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Clinical Pharmacokinetics (2026) 65:621–632
https://doi.org/10.1007/s40262-025-01610-4

ORIGINAL RESEARCH ARTICLE

Model-Based Alternative Dosing Strategies for Subcutaneous Nivolumab to Improve Cost Effectiveness

Yan Wang[1] · Laura H. Bukkems[1] · Rob ter Heine[2] · J. G. C. van Hasselt[3] · S. L. W. Koolen[4,5] · J. J. M. A. Hendrikx[6,7] · Tom Van der Hulle[8] · Ellen Kapiteijn[8] · Juliette Zwaveling[1] · Annemarie Becker[9] · Michel M. van den Heuvel[10] · Willemijn S. M. E. Theelen[11] · Thijs H. Oude Munnink[12] · Egbert F. Smit[13] · Henk-Jan Guchelaar[1] · Dirk Jan A. R. Moes[1]

Received: 1 October 2025 / Accepted: 8 December 2025 / Published online: 12 January 2026

Abstract

Background The increasing use of the immune checkpoint inhibitor nivolumab places a significant financial burden on healthcare systems, contributes to environmental concerns, and strains hospital capacities. The nivolumab average exposure and exposure variation of a fixed subcutaneous (SC) dosing regimen (1200 mg every 4 weeks) is significantly higher compared with 3-mg/kg every 2 weeks intravenous dosing.

Objectives We aimed to develop alternative dosing regimens for SC nivolumab to reduce drug expenses and lower the treatment burden for patients while ensuring effective exposure.

Methods Population pharmacokinetic simulation was conducted using a population pharmacokinetic model developed by the license holder to explore alternative SC regimens. In this process, patients were divided into three weight groups: less than 60 kg, 60–90 kg, and more than 90 kg. Furthermore, two experimental progressive alternative dosing regimens were developed, one based on a minimum effective concentration-driven approach. The second progressive alternative regimen was based on using the 1200-mg SC formulation as an intravenous infusion.

Results We developed an alternative bodyweight-based regimen consisting of SC 1200 mg every 7 weeks (<60 kg), 1200 mg every 6 weeks (60–90 kg), and 1200 mg every 5 weeks (>90 kg). This new alternative dosing regimen would save an average of €24,345 (35%) per patient per year compared with SC 1200 mg every 4 weeks. The results for the first experimental, progressive, extended-interval dosing regimen for patients with melanoma indicate that 95% of patients exceed a steady-state trough concentration of 2.5 mg/L when administered SC 1200 mg every 10 weeks. This dosing regimen would decrease the yearly cost from €68,870 to €27,548 (60% less) per patient per year. The second experimental progressive regimen using SC 1200 mg as an intravenous administration every 7 weeks leads to a potential saving of €29,516, which is a 43% decrease compared with the SC 1200-mg approved regimen.

Conclusions The developed dosing regimen with a bodyweight-dependent interval offers a cost-effective and patient-friendly method to optimize SC nivolumab use while ensuring adequate exposure, which can be directly implemented in clinical practice. Moreover, the two experimental progressive proposed regimens provide a rationale for a clinical non-inferiority study in which alternative dose regimens are compared to standard dosing according to the drug label.

1 Introduction

The emergence of cancer immunotherapy has marked a breakthrough in cancer treatment, as programmed cell death protein-1 (PD-1) and programmed death ligand-1 (PD-L1) inhibitors significantly improve clinical outcomes. Nivolumab has been widely applied in various cancers, including melanoma, lung cancer, renal cancer, classical Hodgkin lymphoma, gastric cancer, and others, as monotherapy or in combination with other therapies. Nivolumab is a fully human immunoglobulin G4 antibody, which binds to PD-1 on T cells, thereby preventing inhibitor co-signaling and restoring T-cell activation [1].

Initially, nivolumab was approved for the treatment of multiple solid tumors with intravenous (IV) administration of a dose of 3 mg/kg every 2 weeks (Q2W) [2]. In silico modeling and simulation subsequently allowed the amendment of this dosage to fixed dosing of either 240 mg Q2W or

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Key Points

By using population pharmacokinetic modeling, evidence-based rational dosing regimens for subcutaneous nivolumab were developed that resulted in drug exposure within the therapeutic range while minimizing financial toxicity, to improve treatment access.

One developed dosing regimen with a bodyweight-dependent interval offers a cost-effective and patient-friendly method to optimize subcutaneous nivolumab use while ensuring adequate exposure, which can be directly implemented in clinical practice.

Two developed experimental progressive regimens with a significant cost reduction provide a rationale for a clinical non-inferiority study in which alternative dose regimens are compared to standard dosing according to the drug label.

480 mg every 4 weeks (Q4W) [3]. Conventional IV administration has some disadvantages, such as overloaded infusion centers and therefore reduced convenience for patients. A subcutaneous (SC) formulation combined with the recombinant human hyaluronidase PH20 enzyme (rHuPH20), which is already used in combination with many other monoclonal antibodies, can reduce administration time, increase IV infusion center capacity, and is generally preferred by patients [4]. Recently, both the European Medicines Agency and the US Food and Drug Administration (FDA) approved nivolumab co-formulated with an rHuPH20 SC injection as an additional dosage form for nivolumab. The approved SC regimen includes a dose of 600 mg Q2W, 900 mg every 3 weeks (Q3W), or 1200 mg Q4W for all patients regardless of the tumor type [5].

Treatment with nivolumab is associated with high costs, which places a significant financial burden on healthcare systems; therefore, cost-effective alternative dosing regimens might be of interest. The FDA has issued a guidance document for industry that supports alternative dosing of PD-1 and PD-L1 inhibitors by pharmacokinetic (PK) modeling and simulation; and is commonly used to register a flat dose after an initial mg/kg registration [6]. Alternatively, this guidance has also successfully been used as a framework for the development of cost-effective alternative dosing regimens based on body weight currently applied in clinical practice [7–11]. Notably, the nivolumab exposure in the SC dosing regimen varied within different bodyweight groups and was much higher than the exposure reached with initial 3-mg/kg Q2W IV dosing [2]. Subcutaneous nivolumab was approved based on PK endpoints, which provides possibilities to explore different administration intervals based on bodyweight within the guidelines set by the FDA. Moreover, the latest approval of SC pembrolizumab was also based on PK endpoints only [12], providing a solid rationale for exploring alternative dosing regimens using the PK/pharmacodynamic modeling approach.

There is a flat nivolumab exposure–response relationship in patients with melanoma and renal cell carcinoma, indicating that a higher steady-state trough concentrations ($C_{trough,ss}$) does not increase the probability of an objective response [13]. Objective response rates (ORRs) were similar across doses (0.1–10 mg/kg) in melanoma and renal cell carcinoma (1–10 mg/kg), while for non-small-cell lung cancer the nivolumab exposure seems more critical (a higher ORR observed at 3 mg/kg and 10 mg/kg compared with 1 mg/kg) [13]. The $C_{trough,ss}$ of nivolumab associated with 0.1-mg/kg dosing in melanoma was reported to be 2.5 mg/L [14].

Another interesting potential cost-saving approach is related to the fact that in theory the SC formulation could also be injected intravenously because earlier studies have shown that IV administration of up to 30,000 U of HuPH20 in healthy volunteers was well tolerated, rapidly cleared from the plasma, and did not appear to be associated with any serious adverse effects at doses used in SC therapeutic products [15]. Furthermore, the production processes for IV and SC formulations of nivolumab are the same, and the SC formulation is an isotonic aqueous solution. This option would potentially provide healthcare providers more milligrams of nivolumab for the same price assuming the standard price of the SC dose will be similar to the price of the standard IV dose.

With the above-mentioned knowledge in mind, the aim of the current study was to develop alternative dose interval extension regimens for SC nivolumab to reduce drug expenses while ensuring effective exposure. A weight-based extended-interval dosing strategy maintains equivalent systemic drug exposure compared to the IV 3-mg/kg Q2W regimen guided by the FDA guideline for in silico dose adjustments for PD-1 and PDL-1 inhibitors. Furthermore, two experimental progressive alternative dosing regimens were investigated, one was based on a minimum effective concentration-driven approach and finally a regimen based on using the 1200-mg SC formulation as an IV infusion.

2 Methods

2.1 FDA Principle for Simulated Dosing Regimens

We developed three alternative dose-interval extension strategies based on PK modeling and simulation. The first dosing regimen was based on patients' bodyweight while maintaining equivalent systemic drug exposure compared to the IV 3-mg/kg Q2W regimen by adhering to the FDA guideline

for in silico dose adjustments for PD-1 and PDL-1 inhibitors. The second dosing regimen specifically designed as an experimental regimen for patients with melanoma aimed to maintain a minimum nivolumab concentration above the suggested 2.5-mg/L $C_{trough,ss}$ threshold in melanoma [14]. The third strategy consists of using the 1200-mg SC formulation as an IV administration. Subsequently, potential cost savings were calculated between the alternative regimens and the approved SC regimen.

We calculated the area under the curve (AUC) and trough concentration (C_{trough}) for the first cycle and at steady state for every regimen. We assumed IV administration using 40-mg vials (the smallest available dosage form) and rounded up the numbers of vials required per dose. Subsequently potential cost savings were calculated between the alternative regimens and the approved SC regimen. The list prices for nivolumab from the Dutch Institute for Health Care (Zorginstituut Nederland www.medicijnkosten.nl) were used.

2.2 Virtual Patient Population and Simulations

We used the PopGen population generator, which is based on the International Cancer Research Partnership database for European patients, to simulate 500 virtual patients [16]. The age distribution was based on the clinical trial [17]. The median age of the population was 64 years. The median weight of the population was 67 kg. One-hundred percent of the participants were male (higher nivolumab clearance compared to females). For more details about the virtual patient population, see Table 1. The initial approved IV dose of nivolumab was 3 mg/kg Q2W administered intravenously over 60 minutes and the approved SC dose of nivolumab is 1200 mg every 4 weeks. We simulated the concentration at the first week and at steady state for these doses.

2.3 PK Modeling Implementation

The SC and IV population PK models used for simulation were developed by the license holder of nivolumab [2]. During simulation for SC administration, we set the following covariates to the most frequent value performance status (PS) = 1, white race, and SC administration with rHuPH20. Bodyweight and sex were simulated using PopGen. We used non-small-cell lung cancer as the tumor type for initial exploration of the dosing regimens. The final bodyweight-adjusted extended alternative SC dosing regimen was checked for sensitivity with other tumor types. Based on the FDA guidance [6], we calculated key PK parameters, including C_{trough}, maximum concentration (C_{max}), and AUC. Additionally, we calculated the geometric mean (GM) for them. As a comparator metric, the average concentration at steady state ($C_{average,ss}$) was also calculated.

Table 1 Demographic characteristics of virtual patient population (N = 500)

N = 500	
Sex, n (%)	
Male	500 (100%)
Age, median (range), years	64 (27–85)
Weight, median (range), kg	67 (31–128)
Height, median (range), cm	166 (142–194)

N number of patients

2.4 Simulation and Alternative Dose Acceptance Criteria

The acceptance criteria were set in accordance with the requirements of the FDA guidance on alternative dosing regimens for PD-1 and PDL-1 inhibiting antibodies. As a reference dosing regimen, we selected 3 mg/kg Q2W, as this regimen has been used to establish efficacy in clinical trials. The alternative regimen should meet the following requirements: (1) the GM of the AUC or $C_{average}$ and C_{trough} at steady state and/or during the first interval should not be more than 20% lower compared to the reference dosing regimen and (2) the C_{max} following the alternative dosing regimen does not increase more than 25% compared to that of the reference dosing regimen, unless there is adequate clinical evidence that the steady-state C_{max} for the new regimen is unlikely to be associated with an unacceptable safety profile. As a SC alternative dosing regimen is compared to an IV dosing regimen, in general, the C_{max} will be naturally lower because of the SC absorption process. In addition, a higher C_{max} will unlikely be associated with an unacceptable safety profile as nivolumab has been proven safe up to a dose of 10 mg/kg Q2W.

2.5 Software

Simulations were performed using the non-linear mixed-effects modeling software package NONMEM Version 7.5 (Icon, Dublin, Ireland). Data management was conducted using R Statistical Software (v4.4.2; R Core Team 2023) with the base (v4.4.2; R Core Team 2024), dplyr (v1.1.4; Wickham et al. 2023), and tidyverse (v2.0.0; Wickham et al. 2019) packages. Data visualization was performed using the ggplot2 package (v3.5.1; Wickham 2016).

3 Results

3.1 Comparison Between Approved SC and IV Dosing Regimens

Figure 1A, C show the predicted nivolumab concentration over 1 year for the approved IV 3 mg/kg Q2W and SC 1200 mg Q4W. With the administration of SC 1200 mg Q4W, the predicted $C_{trough,ss}$ values were generally higher than the GM for the administration in IV 3 mg/kg Q2W (Fig. 2). The GM ratio of predicted $C_{trough,ss}$ at the first cycle and at steady state were 3.24 and 2.07, respectively. The GM ratio of the AUC of the SC regimen at the first cycle and the AUC at steady state (intervals: 2 weeks) to the IV regimen is 2.79 and 2.17.

The list price of a 40-mg vial of IV nivolumab is €441.48 and a 600-mg vial of SC nivolumab is €2648.86 in the Netherlands in 2025 [18], which demonstrates that IV 480 mg is equally expensive as SC 1200 mg. In our study, administration of a nivolumab dose of SC 1200 mg every 4 weeks to all patients resulted in less savings in drug expenses than administration of IV 3 mg/kg every 2 weeks (Table 2). This is because our median-simulated patient weight is lower than 80 kg, which results in lower costs.

3.2 Extended Interval Dosing: Bodyweight-Adjusted Alternative SC Dosing

Based on the predefined alternative dose acceptance criteria, we selected the following alternative weight-based regimens for SC 1200 mg: every 7 weeks (Q7W) [<60 kg], every 6 weeks (Q6W) [60–90 kg], and every 5 weeks (Q5W) [>90 kg]. The concentration versus time curve of the simulations are presented in Fig. 1B. The GM of $C_{trough,ss}$ for the SC 1200 mg every 7/6/5 weeks (50.1 mg/L) was close to the approved IV regimen (50.9 mg/L) [Fig. 2]. As shown in Table 2, the $C_{trough,ss}$ in SC 1200-mg weight-based 7/6/5 weeks was in agreement with the FDA criteria compared with the IV 3-mg/kg Q2W regimen, as the ratio of $C_{trough,ss}$ to the IV regimen was 0.98. The ratio of AUC at steady state per week of the SC regimen to the IV regimen is 1.38. As observed, SC administration of 1200 mg Q4W (GM: 148 mg/L) and every 7/6/5weeks (GM: 94.1 mg/L) results in higher predicted $C_{average,ss}$ values compared with IV 3-mg/kg dosing Q2W (GM: 68.1 mg/L) [Fig. 3]. The achieved C_{max} values are presented in Figs. S1 and S2 of the Electronic Supplementary Material (ESM).

The plots (Figs. 4, 5A) demonstrate that the $C_{average,ss}$ after the alternative SC dose was slightly higher than after the IV dose. For patients weighting more than 90 kg, the GM of $C_{trough,ss}$ is 47.59 and 58.30 mg/L, respectively, after the alternative SC strategy and IV 3-mg/kg Q2W regimen (Fig. 5B).

Based on the list price of the SC nivolumab formulation, our new alternative dosing regimen would reduce the cost to €13,774 to €29,516 every year (20–43%) compared with the approved SC 1200-mg Q4W regimen, dependent on the weight of the patient (Table S1 of the ESM). The weight-adjusted alternative regimen of 1200 mg every 7, 6, or 5 weeks would reduce the annual cost by €9321–€25,063 (14–39%) compared with IV 3 mg/kg Q2W (Table S1 of the ESM).

We also tested different tumor types because of different observed nivolumab clearances [2], with the highest clearance observed in gastric cancer and the lowest clearance in patients with classical Hodgkin lymphoma. The alternative weight-based SC regimen, 1200 mg Q7W (<60 kg), Q6W (60–90 kg), and Q5W (>90 kg), fulfilled the FDA criteria for all tumor types when compared with the IV regimen at the dose of 3 mg/kg every 2 weeks (Table 3).

3.3 Alternative SC Dosing Regimen for Melanoma

As the ORRs were similar across doses (0.1–10 mg/kg) in patients with melanoma, we also designed a progressive alternative dose regimen using the 2.5-mg/L threshold as a target (mean steady-state minimum concentration observed in patients treated with nivolumab 0.1 mg/kg Q2W in a phase I trial) [19]. By simulating SC 1200 mg every 10 weeks, $C_{trough,ss}$ was maintained above 2.5 mg/L in 95% of the patients with melanoma. Figure 1D presents the predicted nivolumab exposure for this regimen. The GM (5th–95th percentile) $C_{trough,ss}$ in simulated patients was 18.34 (3.06–69.60). This regimen would hypothetically save around 60% of nivolumab compared to the approved SC regimen (SC 1200 mg Q4W) [Table 4].

3.4 A General Alternative Using the SC Formulation as IV Administration

The SC 1200-mg dose transformed to a IV dose given every 7 weeks (Q7W) meets the FDA's criteria based on the GM of $C_{trough,ss}$ (43.11 mg/L vs 50.88 mg/L) for the IV-approved regimen (3 mg/kg Q2W). This option would save around €29,516 (43%) in comparison with a standard SC regimen (1200 mg Q4W). More details are provided in Tables S2 and S3 of the ESM. Figure S3 of the ESM shows more details on IV 1200 mg Q7W.

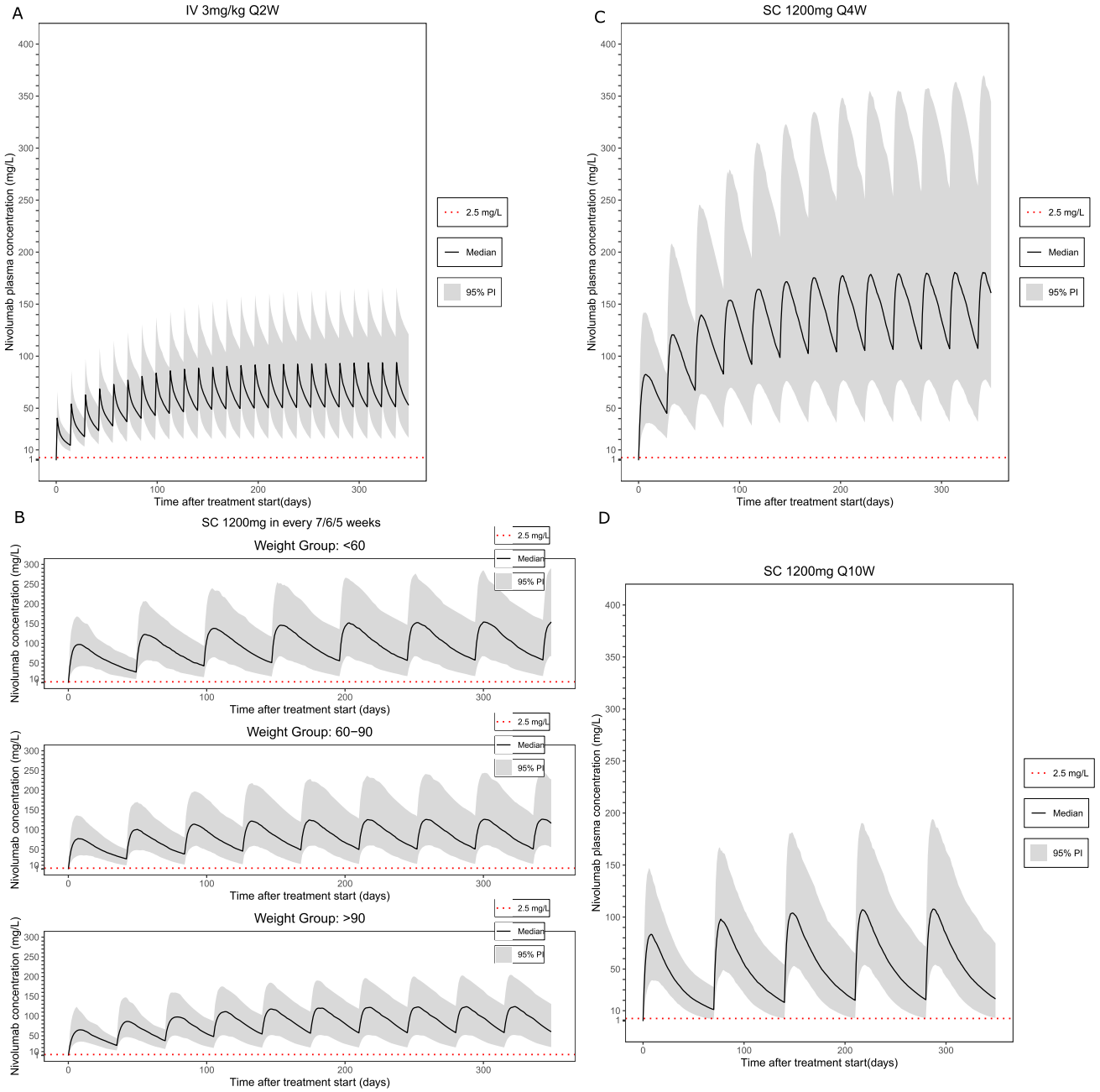

Fig. 1 Predicted nivolumab plasma concentration and time curve based on the modeling simulation results, **A** intravenous (IV) 3 mg/kg every 2 weeks (Q2W); **B** subcutaneous (SC) 1200 mg every 7, 6, or 5 weeks in three weight groups (less than 60 kg, 60–90 kg, and more than 90 kg); **C** SC 1200 mg every 4 weeks (Q4W); and **D** SC 1200 mg every 10 weeks (Q10W). The solid black line represents the median of the nivolumab concentration of the simulated population and the gray shaded areas represent the 95% prediction interval (PI). The red dotted line represents a 2.5-mg/L concentration

4 Discussion

In this study, we developed cost-saving dosing strategies for the PD-1 inhibitor nivolumab. We simulated the administration of the initially approved IV 3 mg/kg Q2W, the recently approved SC 1200 mg Q4W, and the alternative SC 1200-mg extended-dose regimens in a virtual population. The primary goal for examining alternatives to the approved fixed SC 1200-mg Q4W regimen was to improve cost effectiveness and concomitant patient friendliness. Subcutaneous nivolumab fixed-dose treatment is associated with relatively high expenses and registration data show that drug concentrations measured during SC dosing are higher as compared

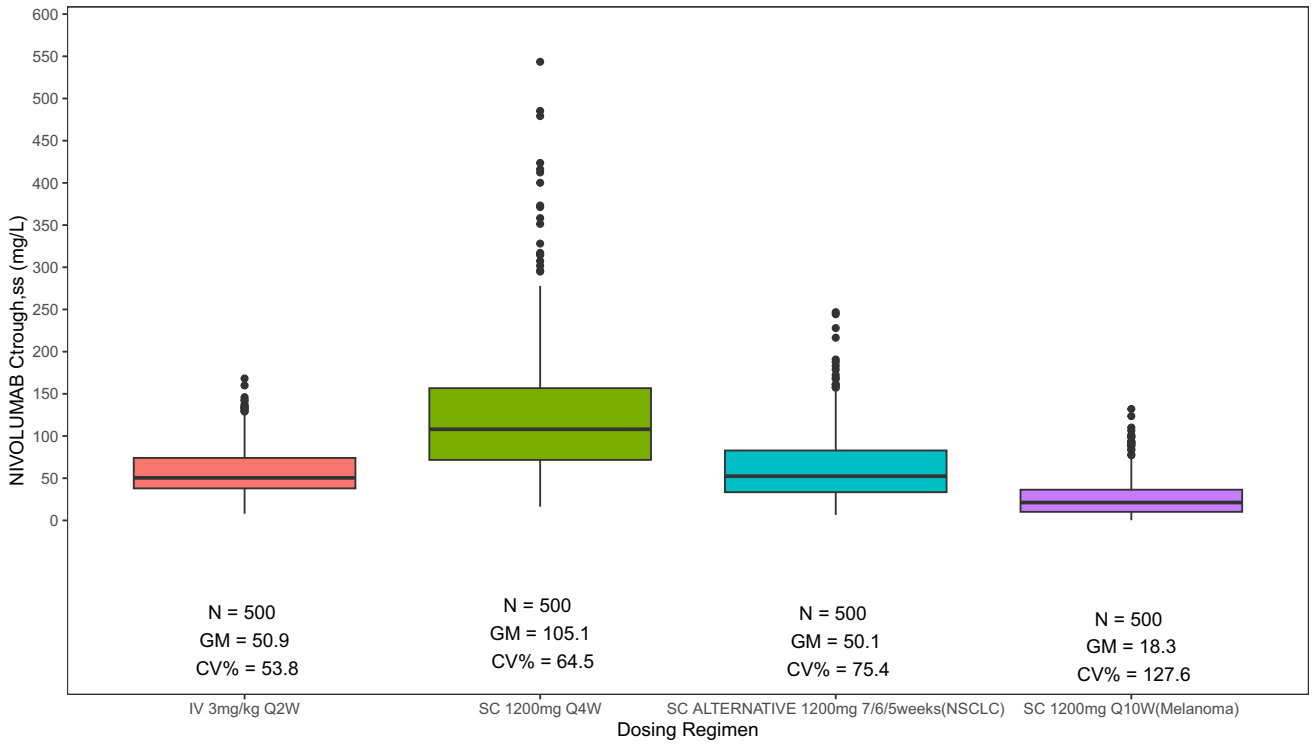

Fig. 2 Box plot of predicted nivolumab plasma concentration at steady-state trough ($C_{trough,ss}$) in four regimens. The median black line shows the median, the box extends to 25th and 75th percentiles. The subcutaneous (SC) 1200-mg every 10 weeks (Q10W) regimen is simulated in patients with melanoma and the other three regimens are simulated in patients with non-small-cell lung cancer (NSCLC). *CV%* percent coefficient of variation, *GM* geometric mean, *IV* intravenous, *N* number of simulated individuals, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q10W* every 10 weeks

Table 2 Comparison of SC 1200 mg weight-based (7/6/5-week) dosing with IV 3 mg/kg Q2W and SC 1200 mg Q4W for US FDA criteria in a non-small cell lung cancer virtual population

Dosing regimen	GM $C_{trough1st}$, (%CV)	GM $C_{trough,ss}$, (%CV)	GM AUC_{1st}/week, (%CV)	GM AUC_{ss}/week, (%CV)	GM $C_{average,ss}$, (%CV)	Annual drug costs per patient (€)
IV 3 mg/kg Q2W	14.37 mg/L (32%)	50.88 mg/L (54%)	162.59 mg day/L (27%)	476.44 mg day/L (42%)	68.06 mg/L (42%)	64,417.23
SC 1200 mg Q4W	46.56 mg/L (42%)	105.10 mg/L (64%)	453.96 mg day/L (39%)	1035.75 mg day/L (51%)	147.96 mg/L (51%)	68,870.36
SC 1200 mg Q7W (<60 kg), Q6W (60–90 kg) and Q5W (>90 kg)	26.71 mg/L (56%)	50.07 mg/L (75%)	386.16 mg day/L (39%)	659.01 mg*day/L (48%)	94.14 mg/L (48%)	44,525.67
GM ratio (IV vs SC Q7/6/5)	1.86	0.98	2.38	1.38	1.38	0.69 (−31%)

AUC_{1st} area under the curve after the first dose, AUC_{ss} area under the curve at steady state, $C_{average,ss}$ average concentration at steady state, *CV* coefficient of variation, $C_{trough1st}$ trough concentration after the first dose, *FDA* Food and Drug Administration, *GM* geometric mean, *IV* intravenous, $C_{trough,ss}$ steady-state trough concentration, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q5W* every 5 weeks, *Q6W* every 6 weeks, *Q7W* every 7 weeks, *SC* subcutaneous

with IV dosing, which implies unnecessary drug waste. Furthermore, extended dose intervals reduce the number of visits to the clinic, which improve the patients' health-related quality of life. Therefore, it is important to explore dose strategies that minimize wastage while maintaining efficacy. Our simulations of SC nivolumab regimens showed that the 4-week intervals for the 1200-mg dose could be extended to 7 weeks for patients <60 kg, 6 weeks for patients between 60

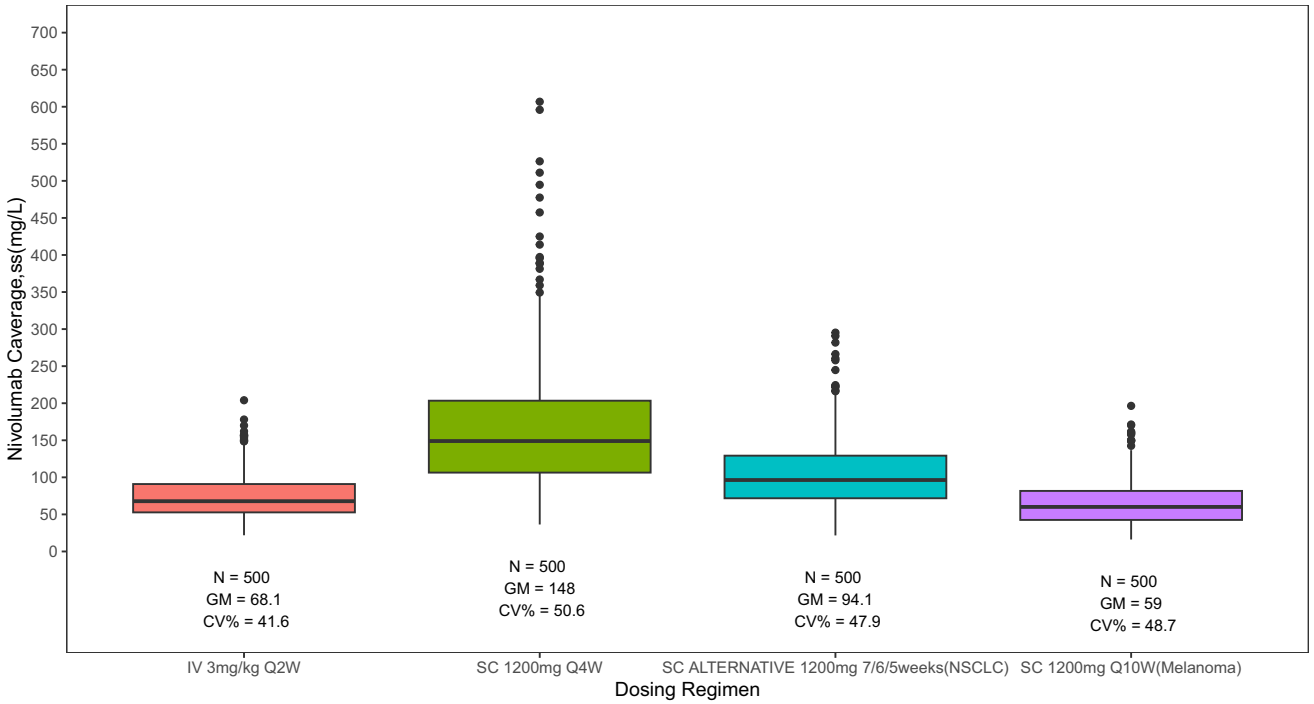

Fig. 3 Box plot of predicted nivolumab plasma average concentration at steady state ($C_{average,ss}$) in four regimens. The median black line shows the median, the box extends to 25th and 75th percentiles. The subcutaneous (SC) 1200-mg every 10 weeks (Q10W) regimen is simulated in patients with melanoma and the other three regimens are simulated in patients with non-small-cell lung cancer (NSCLC). *CV%* percent coefficient of variation, *IV* intravenous, *GM* geometric mean, *N* number of simulated individuals, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q10W* every 10 weeks

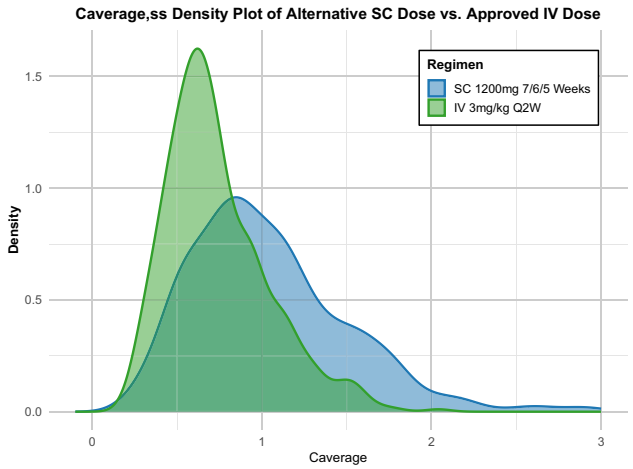

Fig. 4 Density plot of the predicted nivolumab plasma average concentration at steady state ($C_{average,ss}$) in two regimens. The blue shaded line represents the density distribution of $C_{average,ss}$ in subcutaneous (SC) 1200 mg every 7, 6, or 5 weeks (<60 kg, 7 weeks; 60–90 kg, 6 weeks; >90 kg, 5 weeks). The *green shaded line* represents the density distribution of $C_{average,ss}$ in intravenous (IV) 3 mg/kg every 2 weeks (Q2W)

and 90 kg, and 5 weeks for patients >90 kg while maintaining equivalent exposure compared to the IV 3-mg/kg Q2W regimen. As a concept, we explored two more experimental progressive alternative dosing regimens. It was demonstrated in this experimental regimen in patients with melanoma that the SC nivolumab interval could potentially be extended to a maximum of one dose every 10 weeks, while theoretically still achieving effective plasma concentrations. In addition, another experimental regimen in patients who require an IV infusion of nivolumab, using the SC 1200-mg formulation as an IV infusion would enable dosing every 7 weeks without compromising equivalent exposure compared to IV 3 mg/kg, resulting in a more cost-effective administration of nivolumab.

Our study showed that when dosed according to the drug label, costs of SC administration are 6% more in drug expenses than the original IV regimen (3 mg/kg every 2 weeks) and are equal to the flat dose regimen (240 mg/Q2W). However, SC administration might be more convenient for patients and is supposed to reduce the logistic burden accompanied with IV administration.

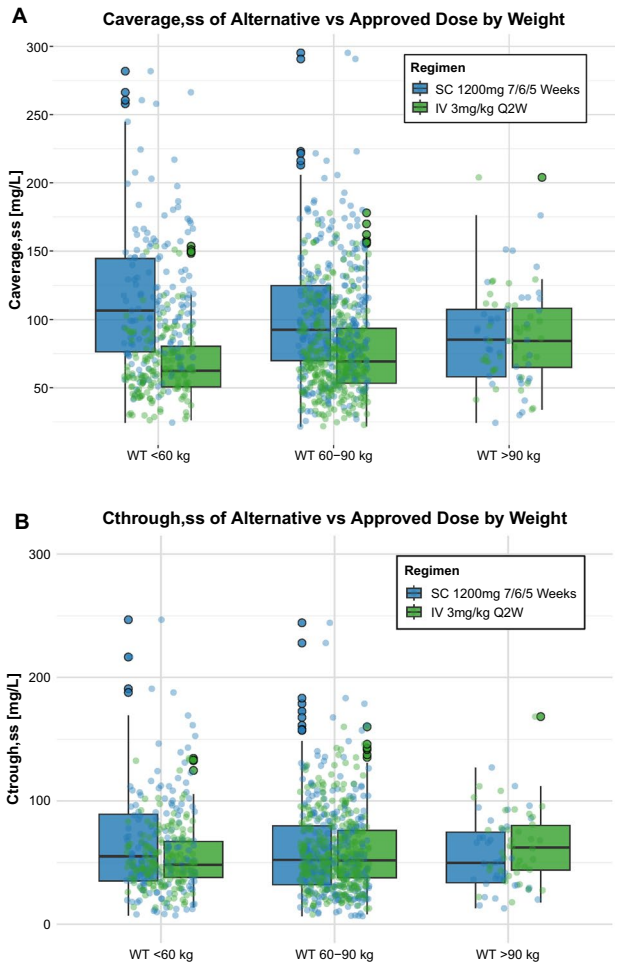

Fig. 5 Box plot of predicted nivolumab plasma concentration at steady-state trough ($C_{trough,ss}$) and average concentration at steady state ($C_{average,ss}$) in two regimens by three weight (WT) groups. The blue box represents subcutaneous (SC) 1200 mg every 7, 6, or 5 weeks (<60 kg, 7 weeks; 60–90 kg, 6 weeks; >90 kg, 5 weeks). The green box represents intravenous (IV) 3 mg/kg every 2 weeks (Q2W). Both solid and transparent points present individual predicted concentrations. The median black line shows the median, the box extends to 25th and 75th percentiles. **A** The box plot of predicted nivolumab plasma $C_{average,ss}$ in two regimens by three WT groups (<60 kg; 60–90 kg; >90 kg). **B** The box plot of predicted nivolumab plasma $C_{trough,ss}$ in two regimens by three WT groups (<60 kg; 60–90 kg; >90 kg). *WT* weight

The first developed alternative regimen is dependent on bodyweight and showed that predicted GM ratios for $C_{trough,ss}$ between IV and alternative dosing regimens adjusted by bodyweight is 1.06. The GM ratios are within the 20% difference in the PK-based approach as provided by the FDA criteria [6] for PD-1-blocking or PD-L1-blocking antibodies based on modeling and simulations. As for the AUC, both the AUC_{1st} and AUC_{ss} are not within range, with 2.38 and 1.48 for predicted GM ratios, respectively. The exposure is higher than the IV 3-mg/kg regimen but lower than the approved 1200 mg Q4W and 10 mg/kg Q2W regimens. Compared with the approved SC regimen (1200 mg Q4W), the alternative weight-based dosing shows a lower AUC but is higher than the 3-mg/kg IV regimen and therefore is unlikely to cause additional side effects or reduced efficacy. Moreover, the AUC of this weight-adjusted alternative SC regimen is higher than the IV 3 mg/kg Q2W regimen. Therefore, our alternative regimen (SC 1200 mg Q7W [<60 kg], Q6W [60–90 kg], and Q5W [>90 kg]) is FDA guideline compliant and could directly be implemented in clinical practice. It is important to note that electronic rounding and hybrid dosing with IV 3-mg/kg Q2W administration has already been applied to save costs, which is not taken into account in this analysis [20].

The first progressive alternative regimen was designed for patients with melanoma. Specifically, in melanoma, IV nivolumab showed a flat exposure–response relationship at a dose that ranged from 0.1 to 10.0 mg/kg Q2W [13]. When comparing 10 mg/kg with 3 mg/kg, the lower dose showed a higher ORR, 20.0 and 41.2%, respectively. In addition, dose escalation from 0.1 mg/kg to 1.0 mg/kg showed no increased response and performed similar to the 3-mg/kg dose: ORR 35.3% [21–27]. These characteristics combined provided an opportunity for exploring a more progressive regimen for patients with melanoma. Our simulation predicted that $C_{trough,ss}$ of SC 1200 mg Q4W (GM >105 mg/L) would be 6.6 times higher than dosing with IV 3 mg/kg Q2W and this is an impressive 1050 times higher than half-maximal effective concentration (0.1 mg/L). The $C_{trough,ss}$ for the 0.1-mg/kg Q2W regimen, which reached near-complete target saturation in patients with melanoma [21, 28] is 2.5 mg/L. Therefore, in the current study, we suggested 2.5 mg/L as a possible threshold for determining the maximum interval for the SC 1200-mg regimen in this specific patient subgroup. However, this threshold should be further validated in a survival outcome study before implementation could be considered. Topalian et al. measured PD-1 occupancy in circulating lymphocytes, which act as transient cells, rather than infiltrated lymphocytes that are found in the tumor, casting uncertainty on whether the 2.5-mg/L threshold is sufficient for an optimal outcome. A second general limitation of this approach is that the half-maximal inhibitory concentration for T-cell functional activity is significantly higher than that required for receptor saturation [29], which means that T-cell activity can increase even when receptor occupancy is saturated. A similar observation has also been reported for pembrolizumab [30]. NCT04295863 [31] is trying to assess the non-inferiority margin and efficacy of extended-interval nivolumab dosing (IV 240 mg Q2W or IV 480 mg Q4W) compared to standard dosing, which

Table 3 Comparison of SC 1200-mg weight-based (7/6/5-week) dosing with IV 3 mg/kg Q2W in all tumor types

Tumor type	Clearance (mL/h)	IV 3 mg/kg Q2W, $C_{trough,ss}$	SC 1200 mg Q7/6/5W, $C_{trough,ss}$	Difference
Classical Hodgkin lymphoma	7.82	70.41	82.32	+16.92%
NSCLC	10.80	50.88	50.07	−1.59%
Other solid tumors (including melanoma)	11.04	47.43	48.29	+1.81%
Gastric cancer	12.98	38.68	36.50	−5.64%

$C_{trough,ss}$ steady-state trough concentration, *IV* intravenous, *NSCLC* non-small cell lung cancer, *Q2W* every 2 weeks, *Q5W* every 5 weeks, *Q6W* every 6 weeks, *Q7W* every 7 weeks, *SC* subcutaneous

Table 4 Prediction of C_{trough} and AUC for the maximum extended-interval dosing regimen of nivolumab for patients with melanoma

	GM $C_{trough1st}$, (%CV)	GM $C_{trough,ss}$, (%CV)	GM AUC_{1st}/week (%CV)	GM AUC_{ss}/week, (%CV)	GM $C_{average,ss}$, (%CV)	Annual drug costs (€)
SC 1200 mg Q4W	45.64 mg/L (42%)	102.10 mg/L (65%)	449.64 mg day/L (39%)	1013.91 mg day/L (51%)	144.84 mg/L (51%)	68,870.36
SC 1200 mg Q10W	12.25 mg/L (106%)	18.34 mg/L (128%)	310.76 mg day/L (39%)	413.30 mg day/L (49%)	59.04 mg/L (49%)	27,548.14 (−60%)
GM ratio (Q4W vs Q10W)	0.27	0.18	0.69	0.41	0.41	0.4

AUC area under the curve, AUC_{1st} area under the curve after the first dose, AUC_{ss} area under the curve at steady state, $C_{average,ss}$ average concentration at steady state, $C_{trough1st}$ trough concentration after the first dose, $C_{trough,ss}$ steady-state trough concentration, *CV* coefficient of variation, *GM* geometric mean, *IV* intravenous, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *SC* subcutaneous

used a C_{trough} above 1.5 µg/mL as criteria for PK success. In addition, EudraCT 2021-001707-32 [32] aims to explore the difference between the mean C_{trough} at 4 weeks by comparing nivolumab at a dose of 480 mg Q4W and an extended interval regimen of 240 mg Q4W. As our proposed regimen of SC 1200 mg every 10 weeks does not meet the FDA criteria, this regimen should be evaluated in a non-inferiority study before potential implementation in clinical practice.

The second progressive regimen that simulated the use of the SC 1200-mg Q7W formulation for an IV administration also leads to significant savings and meets the criteria for at least equivalent exposure compared to the 3-mg/kg Q2W approved regimen. From a FDA guideline perspective, this regimen would be a candidate for implementation in clinical practice although for a higher expected C_{max}, as 1200 mg exceeds even the 10-mg/kg boundary for most patients. In addition, the safety of an IV injection of rHuPh20 should be addressed in more detail. Concerns about the safety of injecting rHuPH20 have been investigated in healthy volunteers in an earlier study, which has shown that IV administration of up to 30,000 U of rHuPH20 was well tolerated, rapidly cleared from the plasma, and did not appear to be associated with any serious adverse effects at doses used in SC therapeutic products [15]. The SC nivolumab 1200-mg formulation consists of 20,000 U of rHuPH20 and falls therefore within the investigated range [5]. However, to our knowledge, long-term safety has so far not been evaluated in clinical studies. Other factors, such as osmolality, pH, and polysorbate content, should also be evaluated. This safety issue should therefore be addressed in a longer clinical study with nivolumab before potential implementation in clinical practice.

Until now, in most proposed more progressive regimens, maintaining a C_{trough} above a threshold value is regarded as a rule for all immune checkpoint inhibitors in order to maintain efficacy. As immune checkpoint inhibitors work through the immune system on tumor cells, the immune reaction cascade might not require the same C_{trough} throughout the entire period of treatment. This question, however, warrants further investigation.

Concerning the study limitations, our study was based on a virtual patient population, which may deviate slightly from

real-world patients. However, this in silico concept is widely applied and accepted as shown in earlier studies [33–35]. The FDA guideline does not yet specifically mention specific criteria when changing from an IV to a SC formulation or vice versa instead of an IV to an IV formulation. One could argue that SC has higher variability and would require additional criteria. Nevertheless, we think that the proposed regimen (1200 mg SC Q7W [<60 kg], Q6W [60–90 kg], and Q5W [>90 kg]) results in exposure for every single patient within the efficacy and safety range of nivolumab. There is an inherent difference between the two different routes of administration, which made some metrics, including C_{trough} in the first cycle and AUC in the first cycle, less meaningful as nivolumab has been proven tolerable (also in 1200 mg Q4W and 10 mg/kg Q2W) in even higher concentrations without an increase in toxicity. Although the developed alternative dosing regimens contribute to less drug expenses in the short term, we argue that high drug expenses are symptoms of an underlying drug pricing system that should be fixed. Furthermore, our study calculated cost reductions with list prices for nivolumab because real prices are not known, as prices of medicines with a high national budget impact are negotiated by the government and are confidential in the Netherlands. Finally, list prices may differ by country, as may the savings, especially when an expiring patent of the IV formulation would also reduce the price of the SC formulation.

5 Conclusions

To conclude, the present work shows that the dose interval of SC nivolumab can be extended dependent on bodyweight maintaining effective exposure, which is compliant with the FDA guideline. Using this extended-dosing interval, expenses can be reduced significantly, as well as the number of patients' hospital visits, which will improve the quality of life of the oncologic patients. This regimen can be implemented in clinical practice directly. The more experimental progressive proposed regimens provide a solid basis for clinical and non-inferiority study designs to investigate that the outcomes of both the approved and alternative regimens are not different from each other.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40262-025-01610-4.

Funding The work of Yan Wang was supported by the China Scholarship Council (202306100051).

Declarations

Conflict of interest Dirk Jan A.R. Moes is an Editorial Board member of *Clinical Pharmacokinetics*. He was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. All other authors declare no conflicts of interest related to this work.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Data are available from the corresponding author upon reasonable request.

Code availability All the model codes are provided in the supplementary materials.

Author contributions YW, LHB, EFS, RH, HJG, and DJARM contributed to the research design, YW, LHB, and DJARM performed the research, analyzed the data, and wrote the manuscript, and RH, JGCH, SLWK, JJMA, TH, EK, JZ, AB, MMH, WT, THOM, EFS, and HJG reviewed and revised the manuscript.

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Authors and Affiliations

Yan Wang[1] · Laura H. Bukkems[1] · Rob ter Heine[2] · J. G. C. van Hasselt[3] · S. L. W. Koolen[4,5] · J. J. M. A. Hendrikx[6,7] · Tom Van der Hulle[8] · Ellen Kapiteijn[8] · Juliette Zwaveling[1] · Annemarie Becker[9] · Michel M. van den Heuvel[10] · Willemijn S. M. E. Theelen[11] · Thijs H. Oude Munnink[12] · Egbert F. Smit[13] · Henk-Jan Guchelaar[1] · Dirk Jan A. R. Moes[1]

✉ Dirk Jan A. R. Moes
d.j.a.r.moes@lumc.nl

1 Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands

2 Department of Pharmacy, Pharmacology and Toxicology, Radboudumc, Nijmegen, The Netherlands

3 Leiden Academic of Drug Research, Leiden, The Netherlands

4 Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

5 Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, The Netherlands

6 Department of Pharmacy and Pharmacology, Netherlands Cancer Institute, Amsterdam, The Netherlands

7 Department of Nuclear Medicine, Netherlands Cancer Institute, Amsterdam, The Netherlands

8 Department of Medical Oncology, Leiden University Medical Center, Leiden, The Netherlands

9 Department of Pulmonology, Amsterdam University Medical Center, Amsterdam, The Netherlands

10 Department of Pulmonology, University Medical Center Utrecht, Utrecht, The Netherlands

11 Department of Thoracic Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands

12 Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, The Netherlands

13 Department of Pulmonology, Leiden University Medical Center, Leiden, The Netherlands