Distinct genomic landscapes characterize mismatch-repair deficiency(dMMR)/microsatellite instability-high (MSI-H) gastrointestinal (GI) cancers stratified by tumor mutation burden (TMB)

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Background

- TMB-H was reported to be predictive of response to immune checkpoint inhibitors[1-2].
- However, genomic signatures contributing to TMB-H independent from dMMR/MSI-H status are not well-studied.
- We aimed to characterize specific molecular features of a large cohort of MSS GI tumors with TMB-H.

Methods

- NGS was performed on genomic DNA isolated from formalin-fixed paraffin-embedded tumor samples using the NextSeq or NovaSeq 6000 platforms (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%[3].
- Microsatellite instability (MSI)/ MMR status was determined by a combination of NGS (>=46 loci), IHC and fragment analysis.
- TMB-H were defined using differing TMB cutoffs (10, 20, 50 mutations/Mb), according to the standard algorithm by Friends of Cancer Research TMB Harmonization Project[4].
- .Molecular features were compared in four groups (TMB<10 vs 10-20 vs 20-50 vs ≥50mutations/Mb) using Fisher-Exact or Chi-square and adjusted for multiple comparison by Benjamini-Hochberg.
- Significance was determined by q<.05.

Reference:
1.Ann Oncol. 2019 Jul 1;30(7):1096-1103. 2.Oncologist. 2020 Sep;25(9):803-809.
3. Lancet Oncol. 2023 Feb;24(2):151-161. 4. J Immunother Cancer 2020; 8.

Results

Fig 1. Tumors with TMB over 10, 20, 50 mutations/Mb were observed in 95.38%, 86.05% and 14.47% respectively in the dMMR/MSI-H GI cohort (n=2272).

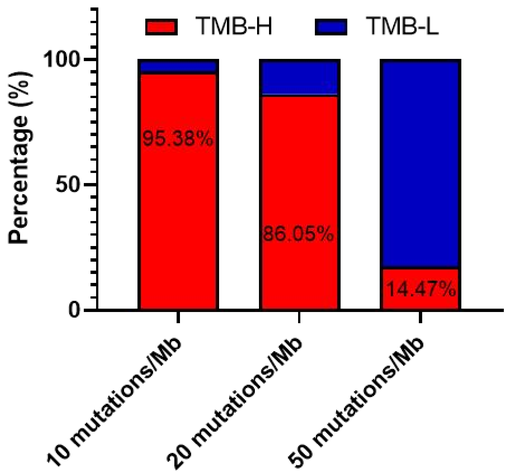


Fig 2. Distinct mutational landscapes according to different TMB levels (all P_{adj}<0.0001).

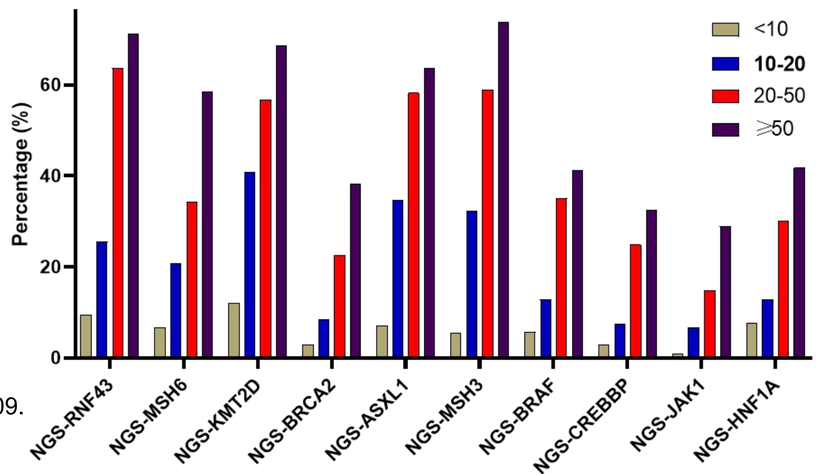


Fig 3. The rates of CNNE1 amplification and HER2 overexpression were the highest in tumors with TMB below 10 mutations/Mb (all Padj<0.05).

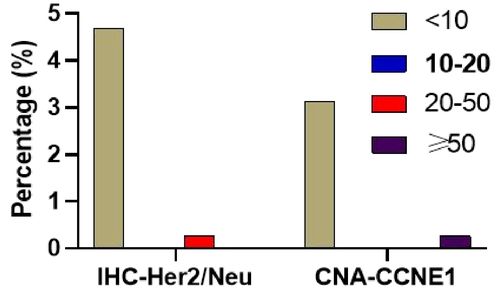
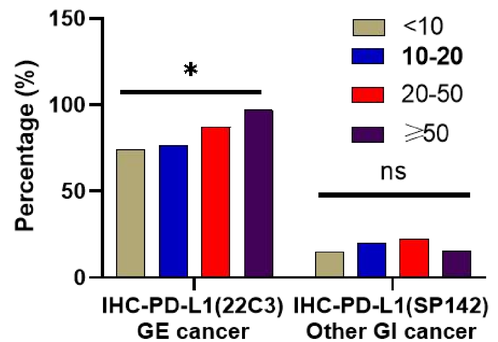


Fig 4. The association between PD-L1 positivity and TMB levels was only observed in gastroesophageal cancers.



Conclusion

This is the largest study to investigate the distinct molecular landscape of dMMR/MSI-H GI cancers with different degrees of TMB. These data may inform our understanding of the efficacy of ICB in dMMR/MSI-H GI tumors.