Tumor-immune signatures associated with response or resistance to tislelizumab in patients with previously treated advanced hepatocellular carcinoma (HCC)

Authors:

Chiun Hsu[1], Julien Edeline[2], Gianluca Masi[3], Yuk Ting Ma[4,5], Weilin Wang[6], Henning Wege[7], Cong Fei[8], Chen Ling[8], Xiaopeng Ma[9], Pei Zhang[9], Ruiqi Huang[8], Xikun Wu[8], Zhirong Shen[9], Bai Li[9], Sandra Chica Duque[10], Zhiqiang Meng[11]

Affiliations:

[1]Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei, Taiwan; [2]Centre Eugène Marquis, Rennes, France; [3]Department of Translational Research and New Technologies in Medicine, University of Pisa, Pisa, Italy; [4]University of Birmingham, Birmingham, UK; [5]University Hospital Birmingham NHS Foundation Trust, Birmingham, UK; [6]Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [7]Department of Medicine, Gastroenterology and Hepatology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [8]BeiGene (Shanghai) Co., Ltd., Shanghai, China; [9]BeiGene (Beijing) Co., Ltd., Beijing, China; [10]BeiGene (San Mateo) Co., Ltd., San Mateo, CA, USA; [11]Department of Integrative Oncology, Fudan 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:

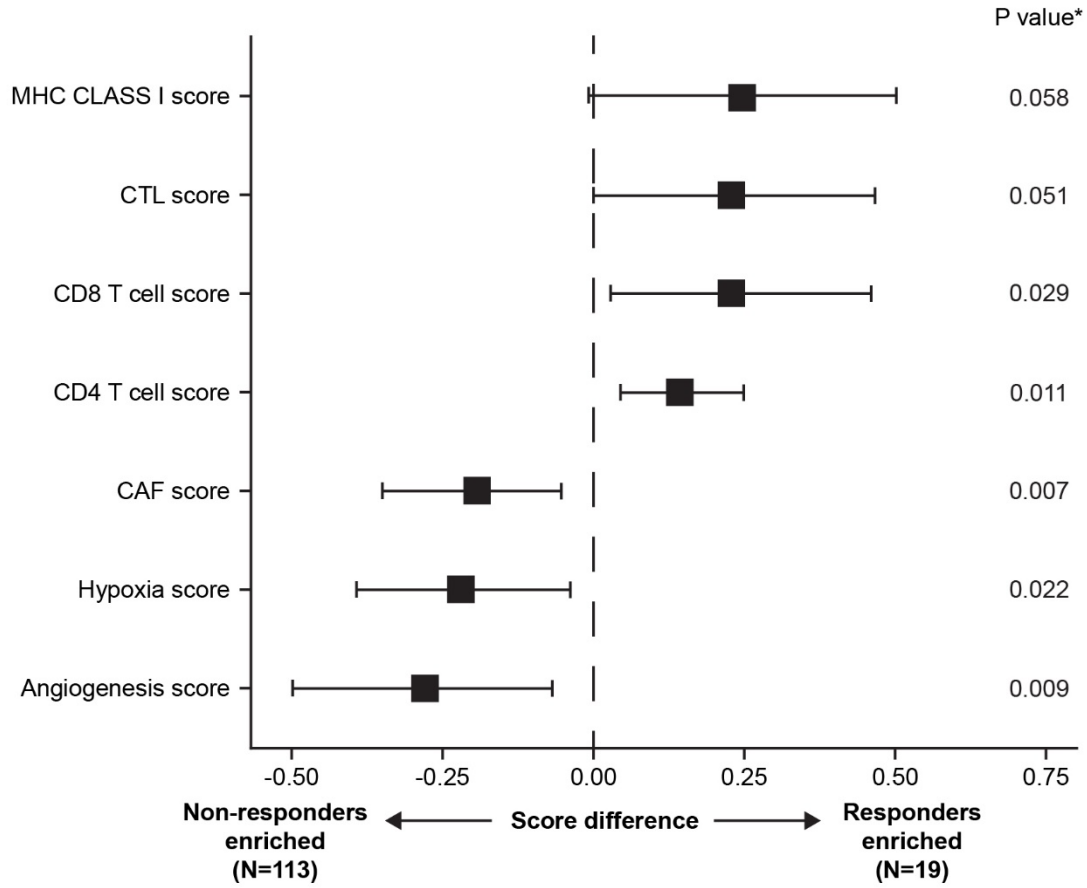
249 patients were enrolled and received ≥1 dose of tislelizumab; 138 patients had evaluable GEP data, of which 132 patients had evaluable GEP and tumor response data. GEP analysis demonstrated that CD4 T cell, CD8 T cell, cytotoxic T lymphocyte and major histocompatibility complex class I signatures 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.**

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 on-going Phase 3 study (NCT03412773).

Figures/tables:

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



*Median of the difference (Wilcoxon test) and the nonparametric confidence interval
MHC, major histocompatibility complex; CTL, cytotoxic T-cell; CAF, cancer-associated fibroblasts

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