Abstract #835: Characterization of the tumor immune microenvironment (TIME) and somatic landscape in gastrointestinal (GI) malignancies with *MTAP* deletions (del)

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Background

PRMT5 is a synthetic lethality target in patients (pts) with *MTAP* del and early phase trials of inhibitors are underway. *MTAP* del are also associated with a less immunogenic TIME and reduced efficacy of immunotherapy, but research in GI malignancies is scarce. Thus, we investigated the TIME and somatic landscape in GI malignancies with *MTAP* del.

Methods

From the Tempus Database, we retrospectively analyzed de-identified NGS data generated by the Tempus xT and xR assays from pts across GI malignancies, including pancreatic (n=11,217), gastroesophageal (GE, n=5,803), cholangiocarcinoma (CCA, n=3,244), and colorectal (CRC, n=17,537) cancers.

MTAP del were defined as two-copy losses. Somatic alterations (alts), immune cell infiltration predicted from gene expression patterns, PD-L1 from IHC, TMB, and MSI were evaluated. Fusions were only analyzed in pts with tumor cell content ≥30% to avoid any potential bias. Chi-squared/Fisher's Exact tests or Kruskal-Wallis tests were used to assess statistical significance ($p<0.05$, $q<0.05$ for false discovery rate correction for multiple testing).

Cohort Overview

Characteristic	Pancreatic (n=11,217)	GE (n=5,803)	CCA (n=3,244)	CRC (n=17,537)
Age at Dx, median (IQR)	67 (60, 74)*	65 (57, 73)*	66 (59, 73)	60 (51, 70)
Male, n (%)	5,965 (53)	4,327 (75%)	1,579 (49%)	9,926 (57%)
Female, n (%)	5,252 (47%)	1,476 (25%)	1,665 (51%)	7,611 (43%)
White, n (%)†	5,389 (81%)	2,607 (80%)	1,441 (80%)	7,858 (76%)
Black or African American, n (%)†	656 (9.9%)	279 (8.6%)	168 (9.3%)	1,294 (12%)
Other, n (%)†	344 (5.2%)	235 (7.2%)	114 (6.3%)	782 (7.6%)
Asian, n (%)†	235 (3.5%)	135 (4.1%)	87 (4.8%)	419 (4.0%)
MTAP del, n (%)	1,662 (14.8%)	426 (7.3%)	369 (11.4%)	157 (0.9%)

*P<0.05 by *MTAP* del status // †% of known data.

This is the largest analysis of the TIME and somatic landscape of *MTAP* loss across GI malignancies.

In pts with MTAP del and pancreatic cancer, CCA, and CRC, we observed a less immunogenic TIME pattern, indicating the evaluation of immunotherapy implications in these GI malignancies with MTAP del is warranted. Our findings are hypothesis-generating, providing further rationale to study synthetic lethality and novel combinatorial therapeutic strategies in GI malignancies with MTAP del.

Results/Graphs/Data

Associations between *MTAP* del and immune infiltration

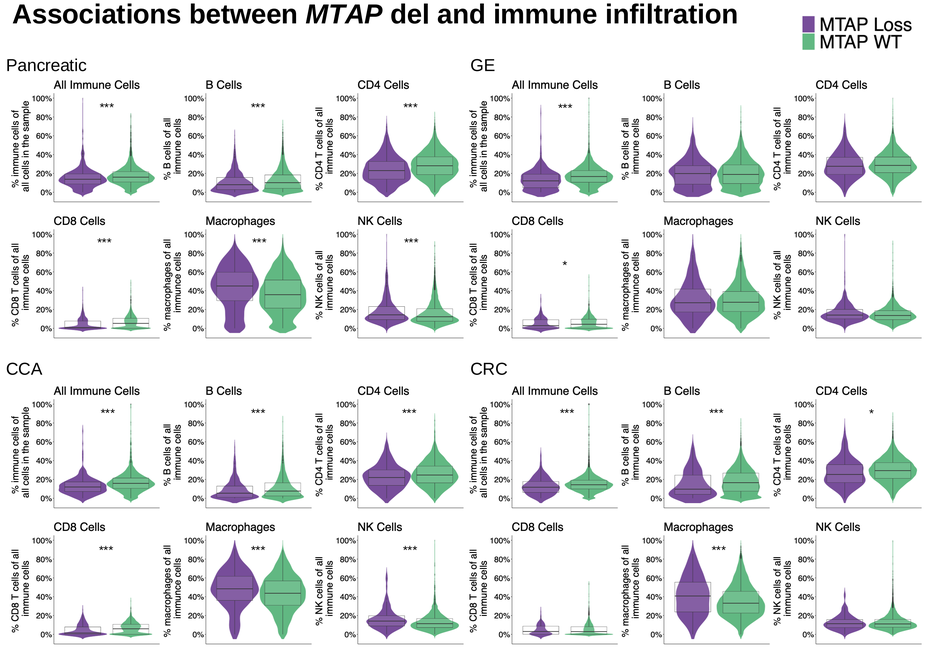

Figure 1. In pancreatic, CCA, and CRC pts, *MTAP* del was associated with a reduced proportion of B cells and CD4 T cells, and there were higher percentages of macrophages vs pts with *MTAP* WT status ($p<0.001$ for all). Reductions in proportion of CD8 T cells were also associated with *MTAP* del in pancreatic and CCA pts ($p<0.001$ for both). ***p≤0.001, **p≤0.01, *p≤0.05

Associations between *MTAP* del and Somatic Alterations

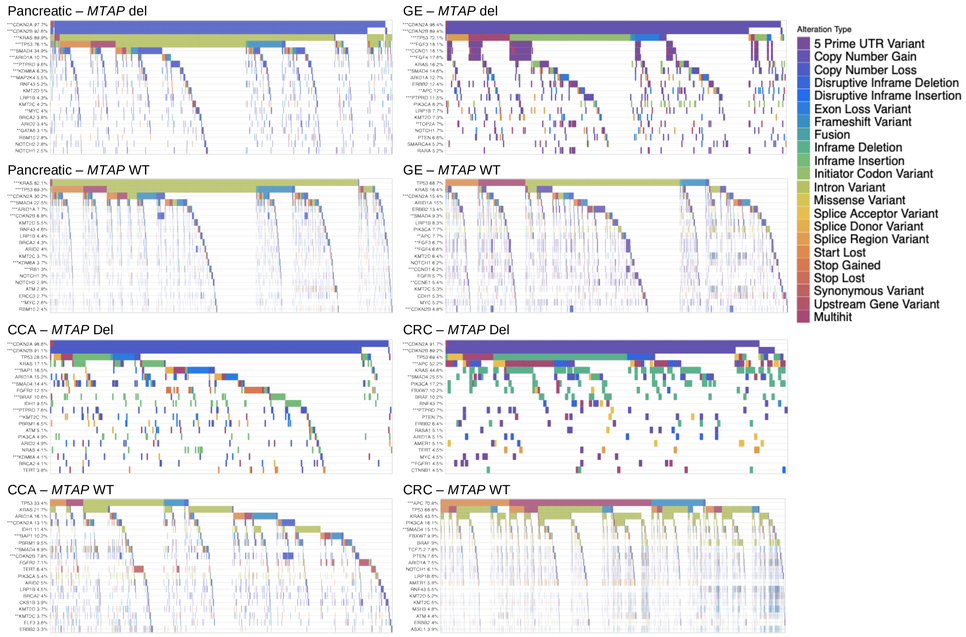

Figure 2. *SMAD4* alterations, a marker of reduced immune infiltrates, were more prevalent in pts with *MTAP* del across GI malignancies ($q<0.005$). In the CCA cohort, there was a higher percentage of *BRAF* alt and *FGFR2* fusions (*MTAP* del=13%, *MTAP* WT=8.7%, data not shown) in pts with *MTAP* loss ($q<0.001$, $q=0.028$), while *KRAS* alt were higher in pancreatic cases with *MTAP* loss ($q<0.001$). ***q≤0.001, **q≤0.01.

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