High-resolution transcriptional signature predicts survival benefit in colorectal cancer (CRC) treated with EGFR inhibitors (EGFRi) independent of *RAS/BRAF* mutation status or tumor sidedness

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Background

- Cetuximab (CTX) and Panitumumab (PMB) therapies directed at EGFR have been restricted to left-sided CRC harboring wild-type *KRAS* (*KRAS*^{WT}), limiting their utility.
- Approximately 50% of mCRC fail to respond to EGFRi, thus identification of predictive biomarkers is an unmet need.
- Here we evaluate a CTX sensitivity score (CTX-S) that we previously reported (Yang M. et al., 2019), in a large, real-world population of *RAS/BRAF* mutant *vs* wild-type and in right- vs left-sided tumors.

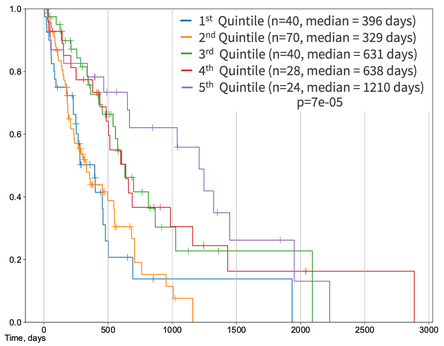
Objectives and Methods

- CTX/PMB-treated CRC specimens (n = 1124) with clinical outcomes, NextGen Sequencing of DNA (592-gene panel or whole exome sequencing) and RNA (whole transcriptome sequencing) were tested at Caris Life Sciences (Phoenix, AZ).
- 1097 specimens were MSS as determined by IHC of MMR proteins and/or NGS.
- Association of CTX-S with *RAS/BRAF* mutation and tumor sidedness was performed in MSS tumors.
- Tumors with likely pathogenic mutations in *KRAS*, *NRAS* or *BRAF* were considered as *RAS*^{MUT}/*BRAF*^{MUT}, or *RAS*^{WT}/*BRAF*^{WT} if no mutation was detected for each gene.
- Samples were stratified based on CTX-S quintiles.
- Survival on EGFRi was calculated from the initiation of EGFRi to last contact using Kaplan-Meir method.

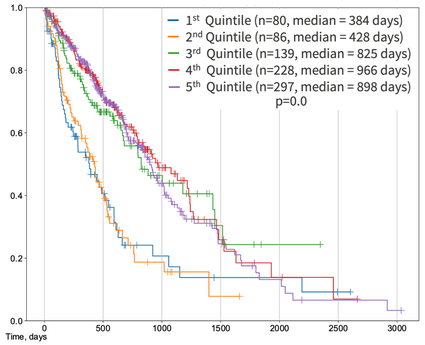
Results

Figure 1: Association of CTX-S with survival on EGFRi in the context of RAS/BRAF mutations

RAS^{MUT}/*BRAF*^{MUT}: EGFRi-OS



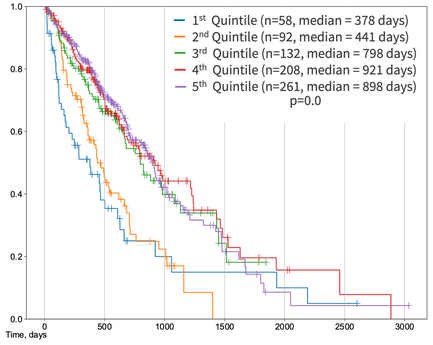
RAS^{WT}/*BRAF*^{WT}: EGFRi-OS



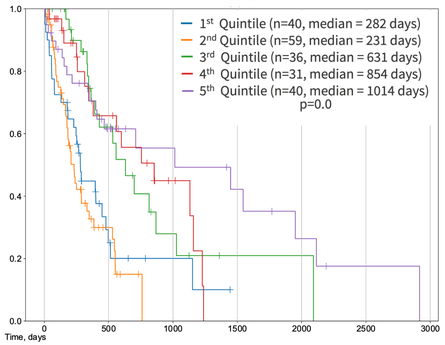
Higher CTX-S quintiles are associated with improved survival on EGFRi in both RAS/BRAF mutant and wild-type tumors

Figure 2: Association of CTX-S with survival on EGFRi in the context of tumor sidedness

LCRC: EGFRi-OS



RCRC: EGFRi-OS



Higher CTX-S quintiles are associated with improved survival on EGFRi in both left- and right-sided tumors

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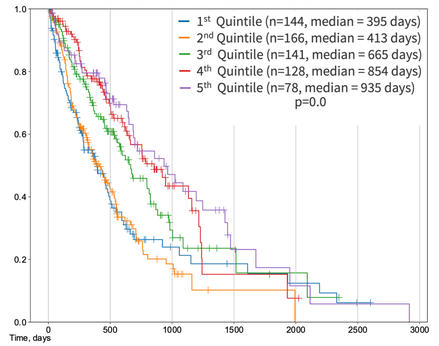
Figure 3: Association of CTX-S with survival on EGFRi in the context of nonCMS2-CRC

nonCMS2: EGFRi-OS



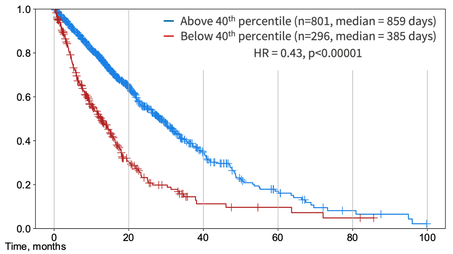
While no significant association are observed between CTX-S and improved survival on EGFRi in CMS2-CRC (data not shown), higher CTX-S quintiles are associated with improved response on EGFRi in nonCMS2-CRC.

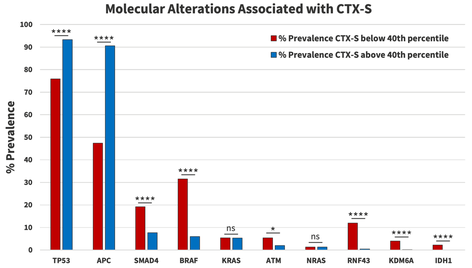
Table 1: Distribution of CMS by CTX-S Quintiles

CMS Subtype	CTX-S				
	1st Quintile (n=2551)	2nd Quintile (n=2552)	3rd Quintile (n=2536)	4th Quintile (n=2545)	5th Quintile (n=2551)
CMS1	941 (36.89%)	754 (29.55%)	278 (10.96%)	83 (3.26%)	18 (0.71%)
CMS2	0 (0.00%)	55 (2.16%)	619 (24.41%)	1398 (54.93%)	1988 (77.93%)
CMS3	537 (21.05%)	785 (30.76%)	614 (24.21%)	217 (8.53%)	23 (0.90%)
CMS4	1061 (41.59%)	945 (37.03%)	1015 (40.02%)	842 (33.08%)	514 (20.15%)
Unclear	12 (0.47%)	13 (0.51%)	10 (0.39%)	5 (0.20%)	8 (0.31%)

Enrichment of CMS2 and a decrease in CMS1 with increasing CTX-S quintiles.

Figure 4: Association of survival on EGFRi and molecular alterations with CTX-S





Patients with CTX-S above the 40th percentile are associated with improved survival on EGFRi. Further, tumors with CTX-S > 40th percentile are associated with an in increased prevalence of mutations in TP53 and APC and a decreased prevalence of mutations in SMAD4, BRAF, ATM, RNF3, KDM6A and IDH1.

Conclusions

- Our data suggest that CTX-S may predict longer survival on EGFRi, surprisingly independent of *RAS/BRAF* mutation status as well as tumor sidedness.
- Patients with high CTX-S had increased prevalence of CMS2 and harbored more *APC* and *TP53* mutations. A strong EGFRi biomarker would likely expand the utility of EGFRi to right-sided tumors and possibly to *RAS*^{MUT} tumors.
- Further validation of these biomarkers in a prospective clinical trial is warranted and could change our current standard of care for CRC.