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#### POTENTIAL MECHANISMS OF RESISTANCE IDENTIFIED THROUGH ANALYSIS OF MULTIPLE BIOMARKERS IN IMMUNE HOT NON-RESPONDERS WITH NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH TISLELIZUMAB

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**Background** Tislelizumab, an anti-PD-1 monoclonal antibody, has demonstrated clinical benefit for patients with NSCLC. The underlying response and resistance mechanisms to tislelizumab treatment remain unknown.

**Methods** Baseline tumor samples from 59 nonsquamous (NSQ) and 41 squamous (SQ) NSCLC patients treated with tislelizumab monotherapy (NCT02407990 and NCT04068519) were tested for gene mutations using large panel next generation sequencing and RNA expression using gene expression profiling (GEP; Precision Immuno-Oncology Panel, HTG Molecular

Diagnostics). GEP analyses of NSQ and SQ NSCLC were performed separately due to different gene expression patterns.

**Results** The ORR, mPFS, and mOS in this pooled NSCLC cohort were 15.2% (95% CI: 9.0, 23.6), 4.1 months (95% CI: 2.20, 6.11), and 15.1 months (95% CI: 11.20, NE), respectively, with a median study follow-up of 15.3 months (95% CI: 14.06, 15.90). Non-responders (NRs) exhibited distinct tumor and immune gene signature profiles and could be clustered into two subgroups: NR1 and NR2. Compared with responders, NR1 had elevated cell cycle signatures in both NSQ (P=0.2) and SQ (P=0.03) cohorts, and a trend of decreased inflamed gene signature profiles. However, NR2 showed comparable or even higher tumor inflammation (18-gene), and CD8+ T-cell signature scores in both NSQ and SQ cohorts and could be classified as immune hot. To explore the resistance mechanisms of immune hot NRs, differentially expressed gene analyses between immune hot NR2 and responders were performed. M2 macrophage and Treg signature scores were higher in NR2 in both NSQ (M2, P=0.05; Treg, P=0.03) and SQ (M2, P=0.05 [subgroup of NR2]; Treg, P=0.03) cohorts; significantly higher expression of immune regulatory genes included PIK3CD, CCR2, CD244, IRAK3, and MAP4K1 (P<0.05) in NSQ and PIK3CD, CCR2, CD40, CD163, and MMP12 (P<0.05) in SQ. Significantly higher epithelial-mesenchymal transition (EMT) and angiogenesis gene expression, including SNAI1, FAP, VEGFC, and TEK (P<0.05) genes, were also observed in SQ NR2. Moreover, gene mutation analysis identified seven immune hot NR patients harboring either driver mutations (RET fusion, ROS1 fusion, BRAF, and PIK3CA amp) or well-established resistance mutations (loss of function mutation in JAK2, STK11, and MDM2 amplification).

**Conclusions** Despite the presence of immune hot features, a subgroup of tislelizumab NRs with NSCLC were identified. High levels of immune suppressive factors, such as M2 macrophage and Treg signatures, angiogenesis, and EMT genes, as well as the existence of driver/resistance mutations, may indicate mechanisms of resistance of immune hot NRs, highlighting potential novel treatment targets.

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**Trial Registration** NCT02407990 and NCT04068519

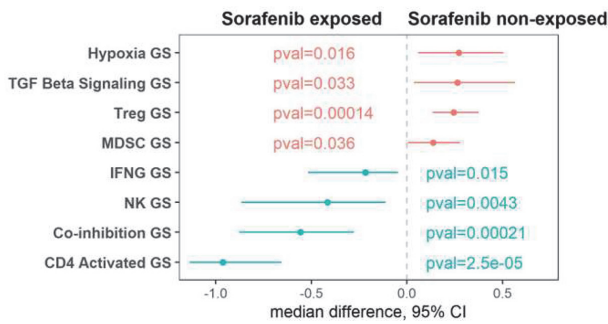
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#### ASSOCIATION BETWEEN PROGRAMMED DEATH-LIGAND 1 (PD-L1) EXPRESSION AND GENE SIGNATURES OF RESPONSE OR RESISTANCE TO TISLELIZUMAB MONOTHERAPY IN HEPATOCELLULAR CARCINOMA (HCC)

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**Background** PD-1/L1 inhibitors are treatment options for patients with HCC who have progressed after first-line



**Abstract 77 Figure 1** Median difference in gene signatures before and after sorafenib exposure

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<sup>+</sup> (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<sup>+</sup> 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<sup>+</sup> than PD-L1<sup>-</sup> sorafenib-exposed samples (23.8% vs 0%; P=0.049). DEG analysis in sorafenib-exposed samples demonstrated 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).

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**T-CELL, MHC I, AND TUMOR INTRINSIC GENE SIGNATURES PREDICT CLINICAL BENEFIT AND RESISTANCE TO TISLELIZUMAB MONOTHERAPY IN PRETREATED PD-L1+ UROTHELIAL CARCINOMA**

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**Background** Tislelizumab, an anti-PD-1 monoclonal antibody, demonstrated efficacy as monotherapy in patients with previously treated PD-L1+ urothelial carcinoma (UC) during a phase 2 study (NCT04004221). Here, gene expression profiles correlating with response and resistance to tislelizumab treatment are reported.

**Methods** Gene expression profiling (GEP) was conducted on baseline tumor samples from 100 Chinese patients with UC enrolled in the phase 2 tislelizumab study using a 1,392-gene panel by HTG EdgeSeq. Gene Signature (GS) scores were calculated using the Gene Set Variation Analysis package. Differential gene expression (DEG) analysis was performed between responders and non-responders using the Wilcoxon test; survival was evaluated using the Cox proportional hazards model and the odds of tumor response for subgroup analysis was estimated by logistic regression.

**Results** Of patients with available confirmed response results (n=85), DEG analysis found that responders had significantly higher T-cell GS (CD3D, CD3E, CD3G, CD6, SH2D1A, TRAT1) (P=0.04) and MHC I GS (HLA-A, TAP1) (P=0.05), respectively. Using median GS scores as a cutoff, improvement in overall survival (OS) was observed in T-cell-high versus T-cell-low groups (P=0.01) and a trend of longer OS was seen between MHC I-high versus MHC I-low groups. Patients in T-cell and MHC I-double-high subgroups showed further

**Abstract 78 Table 1** T-cell and MHC I gene signatures associated with clinical efficacy of tislelizumab in patients with UC

Population	N	ORR, %	Odds Ratio* (P value; 95% CI)	Median OS, mo (95% CI)	Hazard Ratio* (95% CI)	Median PFS, mo (95% CI)	Hazard Ratio* (95% CI)
Biomarker-evaluable	100	23	NA	9.82 (8.25, 13.01)	NA	2.1 (2.07, 4.07)	NA
T-cell high & MHC I high	30	40	NA	15.2 (10.8, NA)	NA	5.26 (3.58, 13.47)	NA
T-cell high/MHC I low & T-cell low/MHC I high	40	20	0.30 (P=0.03; 0.1, 0.91)	8.25 (4.8, NA)	1.66 (0.91-3.06)	2.07 (2, 4.4)	1.38 (0.80-2.4)
T-cell low/MHC I low	30	10	0.16 (P=0.01; 0.04, 0.69)	8.15 (5.32, 12.19)	2.15 (1.14-4.04)	2.07 (1.91, 2.96)	2.15 (1.14-3.51)

\*T-cell high & MHC I high as reference for all subgroup analysis.