APC is a high-utility mutational biomarker that may identify subpopulations of mutant *RAS*/*BRAF* and right-sided colorectal cancer (CRC) patients who derive benefit from EGFR inhibitors (EGFRi)

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Background

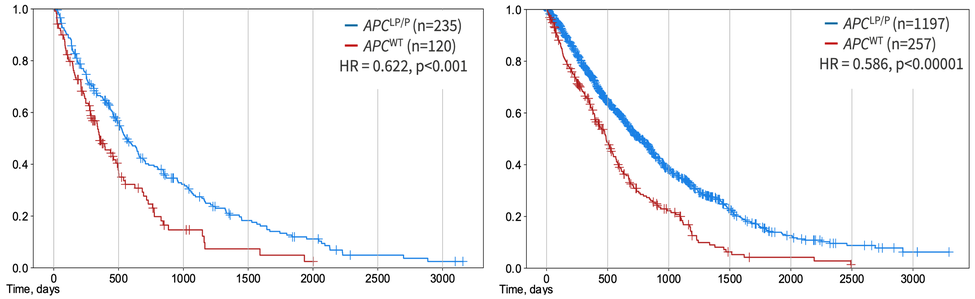
- Cetuximab (CTX) and Panitumumab (PMB) therapies directed at EGFR have been restricted to left-sided CRC harboring wild-type *KRAS* (*KRAS*^{WT}), limiting their utility.
- Approximately 50% of mCRC fail to respond to EGFRi, thus identification of predictive biomarkers is an unmet need.
- Here we evaluate a prespecified 203 gene expression score measuring cetuximab sensitivity (CTX-S) 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 samples were analyzed at Caris Life Sciences (Phoenix, AZ) with DNA-based next-generation sequencing (NGS; 592 genes, NextSeq) or whole-exome sequencing (NovaSeq) and with RNA-based whole-transcriptome sequencing (WTS, NovaSeq).
- 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.

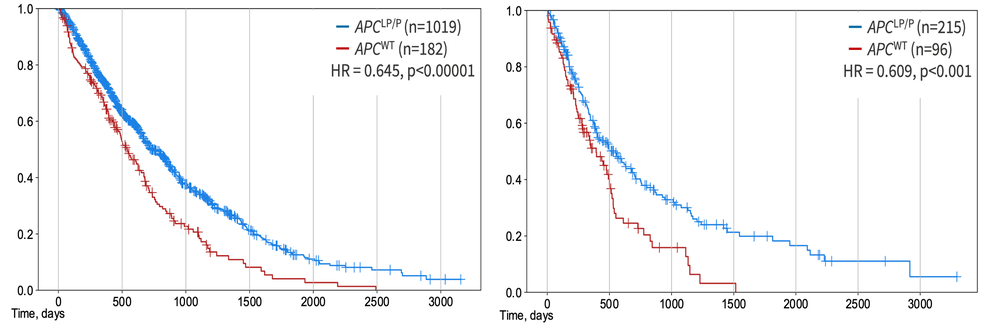
Results

Figure 1: Association of *APC* mutation status with survival on EGFRi in the context of RAS/BRAF mutations



Compared to wild-type, *APC* mutations were associated with improved survival on EGFRi in both *RAS*/*BRAF* mutant as well as *RAS*/*BRAF* wild-type tumors

Figure 2: Association of *APC* mutation status with survival on EGFRi in the context of tumor sidedness



Compared to wild-type, *APC* mutations were associated with improved survival on EGFRi in both left- and right-sided CRC

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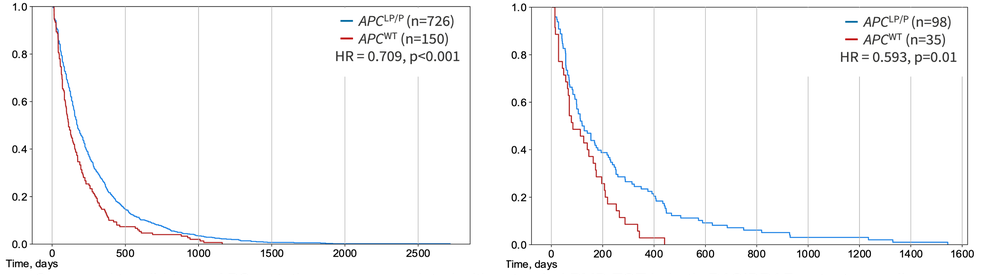
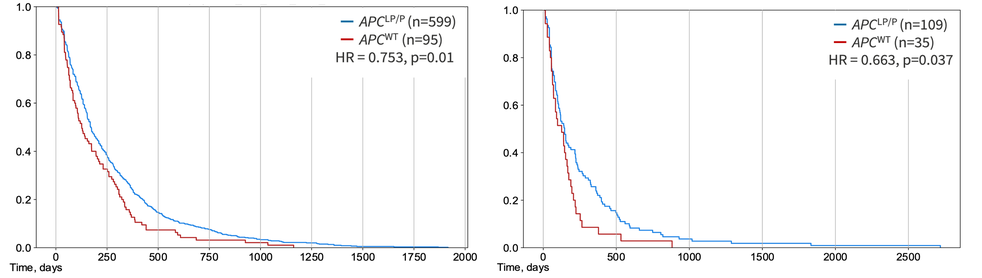
Figure 3: Association of *APC* mutation status with PMB-TOT in the context of RAS/BRAF mutations



Compared to wild-type, *APC* mutations were associated with extended PMB-TOT in both *RAS*/*BRAF* mutant as well as RAS/BRAF wild-type tumors. Similar benefit was not observed in CTX-treated CRC

Figure 4: Association of *APC* mutation status with PMB-TOT in the context of tumor sidedness



Compared to wild-type, *APC* mutations were associated with extended PMB-TOT in both left- and right-sided CRC. Similar benefit was not observed in CTX-treated CRC

Conclusions

- Our data suggests that the simple application of a high-utility mutational biomarker (*APC*), may increase the eligibility for successful EGFRi therapy in a substantial subpopulation of *RAS/BRAF* mt patients as well as right-sided CRC, potentially altering the standard of care.
- Further validation of this biomarker in a prospective clinical trial is warranted.