

ORIGINAL ARTICLE

Assessment of nivolumab exposure and clinical safety of 480 mg every 4 weeks flat-dosing schedule in patients with cancer

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Background: A nivolumab monotherapy flat-dosing regimen of 480 mg every 4 weeks (Q4W) has been approved in several markets, including the United States, Canada, and European Union, as an alternative dosing regimen for several indications. Approvals of this Q4W regimen were based on population pharmacokinetic (PK) analyses, established flat exposure–response relationships, and clinical safety. The objective of this study was to compare the PK exposure of 480 mg Q4W with 3 mg/kg every 2 weeks (Q2W) and 240 mg Q2W using modeling and simulation, and to evaluate clinical safety of the Q4W regimen.

Patients and methods: Nivolumab PK exposure for the 480 mg Q4W schedule was simulated for 3817 patients across multiple tumor types and compared with those for the 3 mg/kg Q2W and 240 mg Q2W schedules. The safety profile of the Q4W schedule was assessed by analysis of clinical data from 61 patients who transitioned to nivolumab 480 mg Q4W from 3 mg/kg Q2W during four phase III clinical trials.

Results: Compared with 3 mg/kg Q2W, nivolumab 480 mg Q4W produced similar time-averaged concentration, approximately 16% lower trough concentration, and 45% higher peak concentration at steady state. The peak concentration for 480 mg Q4W was significantly lower than that of 10 mg/kg Q2W, a dose previously shown to have an acceptable tolerability and safety profile. Treatment-related adverse events (TRAEs) that started after transitioning from 3 mg/kg Q2W to 480 mg Q4W were reported in 14.8% of patients, with 1.6% of patients reporting grades 3–4 TRAEs. Pooled safety data for these patients are consistent with those for the 3 mg/kg Q2W schedules, and no new safety signals were identified.

Conclusions: The time-averaged steady-state exposure and safety profile of nivolumab 480 mg Q4W are consistent with that of 3 mg/kg Q2W across multiple tumor types. Nivolumab 480 mg Q4W represents a new dosing schedule option, and in addition to 240 mg Q2W, provides convenience and flexibility for patient care.

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Key words: nivolumab, Q4W, PK exposure, safety, immuno-oncology, solid tumors

Introduction

Nivolumab is a fully human immunoglobulin G4 monoclonal antibody that targets the interaction between the programmed

death-1 (PD-1) immune checkpoint and its ligands, programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2) [1, 2]. Nivolumab is approved globally, including in the United States, European Union, and Japan, for several cancer types,

including melanoma, renal cell carcinoma (RCC), non-small-cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma (UC), microsatellite instability-high or mismatch repair deficient colorectal cancer (MSI-H/dMMR CRC), hepatocellular carcinoma (HCC), and classical Hodgkin lymphoma (cHL) [1, 2].

Nivolumab has a wide therapeutic index, with doses from 0.1 to 10 mg/kg every 2 weeks (Q2W) found to be well tolerated based on early phase dose-ranging data [3, 4]. The pharmacokinetics (PK) of nivolumab is linear, resulting in dose-proportional increases in exposure over this dose range [5]. The 3 mg/kg Q2W intravenous (IV) dose investigated in initial phase III studies was shown to be efficacious across multiple tumor types and indications, and has been approved by regulatory authorities across the world [1–3].

Most monoclonal antibodies, including immune checkpoint inhibitors, have historically been dosed based on body weight (BW) because this generally results in lower interpatient variability in drug exposure [6]. However, the wide therapeutic index for checkpoint inhibitors has encouraged evaluation of fixed dosing, because this option can reduce dosing errors and facilitate preparation, thus ensuring consistent dosing [6].

Several health authorities, including the US Food and Drug Administration (FDA), Health Canada, and the European Medicines Agency (EMA), have approved the nivolumab 240 mg Q2W flat dose, which replaces the 3 mg/kg Q2W dose in all monotherapy indications [1, 2, 7]. These changes in dose were based on population PK (PPK) and exposure–response (E–R) analyses demonstrating comparability in the exposure, safety, and efficacy of 240 mg Q2W flat dosing with the initially approved 3 mg/kg Q2W schedule [6].

The US FDA recently approved nivolumab 480 mg every 4 weeks (Q4W) administered IV over 30 min for eight previously approved monotherapy indications as an alternative dose to the 240 mg Q2W regimen [1]. The EMA approved this additional 480 mg monotherapy dose for advanced melanoma and RCC [2]. The approvals were primarily based on modeling and simulation to inform similar benefit–risk of nivolumab 480 mg Q4W flat dosing to 3 mg/kg Q2W weight-based dosing [8]. This optional dose will provide increased convenience and flexibility for patients and caregivers through the availability of less frequent treatment, which may be particularly beneficial to patients receiving nivolumab over long periods of time or those residing far from treatment centers. Patients who start on a nivolumab Q2W regimen may also be given the option of moving to the 480 mg Q4W regimen. Less frequent flat dosing is also likely to reduce the scheduling burden on cancer care institutions, dosage preparation time compared with BW-based dosing, and overall burden on pharmacy staff [6].

Here, we report results of a comparison of the predicted steady-state PK exposures for the nivolumab 480 mg Q4W and 240 mg Q2W regimens with those for the initially approved 3 mg/kg Q2W dose, and PK exposure simulations supporting the switch from nivolumab 240 mg Q2W to 480 mg Q4W. We also describe the results of an analysis of the safety of patients with advanced melanoma, RCC, nonsquamous NSCLC, and squamous NSCLC who transitioned to Q4W dosing from Q2W dosing of nivolumab, or from a comparator arm in four phase III clinical trials [9–12].

Methods

Comparison of nivolumab exposures

A pooled PK dataset was created with data from 3817 patients with melanoma, RCC, NSCLC, SCCHN, UC, cHL, small-cell lung cancer (SCLC), HCC, CRC, or gastric cancer (GC) enrolled in nivolumab clinical trials. Nivolumab concentration–time profiles and the summary measures of exposure were predicted using a previously developed PPK model [6]. Steady-state peak, trough, and time-averaged concentrations ($C_{\max\text{ss}}$, $C_{\min\text{ss}}$, and C_{avgss} , respectively) were calculated for patients receiving 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W or 240 mg Q2W followed by 480 mg Q4W schedules, and analyzed by tumor type. Exposure comparisons for the 480 mg Q4W dosing regimen were also carried out with respect to BW.

Safety evaluation of nivolumab 480 mg Q4W

Clinical safety data were available for 61 patients from four ongoing phase III clinical trials: CheckMate 066 ($N=25$), 025 ($N=21$), 057 ($N=12$), and 017 ($N=3$) (supplementary Figure S1, available at *Annals of Oncology* online) [9–12]. Study designs for these studies have been published previously and are presented in supplementary Figure S1, available at *Annals of Oncology* online [9–12]. In open-label extension phases of these studies, eligible patients who had received nivolumab 3 mg/kg Q2W without disease progression could transition to nivolumab 480 mg Q4W administered IV over 30 min, and eligible patients in comparator arms no longer deriving benefit could cross over to nivolumab, either 3 mg/kg Q2W or 480 mg Q4W, until documented disease progression, discontinuation, or consent withdrawal.

To compare the treatment-related adverse event (TRAE) rates for the 480 mg Q4W dosing regimen with those of the 3 mg/kg Q2W dosing regimen, TRAEs were characterized from first dose of nivolumab 480 mg Q4W until 30 days following last dose and graded according to the Common Terminology Criteria for Adverse Events v4.0. In addition, TRAE rates with the 480 mg Q4W dosing regimen were compared with respect to BW to assess whether the TRAEs were associated with differences in exposure across the BW range.

Results

Comparison of nivolumab exposures

C_{avgss} values were comparable (<6% difference) between 480 mg Q4W and 3 mg/kg Q2W (Table 1). Additionally, $C_{\min\text{ss}}$ was approximately 16% lower with 480 mg Q4W compared with 3 mg/kg Q2W, whereas $C_{\max\text{ss}}$ was approximately 45% higher. All three measures of exposures with 240 mg Q2W were similar to those of 3 mg/kg Q2W (Table 1).

Although the $C_{\max\text{ss}}$ with 480 mg Q4W was higher than that of either 3 mg/kg or 240 mg Q2W, it was 57% lower than with the $C_{\max\text{ss}}$ produced in patients receiving 10 mg/kg Q2W (Figure 1), a dose that has previously been demonstrated to have an acceptable tolerability and safety profile [3, 13]. Nivolumab 480 mg Q4W resulted in a modest increase in the interpatient variability in exposure relative to 3 mg/kg Q2W [$<15\%$ increase in coefficient of variation (CV), Table 1].

Nivolumab serum concentration was simulated for patients receiving nivolumab 240 mg Q2W for 4 months (i.e. 8 doses) immediately followed by 480 mg Q4W for up to a total of 12 months, and compared with the serum concentration of patients continuing to receive nivolumab 240 mg Q2W for

Table 1. Comparison of predicted steady-state PK exposures for nivolumab 240 mg Q2W and 480 mg Q4W versus 3 mg/kg Q2W (N = 3817)

PK exposure	3 mg/kg Q2W	240 mg Q2W		480 mg Q4W	
	GM, $\mu\text{g/mL}$ (% CV)	GM, $\mu\text{g/mL}$ (% CV)	% difference in GMs ^a	GM, $\mu\text{g/mL}$ (% CV)	% difference in GMs ^a
C_{avgss}	85.1 (43.4)	90.0 (46.4)	5.76	90.0 (46.4)	5.76
C_{minss}	65.7 (51.9)	69.5 (54.7)	5.78	55.2 (62.9)	-16.0
C_{maxss}	127 (45.0)	134 (48.5)	5.51	184 (57.7)	44.9

^aCompared with 3 mg/kg Q2W.

C_{avgss} , time-averaged concentration at steady state; C_{maxss} , peak concentration at steady state; C_{minss} , trough concentration at steady state; CV, coefficient of variation; GM, geometric mean; PK, pharmacokinetic; Q2W, every 2 weeks; Q4W, every 4 weeks.

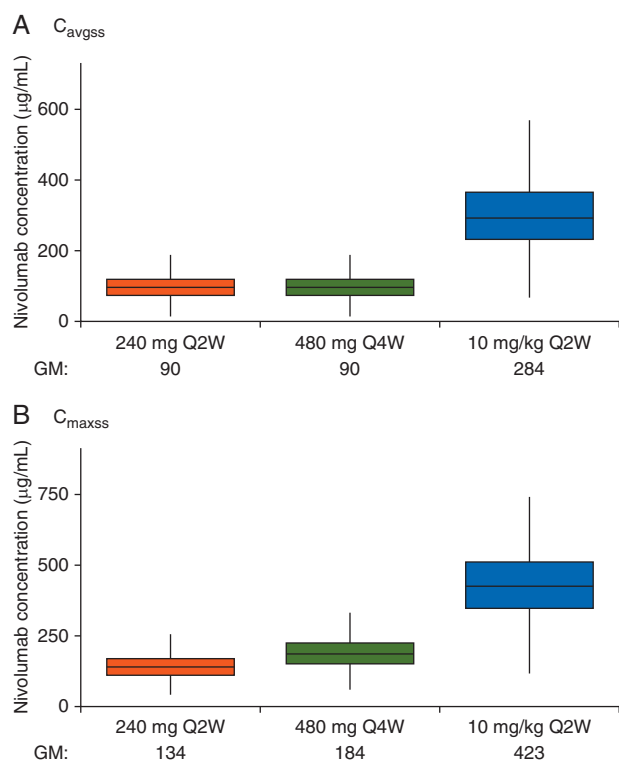


Figure 1. Predicted exposure range for nivolumab flat dosing at 240 mg Q2W and 480 mg Q4W compared with 10 mg/kg Q2W (N = 3817). The boxes show the median, 25th, and 75th percentile per group. The whiskers extend to 1.5 times the interquartile range or the most extreme value (whichever is closer to the median value), and the values outside this range are not shown. C_{avgss} , time-averaged concentration at steady state; C_{maxss} , peak concentration at steady state; GM, geometric mean; Q2W, every 2 weeks; Q4W, every 4 weeks.

12 months. The simulations show that, in each 4-week dosing interval of 480 mg Q4W, nivolumab serum concentration is expected to be higher for the first 2 weeks and slightly lower for the second 2 weeks, compared with continuing treatment with 240 mg Q2W (Figure 2). Serum concentrations after the first 480 mg infusion (month 4) rapidly approached steady-state concentration levels ($\geq 90\%$) of 480 mg Q4W and were maintained for the entire treatment duration (Figure 2 and [supplementary](#)

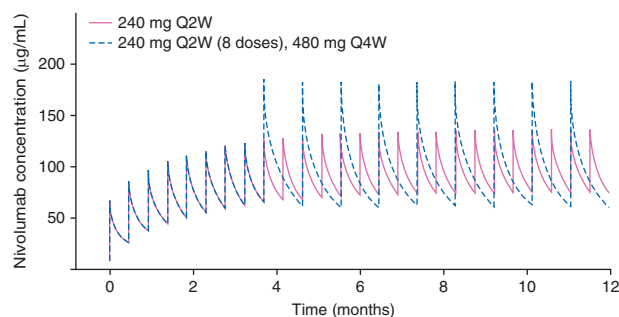


Figure 2. Predicted geometric mean nivolumab concentration-time profiles of 240 mg Q2W and 240 mg Q2W (eight doses) followed by 480 mg Q4W over 1 year (N = 3817). Q2W, every 2 weeks; Q4W, every 4 weeks.

[Table S1](#), available at *Annals of Oncology* online). Serum concentrations with the continuous 240 mg Q2W schedule at month 4 were also approximately 90% of simulated steady-state levels of 240 mg Q2W.

The predicted exposures were reviewed by tumor type. Observed differences in C_{avgss} of 480 mg Q4W relative to C_{avgss} of 3 mg/kg Q2W between tumor types (range: -3.61%, 21.40%) were associated with variations in median BW (range: 66.0 kg, 82.3 kg) ([supplementary Table S2](#), available at *Annals of Oncology* online).

Exposure comparison by BW group is presented in [supplementary Figure S2](#), available at *Annals of Oncology* online. Despite the higher predicted exposures in lighter patients receiving the flat dosing, exposure measures in the low BW group (< 70 kg) are well below those with nivolumab 10 mg/kg Q2W (Figure 1).

Clinical safety of nivolumab 480 mg Q4W

Clinical safety data with 480 mg Q4W were available for 61 patients [CheckMate 066 (N = 25), 025 (N = 21), 057 (N = 12), and 017 (N = 3)] who transitioned from nivolumab dosing of 3 mg/kg Q2W to 480 mg Q4W, and clinical safety data with 3 mg/kg Q2W were available for 1030 patients [CheckMate 066 (N = 206), 025 (N = 406), 057 (N = 287), and 017 (N = 131)] (Table 2 and [supplementary Figure S1](#), available at *Annals of Oncology* online). There were a limited number of patients

($N=15$) in the low BW group (<70 kg). The lowest baseline BW was 36 kg (supplementary Table S3, available at *Annals of Oncology* online). Average duration of exposure to nivolumab 480 mg Q4W was 2.06 months, with 19.7% of patients treated with nivolumab for longer than 3 months. Patients received a median of three doses and nearly 92% of patients had a relative dose intensity greater than 90% (Table 2).

The incidence of TRAEs observed in patients who transitioned from nivolumab 3 mg/kg Q2W to 480 mg Q4W was comparable with that of the overall population reported during the nivolumab weight-based treatment phase and was consistent across studies (Table 2). Pooled data from all four studies showed that TRAEs that started after transitioning to nivolumab 480 mg Q4W were reported in 14.8% of patients (Table 2), which is comparable with what would be expected for patients who continued the Q2W dose schedule. The most commonly reported TRAEs were upper abdominal pain, diarrhea, fatigue, and nausea, which occurred in two patients (3.3%) each, all of which were grades 1–2. There was no increased incidence of TRAEs associated with low BW (supplementary Table S3, available at *Annals of Oncology* online).

The incidence of serious adverse events (SAEs) was comparable between BW groups (supplementary Table S3, available at *Annals of Oncology* online), indicating that the higher exposure of patients in the lower BW group was not associated with increased risk of SAEs. One patient (1.6%) in the ≥ 70 and <90 kg BW group experienced an SAE related to nivolumab (grade 3 immune-mediated renal failure) (Table 2), which was treated with immune-modulating therapy. No infusion reactions were reported. No AEs led to treatment discontinuation and no deaths were attributed to study-drug toxicity. No new safety concerns were identified.

Discussion

This analysis evaluated PK exposure and clinical safety of nivolumab 480 mg Q4W compared with 240 mg Q2W and 3 mg/kg Q2W dosing schedules using quantitative clinical pharmacology approaches and pooled safety data from four phase III clinical trials. A flat dose of 240 mg Q2W was previously approved by the FDA based on modeled comparisons of exposure, and bridging of efficacy and safety data demonstrating comparability with 3 mg/kg Q2W [6]. More recently, a less frequent flat dose of 480 mg Q4W was approved as an additional option for several monotherapy indications, based on a similar modeling approach together with clinical safety data [8].

We demonstrated the comparability of overall exposure at steady state (C_{avgss}) with nivolumab 480 mg Q4W and 3 mg/kg Q2W or 240 mg Q2W, with similar PK exposures across tumor types. These findings are consistent with previously reported data that indicate similar overall PK exposures with flat and weight-based dosing of immuno-oncology agents, including nivolumab 240 mg Q2W and 3 mg/kg Q2W [6], pembrolizumab 200 mg every 3 weeks (Q3W) and 2 mg/kg Q3W [14], and durvalumab 1500 mg Q4W or 750 mg Q2W and 10 mg/kg Q2W [15].

Pooled safety data from the CheckMate 066, 025, 057, and 017 studies for 61 patients who transitioned from nivolumab 3 mg/kg Q2W to 480 mg Q4W are consistent with the established safety profile of nivolumab 3 mg/kg Q2W and 240 mg Q2W [1]. We did not observe increased frequencies or severity of AEs in the lowest BW subgroup (<70 kg) compared with higher BW subgroups (≥ 70 and ≥ 90 kg) or compared with pooled safety data from patients with melanoma, NSCLC, RCC, SCCHN, UC, and cHL who were treated with weight-based nivolumab up to 10 mg/kg [3, 13]. Previous results from a nivolumab dose-escalation study in 306 patients did not identify a maximum tolerated dose and

Table 2. Summary of TRAEs during weight-based nivolumab treatment across CheckMate 066, 025, 057, and 017, and the pooled patient cohort that transitioned to nivolumab 480 mg Q4W^a

N (%)	3 mg/kg Q2W				480 mg Q4W
	CheckMate 066 [9] (N = 206)	CheckMate 025 [10] (N = 406)	CheckMate 057 [11] (N = 287)	CheckMate 017 [12] (N = 131)	Pooled cohort (N = 61)
Number of nivolumab doses received, median, N	12	12	6	8	3 ^b
TRAEs (all grades)	153 (74.3)	319 (78.6)	199 (69.3)	76 (58.0)	9 (14.8)
Grades 3–4	24 (11.7)	76 (18.7)	30 (10.5)	9 (6.9)	1 (1.6) ^c
Treatment-related SAEs (all grades)	19 (9.2)	47 (11.6)	21 (7.3)	9 (6.9)	1 (1.6)
Grades 3–4	12 (5.8)	32 (7.9)	15 (5.2)	3 (2.3)	1 (1.6) ^c
TRAEs leading to discontinuation (all grades)	5 (2.4)	31 (7.6)	14 (4.9)	4 (3.1)	0
Grades 3–4	4 (1.9)	19 (4.7)	11 (3.8)	2 (1.5)	0
Treatment-related deaths	0	0	1 (0.3) ^d	0	0

^aPooled data include patients in CheckMate 066, 025, 057, and 017 who transitioned to nivolumab 480 mg Q4W after receiving nivolumab 3 mg/kg Q2W.

^bMean duration of exposure to nivolumab 480 mg Q4W was 2.06 months, with 19.7% of patients treated with nivolumab for longer than 3 months. Nearly 92% of patients had a relative dose intensity greater than 90%.

^cOne patient with a body weight ≥ 70 and <90 kg experienced an SAE of grade 3 renal failure.

^dCause of death was encephalitis attributed to nivolumab.

Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event; TRAE, treatment-related adverse event.

established that the safety profile was similar across tumor types and dose levels (0.1–10 mg/kg) [4]. Probabilities of both grade ≥ 3 TRAEs and those leading to discontinuation were similar between 3 and 10 mg/kg doses [4]. Low BW patients may be receiving a higher nivolumab exposure with 480 mg Q4W than Q2W dosing; however, exposure measures in the low BW group (< 70 kg) are well below those with 10 mg/kg Q2W in our model and doses up to 10 mg/kg Q2W had a similar safety profile to 3 mg/kg Q2W [3, 13].

Most AEs from anti-PD-1 therapy occur during the first 3 months of treatment [16], and patients who received nivolumab 480 mg Q4W in our analysis transitioned from a prior regimen where they received and tolerated 3 mg/kg Q2W dosing. Only a small number of patients, particularly in low BW groups, were available for the overall safety analysis, and follow-up was relatively short. However, nivolumab concentrations reached steady state immediately after transitioning to 480 mg Q4W at approximately week 16, and were maintained throughout the duration of treatment. To further evaluate the 480 mg Q4W schedule, this dose schedule is included in ongoing nivolumab clinical trials, including the phase IIIB/IV CheckMate 384 study (NCT02713867) and the phase III CheckMate 511 study (NCT02714218), in patients with NSCLC and melanoma, respectively.

Consistent with other reports of flexible/individualized dose scheduling [17–19], nivolumab 480 mg Q4W may provide increased convenience to patients, particularly those on long-term therapy, with less frequent visits to cancer care institutions and lower healthcare costs. Patients may either start treatment on the Q4W regimen or switch to it during treatment at their next scheduled infusion [2]. The burden on patients is considerably reduced with less frequent dosing, especially for those who have a long journey to their infusion center. Increased flexibility potentially allows for the scheduling of the infusions to be optimized. Less frequent dosing of nivolumab may improve efficiencies in pharmacies and infusion centers by decreasing demand for infusion chairs, patient time in centers, and amount of required infusion supplies, which could ultimately lower costs for infusion center infrastructure [6]. Fewer patient visits may lead to concerns regarding reduced in-person surveillance during initial treatment, but these may be mitigated by follow-up telephone calls to patients, for example.

Conclusion

Nivolumab 480 mg Q4W is predicted to have a similar overall exposure and safety profile to 3 mg/kg Q2W and 240 mg Q2W dosing across patients with various tumor types. The 480 mg Q4W flat dose has the potential to be practice-changing and is expected to improve ease of administration, shorten patient waiting time, and reduce costs incurred by patients and cancer care institutions. This alternative dosing schedule will provide enhanced freedom and flexibility to patients, clinicians, and caregivers, and will ultimately optimize patient care.

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