Association of tumor mutation burden and genomic alterations with clinical outcomes in Chinese patients with advanced solid tumors treated with tislelizumab

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Introduction

- High tumor mutation burden (TMB-H) has been reported to positively correlate with the efficacy of antibodies targeted against the immune checkpoints programmed death protein-1/programmed death ligand-1 (PD-1/PD-L1)[1,2]
  - Consequently, the US Food and Drug Administration have approved an anti-PD-1 therapy for patients with TMB-H solid tumors (F1CDx, TMB ≥ 10 mutations/mega base [mut/Mb])[3]
- The association of other genomic alterations with the clinical efficacy of an anti-PD-1 antibody also warrants investigation
- Tislelizumab, an anti-PD-1 monoclonal antibody with high affinity and binding specificity for PD-1,[4,5] has been approved by the National Medical Products Administration for the treatment of patients with multiple tumor types, including classical Hodgkin lymphoma, urothelial carcinoma, non-small cell lung cancer, and hepatocellular carcinoma[6-10]
- Here, we report the association between TMB and other genomic alterations with clinical outcomes following treatment with tislelizumab monotherapy in patients with solid tumors from a Phase 1/2 study (NCT04068519)

Methods

BGB-A317-102 study design

- Chinese patients with advanced solid tumors who received tislelizumab monotherapy and had tissue samples available for genomic testing were eligible for this retrospective analysis
  - 156 patients had evaluable tumor samples for genomic analysis
- Study design has been previously described; scan QR code to red full study methods for BGB-A317-102 (NCT04068519), including the various types of solid tumors enrolled in the study[11]

Genomic profiling

- Genomic profiling was assessed in formalin-fixed paraffin-embedded tumor tissues at baseline using the BurningRock OncoScreen Plus 520 next-generation sequencing (NGS) panel[12]
- TMB status was determined using a validated algorithm in the NGS panel[12]
- Patients were classified as having hyper-amplification if their genome harbored ≥ 1 amplified gene with a copy number > 5

Statistical analysis

- Investigator-assessed overall response rate (ORR), in different tumor types, was determined by RECIST v1.1 and a two-sided binomial exact 95% confidence interval (CI) of ORR was constructed
- Survival was analyzed using the Kaplan-Meier method
  - Cox proportional-hazards method was used to estimate the association of TMB with progression-free survival (PFS) and overall survival (OS)
- All statistical analysis results are *post-hoc* exploratory and thereby p values are descriptive

Results

Baseline characteristics and clinical outcomes

- As of May 2020, 300 patients were enrolled, and 156 patients had their TMB status evaluated
- Baseline characteristics and clinical outcomes of TMB-evaluable patients were comparable with the overall population (**Table 1**)

Table 1. Baseline characteristics and clinical outcomes

Characteristic	Overall (N=300)	TMB-evaluable patients (n=156)
Age, median (range)	56.5 (18.0–82.0)	54.5 (22.0–77.0)
Sex, n (%)		
Female	93 (31.0)	52 (33.3)
Male	207 (69.0)	104 (66.7)
ECOG PS, n (%)		
0	80 (26.7)	36 (23.1)
1	220 (73.3)	120 (76.9)
Tumor stage, n (%)		
III	7 (2.3)	5 (3.2)
IV	293 (97.7)	151 (96.8)
Prior lines of systemic therapy, n (%)		
0	10 (3.3)	4 (2.6)
1	85 (28.3)	44 (28.2)
2	69 (23.0)	43 (27.6)
≥ 3	73 (24.3)	39 (25.0)
Missing	63 (21.0)	26 (16.7)
Clinical outcomes		
ORR*, % (95% CI)	17.0 (12.9, 21.7)	16.0 (10.6, 22.7)
Median PFS, months (95% CI)	2.4 (2.2, 4.0)	2.3 (2.2, 2.9)
Median OS, months (95% CI)	12.4 (9.6, 14.8)	12.5 (8.5, 17.6)
Median follow-up, months (95% CI)	29.4 (26.8, 31.4)	28.6 (26.7, 32.5)

*Data cut-off: May 31, 2020; *Patient with non-evaluable response is included in non-response group in all efficacy analysis*
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TMB, tumor mutation burden

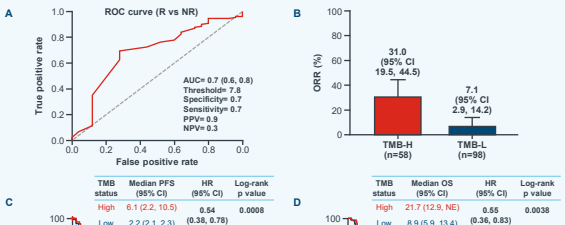
Conclusions

- **This study demonstrated that TMB-H status was associated with an improvement in the efficacy of tislelizumab monotherapy in patients with advanced solid tumors**
- **In patients with TMB-H tumors, hyper-amplification of genes in the RTK-RAS-PI3K pathway more frequently occurred in patients who did not respond to tislelizumab treatment, and was associated with poor clinical outcomes**
- **These results suggest that hyper-amplification of genes in the RTK-RAS-PI3K pathway may be associated with potential mechanisms of resistance to tislelizumab in patients with TMB-H tumors**
- **These findings enhance our understanding of the association of TMB and the hyper-amplification of genes with clinical outcomes of tislelizumab monotherapy in a pan-cancer setting**

Association of TMB-H with clinical outcomes following tislelizumab monotherapy

- Patients with TMB-H were defined as ≥ 8 mut/Mb according to the receiver operating characteristic (ROC) curve (**Figure 1A**)
  - Several TMB thresholds were tested between 6–10 mut/Mb, with 8 mut/Mb being the recommended cut-off
- Patients with TMB-H had a higher ORR compared with patients with low TMB (TMB-L) (31.0% vs 7.1%) (**Figure 1B**)
- Improved PFS (**Figure 1C**) and OS (**Figure 1D**) were observed in patients with TMB-H compared with patients with TMB-L

Figure 1. Patients with TMB-H demonstrated superior clinical efficacy compared with patients with TMB-L



TMB status	Median PFS (95% CI)	HR (95% CI)	Log-rank p value
High	6.1 (2.2, 10.5)	0.54 (0.38, 0.78)	0.0008
Low	2.2 (2.1, 2.3)		

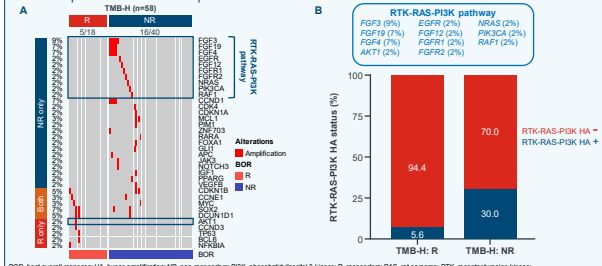
TMB status	Median OS (95% CI)	HR (95% CI)	Log-rank p value
High	21.7 (12.9, NE)	0.55 (0.36, 0.83)	0.0038
Low	8.9 (5.9, 13.4)		

AUC, area under curve; CI, confidence interval; HR, hazard ratio; NE, non-evaluable; NPV, negative predictive value; NR, non-responders; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PPV, positive predictive value; R, responders; ROC, receiver operating characteristic; TMB-H, high tumor mutation burden; TMB-L, low tumor mutation burden

Hyper-amplified genes in the RTK-RAS-PI3K pathway were more frequently observed in patients with TMB-H who did not respond to tislelizumab treatment

- To further explore the resistance mechanism in patients with TMB-H, additional genomic alterations (such as hyper-amplification) that were not included in the TMB algorithm were investigated
- In patients with TMB-H, a numerically higher frequency of hyper-amplifications occurred in patients who did not respond to tislelizumab treatment (40.0%, 16/40) compared with patients who did respond (27.8%, 5/18, **Figure 2A**)
- In the TMB-H population, hyper-amplified genes were highly enriched in the RTK-RAS-PI3K pathway
  - 31.4% (11/35) of all hyper-amplified genes identified were in the RTK-RAS-PI3K pathway (**Figure 2A, 2B**), and 90.9% (10/11) of these RTK-RAS-PI3K-amplified genes were enriched in patients who did not respond to tislelizumab treatment (**Figure 2A**)
  - The proportion of tumors with hyper-amplified genes within this specific pathway was higher in patients who did not respond to tislelizumab treatment (30.0%, 12/40) compared with patients who did respond (5.6%, 1/18) in TMB-H population (**Figure 2B**)
- These results suggest a potential role of hyper-amplified genes in the RTK-RAS-PI3K pathway in resistance to tislelizumab treatment in patients with TMB-H tumors

Figure 2. In TMB-H patients, a higher frequency of hyper-amplified genes in the RTK-RAS-PI3K pathway occurred in patients who did not respond to tislelizumab treatment

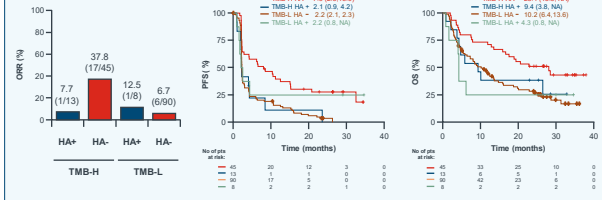


BOR, best overall response; HA, hyper-amplification; NR, non-responders; PI3K, phosphatidylinositol 3-kinase; R, responders; RAS, rat sarcoma; RTK, receptor tyrosine kinase; TMB-H, high tumor mutation burden

Hyper-amplification of genes in the RTK-RAS-PI3K pathway was associated with poor response and survival in patients with TMB-H

- In patients with TMB-H, hyper-amplification of genes in the RTK-RAS-PI3K pathway was associated with poor clinical outcomes
  - Patients with TMB-H who did not have hyper-amplification of genes in the RTK-RAS-PI3K pathway had a higher ORR compared with patients who had hyper-amplification of genes in this pathway (37.8% vs 7.7%, **Figure 3A**)
  - Survival was also improved in patients with TMB-H who did not have hyper-amplification of genes in the RTK-RAS-PI3K pathway; median PFS was 7.9 versus 2.1 months and median OS was 28.1 versus 9.4 months for patients without RTK-RAS-PI3K hyper-amplifications compared with patients with RTK-RAS-PI3K hyper-amplifications, respectively (**Figure 3B, 3C**)
- In contrast, hyper-amplification of genes in the RTK-RAS-PI3K pathway was not associated with poor clinical outcomes (ORR and PFS) in patients with TMB-L tumors (**Figure 3**)
  - Further exploration is required in a balanced population; in the TMB-L population, only 8 patients had hyper-amplification of genes in the RTK-RAS-PI3K pathway compared with 90 patients who did not have hyper-amplification of these genes

Figure 3. Hyper-amplification of genes in the RTK-RAS-PI3K pathway is associated with worse clinical outcomes with tislelizumab treatment in patients with TMB-H



All HA+/HA- groups are in the RTK-RAS-PI3K pathway
HA, hyper-amplification; NA, not available; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; RAS, rat sarcoma; RTK, receptor tyrosine kinase; TMB-H, high tumor mutation burden; TMB-L, low tumor mutation burden

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