The landscape of *MAP3K1/MAP2K4* alterations in gastrointestinal (GI) malignancies.

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Background

- Inactivating alterations in *MAP3K1/MAP2K4* occur in various solid tumors, sensitize cancer models to MEK inhibitors, and have co-mutation partners which may enable therapeutic targeting.

Methods

- We retrospectively reviewed 20,290 GI malignancy patients (pts), comprised of 9986 colorectal carcinoma (CRC) and 10,304 non-CRC, whose tumors were profiled with Caris Life Sciences from 2015-2019.
- Testing included:
  - Next-generation sequencing (NGS) was performed on genomic DNA isolated from FFPE tumor samples using the NextSeq platform and a custom-designed SureSelect XT assay to enrich 592 cancer-related whole-gene targets.
  - Immunohistochemistry (IHC) for programmed death ligand-1 (PD-L1) utilized the SP142 antibody with a positive threshold of ≥2+ stain intensity and ≥5% cancer cell staining. In non-CRC, the PD-L1 22c3 antibody was also utilized (CPS scoring method with positive threshold dependent on cancer type).
  - Microsatellite instability-high (MSI-H)/deficient mismatch repair (dMMR) status was evaluated by a combination of fragment analysis, IHC and NGS.
  - Tumor mutational burden (TMB) was measured (592 genes and 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. The threshold to define TMB-high was ≥17 mutations/MB.
- Genetic variants identified were interpreted by board-certified molecular geneticists. All truncating *MAP3K1/MAP2K4*-alterations (*MAP3K1/MAP2K4*-MT) were considered presumed pathogenic, and all patients (pts) with pathogenic/presumed pathogenic were included in the *MAP3K1/MAP2K4*-MT cohort. Variants of undetermined significance (VUS) were classified as presumed benign and not included.
- Statistical analysis was performed using Chi-square or Fisher's exact tests where appropriate, with significant differences determined by p-values of <0.05 (*denotes raw p<0.05, and **denotes p<0.05 following correction for multiple hypothesis testing using the Benjamini & Hochberg method).

Results

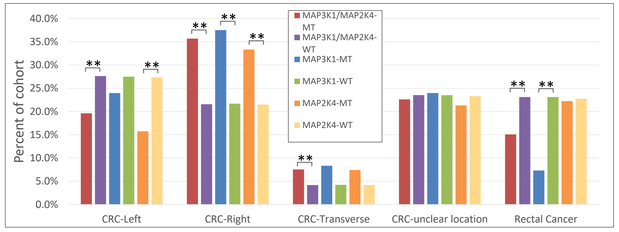
Table 1. – Patient characteristics

Characteristic	All GI Malignancies	CRC MAP3K1/MAP2K4-MT	CRC MAP3K1/MAP2K4-WT	Non-CRC MAP3K1/MAP2K4-MT	Non-CRC MAP3K1/MAP2K4-WT
Total, N cases	20,290	200	9786	121	10,183
Median Age, years (SD) - Age Range, years	63 (12.6) 0-90+	61 (13.4) 18-90+	61 (13.0) 14-90+	69 (11.9)* 33-90+	65 (11.9) 0-90+
Female/Male, N cases - (% Female)	8831/11,459 (43.5%)	83/117 (41.5%)	4420/5366 (45.2%)	62/59 (51.2%)*	4266/5917 (41.9%)

*denotes p < 0.05.

- *MAP3K1/MAP2K4*-MT were more frequent in CRC than non-CRC pts (2.0% v. 1.2%, p<0.0001), with truncating mutations representing the majority.

Figure 1. – Association of *MAP3K1/MAP2K4*-MT by sidedness in CRC.

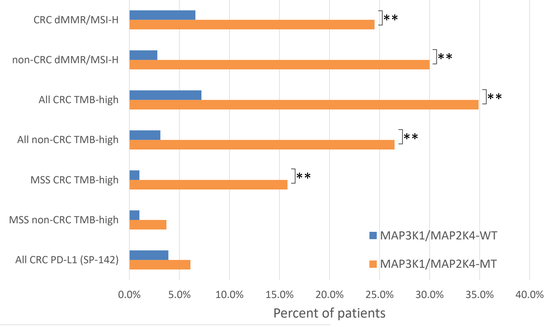


- *MAP3K1/MAP2K4*-MT CRC pts were more frequently right-sided (36% v. 22%, p<0.0001) and transverse (8% v. 4%, p<0.05) compared to WT, whereas WT cases were more frequently left-sided (20% v. 28%, p<0.05) and rectal (15% v 23%, p<0.05).
- No difference in PD-L1 IHC (SP142 or 22c3) in non-CRC malignancies was observed.

Table 2. – Frequency of *MAP3K1/MAP2K4*-MT by GI malignancy site.

Cancer Type	Total cases	MAP3K1 and/or MAP2K4-mutated	% MAP3K1 and/or MAP2K4-mutated
Colorectal Adenocarcinoma	**9986**	**200**	**2.0%**
Non-Colorectal Adenocarcinoma	**10304**	**121**	**1.2%**
Small Intestine	560	16	2.9%
Gastric	1495	31	2.1%
Cholangiocarcinoma	1668	23	1.4%
Pancreatic	3430	31	0.9%
Appendiceal	523	4	0.8%
Esophageal	1366	9	0.7%
Esophagogastric Junction	595	4	0.7%
Hepatocellular Carcinoma	386	2	0.5%
Anal Carcinoma	281	1	0.4%
Total	**20290**	**321**	**1.6%**

Figure 2. – Immune biomarker comparison of *MAP3K1/MAP2K4*-MT with WT.



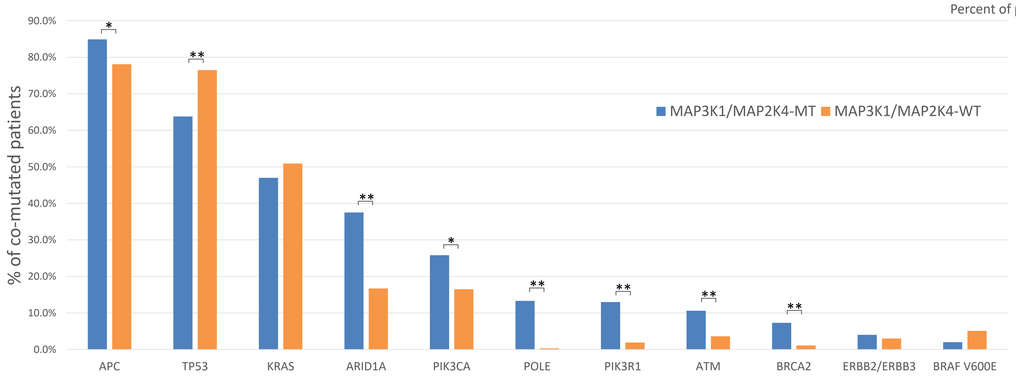
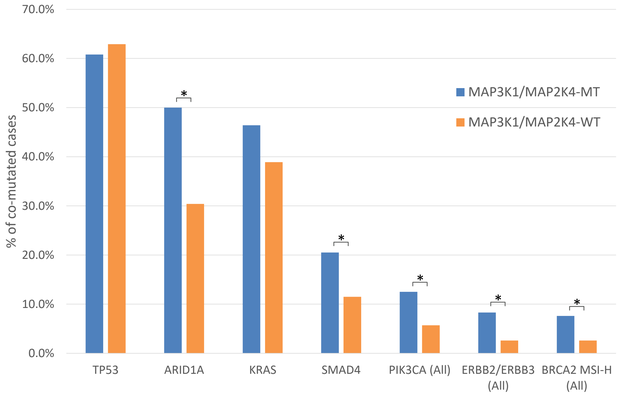


Figure 3. – Comparison of selected co-mutation rates of *MAP3K1/MAP2K4*-MT versus WT CRC MSS patients.

Results, continued

Figure 4. – Comparison of selected co-mutation rates of *MAP3K1/MAP2K4*-MT versus WT non-CRC patients (all MSS except as noted).



Conclusions

- Truncating *MAP3K1/MAP2K4* alterations occur in nearly 2% of GI malignancy pts and are more commonly associated with dMMR/MSI-H, higher TMB and other immune biomarkers than WT.
- In CRC, *MAP3K1/MAP2K4*-MT pts had a greater tendency for *PIK3CA* and *APC* co-mutation and significantly lower *TP53* co-mutation versus WT pts; no difference was seen in *BRAF V600E*, *ERBB2/ERBB3*, or *KRAS*.
- Potentially targetable co-mutation partners implicated in PI3K and MAPK pathways as well as *POLE*, *BRCA2* and *ATM* warrant further evaluation, as well as a high co-mutation rate with *ARID1A*.

References

1. Xue Z, Vis DJ, Bruna A, et al. *MAP3K1* and *MAP2K4* mutations are associated with sensitivity to MEK inhibitors in multiple cancer models. *Cell Res*, 2018.
2. Avivar-Valderas A, McEwen R, Taheri-Ghahfarokhi A, et al. Functional significance of co-occurring mutations in *PIK3CA* and *MAP3K1* in breast cancer. *Oncotarget, 2018.*