Tumor Microenvironment Associated with Complete Response to Tislelizumab Monotherapy in Relapsed/Refractory Classical Hodgkin Lymphoma Reveals a Potentially Different Mechanism of Action

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Background: Tislelizumab, a humanized immunoglobulin 4 monoclonal anti-programmed cell death protein 1 (anti–PD-1) antibody, has an engineered Fc region that minimizes binding to Fcγ receptor (FcγR) on macrophages, thereby abrogating antibody-dependent phagocytosis (ADCP)-induced T-cell clearance. Tislelizumab demonstrated an overall response rate of 87.1% with a high complete response (CR) rate (62.9%) and was generally well tolerated in a phase 2 study in Chinese patients with relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL) (BGB-A317-203 study; clinicaltrials.gov identifier: NCT03209973). The present study explored the underlying mechanism of action (MOA) of tislelizumab and its potential contribution to the high CR rate associated with it in patients with R/R cHL.

Methods: Seventy patients with confirmed R/R cHL were included in this study. Tissue samples were collected at baseline for biomarker testing. Forty-one samples were evaluable for multiple immunohistochemistry (mIHC) assays, and 36 samples were evaluable for gene expression profiling (GEP). For programmed death-ligand 1 (PD-L1), CD8 (cytotoxic T-cell marker), CD68 (macrophage pan-marker), CD64 (FcγRI), and CD30, mIHC samples were stained using Opal 7-Color IHC kit. Spatial analysis for the markers was conducted using HALO software. GEP utilized the HTG EdgeSeq Precision Immuno-Oncology panel. Genes expressed differentially in CR and non-CR were identified using the Lima R Bioconductor package. Gene signature score was calculated by the gene set variation analysis method. Median value across the biomarker population was used as the cutoff to define biomarker high versus low group. Differential biomarker tests between CR and non-CR were conducted by Wilcoxon rank-sum test.

Results: For anti-PD-1 antibodies with a functional Fc, the Fc/FcγR interaction resulted in macrophage-induced T-cell clearance and dampened anti-tumor activity, while tislelizumab activity was not affected by macrophages in the mouse cancer model (Zhang T, et al. *Cancer Immunol Immunother.* 2018;67:1079–1090). In cHL clinical samples, we observed a similar CR rate for tislelizumab in FcγRI+ macrophages (CD68+CD64+) high versus low group (71.4% vs 60%, *P*=0.85 by Fisher-test). In the CD8+ T-cell high microenvironment where ADCP-induced T-cell clearance is more likely, neither the total number of CD68+/CD64+ cells (CR rate 86.6% for high vs 85.7% for low, n.s. by Fisher-test) nor the average number of CD68+CD64+ cells within 30 μm of CD8+ T cells (85.7% vs 80%, n.s. by Fisher-test) were observed to affect the CR rate.

Additional tumor microenvironment components that may contribute to the high CR rate were also explored. We found that FcγRI+ and CD8+ cell percentage by mIHC were higher in CR

patients (P=0.04 and P=0.08, CR vs non-CR). GEP results show that the tumor inflammation gene signature (TIS) (eg, CD8A, CCL5, PD-L1, IDO1, IFNG, CXCL9) were higher in CR patients (CR vs non-CR, P=0.04). Specific gene/gene signatures were associated with CR for different histology subtypes. In the mixed cellular subtype, CD8+ T cells by mIHC (P=0.0004) and the TIS gene signature by GEP (P=0.007) showed a larger difference between CR and non-CR. In the nodular sclerosis subtype, the extracellular matrix and fibroblast-related gene signature (eg, ICAM, COL1As, ITGAs, PDGFRB) were higher in CR patients (P=0.04, CR vs non-CR).

Conclusions: Tislelizumab demonstrated a high CR rate regardless of the FcγRI expressing macrophage abundance in the cHL tumor microenvironment, which may be a functional consequence of its engineered Fc region and may differentiate its MOA from the MOAs of other anti-PD-1 agents. CD8+ T-cell abundance and tumor inflammatory gene signatures in the microenvironment may be associated with higher CR rate for cHL patients treated with tislelizumab.