TISLELIZUMAB EXPOSURE-RESPONSE ANALYSES OF EFFICACY AND SAFETY IN PATIENTS WITH ADVANCED TUMORS

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BACKGROUND

- Tislelizumab, an investigational humanized IgG4 monoclonal antibody, was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy
- Tislelizumab is currently tested in clinical studies at the dose of 200 mg every 3 weeks (Q3W). Recently, the approval of alternative dosing regimens for other PD-1 inhibitors such as nivolumab (240 mg every 2 weeks [Q2W] and 480 mg every 4 weeks [Q4W]) and pembrolizumab (200 mg Q3W and 400 mg every 6 weeks [Q6W]) demonstrated feasibility and utility exposure-response (E-R) analysis approach for assessing less frequent dosing regimens
- Tislelizumab E-R relationships for efficacy and safety endpoints in subjects with advanced tumors were evaluated to inform the benefit-risk assessment and to explore the feasibility of alternative extended dosing schedules

OBJECTIVES

- Explore the E-R relationships between tislelizumab exposure and efficacy and safety endpoints using data collected from three clinical studies (BGB-A317-001, BGB-A317-102, and BGB-A317-203)
- Explore and evaluate the feasibility of a Q6W dosing regimen for tislelizumab using the E-R analysis approach

METHODS

Analysis Dataset

- The E-R relationships for both efficacy and safety endpoints were explored based on the data from studies BGB-A317-001, BGB-A317-102, and BGB-A317-203
- The efficacy and safety data files were created using R and the model-predicted exposure metrics were computed using the Bayesian post-hoc pharmacokinetic (PK) parameters following administration of tislelizumab with different dose regimens

Exposure Metrics

- The previously developed population PK model was used to simulate tislelizumab exposure
- The following individual model-predicted PK parameters were used as the exposure measures for tislelizumab E-R analysis:
  - $C_{min,ss}$: steady-state trough concentration
  - $C_{max,ss}$: steady-state peak concentration
  - $C_{avg,D42}$: time-averaged concentration over the first 42 days
  - $C_{avg,ss}$: time-average concentration at steady-state

Response Measures

- The efficacy endpoint analyzed in the report was objective response rate (ORR). The objective responders (OR) were those patients whose best overall response was either complete response or partial response; otherwise, the patients were classified as non-objective responders. The E-R analysis for efficacy was performed separately for solid tumors and classical Hodgkin's lymphoma (cHL)
- The following safety endpoints were characterized by incidence only, and data from all the three studies, BGB-A317-001, BGB-A317-102, and BGB-A317-203, were used in the analysis:
  - Immune-related adverse events (AEs)
  - Infusion-related AEs
  - AEs greater than grade 3
  - AEs leading to dose modification
  - AEs leading to drug discontinuation

Modelling Methods

- The association between tislelizumab exposures and the probability of achieving response (efficacy and safety) in patients with advanced tumors was examined by a logistic regression model

$$logit(Pr_i) = \beta_{0,\text{tumor type}} + \theta_{PK} \times PK_i$$

- Where:
  - logit is the logit transform
  - Pr_i is the probability of response for patient i
  - PK_i is the PK exposure value
  - θ_{PK} is the coefficient for PK_i
- Continuous exposures could be used as their original values or transformed values (eg, log-transformed) based on the model selection criteria of smaller Akaike's information criteria. The significance level was based on α=0.05
- Models were evaluated by comparison of the model-predicted probability curve, with predicted probability curves of 1000 bootstrap samples, magnitude and sign of parameter estimates, and the standard errors of the parameter estimates

Summary of Efficacy Data

- The tumor types were collapsed into seven categories for E-R analysis of solid tumor, esophageal carcinoma, gastric cancer, hepatocellular cancer, non-small cell lung cancer, ovarian cancer, urothelial bladder cancer, and other (**Table 1**)

Table 1: Summary of Efficacy Data

Tumor Type		N	% of Responders (Yes/No)
Solid tumors	Esophageal cancer	79	10.1% (8/71)
	Gastric cancer	77	14.3% (11/66)
	Hepatocellular carcinoma	66	10.6% (7/59)
	Non-small cell lung cancer	107	12.1% (13/94)
	Ovarian cancer	51	9.8% (5/46)
	Urothelial bladder cancer	40	17.5% (7/33)
	Other tumors	325	11.4% (37/288)
	Total	745	11.8% (88/657)
Hematologic cancer	Classical Hodgkin's lymphoma	70	85.7% (60/10)

Note: Subjects with missing response data were treated as non-responders in this analysis.

RESULTS

E-R Relationship for Efficacy

- The summary of parameters and trends of OR with the range of $C_{max,ss}$ and $C_{avg,D42}$ of solid tumors and cHL are provided in **Figure 1**
- **Solid tumors** (N=745, BGB-A317-001 and BGB-A317-102):
  - The probability plots of ORR versus model-predicted exposures showed a slight trend for $C_{max,ss}$, but not for $C_{min,ss}$, $C_{avg,ss}$, and $C_{avg,D42}$. The logistic regression model with $C_{max,ss}$ suggested a statistically significant association between ORR and $C_{max,ss}$ (P=0.034 for slope). However, the observed rate of OR over the exposure quantiles was less than 25%, indicating the increase in response is not clinically significant. There is no significant difference in ORR among tumor types.
- **cHL patients** (N=70, BGB-A317-203):
  - The probability plots of ORR versus model-predicted exposures showed no observed trend

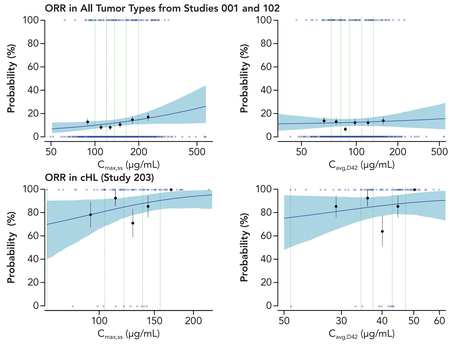
E-R Relationship for Safety

- The trends of safety measures with the range of $C_{max,ss}$ of solid tumors and cHL are provided in **Figure 2**
- No E-R relationship was observed for:
  - Immune-related AEs, infusion-related AEs, AEs greater than grade 3, and AEs leading to drug discontinuation. However, the probability of immune-related AEs, infusion-related AEs, and AEs greater than grade 3 among tumor type was different (P<0.05). There was no significant difference in AEs leading to drug discontinuation among tumor types (P>0.05)
- AEs leading to dose modification:
  - The logistic regression model with $C_{max,ss}$ suggested a statistically significant association between AEs leading to dose modification and $C_{max,ss}$ (P=0.040 for slope); however the increase in AEs with Cmax,ss is clinically not significant. There is no significant difference in AEs leading to dose modification among tumor types (P>0.05)

Feasibility of Alternate Q6W Dosing

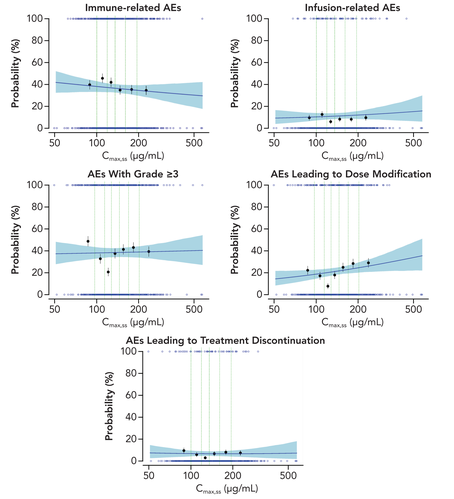
- The model-predicted tislelizumab PK profiles of 200 mg Q3W and 400 mg Q6W during the first 42 days and steady-state are provided in **Figure 3** and **Table 2**
- The model-predicted safety and efficacy endpoints are comparable between 200 mg Q3W and 400 mg Q6W (**Figures 4 and 5**), indicating that both regimens may be used interchangeably with similar efficacy and safety profiles and supporting further evaluation of the 400 mg Q6W regimen in clinical studies

Figure 1: No Clinically Significant E-R Relationships Observed for Efficacy Endpoint (ORR) in Solid Tumors and cHL



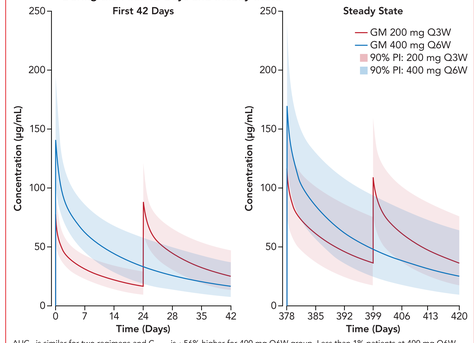
Abbreviations: $C_{avg,D42}$, time-averaged concentration at Day 42 after first dose; $C_{max,ss}$, steady-state peak concentration; D, day; E-R, exposure-response; ORR, objective response rate.

Figure 2: No Clinically Significant E-R Relationships Observed for Safety Endpoints



The open blue circles are 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 100x(1/q)th percentiles, vertical dotted lines) of exposures (plotted at the median value within each quantile). The blue line is the model-predicted probability. The light blue shaded areas are the 95% prediction intervals based on 1000 bootstrap samples.
Abbreviations: AE, adverse event; $C_{max,ss}$, steady-state peak concentration; E-R, exposure-response; SE, standard error.

Figure 3: Tislelizumab Model-Predicted PK Profiles of 200 mg Q3W and 400 mg Q6W During the First 42 Days and Steady-State



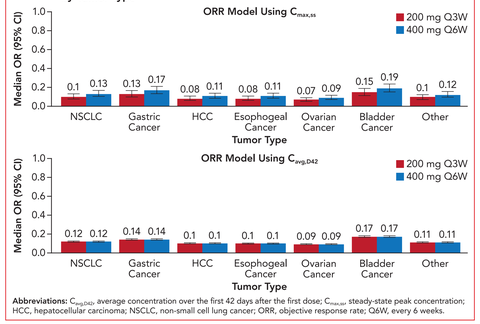
AUC_{ss} is similar for two regimens and $C_{max,ss}$ is ~56% higher for 400 mg Q6W group. Less than 1% patients at 400 mg Q6W are predicted to have $C_{min,ss}$ lower than that for 200 mg Q3W.
Abbreviations: AUC_{ss} steady-state area-under-the-curve; $C_{max,ss}$, steady-state peak concentration; $C_{min,ss}$, steady-state trough concentration; GM, geometric mean; PK, pharmacokinetic; PI, prediction interval; Q3W, every 3 weeks; Q6W, every 6 weeks.

Table 2: Comparison of Predicted First-Dose And Steady-State PK Exposures for 200 mg Q3W and 400 mg Q6W

Exposure (μg/mL)		200 mg Q3W GM (% CV)	400 mg Q6W GM (% CV)
After the first dose	$C_{avg,D42}$	35 (22.6)	41 (24.6)
	C_{min1}	17 (34.7)	17 (50.9)
	C_{max1}	70 (19.9)	141 (19.9)
Steady state	$C_{avg,ss}$	57 (32.6)	57 (33.3)
	$C_{min,ss}$	36 (47.2)	25 (61.2)
	$C_{max,ss}$	108 (23.7)	169 (21.5)

Abbreviations: $C_{avg,D42}$, average concentration over the first 42 days after the first dose; $C_{avg,ss}$, steady-state average concentration; $C_{max,ss}$, steady-state peak concentration; C_{max1}, peak concentration after the first dose; $C_{min,ss}$, steady-state trough concentration (at day 21 for Q3W, at day 42 for Q6W, and at day 14 of Q2W of last dose); C_{min1}, trough concentration after the first dose (at day 21 for Q3W, at day 42 for Q6W, and at day 14 of Q2W after the first dose); CV, coefficient of variation; D, day; GM, geometric mean; PK, pharmacokinetic; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks.

Figure 4: Model-Predicted ORR for Tislelizumab Between 200 mg Q3W and 400 mg Q6W by Tumor Type

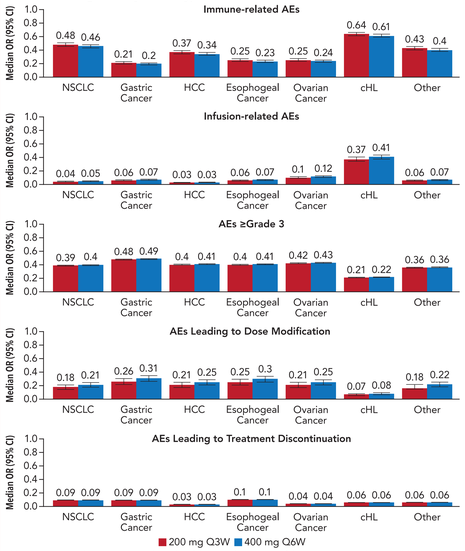


Abbreviations: $C_{avg,D42}$, average concentration over the first 42 days after the first dose; $C_{max,ss}$, steady-state peak concentration; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; ORR, objective response rate; Q6W, every 6 weeks.

CONCLUSIONS

- There were a lack of clinically significant E-R relationships for ORR and safety endpoints across a variety of advanced solid tumors and cHL for tislelizumab, supporting evaluation of the 400 mg Q6W regimen in future clinical trials
- With the clinical data across multiple tumor types and well-characterized E–R relationships for efficacy and safety for tislelizumab, the 400 mg Q6W regimen is not expected to be clinically different from the 200 mg Q3W in terms of safety or efficacy outcomes

Figure 5: Model-Predicted Safety Events for Tislelizumab Between 200 mg Q3W and 400 mg Q6W by Tumor Type



Abbreviations: AE, adverse event; cHL, classical Hodgkins Lymphoma; CI, confidence interval; HCC, hepatocellular carcinoma; irAE, immune-related adverse event; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; Q6W, every 6 weeks.

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CONFLICTS OF INTEREST

CW: Employee- BeiGene USA, Inc; **TT:** Employee- BeiGene USA, Inc; **LL:** Employee- Shanghai Qiang shi information Technology; **YB:** Employee- BeiGene USA, Inc.; **SS:** Employee- BeiGene USA, Inc.

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Please address any questions or comments regarding this poster to Clinicaltrials@beigene.com