 95% CIs for grade 3+ AEs and grade 2+ IMAEs, are presented in Figure 3 and Tables S5 and S6, respectively.

Cmax1 was not a significant predictor of grade 3+ AEs. Grade 3+ AE risk was significantly lower (~47%) in patients with melanoma treated in the adjuvant setting versus advanced melanoma. Patients with ECOG PS greater than zero and patients receiving second-line or higher therapy had a greater risk of grade 3+ AEs (70% and 33%, respectively) than patients with an ECOG PS of zero and patients receiving first-line therapy, respectively. Additional covariates, except for other tumor types, were not significantly associated with grade 3+ AE risk. Conversely, an increase in Cmax1 was a significant predictor of grade 2+ IMAEs, where higher Cmax1 was associated with a higher risk of grade 2+ IMAEs (approximately 19% from a median of 58 μg/ml to the 95th percentile of 169 μg/ml). Risk of grade 2+ IMAEs was numerically lower in patients with melanoma treated in the adjuvant setting versus patients with advanced melanoma, although the difference was not statistically significant. Female patients and patients with ECOG PS greater than or equal to one had a greater risk of grade 2+ IMAEs (20% and 33%, respectively) than male patients and patients with an ECOG PS of zero. Other covariates, except for other tumor types, were not significantly associated with grade 2+ IMAE risk.

Performance of E–R models of grade 3+ AEs and grade 2+ IMAEs was evaluated by comparing observed and predicted median cumulative probabilities of AEs for the nivolumab 3 mg/kg q2w regimen using the development cohort (Figure S3). Model-predicted probabilities of grade 3+ AEs

and grade 2+ IMAEs were consistent with the observed probabilities of events across all tumor types. Overall, grade 3+ AEs and grade 2+ IMAEs were reasonably predicted by the model in patients with melanoma treated in the adjuvant setting.

Model application

The E–R efficacy and safety models were applied for the benefit–risk assessment of alternative dosing regimens.

To align measurements of trough concentrations across dosing regimens, exposure measures of Cmind14 (one dose for 240 mg q2w and 3 mg/kg q2w) and Cmind28 (one dose for 480 mg q4w and two doses for 3 mg/kg q2w) were used in E–R efficacy analyses. The Cmind14 and Cmind28 models were used to predict 240 mg Q2W and 480 mg q4w efficacy, respectively. The model-predicted cumulative probabilities of RFS and DMFS for nivolumab 3 mg/kg q2w, 240 mg q2w, and 480 mg q4w at 1 and 2 years were all similar (less than 1% difference; Tables S7 and S8) but higher than the ipilimumab control arm (Figure 4). The model predicted the ranges of Cmax1 associated with nivolumab 240 mg q2w and 480 mg q4w may result in similar rates of grade 3+ AEs and grade 2+ IMAEs relative to nivolumab 3 mg/kg q2w (Figure 5). At 6 months, the model-predicted differences in the probabilities of experiencing grade 3+ AEs and grade 2+ IMAEs with nivolumab 480 mg q4w relative to 3 mg/kg q2w were less than 1% and 2.4%, respectively (Tables S9 and S10). At 12 months, the model-predicted differences in the probabilities of experiencing grade 3+ AEs and grade 2+ IMAEs with nivolumab 480 mg q4w relative to 3 mg/kg q2w were 1.2% and 3%, respectively (Tables S9 and S10).

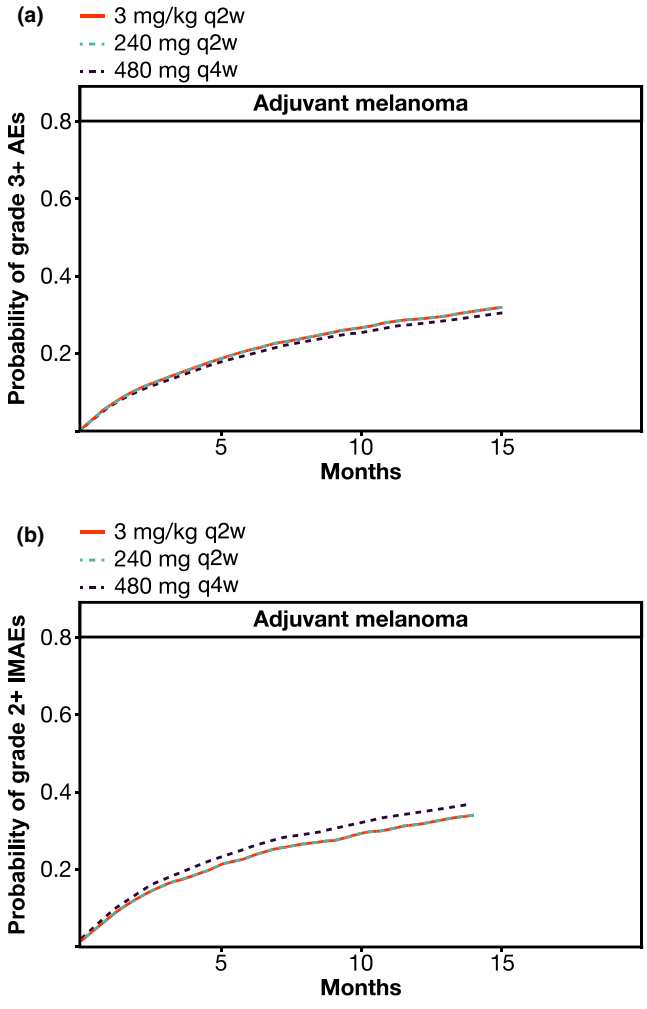

FIGURE 5 Kaplan–Meier curves for model-predicted mean probability for (a) grade 3+ AEs and (b) grade 2+ IMAEs with nivolumab 3 mg/kg q2w, 240 mg q2w, and 480 mg q4w in adjuvant melanoma. AE, adverse event; IMAE, immune-mediated adverse event; q2w, every 2 weeks; q4w, every 4 weeks

DISCUSSION

We present a comprehensive E–R analysis of nivolumab monotherapy for efficacy and safety end points in the adjuvant treatment of melanoma. The E–R relationship for efficacy was characterized using RFS and DMFS. The E–R relationship for safety was characterized using grade 3+ AEs and grade 2+ IMAEs, pooling data from a range of nivolumab monotherapy doses in advanced and resected tumors.

Trough concentration after the first dose provided a conservative assessment, as other earlier measures with 240 mg q2w or 480 mg q4w were higher, relative to 3 mg/kg q2w. This approach ensures evaluation of the largest potential impact of proposed dosing regimens on efficacy. Previous analyses in advanced tumors demonstrated that other summary measures of nivolumab exposure, such as time-averaged steady-state concentration (Cavgss) [Correction added on 30 June 2021, after first online publication: abbreviation (Cavgss) was included after its definition, 'time-averaged steady-state concentration'] and time-averaged concentration after the first dose (Cavg1), were not significant predictors of efficacy in E–R analyses in other tumor types.[12,15–17] Similar to the results from the advanced melanoma setting that used Cavg1 as the exposure metric for E–R efficacy analysis,[12,16,17] nivolumab exposures (Cmind14 or Cmind28) were not significant predictors of efficacy for RFS or DMFS.

Current analyses in the adjuvant setting identified higher baseline age and lower LDH levels as significant predictors of recurrence or death. Higher age also associated with greater risk of distant metastases or death. Although baseline body weight was not a significant covariate in adjuvant melanoma, the directionality of the body-weight effect was the same across adjuvant and advanced melanoma, with lower baseline body weight predicting a higher risk of death or tumor recurrence.[17] Lower body mass index, higher age, and elevated LDH can be indicators of disease severity and are associated with poor prognosis in patients with melanoma.[21–24] In adjuvant melanoma,

the range of baseline LDH (× ULN) was generally within the normal range (median [5th–95th percentile], 0.73 [0.51–1.06]) and narrower than that observed in advanced melanoma in earlier trials (median [5th–95th percentile], 1 [0.573–3.16]),[17] indicating better health status in patients receiving adjuvant therapy. Furthermore, in evaluating for prognostic biomarkers, baseline LDH was not a significant marker of efficacy in adjuvant melanoma.[25] Therefore, although the effect of LDH is statistically significant, it is not expected to be clinically relevant in the adjuvant treatment of melanoma. Similar to previous analyses in advanced melanoma, PD-L1 expression greater than 5% showed lower risk of recurrence, distant metastases, or death with nivolumab as adjuvant therapy than PD-L1 expression less than 5%.[16] As PD-L1 is expressed on tumor cells, PD-L1 expression levels may be a surrogate for interferon-γ release from neighboring activated T cells and, in some treatment settings, may associate with immunotherapy responses.[26]

The E–R safety analyses were conducted with pooled safety data over a wide range of nivolumab doses (1–10 mg/kg q2w or q3w) and tumor types. The end points of E–R safety analyses were grade 3+ AEs and grade 2+ IMAEs, which were selected to represent the overall safety profile of cancer immunotherapy. Grade 3+ AEs could affect overall survival, whereas grade 2+ IMAEs are related to the nivolumab mechanism of action and have been found to be the most sensitive with respect to the E–R relationship.[11]

Cmax1 represented the most extreme exposure difference across regimens and therefore provided a conservative worst-case assessment of the largest potential impact of the proposed dosing regimens on safety. Nivolumab Cmax1 was not a significant predictor for grade 3+ AEs, indicating factors other than drug exposure may drive this safety end point. However, Cmax1 was a significant predictor for the risk of grade 2+ IMAEs, although the magnitude of risk with higher exposure was small. Similar to previous E–R safety analyses in advanced tumor types, nivolumab exposures of Cavg1 or maximum concentration during the first 28 days cycle (Cmaxd28) [Correction added on 30 June 2021, after first online publication: abbreviation (Cmaxd28) was included after its definition, 'maximum concentration during the first 28 days cycle'] were not associated with an increased risk of various AEs.[12,15,17,27]

An ECOG PS greater than or equal to one significantly increased the risk of grade 3+ AEs and grade 2+ IMAEs, consistent with observations in a previous analysis of other tumor types conducted using AEs leading to discontinuation or death as the end point.[15] Grade 3+ AE risk was also significantly increased in patients who received second-line or higher therapy. These results suggest that patients with a poor ECOG PS, varied comorbidities, and residual effects from prior therapy may have a worse prognosis and experience more AEs than patients with improved ECOG PS. Our analysis showed that patients with melanoma treated in the adjuvant setting had a substantially lower (~47%) incidence of grade 3+ AEs than patients with advanced melanoma, supporting the hypothesis that healthy patients with fewer comorbidities have a higher tolerance to immunotherapy. However, the incidence of grade 2+ IMAEs in patients with melanoma treated in the adjuvant setting was similar to the incidence observed in patients with advanced melanoma, reflecting the association of IMAEs with the mechanism of action of nivolumab.

Different model evaluation strategies were applied to E–R efficacy and safety analyses. E–R efficacy analyses were performed using a smaller data set (all nivolumab data from CheckMate 238 [$n = 448$]) than that used for safety analyses; thus, fivefold cross-validation was conducted in which model predictions were compared with the observed data from patients who were not included in the estimation of the model. Overall, the average bias in the prediction of the cross-validation models was similar in magnitude to the bias in the original models. In contrast, E–R safety analyses were conducted using a larger pooled data set comprising 3008 patients across multiple tumor types and dose ranges. Therefore, data for one-third of the patients with melanoma receiving adjuvant nivolumab were left out of model development for an external validation. Grade 3+ AEs and grade 2+ IMAEs were, for the most part, adequately predicted for patients in the model development and validation data sets. The model predictions mirrored the observed Kaplan–Meier curves for grade 3+ AEs and grade 2+ IMAEs, even though the model parameter estimates were largely influenced by other tumor types and the limited number of patients with melanoma receiving adjuvant nivolumab included in the data set.

The RFS and DMFS predictions were similar across the compared dosing regimens, supporting nivolumab flat-dosing regimens in the adjuvant setting. The incidences of grade 3+ AEs and grade 2+ IMAEs were predicted to be similar with nivolumab 240 mg q2w or 480 mg q4w compared with 3 mg/kg q2w, with a small increase in the risk of grade 2+ IMAEs at 6 and 12 months. Overall, based on inclusion of nivolumab doses up to 10 mg/kg q2w and the model performance, predictions of E–R safety at the higher 480 mg q4w dose were considered appropriate in patients with melanoma treated in the adjuvant setting. Furthermore, pooled clinical safety data from patients who switched from 3 mg/kg q2w to 480 mg q4w in other tumor types demonstrate adequate safety of this dose.[28]

In conclusion, the current analyses of nivolumab in adjuvant melanoma treatment are the most comprehensive E–R analyses to date, covering efficacy and safety outcomes. Nivolumab exposures (Cmind14 and Cmind28) were not significantly associated with efficacy (measured by RFS and DMFS) at the dose of 3 mg/kg q2w. Nivolumab exposures (Cmax1) were marginally significant for grade 2+ IMAEs, but not for grade 3+ AEs, which is consistent with observations in other tumor types.[11,15,27] The models were successfully applied to support dose optimization to 240 mg

q2w and 480 mg q4w flat-dosing regimens of nivolumab. This robust characterization of E–R relationships forms a basis for evaluating the relative contribution of nivolumab to safety and efficacy in future studies of immune checkpoint inhibitor combinations for the adjuvant treatment of melanoma.

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CONFLICT OF INTEREST

K.S., P.V., L.H., A.R., and S.S. are employees of Bristol Myers Squibb. K.S., A.R., S.S., and L.H own shares in Bristol Myers Squibb. V.I. declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

K.S., L.H., A.R., and S.S. wrote the manuscript. K.S., L.H., A.R., and S.S. designed the research. K.S., P.V., and V.I. performed the research. K.S., V.I., L.H., A.R., and S.S. analyzed the data.

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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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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