ASSOCIATION BETWEEN PROGRAMMED DEATH-LIGAND 1 (PD-L1) EXPRESSION AND GENE SIGNATURES OF RESPONSE OR RESISTANCE TO TISLELIZUMAB MONOTHERAPY IN HEPATOCELLULAR CARCINOMA (HCC)

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 1). 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=0.08) and immune-cell activation signatures along with co-inhibition molecules. In sorafenib-exposed samples, PD-L1 expression was positively correlated with CB (P=0.0027) 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=0.049). DEG analysis in sorafenib-exposed samples showed that NK-mediated cytotoxicity GS was positively correlated with CB (P=0.03), 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=0.01), including TEK, KDR, HGF, and EGR1. Despite high inflamed tumor signatures, NR2 had increased expression of T-cell inhibition GS scores (P=0.01), including CD274, CTLA4, TIGIT, and CD96. The NR3 subgroup showed higher cell-cycle GS scores compared with responders (P=0.05), 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).

Acknowledgements This study was sponsored by BeiGene, Ltd. Writing and editorial assistance was provided by Regina Switzer, PhD, and Elizabeth Hermans, PhD (OPEN Health Medical Communications, Chicago, IL), and funded by the study sponsor.

Trial Registration NCT02407990, NCT04068519