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

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BACKGROUND

- Liver cancer was the sixth most common type of cancer and the fourth leading cause of cancer death worldwide in 2018, with 841,080 new cases worldwide[1,2]
  - Hepatocellular carcinoma (HCC) accounted for 85% to 90% of all reported liver cancer cases[1,2]
- Sorafenib as a treatment option for advanced-stage HCC yields moderate survival benefit[3]
- Recently, treatment with programmed cell death protein-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors in HCC have shown clinical benefit[4,5,6]
  - Response or resistance mechanisms are not yet clear, highlighting an unmet need to identify optimal biomarkers that can predict response
- Exploring immune- and tumor-transcriptomic features and their association with anti-PD-1 efficacy may increase the understanding of the tumor microenvironment in HCC and aid in the identification of potential response/resistance mechanisms
- Tislelizumab, an anti-PD-1 monoclonal antibody, has demonstrated single-agent antitumor activity in patients with advanced, previously treated HCC in two phase 1 studies (BGB-A317-001 [NCT02407990], BGB-A317-102 [NCT04068519])
  - Biomarkers, including PD-L1 expression and gene expression profiles (GEPs), and their association with response and resistance to tislelizumab were explored in these studies

METHODS

Study Design

- Pooled analysis from two clinical trials were used:
  - BGB-A317-001 (NCT02407990): First-in-human, multicenter, phase 1a/1b dose-escalation/indication-expansion study
  - BGB-A317-102 (NCT04068519): Chinese, multicenter, phase 1/2 study
  - Samples from both studies were analyzed from patients with previously treated advanced HCC
- Previous reports have shown increased PD-L1 expression on tumor cells (TCs) after sorafenib treatment[7]
- In this study, sorafenib exposed samples were defined as tissue samples collected after a record of sorafenib treatment and sorafenib non-exposed samples were defined as tissue samples collected prior to record of sorafenib treatment
- PD-L1 expression was evaluated on TCs using the VENTANA PD-L1 (SP263) assay in baseline tumor samples from 62 patients
- Clinical benefit (CB) was defined as the proportion of patients who have complete response, partial response, and stable disease that is ≥24 weeks in duration per Response Evaluation Criteria in Solid Tumors v1.1

Gene Expression Profiling

- Gene expression profiling using the HTG EdgeSeq Precision Immuno-Oncology Panel was performed on baseline tumor samples (formalin-fixed, paraffin-embedded blocks or cut slides)
- Signature scores were calculated using the Gene Set Variation Analysis package with publicly available gene signatures
- Differentially expressed gene signature (DEG) analysis was performed between responders (Rs) and non-responders (NRs) using a Wilcoxon rank-sum test
- Non-responder subgroups were hierarchically clustered by one minus Pearson's correlation with average linkage by columns

Statistical Analysis

- Kruskal-Wallis test was used to detect overall response effect, and pairwise Wilcoxon test was used to detect differences between two response subgroups
  - Bonferroni method was used to adjust multiple comparisons for each signature
- Potential associations with survival were analyzed using a log-rank test and Cox proportional hazards model

RESULTS

Patient Characteristics

- Of the 68 HCC patients enrolled in the BGB-A317-001 and -102 studies, 62/68 (91%) had sample collection and sorafenib treatment records available for analysis
  - Patient baseline characteristics and clinical efficacy are shown in Table 1

Table 1: Baseline Characteristics and Clinical Outcome

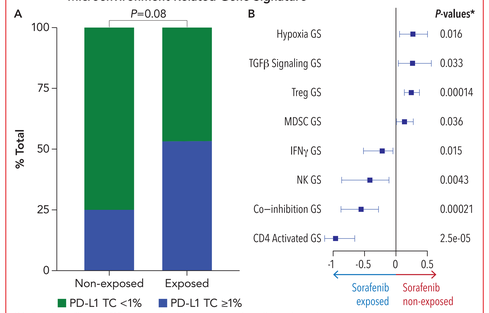
Characteristic		ITT (N=68)	GEP (N=62)
Age, n (%)	<65	52 (76.5)	47 (75.8)
	≥65	16 (23.5)	15 (24.2)
Sex, n (%)	Male	56 (82.4)	51 (82.3)
	Female	12 (17.6)	11 (17.7)
Tumor stage, n (%)	Stage III	4 (5.9)	2 (3.2)
	Stage IV	64 (94.1)	60 (96.8)
Histologic grade at baseline, n (%)	Well differentiated	19 (50.0)	17 (47.2)
	Moderately differentiated	12 (31.6)	12 (33.3)
	Poorly differentiated	7 (18.4)	7 (19.4)
ECOG score at baseline, n (%)	0	27 (39.7)	23 (37.1)
	1	41 (60.3)	39 (62.9)
AFP (ng/ml), n (%)	≥400	28 (29.4)	26 (41.9)
	<400	30 (44.1)	26 (41.9)
Objective response rate, % (95% CI)		13.24 (6.23, 23.64)	14.52 (6.86, 25.78)
Median PFS, months (95% CI)		3.33 (2.10, 4.07)	3.57 (2.13, 4.07)
Median OS, months (95% CI)		13.3 (11.13, NE)	12.97 (11.13, NE)
Median follow-up, months (95% CI)		14.47 (8.50, 17.47)	14.03 (8.50, 17.47)

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GEP, gene expression profile; ITT, intent-to-treat; NE; not evaluable; OS, overall survival; PFS, progression-free survival; SD, standard deviation.

Prevalence of PD-L1 TC ≥1% and GEP Analysis Showed Different Patterns in Sorafenib Exposed and Non-Exposed Samples

- Sorafenib-exposed (n=41) samples had a higher prevalence of PD-L1 TC ≥1% compared with non-exposed samples (n=16) (53.7% vs 25%; *P*=0.08; Figure 1A)
- In sorafenib non-exposed samples, multiple immune suppressive factors were enriched, including immune-related (regulatory T cell [Treg] and myeloid-derived suppressor cell) and tumor intrinsic (TGFβ and hypoxia) signatures
- In sorafenib-exposed samples, immune cell activation signatures were enriched along with the co-inhibition signature (Figure 1B)

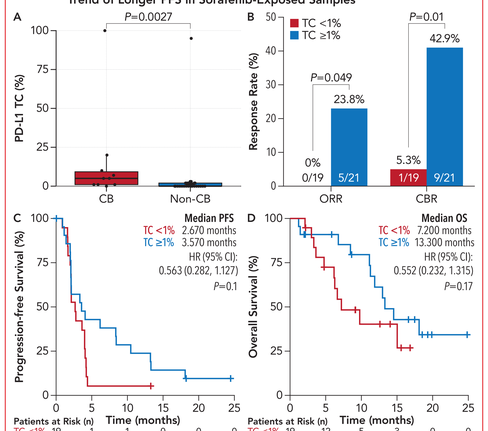
Figure 1: Prior Sorafenib Exposure May Affect PD-L1 Expression as Well as Tumor Microenvironment-Related Gene Signature



*Median of the difference (Wilcoxon test) and the nonparametric confidence interval.
Abbreviations: GS, gene signature; IFNγ, interferon gamma; MDSC, myeloid-derived suppressor cell; NK, natural killer; PD-L1; programmed death-ligand 1; TC, tumor cell; TGFβ, transforming growth factor beta; Treg, regulatory T cell.

- In sorafenib-exposed samples, PD-L1 TC expression was significantly higher in patients with CB versus patients with no clinical benefit (non-CB) as revealed by DEG and box-plot analysis (*P*=0.0027; Figure 2A)
- Higher objective response rates (ORRs) were observed in patients with PD-L1 TC ≥1% compared with patients with PD-L1 TC <1% (ORR=23.8% vs 0%; *P*=0.049; Figure 2B)
- A longer progression-free survival (PFS) and overall survival (OS) trend were linked to patients with PD-L1 TC ≥1%, and separation of Kaplan-Meier curves between the 2 arms was observed (Figure 2C and 2D)

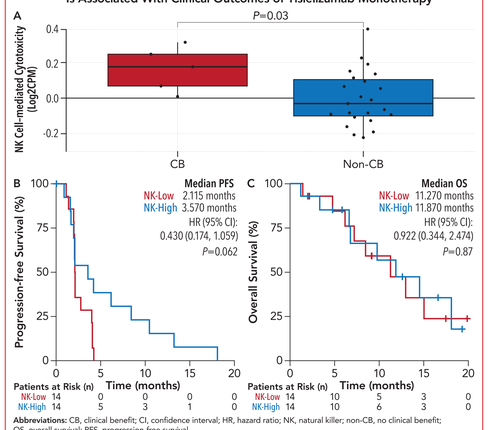
Figure 2: PD-L1 Expression Was Positively Correlated With Clinical Benefit and a Trend of Longer PFS in Sorafenib-Exposed Samples



Abbreviations: CB, clinical benefit; CBR, clinical benefit rate; CI, confidence interval; HR, hazard ratio; non-CB, no clinical benefit; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TC, tumor cell.

- In sorafenib-exposed samples, the natural killer (NK) cell–mediated cytotoxicity signature was significantly higher in tumors from CB versus non-CB as revealed by DEG and box-plot analysis (*P*=0.03; Figure 3A)
- A trend of improved PFS was observed in patients with NK cytotoxicity-high versus NK cytotoxicity-low signatures (median PFS: 3.57 vs 2.12, *P*=0.062; Figure 3B)
- No significant association between NK cytotoxicity signature and OS was observed (Figure 3C)

Figure 3: In Sorafenib-Exposed Samples, Natural Killer Cell–Mediated Cytotoxicity Is Associated With Clinical Outcomes of Tislelizumab Monotherapy



Abbreviations: CB, clinical benefit; CI, confidence interval; HR, hazard ratio; NK, natural killer; non-CB, no clinical benefit; OS, overall survival; PFS, progression-free survival.

- Monotherapy NRs could be clustered into three distinct GEP subgroups according to the immune and gene signatures listed in Table 2

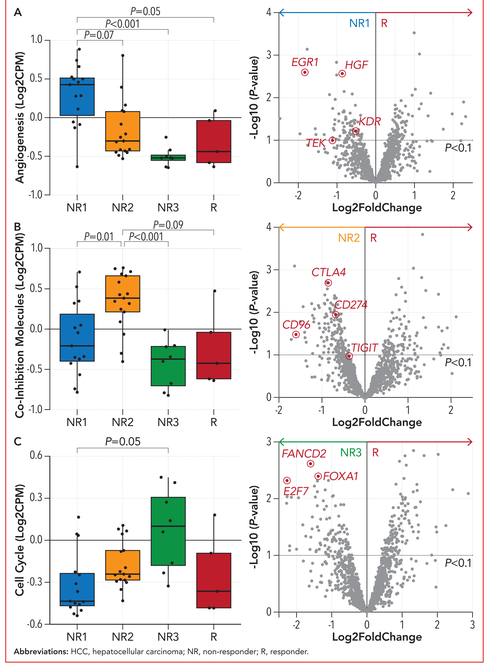
Table 2: Immune and Tumor Gene Signatures Utilized for NR Subgroup Clustering

Antitumor Immune Activity		Immune Cell Population Abundance			Feature of Tumor	
Antigen presentation	IFNγ	CD4/CD8	Mast cell	NK cell	Cell cycle	DNA repair
Cytotoxicity	Immune checkpoint	Exhausted CD8	Dendritic cell	Neutrophil	TGFβ	Angiogenesis
Inflammatory		Macrophage	Treg	MDSC		

Abbreviations: IFNγ, interferon gamma; MDSC, myeloid-derived suppressor cell; NK, natural killer; TGFβ, transforming growth factor beta; Treg, regulatory T cell.

- Differentially expressed gene signatures and PFS/OS among distinct NR subgroups and Rs are shown in Figure 4 and Figure 5
  - NR1 had significantly higher angiogenesis signatures than R (adjusted *P*=0.05) (driven by *TEK*, *KDR*, *HGF*, and *EGR1*, etc.), as well as the lowest median PFS and OS (1.97 months and 6.63 months, respectively; Figure 4A and Figure 5)
  - NR2 had a trend of higher expression of the T-cell inhibition signature than R (adjusted *P*=0.09) (driven by *CD274*, *CTLA4*, *TIGIT*, and *CD96*), with a median PFS of 2.13 months and median OS of 9.77 months (Figure 4B and Figure 5)
  - NR3 had the highest cell cycle signature, which was driven by *E2F7*, *FOXA1*, and *FANCD2*, with a median PFS of 5.17 months and median OS of 15.03 months (Figure 4C and Figure 5)

Figure 4: Tumor-Immune Profiles of Responder and Non-Responder Subgroups of Tislelizumab in HCC

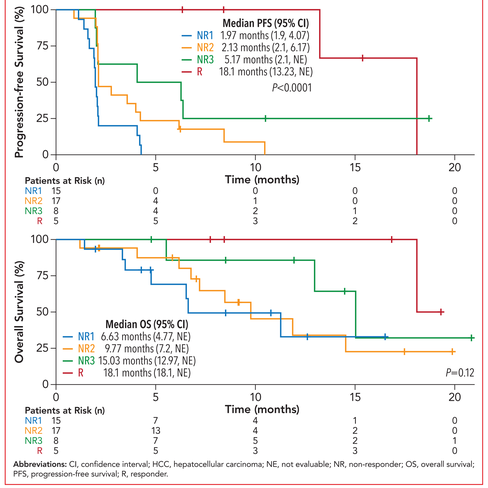


Abbreviations: HCC, hepatocellular carcinoma; NR, non-responder; R, responder.

CONCLUSIONS

- Sorafenib exposure may affect the predictive value of PD-L1 expression and tumor microenviroment-related gene signatures to anti-PD-1 therapy
  - In sorafenib exposed tissue samples, there was an association of PD-L1 expression and NK cell-mediated cytotoxicity signatures with clinical outcomes from tislelizumab monotherapy
- Elevated angiogenesis, immune checkpoint expression, and cell cycle signatures were observed in distinct non-responder subgroups of tislelizumab monotherapy, which may indicate resistance to single-agent PD-1 inhibitors and may potentially identify novel combination treatment strategies
- These findings increase our understanding of PD-L1 expression levels and tumor-immune profiles in HCC that are associated with the clinical efficacy of anti-PD-1 monotherapy
  - Further validation will be considered in an ongoing phase 3 study (BGB-A317-301, RATIONALE 301 [NCT03412773])

Figure 5: Progression-Free Survival and Overall Survival of Responder and Non-Responder Subgroups of Tislelizumab in HCC



Abbreviations: CI, confidence interval; HCC, hepatocellular carcinoma; NE, not evaluable; NR, non-responder; OS, overall survival; PFS, progression-free survival; R, responder.

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