Molecular correlates of PD-L1 expression in patients (pts) with gastroesophageal cancers.

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Background

- Immune checkpoint inhibitors (ICIs), especially anti-PD-(L)1 antibodies, have become an important paradigm shift in the treatment of various solid tumors, including gastroesophageal (GE) cancers.
- The increased PD-L1 expression evaluated by combined positive score (CPS) is associated with improved efficacy of immunotherapy in GE cancers.
- Specific molecular alterations (e.g. EBV infection) associated with higher PD-L1 expression may influence the efficacy of anti-PD-(L)1 therapy.
- Systematic study of the impact of tumor molecular alterations on PD-L1 expression is still not well-studied.
- We aimed to characterize specific molecular features of tumors with different CPS levels in GE cancers.

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 measured by IHC (22c3) was evaluated by CPS scores.
- Molecular alterations were compared in three groups (CPS>=10, H; CPS =1~9, M; CPS=0, L) using Fisher-Exact or Chi-square and adjusted for multiple comparison by Benjamini-Hochberg. Significance was determined by p <.05.

References

[1] Metges J., et al. *ANN ONCOL 2019;30 Suppl 4: v130.*
[2] Fashoyin Aje Lola,et al. *The Oncologist 2018;24: 103-9.*
[3] Zev A. Wainberg ., et al. *J CLIN ONCOL 2020;4_suppl: 427.*
[4] Kim S. T., et al. *NAT MED* 2018;24: 1449-58.

Results

1. PD-L1 expression and cancer type.

Table 1. PD-L1 expression

Cancer Type	Total	Low	Mediate	High
	n (%)	n (%)	n (%)	n (%)
Esophageal Adenocarcinoma	856 (32)	235 (27)	497 (58)	124 (14
Esophageal Squamous cell carcinoma	75 (3)	9 (12)	34 (45)	32 (43)
Gastric cancer	1662 (61)	482 (29)	862 (52)	318 (19)
Esopphageal, other	64 (2)	24 (38)	25 (39)	15 (23)
Gastroesophageal, unclear	50 (2)	15 (30)	30 (60)	5 (10)
Total	2707 (100)	765 (28)	1448 (53)	494 (18)

2. Association between TMB and PD-L1 expression.

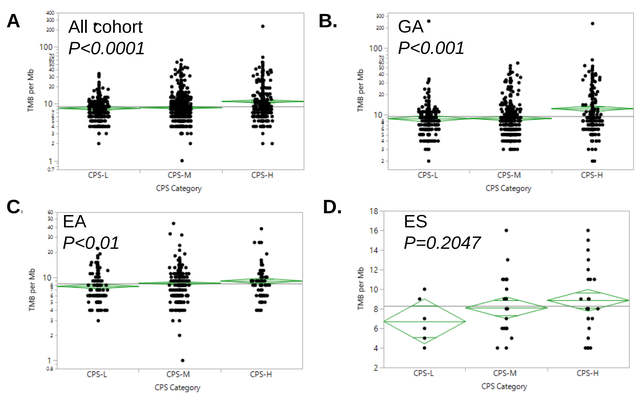

Fig 1. Correlation of TMB with PD-L1 expression. **A.** Overall, TMB was similar between L and M, but was significantly increased in H (average TMB: 8.4 vs. 8.6 vs. 11 mut/MB); **B.** the same was seen in gastric/GEJ adenocarcinoma (GA) (average TMB=8.7 vs. 8.7 vs. 12.3 mut/MB). **C.** In esophageal adenocarcinoma (EA), TMB was significantly elevated in CPS-M and H, compared to CPS-L (average TMB = 7.8 vs. 8.5 vs. 9 mut/MB). **D.** However, no significant association was found between TMB and PD-L1 expression in esophageal squamous cell carcinoma(ES).

3. Association between MSI-H/dMMR status and PD-L1 expression.

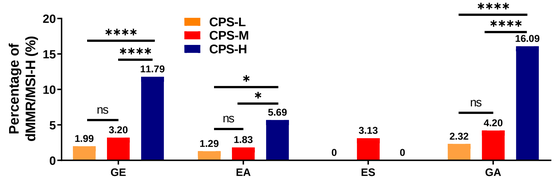

Fig 2. Correlation of MSI-H/dMMR status with PD-L1 expression in GE tumors. MSI-H/dMMR was significantly enriched in CPS-H, compared to CPS-L and M groups. This association remained in GA and EA. Notably, only one patient (3.1%, 1/32) with MSI-H was found in CPS-M group of ES . Ns, not significant; **, p<0.05, ****, p<0.0001.*

4. Association between gene amplification and PD-L1 expression.

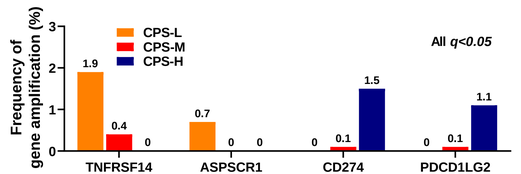

Fig 3. Correlation of copy number amplifications with different PD-L1 expression levels. Amplifications of PD-L1 (H: 1.5%, M: 0.1% and L: 0) and PD-L2 (H: 1.1%, M: 0.1%, L: 0) were the highest in CPS-H, while ASPSCR1 (H: 0, M: 0, L: 1%) and TNFRSF14 (H: 0, M: 0.4, L: 2%) were the lowest.

5. Association between gene mutation and PD-L1 expression (top 10).

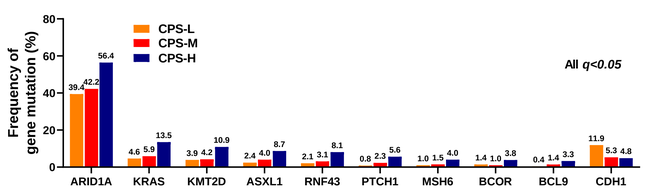

Fig 4. Correlation of gene mutations with different PD-L1 expression levels. Genes involved in epigenetic modification (e.g. *ARID1A*, *ASXL1*, *BCL9*, *BCOR*) and MAPK (*KRAS*, *MAP2K1*) had the highest mutation rates in CPS-H, compared to M and L. In contrast, *CDH1* had higher mutation rates in CPS-L, as compared to M and H.

Conclusions

- This is the largest study to investigate the distinct molecular landscape of pts with different PD-L1 expression levels in GE cancers.
- TMB and the proportion of MSI-H/dMMR were only significantly increased in patients with CPS-H, while no significant difference was seen between CPS-L and M in the overall analysis.
- Our data may provide novel insights for pt selection (e.g. pts with gene mutations involved in epigenetic modification) and the development of rational combination immunotherapy (e.g. drugs targeting MAPK pathway) in GE cancers.