

ORIGINAL ARTICLE

Model-based evaluation of the efficacy and safety of nivolumab once every 4 weeks across multiple tumor types

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Background: Nivolumab 480 mg every 4 weeks (Q4W) is approved in the European Union, United States, and several other markets across multiple tumor types. Its approval was supported by quantitative efficacy/safety analyses bridging to 3 mg/kg every 2 weeks (Q2W).

Patients and methods: The benefit–risk profile of nivolumab 480 mg Q4W relative to 3 mg/kg Q2W was evaluated using population pharmacokinetic modeling and exposure–response (E–R) analyses for safety and efficacy. Pharmacokinetic exposures were predicted for 3203 patients with melanoma, non-small-cell lung cancer (NSCLC), renal cell carcinoma (RCC), squamous cell carcinoma of the head and neck, urothelial carcinoma, or classical Hodgkin lymphoma. Quantitative models analyzed E–R to predict 480-mg Q4W safety across all indications and efficacy for melanoma, NSCLC, and RCC. Intratumoral receptor occupancy (RO) was predicted for parameters representing different tumor types.

Results: Time-averaged concentrations for 480 mg Q4W versus 3 mg/kg Q2W were higher during the first 28 days (26.8%) and similar at steady state (5.2%). The maximum concentration (C_{max}) after the first dose was higher (110.4%), and the trough concentration at day 28 was lower (–22.1%) with 480 mg Q4W versus 3 mg/kg Q2W. The C_{max} achieved with 480 mg Q4W was lower than the previously established safe dose of 10 mg/kg Q2W. The probability of adverse events for key safety end points was similar for 480 mg Q4W and 3 mg/kg Q2W. The predicted overall survival and objective response rates with 480 mg Q4W were comparable to 3 mg/kg Q2W. The predicted high intratumoral RO provided additional evidence to support 480 mg Q4W across tumor types.

Conclusions: The benefit–risk profile for nivolumab 480 mg Q4W was predicted to be similar to that of 3 mg/kg Q2W across tumor types while providing a convenient and flexible option for patients and their caregivers.

Key words: clinical pharmacology, exposure–response, immuno-oncology, model-informed drug development, nivolumab, Q4W dosing frequency

INTRODUCTION

Nivolumab is a highly selective anti-programmed death-1 (PD-1) human monoclonal immunoglobulin G4 (IgG4) antibody approved as a cancer immunotherapeutic agent for multiple tumor types.^{1,2} The antitumor activity of nivolumab was first established in melanoma, renal cell carcinoma (RCC), and squamous/nonsquamous non-small-cell lung cancer (SQ/NSQ NSCLC) in a phase I dose-ranging study (NCT00730639),³ with robust maximal responses at doses of ≥ 1 mg/kg every 2 weeks (Q2W) for melanoma and RCC, and ≥ 3 mg/kg Q2W for NSCLC.⁴ Nivolumab has a wide

therapeutic index with no maximum tolerated dose identified up to 10 mg/kg Q2W.^{3,4} Therefore nivolumab 3 mg/kg Q2W was selected for development across tumor types.⁴ Pivotal studies using 3 mg/kg Q2W demonstrated objective response rates (ORRs) and overall survival (OS) benefit over standard of care (SOC) in several tumor types, with well-established safety profile, leading to approvals of 3 mg/kg Q2W weight-based dosing.^{5–9}

Nivolumab 240 mg Q2W was approved based on population pharmacokinetics (PPK) and dose/exposure–response (E–R) analyses demonstrating comparability of the regimen's pharmacokinetic (PK) exposure, safety, and efficacy of 240 mg Q2W to 3 mg/kg Q2W.^{10,11} In addition, a less frequent flat-dosing option of 480 mg every 4 weeks (Q4W), which is approved across various markets, allows health care professionals greater flexibility in patient care by increasing the time between clinic administration visits without compromising efficacy or safety.

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Nivolumab dose optimization from 3 mg/kg Q2W to 240 mg Q2W and 480 mg Q4W was enabled by understanding its pharmacokinetics and E–R. Nivolumab's pharmacokinetics are linear for doses ranging from 0.1 to 10 mg/kg Q2W and every 3 weeks (Q3W).¹² E–R analyses demonstrated that nivolumab systemic exposure is not identified as a significant predictor for efficacy or safety in tumor types for which dose-ranging data are available, including melanoma, NSCLC, and RCC, suggesting a relatively flat E–R relationship.^{4,13–15}

Nivolumab 480 mg Q4W was selected based on similar time-averaged PK exposure relative to 3 mg/kg Q2W. We describe a model-based approach bridging the benefit–risk profile of nivolumab 480 mg Q4W relative to 3 mg/kg Q2W across tumor types to (i) predict and compare exposures for 480 mg Q4W and 3 mg/kg Q2W, (ii) evaluate the exposure margin for safety based on the well-tolerated 10 mg/kg Q2W dose, and (iii) assess the impact of differences in exposure on efficacy and safety. These results, together with clinical safety data, led to the approval of the optional nivolumab flat-dosing regimen of 480 mg Q4W in several markets across multiple tumor types,^{1,2,16,17} providing health care professionals the flexibility to customize patient care.

PATIENTS AND METHODS

Patients

The pooled analysis dataset used to simulate nivolumab exposure was derived from a PPK analysis dataset of PK and covariate data from 3203 patients with melanoma, RCC, NSCLC, squamous cell carcinoma of the head and neck (SCCHN), classical Hodgkin lymphoma (cHL), and urothelial carcinoma (UC). The safety-bridging analysis included data from 2560 patients with melanoma, RCC, SQ NSCLC, NSQ NSCLC, SCCHN, cHL, UC, and other tumor types, and the efficacy-bridging analysis included data from patients with melanoma, RCC, SQ NSCLC, and NSQ NSCLC ($n = 1579$ and $n = 1615$ for ORR and OS analyses, respectively; [supplementary Table S1](#), available at *Annals of Oncology* online).

Comparison of nivolumab exposures

Nivolumab concentration–time profiles were predicted based on individual PK parameter estimates derived from a previously well-established PPK model.¹² These predictions were used to determine the following summary measures of exposure: peak, trough, and time-averaged concentrations after first dose ($C_{\max 1}$, $C_{\min 1}$, and $C_{\text{avg}1}$) and at steady state ($C_{\max \text{ss}}$, $C_{\min \text{ss}}$, and C_{avgss}), and time-averaged and trough concentrations over the first 28 days ($C_{\text{avgd}28}$ and $C_{\text{mind}28}$). Time-varying average concentration over each day for which a patient is at risk for a specific adverse event (C_{avgday}) was generated for time-to-event safety analysis.

The concentration–time profiles and summary measures of exposures for 480 mg Q4W and 3 mg/kg Q2W were compared. The 240-mg Q2W regimen was included for comparison purposes, as it replaced the 3-mg/kg Q2W dosing regimen in several markets.

Safety-bridging evaluation

Safety bridging was performed by (i) comparing nivolumab exposures for 480 mg Q4W with the established safe dose of 10 mg/kg Q2W, and (ii) using E–R safety analyses to predict the probability of experiencing adverse events (AEs) with 480 mg Q4W.

The E–R safety analyses were conducted with pooled data across 2560 patients with melanoma, RCC, SQ NSCLC, NSQ NSCLC, SCCHN, cHL, UC, and other tumor types, who received nivolumab 1 to 10 mg/kg Q2W and 0.3 to 10 mg/kg Q3W. The impact of exposure on safety was assessed using time-to-event models and logistic regression analyses ([supplementary Table S1](#), available at *Annals of Oncology* online).

The safety analyses' exposure measures were C_{avgday} and $C_{\max 1}$. C_{avgday} was selected as the primary exposure measure for time-to-event safety analyses because it provides a close approximation of the continuously varying concentration–time profile, providing differences in peak and overall exposure. $C_{\text{avgd}28}$ was selected as the main exposure measure for logistic regression because it

Table 1. Comparison of PK exposure parameters for nivolumab 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W

PK exposure parameter, µg/ml	Nivolumab dosage ($N = 3203$)			Difference between 3 mg/kg Q2W and 240 mg Q2W, % ^b	Difference between 3 mg/kg Q2W and 480 mg Q4W, % ^b
	3 mg/kg Q2W ^a (CV)	240 mg Q2W ^a (CV)	480 mg Q4W ^a (CV)		
$C_{\text{avg}1}$	27.5 (23.6)	29.0 (27.2)	44.0 (29.4)	5.5	59.6
$C_{\min 1}$	18.0 (28.1)	19.0 (32.6)	22.6 (39.3)	5.6	25.5
$C_{\max 1}$	58.7 (72.9)	61.8 (76.4)	123.5 (76.4)	5.3	110.4
$C_{\text{avgd}28}$	34.7 (24.5)	36.5 (28.4)	44.0 (29.4)	5.2	26.7
$C_{\text{mind}28}$	29.0 (30.0)	30.6 (34.6)	22.6 (39.3)	5.5	–22.1
C_{avgss}	86.7 (44.2)	91.2 (47.3)	91.2 (47.3)	5.2	5.2
$C_{\min \text{ss}}$	67.2 (52.8)	70.6 (55.7)	56.3 (63.9)	5.1	–16.2
$C_{\max \text{ss}}$	129.1 (46.1)	136.0 (50.0)	185.1 (58.3)	5.4	43.4

$C_{\text{avg}1}$, time-averaged concentration after the first dose; $C_{\text{avgd}28}$, time-averaged concentration over the first 28 days; C_{avgss} , time-averaged concentration at steady state; $C_{\max 1}$, peak concentration after the first dose; $C_{\max \text{ss}}$, peak concentration at steady state; $C_{\min 1}$, trough concentration after the first dose; $C_{\text{mind}28}$, trough concentration at day 28; $C_{\min \text{ss}}$, trough concentration at steady state; CV, coefficient of variation; PK, pharmacokinetic; Q2W, every 2 weeks; Q4W, every 4 weeks.

^a Values are reported as geometric means.

^b Percentage difference is in reference to the dosage of 3 mg/kg Q2W.

represents the drug concentration over the dosing interval for Q2W and Q4W. $C_{\max 1}$ was selected as a conservative exposure predictor as it yielded the greatest differences between the established and proposed regimens (Table 1).

The probabilities of experiencing safety events were predicted for various dosing regimens across tumor types. For additional details, see [supplementary methods](#), available at *Annals of Oncology* online.

Efficacy-bridging evaluation

Efficacy bridging consisted of E–R analyses for each of the four tumor types/histologies with dose-ranging data (melanoma, RCC, SQ NSCLC, and NSQ NSCLC) and intratumoral receptor occupancy (RO) by modeling to bridge efficacy to additional tumor types. The bridging strategy utilized the understanding that nivolumab is highly specific for the PD-1 receptor, and that the hypothesized mechanism of action (MOA) involves a cascade of events that activate T cells to destroy tumor cells. This MOA suggests that time-averaged

concentration (i.e. C_{avgd28}) is a more relevant driver of efficacy than concentration at a given time point (i.e. peak/trough concentration), and that C_{avgd28} (an early measure of exposure) is not likely influenced by changes in nivolumab clearance during treatment.¹³ C_{mind28} was used as a conservative exposure predictor for efficacy because other early exposure measures were higher in 480 mg Q4W relative to 3 mg/kg Q2W (Table 1).

E–R efficacy was evaluated for ORR and OS, representing early and long-term efficacy of nivolumab, respectively. ORR was assessed by logistic regression and OS by Cox proportional hazards model for each tumor type/histology in patients with melanoma, RCC, SQ NSCLC, and NSQ NSCLC treated with nivolumab 1 to 10 mg/kg Q2W and 0.3 to 10 mg/kg Q3W ([supplementary Table S1](#), available at *Annals of Oncology* online).

The predicted OS and ORR for 480 mg Q4W were compared with those for 3 mg/kg Q2W and with the OS and ORR for SOC by comparing hazard ratios (HRs; for additional details, see the [supplementary methods](#) available at *Annals of Oncology* online).

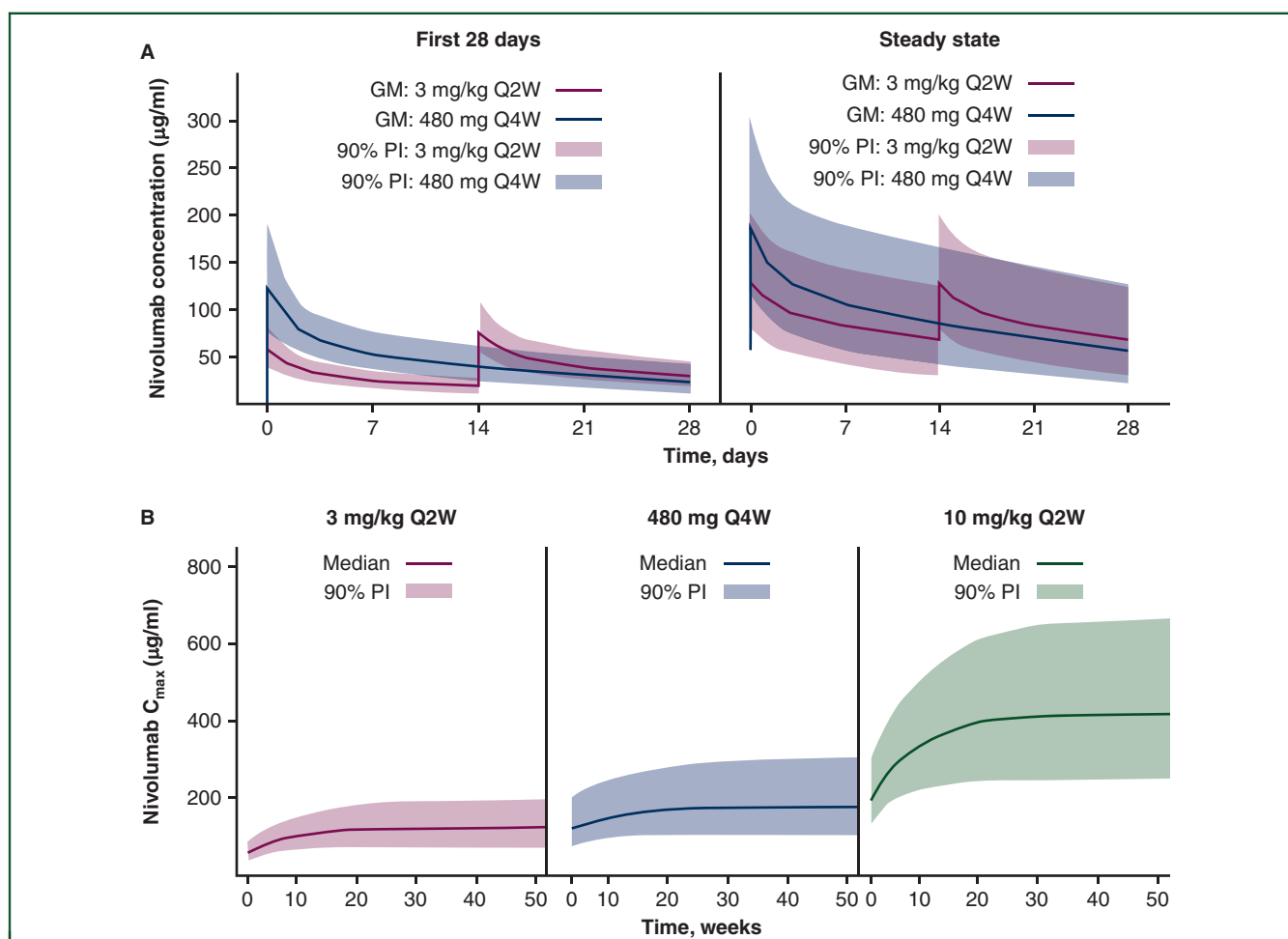


Figure 1. (A) Nivolumab concentration–time profiles of the 3-mg/kg Q2W and 480-mg Q4W regimens over the first 28 days. (B) Predicted exposure ($C_{\max}$) margin of safety over time for nivolumab 480 mg Q4W compared with 3 mg/kg Q2W and 10 mg/kg Q2W in patients with multiple tumor types.

Analysis was conducted in patients with melanoma, non-small-cell lung cancer, renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, and urothelial carcinoma. Plotted are the median values with 90% prediction intervals.

$C_{\max}$, peak concentration; GM, geometric mean; PI, prediction interval; Q2W, every 2 weeks; Q4W, every 4 weeks.

A quantitative systems pharmacology (QSP) model of intratumoral PD-1 RO was developed to assess the effect of 480 mg Q4W versus 3 mg/kg Q2W on intratumoral RO at the site of action of nivolumab.¹³ Intratumoral RO was predicted for a range of physiological parameters, representing highly perfused and stromal tumor types. Given nivolumab's specificity for the PD-1 receptor,¹ alternative dosing regimens with similar intratumoral RO are expected to have similar efficacy because they should block inhibitory signaling through PD-1 receptors to a similar extent.

RESULTS

Comparison of nivolumab exposures

Comparison of nivolumab concentration–time profiles during the first 28 days and at steady state for the 480-mg Q4W and 3-mg/kg Q2W dosing regimens demonstrated that 480 mg Q4W achieves higher concentrations over the first 14 days of each 4-week interval relative to 3 mg/kg Q2W (Figure 1A). Following the initiation of treatment, the lowest concentration (C_{min1}) predicted with 480 mg Q4W was greater than that predicted with 3 mg/kg Q2W (Figure 1A and Table 1).

A comparison of key summary measures of exposures for the 3-mg/kg Q2W, 240-mg Q2W, and 480-mg Q4W dosing regimens is presented in Table 1. C_{avgd28} for 480 mg Q4W was higher than 3 mg/kg Q2W during the first 28 days

(26.7%), and C_{avgss} was similar (5.2%). C_{min1} was higher with 480 mg Q4W versus 3 mg/kg Q2W (25.5%), whereas C_{mind28} and C_{minss} were lower with 480 mg Q4W (−22.1% and −16.2%, respectively). Conversely, C_{max1} and C_{maxss} with 480 mg Q4W were higher versus 3 mg/kg Q2W (110.4% and 43.4% higher, respectively).

Safety-bridging evaluation

Safety bridging used robust clinical data for 10 mg/kg Q2W, which was previously demonstrated to have a similar safety profile to 3 mg/kg Q2W.³ The nivolumab C_{max} values for 480 mg Q4W were well below those achieved with 10 mg/kg (Figure 1B), providing a wide exposure safety margin.

There were negligible differences between the three regimens in the probabilities of experiencing an AE, irrespective of severity or type (Figure 2). The predicted cumulative probability of experiencing grade ≥ 2 immune-mediated AEs (IMAEs), grade ≥ 2 treatment-related AEs (TRAEs), and TRAEs leading to discontinuation or death (TRAEs-DC/D) was similar with nivolumab 480 mg Q4W compared with 3 mg/kg Q2W (Figure 2 and supplementary Table S2, available at *Annals of Oncology* online). Although the exposure difference was greatest at C_{max1} (110.4% higher from 480 mg Q4W relative to 3 mg/kg Q2W), there was a numerical increase in risk of grade ≥ 2 IMAEs with 480 mg Q4W versus 3 mg/kg Q2W when using the C_{max1}

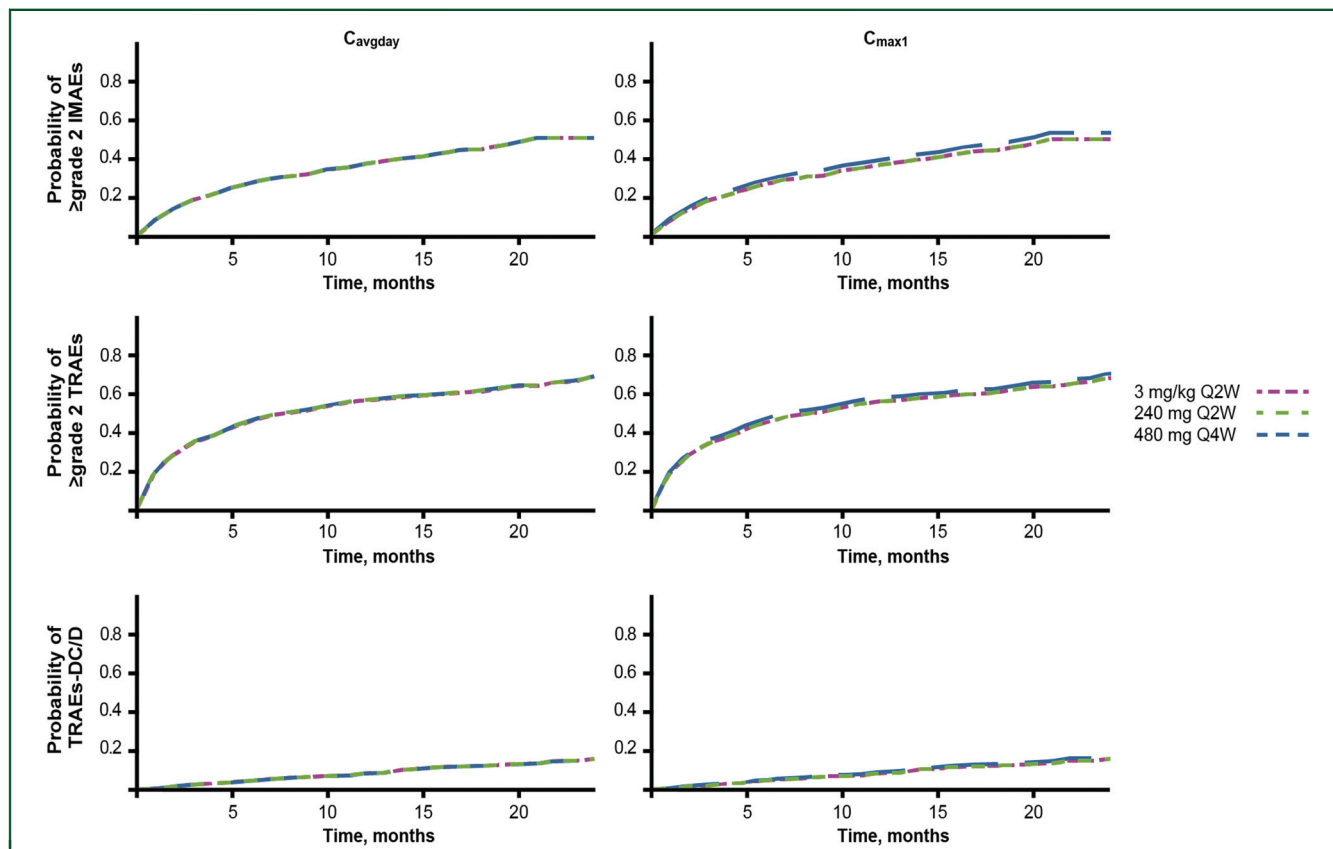


Figure 2. Predicted cumulative probability of having grade ≥ 2 IMAEs, grade ≥ 2 TRAEs, and TRAEs-DC/D for nivolumab exposures (C_{avgday} and C_{max1}) with 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W.

C_{avgday} , time-varying average concentration over each day for which a patient is at risk for an event; C_{max1} , peak concentration after the first dose; IMAE, immune-mediated adverse event; Q2W, every 2 weeks; Q4W, every 4 weeks; TRAEs-DC/D, treatment-related adverse events leading to drug discontinuation or death.

exposure predictor ($\leq 4\%$ increase at year 2; [Figure 2](#) and [supplementary Table S2](#), available at *Annals of Oncology* online). This trend was consistent across tumor types ([supplementary Figure S1](#) and [Table S2](#), available at *Annals of Oncology* online). The risks of grade ≥ 2 IMAEs, grade ≥ 3 AEs, and AEs-DC/D with 480 mg Q4W assessed in the logistic regression analysis were similar to those of 3 mg/kg Q2W ([supplementary Figure S2](#) and [Table S3](#), available at *Annals of Oncology* online).

Efficacy-bridging evaluation

The E–R efficacy analysis between 3 mg/kg Q2W and 480 mg Q4W demonstrated that the HRs for survival with 480 mg Q4W were similar to 3 mg/kg Q2W,

maintaining the superiority over SOC seen in pivotal trials ([Figure 3A](#) and [B](#)).

The predicted ORRs between 480 mg Q4W and 3 mg/kg Q2W were comparable (difference $\leq 2\%$), and were greater than those of the control group across tumor types ([Figure 4A](#)). Although there was a slight trend toward a higher ORR with increased nivolumab exposure in SQ NSCLC, the predicted ORR was similar within the exposure range of 3 mg/kg Q2W and flat dosing of 480 mg Q4W ([Figure 4B](#)).

$C_{\text{mind}28}$ with 480 mg Q4W was 22.1% lower compared with 3 mg/kg Q2W; however, the OS and ORR were predicted to be similar using $C_{\text{mind}28}$, the most conservative exposure measure for efficacy (see [supplementary Figures S3](#) and [S4](#) for OS and ORR, respectively, and [Table S4](#), available at *Annals of Oncology* online).

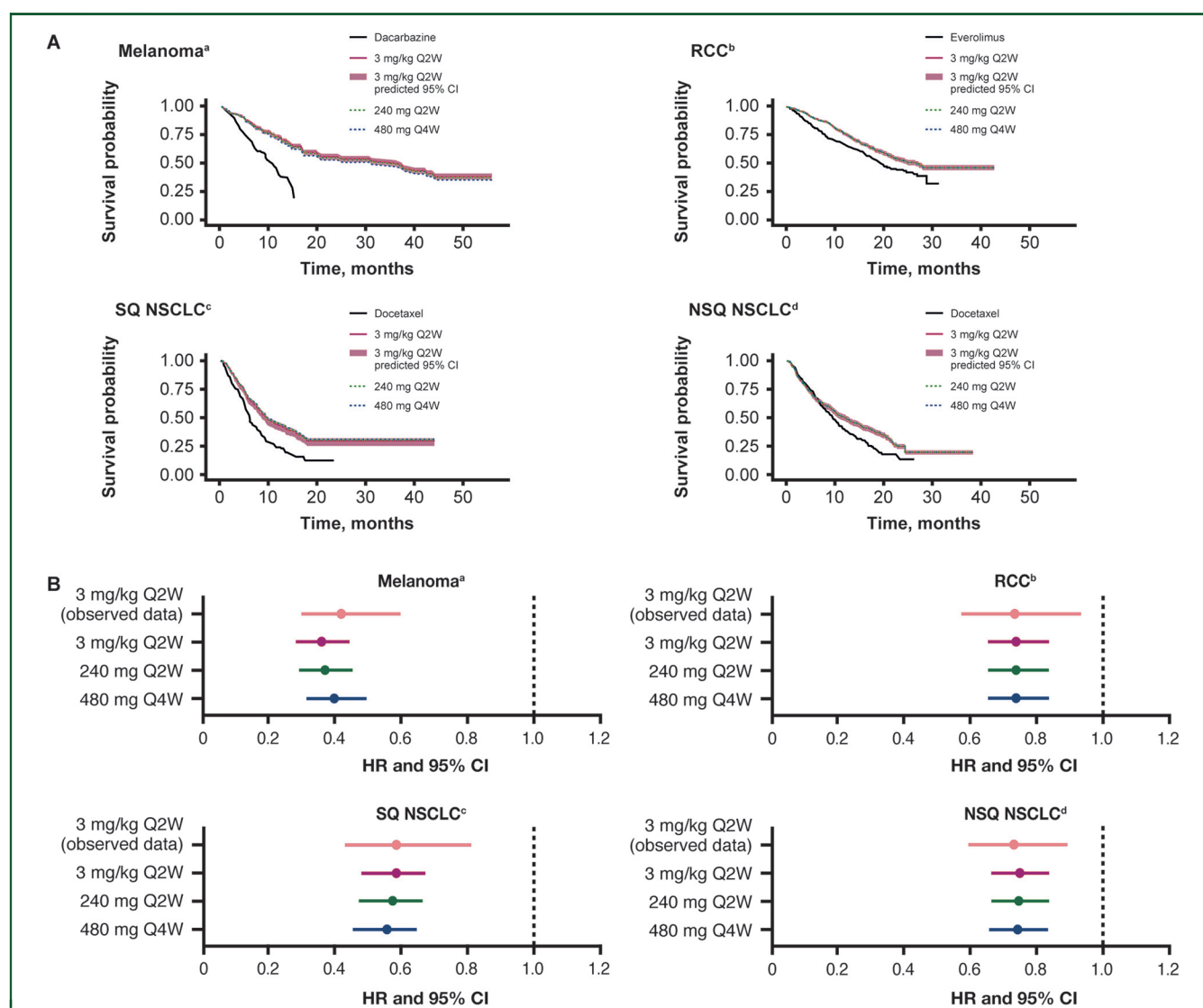


Figure 3. (A) Predicted mean OS (95% CIs) using $C_{\text{avgd}28}$ for nivolumab 3 mg/kg, 240 mg Q2W, and 480 mg Q4W relative to the standard of care in patients with melanoma, RCC, SQ NSCLC, and NSQ NSCLC. (B) Predicted HRs (95% CI) using $C_{\text{avgd}28}$ for nivolumab 3 mg/kg, 240 mg Q2W, and 480 mg Q4W in patients with melanoma, RCC, SQ NSCLC, and NSQ NSCLC.

$C_{\text{avgd}28}$, time-averaged concentration over the first 28 days; CI, confidence interval; HR, hazard ratio; NSCLC, non-small-cell lung cancer; NSQ, nonsquamous; OS, overall survival; Q2W, every 2 weeks; Q4W, every 4 weeks; RCC, renal cell carcinoma; SQ, squamous.

^a Data acquired from CheckMate 066 (NCT01721772).

^b Data acquired from CheckMate 025 (NCT01668784).

^c Data acquired from CheckMate 017 (NCT01642004).

^d Data acquired from CheckMate 057 (NCT01673867).

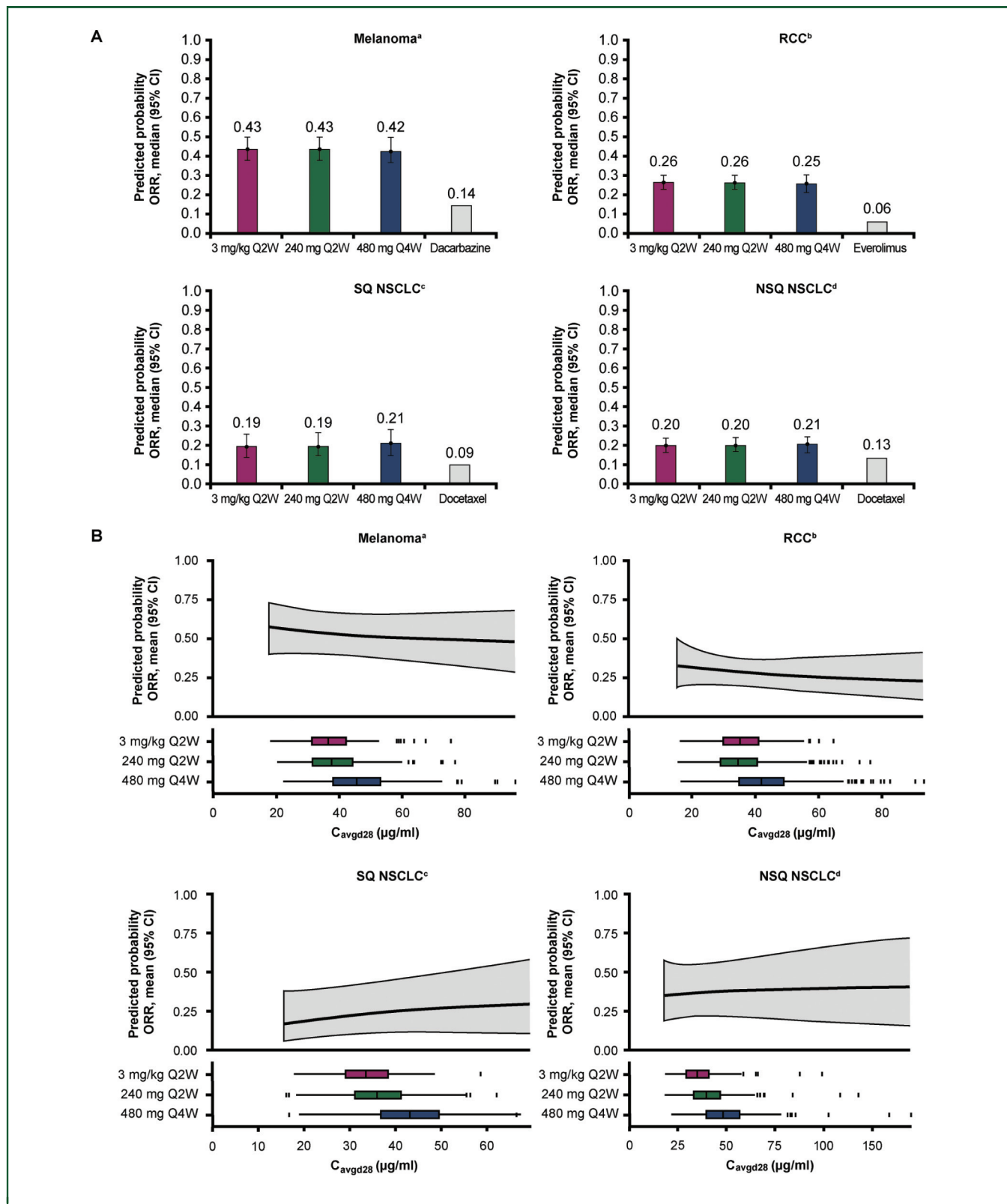


Figure 4. (A) Prediction of ORR (95% CIs) using C_{avgd28} for nivolumab 3 mg/kg, 240 mg Q2W, 480 mg Q4W, and standard of care in patients with melanoma, RCC, SQ NSCLC, and NSQ NSCLC. (B) The E–R relationship of ORR (95% CIs) using C_{avgd28} for nivolumab in patients with melanoma, RCC, SQ NSCLC, and NSQ NSCLC. C_{avgd28} , time-averaged concentration over the first 28 days; CI, confidence interval; E–R, exposure–response; NSCLC, non-small-cell lung cancer; NSQ, nonsquamous; ORR, objective response rate; Q2W, every 2 weeks; Q4W, every 4 weeks; RCC, renal cell carcinoma; SQ, squamous.

^a Data acquired from CheckMate 066 (NCT01721772); standard of care was dacarbazine.

^b Data acquired from CheckMate 025 (NCT01668784); standard of care was everolimus.

^c Data acquired from CheckMate 017 (NCT01642004); standard of care was docetaxel.

^d Data acquired from CheckMate 057 (NCT01673867); standard of care was docetaxel.

A high intratumoral RO was predicted over the 28-day dosing interval for nivolumab 3 mg/kg Q2W and 480 mg Q4W across a range of physiological parameters representing highly vascular or stromal tumor types (supplementary Figure S5, available at *Annals of Oncology* online). The consistent intratumoral RO with 3 mg/kg Q2W and 480 mg Q4W indicates that the immunostimulatory cascade and resulting efficacy will be similar for these regimens.

DISCUSSION

The benefit–risk profile for nivolumab’s Q4W dosing regimen was based on extensive clinical experience, wide therapeutic indices, robust clinical pharmacology, and QSP analyses. The clinical data from E–R and safety analyses across multiple tumor types support similarities in the benefit–risk profiles for 480 mg Q4W and 3 mg/kg Q2W.

Although $C_{\max}$ was higher with 480 mg Q4W versus 3 mg/kg Q2W, the exposure was well below a previously established $C_{\max}$ from a safe dose of 10 mg/kg Q2W. In addition, extensive exposure–safety analyses were conducted with pooled safety data across multiple tumor types and dose ranges (1 to 10 mg/kg Q2W, 0.3 to 10 mg/kg Q3W) for several safety end points. The safety end points of AEs-DC/D and TRAEs-DC/D represent the safety events affecting the treatment duration of nivolumab (including death). The end points of grade ≥ 3 AEs and grade ≥ 2 TRAEs represent the worst-grade events affecting patients’ quality of life, whereas grade ≥ 2 IMAEs reflect a more sensitive safety profile of nivolumab’s immunomodulatory activity. These safety analyses were conducted using C_{avgday} and C_{avgd28} to represent the most likely scenarios and $C_{\max 1}$ as a worst-case scenario, although the peak concentration on the first day of treatment is not likely to be the main driver of safety throughout treatment.

The exposure–safety assessments are further supported by available safety data from patients who switched to 480 mg Q4W infused over 30 min in ongoing clinical trials (NCT02713867)^{1,18} and nivolumab monotherapy maintenance after nivolumab plus ipilimumab (NCT02714218).¹⁹ No new AEs were noted when patients were treated with 480 mg Q4W versus 3 mg/kg Q2W.²⁰ In addition, the frequency and severity of AEs were not higher with the new dosing regimen.²⁰

To bridge the efficacy of nivolumab 480 mg Q4W with the clinically evaluated 3-mg/kg Q2W dosing regimen, extensive E–R analyses were conducted for ORR and OS across four tumor types/histologies of varying immunogenicity with available dose-ranging data (melanoma, RCC, SQ NSCLC, and NSQ NSCLC). The exposure–efficacy analyses demonstrated similarity between 480 mg Q4W and 3 mg/kg Q2W for both ORR, an early measure of treatment, and OS, a measure of the long-term benefit of therapy.

Based on nivolumab’s MOA, we hypothesize that sustained exposure leads to a cascade of long-lasting anti-cancer immunostimulation. Thus E–R analyses were performed using C_{avgd28} as the primary exposure measure representing the relevant drug concentration over the dosing interval for both Q2W and Q4W. The efficacy

analyses were also conducted using C_{mind28} , the only measure of early exposure that was lower with 480 mg Q4W relative to 3 mg/kg Q2W, to evaluate the potential worst-case scenario. However, given nivolumab’s MOA, transient concentration differences are not likely to impact efficacy if overall exposures are similar. The objective response and survival benefit with nivolumab 480 mg Q4W were predicted to be consistent with pivotal trials conducted with 3 mg/kg Q2W in tumor types with differing immunogenicity and tumor mutational burden.

An innovative QSP approach was used to predict the influence of tumor parameters on intratumoral PD-1 RO of nivolumab. Given the breadth of quantitative tumor characteristics explored, insights from the simulations of RO are considered broadly applicable, including when only 3 mg/kg Q2W data are available. The specificity of nivolumab for the PD-1 receptor suggests that its efficacy is mediated by intratumoral RO. Similar to 3 mg/kg, 480 mg Q4W is predicted to maintain a high level of intratumoral RO, indicating that the efficacy will also be similar.

Conclusions

The comprehensive model-based clinical pharmacology analyses supplemented with the rigorous evaluation of the clinical efficacy and safety of nivolumab demonstrate that the benefit–risk profile with nivolumab 480 mg Q4W is predicted to be similar to 3 mg/kg Q2W, which was studied in registered clinical trials across multiple tumor types. The extended dosing frequency of nivolumab is an additional convenient treatment option for patients and health care professionals, which maintains the established anticancer efficacy without compromising safety.

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DISCLOSURE

XZ, JS, YF, BJS, PS, VG, AB, AR, and SA are employees of Bristol-Myers Squibb. BJS, PS, AR, and SA are stockholders of Bristol-Myers Squibb. All remaining authors have declared no conflicts of interest.

DATA SHARING

Bristol-Myers Squibb’s policy on data sharing can be found at <https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html>.

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