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Assessment of nivolumab benefit–risk profile of a 240-mg flat dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors

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Background: Nivolumab 3 mg/kg every 2 weeks (Q2W) has shown benefit versus the standard of care in melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC). However, flat dosing is expected to shorten preparation time and improve ease of administration. With knowledge of nivolumab safety, efficacy, and pharmacokinetics across a wide dose range in body weight (BW) dosing, assessment of the benefit–risk profile of a 240-mg flat dose relative to the approved 3-mg/kg dose was approached by quantitative clinical pharmacology.

Patients and methods: A flat dose of 240 mg was selected based on its equivalence to the 3-mg/kg dose at the median BW of ∼80 kg in patients in the nivolumab program. The benefit–risk profile of nivolumab 240 mg was evaluated by comparing exposures at 3 mg/kg Q2W and 240 mg Q2W across BW and tumor types; clinical safety at 3 mg/kg Q2W by BW and exposure quartiles in melanoma, NSCLC, and RCC; and safety and efficacy at 240 mg Q2W relative to 3 mg/kg Q2W in melanoma, NSCLC, and RCC.

Results: The median nivolumab exposure and its distribution at 240 mg Q2W were similar to 3 mg/kg Q2W in the simulated population. Safety analyses did not demonstrate a clinically meaningful relationship between BW or nivolumab exposure quartiles and frequency or severity of adverse events. The predicted safety and efficacy were similar across nivolumab exposure ranges achieved with 3 mg/kg Q2W or 240 mg Q2W flat dose.

Conclusion: Based on population pharmacokinetic modeling, established flat exposure–response relationships for efficacy and safety, and clinical safety, the benefit–risk profile of nivolumab 240 mg Q2W was comparable to 3 mg/kg Q2W. The quantitative clinical pharmacology approach provided evidence for regulatory decision-making on dose modification, obviating the need for an independent clinical study.

Key words: nivolumab, flat dosing, clinical pharmacology, exposure–response relationship, cancer immunotherapy, solid tumors

Introduction

Nivolumab is a highly selective anti-programmed death 1 (PD-1) human monoclonal IgG4 antibody that potentiates T-cell responses by blocking the binding of PD-1 on activated T cells with its ligands, PD-L1 and PD-L2, expressed on antigen presenting cells and on some tumor cells [1]. Clinical trials with nivolumab

3 mg/kg every 2 weeks (Q2W) showed an overall survival (OS) benefit over standard of care in several cancers, including advanced melanoma [2], squamous [3], and nonsquamous [4] non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC) [5], and squamous cell carcinoma of the head and neck (SCCHN) [6]. Based on clinical benefit including survival and response, nivolumab is approved as a first-line treatment in

patients with unresectable or metastatic melanoma as a single agent or in combination with ipilimumab, and as a second-line treatment in patients with metastatic NSCLC, RCC, classical Hodgkin lymphoma (cHL), SCCHN, and urothelial cancer (UC) as a single agent [7]. To improve the ease of nivolumab use and to meet the needs of patients and healthcare practitioners, our objective is to assess the benefit–risk of the transition to a flat nivolumab dose of 240 mg Q2W, regardless of patient's body weight (BW).

Therapeutic monoclonal antibodies and chemotherapies are often dosed based on BW, with a perception that interpatient variability in drug exposure is lower with this approach compared with flat dosing. However, analysis across a broad range of monoclonal antibodies showed that BW-based dosing does not always offer advantages over flat (BW-independent) dosing [8]. Moreover, a flat dose is expected to shorten dosage preparation time, improve ease of administration, and shorten patient waiting time. Dosing strategies independent of BW are generally favored in drugs with a wide-therapeutic index. In the large, phase 1b, dose-escalation study CA209003, nivolumab was adequately tolerated up to 10 mg/kg across tumor types, including melanoma, NSCLC, and RCC, with no maximum tolerated dose identified [9]. The antitumor activity with respect to objective response rates approached a plateau at 3 mg/kg, with no increased benefit observed at doses of >3 mg/kg. Integrated analyses characterizing dose/exposure–response (E–R) relationships for pharmacodynamic, safety, and efficacy endpoints provided dose selection rationale for nivolumab monotherapy (Q2W) across tumor types [10].

Population pharmacokinetic (PPK) analyses of data from multiple phase 1, 2, and 3 clinical studies showed that the pharmacokinetics (PK) of nivolumab is linear, with dose-proportional exposures over a dose range of 0.1–10 mg/kg, and the PK is similar in patients with melanoma, NSCLC, and RCC [11]. The E–R analyses for efficacy and safety showed that nivolumab exposure was not a significant predictor of OS or the risk of adverse events (AE) leading to drug discontinuation or death (AE–DC/D) in patients with advanced solid tumors [12]. Moreover, the dose/E–R relationships seem to be relatively flat across indications of melanoma, NSCLC, and RCC [10].

The initially approved dose of 3 mg/kg Q2W, which was studied in the pivotal clinical studies, has been replaced with a dose of 240 mg Q2W, and this study describes the basis for this change. The objective of this analysis is to assess the benefit–risk profile of nivolumab 240 mg Q2W relative to 3 mg/kg Q2W through a quantitative clinical pharmacology approach and thereby support posology changes for nivolumab.

Methods

Selection of nivolumab flat dose of 240 mg

To select the appropriate flat dose of nivolumab, a BW distribution assessment was conducted using observed baseline BWs from 3458 patients enrolled in 18 nivolumab clinical studies across tumor types including melanoma, NSCLC, RCC, cHL, SCCHN, UC, gastric cancer (GC), and small cell lung cancer (SCLC) (supplementary Table S1, available at *Annals of Oncology* online). The flat dose was selected such that there was a high degree of overlap in nivolumab exposures over this BW range.

Assessment of the benefit–risk profile of nivolumab 240 mg relative to 3 mg/kg

The benefit–risk profile of nivolumab 240 mg Q2W relative to 3 mg/kg Q2W was assessed by the following analyses: (i) comparison of nivolumab exposures at 240 mg Q2W and 3 mg/kg Q2W across the BW range and tumor types; (ii) evaluation of the exposure margin for safety based on the well-tolerated dose of 10 mg/kg Q2W; (iii) evaluation of clinical safety of nivolumab 3 mg/kg Q2W by BW groups and by exposure quartiles in patients with melanoma, NSCLC, and RCC; (iv) prediction of risk of any-grade AE–DC/D at 240 mg Q2W relative to 3 mg/kg Q2W across indications of melanoma, NSCLC, and RCC; and (v) prediction of risk of death at 240 mg Q2W relative to 3 mg/kg Q2W in patients with melanoma, NSCLC, and RCC. Nivolumab clinical studies and the number of patients included in the analyses are summarized in supplementary Table S1, available at *Annals of Oncology* online.

Comparison of nivolumab exposures at 240 mg and 3 mg/kg. A previously developed PPK model was used to predict the nivolumab exposures resulting from a flat dose in patients across tumor types and compare these exposures with those produced by the 3 mg/kg Q2W dose [11]. In brief, the PK of nivolumab was described by a linear two-compartment model with time-varying clearance. The PPK model incorporated covariate effects of baseline BW, estimated glomerular filtration rate, performance status, sex, race, and tumor type on nivolumab clearance; and baseline BW and sex on volume of distribution.

The PPK model was used to simulate a total of 100 clinical trials in the 3458 cancer patients with covariate values corresponding to those in the original analysis data set. The simulations were carried out using NONMEM (version 7.3, ICON Development Solutions, Hanover, MD). The simulated nivolumab concentrations were used to determine the following summary measures of exposure for each patient: peak, trough, and time-averaged concentration after the first dose (Cmax1, Cmin1, and Cavg1), as well as at steady state (Cmaxss, Cminss, and Cavgss, respectively) across all of the 100 simulated clinical trials to determine the summary exposures of nivolumab. The summary statistics and distribution of nivolumab exposures in the overall population and across the BW range predicted for the selected flat dose of 240 mg were compared with that of the initially approved 3 mg/kg dose.

Evaluation of safety of nivolumab 240 mg. To understand the potential association between patient BW and nivolumab exposure and safety, a thorough review and analyses of clinical safety data from patients treated with nivolumab was conducted based on baseline BW and nivolumab exposure quartiles (Cavgss). Subgroup safety analyses were carried out based on baseline BW categories in patients with melanoma, NSCLC, and RCC ($N = 1781$) treated with nivolumab 3 mg/kg Q2W. Additional subgroup safety analyses were compared based on grouped quartiles of Cavgss in patients ($N = 1696$) with melanoma, NSCLC, and RCC treated with nivolumab 3 mg/kg Q2W and available PK information. Similar subgroup analyses of patients treated with nivolumab 10 mg/kg (all indications) were also conducted by BW groups ($N = 131$) and exposure quartiles ($N = 130$). The primary endpoints included AEs, serious AEs, and AEs leading to discontinuation. The incidences and rates of all, grade 3/4, and grade 5 AEs were summarized for patients in melanoma, NSCLC, and RCC groups.

In addition, the safety of nivolumab 240 mg Q2W dosing relative to 3 mg/kg Q2W was evaluated by the predicted hazard ratios (HRs) of AE–DC/D using an established E–R model. The relationship between nivolumab exposure (represented by Cavg1) and the risk of AE–DC/D was previously characterized by a semiparametric Cox proportional-hazards model in 1768 patients with melanoma, NSCLC, or RCC. In this analysis, PPK model-predicted Cavg1 was selected as the measure of overall nivolumab exposure since Cavg1 was highly correlated with other exposure measures and was expected to have a similar E–R relationship as other exposure measures. At doses ranging from 0.1 to 10 mg/kg, nivolumab exposure was not a significant predictor of any-grade AE–DC/D,

which is consistent with that reported in melanoma patients [12]. To assess the risk of AE–DC/D, the HRs of the 5th and 95th percentiles Cavg1 produced by nivolumab 3 mg/kg Q2W or 240 mg Q2W relative to median Cavg1 were calculated using the estimated exposure effects from the E–R model, together with the summary Cavg1 simulated from the PPK model.

Assessment of efficacy of nivolumab 240 mg. The assessment of nivolumab 240 mg Q2W efficacy in melanoma, NSCLC, and RCC was conducted by predicting the HR of OS relative to 3 mg/kg Q2W dose using previously developed E–R models for each indication. The relationships between nivolumab exposure (represented by Cavg1) and OS (the primary endpoint of efficacy) were described by semiparametric Cox proportional-hazards models in patients with melanoma ($N = 399$), squamous NSCLC ($N = 293$), nonsquamous NSCLC ($N = 354$), and RCC ($N = 569$). Across tumor types, the relationships were consistently flat at the tested dose range (up to 10 mg/kg) [10]. The HR of the 5th and 95th percentile Cavg1 relative to the median Cavg1 was calculated separately for each indication using these estimated exposure effects on risk of death, together with the summary Cavg1 from PPK simulation.

Results

Selection of nivolumab flat dose of 240 mg

The flat dose of nivolumab was selected to achieve a high degree of overlap in exposures with the 3 mg/kg dose. The range of baseline BWs was 34–180 kg, with ∼5% of patients below 50 kg and 6% of patients above 110 kg. A flat dose of 240 mg Q2W was selected by multiplying the initially approved 3 mg/kg Q2W dose by the median BW (∼80 kg) of patients in the nivolumab clinical program (Figure 1A). The exposures produced by the 240 mg dose will therefore be identical to those produced by 3 mg/kg for patients at the median BW of 77 kg.

Comparison of nivolumab exposures at 240 mg and 3 mg/kg

The extent and variability of exposure produced by nivolumab 240 mg Q2W versus 3 mg/kg Q2W dosing were evaluated in a large data set consisting of covariates including baseline BW from 3458 patients across tumor types. The overall difference in geometric means of all summary exposure measures between the two dosing scenarios was <6%, with similar variability (% CV) (Table 1). The median and 90% prediction intervals (5th to 95th percentile) for the simulated nivolumab summary exposure (Cavg1) with 3 mg/kg Q2W and 240 mg Q2W across the range of BWs are presented in Figure 1B. Similar trends were observed with the other five summary exposure measures. Additionally, all six measures of exposure were highly correlated for both the 3 mg/kg Q2W and 240 mg Q2W dosing regimens (correlation coefficient >0.9). Given the relationship between nivolumab PK and BW, a flat dose of nivolumab was expected to lead to higher exposures in lighter patients and lower exposures in heavier patients, in contrast to BW-based dosing. Despite the higher predicted exposures in patients with lower BW receiving the flat dosing regimen, the median and 90% prediction intervals of nivolumab summary exposures across the BW range was maintained well below the corresponding median and 95th percentile exposures observed with nivolumab 10 mg/kg Q2W, the clinically

established safe and tolerable dose [9]. Moreover, the distribution of nivolumab Cavg1 in the simulated population following nivolumab 240-mg flat dose almost entirely overlapped with the distribution achieved with a 3-mg/kg dose (Figure 1C).

Safety of nivolumab 240 mg

The safety of nivolumab 240 mg Q2W was evaluated by reviewing AEs in melanoma, NSCLC, and RCC populations subdivided by BWs and nivolumab exposure quartiles. In addition, the HR for AE–DC/D was predicted for both nivolumab 3 mg/kg Q2W and 240 mg Q2W dosing regimens.

The safety profile following administration of nivolumab 3 mg/kg Q2W is presented by BW groups for patients with melanoma, NSCLC, and RCC (supplementary Table S2, available at *Annals of Oncology* online). Overall, for the 1781 patients treated with 3 mg/kg Q2W or the 131 patients treated with 10 mg/kg (supplementary Table S3, available at *Annals of Oncology* online), safety analyses by BWs did not demonstrate a relationship between BW and increased frequencies for any AEs regardless of causality, serious AEs, or AEs leading to discontinuation. Although interpretation of safety data for nivolumab 3 mg/kg by BW category was limited by the small number of patients ($n = 63$) in the <50 kg BW group, there was a numerically higher rate of grade 5 AEs (grade 5 AEs: 11.1%, <50 kg; 6.0%, ≥50 to <70 kg; 6.8%, ≥70 to <90 kg; 5.7%, ≥90 to <110 kg; 2.8%, ≥110 kg) and serious AEs for the lowest BW group compared with higher-BW groups, and were mainly attributed to malignant neoplasm progression (six of seven patients, grade 5 AEs).

Furthermore, the safety profile following administration of nivolumab 3 mg/kg Q2W is presented by nivolumab exposure quartiles for patients with melanoma, NSCLC, or RCC (supplementary Table S4, available at *Annals of Oncology* online). Overall, for the 1696 patients treated with 3 mg/kg Q2W or the 130 patients treated with 10 mg/kg (supplementary Table S5, available at *Annals of Oncology* online), safety analyses by exposure quartiles did not demonstrate a relationship between higher exposures and increased frequencies for any AEs regardless of causality, grade 3/4 AEs, grade 5 AE, serious AEs, or AEs leading to discontinuation. Of note, serious AEs and grade 5 AEs were most frequently reported in the lowest exposure quartiles, due to malignant neoplasm progression. These data suggest that differences in the AE profile by exposures are likely due to underlying disease and its associated comorbidities rather than drug-related effects.

In addition, based on the quantitative understanding of nivolumab safety across a range of doses, the HR of AE–DC/D was predicted to be similar between 3 mg/kg Q2W and 240 mg Q2W flat dose across melanoma, NSCLC, and RCC (Figure 2A). A flat E–R relationship for safety was also indicated for both regimens, as evidenced by the 95% confidence intervals (CIs) including 1. Thus, the higher exposure with the 240-mg Q2W dose in lower-BW patients is not expected to alter the safety profile relative to that of the 3-mg/kg Q2W dose.

Efficacy of nivolumab 240 mg

The hazard of death following administration of nivolumab 3 mg/kg Q2W and 240 mg Q2W was predicted to be similar in
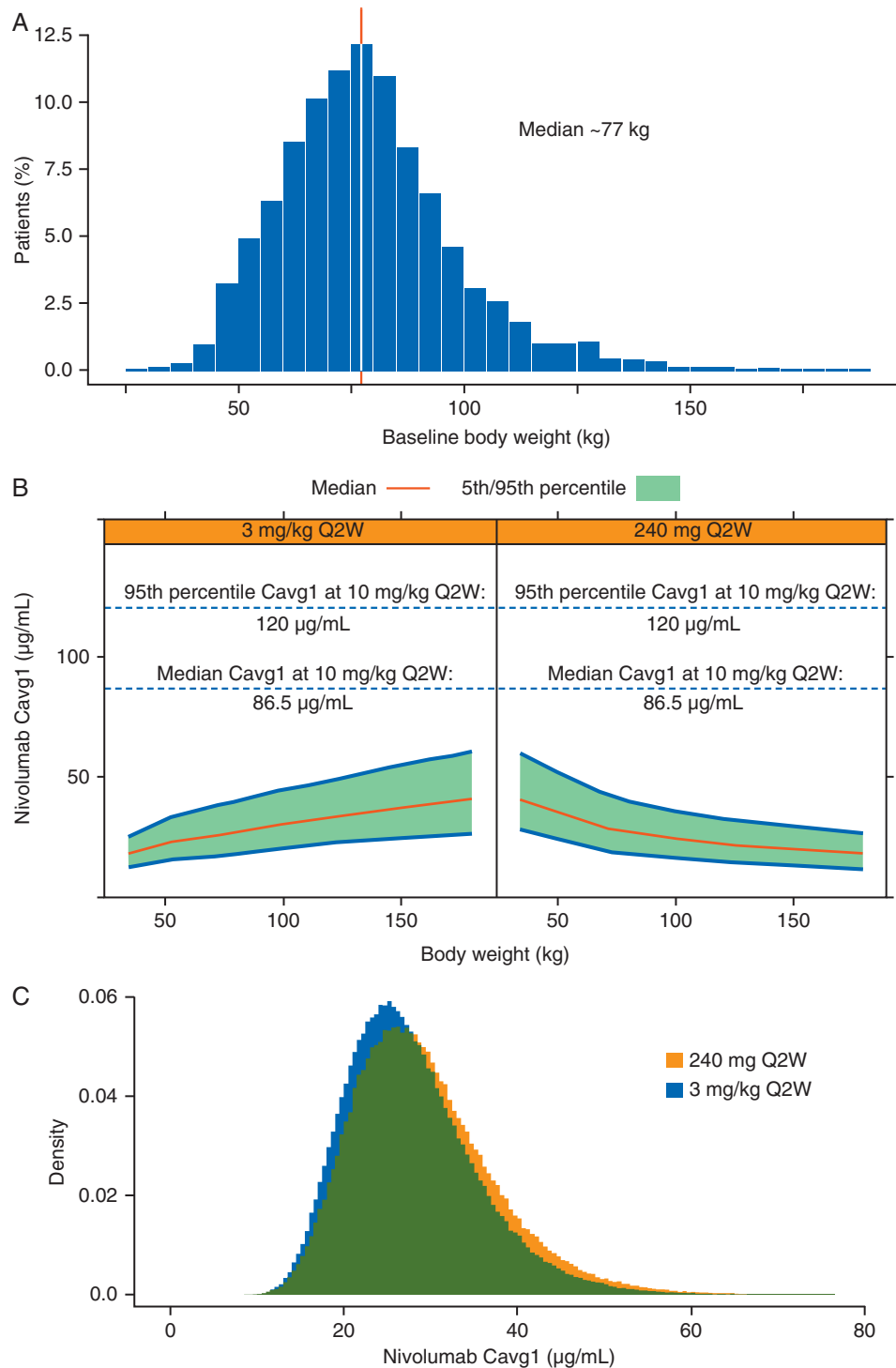
Figure 1. (A) Determination of representative body weight for flat-dose calculation. $N = 3458$ across tumor types including melanoma, NSCLC, RCC, SCCHN, UC, GC, cHL, and others. (B) Simulated nivolumab Cavg1 across body weight in patients across tumor types given 3 mg/kg Q2W and 240 mg Q2W. The solid lines and shaded band represent the simulation-based median and 90% prediction intervals. The dotted lines and values represent median and 95th percentile Cavg1 from observed data. (C) Simulated nivolumab exposure distribution (Cavg1) in patients across tumor types given 240 mg Q2W and 3 mg/kg Q2W. Cavg1, model-predicted average concentration after the first nivolumab dose.

patients with melanoma, squamous NSCLC, nonsquamous NSCLC, and RCC (Figure 2B). The 95% CIs for all HRs included 1, suggesting a flat E–R relationship for OS over the exposure range in either regimen. Hence, the efficacy profile in higher-BW patients when using the 240-mg Q2W flat dosing (nivolumab exposure is expected to be slightly lower) was not expected to be altered compared with the 3-mg/kg Q2W regimen.

Table 1. Comparison of summary of exposures in patients across tumor types

Summary exposure	Nivolumab 3 mg/kg GM, μg/mL (% CV)	Nivolumab 240 mg GM, μg/mL (% CV)	Difference in GMs, %	Nivolumab 3 mg/kg median, μg/mL (P05, P95)	Nivolumab 240 mg median, μg/mL (P05, P95)
Cmin1	17.2 (31.7)	18.1 (33.2)	4.97	17.3 (10.1, 28.6)	18.2 (10.4, 30.8)
Cavg1	26.8 (27.4)	28.1 (28.0)	4.63	26.7 (17.3, 41.7)	28.1 (17.9, 44.3)
Cmax1	57.5 (37.6)	60.4 (42.0)	5.04	57.5 (31.5, 105.0)	60.4 (31.4, 117.0)
Cminss	66.7 (54.5)	70.3 (58.4)	5.40	67.8 (27.2, 155.0)	71.3 (27.3, 172.0)
Cavgss	86.6 (45.9)	91.2 (49.5)	5.31	86.5 (42.6, 177.0)	90.7 (42.9, 196.0)
Cmaxss	130.0 (37.1)	136.0 (41.8)	4.41	129.0 (73.0, 233.0)	135.0 (72.1, 263.0)

CV, coefficient of variation; GM, geometric mean calculated from the formula $\exp[(1/n)\mathrm{Sum}(\log(x))]$. The values in the table are the median of GM, 5th, 50th, and 95th percentiles of each summary exposure measure from 100 simulations.

Overall benefit–risk profile of nivolumab 240 mg

In summary, based on the high confidence in the predicted nivolumab exposures with a 240-mg Q2W flat dose, the well-established safety profile of nivolumab up to the 10-mg/kg dose level, and well-characterized and relatively flat E–R relationships for safety and efficacy, the benefit–risk profile for 240 mg Q2W was comparable to the originally approved 3 mg/kg Q2W dose, which supports the revision of the approved United States prescribing information to reflect a nivolumab flat-dosing regimen of 240 mg Q2W regardless of patient BW.

Discussion

Within the comprehensive nivolumab global development program in multiple tumor types, we are evaluating opportunities to improve the conditions for use of nivolumab to meet the needs of patients and healthcare providers. Thus, one way to improve the ease of use and administration, as well as to reduce prescription errors, would be to change to a flat dose from a weight-based dose.

A flat dose for a therapeutic antibody provides several advantages to patients and healthcare providers as all patients would receive the same dose. In addition, a unified flat dose will require less preparation time and reduce the burden on pharmacy staff, as well as shorten patient waiting time. Flat dosing is already implemented for several cancer immunotherapeutic antibodies, including obinutuzumab (anti-CD20 antibody) [13], pertuzumab (HER2/neu receptor antagonist) [14], pembrolizumab, and atezolizumab (anti-PD-1 antibody) [15, 16]. Clearly, a flat-dosing regimen offers advantages over the current BW-based dosing of nivolumab, including reduction in overall healthcare burden.

This analysis was designed to assess the benefit–risk profile of nivolumab 240 mg Q2W relative to the initially approved 3 mg/kg Q2W using quantitative clinical pharmacology approaches. No new trials were conducted to support this posology change. Based on the BW distribution in patients across tumor types in nivolumab clinical studies and the established efficacious and safe dose of 3 mg/kg, a flat dose of 240 mg Q2W was selected, which is identical to a dose of 3 mg/kg for patients with an approximate BW of 80 kg.

The disposition of single-agent nivolumab was extensively studied in patients across multiple solid tumors and hematologic malignancies, including melanoma, NSCLC, RCC, SCCHN, UC, GC, SCLC, and cHL with mg/kg dosing. Nivolumab concentrations increased proportionally over a dose range of 0.1–10 mg/kg Q2W, and there was no clinically important effect of patient factors, such as baseline BW, on clearance of nivolumab [7]. Nivolumab clearance and volume of distribution were found to increase with increasing BW, but the increase was less than proportional, indicating that BW-based dosing represents an overadjustment for the effect of BW on nivolumab PK at the higher BWs. Therefore, BW-based dosing may lead to higher exposures in obese patients. Conversely, a flat dose was expected to lead to higher exposures in lighter patients. Overall, the ranges of nivolumab exposures resulting from either a 3-mg/kg Q2W or a 240 mg Q2W flat dose were similar. In addition, total endotoxin levels were below the permissible levels with nivolumab 240 mg Q2W over the BW range. The expression of tumor and peripheral biomarkers, including T-cell markers and cytokines, was assessed in patients with melanoma. There was no meaningful changes in biomarkers across all dose levels of nivolumab (0.3, 2, and 10 mg/kg) during the course of treatment [17].

The safety of nivolumab mg/kg dosing was extensively evaluated through our clinical program, and similar profiles were observed across tumor types and dose levels (0.1–10 mg/kg) [10]. Hence, a thorough safety review of AEs across indications for different BW groups and predicted exposure quartiles demonstrated that neither BW nor exposure was associated with AEs. The safety and efficacy of nivolumab in melanoma, NSCLC, and RCC at 3 mg/kg is well established by prolonged survival compared with standard of care in studies from several clinical trials [2–5, 18]. The predicted safety analyses confirmed the lack of relationship between nivolumab exposures at 3 mg/kg Q2W or 240 mg Q2W and the risk of AE–DC/D. Similarly, the predicted hazard of death at nivolumab 3 mg/kg Q2W or 240 mg Q2W were comparable for melanoma, squamous and nonsquamous NSCLC, and RCC. Additional dosing regimens that are convenient for patients, such as every 4 weeks dosing, are under evaluation in nivolumab clinical trials.

Nivolumab in combination with ipilimumab is approved in advanced melanoma and is being evaluated in other tumor types, and therefore drug–drug interaction is an important consideration
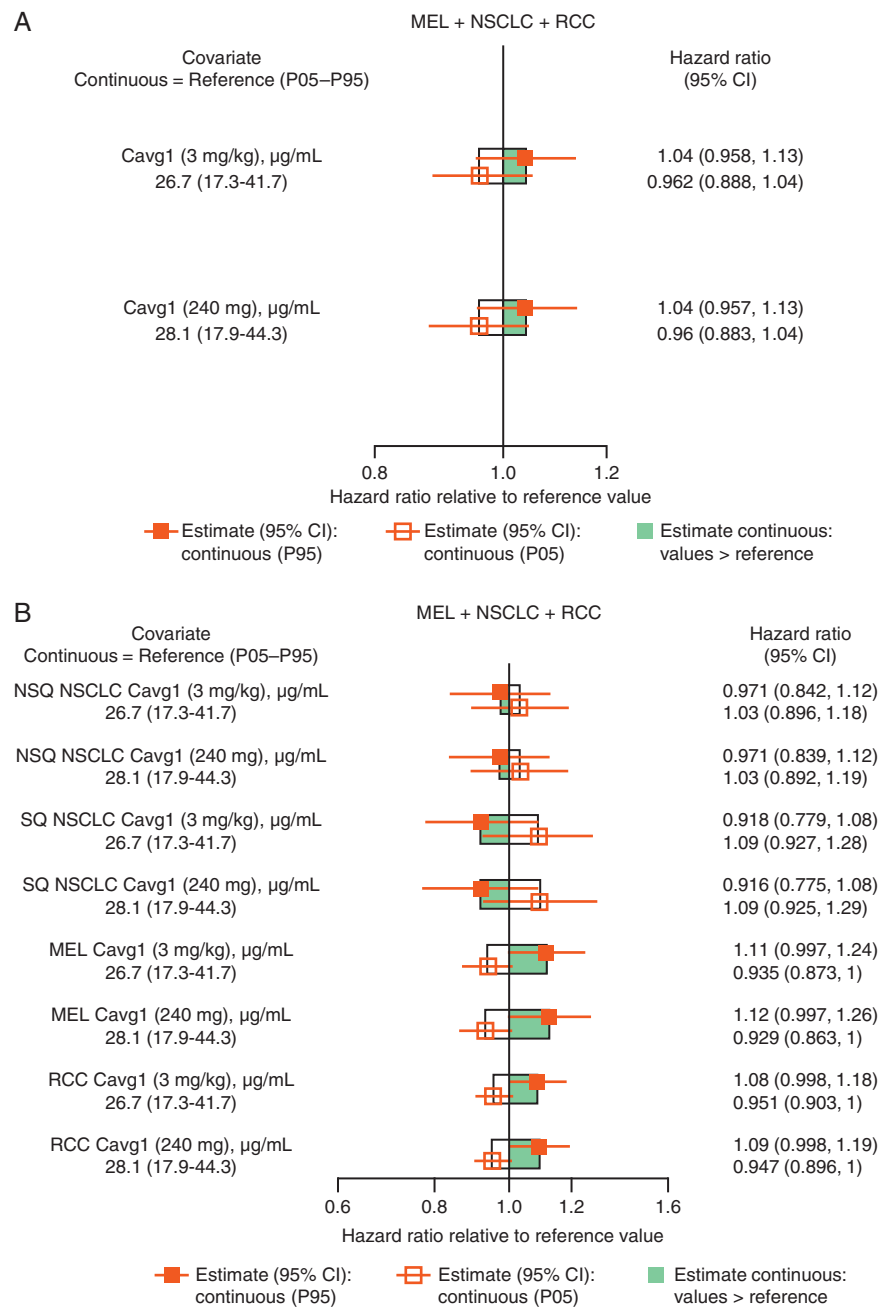
Figure 2. (A) Effect of nivolumab exposure (Cavg1) on safety (AE–DC/D) at 240 mg Q2W and 3 mg/kg Q2W in patients with melanoma, NSCLC, and RCC. (B) Effect of nivolumab exposure (Cavg1) on efficacy (OS) at 240 mg Q2W and 3 mg/kg Q2W in patients with melanoma, NSCLC, and RCC. CI, confidence interval; MEL, melanoma; NSQ, nonsquamous; SQ, squamous.

in dosing regimens. When administered in combination with ipili-mumab, the clearance of nivolumab increased by 24%, but this magnitude of an increase is not considered to be clinically relevant based on the E–R relationship of combination therapy [7]. Furthermore, the increase in clearance would have the same effect on nivolumab exposures produced by 3 mg/kg Q2W or 240 mg Q2W doses of nivolumab, and therefore the relative exposures of nivolumab 3 mg/kg Q2W or 240 mg Q2W would be the same as that without the increase in clearance. Overall, the dosing regimen in the combination phase will remain the same, whereas the dosing of nivolumab monotherapy in the maintenance phase will be modified from 3 mg/kg Q2W to 240 mg Q2W [7].

In conclusion, based on the robust PPK and dose/E–R analyses, the exposure, safety, and efficacy of nivolumab flat dosing were similar to those observed with the initially approved BW-based dosing. This novel quantitative clinical pharmacology approach to modify to nivolumab 240 mg Q2W flat dose simplifies dosing and administration of an oncology agent with an established wide therapeutic margin. Modeling approaches are considered sufficient to support regulatory approval when based on robust scientific data and are well conducted [19]. With quantitative clinical pharmacology approaches, a similar benefit–risk profile was established with confidence obviating the need for an independent clinical study, thereby providing a better dosing option.

This extensive evaluation in predicting safety and efficacy of nivolumab 240 mg relative to 3 mg/kg led to its approval for melanoma, NSCLC, RCC, and UC in the USA [7].

Disclosure

AA is currently an employee of AstraZeneca and was an employee of Bristol-Myers Squibb at the time of the study. All remaining authors are employees of Bristol-Myers Squibb, which funded the study.

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