Association of DNA damage response and repair gene (DDR) mutations and microsatellite instability (MSI), PD-L1 expression, tumor mutational burden (TMB) in gastroesophageal cancers

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BACKGROUND

- DNA damage response and repair genes (DDR) encode proteins that assist in homology-directed repair. These proteins interact with other DNA repair proteins and form a system for DNA damage repair.
- The prevalence of genetic deficiencies in the mechanism of homologous recombination across all tumor lineages has been well characterized.[1] Certain gastric cancers have been shown to harbor deficiencies in the homologous recombination pathway.[2]
- Studies also show DDR mutations upregulate PD-L1, increase tumor mutational burden, and are associated with higher tumor infiltrating lymphocytes.[3,4]
- Therefore deficient homologous recombination and biomarkers for immune checkpoint inhibition are a possible opportunity for immunotherapy in upper GI cancers.[5,6]
- We investigated the association of DDR mutations in gastric (GC), esophageal (EC), and gastroesophageal junction (GEJ) cancers with known predictors for immune checkpoint inhibitors.

OBJECTIVES

- To compare the association of known predictive biomarkers (MSI, PD-L1, TMB) to checkpoint inhibitors in DDR-mutated upper GI malignancies vs. non-DDR-mutated upper GI malignancies
- To correlate specific DDR alterations (e.g. *ARID1A*, *ATRX*, *BRCA2*, *PTEN*, *RAD50*, *WRN*) in gastric, esophageal, and gastroesophageal junction cancers with MSI, PD-L1, and TMB

METHODS

Cancer Type	Tumor Count
Esophageal	709
Gastric	831
Gastroesophageal junction	355
Unclear	40
Total	**1935**

NGS/FA → Microsatellite instability (MSI)

IHC → PD-L1 (22c3 or SP142)

NGS → TMB High/Low (cutoff ≥ 10)

- Molecular profiles of tumors obtained from patients with gastric, esophageal, and gastroesophageal cancers were reviewed to identify DDR mutations and their association with MSI, PD-L1, and TMB. The molecular profiles were generated from tumors submitted to CARIS Life Sciences.
- 20 DDR mutations were tested by Next-Generation Sequencing (NGS) with a 592-gene panel on a total of 1935 (709 Esophageal; 831 Gastric; 355 Gastroesophageal junction) cancers.
- MSI was assessed by NGS or fragment analysis, PD-L1 by IHC (22c3 for CPS or SP142), and TMB by NGS (TMB-high ≥10 mutations/megabase [mt/MB]).

RESULTS

Gastroesophageal DDR mutation rates

- Overall DDR mutation rate when accounting for all Gastroesophageal cancers was 23% ($p < 0.0001$) (Table 1)
- Gastric (GC) had the highest DDR mutation rate compared to Esophageal (EC) and Gastroesophageal Junction (GEJ) (27% vs. 20%, $p = 0.0005$ and 17%, $p = 0.0002$, respectively) (Table 1)

Table 1: DDR Mutation Rates

Cancer Type	Tumor Count	DDR-M Count	DDR-M Rate
Esophageal (EC)	709	140	20%
Gastric (GC)	831	228	27%
Gastroesophageal Junction (GEJ)	355	61	17%
Unclear	40	9	23%
Total Gastroesophageal	1935	438	23%

DDR-mutated cohort vs. non-DDR-mutated cohort

- MSI-High (MSI-H) was significantly more common in the DDR mutated cohort (DDR-M) compared to non-mutated cancers (18% vs. 1%; $p < 0.0001$), TMB-High (≥10 mutations/megabase [mt/MB]) was higher in DDR-M (35% vs. 21%; $p < 0.0001$) (Figure 1)
- DDR mutations were more frequent in the PD-L1 combined positive score (CPS) ≥50 group than CPS 0 (42.9% vs. 24%; $p = 0.037$) and CPS 1-9 (42.9% vs. 20.6%; $p = 0.005$) (Figure 2)
- In the DDR-M cohort GC had the highest TMB compared to DDR-M EC and GEJ (mean: 13.8 vs. 9.4 vs. 10 mt/MB, respectively; $p < 0.0001$) (Table 2) (Figures 3-5)

Figure 1: Biomarker prevalence across cohorts

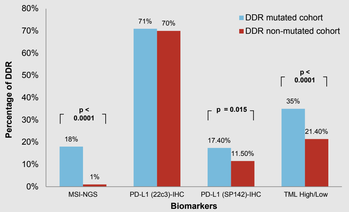


Figure 2: PD-L1 CPS score groups

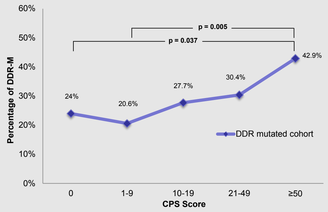


Table 2: TMB mean DDR-M

Cancer Type	Mean DDR-M	Mean DDR-nonmutated	P-value
Gastric (GC)	13.8 mt/MB	7.7 mt/MB	$p < 0.0001$ *
Esophageal (EC)	9.4 mt/MB	8.3 mt/MB	$p = 0.0006$ *
Gastroesophageal Junction (GEJ)	10 mt/MB	7.6 mt/MB	$p = 0.0001$ *
Total Gastroesophageal	11.8 mt/MB	7.9 mt/MB	$p < 0.0001$ *

Figure 3: TMB across gastric tumors

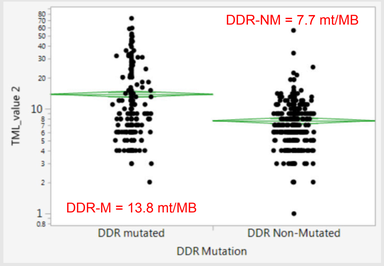


Figure 4: TMB across esophageal tumors

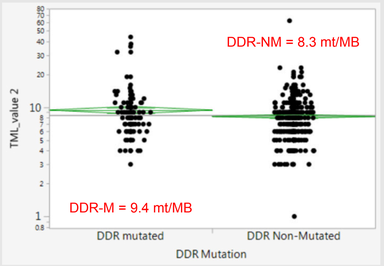
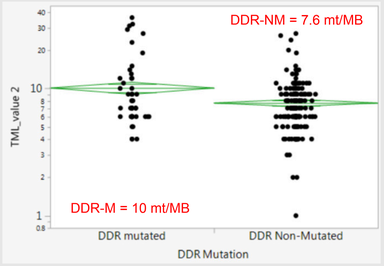


Figure 5: TMB across GEJ tumors



DDR-mutations correlated with biomarkers

- *ARID1A*, *ATRX*, *BRCA2*, and *PTEN* were the most prevalent DDR mutations in MSI-H (87%, 31%, 25%, 24%, respectively) (Figure 6)
- *ARID1A*, *ATRX*, *BRCA2*, and *PTEN* were the most prevalent DDR mutations in TMB-High (47%, 7.7%, 6.7%, 6.8%) (Figure 7)
- *ARID1A*, *BRCA2*, *RAD50*, and *WRN* were the most prevalent DDR mutations in PD-L1 high (CPS > = 10) (48.5% vs. 5.2% vs. 2.5% vs. 3.4%) (Figure 8)

Figure 6: DDR-M correlated with MSI

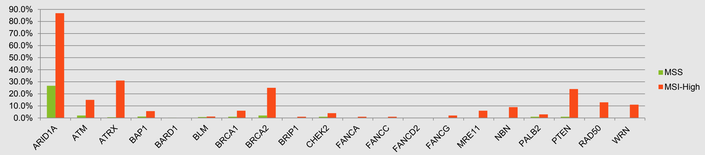


Figure 7: DDR-M correlated with TMB (≥10 mt/MB)

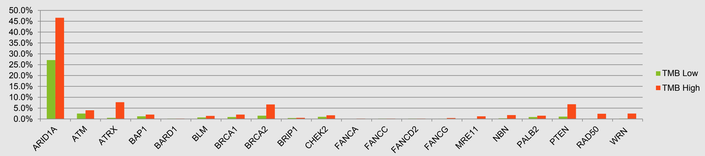
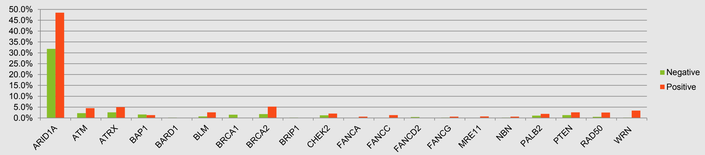


Figure 8: DDR-M correlated with PD-L1 (CPS >10)



CONCLUSIONS

- Based on the molecular profiles examined within this study, DDR mutations are prevalent across all gastroesophageal cancers. Out of esophageal, gastric, and gastroesophageal junction cancers, DDR-mutations are most pronounced in gastric cancers.
- Biomarker expression of MSI-H, TMB-high, and high PD-L1 are significantly more prevalent in the DDR-mutated cohort compared to the non-DDR-mutated cohort.
- Out of the 20 DDR mutations examined, alterations in *ARID1A*, *ATRX*, *BRCA2*, and *PTEN* are correlated with MSI-H and TMB-high. In contrast *ARID1A*, *BRCA2*, *RAD50*, and *WRN* are correlated with increased PD-L1 expression. These highly prevalent DDR mutations should be investigated as possible biomarkers for treatment.
- These findings may help identify patients for tailored immunotherapy approaches in future clinical trials. By further identifying associations of DDR alterations and immuno-oncology predictive biomarkers, rational drug combinations may be implemented in the treatment of upper gastrointestinal cancers.

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