

ORIGINAL ARTICLE

Model-informed drug development approach supporting approval of the 4-week (Q4W) dosing schedule for nivolumab (Opdivo) across multiple indications: a regulatory perspective

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Background: A nivolumab dosage regimen of 480 mg intravenously (i.v.) every 4 weeks (Q4W) was approved by FDA for the majority of the approved indications for nivolumab.

Methods: The proposed new dosage regimen was supported by pharmacokinetic modeling and simulation, dose/exposure–response relationships for efficacy and safety in the indicated patient populations, and the clinical safety data with the 480 mg Q4W dosage regimen. Pharmacokinetic exposures achieved with 480 mg Q4W were predicted for 4166 patients in 21 clinical studies with various types of solid and hematological tumors. Exposure–response analyses were conducted to predict 480 mg Q4W safety and efficacy across all FDA-approved indications for nivolumab.

Results: For the overall population, the geometric mean exposure achieved with 480 mg i.v. Q4W was 5.2% higher for steady state C_{avg} and 15.6% lower for C_{trough} than those with 3 mg/kg i.v. Q2W, the approved dosage regimen. The simulated concentration–time course achieved with 480 mg Q4W regimen was below the median concentration achieved with 10 mg/kg i.v. Q2W that was also studied in clinical trials. The predicted probability of adverse events was similar between 480 mg Q4W and that observed with the 3 mg/kg Q2W regimen. Efficacy results were found to be similar between Q2W and Q3W dosage regimens in patients with renal cell carcinoma. The predicted efficacy for each indication suggested that the efficacy with 480 mg Q4W is unlikely to be compromised compared with that observed with 3 mg/kg Q2W.

Conclusions: The model-informed analyses of predicted exposure, efficacy and safety based on data from extensive clinical experience with nivolumab suggest that the benefit–risk profile of 480 mg Q4W regimen is comparable to the approved 3 mg/kg Q2W regimen, thus providing the regulatory basis for the approval of 480 mg Q4W regimen in the absence of clinical efficacy data with this new dosage regimen.

Key words: nivolumab, Q4W dosing frequency, model-informed drug development, immuno-oncology, clinical pharmacology, regulatory perspective

Introduction

Opdivo (nivolumab; Bristol-Myers Squibb) is a human immunoglobulin subtype G4 (IgG4) monoclonal antibody that blocks the PD-1 pathway-mediated inhibition of the antitumor immune

response by binding to the PD-1 receptor on T cells and blocking the interaction with its ligands PD-L1 and PD-L2 [1].

The US Food and Drug Administration (FDA) has approved Opdivo for the treatment of patients with the cancers: metastatic

melanoma, post-surgical resection of melanoma, metastatic non-small-cell lung cancer (NSCLC), advanced renal cell carcinoma (RCC), urothelial carcinoma (UC), classical Hodgkin's lymphoma (cHL), squamous (SQ) cell carcinoma of the head and neck (SCCHN) and hepatocellular carcinoma (HCC). The first approved dosage regimen of nivolumab was 3 mg/kg administered via intravenous (i.v.) infusion over 60 min once every 2 weeks (Q2W) [2, 3]. Subsequently, the FDA approved the dosage regimen of nivolumab 240 mg i.v. Q2W for all approved indications based on bridging the exposure, safety and efficacy achieved by 240 mg Q2W to those observed with the nivolumab 3 mg/kg Q2W dosage regimen. Clinical studies have shown that nivolumab is also tolerated at 10 mg/kg i.v. Q2W in patients with solid tumors [4].

On 5 March 2018, the FDA added a 480 mg i.v. every 4 weeks (Q4W) new dosage regimen for the majority of the approved nivolumab indications [5]. The applicant sought this new dosage regimen to provide healthcare providers and patients additional flexibility. The proposed new dosage regimen was only supported by the pharmacokinetic (PK) modeling and simulation, dose and exposure–response (E–R) relationships for efficacy and safety in the indicated patient population, and clinical safety data with the 480 mg Q4W dosage regimen. No clinical efficacy data with the nivolumab Q4W dosage regimen was available at the time of this approval. This article explains the regulatory perspectives for the approval of the nivolumab 480 mg i.v. Q4W dosage regimen.

Methods

The assessment of the benefit–risk profile of nivolumab 480 mg i.v. Q4W was based upon the comparison of nivolumab exposures predicted for 480 mg Q4W, 240 mg i.v. Q2W and 3 mg/kg i.v. Q2W dosage regimens pooling the results of clinical trials across all tumor types, the safety evaluation of nivolumab 480 mg Q4W predicted in E–R analyses, and bridging the efficacy of nivolumab from clinical trials using the model-predicted exposures for 480 mg Q4W. A summary of data included for population PKs (popPK), efficacy and safety assessment is provided in [supplementary Table S1](#), available at *Annals of Oncology* online.

Comparison of nivolumab exposures at 480 mg Q4W, 240 mg Q2W and 3 mg/kg Q2W

A previously developed popPK model was applied to predict the nivolumab exposure produced by 480 mg Q4W dosage regimen [6]. The model was built based on data from 4166 patients across tumor types with dosage regimen ranged from 0.1 to 10 mg/kg Q2W and from 0.3 to 10 mg/kg Q3W. No PK data were available for nivolumab 480 mg Q4W dosage regimen.

The predicted individual exposure metrics including time-averaged concentration (C_{avg1st}), peak concentration (C_{max1st}) and trough concentration ($C_{trough1st}$) after the first dose, during the first 28-day cycle (C_{avg28d} , C_{max28d} and $C_{trough28d}$) and at steady state (C_{avgss} , C_{maxss} and $C_{troughss}$) in these patients were generated based on individual post hoc PK parameters. These nivolumab exposure metrics predicted at 480 mg Q4W were compared with those achieved at 3 mg/kg Q2W and 240 mg Q2W.

Evaluation of safety of nivolumab 480 mg Q4W

Safety for 480 mg Q4W were bridged by comparison of predicted exposures with 480 mg Q4W relative to that observed with 10 mg/kg Q2W, which is known to be reasonably safe and tolerable in clinical trials.

Additional safety assessment was conducted by evaluating the nivolumab dose/exposure–safety relationship in 2560 patients with melanoma, SQ NSCLC, nonsquamous (NSQ) NSCLC, RCC, SCCHN, UC and cHL from 13 clinical trials across doses ranging from 0.3 mg/kg Q3W to 10 mg/kg Q2W. The evaluated safety end points were adverse events (AE) leading to discontinuation or death (AE-DC/D), grade 3+ AE (AE-grade 3+) and grade 2+ immune-mediated AE (AE-IM grade 2+).

Efficacy bridging of nivolumab 480 mg Q4W

The dose–response (D–R) relationships for overall survival (OS) and overall response rate (ORR) were evaluated across tumor types (melanoma, RCC, SQ NSCLC and NSQ NSCLC) whenever efficacy data were available across a dose range. The analysis population for D–R of OS included 399 patients with melanoma, 354 patients with NSQ NSCLC, 293 patients with SQ NSCLC and 607 patients with RCC.

The E–R relationships for efficacy were characterized based on primary end points in the clinical trials supporting new or expanded indications: OS, recurrence-free survival and ORR. The model-predicted average (C_{avg28d}) and trough ($C_{trough28d}$) concentrations over the first 28 days (42 days for Q3W) were selected for the primary analyses of E–R. The efficacy of nivolumab 3 mg/kg Q2W, 240 mg Q2W and 480 mg Q4W based on the clinical end points supporting approval were predicted and compared using the established E–R models with $C_{trough28d}$. For additional details on patient population, safety and efficacy bridging analyses, see the [supplementary methods](#), available at *Annals of Oncology* online.

Results

Comparison of nivolumab exposures achieved by 480 mg Q4W, 240 mg Q2W and 3 mg/kg Q2W

The exposure metrics for nivolumab 480 mg Q4W versus 240 mg Q2W and 3 mg/kg Q2W were summarized in [Table 1](#). The C_{avg} of the 480 Q4W regimen was in general similar to that of the 3 mg/kg Q2W; however, the C_{trough} was lower for 480 mg Q4W ([Figure 1A](#)). For the overall population, the geometric means of steady state C_{trough} achieved with 480 mg Q4W was 15.6% lower compared with that with 3 mg/kg Q2W. The differences in steady state C_{trough} between that predicted with 480 mg Q4W and that observed with 3 mg/kg Q2W were within 20% for melanoma, resected melanoma, NSCLC, cHL, UC and HCC and within 25% for RCC and SCCHN. The steady state C_{trough} with nivolumab 480 mg Q4W relative to 240 mg Q2W was ~20% lower for all relevant tumor types.

Evaluation of safety of nivolumab 480 mg Q4W

The simulated concentration–time course achieved with 480 mg Q4W was well below the median concentration achieved with 10 mg/kg Q2W ([Figure 1B](#)), which is known to be reasonably safe and tolerable in clinical trials.

In Study CA209003, 130 patients with various tumor types including melanoma, NSCLC and RCC were tested with 10 mg/kg Q2W dosage regimen [4]. The duration of treatment with 10 mg/kg ranged from 2 to 122 weeks, with a median of 15.9 weeks and a mean of 26.8 weeks. In this trial, treatment with nivolumab 10 mg/kg was tolerable with manageable toxicities. The dose–response analyses for AE-DC/D, AE-grade 3+ and AE-IM grade 2+ also indicated no evident difference between 10 mg/kg Q2W and 3 mg/kg Q2W regimens. In addition, no consistent

Table 1. Comparison of exposure among nivolumab 3 mg/kg Q2W, 240 mg Q2W or 480 mg Q4W in overall population

Summary exposure	3 mg/kg Q2W GM, µg/ml (%CV)	240 mg Q2W GM, µg/ml (%CV)	480 mg Q4W GM, µg/ml (%CV)	%Diff GM 480-3 mg/kg	%Diff GM 480-240 mg
$C_{trough1st}$	18.55 (28.89)	19.52 (32.35)	23.86 (39.97)	28.6	22.2
C_{avg1st}	28.43 (24.17)	29.92 (26.78)	45.81 (29)	61.1	53.1
C_{max1st}	59.53 (86.05)	62.65 (86.69)	125.68 (90.8)	111.1	100.6
C_{avg28}	35.89 (25.16)	37.77 (28.07)	44.17 (28.75)	23.1	16.9
$C_{trough28}$	30.14 (31.26)	31.72 (34.74)	23.86 (39.97)	-20.8	-24.8
C_{max28}	78.57 (68.03)	82.68 (69.29)	125.68 (90.8)	60	52
$C_{troughss}$	69.44 (50.28)	73.08 (52.99)	58.62 (60.47)	-15.6	-19.8
C_{maxss}	132.23 (50.11)	139.16 (52.65)	189.71 (66.62)	43.5	36.3
C_{avgss}	89.18 (42.44)	93.86 (45.26)	93.86 (45.26)	5.2	0

CV, coefficient of variation; GM, geometric mean; C_{avg1st} , time-averaged concentration after the first dose (the first dose for 480 Q4W is twofold increase compared with 240 mg or 3 mg/kg Q2W); $C_{trough28}$, trough concentration at day 28; C_{maxss} , peak concentration at steady state.

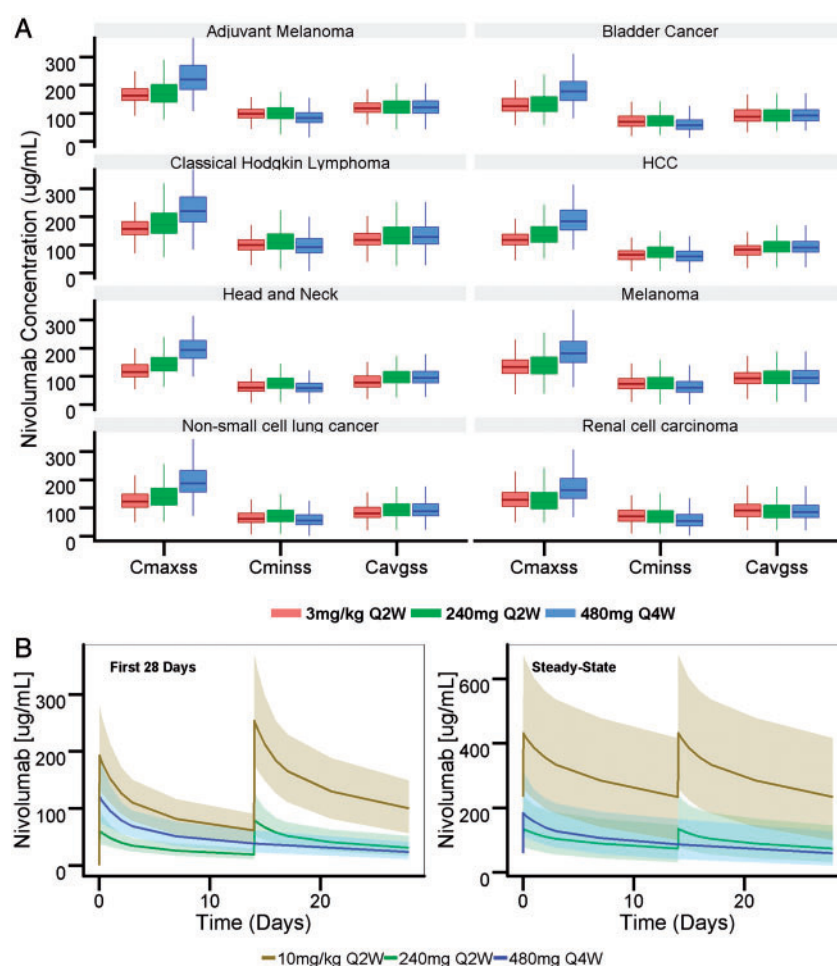


Figure 1. (A) Boxplots of predicted steady-state exposure for nivolumab 3 mg/kg Q2W, 240 mg Q2W and 480 mg Q4W in subjects with melanoma, adjuvant melanoma, NSCLC, RCC, SCCHN, UC, CHL or HCC. (B) Simulated nivolumab concentration–time profile in patients given 240 mg Q2W, 480 mg Q4W or 10 mg/kg Q2W. The dashed (green online), solid (blue online) and dotdash (gold online) lines and shaded bands represent the simulation-based median, 5th and 95th percentile of concentration–time profiles in patients given 240 mg Q2W, 480 mg Q4W or 10 mg/kg Q2W.

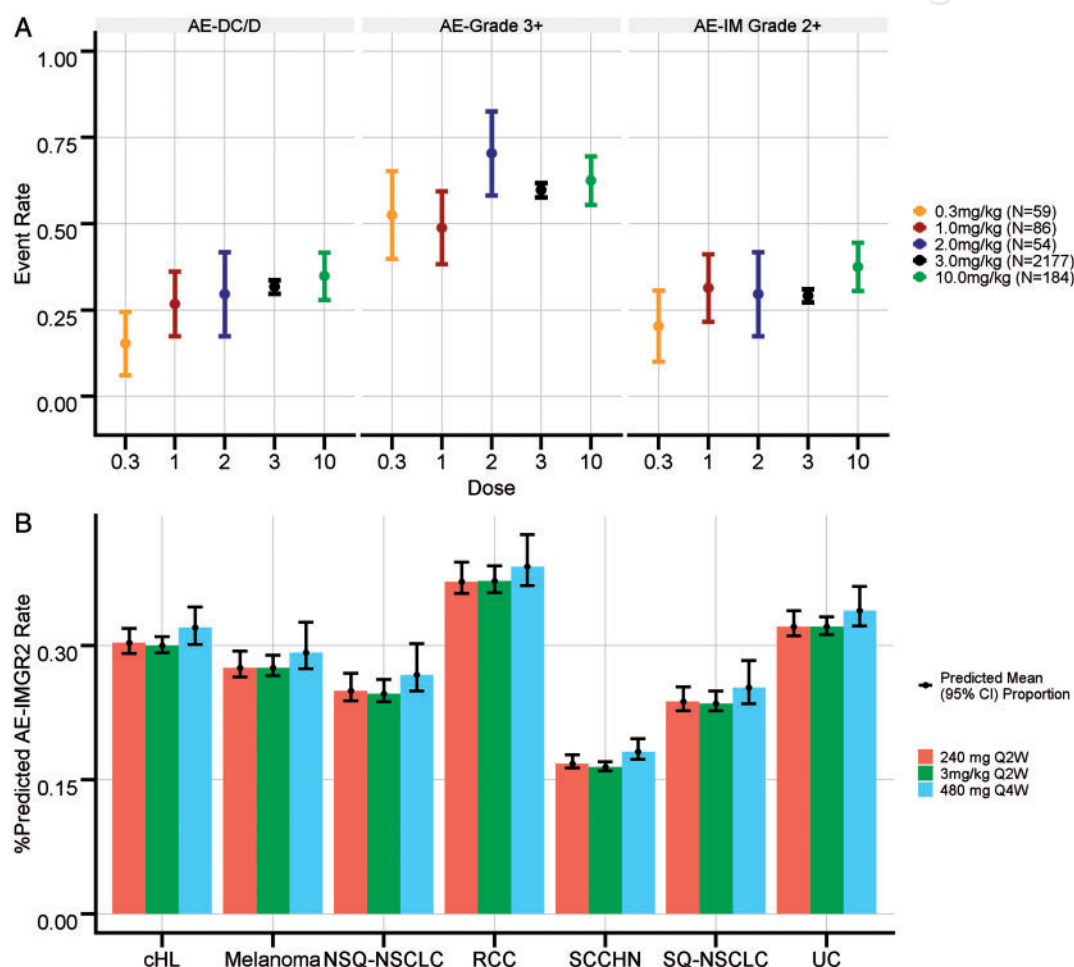


Figure 2. (A) Safety event rates of AE-DC/D, AE-grade 3+ and AE-IM grade 2+ in different tested doses in 2560 patients with melanoma, SQ NSCLC, NSQ NSCLC, RCC, SCCHN, UC and cHL. (B) Model predicted proportion of AE-IM grade 2+ events for 3 mg/kg Q2W, 240 mg Q2W and 480 mg Q4W by tumor type.

associations were found between nivolumab early exposure and event rates of AE-DC/D and grade 3+ AE (Figure 2).

Consistent with dose/exposure–safety relationships, the toxicity profile of 142 patients with unresectable or metastatic melanoma treated with 480 mg Q4W in Study CA209511 also appeared similar to the safety profile observed with nivolumab (240 mg Q2W or 3 mg/kg Q2W administered i.v. over 60 min); no new safety signals were identified.

Efficacy bridging of nivolumab 480 mg Q4W

Extensive dose/E–R analyses were conducted to bridge the efficacy of nivolumab 480 mg Q4W with that observed with the 3 mg/kg Q2W dosage regimen.

Dose–efficacy profiles were available for melanoma, HCC and NSCLC with nivolumab 0.1–10 mg/kg Q2W regimens, and for RCC with 1–10 mg/kg Q2W and 0.3–10 mg/kg Q3W regimens. Flat dose–efficacy relationships were found for HCC, melanoma and RCC (Figure 3). Efficacy results were found to be similar between nivolumab Q2W and Q3W dosage regimens in patients with RCC. For NSCLC, there appeared to be a trend of additional benefit (especially in ORR) at 3 mg/kg Q2W when compared with 1 mg/kg Q2W. However, the efficacy data in patients with

NSCLC at the 1 mg/kg Q2W dosage regimen was based on a small sample size in a dose-finding study and consistent additional benefit at 10 mg/kg over 1 mg/kg was not observed.

The exposure–efficacy relationship for nivolumab was likely to be positively biased based on data submitted to FDA for nivolumab and other PD-1/PD-L1 products, especially if based on a single arm trial with one dose level [7, 8]. These analyses were conducted using the $C_{trough28d}$ in order to predict efficacy as the worst-case scenario for the potential loss of efficacy. No significant associations were identified between $C_{trough28d}$ and OS for patients treated for metastatic or resected melanoma or between $C_{trough28d}$ and ORR for UC, HCC or cHL after adjusting for baseline covariates. The predicted efficacy for those tumor types based on the final E–R models was similar between 3 mg/kg Q2W and 480 mg Q4W. Positive associations were identified between nivolumab exposure and time to OS for RCC and NSQ-NSCLC, but the predicted OS was similar between 3 mg/kg Q2W and 480 mg Q4W (supplementary Tables S2 and S3, available at *Annals of Oncology* online). For SQ-NSCLC and SCCHN, the predicted OS were slightly lower for 480 mg Q4W (median OS: 8.3 months for SQ-NSCLC and 8.8 months for SCCHN) compared with 3 mg/kg Q2W (median OS: 9.2 months for SQ-NSCLC and 9.3 months for SCCHN); however, they were much higher than the

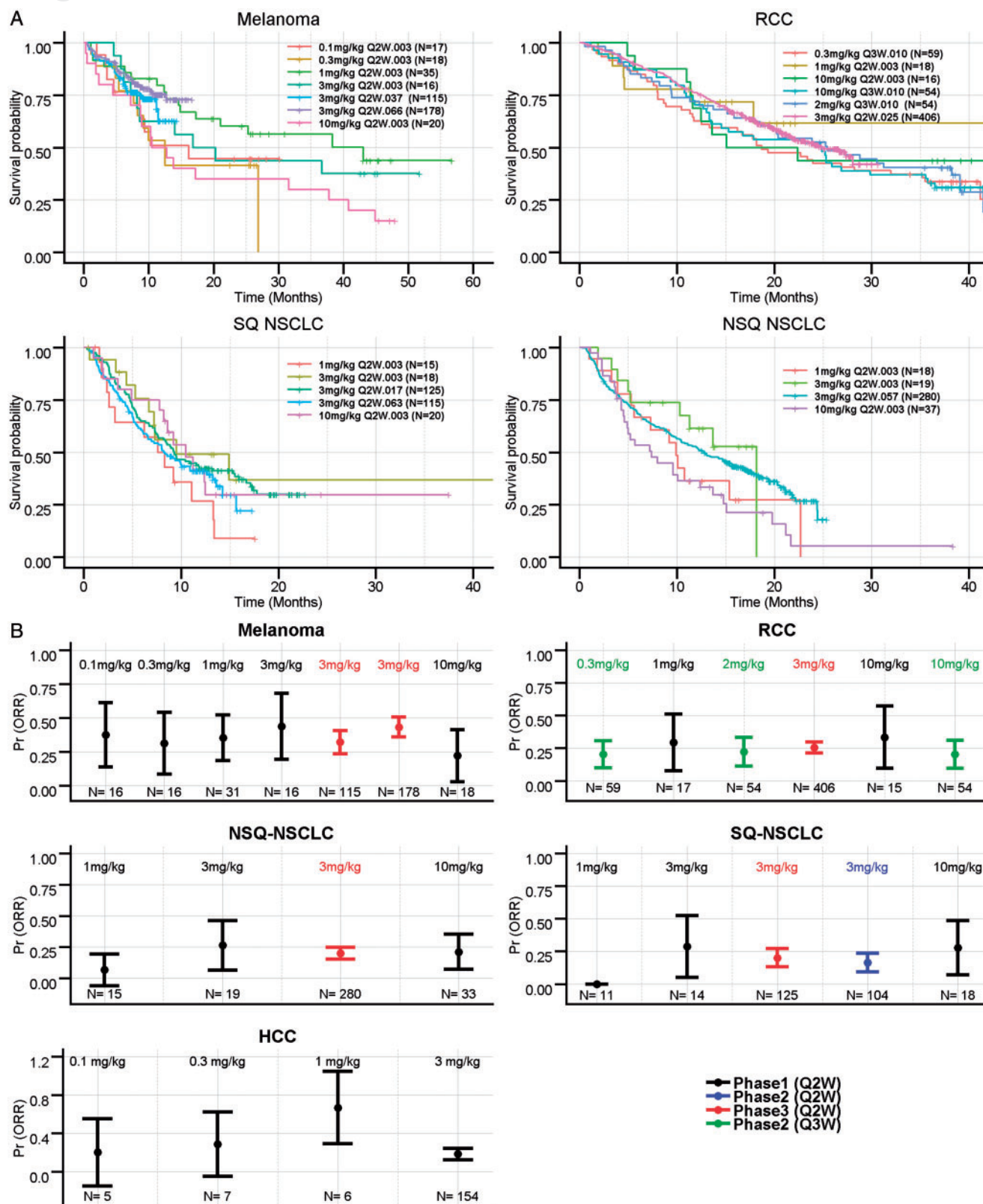


Figure 3. (A) The Kaplan–Meier (KM) curve of overall survival (OS) for doses ranging from 0.1 to 10 mg/kg in patients with melanoma, RCC, SQ and NSQ NSCLC. (B) Overall response rates (ORR) across different tested doses ranging from 0.1 to 10 mg/kg for patients with melanoma, RCC, SQ-NSCLC, NSQ-NSCLC and HCC.

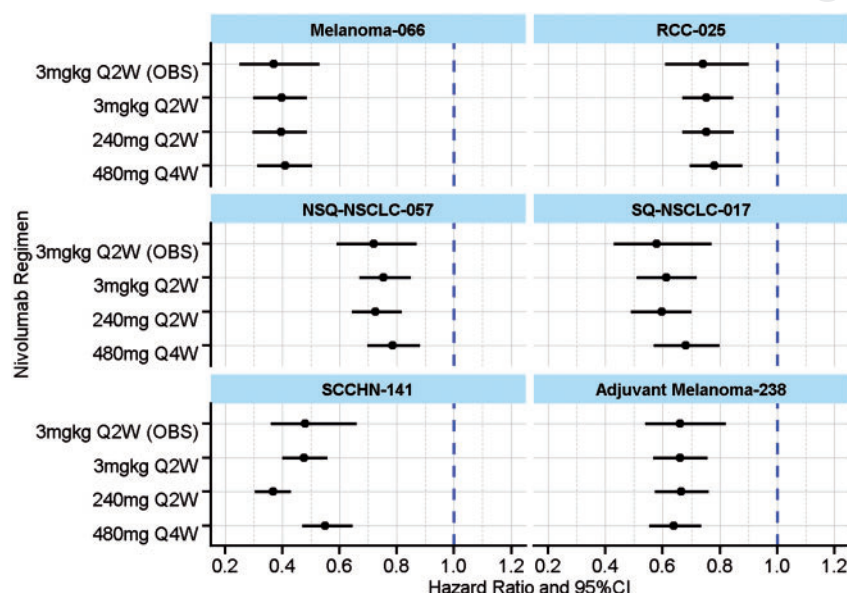


Figure 4. Predicted hazard ratios (HRs) of nivolumab 3 mg/kg Q2W, 240 mg Q2W and 480 mg Q4W relative to comparator arm in pivotal trials across tumor types of melanoma, RCC, NSCLC, SCCHN and adjuvant melanoma. Note: First row in each of the plots represents the observed HR of nivolumab 3 mg/kg Q2W relative to comparator arm. The dot represents the median and the error bar represents the 95% confidence interval.

comparator arms in the pivotal trials (supplementary Table S2, available at *Annals of Oncology* online). The hazard ratios (HRs) of different nivolumab dosage regimens relative to the control arm in the pivotal trials predicted based on the established E–R relationships were shown in Figure 4. The predicted HR of nivolumab 3 mg/kg Q2W versus the control matched the observed HR reasonably well. The predicted HRs with nivolumab 480 mg Q4W treatment relative to the control arm were comparable to 3 mg/kg Q2W for melanoma, adjuvant melanoma, NSQ-NSCLC and RCC, and the predicted HRs of 480 mg Q4W relative to the control arm were higher than the 3 mg/kg Q2W for SQ-NSCLC (0.68 versus 0.61) and SCCHN (0.55 versus 0.48).

Discussion

Per the FDA exposure–response guidance [9], the dose and ‘E–R information is at the heart of any determination of the safety and effectiveness of drugs’ can support, or in some cases provide primary evidence for, approval of different doses, dosage regimens, or dosage forms, or use of a drug in different populations, when effectiveness is already well-established in other settings. The nivolumab 3 mg/kg Q2W regimen has been extensively studied in patients across multiple solid tumors and one hematological malignancy. Robust dose/E–R relationships for nivolumab were established to support an alternative dosage regimen of 480 mg Q4W.

The clinical experience and understanding of the safety profile of nivolumab at doses ranging from 0.1 to 10 mg/kg Q2W or Q3W as well as the predicted exposures for the 480 mg Q4W regimen provided confidence that the 480 mg Q4W regimen would be reasonably safe and tolerable. The extensive dose/E–R analyses of multiple AEs predicted that the safety profile of nivolumab 480 mg Q4W would be similar to the established safety profile at

3 mg/kg Q2W. This was further supported by the observed safety profile with nivolumab 480 mg Q4W in Study CA209511.

The efficacy profiles observed across doses ranging from 0.1 to 10 mg/kg Q2W for melanoma and from 0.3 to 10 mg/kg Q3W for RCC provided primary evidence for efficacy bridging. The exposure–efficacy relationship for nivolumab was likely to be positively biased, especially if it was based on a single arm trial with one dose level. This bias is likely due to the decreased clearance of monoclonal antibodies over time in responders [7, 8]. Based on the effect of nivolumab early exposure (C_{trough} over first 28 days) on OS in patients with RCC shown in supplementary Figure S1, available at *Annals of Oncology* online, the slope of exposure on efficacy for a 3 mg/kg single dose from Study CA209025 was much steeper than the slope for the multiple doses. This inconsistency has been identified previously in the E–R analyses for melanoma [10].

Efficacy with nivolumab 480 mg Q4W was predicted based on positively biased E–R analyses using $C_{trough28d}$ as the worst-case scenario. The comparable efficacy prediction for melanoma, adjuvant melanoma, RCC, cHL, UC, NSQ-NSCLC and HCC, and slightly lower efficacy prediction for SQ-NSCLC and SCCHN with 480 mg Q4W compared with 3 mg/kg Q2W provided further evidence that survival benefit for 480 mg Q4W is unlikely to be compromised. It is worth noting that the above efficacy prediction based on potentially biased E–R relationships probably overpredicted the efficacy loss for the 480 mg Q4W over the 3 mg/kg Q2W for SQ-NSCLC and SCCHN. The difference in nivolumab exposure (C_{avg} and C_{trough}) between low body-weight and high body-weight patients with 3 mg/kg Q2W was larger than that caused by the dosage regimen change. However, body weight was not identified as a significant covariate that affects efficacy, which indicated that a 20% difference in C_{trough} between the 480 mg Q4W and 3 mg/kg Q2W is unlikely to have any meaningful impact on the clinical outcome of nivolumab treatment.

Furthermore, the difference in C_{trough} between 480 mg Q4W and 3 mg/kg Q2W does not represent the exposure difference for the entire dosing interval as the C_{avg} between the two dosage regimens was similar. The similar efficacy between Q2W and Q3W dosage regimen and across 0.3–10 mg/kg Q3W regimens for RCC provided additional confidence that decreasing dose frequency from Q2W to Q4W while maintaining total monthly dose was unlikely to compromise the efficacy. Multiple efficacy trials (e.g. CheckMate 384) [11] using the nivolumab 480 mg Q4W dosage regimen as one of the treatment arms are ongoing. Results from these clinical trials will provide further clinical experience with nivolumab 480 mg Q4W dosage regimen.

The potential to use a less frequent dosage regimen for PD-1 or PD-L1 inhibitors could provide healthcare providers and patients additional flexibility to individualize treatment as well as allowing investigators/pharmaceutical companies flexibility in the design of future clinical trials for PD-1/PD-L1 inhibitors, especially in the setting of combination therapy. The approach to approval of a new dosage regimen described here may inform the dosage regimen change of other anti-PD-1/PD-L1 mAbs and possibly other mAbs. A comprehensive clinical understanding of the drug products and availability of the efficacy and safety data from a wide range of dosage regimens are essential to support the bridging. Available PK data and established E–R relationships in all pivotal trials facilitate the efficacy and safety bridging of an untested dosage regimen. However, one should be cautious when interpreting and applying the E–R relationship for mAbs if the relationship is based on data from a single dose, because exposure can be confounded by target-mediated clearance or interaction between disease response and clearance. Inconsistent results between D–R and E–R relationships for nivolumab and between E–R relationships based on single dose and multiple doses in patients with RCC serves as an example. A well-controlled dose-ranging trial with randomized arms can circumvent the potential confounded E–R relationship.

A well-understood dose–efficacy profile at a lower efficacious nivolumab dose in several tumor types (melanoma, NSCLC and RCC) provides the pivotal evidence for the approval of the 480 mg Q4W dosage regimen. However, for other anti-PD-1 or PD-L1 mAbs or anticancer mAbs, a dose–efficacy profile at a lower efficacious dose with exposure equal to or lower than the exposure with the proposed dosage regimen may not be available. Given that anti-PD-1 or PD-L1 mAbs are generally not with a narrow therapeutic range, the Clinical Pharmacology-based ‘exposure-matching’ approach leveraging the bioequivalence principle to bridge efficacy in support of an untested dosage regimen (assuming safety is covered) might be reasonable. The details of the ‘exposure-matching’ approach is currently under extensive evaluation.

Discussion

Conclusion

Overall, the approval of the 480 mg Q4W dosage regimen for nivolumab was supported by the population PK simulations, flat dose–response relationships for efficacy and safety in the patient populations across clinical studies supporting all approved nivolumab indications, and the available clinical safety data with the 480 mg Q4W and 10 mg/kg Q2W dosage regimens. The similar

OS across 0.3, 2 and 10 mg/kg Q3W dosage in 167 patients with RCC in Study CA209010 provided reassurance that decreasing dosing frequency from Q2W to Q4W while maintaining similar exposure was unlikely to compromise the efficacy. Predictions based on E–R relationships across the various tumor types indicated that the efficacy with 480 mg Q4W is unlikely to be compromised. Multiple efficacy trials using the nivolumab 480 mg Q4W dosage regimen as one of the treatment arms are ongoing.

The model-informed analyses of predicted exposure, efficacy and safety based on extensive clinical experience of nivolumab provided the regulatory basis for the approval of the 480 mg Q4W new dosage regimen in the absence of the empirical clinical efficacy data, since the model has been shown to be robust for prediction of safety, efficacy, and PKs. Where exposure or C_{max} with a new dosage regimen is appreciably higher than that previously studied, additional safety data may be required. With the passage of PUDFA VI, the FDA is committed to advancing model-informed drug development, which will ultimately facilitate drug development and approval of alternative dosage regimens.

Acknowledgements

This analysis was supported by the Office of Clinical Pharmacology and the Office of New Drugs at the FDA. We thank BMS for providing original datasets and codes for the analyses. E–R analyses for efficacy for melanoma, RCC and NSCLC and E–R analyses for safety were conducted by BMS and modified by FDA. E–R analyses for efficacy for other tumor types and D–R analyses for efficacy and safety were conducted by FDA. The QSP model was developed by BMS.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the official views of the FDA.

Funding

None declared.

Disclosure

All listed authors are employees of the Food and Drug Administration of the United States. The authors have declared no conflicts of interest.

References

1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012; 12(4): 252–264.
2. Kazandjian D, Suzman DL, Blumenthal G et al. FDA approval summary: nivolumab for the treatment of metastatic non-small cell lung cancer with progression on or after platinum-based chemotherapy. *Oncologist* 2016; 21(5): 634–642.
3. Hazarika M, Chuk MK, Theoret MR et al. U.S. FDA approval summary: nivolumab for treatment of unresectable or metastatic melanoma following progression on ipilimumab. *Clin Cancer Res* 2017; 23(14): 3484–3488.

4. Topalian SL, Hodi FS, Brahmer JR et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012; 366(26): 2443–2454.
5. Sutharshan K, Gearry RB. Temporary adalimumab dose escalation is effective in Crohn's disease patients with secondary non-response. *J Crohns Colitis* 2013; 7(7): e277–e278.
6. Bajaj G, Wang X, Agrawal S et al. Model-based population pharmacokinetic analysis of nivolumab in patients with solid tumors. *CPT Pharmacometrics Syst Pharmacol* 2017; 6(1): 58–66.
7. Li H, Yu J, Liu C et al. Time dependent pharmacokinetics of pembrolizumab in patients with solid tumor and its correlation with best overall response. *J Pharmacokinet Pharmacodyn* 2017; 44(5): 403–414.
8. Liu C, Yu J, Li H et al. Association of time-varying clearance of nivolumab with disease dynamics and its implications on exposure response analysis. *Clin Pharmacol Ther* 2017; 101(5): 657–666.
9. Guidance for Industry: Exposure–Response Relationships—Study Design, Data Analysis, and Regulatory Applications. Food and Drug Administration, April 2003. <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072109.pdf>.
10. Bajaj G, Gupta M, Feng Y et al. Exposure–response analysis of nivolumab in patients with previously treated or untreated advanced melanoma. *J Clin Pharmacol* 2017; 57(12): 1527–1533.
11. Yao LP. Extrapolation in pediatric drug development: an evolving science. In 2018 ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop, Washington, DC, 13 September 2018.