The combination of hyperamplification and tumor mutational burden as a pan-cancer biomarker in patients treated with tislelizumab

Sanjeev Deva,[1] Michael Millward,[2] Michael Friedlander,[3] Hui K. Gan,[4] Lisa G. Horvath,[5] Jong-Seok Lee,[6] Andrew Hill,[7] Shahneen Sandhu,[8] Liang Liang,[9] Jingwen Shi,[9] Yun Zhang,[9] Yang Shi,[9] Xiaopeng Ma,[9] Xikun Wu,[9] Zhirong Shen,[9] Jayesh Desai[8]*

[1]Auckland Cancer Trials Centre, Auckland City Hospital, Auckland, New Zealand; [2]Cancer Trials, Linear Clinical Research & University of Western Australia, Perth, WA, Australia; [3]Department of Medical Oncology, Prince of Wales Hospital, and Prince of Wales Clinical School, University of New South Wales, Sydney, NSW, Australia; [4]Medical Oncology Department, Austin Health, Heidelberg, VIC, Australia; [5]Chris O'Brien Lifehouse, Camperdown, NSW, Australia; [6]Department of Hematology and Medical Oncology, Seoul National University Bundang Hospital, Seongnam-si, Republic of Korea; [7]Tasman Oncology Research Ltd, Southport, QLD, Australia; [8]Peter MacCallum Cancer Centre and the University of Melbourne, Melbourne, VIC, Australia; [9]BeiGene (Beijing) Co., Ltd., Beijing, China. *Presenting author

Abstract No: LB511

Background

- High tumor mutational burden (TMB-H) is associated with elevated neoantigen expression across tumors, linked with an improved response to immune checkpoint inhibitors[1,2]
- Certain subtypes of genomic alterations (e.g. hyperamplification) that are not included in the TMB algorithm might also be associated with clinical outcomes. However, their role as biomarkers in the pan-cancer setting is unknown and has not been previously investigated in the context of a single clinical study enrolling an unselected patient population
- Tislelizumab is a humanized monoclonal antibody with high affinity and specificity for programmed cell death protein 1 (PD-1) that was specifically designed to minimize FcγR binding on macrophages in order to abrogate antibody-dependent phagocytosis, a potential mechanism of T-cell clearance and resistance to anti PD-1 therapy[3,4]
- Here we report data from the final analysis of a Phase 1 trial that enrolled patients with various solid tumors treated with tislelizumab (NCT02407990). We evaluated the association of TMB with clinical outcomes, integrative biomarker analysis of genomic alterations and gene expression profiling by TMB status

Methods

- A total of 451 patients were enrolled between May 2015 and October 2017 from 27 sites in Australia, Korea, New Zealand, and Taiwan and were treated with different doses of tislelizumab. Baseline tumor tissue was evaluated for gene expression (HTG EdgeSeq Precision Immuno-Oncology Panel) and genomic profiling (FoundationOne CDx)
- TMB-H was defined as ≥ 10 mutations/Mb based on receiver operating characteristic analysis per Youden index (area under curve=0.622 [95% confidence interval {CI}: 0.512, 0.733]). Gene hyperamplification (HA) was defined as a minimum of copy number gain > 5 as per manufacturer's instructions
- For the validation cohort, mutational and clinical data of Memorial Sloan Kettering (MSK) Cancer pan-cancer immunotherapy cohort[5] were downloaded from cbioportal. Only patients treated with PD-(L)1 monotherapy were retained (N=837) for validation of the algorithm in the downstream analysis
- Objective response rate (ORR) and 95% CIs were evaluated using the binomial exact method. Median progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. Genes were ranked according to their fold change and then gene set enrichment analysis was performed using R package "fgsea". p values are provided for descriptive purpose

Results

Table 1. Baseline Characteristics

	Number of patients (%)	
	Overall (N=451)	TMB BEP (n=266)
Median age, years (range)	61.0 (18–81)	60.0 (18–81)
Race		
Asian	130 (28.8)	58 (21.8)
Black/African American	5 (1.1)	4 (1.5)
Caucasian	290 (64.3)	189 (71.1)
Other	26 (5.8)	15 (5.6)
ECOG PS		
0	169 (37.5)	108 (40.6)
1	282 (62.5)	158 (59.4)
Metastatic stage		
I	1 (0.2)	1 (0.4)
II	6 (1.3)	5 (1.9)
III	36 (8.0)	20 (7.5)
IV	401 (88.9)	236 (88.7)
Missing	7 (1.6)	4 (1.5)
ORR, % (95% CI)	13.3 (10.3, 16.8)	13.9 (10.0, 18.7)
mPFS, months (95% CI)	2.1 (2.1, 2.7)	2.1 (2.1, 2.7)
mOS, months (95% CI)	10.3 (8.5, 11.6)	11.2 (8.3, 13.7)

BEP, biomarker evaluable population; CI, confidence intervals; ECOG PS, Eastern Cooperative Oncology Group performance status; mOS, median OS; mPFS, median PFS; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TMB, tumor mutation burden

Conclusions

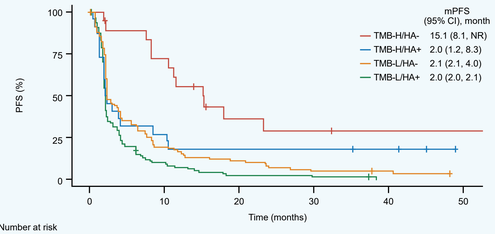
- **TMB-H/HA- could be a potential pan-tumor biomarker to identify patients who are most likely to benefit from PD-(L)1 blockade**
  - The TMB-H/HA- subgroup showed better clinical outcomes with tislelizumab monotherapy treatment compared to other subgroups
  - The TMB and HA joint algorithm was validated in another independent immune checkpoint inhibitor-treated pan-cancer cohort
- **Genes in the RTK-RAS-PI3K pathway were often hyperamplified in TMB-H non-responders and associated with poor clinical outcomes**
- **In TMB-H tumors, elevated cytotoxic T-cell activity and interferon signaling were associated with the absence of HA, which may be associated with the clinical benefit**

Figure 1. In TMB-H (≥ 10 mut/Mb) patients, exclusion of gene HA was associated with improved outcomes with tislelizumab. ORR (**A**), PFS by TMB and HA status (**B**), OS by TMB and HA status (**C**)

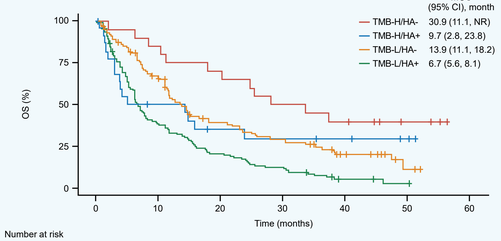
A

	TMB-H			TMB-L		
	Overall	HA-	HA+	Overall	HA-	HA+
n (% in TMB BEP [N=266])	43 (16.2)	20 (7.5)	23 (8.6)	223 (83.8)	103 (38.7)	120 (45.1)
ORR, % (95% CI)	32.6 (19.1, 48.5)	50.0 (27.2, 72.8)	17.4 (5.0, 38.8)	10.3 (6.7, 15.1)	11.7 (6.2, 19.5)	9.2 (4.7, 15.8)
mPFS, months (95% CI)	8.3 (2.0, 11.5)	15.1 (8.1, NR)	2.0 (1.2, 8.3)	2.1 (2.0, 2.1)	2.1 (2.1, 4.0)	2.0 (2.0, 2.1)
mOS, months (95% CI)	20.1 (10.3, 37.4)	30.9 (11.1, NR)	9.7 (2.8, 23.8)	11.1 (7.7, 11.9)	13.9 (11.1, 18.2)	6.7 (5.6, 8.1)

B



C



BEP, biomarker evaluable population; HA, hyperamplification; mOS, median OS; mPFS, median PFS; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TMB, tumor mutation burden; TMB-H, high tumor mutation burden; TMB-L, low tumor mutation burden

Baseline characteristics and updated clinical outcomes

- Median follow-up of the overall study population (N=451) was 8.6 months (range: 0.1–58.9 months) and 87 patients (19.2%) were still alive. This was a heavily pre-treated population with > 95% of the patients having received prior anticancer drug therapies. Baseline characteristics are shown in **Table 1**
- Of the 451 enrolled patients, the confirmed overall ORR was 13.3% (95% CI: 10.3, 16.8), median (m) PFS of 2.1 months (95% CI: 2.1, 2.7), and mOS of 10.3 months (95% CI: 8.5, 11.6). Biomarker evaluable population (BEP) had comparable baseline characteristics and clinical outcomes to the overall study cohort
- Improved clinical outcomes were observed in patients with TMB-H tumors (n=43, 16.2% TMB evaluable patients), with an ORR of 32.6% (95% CI: 19.1, 48.5), median PFS of 8.3 months, and median OS of 20.1 months

Exclusion of gene HA may further improve clinical efficacy in TMB-H patients

- To evaluate the association of other genomic alterations with clinical efficacy and the potential to further optimize TMB-based biomarker, TMB-H subgroup were further stratified by the status of deep deletion, HA, structural variants, or alterations in the telomerase reverse transcriptase promoter region
- Only the presence of HA was found to be associated with poorer clinical outcomes characterized by a lower ORR and shorter PFS and OS than patients without HA in the TMB-H subgroup (**Figure 1**). TMB-H patients without HA achieved superior clinical efficacy with an ORR of 50% (95% CI: 27.2, 72.8), median PFS of 15.1 months (95% CI: 8.1, not reached [NR]), and median OS of 30.9 months (95% CI: 11.1, NR)
- To validate this finding, we applied the same algorithm to a larger independent pan-tumor cohort (N=837 received PD-[L]1 treatment in the MSK immunotherapy cohort). A consistent trend of association between TMB-H/HA- and improved OS vs TMB-H/HA+ was observed (median OS of 34 vs 15 months, respectively)

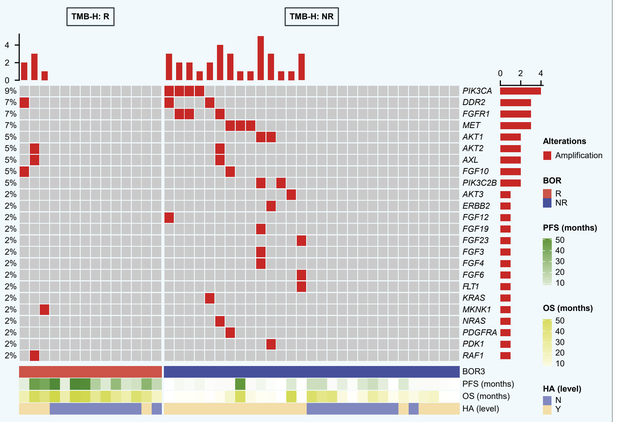
Genes within RTK-RAS-PI3K pathway were frequently hyperamplified and associated with resistance of TMB-H population

- Trend of more amplifications in RTK-RAS-PI3K pathway (including *PIK3CA*, *FGFR1*, *MET*, *AKT1*, etc) were observed in non-responders in the TMB-H population (48% vs 21%, p=0.11) (**Figure 2**)
- When patients with any hyperamplification within RTK-RAS-PI3K genes are excluded, ORR is increased to 42.3% in TMB-H, with mPFS of 15.1 months and mOS of 30.9 months

TMB-H tumors without HA tended to be more immune activated

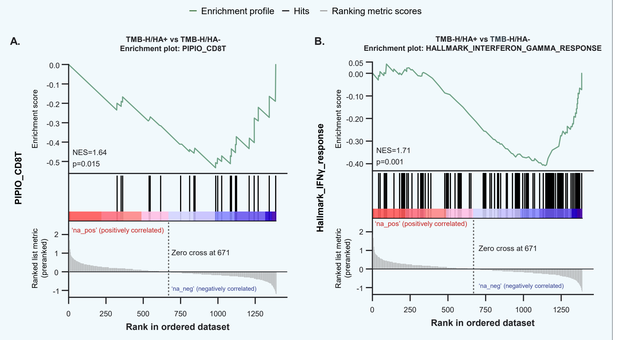
- Next, we sought to understand the characteristics of the tumor microenvironment of different HA status by interrogating the paired gene expression profiles in TMB-H subgroup (HA+ [n=20] vs HA- [n=17])
- Gene set enrichment analysis showed that immune activation-related signatures were heavily enriched in HA-negative tumors, including CD8+ T-lymphocytes (normalized enrichment score [NES]=1.64, p=0.015; **Figure 3A**), as well as a trend towards higher expression of T-cell markers (CD3E, CD3G, CD8A, CD8B), cytotoxicity-associated effector molecules (including *GZMA* and *GZMK*), and T-cell receptor downstream signaling molecules (including *ZAP70, LAT, VAV1*, and *NFATC1*)
- In addition, higher expression of genes involved in IFN gamma signaling pathways were also identified in TMB-H tumors without HA (NES=1.71, p=0.001; **Figure 3B**). Numerous IFN-induced genes such as *IFI6, IFI27, IFIT1, IFIH1, IFIT3, MX1, ISG15*, and *ISG20* were captured among the leading-edge genes

Figure 2. HA profile of responders vs non-responders in the TMB-H subgroup



BOR, best overall response; HA, hyperamplification; N, no; NR, non-responders; OS, overall survival; PFS, progression-free survival; R, responders; TMB-H, high tumor mutation burden; Y, yes

Figure 3. Differentially expressed genes at leading edge showed significantly enriched T-cell signatures (**A**) and significantly enriched IFN signatures (**B**) in HA- vs HA+ tumors in TMB-H patients



IFN, interferon; HA, hyperamplification; NES, normalized enrichment score; TMB-H, high tumor mutational burden

References

1. McGranahan N, et al. Science 2016;351:1463–9
2. Marabelle A, et al. Lancet Oncol 2020;21:1353–65
3. Zhang T, et al. Cancer Immunol Immunother 2018;67:1079–90
4. Dahan R, et al. Cancer Cell 2015;28:285–95
5. Samstein RM, et al. Nat Genet 2019;51:202–6

Acknowledgments

This study was sponsored by BeiGene, Ltd. Medical writing support, under direction of the authors, was provided by Simon Lancaster, BSc, and Louise Oakes, PhD, of Ashfield MedComms, an Ashfield Health company, and was funded by BeiGene, Ltd.

***Author contact details:** Jayesh.Desai@petermac.org (Jayesh Desai)