Background: Colorectal cancer (CRC) especially with KRAS/BRAF mutation (MT) is aggressive and has limited treatment options when metastatic. We used targeted molecular profiling (MP) approach to identify potential treatment options not typically considered for CRC in order to improve the management of this disease.

Methods: We evaluated 6892 CRC cases referred to Caris Life Sciences by MP including sequencing (Sanger/NAS), protein expression (IHC) and gene amplification (CISH/ISH). The cases were analyzed with the Caris Molecular Intelligence (CMI) Engine.

Results: CRC metastases (mets) to liver, brain, ovary or lung (n=1507) showed expression of actionable markers including high TOPO (52%), low RRM1 (57%), TS (71%) and MGMT (39%), suggesting benefit from irinotecan, gemcitabine, SUI/ cetuximab and temozolomide. Brain mets had higher TOP2A (300% vs. 81%), overexpression and lower EGFR (0.3%) compared with other mets (>0.5%). Brain and lung mets had higher MGMT (65% and 99%) compared with other mets (47%, p<0.01), suggesting poor response to EGFR inhibitors (EGFRi). Additional analysis at other metastatic sites will be presented. BRAF-mutated CRC (n=455) showed high levels of RRM1 (52%) compared to wildtype (53%) and low PDGFR (22%) compared with wildtype (36%). BRAF MT also displayed increased expression of TOPO, cMET, cMET/IGF1R, or FGFR2 than wildtype.

Conclusions: Of 6892 CRC cases identified significant differences among tumors with BRAF/KRAS-MT and metastasis, prompting unexpected treatment options. Agents uncommonly used in CRC metastases such as temozolomide are suggested, and etoposide or taxanes are suggested for brain or ovarian mets, respectively. Targeted therapies could be considered for KRAS or BRAF mutated tumors based on actionable targets revealed by MP.

Background: Metastatic colorectal cancers, especially those with distal metastases carry a dismal prognosis despite progress made in treatments in recent years. Main sites of colorectal metastases are liver, lung and peritoneum, and rare metastatic sites include ovary, brain, adrenal gland, bone and bladder. Systematic evaluation of different treatments for these various metastases is lacking, especially for the rare metastases.

KRAS and BRAF mutations also present treatment challenges for colorectal cancers, as KRAS-mutated patients do not benefit from cetuximab and panitumumab, and that BRAF indicates a significantly poorer prognosis.

Our study aims to investigate therapeutic biomarker profiles of colorectal cancers that are difficult to treat, including the distant metastases and KRAS and BRAF-mutated, and to identify potential treatment options.

References:
2. NCCN Clinical Practice Guidelines in Oncology Version 2, 2013