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 exposure-response (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 dosing schedules.

Method:

The analyses used data from patients with advanced solid tumors (n = 745) and classical Hodgkin lymphoma (cHL, n = 70) from three clinical studies who received tislelizumab doses ranging from 0.5 to 10 mg/kg (including current recommended dose of 200 mg Q3W). E-R efficacy analyses were performed for overall response rate (ORR) and E-R safety analyses were performed for immune-related adverse events (irAEs), infusion-related AEs, and AEs ≥ grade 3, AEs leading to dose modification, and drug discontinuation using logistic regression models. Impact of tumor type on E-R efficacy and safety analyses were also investigated.

Results:

E-R analysis indicated that there was slight trend for increase in ORR in solid tumors with steady-state maximum concentration, minimum concentration and average concentrations over the dose range tested. However, the increase in ORR over the exposure range was not considered to be clinically significant. Tislelizumab exposure was not associated with ORR in cHL patients. No E-R relationships were observed for safety endpoints irAEs, infusion-related AEs, AEs ≥ grade 3, AEs leading to drug discontinuation or dose modification among tumor types. Predictions with an alternate dose regimen of 400 mg Q6W showed that clinically significant differences in ORR and safety were not expected, compared with 200 mg Q3W.

Conclusion:

There was a lack of clinically significant E-R relationships for ORR and safety endpoints across a variety of advanced solid tumors and cHL for tislelizumab. These findings support the current dose regimen of 200 mg Q3W and further clinical testing of alternative dosing schedules that produce comparable exposure (eg, 400 mg Q6W).