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ARTICLE

Model-informed drug development supporting the approval of the avelumab flat-dose regimen in patients with advanced renal cell carcinoma

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Abstract

Avelumab is an anti–PD-L1 monoclonal antibody approved as monotherapy for Merkel cell carcinoma (MCC) and urothelial carcinoma (UC), and in combination with axitinib for advanced renal cell carcinoma (aRCC). Although initially approved with weight-based dosing (10 mg/kg intravenously [IV] every 2 weeks [Q2W]), avelumab was subsequently approved for flat dosing (800 mg IV Q2W) based on population pharmacokinetic (PopPK), exposure-efficacy, and exposure-safety modeling in MCC and UC. Here, through modeling and simulation, we provide justification for a flat-dose regimen of avelumab plus axitinib in aRCC. Simulated exposure metrics from the previous monotherapy PopPK model (1827 patients) for both weight-based and flat-dose regimens were compared with exposure metrics from treatment-naive patients with aRCC who received avelumab plus axitinib (488 patients). The aRCC population exposures were derived from a fit-for-purpose PopPK model developed using data from monotherapy and combination studies and the existing base structural PopPK model. Exposure-response relationships for safety were analyzed, including grade ≥3 treatment-emergent adverse events (TEAEs), any-grade infusion-related reactions, and TEAE any-grade immune-related adverse events (irAEs). Weight-based dosing of avelumab in the aRCC population yielded similar PK exposures to the flat-dose regimen reference exposures in the monotherapy population. Increased avelumab exposure was not associated with increased probabilities of grade ≥3 TEAEs or any-grade IRRs, although there was a weak association with an increased probability of any-grade irAEs. Overall, models in aRCC suggest that the avelumab 800-mg Q2W

Satjit Brar was at this affiliation at the time the study was conducted.

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flat-dose regimen would provide similar benefits compared with weight-based dosing with no meaningful change in the probability of AEs.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
There is an ongoing shift in oncology from weight-based dosing to flat-dose regimens for immune checkpoint inhibitors.

WHAT QUESTION DID THIS STUDY ADDRESS?
Does a flat dosing regimen of avelumab plus axitinib provide similar exposure and safety as (1) weight-based dosing in a population of patients with advanced renal cell carcinoma (aRCC) and (2) avelumab monotherapy in previously established and marketed solid tumor indications?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
Population modeling and simulation predicted no difference in avelumab exposure and safety profile for flat-dose avelumab plus axitinib therapy in patients with aRCC versus weight-based dosing or monotherapy treatment.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
Our analyses support the approval of an avelumab 800-mg flat dose Q2W for patients with aRCC, even though pivotal study dosing was weight-based. Our fit-for-purpose modeling and simulation approach might be useful for therapies under development for additional indications or dosing approaches.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies (mAbs) that are used to elicit antitumor immune responses in various tumor types. ICIs that block the immunosuppressive interaction between programmed death 1 (PD-1) on T cells and its ligand (PD-L1) on the surface of tumor cells are of particular importance. Blocking this immunosuppressive interaction with either anti–PD-1 antibodies, such as pembrolizumab and nivolumab, or anti–PD-L1 antibodies, such as avelumab, atezolizumab, or durvalumab, allows the host antitumor immune response to take effect in the tumor microenvironment.[1]

Avelumab is a human immunoglobulin G1 anti–PD-L1 mAb that has been approved by health authorities around the world as monotherapy for the treatment of metastatic Merkel cell carcinoma (mMCC) and advanced or metastatic urothelial carcinoma (UC), and in combination with axitinib for metastatic RCC.[2–4] In addition to its approved indications, avelumab has shown activity across several tumor types.[5,6] Avelumab's initial approval, based on results from the JAVELIN Merkel 200 clinical trial[7] and UC cohorts of the JAVELIN Solid Tumor trial,[8,9] was a dose of 10 mg/kg administered every 2 weeks (Q2W). An initial weight-based dosing schema is common for mAbs, including ICIs.[10]

Various pharmacokinetic (PK) modeling and simulation studies have demonstrated that ICIs show similar variability in exposure across patient populations in weight-based and flat-dosing regimens.[11–16] Flat-dose regimens offer several advantages over weight-based regimens, including ease of dose preparation, reduction of errors, cost savings, and minimal drug waste.[17–19] Analyses of PK might appear to support weight-based dosing due to the finding of a statistically significant effect of body size on PK parameter(s), but PK are rarely proportional to body size. As such, weight-based dosing may overadjust for the body size effect.[10] For these and other reasons, there has been a recent shift in oncology from weight-based dosing to flat-dose regimens for ICIs.[18,19]

Previous population PK (PopPK), exposure-efficacy, and exposure-safety models and simulations in mMCC and UC[16,20] patient populations provided the basis for the subsequent approval of an avelumab 800-mg flat dose Q2W by the US Food and Drug Administration, the European Medicines Agency, and other health authorities around the world.[4,21] A flat dose of avelumab 800 mg was selected based on the median (~80 kg) body weight of patients with various solid tumors being treated with avelumab at 10 mg/kg.[14,16] Although median body weight varies in different countries, exposure simulations across weight quartiles overlapped, with only minor differences between the lightest and heaviest weight quartiles. Thus, the 800-mg

flat dose was expected to preserve the clinical activity and safety profile associated with the approved weight-based dose while decreasing variability in exposures.[16] Although these analyses were instrumental in recommending a flat-dose regimen of avelumab monotherapy, use of a flat-dose regimen as part of a combination treatment paradigm has not been previously explored.

In previously untreated patients with advanced renal cell carcinoma (aRCC), avelumab (10 mg/kg Q2W) in combination with axitinib, a vascular endothelial growth factor receptor inhibitor, improved progression-free survival and overall survival (OS) over sunitinib, the standard of care.[22,23] Here, we provide support for a flat dose of avelumab in combination with axitinib for the treatment of patients with aRCC through PopPK and exposure-safety modeling and simulation. We conducted a PopPK analysis leveraging the existing base structural component of the avelumab monotherapy model to estimate individual PopPK parameters in the aRCC analysis population,[20] comparing the predicted avelumab exposures from the aRCC population with the reference simulations of the 10 mg/kg Q2W and flat-dosing regimen of 800 mg Q2W. We then evaluated the relationship between avelumab exposure and the probability of certain key adverse events (AEs). We observed a flat trend across the range of exposures, suggesting that the probability of AEs was similar between weight-based and flat-dosing regimens in this patient population.

METHODS

Study overview

Clinical trials were conducted in accordance with the ethics principles of the Declaration of Helsinki and the Good Clinical Practice guidelines, defined by the International Council for Harmonization. Patients provided written informed consent. The protocol, amendments, and informed-consent forms were approved by the institutional review board or independent ethics committee at each trial site. An independent external data monitoring committee reviewed efficacy and safety.

We used data from two clinical trials to generate PopPK models and exposure-response (E-R) analyses for avelumab in patients with treatment-naive aRCC, which included demographic, dosing, PK, and safety information, for a total of 488 patients from JAVELIN Renal 100 and JAVELIN Renal 101 (treatment arm only; Table S2 and Table S3), referred to as the aRCC analysis population. JAVELIN Renal 100 (NCT02493751) was a phase Ib study in which a combination of avelumab 10 mg/kg and axitinib 5 mg was administered to patients with previously untreated aRCC.[24] JAVELIN Renal 101 (NCT02684006) is an ongoing phase III trial in which patients with previously untreated aRCC have been randomized (1:1) to be treated with a combination of avelumab 10 mg/kg and axitinib 5 mg (treatment arm) or sunitinib 50 mg (control arm), which was the standard of care at the start of the trial.[22] Only for PopPK, the analysis population was represented in a pooled dataset, including 2315 patients in total: the aforementioned 488 combination treatment patients with aRCC and 1827 monotherapy treatment patients with solid tumors included in the previous PopPK analysis.[20]

The PopPK model was a fit-for-purpose two-compartment structural model with time-dependent clearance, which also included the fixed effects of body weight by allometric scaling on baseline clearance (CL), central volume (V_1), peripheral volume (V_2), and intercompartmental clearance (Q), with exponents estimated on CL, V_1, and V_2, and fixed to 1 for Q; this represented the base structural component of the established, full-covariate PopPK model developed previously.[20] The PopPK model of avelumab characterized for the aRCC analysis population was used to: estimate the baseline clearance and time-dependent CL effects in the aRCC analysis population, including comparison with the CL estimated in the solid-tumor monotherapy population; and compare avelumab exposures following a single dose and at steady-state in the aRCC analysis population with reference exposures following both 10 mg/kg Q2W and 800 mg Q2W. The characterization of avelumab PopPK was performed using NONMEM version 7.3 (Icon Development Solutions, Dublin, Ireland), with the first-order conditional estimation method with interaction (FOCEI) for estimation of all parameters in this pooled analysis population, maintaining consistency with the previous modeling approach.

Reference exposure used to support flat dosing in aRCC

Previously, to support the conversion to flat dosing of avelumab in mMCC and UC, the PopPK model results from avelumab monotherapy in patients with solid tumors were used to derive single-dose and steady-state exposure metrics of area under the plasma concentration-time curve (AUC), maximum plasma concentration (C_{max}), and trough plasma concentration (C_{trough}), simulated following both 10 mg/kg Q2W (clinical regimen) and a flat-dose regimen of 800 mg Q2W, as separately described.[16,20] These were considered the reference exposures for comparison. Avelumab exposure metrics after single dose and at steady-state in the aRCC analysis population were derived from the individual

parameter estimates from the final aRCC PopPK model (using the closed form solution of the PopPK model, as done previously[20]) and were then plotted alongside the reference exposure metrics for both weight-based and flat-dose regimens.[16] The model was then used to obtain simulated avelumab exposures in patients with aRCC at the extremes of bodyweight (2.5th, 50th, and 97.5th percentiles) following both weight-based and flat-dosing regimens, through the $SIMULATION method in NONMEM using the final parameter estimates (including intersubject and residual error) with 1000 repetitions for each bodyweight.

Exposure-response safety analyses

Avelumab monotherapy E-R relationships for safety have been previously characterized in mMCC and UC patient populations receiving monotherapy.[16] For the aRCC patient population, safety and PK data were collected from 488 treatment-naive patients from the JAVELIN Renal 100 and Renal 101 (treatment arm only) trials and were used to build exposure-safety models. The relationships were evaluated between avelumab single-dose and steady-state exposure metrics from the aRCC PopPK model and the probability of experiencing the following AEs: treatment-emergent AEs (TEAEs) grade ≥3, immune-related AEs (irAEs) of any grade, and infusion-related reactions (IRRs) of any grade. Other AE end points of interest were not evaluated due to insufficient data.

A base model was developed for each of the safety end points using binomial logistic regression with a logit link function. The most significant avelumab exposure metric, as determined using the model deviance, was selected for incorporation into each respective base model. For model adequacy, the Hosmer-Lemeshow (HL) test[25,26] was used to assess whether or not the observed event rates matched the expected event rates in subgroups of the model population; evaluation included the observed and predicted function values as well as χ^2 value of the HL, degrees of freedom, and p value of the HL test. Calibration plots of observed versus predicted event rates in these subgroups were also used to assess goodness of fit. For model validation, the C index (or area under the receiver-operating characteristic [ROC] curve) was calculated and used to evaluate the performance of the model by quantifying the ability of the model to discriminate between patients having or not having the outcome of interest. The characterization of avelumab E-R for safety was performed using R version 3.4.1 and implementing the glm (family = "binomial") functions in R.

In addition to the exposure metrics derived from the clinical regimen, steady-state exposures in the aRCC population were predicted following a flat-dose regimen of 800 mg Q2W. The predicted avelumab exposures after a 10 mg/kg Q2W regimen and an 800 mg Q2W regimen in the aRCC patient population were used along with the final exposure-safety models to simulate the predicted probability of the key safety events under both dosing regimens.

RESULTS

Population PK analysis

The PopPK analysis contained dosing information, serum avelumab concentration information, and various demographic treatment information for 2315 patients receiving avelumab (1827 patients were from the avelumab solid-tumor monotherapy PopPK data set, and 488 patients were from the 2 aRCC clinical trials investigating avelumab plus axitinib combination therapy). Patients in this study had a median baseline weight of 81.5 kg (range, 44.2–143.0 kg). The serum avelumab concentrations, particularly C_{trough} values (which represented most of the observed data in aRCC), overlapped in both aRCC clinical trials; furthermore, they overlapped with the previous solid-tumor monotherapy populations (Figure S1).

Based on our PopPK model for avelumab, the parameters and distributions were similar in patients with aRCC receiving avelumab plus axitinib combination therapy and patients with solid tumors receiving avelumab monotherapy (Table 1; Table S1). Furthermore, no changes were notable in the parameter estimates from this model compared with the previous full PopPK model.[20] The mean (coefficient of variation [%CV]) baseline CL of avelumab in the aRCC population is 0.0279 L/h (28%), similar to the prior estimated CL of 0.0289 L/h (30%), based on the model using avelumab monotherapy. There is no evidence of drug-drug interaction (DDI) or altered PK of avelumab when administered in combination with axitinib in this population, and neither antidrug antibody (ADA) nor PD-L1 status appeared to affect avelumab PK to a clinically meaningful extent.

The PK data were generally well-described by the model. There was no evidence of model mis-specification, such that the pre-established PopPK structural model without full covariate effects, as used to characterize the solid-tumor monotherapy treatment population, was still appropriate for characterizing the PopPK of avelumab when used in combination with axitinib in treatment-naive patients with aRCC (Figure S2).

TABLE 1 Final parameter estimates for PopPK model to characterize avelumab PK in patients with aRCC[a]

Parameter	Value	RSE (%)	95% CI	Shrinkage, %
θ_{CL}, L/h	0.0269	1.026	0.02636–0.02744	13.92
θ_{V1}, L	3.196	0.7824	3.147–3.245	38.8
θ_{V2}, L	0.7278	6.505	0.635–0.8206	54.68
θ_{Q}, L/h	0.3352	12.24	0.02548–0.04157	–
$\theta_{I_{max}}$	−0.08533	16.75	−0.1134 to −0.05732	34.48
$\theta_{T_{50}}$, days	99.24	6.931	85.76–112.7	–
θ_{γ}	2.086	5.294	1.87–2.303	–
$\theta_{\text{weight on CL}}$	0.4714	6.402	0.4123–0.5306	–
$\theta_{\text{weight on V1}}$	0.4694	6.79	0.4069–0.5319	–
$\theta_{\text{weight on V2}}$	0.5826	5.183	0.5234–0.6418	–
$\sigma_{\text{proportional error}}$[b]	0.1742	2.416	0.1659–0.1824	13.79
$\sigma_{\text{additive error}}$[b]	2.168	7.382	1.845–2.482	–
ω^2_{CL}	0.09339	30.56	0.084–0.1028	–
$\omega^2_{V_1}$	0.03776	19.43	0.03229–0.04323	–
cov_{CL-V_1}	0.03048	17.46	0.02416–0.03681	–
$\omega^2_{V_2}$	1.204	109.7	0.9567–1.451	–
cov_{CL-V_2}	0.08418	29.01	0.04497–0.1234	–
$\text{cov}_{V_1-V_2}$	0.01799	13.41	−0.01453 to 0.0505	–
$\omega^2_{I_{max}}$	0.1052	32.44	0.07588–0.1346	–

Abbreviations: aRCC, advanced renal cell carcinoma; CI, confidence interval; CL, baseline clearance (at time = 0); cov, covariance between the interindividual variability of the two parameters; I_{max}, the maximal effect of time on CL; PK, pharmacokinetic; PopPK, population pharmacokinetic; Q, intercompartmental clearance; RSE, relative standard error; T_{50}, time at which 50% of I_{max} is achieved; V_1, central volume; V_2, peripheral volume; γ, shape parameter.

[a]Final model results, including 2315 patients in PopPK analysis data set (solid-tumor monotherapy and aRCC combination treatment populations).

[b]Shrinkage reported in table row for proportional error is the shrinkage corresponding to both σs (proportional and additive).

Simulations to support flat dosing of avelumab in aRCC

Across all metrics, the predicted exposures for avelumab plus axitinib in the aRCC analysis population overlapped with the prior reference simulations in the solid-tumor monotherapy treatment population for the 10 mg/kg Q2W regimen, and to a greater degree for the 800 mg Q2W flat-dose regimen (Figure 1; Figure S3). Furthermore, the simulated exposure distributions overlapped across body-weight extremes (percentiles of 2.5, 50, and 97.5) with weight-based or flat dosing (Figure 2).

Exposure-response analysis for safety in aRCC

Univariate analysis of TEAEs of grade ≥3 indicated that the most significant exposure metric based on model deviance was C_{trough} after a single dose ($C_{trough,sd}$), with an odds ratio of 0.970 (95% confidence interval [CI]: 0.954–0.987) per μg/ml change in concentration. For any-grade irAEs, no exposure metrics were significantly associated, but the strongest (yet still insignificant) association was avelumab C_{max} after a single dose ($C_{max,sd}$), with an odds ratio of 1.000 (95% CI: 0.999–1.010) per μg/ml change in concentration (Table 2; Figure 3). Translated, a relatively large increase in exposure, such as that between the 5th and 95th percentile of single-dose C_{max} in the aRCC population, is estimated to increase the probability of an irAE of any grade by no more than 11%. This demonstrates a relatively flat E-R relationship. The $C_{trough,sd}$ was the most significant exposure metric associated with any-grade IRRs, with an odds ratio of 0.963 (95% CI: 0.944–0.981) per μg/ml change in concentration (Table 2). All E-R models had insignificant HL test results, suggesting good agreement between the observed and predicted probabilities; combined with other evaluations, there were no signs of lack of goodness of fit for any model. Based on the C index, all E-R models had no better than "poor" model discrimination.

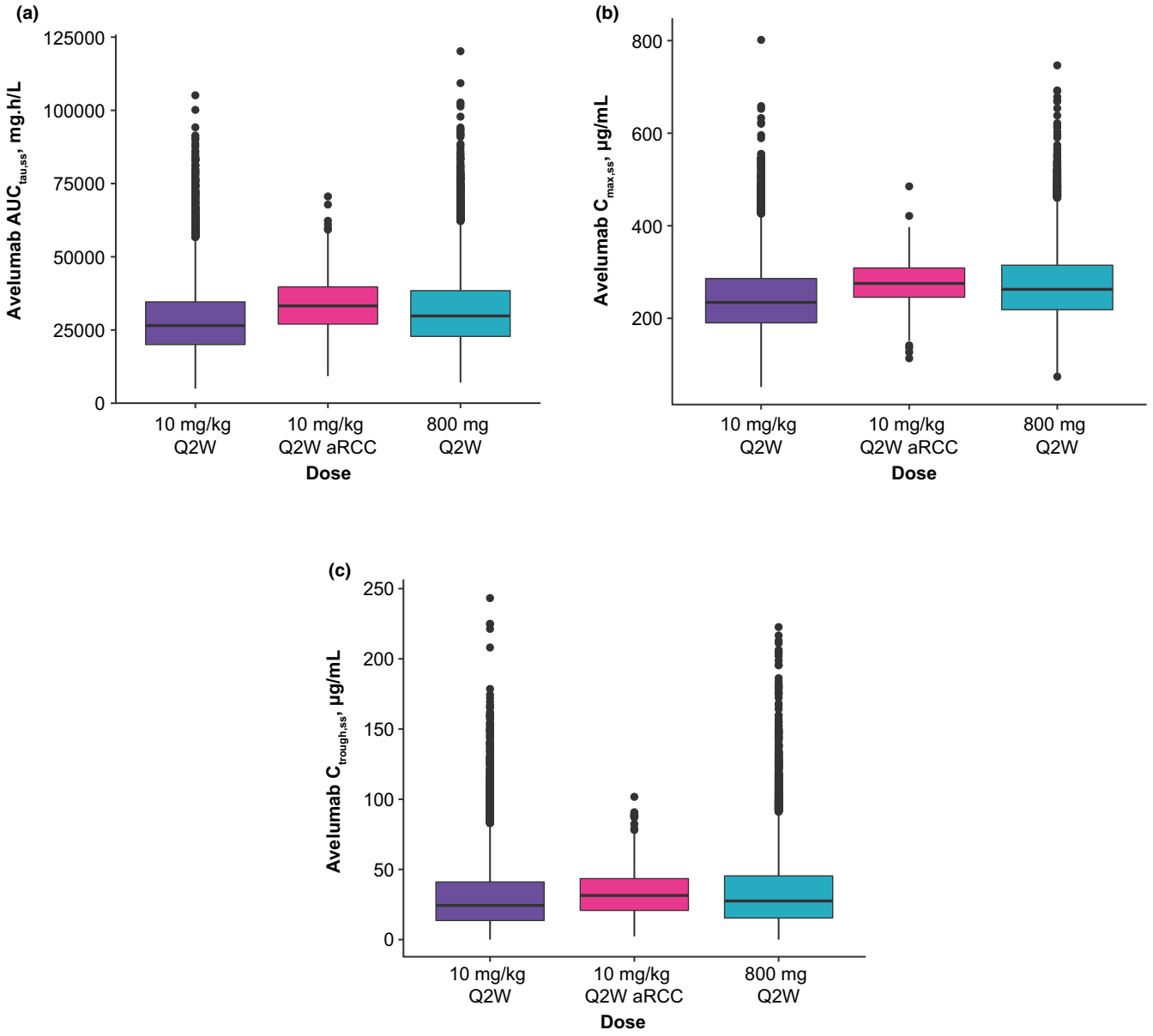

FIGURE 1 Exposures for avelumab plus axitinib in the aRCC population: (a) $AUC_{tau,ss}$, (b) $C_{max,ss}$, and (c) $C_{trough,ss}$. Pink boxplot is exposure (derived from individual parameters) in aRCC population (488 patients) receiving combination treatment avelumab 10 mg/kg Q2W plus axitinib using the current PopPK model (described in this report). The purple and teal boxplots are previously simulated reference exposures following 10 mg/kg Q2W and 800 mg Q2W, respectively, using the previous PopPK model in solid-tumor monotherapy populations. aRCC, advanced renal cell carcinoma; $AUC_{tau,ss}$, steady-state area under the concentration-time profile of dosing interval; $C_{max,ss}$, steady-state maximum concentration; $C_{trough,ss}$, steady-state trough concentration; PopPK, population pharmacokinetic; Q2W, every 2 weeks

In all E-R models, additional covariates were explored with the avelumab exposure metric retained in the model. No intrinsic or extrinsic factors were found to have a clinically meaningful impact on the incidence of the various AE categories, including ADA status, PD-L1 status, race, and body weight. Of important note, the simulated probability of experiencing any of these described AEs for the overall aRCC population showed a completely overlapping distribution between the two dose regimens (weight-based and flat dosing), with no change in the mean probability between groups (Figure 4).

DISCUSSION

The collection of PopPK and E-R modeling and simulation work presented here was conducted to support a supplemental application and amendment to the approved prescribing information for avelumab administration in multiple

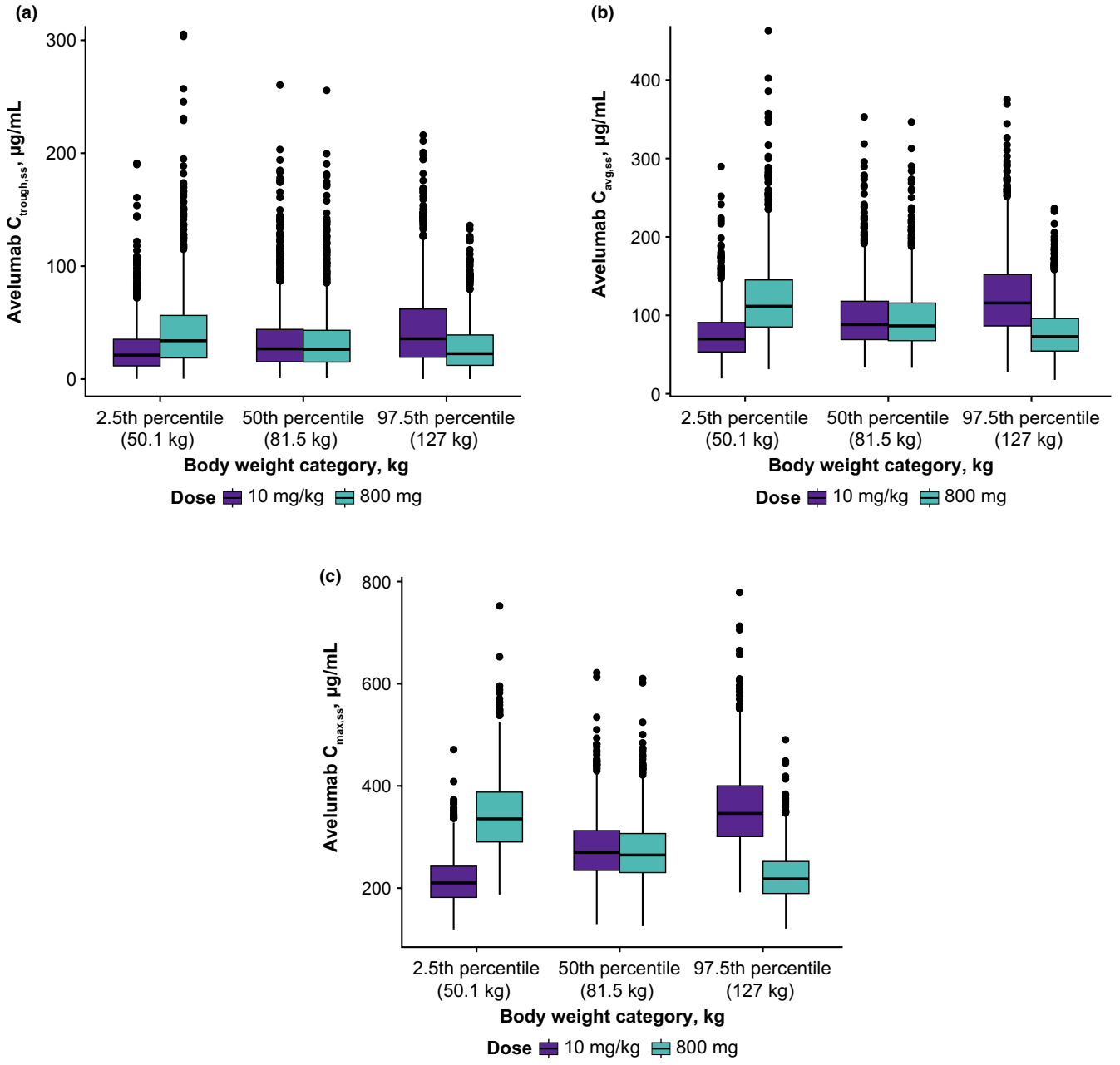

FIGURE 2 Box and whisker plots for the simulated (a) $C_{trough,ss}$, (b) $C_{avg,ss}$, and (c) $C_{max,ss}$ at steady state for the weight-based (10 mg/kg Q2W) and flat (800 mg Q2W) dosing regimens by extremes of weight in the aRCC population. aRCC, advanced renal cell carcinoma; $C_{avg,ss}$, steady-state average concentration; $C_{max,ss}$, steady-state maximum concentration; $C_{trough,ss}$, steady-state trough concentration; PopPK, population pharmacokinetics

TABLE 2 Exposure-response safety analysis by safety end point and model

	Grade ≥3 TEAEs		Any-grade irAEs		Any-grade IRRs	
	Variable	**OR[a] (95% CI)**	**Variable**	**OR[a] (95% CI)**	**Variable**	**OR[a] (95% CI)**
Base model	$C_{trough,sd}$	0.970 (0.954–0.987)	$C_{max,sd}$	1.000 (0.999–1.010)	$C_{trough,sd}$	0.963 (0.944–0.981)

Abbreviations: CI, confidence interval; $C_{max,sd}$, maximum concentration after single dose; $C_{trough,sd}$, trough concentration after single dose; irAE, immune-related adverse event; IRR, infusion-related reaction; NA, not applicable; OR, odds ratio; TEAE, treatment-emergent adverse event.

[a]Per single unit (1 µg/ml).

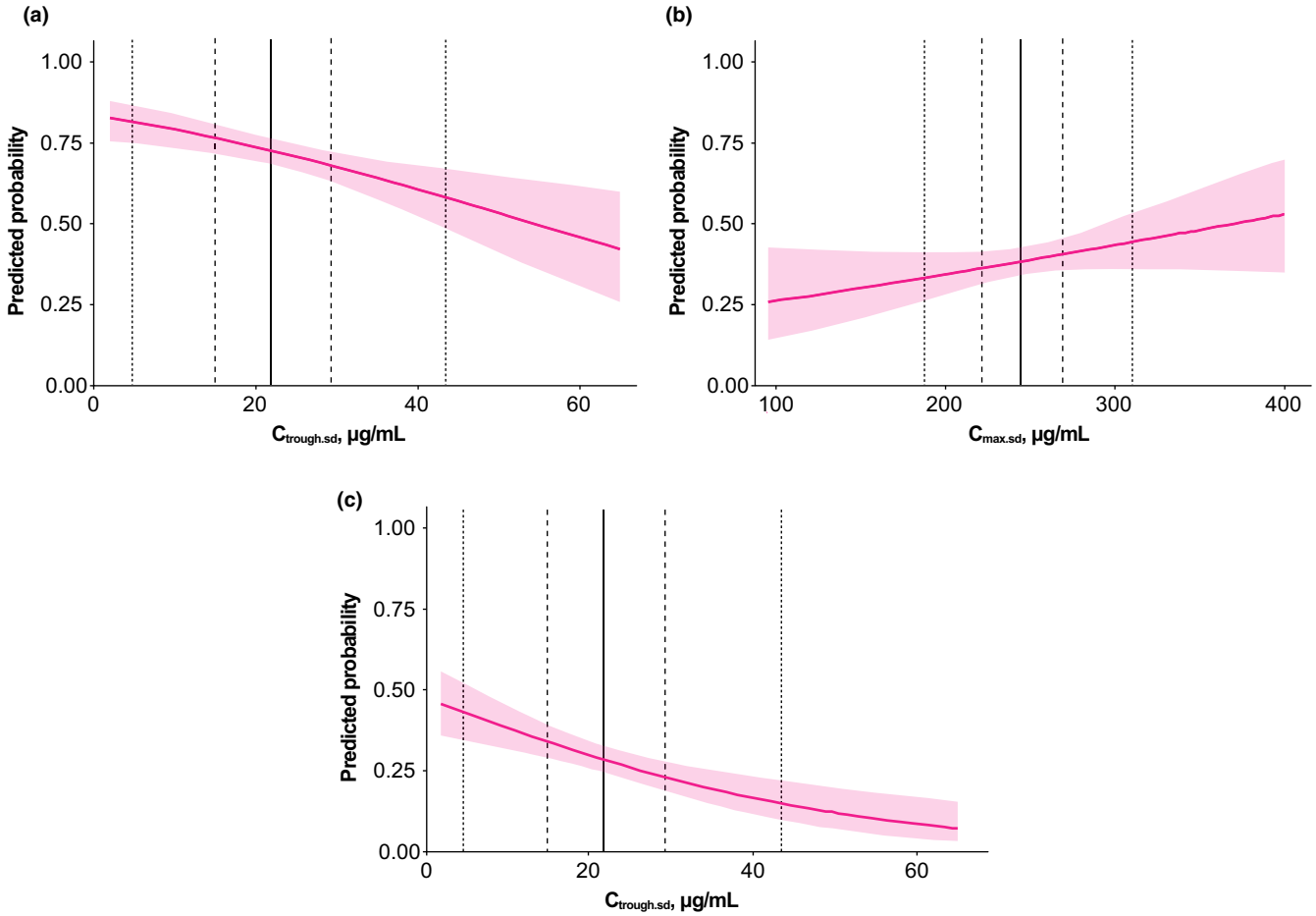

FIGURE 3 Probability of (a) TEAEs grade ≥3 by avelumab $C_{trough,sd}$, (b), any-grade irAEs by $C_{max,sd}$, and (c) any-grade IRRs by $C_{trough,sd}$. Horizontal line and corresponding shaded region represent predicted probability and 95% CI. Solid gray line represents the median $C_{trough,sd}$ or $C_{max,sd}$. Gray dashed lines represent the 25th and 75th percentiles and Dotted gray lines represent the fifth and 95th percentiles. CI, confidence interval; $C_{max,sd}$, maximum concentration after single dose; $C_{trough,sd}$, trough concentration after single dose; irAE, immune-related adverse event; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event

jurisdictions; importantly, this work, along with additional exposure-efficacy analyses,[27] supports a dosing regimen that was not used in the pivotal study for this indication. To date, this method has been used to support successful approvals in regions including the United States and Europe.[4,21]

Population PK analysis

Here, we compare the PopPK of avelumab in combination with axitinib in previously untreated patients with aRCC with the PK of avelumab in patients with solid tumors treated with avelumab monotherapy. It was assumed that DDI potential between the two agents would be minimal; PK evaluation of axitinib demonstrated comparable exposure to that following single agent use, with no evidence of avelumab impacting axitinib PK.[28] Furthermore, axitinib was not expected to impact avelumab PK, as large molecule drugs are primarily eliminated through proteolytic degradation and have minimal DDIs with small molecule therapeutics. We demonstrate that the PK of avelumab are similar in aRCC and solid tumor populations, as evidenced by overlapping exposures and the resulting PK parameters being nearly unchanged; thus, there is no evidence of DDIs or altered PK of avelumab when administered in combination with axitinib in this population. Specifically, the baseline CL of avelumab estimated in our PopPK model was similar to that estimated in the monotherapy model, and the change in CL over time of less than 10% was in line with the solid tumor population, for which various tumor types were uniquely characterized. Based on goodness-of-fit plots and diagnostics, our model is suitable for making predictions and simulations of avelumab exposure in this population of patients with aRCC treated in combination with axitinib, to support flat-dose conversion and E-R analyses for safety and efficacy.

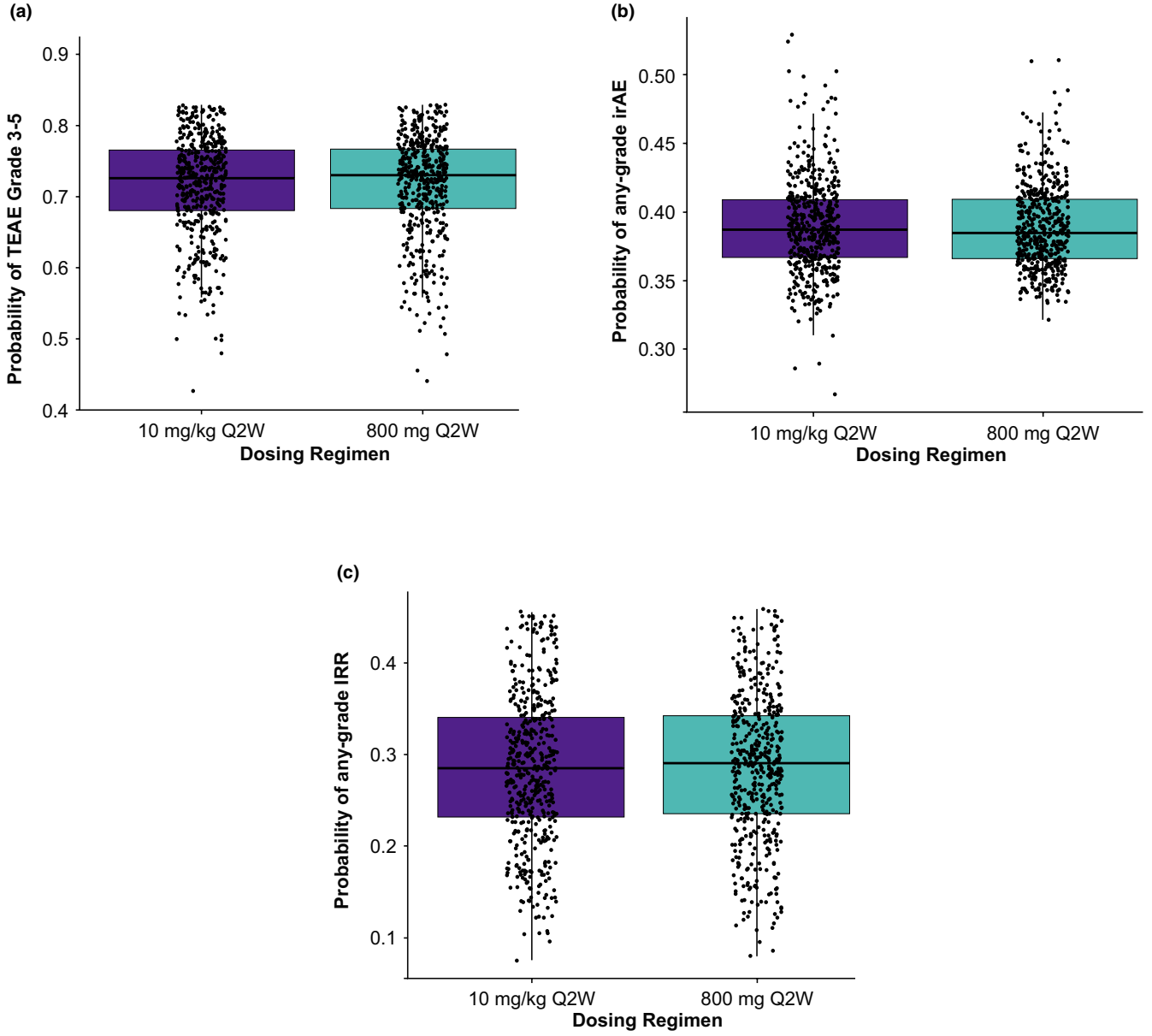

FIGURE 4 Probability of experiencing (a) grade ≥3 TEAEs, (b) any-grade irAEs, and (c) any-grade IRRs for the avelumab weight-based 10 mg/kg Q2W and flat 800 mg Q2W doses in the aRCC population receiving combination therapy with axitinib. irAE, immune-related adverse reaction; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event; Q2W, every 2 weeks

The present PopPK analysis to characterize avelumab PK in the aRCC population leveraged the rich prior information available on the PK behavior of avelumab when administered as monotherapy in patients with solid tumors,[16,20] work that included extensive evaluation and characterization of intrinsic and extrinsic factors. Traditional model building and formal evaluation of covariates impacting the PK of avelumab in the aRCC population was not pursued, as the structural PK model was already established, and the previous PopPK model results served as a robust comparison. In agreement with the previous avelumab and other mAb PopPK models, the only covariate used in this model was that of body weight on CL and volume parameters. The appropriateness of the current, streamlined modeling approach is supported by the similarity of the results across models and populations, as well as the model diagnostics. This "fit-for-purpose" approach to postapproval dose optimization and confirmation, which entailed using the base structural component of an already established, full-covariate PopPK model built with robust PK data across dose levels, may work well for other agents in which initial indications or regulatory approvals have been established and additional indications and/or treatment combinations are introduced.

Simulations to support flat dosing of avelumab in aRCC

The predicted exposures of avelumab 10 mg/kg in combination with axitinib, derived from the individual estimates obtained from the aRCC PopPK model, substantially overlapped with previously simulated exposures generated to support the approved 800-mg flat-dose regimen for avelumab monotherapy in patient populations with mMCC and UC.[16,20] This similarity in exposure served as the primary evidence to support a flat-dose extension in this patient population and treatment setting, with additional support from exposure-safety and exposure-efficacy analyses. Of note, the range of baseline body weight in the aRCC analysis population (median: 81.5 kg [range: 44.2–143 kg]) differed slightly from the population in the previous PopPK model and subsequent simulations to support flat dosing in mMCC and UC (median: 70.6 kg [range: 30.4–204 kg). This likely accounts for the minor differences in exposure (particularly the median) following weight-based dosing in the two populations. Furthermore, across body-weight extremes (percentiles of 2.5, 50, and 97.5), there was overlap in the distributions of exposure simulated following weight-based or flat dosing (Figure 2) in the aRCC population. Similar to the mMCC and UC findings,[16] the exposure-weight relationship is reversed with the flat-dose regimen; that is, low-weight patients experience the highest exposure and vice versa.

Exposure-response analysis for safety in aRCC

In the combination setting of avelumab and axitinib, there was no specific expectation of potentiation of toxicities, and clinical trial results demonstrated the frequency and severity of AEs were generally consistent with monotherapy.[22] In exposure-safety analyses, no observed trend in the E-R relationship was considered clinically relevant. Overall, none of the exposure parameters or any other covariates explored were strong predictors of the AE endpoints of interest; model discriminatory performance for all models was "failed" or "poor" as assessed by ROCs. The directionally negative association with exposure estimated for TEAEs grade ≥3 and any-grade IRRs, suggesting a lower probability of AEs at higher exposure, is likely confounded by multiple factors, including disease burden, infusion interruptions, and treatment delays; furthermore, the PK sample collection schedule (mostly collection at C_{trough}) limited the avelumab exposure information available in cases of infusion interruptions. Caution is needed in the interpretation of these results due to confounded exposure-safety relationships; these analyses evaluate association and not causation.

The E-R analyses for safety end points were similar to those previously estimated for avelumab monotherapy in populations of patients with MCC and UC, and no appreciable differences were noted in the exposure-safety relationship when used in the aRCC population in combination with axitinib. Importantly, the simulated probability of any safety event was indistinguishable between the two dosing regimens (10 mg/kg Q2W vs. 800 mg Q2W), with a completely overlapping distribution and no change in the mean probability between groups. The probability of an irAE of any grade does not change more than ~10% for either the low weight (2.5th percentile) or high weight (97.5th percentile) patients, when switching between a weight-based and flat dosing regimen for avelumab. Similarly, with flat dosing, the difference in predicted single-dose C_{max} between patients at the extremes of bodyweight (~54% higher exposure for low weight patients), is also not projected to alter the probability of an irAE by more than ~10%. Therefore, the exposure-safety predictions provide additional justification for the change to a flat 800 mg Q2W avelumab dosing regimen in combination with axitinib in aRCC.

CONCLUSION

These analyses using PK and E-R modeling and simulation provide support for the labeling of an 800-mg flat dose of avelumab in combination with axitinib in patients with treatment-naive aRCC.

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CONFLICT OF INTEREST

J.C. Masters and A. di Pietro are employees of Pfizer, and own stock and other ownership interests in Pfizer. A. Khandelwal is an employee of the healthcare business of Merck KGaA, Darmstadt, Germany, owns stock and other ownership interests in Merck KGaA, Darmstadt, Germany, and holds patents, royalties, or other intellectual property in the healthcare business of Merck KGaA, Darmstadt, Germany. H. Dai is an employee of EMD Serono, and owns stock and other ownership interests in Merck KGaA, Darmstadt, Germany. S. Brar was an employee of Pfizer.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. J.M., S.B., A.dP., and A.K. designed the research. J.M. and S.B. performed the research. J.M. analyzed the data. J.M., S.B., A.K., and H.D. contributed new reagents/analytical tools.

DATA AVAILABILITY STATEMENT

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

REFERENCES

1. Darvin P, Toor SM, Sasidharan Nair V, Elkord E. Immune checkpoint inhibitors: recent progress and potential biomarkers. *Exp Mol Med*. 2018;50:1-11.
2. Boyerinas B, Jochems C, Fantini M, et al. Antibody-dependent cellular cytotoxicity activity of a novel anti-PD-L1 antibody avelumab (msb0010718c) on human tumor cells. *Cancer Immunol Res*. 2015;3:1148-1157.
3. Hamilton G, Rath B. Avelumab: combining immune checkpoint inhibition and antibody-dependent cytotoxicity. *Expert Opin Biol Ther*. 2017;17:515-523.
4. Bavencio (avelumab). *Prescribing Information*. EMD Serono; 2020.
5. Chin K, Chand VK, Nuyten DSA. Avelumab: clinical trial innovation and collaboration to advance anti-PD-L1 immunotherapy. *Ann Oncol*. 2017;28:1658-1666.
6. Marciscano AE, Gulley JL, Kaufman HL. Avelumab: is it time to get excited? *Expert Rev Anticancer Ther*. 2018;18:815-821.
7. Kaufman HL, Russell J, Hamid O, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncol*. 2016;17:1374-1385.
8. Apolo AB, Infante JR, Balmanoukian A, et al. Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: results from a multicenter. *Phase Ib Study. J Clin Oncol*. 2017;35:2117-2124.
9. Patel MR, Ellerton J, Infante JR, et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. *Lancet Oncol*. 2018;19:51-64.
10. Bai S, Jorga K, Xin Y, et al. A guide to rational dosing of monoclonal antibodies. *Clin Pharmacokinet*. 2012;51:119-135.
11. Freshwater T, Kondic A, Ahamadi M, et al. Evaluation of dosing strategy for pembrolizumab for oncology indications. *J Immunother Cancer*. 2017;5:43.
12. Lala M, Li TR, de Alwis DP, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. *Eur J Cancer*. 2020;131:68-75.
13. Stroh M, Winter H, Marchand M, et al. Clinical pharmacokinetics and pharmacodynamics of atezolizumab in metastatic urothelial carcinoma. *Clin Pharmacol Ther*. 2017;102:305-312.
14. Zhao X, Suryawanshi S, Hruska M, et al. 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. *Ann Oncol*. 2017;28:2002-2008.
15. Long GV, Tykodi SS, Schneider JG, et al. Assessment of nivolumab exposure and clinical safety of 480mg every 4 weeks flat-dosing schedule in patients with cancer. *Ann Oncol*. 2018;11:2208-2213.
16. Novakovic AM, Wilkins JJ, Dai H, et al. Changing body weight-based dosing to a flat dose for avelumab in metastatic Merkel cell and advanced urothelial carcinoma. *Clin Pharmacol Ther*. 2020;107:588-596.
17. Hendrikx JJMA, Haanen JBAG, Voest EE, Schellens JHM, Huitema ADR, Beijnen JH. Fixed dosing of monoclonal antibodies in oncology. *Oncologist*. 2017;22:1212-1221.
18. Baik CS, Rubin EH, Forde PM, et al. Immuno-oncology clinical trial design: limitations, challenges, and opportunities. *Clin Cancer Res*. 2017;23:4992-5002.
19. Louedec FL, Leenhardt F, Marin C, Chatelut É, Evrard A, Ciccolini J. Cancer immunotherapy dosing: a pharmacokinetic/pharmacodynamic perspective. *Vaccines*. 2020;8:632.
20. Wilkins JJ, Brockhaus B, Dai H, et al. Time-varying clearance and impact of disease state on the pharmacokinetics of avelumab in Merkel cell carcinoma and urothelial carcinoma. *CPT Pharmacometrics Syst Pharmacol*. 2019;8:415-427.
21. Bavencio (avelumab). *EPAR Product Information*. EMD Serono; 2021.
22. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380:1103-1115.
23. Choueiri TK, Motzer RJ, Rini BI, et al. Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma. *Ann Oncol*. 2020;31:1030-1039.
24. Choueiri TK, Larkin J, Oya M, et al. Preliminary results for avelumab plus axitinib as first-line therapy in patients with advanced clear-cell renal-cell carcinoma (JAVELIN Renal 100): an open-label, dose-finding and dose-expansion, phase 1b trial. *Lancet Oncol*. 2018;19:451-460.
25. Hosmer DW, Lemeshow S, Sturdivant RX. *Applied Logistic Regression*, 3rd ed. Wiley; 2013.
26. Agresti A, Kateri M. Categorical data analysis. In: Lovric M, ed. *International Encyclopedia of Statistical Science*. Springer-Verlag, Berlin Heidelberg; 2011:206-208.
27. Bello C, Brar S, Masters JC, et al. Exposure-response (E-R) analysis of efficacy for avelumab in combination with axitinib in patients with advanced renal cell carcinoma (aRCC) in JAVELIN Renal 101. *Proc Annu Meet Am Assoc Cancer Res*. 2021;81(13_Suppl): Abstract 1364.
28. Inlyta (axitinib). *Prescribing Information*. Pfizer; 2020.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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