T-CELL-, MHC I-, AND TUMOR-RELATED GENE SIGNATURES PREDICT CLINICAL BENEFIT AND RESISTANCE TO TISLELIZUMAB MONOTHERAPY IN PRETREATED PD-L1–HIGH UROTHELIAL CARCINOMA

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BACKGROUND

- Urothelial carcinoma (UC) is the most common histologic type of bladder cancer and has a low 5-year survival rate when diagnosed at an advanced stage[1]
  - In China, UC is the sixth most common cancer in men and the thirteenth most common in women[2]
- While several FDA-approved anti-programmed cell death protein-1/programmed death-ligand 1 (PD-1/PD-L1) therapies have exhibited improved efficacy in late-line UC,[3] the mechanisms of response or resistance are not clear and warrant further exploration
- Tislelizumab, a humanized IgG4 monoclonal antibody with high affinity and binding specificity for PD-1[4] is the first PD-1/PD-L1 blockade approved in PD-L1–high UC[5] by the National Medical Products Administration (NMPA) in China (April 2020)
- Here, retrospective analyses of gene expression profiles correlating with response and resistance to tislelizumab treatment are presented

METHODS

Study Design

- This phase 2 trial (BGB-A317-204; NCT04004221) conducted in China and Korea assessed the safety, tolerability, and efficacy of tislelizumab (200 mg every 3 weeks) in patients with PD-L1–high UC previously treated with ≥1 platinum-containing therapy
- Patients were considered PD-L1–high if ≥25% of tumor/immune cells expressed PD-L1 as assessed by the VENTANA™ PD-L1 (SP263) assay
- One hundred Chinese patients had evaluable gene expression profiling (GEP) data and were further analyzed

Gene Expression Profiling

- GEP analysis was conducted on baseline tumor samples (formalin-fixed, paraffin-embedded) using HTG EdgeSeq Precision Immuno-oncology panel
- Gene signature scores were calculated using the Gene Set Variation Analysis package and publicly available gene signatures
- Non-responder subgroups were hierarchically clustered by Euclidean distance metrics with average linkage by columns

Statistical Analysis

- Objective response rate (ORR) and Clopper-Pearson 95% confidence intervals (CIs) were calculated
- The Kaplan-Meier method was used to estimate median overall survival (OS), progression-free survival (PFS), and 95% CIs
- Differential gene expression (DEG) analysis was performed between responders and non-responders using the Wilcoxon rank-sum test; the Bonferroni method was used to adjust for multiple comparisons
- Kaplan-Meier curves of biomarker subgroups were compared using the log-rank test; hazard ratios were estimated using the Cox proportional hazard model

RESULTS

Patient Characteristics

- Baseline characteristics and clinical outcomes of the 100 GEP-evaluable patients were comparable with the overall population in this trial (Table 1)

T-cell and MHC I Signatures Were Associated With Response and Survival Benefits

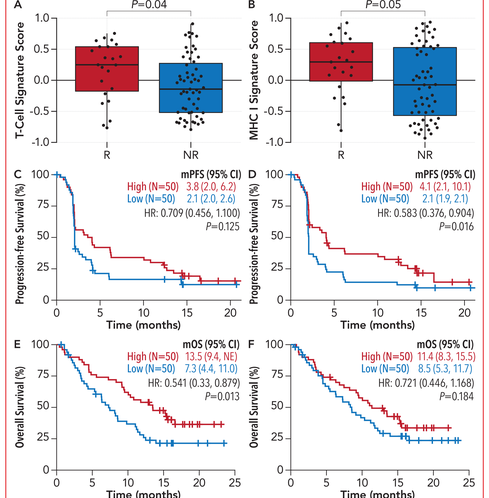
- T-cell[6] (*CD3D, CD3E, CD3G, CD6, SH2D1A, TRAT1*) and major histocompatibility complex class I (MHC I) signatures[7] (*HLA.A, TAP1*) were enriched in responders (Figure 1A and 1B)
- Using median signature score as the cutoff:
  - Significant improvement of OS (median OS: 13.5 vs 7.3 months, *P*=0.013, Figure 1E) and a trend of longer PFS (median PFS: 3.8 vs 2.1 months, *P*=0.125, Figure 1C) was observed in the T-cell–high group versus the T-cell–low group
  - Significant improvement of PFS (median PFS: 4.1 vs 2.1 months, *P*=0.016, Figure 1D) and a trend of longer OS (median OS: 11.4 vs 8.5 months, *P*=0.184, Figure 1F) was observed in the MHC I–high group versus the MHC I–low group

Table 1: Baseline Characteristics and Clinical Outcomes

Characteristic		Overall (n=113)	GEP Evaluable (n=100)
Age, n (%)	<65	44 (38.9)	34 (34.0)
	≥65	69 (61.1)	66 (66.0)
Sex, n (%)	Male	84 (74.3)	75 (75.0)
	Female	29 (25.7)	25 (25.0)
Known metastasis, n (%)	Lymph node only	25 (22.3)	23 (23.0)
	Liver metastasis	33 (29.5)	29 (29.0)
	Visceral metastasis	87 (77.7)	77 (77.0)
Number of previous regimens, n (%)	1	69 (61.1)	61 (61.0)
	2	37 (32.7)	32 (32.0)
	≥3	7 (6.2)	7 (7.0)
Response, n (%)	CR	10 (8.8)	10 (10.0)
	PR	15 (13.2)	13 (13.0)
	SD	15 (13.2)	12 (12.0)
	PD	51 (45.1)	47 (47.0)
	Non-CR/Non-PD	4 (3.5)	3 (3.0)
	NE	18 (15.9)	15 (15.0)
ORR, % (95% CI)[a]		22 (14.9, 30.9)	23 (15.2, 32.5)
Median PFS, months (95% CI)		2.2 (2.1, 3.9)	2.1 (2.1, 4.0)
Median OS, months (95% CI)		9.8 (7.5, 12.5)	9.8 (7.5, 12.2)

[a]Objective response rate was the proportion of patients with confirmed complete/partial responses using RECIST v1.1 in the overall /GEP-evaluable population.
Abbreviations: CI, confidence interval; CR, complete response; GEP, gene expression profile; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Figure 1: DEG Analysis by Clinical Response and Kaplan-Meier Curves for PFS and OS by T-cell and MHC I Signatures

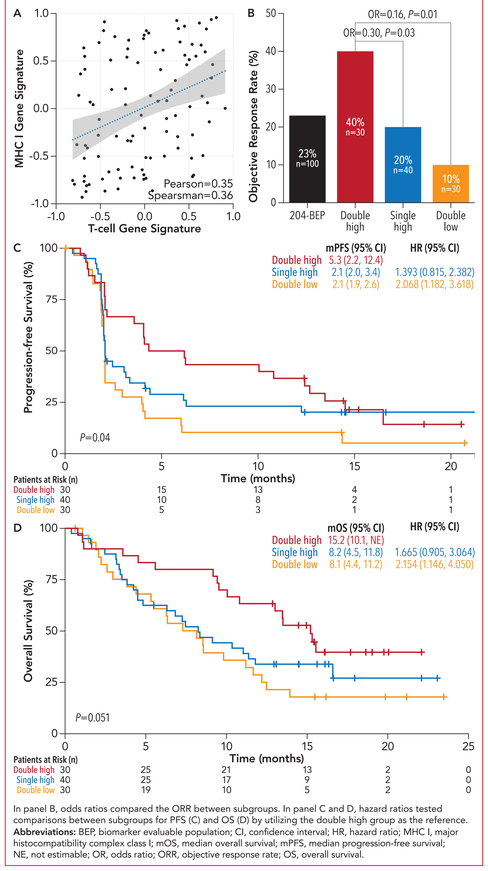


Abbreviations: CI, confidence interval; HR, hazard ratio; MHC I, major histocompatibility complex class I; mOS, median overall survival; mPFS, median progression-free survival; NE, not estimable; NR, non-responder; OS, overall survival; PFS, progression-free survival; R, responder.

Double-High Signature Score Subgroup Showed the Highest ORR and the Longest Survival Benefit

- Correlation of T-cell and MHC I signatures were low (Figure 2A)
- Using the median as a cutoff, three subgroups were identified by combining both signatures: double high (30/100), single high (40/100), and double low (30/100)
- The double-high subgroup (T-cell–high and MHC I–high groups; ORR=40%) had higher ORR compared with either the single-high (ORR=20%, *P*=0.03) or double-low (ORR=10%, *P*=0.01) subgroups (Figure 2B)
- Significantly longer PFS (*P*=0.04) and OS (*P*=0.05) were observed for patients with double-high signature score (Figure 2C and 2D)

Figure 2: DEG Analysis by Clinical Response and Kaplan-Meier Curves for PFS and OS by T-cell Signature and MHC I Signature

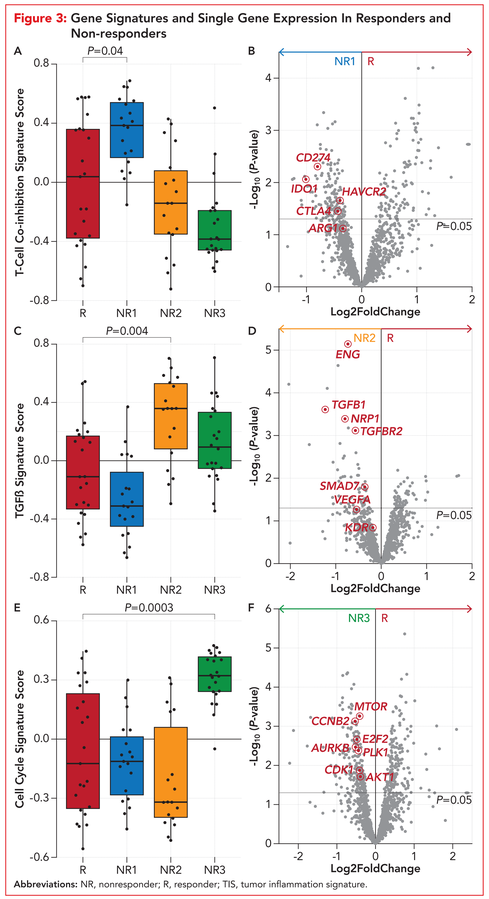


In panel B, odds ratios compared the ORR between subgroups. In panel C and D, hazard ratios tested comparisons between subgroups for PFS (C) and OS (D) by utilizing the double high group as the reference.
Abbreviations: BEP, biomarker evaluable population; CI, confidence interval; HR, hazard ratio; MHC I, major histocompatibility complex class I; mOS, median overall survival; mPFS, median progression-free survival; NE, not estimable; OR, odds ratio; ORR, objective response rate; OS, overall survival.

Differential Signature and Single Gene Expression Between Responders and Non-responders

- Non-responders were clustered into three distinct subgroups (NR1, NR2, and NR3) according to immune- and tumor-related gene signatures (Table 2)
- With a comparable tumor inflammation signature (TIS) to responders, NR1 had significantly higher expression of T-cell co-inhibition signatures (Figure 3A, *P*=0.04)
- NR2 was enriched for TGFβ signaling (Figure 3C, *P*=0.004)
- NR3 exhibited non-inflamed features (decreased TIS [Supplemental Figure 1, *P*=0.01]), but was enriched for cell cycle signatures (Figure 3E, *P*=0.0003)
- Key genes enriched in each non-responder group are shown in Figure 3B, 3D, and 3F

Figure 3: Gene Signatures and Single Gene Expression In Responders and Non-responders



Abbreviations: NR, nonresponder; R, responder; TIS, tumor inflammation signature.

CONCLUSIONS

- T-cell and MHC I signatures were associated with better clinical response and longer PFS and OS after tislelizumab treatment
- Combining high T-cell signatures with high MHC I signatures identified a subgroup with improved clinical benefit (40% ORR, 5.26-month median PFS and 15.2-month median OS)
- Distinct gene expression profiles were negatively correlated with clinical benefit, indicating the presence of a potential resistance signal:
  - Elevated immune checkpoint and suppressive immune cell signatures in inflamed non-responders
  - High expression of TGFβ signaling and angiogenesis-related genes
  - Low tumor inflammation signature with enriched cell cycle signature
- The association between gene expression biomarkers and clinical benefit could enhance our understanding of the process of adaptive antitumor immunity and also indicate a potential novel combination treatment strategy
- Due to the limitations associated with a single-arm study, the potential predictive role of the gene signatures discussed above warrant further exploration in an ongoing phase 3 study (RATIONALE 310; BGB-A317-310; NCT03967977)

Non-responders Could Be Clustered Into Three Distinct Subgroups According to the Immune- and Tumor-related Gene Signatures

Table 2: Immune and Tumor Gene Signatures Utilized for Non-responder Subgroups Clustering

Antitumor Activity	Immune Cells		Feature of Tumor
TIS	Macrophage	CD8 T cell	Endothelial cells
Cytotoxic activity	M1 Macrophage	T cell	Focal adhesion
IFNγ	M2 Macrophage	DC	EMT
MHC class I	Mast cell	NK	Angiogenesis
Checkpoint-T cell	Neutrophils	MDSC	TGFβ signaling
Checkpoint-APC		B cell	Cell cycle

Abbreviations: APC, antigen presentation cell; DC, dendritic cell; EMT, epithelial-mesenchymal transition, MDSC, myeloid-derived suppressor cell; MCH, major histocompatibility complex; NK, natural killer cell; TIS, tumor inflammation signature.

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