

Association Between Programmed Death-Ligand 1 (PD-L1) Expression and Gene Signatures of Response or Resistance to Tislelizumab Monotherapy in Hepatocellular Carcinoma (HCC)

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Background: PD-1/L1 inhibitors are treatment options for patients with HCC who have progressed after first-line sorafenib treatment. Tislelizumab, an anti-PD-1 monoclonal antibody, has demonstrated single-agent antitumor activity in patients with advanced, previously treated HCC in two early phase studies (NCT02407990, NCT04068519). Association of biomarkers, including PD-L1 expression and gene expression profiles (GEP), with response and resistance to tislelizumab were explored.

Methods: PD-L1 expression was evaluated on tumor cells (TC) using the VENTANA PD-L1 (SP263) assay in baseline tumor samples collected before or after sorafenib treatment. GEP were assessed using the 1392-gene HTG GEP EdgeSeq panel. Signature scores were calculated using the Gene Set Variation Analysis package with publicly available gene signatures (GS). Wilcoxon rank-sum test was used to analyze differential gene signatures (DEG); GS association with PFS and OS was evaluated using Cox proportional hazards models.

Results: Single-agent tislelizumab demonstrated antitumor activity in advanced, previously treated HCC (ORR=13%; CB [PR+SD >6 months]=31%, median PFS=3.3 months; median OS=13.3 months). PD-L1⁺ (TC≥1%) prevalence and GEP showed different patterns in samples collected before and after sorafenib exposure (**Figure**). While non-exposed samples (n=16) were enriched for immune suppressive signatures, sorafenib-exposed samples (n=41) showed higher PD-L1⁺ prevalence (53.7% vs 25%; $P=.08$) and immune-cell activation signatures along with co-inhibition molecules. In sorafenib-exposed samples, PD-L1 expression was positively correlated with CB ($P=.0027$) and a trend of longer PFS (HR=0.56, 95% CI:0.28-1.13). ORR was higher in PD-L1⁺ than PD-L1⁻ sorafenib-exposed samples (23.8% vs 0%; $P=.049$). DEG analysis in sorafenib-exposed samples demonstrated that NK-mediated cytotoxicity GS was positively correlated with CB ($P=.03$), as well as a trend of longer PFS (HR=0.43, 95% CI:0.17-1.06). Across the different analyses, no correlation with OS was

observed. Patients considered non-responders (NRs) were found clustered into three distinct GEP subgroups (NR1, NR2, NR3). Compared with responders, NR1 had enhanced angiogenesis signatures ($P=.01$), including TEK, KDR, HGF, and EGR1. Despite high inflamed tumor signatures, NR2 had increased expression of T-cell inhibition GS scores ($P=.01$), including CD274, CTLA4, TIGIT, and CD96. The NR3 subgroup showed higher cell-cycle GS scores compared with responders ($P=.05$), including E2F7, FOXA1, and FANCD2.

Conclusions: Prior sorafenib exposure appears to be associated with increased PD-L1 expression and tumor microenvironment-related GS, as well as response and PFS from tislelizumab in advanced HCC patients. Elevated angiogenesis, immune exhaustion, and cell-cycle GS levels may indicate resistance to single-agent PD-1 inhibitors and is suggestive of potential treatment strategies. Validation is warranted in future clinical trials (NCT03412773).

Figure

