The molecular binding mechanism of tislelizumab, an investigational anti-PD-1 antibody, is differentiated from pembrolizumab and nivolumab

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Programmed cell death protein 1 (PD-1) is an immune checkpoint receptor expressed by activated T, B, and NK cells, which interacts with its ligand PD-L1/L2 to inhibit T-cell proliferation and effector functions such as tumor cell killing and cytokine production. Two anti-PD-1 antibodies approved by the FDA, pembrolizumab and nivolumab, have shown efficacy in many cancer types, nevertheless there are some indications where limited efficacy is observed. Tislelizumab (BGB-A317), an investigational anti-PD-1 antibody, has demonstrated significant clinical activity (85.7% ORR, including 61.4% CR) in relapsed/refractory classical Hodgkin's lymphoma (R/R cHL). Additionally, tislelizumab is being studied in global pivotal trials in a number of malignancies, including non-small cell lung cancer, hepatocellular carcinoma, and esophageal squamous cell carcinoma. However, how tislelizumab binds to PD-1 has yet to be shown, particularly in comparison to pembrolizumab and nivolumab. Here we report the co-crystal structure of PD-1 extracellular domain and the Fab of tislelizumab. Tislelizumab interacts with IgV-like domain of PD-1 with an interface area of 1112 $Å^2$. Structure-guided mutagenesis of PD-1 and surface plasmon resonance were performed to compare the binding of tislelizumab, pembrolizumab and nivolumab to mutant and wild type PD-1. The dissociation rate (K_d) of tislelizumab from wild type PD-1 is about 100-fold and 50-fold slower than that of pembrolizumab and nivolumab, respectively. Gln75, Thr76, Asp77 and Arg86 on PD-1 are critical epitopes for tislelizumab, but mutation of them showed little effect on binding of PD-1 to pembrolizumab and nivolumab. Both the co-crystal structure and mutagenesis study identified the unique epitopes of tislelizumab that correlate to the extremely slow-off property of tislelizumab after binding to PD-1. In conclusion, we observed that tislelizumab is differentiated from pembrolizumab and nivolumab by its unique binding epitopes as well as binding kinetics.