

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

Introduction

- Subcutaneous formulation in Nivolumab has been approved by EMA and FDA with a fixed dose of **1200 mg Q4W** for all patients;
- The standard SC dosing regimen (**1200 mg Q4W**) results in variable exposure across different bodyweight groups and was on average much higher than the exposure reached with the 3 mg/kg IV dosing regimen [1];
- Maintaining nivolumab steady-state trough concentration ($C_{min,ss}$) ≥ 2.5 mg/L could achieve maximum therapeutic effect for melanoma [2,3]. Because nivolumab binds to PD-1 receptor and acts via the immune system, this threshold may also relate to NSCLC.

Objectives

- Develop alternative nivolumab dosing strategies based on patients' bodyweight while maintaining equivalent systemic drug exposure compared to the 3 mg/kg IV Q2W regimen;
- Develop alternative nivolumab dosing strategies based on maintaining a minimum $C_{min,ss}$ (2.5 mg/L).

Methods

Dataset:

- 500 virtual NSCLC patients generated by PopGen population generator.

Population PK modeling and Simulation:

- Software:** NONMEM® 7.4.4., R 4.1.3.
- Model:** Combined nivolumab s.c./i.v. PopPK model developed by the license holder [1].

Simulations:

- Criteria and comparison:** FDA criteria [4] for in silico dose adjustments for PD-1 and PDL-1 inhibitors in the comparison with the 3mg/kg Q2W IV regimen.
- Body weight-adjusted SC nivolumab dosing strategies:** Different dose intervals per bodyweight category with the fixed SC dose of 1200mg.
- Maximum stretched dosing intervals:** Using the fixed SC dose of 1200mg with the requirement of 95% the patients $C_{min,ss}$ exceeding 2.5 mg/L.

Results

- The median age, weight, and height are 36years, 67kg and 166cm respectively. 46% of our simulated population was male.
- Figure 1(A) and (C) described the simulation-predicted nivolumab concentration over one year for the registered IV in 3 mg/kg Q2W and SC in 1200 mg Q4W SC.
- Alternative weight-based regimen for 1200mg SC and the dosing interval was as follows: Q7W (<60kg), Q6W (60-90kg) and Q5W (>90kg). The simulation results are presented in Figure1(B).
- The geometric mean(GM) (5th–95th percentile) $C_{trough,ss}$ in simulated patients was 19.26 (3.28–71).
- This maximum extended intervals regimen would save around 60% compared to the approved SC regimen(SC 1200mg Q4W) (Table1).

Table 1. Prediction of C_{trough} and AUC for maximum extended-interval dosing regimens of nivolumab

Regimen	$C_{1trough}$ (CV%)(mg/L)	$C_{trough,ss}$ (mg/L)	AUC1/Week (mg*day/L)	AUCss/Week (mg*day/L)	Annual Cost (euro)
IV 3mg/kg Q2W	14.4 (32%)	50.9 (49%)	162.6 (27%)	476.4 (42%)	64,417
SC 1200mg Q4W	46.6 (42%)	105.1 (64%)	454.0 (39%)	1035.8 (51%)	68,870
SC 1200mg Q10W	12.8 (103%)	19.3 (125%)	315.6 (38%)	422.4 (49%)	27,548 (-60%)
Ratio	0.28	0.18	0.70	0.41	0.40
SC 1200mg 7/6/5W	26.7 (56%)	50.1 (75%)	386.2 (39%)	659.0 (48%)	44,526
Ratio	0.57	0.48	0.85	0.64	0.65

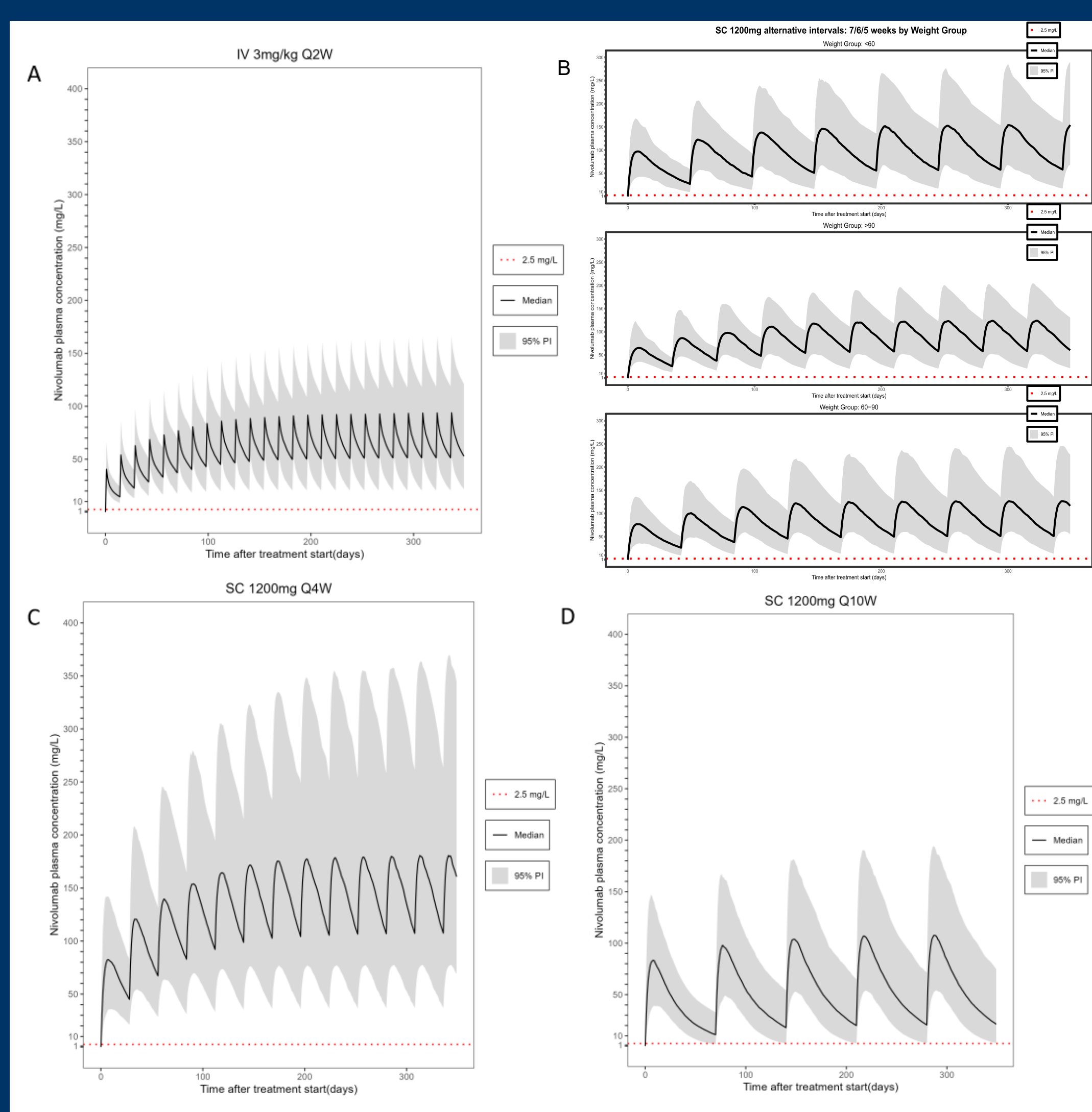


Figure 1. Simulation of Nivolumab Concentration-Time (C-T) Curves

- $C_{trough,ss}$ and AUCss in 1200mg SC weight-based 7/6/5 weeks fulfilled the FDA criteria compared with IV 3mg/kg Q2W regimen, which is not more than 20% lower.
- Based on SC administration estimated price, the weight adjusted alternative regimen-1200mg every 7, 6 or 5 weeks would save the annual cost **€19,892 (31%)**.

- Figure 2 shows the AUCss in the following regimens : IV 3mg/kg Q2W, SC 1200mg Q4W, alternative dosing regimen(1200mg SC in 7/6/5 weeks) and maximum extended intervals dosing regimen(SC 1200mg Q10W).

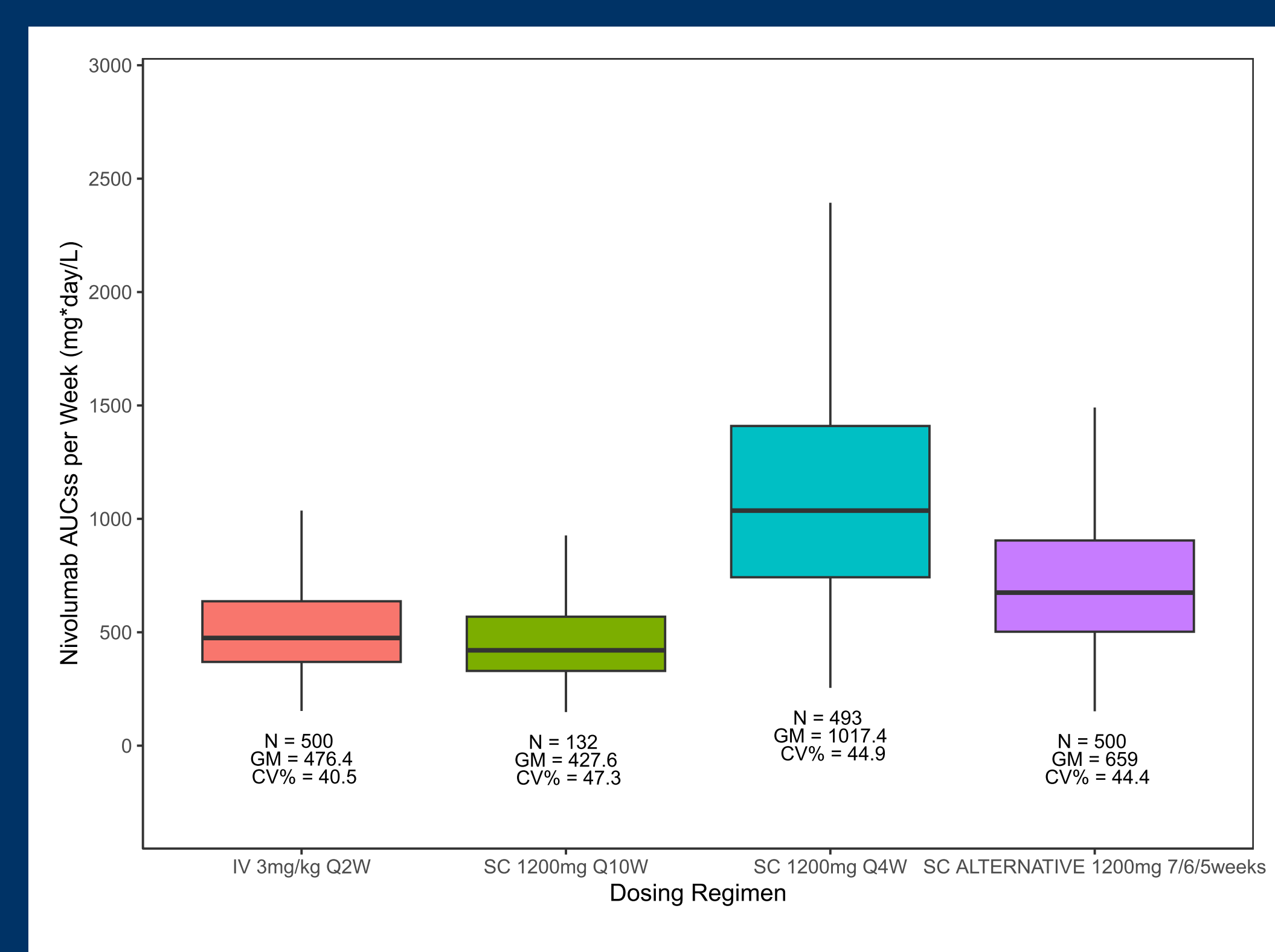


Figure 2. Model-Predicted Nivolumab for Area Under the Curve at Steady-State (AUCss) Per Week Distribution

Conclusions

- The weight-based regimen: 1200mg SC every 5 weeks for more than 90 kg, 6 weeks for 60–90 kg, and 7 weeks for less than 60 kg, offers a cost-effective way to optimize subcutaneous nivolumab use, reduce healthcare burdens and environmental impact while ensuring adequate drug exposure and could be evaluated in a PK equivalence study.
- The more progressive proposed scheme (1200 mg Q10W) provides a solid basis for a non-inferiority study compared to standard dosing.

References:

- Zhao Y et al. Clin Pharmacol. (2024) 115(3):488-97
- FDA Approves Nivolumab and Hyaluronidase-nvhy for Subcutaneous Injection 2024
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- Op 't Hoog CJ et al. Cancer Chemother Pharmacol. (2025) 95(1):36.

Contact information:

Email: y.wang11@lumc.nl

LinkedIn: Scan QR-code on the right

