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Alternative Dosing Regimens of Tislelizumab Using a Pharmacometrics Model-Based Approach

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ABSTRACT

Tislelizumab 200 mg once every 3 weeks (Q3W) is approved for the treatment of multiple cancers. We used a model-based approach to propose three alternative dosing regimens, 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W, with the aims of providing flexible treatment regimens compatible with background chemotherapy and/or reducing infusion visits. A previously developed population pharmacokinetic model was used to simulate pharmacokinetic exposure of the alternative regimens. Regulatory guidance on alternative dosing was used to define pharmacokinetics-based criteria. Alternative doses were selected by simulation, exposure matching, and comparison to the reference regimen of 200 mg Q3W. Deviations from pharmacokinetics-based criteria were bridged using appropriate safety and efficacy references and exposure–response analyses. All three alternative dosing regimens produced comparable exposures versus 200 mg Q3W. Although simulated peak serum concentration (C_{max}) at 300 mg Q4W and 400 mg Q6W was higher versus 200 mg Q3W, this was below the C_{max} of the 5 mg/kg Q3W safety reference. And while the trough serum concentration (C_{trough}) for 400 mg Q6W was slightly lower versus 200 mg Q3W, it was 10.7% higher than the 2 mg/kg efficacy reference C_{trough}, and therefore, within the concentration range in which a flat exposure–efficacy relationship of tislelizumab has been established. Tislelizumab regimens of 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W are expected to result in similar safety and efficacy as 200 mg Q3W.

1 | Introduction

Tislelizumab (BGB-A317) is a humanized immunoglobulin G4 monoclonal anti–programmed cell death protein-1 (PD-1) antibody that binds to PD-1 with high affinity and specificity [1]. Engineered to minimize Fc gamma receptor 1 binding on macrophages, tislelizumab limits antibody-dependent cellular phagocytosis, a process that activates antibody-dependent, macrophage-mediated killing of T effector cells and has been shown to compromise the antitumor activity of other anti–PD-1 monoclonal antibodies [1]. Tislelizumab is being developed for the treatment of patients with solid tumors as a monotherapy and/or in combination with other therapies and has been evaluated across a range of doses (0.5–10 mg/kg

Tian Yu and Srikumar Sahasranaman were employed at BeiGene at the time this study was initiated.

Summary

- What is the current knowledge on the topic?
  - Pharmacokinetic modeling supports a flat-dose regimen for tislelizumab, an anti–PD-1 antibody, across multiple oncologic indications. No dose modifications of tislelizumab are needed based on intrinsic and extrinsic factors, and there is no clinically relevant dose or exposure dependency in terms of efficacy and safety measures for tislelizumab. The approved dose of tislelizumab is 200 mg once every 3 weeks (Q3W).
- What question did this study address?
  - Do the alternate regimens of tislelizumab, 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W, meet the FDA's guidance on the pharmacokinetics-based criteria for the approval of alternative dosing regimens for PD-1/PD-L1 inhibitors and/or have sufficient clinical data to support similar safety and efficacy compared with the 200 mg Q3W regimen?
- What does this study add to our knowledge?
  - These analyses support the lack of a clinically relevant dose or exposure dependency for tislelizumab in terms of objective response rate and safety measures among patients with advanced/metastatic solid tumors. The proposed 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W alternative dosing regimens have similar safety and efficacy outcomes to the 200 mg Q3W regimen.
- How might this change clinical pharmacology or translational science?
  - A model-based approach may be used to support approvals of alternate dosing regimens while maintaining the same therapeutic benefit. The alternative dosing regimens of tislelizumab have the potential to offer patients flexible treatment options that are compatible with background chemotherapy, and/or reduce the number of infusion visits.

intravenously once every 2 weeks [Q2W] or Q3W) in the phase I BGB-A317-001 study [2]. After demonstrating robust antitumor efficacy and a tolerable safety profile, tislelizumab—as monotherapy or in combination with chemotherapy at a fixed dose of 200 mg Q3W administered by intravenous infusion—received approval from the National Medical Products Administration in China for 13 indications, from the European Medicines Agency for six indications [3], and from the US Food and Drug Administration (FDA) for three indications [4]. Alternative dose regimens of tislelizumab are not currently approved by any regulatory agency yet.

Alternative dosing regimens of tislelizumab have the potential to provide flexible treatment options that are compatible with background chemotherapy and to reduce the number of infusion visits for patients. Several alternative dosing regimens have been approved for other anti–PD-1 and anti–programmed death-ligand 1 (PD-L1) antibodies, such as pembrolizumab, nivolumab, and atezolizumab, using modeling and simulation-based approaches [5–9].

Recently, the FDA published guidance on the pharmacokinetics-based criteria for approval of alternative dosing regimens for PD-1/PD-L1 inhibitors [10]. The clinical pharmacology characteristics of tislelizumab, pharmacometrics-based analyses, and clinical evidence presented here collectively form the basis of proposing alternative doses of tislelizumab.

A population pharmacokinetic (popPK) model for tislelizumab based on pharmacokinetic data from 2596 patients across 12 clinical studies of tislelizumab has been published previously [11, 12]. Pharmacokinetic data obtained after both Q2W and Q3W regimens were included in the model building. PopPK modeling of tislelizumab in patients with solid tumors and hematological cancer demonstrated that the pharmacokinetic profile of tislelizumab is linear. The absence of covariate effects with clinical relevance supported a consistent dosing regimen for tislelizumab and that dose adjustment is not required for specific patient populations [11–13]. In clinical trials, tislelizumab did not have any dose-limiting toxicities up to 10 mg/kg Q2W [11–13]. Model-based analyses have demonstrated that the pharmacokinetic profile of tislelizumab is similar across ethnicities and tumor types, and that tislelizumab demonstrated a relatively flat exposure–response relationship across a broad range of exposures [11–13].

The popPK model was evaluated by external model validation against the pharmacokinetic profiles of patients receiving alternative dosing regimens from the following clinical studies: BGB-A317-315 (tislelizumab adjuvant phase, 400 mg Q6W), BGB-A317-212 (tislelizumab 400 mg Q6W), and BGB-A317-Fruquintinib-201 (tislelizumab 300 mg Q4W). The popPK model adequately described the central tendency and variability of the observed serum tislelizumab concentrations following intravenous administration of the alternative dosing regimens, indicating the model's robustness in the simulation of alternative dosing regimens [11–13]. This was followed by simulations in which the pharmacokinetic exposure parameters for 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W alternative dosing regimens were compared with the reference dosing regimen of 200 mg Q3W and with additional efficacy/safety references.

To further demonstrate the comparable efficacy and safety of the alternative dosing regimens to the approved reference dosing regimen of 200 mg Q3W, we conducted exposure–response analyses using data from four clinical studies that encompassed an exposure range that covered the simulated exposures of the alternative doses and also included non-small cell lung cancer (NSCLC), esophageal squamous cell carcinoma (ESCC), and gastric cancer (GC) as the indications of key interest.

In this study, we provide the results of a pharmacometrics-based approach used to determine the proposed 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W alternative dosage regimens of tislelizumab. The simulated exposures were verified against the FDA guidance on alternative doses for anti–PD-(L)1 antibodies. Additional clinical evidence has been provided where applicable.

2 | Methods

2.1 | Study Design and Procedures

All relevant institutional review boards/independent ethics committees reviewed the protocols and amendments and approved the studies, which were carried out in accordance with the International Conference on Harmonisation Good Clinical Practice Guideline, the principles of the Declaration of Helsinki, and local laws and regulations.

2.1.1 | Pharmacometric Analysis

2.1.1.1 | External Model Validation and Selection of Doses for the Alternative Dosing Regimens. The alternative dosing regimens of tislelizumab 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W administered intravenously were determined by performing simulations using the previously developed popPK model that was based on data from 12 clinical studies [11, 12]. In accordance with FDA guidance [10], the alternative dosing regimens were selected by exposure matching to the reference dosing regimen of 200 mg Q3W to ensure that the average serum concentration ($C_{average}$) and trough serum concentration (C_{trough}) following the alternative dosing regimen at steady state and/or in the first least-common time interval were no more than 20% lower compared with those of the reference dosing regimen; and the geometric mean of peak serum concentration at steady state ($C_{max,ss}$) following the alternative dosing regimen did not increase more than 25% compared with that of the reference dosing regimen. The popPK model was externally validated using pharmacokinetic data collected from studies BGB-A317-212 [14], BGB-A317-315 [15], and BGB-A317-201 (validation dataset) in which alternative doses of tislelizumab were administered (Table S1). Model parameter estimation and model evaluation were implemented with NONMEM 7, version 7.5 (ICON Development Solutions, Ellicott City, Maryland, USA). Prediction-corrected visual predictive check (pcVPC) was used to show the time course of the predicted median and spread of concentrations (2.5th to 97.5th percentile) versus the observed data. A total of 1000 trial replicates were simulated using the observed covariates and dose regimens for each subject, the final model parameter estimates, simulated patient-specific random effects, and residual errors. The 95% prediction interval from the 1000 simulated trials of the median, 2.5th, and 97.5th percentiles of the concentration–time profiles, normalized with dose and covariate effects, were overlaid with the corresponding observed data to assess the overall agreement of the model predictions (Figure S1).

2.1.1.2 | Simulation of Exposures for Alternative Dosing Regimens. The pharmacokinetic profiles were simulated over the first least common dose interval (6 weeks for the 150 mg Q2W and 400 mg Q6W regimens and 12 weeks for the 300 mg Q4W regimen) and at steady state using the post hoc model individual pharmacokinetic parameters from the externally validated popPK model previously developed based on 12 studies. The pharmacokinetic parameters that were generated for each patient are listed in Table S2 for reference. These were C_{max}, $C_{average}$, and C_{trough} in the first least common multiple of the dosing interval relative to the 200 mg Q3W reference regimen and at steady state for 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W along with the reference dosing regimens for different simulation scenarios. Area under the concentration–time curves (AUCs) were calculated using the linear up/log down variant of the trapezoidal rule using R software version 4.2.3 (The R Foundation for Statistical Computing, Vienna, Austria). $C_{average}$ was calculated as the AUC over the respective time interval divided by the time of the interval. The aim of these comparisons was to ensure that the pharmacokinetic parameters of the alternative dosing regimens were in line with the pharmacokinetics-based criteria specified in the FDA guidance on supporting alternative dosing regimens of anti–PD-(L)1 treatments for patients with cancer [10].

Deviations from pharmacokinetics-based criteria were bridged using appropriate safety and efficacy references and supportive exposure–response analyses for efficacy and safety using a pool of four clinical studies that encompassed a range of tumor types and pharmacokinetic exposures. For the alternative dosing regimens of 300 mg Q4W and 400 mg Q6W, appropriate safety and efficacy references were also used, as the $C_{max,ss}$ was expected to be higher than the reference regimen of 200 mg Q3W and to account for any exposure differences for the longer dosing intervals.

The 2 mg/kg Q3W dose was selected as the efficacy reference as previous evaluation of the exposure–response relationship of tislelizumab demonstrated similar efficacy and a flat exposure–response relationship in the range of doses from 2 mg/kg and above [12]. The 5 mg/kg Q3W dose was selected as the safety reference because tislelizumab exposures at 5 mg/kg Q3W were higher than 400 mg Q6W, flat exposure–response relationships for safety endpoints, and also because clinical safety and tolerability data were available in a large number of patients in the BGB-A317-001 study (Table S1).

2.1.2 | Exposure–Response Analysis

Pooled exposure–response analyses were conducted using four clinical studies that included 1536 patients with ESCC, NSCLC, GC, and other solid tumors to bridge the benefit-risk profile of tislelizumab for the proposed 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W dosing regimens relative to the 200 mg Q3W reference regimen. The study pool of four clinical studies of tislelizumab monotherapy included two pivotal phase III studies, the BGB-A317-302 study in ESCC ($N = 254$) and the BGB-A317-303 study in NSCLC ($N = 532$), both of which used the dosing regimen of 200 mg Q3W, in addition to the phase IA/IB BGB-A317-001 study in solid tumors ($N = 450$) and the phase I/II BGB-A317-102 study in solid tumors ($N = 300$). Together, these studies encompassed a range of doses from 0.5 mg/kg to 10 mg/kg (Q2W or Q3W) as well as the 200 mg Q3W dose (Table S1). A summary of patient characteristics and demographics is presented in Table S3; a summary of clinical characteristics by objective response rate (ORR) is presented in Table S4 and a summary of ORR by tumor type in the

exposure–efficacy analysis dataset for patients with solid tumors is presented in Table S5.

ORR was the efficacy endpoint in the exposure–response efficacy analysis, and the safety endpoints comprised any treatment-emergent adverse event (TEAE) of grade ≥3, immune-mediated TEAEs, TEAEs leading to treatment discontinuation, infusion-related reactions (IRRs), TEAEs leading to dose modification, TEAEs of special interest (combination of immune mediated TEAEs and IRRs), and serious TEAEs.

Empirical Bayesian estimates of individual pharmacokinetic parameters for all of the tislelizumab-treated patients were derived from the popPK model previously described in Budha et al., 2023 [11]. The model-predicted $C_{average}$ of the first dose ($C_{avg,dose1}$) was used as the primary exposure endpoint in the exposure–response efficacy analysis, while the model-predicted $C_{max,ss}$ was used as the primary exposure endpoint in the exposure–response safety analysis.

The efficacy endpoint, ORR, and all safety endpoints were evaluated as binary outcomes (yes/no). Boxplots of tislelizumab exposures stratified by each endpoint were generated. The probability of response versus exposure in tislelizumab-treated patients was plotted, with probabilities calculated across sets of patients binned by exposure quantile. If an exposure–response trend was observed, further analysis with linear logistic regression models was performed with exposure metrics and other baseline covariates as potential predictors of the probability of events using R statistical software version 4.2.3.

2.1.3 | Safety Analysis Using Clinical C_{max} Cutoffs

Clinical data from the BGB-A317-001 study ($N=451$) was used to assess whether the safety profile at the 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W proposed dosing regimens would be comparable to the clinically evaluated safety profile in BGB-A317-001. In this methodology, the predicted geometric mean C_{max} for each alternative dosing regimen was used to categorize the incidence of selected TEAEs into two groups: patients with predicted $C_{max,ss}$ greater than and less than or equal to the predicted geometric mean C_{max}.

3 | Results

3.1 | External Model Validation and Selection of Doses for the Alternative Dosing Regimens

Simulated pharmacokinetic exposures of the 300 mg Q4W and 400 mg Q6W tislelizumab regimens were consistent with observed data supporting the robustness of the model. The pcVPC plots showed that the observed median, 2.5th, and 97.5th percentiles of the concentration–time profiles were generally contained within the simulation-based 95% confidence intervals for the corresponding model-predicted median in all validation patients (Figure S1). Therefore, the predictive performance of the model was considered satisfactory, with most of the observed data lying within the prediction intervals.

The 150 mg Q2W dosing regimen was determined via simulations and exposure matching to the reference regimen as tislelizumab at the dosing interval of Q2W was tested across a range of doses (0.5–10 mg/kg) in the phase I study, and those data were used to develop the popPK model. As shown in Figure 1a, the steady state peak concentrations were very similar, and trough concentrations were maintained above that of the 200 mg Q3W reference. Overlays of the pharmacokinetic profiles for tislelizumab 300 mg Q4W and 400 mg Q6W dosing regimens with the 200 mg Q3W reference over the first common time interval and at steady state are shown in Figure 1b,c, respectively. The peak concentrations at these higher doses were greater than the 200 mg Q3W reference; however, they were lower than the 5 mg/kg dose of tislelizumab safety reference, tested clinically in approximately 355 patients (phase IA and phase IB of BGB-A317-001, Table S1). Although the C_{trough} of the longer dosing interval of 400 mg Q6W trended slightly lower than the 200 mg Q3W reference, it was maintained above the 2 mg/kg Q3W tislelizumab efficacy reference (Figure S2).

3.2 | Simulation of Exposures for Alternative Dosing Regimens

3.2.1 | 150 mg Q2W

All pharmacokinetics-based criteria mentioned in the FDA guidance were met for the tislelizumab 150 mg Q2W dosing regimen. The $C_{average}$ and C_{trough} were not lower than those of the 200 mg Q3W reference regimen, and the $C_{max,ss}$ was not higher than that of the 200 mg Q3W reference regimen (Table 1).

3.2.2 | 300 mg Q4W

For the 300 mg Q4W dosing regimen, $C_{average}$ and C_{trough} met the prespecified pharmacokinetics-based criteria. Although C_{max} was 6.4% higher than the recommended limit of 25%, it was 18.7% lower when compared with the safety reference dosing regimen of 5 mg/kg Q3W (Table 2).

3.2.3 | 400 mg Q6W

For the 400 mg Q6W dosing regimen, $C_{average}$ met the prespecified pharmacokinetics-based criteria. However, C_{trough} was 28.4% lower and $C_{max,ss}$ was 52.2% higher than the reference dosing regimen of 200 mg Q3W and did not meet the pharmacokinetics-based criteria of 20% and 25%, respectively (Table 3). As a result, C_{trough} at steady state ($C_{trough,ss}$) at 400 mg Q6W was compared with the $C_{trough,ss}$ of 2 mg/kg Q3W as an efficacy reference because it is within the dose range for which tislelizumab exposure–response has been shown to be flat. Similarly, $C_{max,ss}$ of the 400 mg Q6W dosing regimen was compared with $C_{max,ss}$ of 5 mg/kg Q3W and 10 mg/kg Q2W as safety

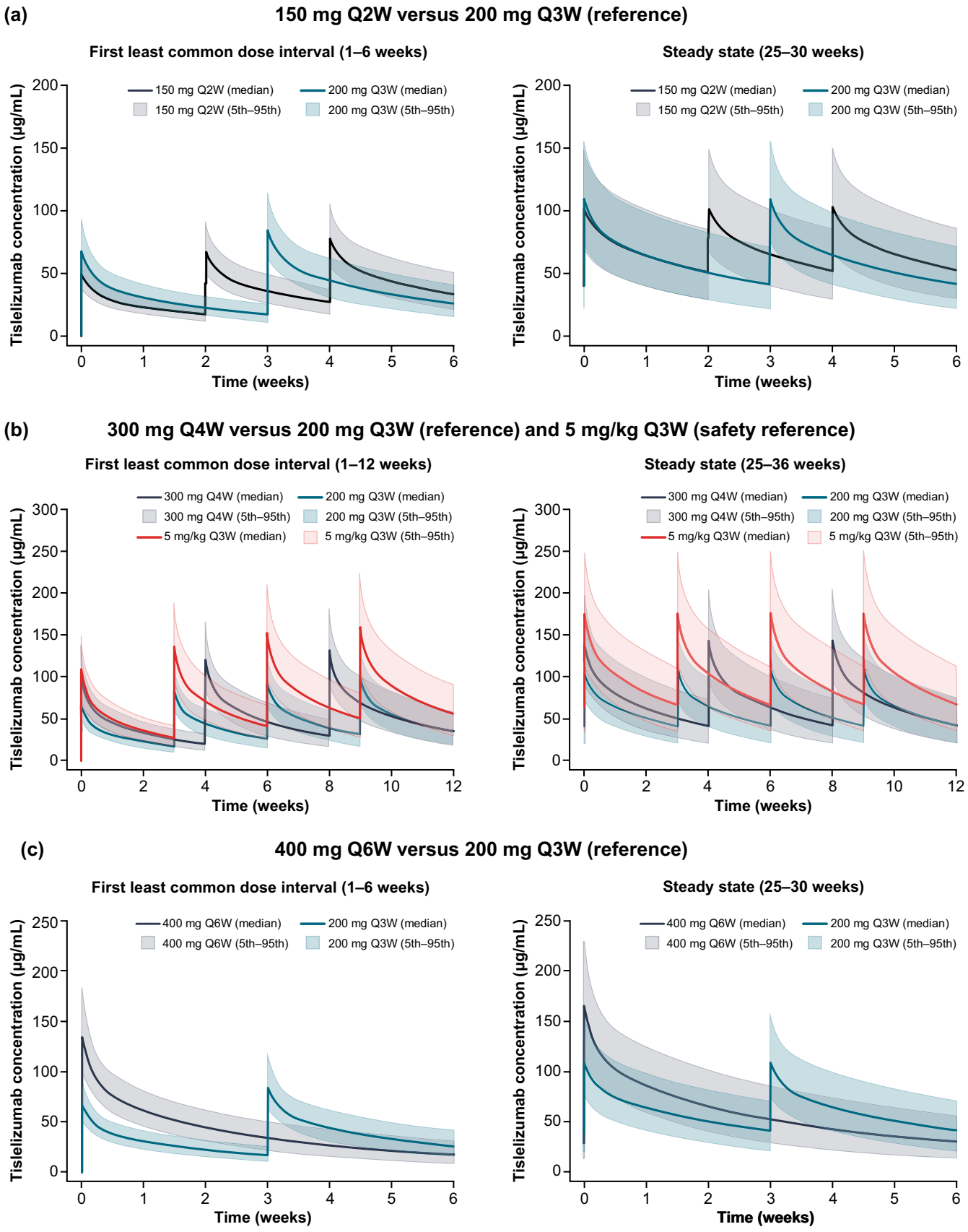

FIGURE 1 | Pharmacokinetic profiles (median and 90% prediction interval) for the 150 mg Q2W (a), 300 mg Q4W (b), and 400 mg Q6W (c) alternative dosing regimens compared with the tislelizumab 200 mg Q3W reference dosing regimen during early treatment and steady state. For each dosing regimen, pharmacokinetic profiles were simulated over the first least common dose interval and at steady state using the individual post hoc model parameters from the final popPK model previously developed based on 12 studies. The solid line represents the median and the shaded area represents the 90% prediction interval. popPK, population pharmacokinetic; Q2/3/4/6 W, once every 2/3/4/6 weeks.

TABLE 1 | Pharmacokinetic exposure metrics for the tislelizumab 150 mg Q2W dosing regimen compared with the 200 mg Q3W reference dosing regimen.

	Test	Reference	
Exposure parameter	**150 mg Q2W[a]**	**200 mg Q3W[a,b]**	**Percentage difference[c]**
First least common dose interval			
$C_{max,1\text{-}6w}$, μg/mL	77.4 (76.9, 78.0)	84.8 (84.2, 85.4)	−8.7
$C_{average,1\text{-}6w}$, μg/mL	36.1 (35.9, 36.4)	34.6 (34.4, 34.9)	4.4
$C_{trough,6w}$, μg/mL	32.6 (32.2, 32.9)	25.0 (24.7, 25.3)	30.2
Steady state			
$C_{max,25\text{-}30w}$, μg/mL	102.5 (101.6, 103.4)	108.8 (107.9, 109.7)	−5.8
$C_{average,25\text{-}30w}$, μg/mL	66.8 (66.1, 67.5)	59.5 (58.9, 60.1)	12.3
$C_{trough,24w}$, μg/mL	49.8 (49.2, 50.5)	39.2 (38.6, 39.7)	27.2

Abbreviations: $C_{average,1\text{-}6w}$, average serum concentration at the first least common dose interval (1–6 weeks); $C_{average,25\text{-}30w}$, average serum concentration at steady state (25–30 weeks); CI, confidence interval; $C_{max,1\text{-}6w}$, peak serum concentration the first least common dose interval (1–6 weeks); $C_{max,25\text{-}30w}$, peak serum concentration at steady state (25–30 weeks); $C_{max,ss}$, peak serum concentration at steady state; $C_{trough,6w}$, trough serum concentration the first least common dose interval (6 weeks); $C_{trough,24w}$, through serum concentration at steady state (24 weeks); FDA, US Food and Drug Administration; GM, geometric mean; Q2/3W, once every 2/3 weeks.
[a]Data are presented as GM [95% CI]. The back transformed GM and 95% CIs were calculated using natural log transformed values with 95% CIs obtained based on the t distribution.
[b]Per FDA guidance [10], the reference dosing regimen used for the comparison was the dosing regimen used to establish efficacy in the clinical trial(s) that served as the basis for approval of the original biologics licensing application.
[c]Percentage difference was calculated as $([GM_{test}—GM_{reference}]/GM_{reference})\times 100$.

TABLE 2 | Pharmacokinetic exposure metrics for the tislelizumab 300 mg Q4W dosing regimen compared with the 200 mg Q3W reference dosing regimen and safety reference.

	Test	Reference		Safety reference	
Exposure parameter	**300 mg Q4W[a]**	**200 mg Q3W[a,b]**	**Percentage difference[c]**	**5 mg/kg Q3W[a,d]**	**Percentage difference[c]**
First least common dose interval					
$C_{max,1\text{–}12w}$, μg/mL	131.2 (130.3, 132.2)	98.9 (98.2, 99.7)	32.7	159.9 (158.7, 161.2)	−17.9
$C_{average,1\text{–}12w}$, μg/mL	49.0 (48.6, 49.4)	42.1 (41.7, 42.4)	16.5	68.0 (67.4, 68.7)	−28.0
$C_{trough,12w}$, μg/mL	33.3 (32.8, 33.8)	33.5 (33.1, 34.0)	−0.7	54.2 (53.5, 54.9)	−38.6
Steady state					
$C_{max,25\text{–}36w}$, μg/mL	143.9 (142.8, 145.1)	109.5 (108.6, 110.4)	31.4	177.0 (175.6, 178.5)	−18.7
$C_{average,25\text{–}36w}$, μg/mL	67.4 (66.7, 68.1)	59.8 (59.2, 60.5)	12.6	96.8 (95.8, 97.8)	−30.3
$C_{trough,24w}$, μg/mL	39.2 (38.6, 39.8)	39.2 (38.6, 39.7)	0.1	63.3 (62.5, 64.2)	−38.1

Abbreviations: $C_{average,1\text{–}12w}$, average serum concentration at the first least common dose interval (1–12 weeks); $C_{average,25\text{–}36w}$, average serum concentration at steady state (25–36 weeks); $C_{max,1\text{–}12w}$, peak serum concentration at the first least common dose interval (1–12 weeks); $C_{max,25\text{–}36w}$, peak serum concentration at steady state (25–36 weeks); $C_{trough,12w}$, minimal serum concentration at the first least common dose interval (12 weeks); $C_{trough,24w}$, minimal serum concentration at steady state (24 weeks); FDA, US Food and Drug Administration; GM, geometric mean; Q3/4W, once every 3/4 weeks.
[a]Data are presented as GM [95% CI]. The back transformed GM and 95% CIs were calculated using natural log transformed values with 95% CIs obtained based on the t distribution.
[b]Per FDA guidance [10], the reference dosing regimen used for the comparison was the dosing regimen used to establish efficacy in the clinical trial(s) that served as the basis for approval of the original biologics licensing application.
[c]Percentage difference was calculated as $([GM_{test}—GM_{reference}]/GM_{reference})\times 100$.
[d]Per FDA guidance [10], the safety reference regimen used for comparison is the dosing regimen that was used in early clinical development to characterize the pharmacokinetics and efficacy of the product.

references. The safety references have previously been tested clinically in a large number of patients (phase IA and phase IB parts of the BGB-A317-001 study) and were well tolerated. Therefore, the higher $C_{max,ss}$ for the 400 mg Q6W regimen is unlikely to be associated with an unacceptable clinical safety profile. Results demonstrate that the 400 mg Q6W dosing regimen would maintain $C_{trough,ss}$ levels 10.7% higher than the 2 mg/kg Q3W efficacy reference dosing regimen and the predicted $C_{max,ss}$ was well below those of the safety references of 5 mg/kg Q3W (25.1% lower) and 10 mg/kg Q2W (62.5% lower) (Table 3).

TABLE 3 | Pharmacokinetic exposure metrics for the tislelizumab 400 mg Q6W dosing regimen compared with the 200 mg Q3W reference dosing regimen and efficacy and safety references.

	Test	Reference		Efficacy reference		Safety reference		Safety reference	
Exposure parameter	**400 mg Q6W[a]**	**200 mg Q3W[a,b]**	**Percentage difference[c]**	**2 mg/kg Q3W[a,d]**	**Percentage difference[c]**	**5 mg/kg Q2W[a,d]**	**Percentage difference[c]**	**10 mg/kg Q2W[a,d]**	**Percentage difference[c]**
First least common dose interval									
$C_{max,1–6wk}$, μg/mL	135.6 (134.6, 136.5)	84.8 (84.2, 85.4)	59.9	54.8 (54.4, 55.2)	147.2	166.9 (165.7, 168.2)	−18.8	333.8 (331.3, 336.3)	−59.4
$C_{average,1–6wk}$, μg/mL	40.6 (40.3, 40.9)	34.6 (34.4, 34.9)	17.3	22.4 (22.2, 22.6)	81.3	77.9 (77.3, 78.6)	−48.0	155.9 (154.6, 157.1)	−74.0
$C_{trough,6w}$, μg/mL	16.9 (16.6, 17.1)	25.0 (24.7, 25.3)	−32.5	16.2 (16.0, 16.4)	4.4	70.2 (69.4, 70.9)	−76.0	140.4 (138.8, 141.9)	−88.0
Steady state									
$C_{max,25–30w}$, μg/mL	165.6 (164.4, 166.9)	108.8 (107.9, 109.7)	52.2	70.4 (69.8, 70.9)	135.4	221.0 (219.1, 223.0)	−25.1	442.1 (438.3, 445.9)	−62.5
$C_{average,25–30w}$, μg/mL	59.7 (59.1, 60.4)	59.5 (58.9, 60.1)	0.4	38.5 (38.1, 38.9)	55.2	144.1 (142.6, 145.6)	−58.5	288.2 (285.2, 291.2)	−79.3
$C_{trough,24w}$, μg/mL	28.0 (27.6, 28.5)	39.2 (38.6, 39.7)	−28.4	25.3 (25.0, 25.7)	10.7	107.4 (106.1, 108.7)	−73.9	214.8 (212.1, 217.5)	−86.9

Abbreviations: $C_{average,1–6w}$, average serum concentration at the first least common dose interval (1–6 weeks); $C_{average,25–30w}$, average serum concentration at steady state (25–30 weeks); $C_{max,1–6w}$, peak serum concentration at the first least common dose interval (1–6 weeks); $C_{max,25–30w}$, peak serum concentration at steady state (25–30 weeks); $C_{trough,6w}$, trough serum concentration at the first least common dose interval (6 weeks); $C_{trough,24w}$, trough serum concentration at steady state (24 weeks); FDA, US Food and Drug Administration; GM, geometric mean; Q2/3/6 W, once every 2/3/6 weeks.

[a]Data are presented as GM [95% CI]. The back transformed GM and 95% CIs were calculated using natural log transformed values with 95% CIs obtained based on the t distribution.

[b]Per FDA guidance [10], the reference dosing regimen used for the comparison was the dosing regimen that was used to establish efficacy in the clinical trial(s) that served as the basis for approval of the original biologics licensing application.

[c]Percentage difference was calculated as $([GM_{test}—GM_{reference}]/GM_{reference})\times100$.

[d]Per FDA guidance [10], the efficacy and safety reference regimens used for comparison are the dosing regimens that were used in early clinical development to characterize the pharmacokinetics and efficacy of the product.

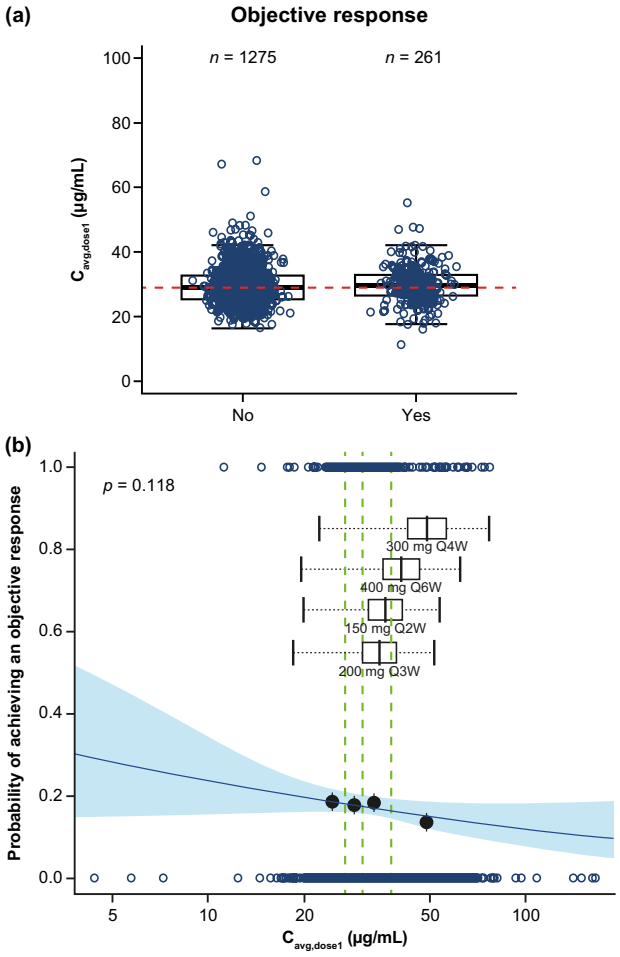

FIGURE 2 | Exposure–response analysis between tislelizumab exposure and ORR (a) and the predicted probability of patients achieving an objective response (b) in the context of the exposures of the 200 mg Q3W, 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W dosing regimens. In panel a, open blue circles represent the model-predicted exposure metrics. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentiles (the lower and upper quartiles, respectively). The bars extend to the most extreme data point, which is no more than 1.5×IQR from the box. The dashed red horizontal line represents the median value in the BGB-A317-001, BGB-A317-102, BGB-A317-302, and BGB-A317-303 studies. Tislelizumab exposure was normalized to a dose of 200 mg. The means (SD) of normalized $C_{avg,dose1}$ are 29.4 (5.48) μg/mL and 29.7 (5.64) μg/mL for the groups categorized as "No" and "Yes" respectively. In panel b, open blue circles reflect the observed events. The filled black symbols are the observed probability of events, and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100×(1/4)th percentiles) of exposures (plotted at the median value within each quantile). The blue line is the model-predicted probability. The blue line and light blue shaded area are the median and 95% prediction interval based on the 1000 bootstrap samples of the model. The horizontal box plots represent the exposure values of 200 mg Q3W, 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point, which is no more than 1.5×IQR from the box. $C_{avg,dose1}$, average serum concentration of the first dose; IQR, interquartile range; N, number of patients; ORR, objective response rate; P, probability; Q2/3/4/6 W, once every 2/3/4/6 weeks; SD, standard deviation; SE, standard error; sqrt, square root.

3.3 | Exposure–Response Analysis for Efficacy

In the pooled exposure–response analysis for efficacy, the median $C_{avg,dose1}$ values were similar between responders and non-responders in patients with solid tumors, as shown in the boxplots of exposure stratified by ORR binary response (Figure 2a). Consistent with these observations, the results from the exposure–response relationships for ORR, explored by plotting the probability of objective response versus the exposure of tislelizumab (with probabilities calculated across sets of patients binned by exposure quantiles), showed that $C_{avg,dose1}$ was not associated with the probability of objective response in tislelizumab-treated patients across solid tumor types in this pool, which included ESCC, NSCLC, and GC among others (Figure S3). Finally, a logistic regression model was developed, and the result of the model, based on patients with solid tumors, showed no significant association between the ORR and $C_{avg,dose1}$ ($p = 0.118$) in the predicted exposure range of the 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W alternative dose regimens (Figure 2b).

3.4 | Exposure–Response Analysis for Safety

TEAEs across the seven selected safety outcomes were generally consistent across each of the individual studies in the exposure–response analysis dataset and when pooled across the four studies, both between tumor types and across the dosing range (Table 4). The probabilities of occurrence of the selected TEAE categories by quantiles of tislelizumab exposure (C_{max} of the first dose [$C_{max,dose1}$]) were explored. Similar ranges of tislelizumab exposure were observed in patients regardless of whether they experienced one of the selected TEAE categories or not (Figure S4). There were no apparent relationships between tislelizumab exposure and any of the safety endpoints evaluated (including grade ≥3 TEAEs, immune-mediated TEAEs, TEAEs leading to treatment discontinuation or dose modification, TEAEs of special interest, and serious TEAEs) among tislelizumab-treated patients (Figure S4); therefore, no logistic regression models were developed for these endpoints.

Generally, the safety profile of tislelizumab is consistent with the anti–PD-1 therapeutic class, with a relatively low rate of treatment-related grade ≥3 toxicity. There was a slight trend for a relationship between tislelizumab exposure and the probability of IRRs. Therefore, an exposure–response logistic regression model for IRRs with $C_{max,ss}$ was developed based on tislelizumab-treated patients, which showed a significant association between the IRRs and $C_{max,ss}$. An imbalance in the incidence of IRRs between BGB-A317-001 and the other studies included in the pool appeared to be contributing to the observed positive exposure–response relationship; the BGB-A317-001 study evaluated higher doses (5 and 10 mg/kg), while the other studies included in the analysis evaluated a single dose (200 mg Q3W) and reported a lower incidence of IRRs. To address the issue of confounding, an exposure–response analysis was conducted using only data from BGB-A317-001. The result showed no significant association between the IRRs and $C_{max,ss}$ ($p = 0.0727$; Figure S5). Therefore, the relationship between IRRs and tislelizumab exposures is not clinically meaningful.

TABLE 4 | Summary of selected safety outcomes in the exposure–response dataset.

Safety endpoints, *n* (%)	BGB-A317-001 (*n* = 450 patients with solid tumors)	BGB-A317-102 (*n* = 300 patients with solid tumors)	BGB-A317-302 (*n* = 254 patients with ESCC)	BGB-A317-303 (*n* = 532 patients with NSCLC)	Overall (*N* = 1536)
Grade ≥ 3 TEAEs	207 (46.0)	137 (45.7)	123 (48.4)	230 (43.2)	697 (45.4)
Immune-mediated TEAEs	131 (29.1)	89 (29.7)	87 (34.3)	186 (35.0)	493 (32.1)
TEAEs leading to treatment discontinuation	39 (8.7)	34 (11.3)	49 (19.3)	65 (12.2)	187 (12.2)
Infusion-related reactions	55 (12.2)	7 (2.3)	11 (4.3)	4 (0.8)	77 (5.0)
TEAEs leading to dose modification	129 (28.7)	94 (31.3)	59 (23.2)	142 (26.7)	424 (27.6)
TEAEs of special interest	156 (34.7)	89 (29.7)	90 (35.4)	188 (35.3)	523 (34.0)
Serious TEAEs	169 (37.6)	85 (28.3)	109 (42.9)	189 (35.5)	552 (35.9)

Abbreviations: ESCC, esophageal squamous cell carcinoma; NSCLC, non-small cell lung cancer; TEAE, treatment-emergent adverse event.

3.5 | Additional Safety Analysis Using Clinical C_{max} Cutoffs

Overall, the safety profiles were comparable and consistent between patients with a $C_{max,ss}$ greater than the predicted geometric mean C_{max} for the 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W dosing regimens and patients with a $C_{max,ss}$ less than or equal to the predicted geometric mean C_{max}. Therefore, this safety analysis did not show any clinically meaningful difference in the safety profiles between the two exposure groups for any of the alternative dose regimens (Table S6).

4 | Discussion

The clinical pharmacologic profile of tislelizumab has been extensively evaluated, supported by robust pharmcokinetic characterization and an extensive understanding of exposure–efficacy and exposure–safety relationships from multiple clinical trials across a wide range of tumor types and multiple dosing regimens. Using a pharmacometrics-based approach, we investigated whether alternative dosing regimens of tislelizumab at 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W met pre-specified pharmacokinetic criteria compared with the reference regimen of 200 mg Q3W. Based on this analysis and supportive clinical data, the tislelizumab dosing regimens of 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W are expected to result in similar safety and efficacy as the tislelizumab 200 mg Q3W reference regimen.

As observed clinical pharmacokinetic data after alternative dosing regimens were available from three clinical studies, the 12-study tislelizumab popPK model, previously developed using the Q2W and Q3W regimens, was used to describe the observed pharmacokinetic profiles of the external datasets and verified using pcVPC. The predictive performance of the tislelizumab popPK model was satisfactory, with most of the observed data lying within the prediction intervals. Therefore, the pharmacokinetics parameters for the 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W dosing regimens could be simulated using this model and pharmacokinetic exposure parameters compared with the reference dosing regimen of 200 mg Q3W.

Per FDA guidance, pharmacokinetic parameters for the 150 mg Q2W regimen met all pharmacokinetics-based criteria. Both geometric means of $C_{average}$ and C_{trough} at the steady state and in the first least common time interval were no more than 20% lower compared to those of the reference dosing regimen. Additionally, the geometric mean of steady state and C_{max} did not increase more than 25% compared to that of the reference 200 mg Q3W dosing regimen.

For the 300 mg Q4W regimen, all pharmacokinetics-based criteria in comparison with the 200 mg Q3W reference regimen were met, except for the $C_{max,ss}$, which was 31.4% higher than that of the reference regimen. Although C_{max} was 6.4% higher than the recommended limit of 25%, it was 18.7% lower when compared with the safety reference of 5 mg/kg Q3W. The 5 mg/kg Q3W safety reference has been tested clinically in approximately 355 patients (phase IA and phase IB of BGB-A317-001) and was demonstrated to be well tolerated. Therefore, the higher $C_{max,ss}$ for the 300 mg Q4W regimen is unlikely to be associated with an unacceptable clinical safety profile.

For the proposed tislelizumab 400 mg Q6W dosing regimen, pharmacokinetics-based criteria for the primary efficacy parameter of $C_{average}$ were met. The $C_{trough,ss}$ for the 400 mg Q6W dosing regimen was lower than the 200 mg Q3W reference regimen (28.4% vs. the guidance limit of 20.0%); however, the established flat exposure–response relationship of tislelizumab over

a wide range of exposures supports the expectation that 400 mg Q6W will produce similar efficacy to the 200 mg Q3W reference regimen. In addition, the $C_{max,ss}$ for the 400 mg Q6W dosing regimen was higher than that of the 200 mg Q3W reference regimen (52.2% vs. the guidance limit of 25.0%); however, it was well below the clinically evaluated safety references of 5 mg/kg Q3W (25.1% lower) and 10 mg/kg Q2W (62.5% lower). Taken together, the safety data for tislelizumab up to 10 mg/kg Q2W, the observed clinical safety data from the BGB-A317-315 and BGB-A317-212 studies [14, 15], and additional safety assessment of the 400 mg Q6W regimen using clinical C_{max} cutoffs, provide adequate safety margins for the higher C_{max} with the 400 mg Q6W regimen.

In conclusion, the modeling and simulation results, along with the lack of an exposure–response relationship and the clinical safety data from studies evaluating alternative dosing regimens of tislelizumab, indicate that the 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W regimens are expected to result in similar safety and efficacy as the 200 mg Q3W reference regimen, and may be used interchangeably for the indications for which the dosing regimen of 200 mg Q3W is approved. While maintaining the same therapeutic benefit across regimens, the alternative dosing regimens of tislelizumab have the potential to offer patients flexible treatment options that are compatible with background chemotherapy, and to reduce the number of infusion visits.

Author Contributions

All authors wrote the manuscript; A.R., S.S., and N.B. designed the research; A.R., T.Y., Y.W., J.W., and N.B. performed the research; A.R., Y.G., K.W., F.X., J.W., and N.B. analyzed the data.

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Conflicts of Interest

All listed authors except Y.G., K.W., and F.X. are current or previous employees of BeiGene Ltd. at the time the analysis was conducted and may own shares in BeiGene Ltd. Y.G., K.W., and F.X. received consultancy fees from BeiGene.

Data Availability Statement

BeOne Medicines (formerly known as BeiGene) voluntarily shares anonymous data on completed studies responsibly and provides qualified scientific and medical researchers access to anonymous data and supporting clinical trial documentation for clinical trials in dossiers for medicines and indications after submission and approval in the United States, China, and Europe. Clinical trials supporting subsequent local approvals, new indications, or combination products are eligible for sharing once corresponding regulatory approvals are achieved. BeOne Medicines shares data only when permitted by applicable data privacy and security laws and regulations. In addition, data can only be shared when it is feasible to do so without compromising the privacy of study participants. Qualified researchers may submit data requests/research proposals for BeOne Medicines review and consideration through BeOne Medicines' Clinical Trial Webpage at https://www.beigene.com/our-science-and-medicines/our-clinical-trials/.

References

1. T. Zhang, X. Song, L. Xu, et al., "The Binding of an Anti-PD-1 Antibody to FcγRI has a Profound Impact on Its Biological Functions," *Cancer Immunology, Immunotherapy* 67, no. 7 (2018): 1079–1090.

2. J. Desai, S. Deva, J. S. Lee, et al., "Phase IA/IB Study of Single-Agent Tislelizumab, an Investigational Anti-PD-1 Antibody, in Solid Tumors," *Journal for Immunotherapy of Cancer* 8, no. 1 (2020): e000453.

3. European Medicines Agency, "Ttislelizumab EPAR Medicine Overview," 2024, https://www.ema.europa.eu/en/documents/overview/tevimbra-epar-medicine-overview_en.pdf.

4. BeiGene Ltd., "BeiGene Receives FDA Approval for TEVIMBRA® for the Treatment of Advanced or Metastatic Esophageal Squamous Cell Carcinoma After Prior Chemotherapy," https://ir.beigene.com/news/beigene-receives-fda-approval-for-tevimbra-for-the-treatment-of-advanced-or-metastatic-esophageal-squamous/20eb032c-15ce-456a-a852-39c88a28d811/.

5. US Food and Drug Administration, "Nivolumab (Package Insert)," https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125554s114lbl.pdf.

6. European Medicines Agency, "Opdivo Summary of Product Characteristics," https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf.

7. European Medicines Agency, "Assessment Report Yervoy Opdivo Procedure no. EMEA/H/C/xxxx/WS/1881," https://www.ema.europa.eu/en/documents/variation-report/opdivo-emea/h/c/ws1881-epar-assessment-report-variation_en.pdf.

8. M. Lala, T. R. Li, D. P. de Alwis, et al., "A Six-Weekly Dosing Schedule for Pembrolizumab in Patients With Cancer Based on Evaluation Using Modelling and Simulation," *European Journal of Cancer* 131 (2020): 68–75.

9. K. M. Morrissey, M. Marchand, H. Patel, et al., "Alternative Dosing Regimens for Atezolizumab: An Example of Model-Informed Drug Development in the Postmarketing Setting," *Cancer Chemotherapy and Pharmacology* 84, no. 6 (2019): 1257–1267.

10. US Food and Drug Administration, "Pharmacokinetic-Based Criteria for Supporting Alternative Dosing Regimens of Programmed Cell Death Receptor-1 (PD-1) or Programmed Cell Death-Ligand 1 (PD-L1) Blocking Antibodies for Treatment of Patients with Cancer: Guidance for Industry," https://www.fda.gov/media/151745/download.

11. N. Budha, C. Y. Wu, Z. Tang, et al., "Model-Based Population Pharmacokinetic Analysis of Tislelizumab in Patients With Advanced Tumors," *CPT: Pharmacometrics & Systems Pharmacology* 12, no. 1 (2023): 95–109.

12. T. Yu, X. Liu, C. Y. Wu, et al., "Clinical Dose Rationale of Tislelizumab in Patients With Solid or Hematological Advanced Tumors," *Clinical and Translational Science* 17, no. 3 (2024): e13769.

13. T. Yu, C.-Y. Wu, S. Sahasranaman, et al., "Clinical Pharmacology Overview of Tislelizumab in Patients With Advanced Tumors With a Focus on Racial Impact," *Clinical and Translational Science* 18, no. 5 (2025): e70221.

14. Y. Liu, Z. He, M. Zhang, et al., "BGB-A317-212: A Multicenter, Open-Label, Phase II Study to Evaluate the Efficacy and Safety of Tislelizumab in Combination With Lenvatinib in Patients With Selected Solid Tumors," *Journal of Clinical Oncology* 42, no. Suppl 16 (2024): 2610.

15. D. Yue, W. Wang, H. Liu, et al., "Perioperative Tislelizumab Plus Neoadjuvant Chemotherapy for Patients With Resectable Non-Small-Cell Lung Cancer (RATIONALE-315): An Interim Analysis of a Randomised Clinical Trial," *Lancet Respiratory Medicine* 13, no. 2 (2024): 119–129.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.