Comprehensive molecular analysis of Microsatellite-Stable (MSS) Tumors with High Mutational Burden in gastrointestinal (GI) cancers.

Jingyuan Wang[1], Joanne Xiu[2], Francesca Battaglin[1], Hiroyuki Arai[1], Shivani Soni[1], Wu Zhang[1], Anthony F. Shields[3], Axel Grothey[4], Benjamin A. Weinberg[5], John L. Marshall[5], Emil Lou[6], Moh'd Khushman[7], Davendra P.S. Sohal[8], Michael Hall[9], W. Michael Korn[2], and Heinz-Josef Lenz[1].

[1] Division of Medical Oncology, Norris Comprehensive Cancer Center, University of Southern California. [2] Caris Life Sciences, Phoenix, Arizona.[3] Karmanos Cancer Institute.[4] West Cancer Center and Research Institute.[5] Lombardi Comprehensive Cancer Center. [6] University of Minnesota.[7] Mitchell Cancer Institute. [8] University of Cincinnati.[9] Fox Chase Cancer Center.

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wangjingyuan@bjmu.edu.cn

Background

- High tumor mutation burden (TMB-H) is associated with improved survival in patients receiving immunotherapy across a wide variety of cancer types, including GI cancers [1-2].
- Mutational signatures contributing to high tumor mutation burden (TMB-H) independent from microsatellite instability-high (MSI-H) status are not well-studied systematically, despite of some known individual genes, including *BRCA1/2, APOBEC* signature, TP53, *POLE* and *MUC16* [3].
- We aimed to characterize specific molecular features of a large cohort of GI tumors with TMB-H & MSS.

Methods

- NGS was performed on genomic DNA isolated from FFPE tumor samples using the NextSeq (592-genes) (Illumina, Inc., San Diego, CA). All variants were detected with greater than 99% confidence based on allele frequency and amplicon coverage, with an average sequencing depth of coverage of greater than 500 and an analytic sensitivity of 5%.
- Microsatellite instability (MSI)/ MMR status was determined by a combination of NGS (>=46 loci), IHC and fragment analysis.
- Tumor mutational burden (TMB) was estimated from 592 genes (1.4 megabases [MB] sequenced per tumor) by counting all non-synonymous missense mutations found per tumor that had not been previously described as germline alterations. Tumors with TMB≥17 mutations/Mb were defined as TMB-H.
- PD-L1 expression was measured by IHC (22c3) [22C3 (CPS score, positivity: CPS≥1) in GE tumors and SP142 (Positivity: TPS≥5%) in other cancers]
- Findings were compared in four groups (TMB-H/L & MSI-H/MSS) using Fisher-Exact or Chi-square and adjusted for multiple comparison by Benjamini-Hochberg. Significance was determined by q<.05.

References

[1]. Benedikt Martin, et al., Visc Med. 2019.
[2]. Robert M. Samstein, et al., Nature Genetics, 2019.
[3]. C. Luchini, et al., Annals of Oncology, 2019.

Results

Figure 1. cancer type.

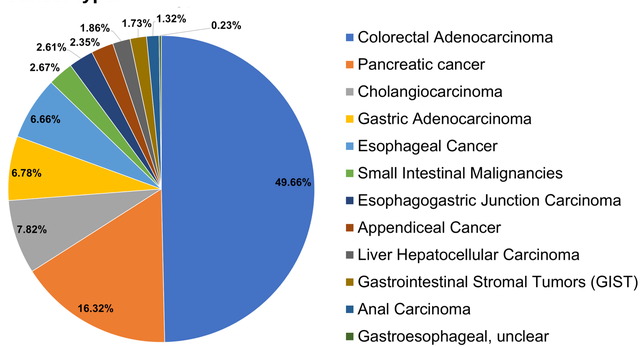
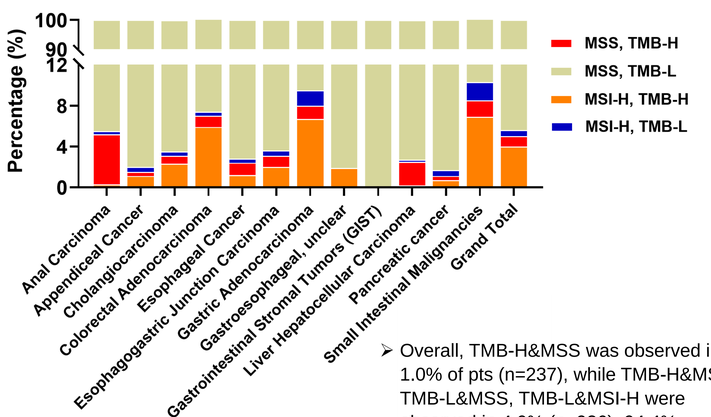
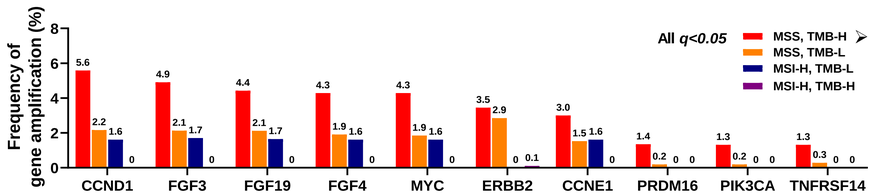


Figure 2. Association between TMB and PD-L1 expression.



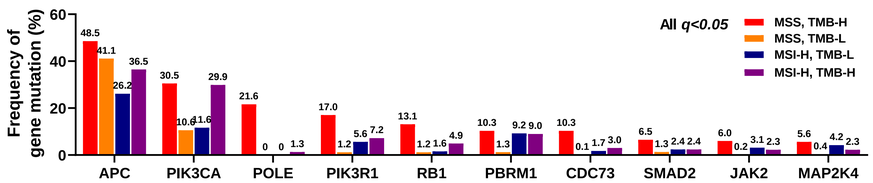
➢ Overall, TMB-H&MSS was observed in 1.0% of pts (n=237), while TMB-H&MSI-H, TMB-L&MSS, TMB-L&MSI-H were observed in 4.0% (n=936), 94.4% (n=22089) and 0.6% (n=130) respectively.

Figure 3. Copy number amplifications in GI Cancers 。



➢ Compared to other groups, TMB-H&MSS showed the most prevalent amplifications (AMPs), including CCND1 (5.6%), FGF3/4/19 (4.9%, 4.3%, 4.4%), MYC (4.3%).

Figure 4. Gene mutations in GI cancers.



➢ Compared to other groups, TMB-H&MSS showed the highest mutation rates in *POLE* (21.6%), *RB1* (13.1%), *CDC73* (10.3%), genes involved in PI3K&MAPK (*PIK3R1* 17%, *mTOR* 3.4%, *MAP2K1* 3.8%, *MAP2K4* 5.6%) and Wnt (*APC* 48.5%, *SMAD2* 6.5%, *TCF7L2* 3.8%) pathways (*q<.05*).

Table 1. The status of HER2 and PD-L1 among four groups (TMB-H/L & MSI-H/MSS)

Molecular	TMB-H & MSS (%)	TMB-L & MSS (%)	TMB-H & MSI-H (%)	TMB-L & MSI-H (%)	Adj *p*
HER2					
High expression (IHC)	**9.9**	4.5	0.3	0	*<.0001*
Amplification (CISH)	**3.4**	2.9	0.1	0	*<.0001*
PD-L1 positivity					
GE cancers (22C3)	73.9	71.4	**87.9**	73.9	*<.01*
Other GI cancers (SP142)	16.8	7.1	**22.9**	14.9	*<.0001*

Conclusions

This is the largest study to investigate the special molecular landscape of pts with TMB-H & MSS in GI cancers. Our data may provide novel insights for pt selection and more effective targeted combination immunotherapies (e.g. HER2, PI3K inhibitors) in MSS GI cancers.