TUMOR-IMMUNE SIGNATURES ASSOCIATED WITH RESPONSE OR RESISTANCE TO TISLELIZUMAB IN PATIENTS WITH PREVIOUSLY TREATED ADVANCED HEPATOCELLULAR CARCINOMA (HCC)

¹Chiun Hsu*, ²Julien Edeline, ³Gianluca Masi, ⁴Yuk Ting Ma, ⁵Weilin Wang, ⁶Henning Wege, ⁷Cong Fei, ⁷Chen Ling, ⁸Xiaopeng Ma, ⁸Pei Zhang, ⁷Ruiqi Huang, ⁷Xikun Wu, ⁸Zhirong Shen, ⁸Bai Li, ⁹Sandra Chica Duque, ¹⁰Zhiqiang Meng. ¹National Taiwan University College of Medicine, Taipei City, Taiwan; ²Centre Eugène Marquis, Rennes, France; ³University of Pisa, Pisa, Italy; ⁴University of Birmingham, Birmingham, UK; ⁵First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; ⁶Gastroenterology and Hepatology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; ⁷BeiGene (Shanghai) Co., Ltd., Shanghai, China; ⁸BeiGene (Beijing) Co., Ltd., Beijing, China; ⁹BeiGene (San Mateo) Co., Ltd., San Mateo, CA, USA; ¹⁰Fudan University Shanghai Cancer Center, Shanghai, China

Background Tislelizumab, an anti-programmed cell death protein-1 monoclonal antibody, demonstrated clinical activity and was well tolerated in patients with previously treated advanced HCC in the open-label, multicenter, Phase 2 RATIONALE-208 study (NCT03419897). We report exploratory analysis of the association of gene expression profiles (GEPs) with response to tislelizumab in patients with previously treated advanced HCC.

Methods Eligible patients who had received ≥ 1 prior line of systemic therapy for advanced HCC received tislelizumab (200 mg) intravenously once every 3 weeks and tumor response was evaluated per RECIST v.1.1. Baseline tumor sampling was optional and GEP analysis was performed using HTG EdgeSeq Precision Immuno-Oncology panel in 138 tumor samples (fresh tumor, n=6; archival tumor, n=132). Signature scores were calculated using Gene Set Variation Analysis package with publicly available gene signatures (GS). GS or genes differentially expressed between responders and non-responders (NRs) were determined using Wilcoxon rank-sum test and modified t-test with limma. Distributions of overall survival (OS) and progression-free survival (PFS) for GS subgroups (high vs low) were estimated by Kaplan-Meier method. Hierarchical clustering of NRs was achieved using 1-Pearson's correlation and average linkage. All statistical analysis results are post-hoc exploratory and thereby p values are descriptive.

Results 249 patients were enrolled and received ≥ 1 dose of tislelizumab; 138 patients had evaluable GEP data, of which 132 patients had evaluable GEP and tumor response data. GEP analysis demonstrated that CD4 T cell, CD8 T cell, cytotoxic T lymphocyte and major histocompatibility complex class I signatures were enriched in responders, and cancer-associated fibroblasts, angiogenesis and hypoxia signatures were enriched in NRs (figure 1). CD8B_PDCD1_9, a novel GS identified, comprises 9 genes highly expressed in responders: CD8B, CXCL13, KLRD1, NKG7, HLA-A, HLA-G, LAG3, PDCD1 and KREMEN1. Higher objective response rate (ORR; $p < 0.0001$, by Fisher's exact test) and longer PFS ($p = 0.005$, by log rank test) were observed in patients with high vs low CD8B_PDCD1_9 score (ORR: 26% vs 3%; median PFS: 2.8 months vs 1.8 months). To explore the heterogeneity of molecular features in NRs, NRs were clustered into 3 subgroups using a series of tumor-immune GS. OS and PFS for the 3 NR subgroups with distinct GS are summarized in table 1.

Abstract 360 Figure 1 Correlation between GS and ORR in patients with previously treated advanced HCC treated with tislelizumab monotherapy

Abstract 360 Table 1 OS and PFS of NR subgroups

NR subgroups	N	Highly enriched GS	Median OS months, (95% CI)	Median PFS months, (95% CI)
NR1	36	DNA repair Cell cycle	14.0 (9.7, NE)	1.4 (1.4, 2.7)
NR2	10	Pembro 18 genes Treg genes Immune inhibition	14.3 (3.1, NE)	5.8 (2.6, 14.4)
NR3	67	Angiogenesis Hypoxia	8.6 (6.8, 12.4)	1.4 (1.4, 2.7)

CI, confidence interval; NE, not evaluable; GS, gene signature; NR, non-responder; OS, overall survival; PFS, progression-free survival

Conclusions This exploratory analysis identified distinct GS associated with tumor response and resistance to tislelizumab monotherapy in patients with previously treated advanced HCC and increases our understanding of the tumor microenvironment. Further GEP analyses will be undertaken in an ongoing Phase 3 study (NCT03412773).

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Trial Registration NCT03419897

Ethics Approval This study was conducted according to the ethical principles of the Declaration of Helsinki, Good Clinical Practice guidelines, the principles of informed consent and the requirements of the public registration of clinical trials. Written informed consent was obtained from each patient prior to screening. The protocol was approved by the institutional ethics committee and was monitored by a safety monitoring committee.

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