Alternative dosing regimens of tislelizumab proposed using modeling and simulation

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ABSTRACT

Background: Tislelizumab (TIS; BGB-A317) is approved for the treatment of multiple solid tumors, administered at 200 mg every 3 weeks (Q3W), and has demonstrated a flat exposure–response relationship across a wide range of doses. We evaluated alternative dosing regimens of TIS at 150 mg every 2 weeks (Q2W), 300 mg every 4 weeks (Q4W), and 400 mg every 6 weeks (Q6W) using a model-based approach with the aim of alleviating patient burden by providing longer dosing intervals and/or treatment flexibility compatible with background chemotherapy to meet the needs of patients and healthcare practitioners.

Methods: A previously developed population pharmacokinetic (PK) model was used for simulating PK exposure of the alternative regimens, which were selected by exposure-matching to the reference dose of 200 mg Q3W. PK-based criteria (peak concentration [C_{max}] within 25% and trough concentration [C_{trough}] within 20% of the reference dose were also used. Alternative dosing regimen exposures in the first least common time interval and at steady state were compared with the reference. Deviations from PK-based criteria were bridged using appropriate safety and efficacy references and exposure–response analyses using data from four phase 1, 2, and 3 clinical trials of TIS in patients with solid tumors, including gastric cancer and esophageal squamous cell carcinoma.

Results: Simulations at steady state shown here demonstrate that the TIS alternative dosing regimens of 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W produce comparable exposures to the 200 mg Q3W reference regimen. Although the simulated C_{max} at 300 mg Q4W and 400 mg Q6W were higher than with the 200 mg Q3W reference dose, these were below the C_{max} of the 5 mg/kg Q3W safety reference (Table). And while the C_{trough} for the 400 mg Q6W dosing regimen was lower than with the 200 mg Q3W reference dose, it was 10.7% higher compared with the 2 mg/kg efficacy reference dose; therefore, it was within the concentration range where a flat exposure–efficacy relationship of TIS has previously been established.

Conclusions: TIS alternative dosing regimens of 150 mg Q2W, 300 mg Q4W, and 400 mg Q6W are expected to result in similar safety and efficacy profiles as the 200 mg Q3W reference dosing regimen and may be used interchangeably for indications where 200 mg Q3W is approved.

Table. Steady-state PK exposure metrics for alternative TIS doses vs reference doses

Parameter	150 mg Q2W vs 200 mg Q3W	300 mg Q4W vs 200 mg Q3W	300 mg Q4W vs 5 mg/kg Q3W[a]	400 mg Q6W vs 200 mg Q3W	400 mg Q6W vs 5 mg/kg Q3W[a]	400 mg Q6W vs 2 mg/kg Q3W[b]
C_{max}	−5.8 (Yes)	31.4 (No)	−18.7 (Yes)	52.2 (No)	−5.8 (Yes)	–
$C_{average}$	12.3 (Yes)	12.6 (Yes)	–	0.4 (Yes)	–	–
C_{trough}	27.2 (Yes)	0.1 (Yes)	–	−28.4 (No)	–	10.7 (Yes)

Data are presented as difference (% = [GM_{test} − $GM_{reference}$/$GM_{reference}$] × 100) vs the 200 mg Q3W reference, [a]safety reference, or [b]efficacy reference (meets regulatory criteria, Yes/No).
$C_{average}$, average concentration; GM, geometric mean.