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Molecular profiling of 6,892 colorectal cancer patients to identify potential targeted treatment options

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Abstract

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

Methods: We evaluated 6892 CRCs referred to Caris Life Sciences by MP including sequencing (Sanger/NGS), protein expression (IHC) and gene amplification (CISH/FISH).

Results: CRC metastases (mets) to liver, brain, ovary or lung (n=1507) showed expression of actionable markers including high TOPO1 (52%), low RRM1 (57%), TS (71%) and MGMT (39%), suggesting benefit from irinotecan, gemcitabine, 5FU/capecitabine and temozolomide. Brain mets had higher TOP2A (100% vs. 81%), while ovarian mets had lower TUBB3 (16% vs. 43%) than the other mets ($p<0.05$). Brain and lung mets had higher KRAS mutations (65% and 59%) than other mets (47%, p=0.07, <0.01), suggesting poor response to EGFR inhibitors (EGFRi). Additional analysis at other metastatic sites will be presented. BRAF-mutated CRC (n=455) showed coincident high IHC of RRM1 (56%), TS (53%) and low PDGFR (22%) compared with wild type, suggesting decreased response to gemcitabine, 5FU/capecitabine, or antiangiogenics. Mutation in other genes (APC, PTEN, HNF1A, ABL1, and RB1) may also suggest targeted therapies for these patients. KRAS-mutated CRC had higher cMET (47% vs. 36%) and lower MGMT (56% vs. 63%), suggesting the benefit of cMETi and temozolomide. KRAS-mutated CRC also had high TUBB3 (42% vs. 33%) and low HER2 by IHC (0.5%) and FISH (3%), indicating less benefit from taxanes or HER2i ($p<0.05$). MP of CRC of ascending, descending colon or rectum showed KRAS mutations in 43%, 23%, 43%; PIK3CA in 29%, 25% and 10% or BRAF in 27%, 18% and 3.3%, respectively.

Conclusions: MP of 6892 CRCs identified significant differences among tumors with BRAF/KRAS-MT and metastases, 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 the recent years. Main sites of colorectal cancer metastases are liver, lung and peritoneum, and rarer metastatic sites include ovary, brain, adrenal gland, bone and bladder. Systemic evaluation of differential treatments for these various metastases is lacking, especially for the rarer 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 theranostic biomarker profiles of colorectal cancers that are difficult to treat, including the distant metastases and KRAS-mutated and BRAF-mutated cancers, and to identify potential treatment options.

Methods

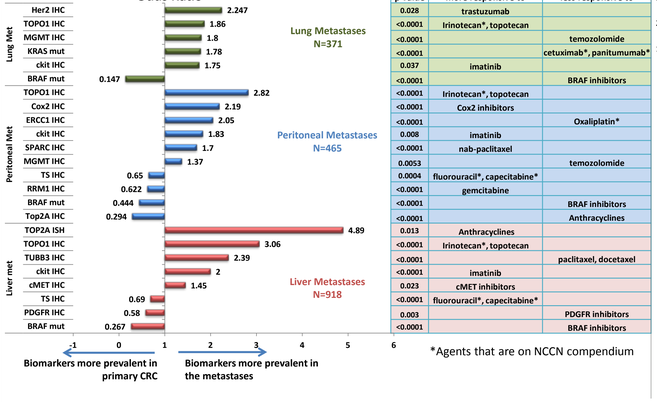
All CRC cases referred to Caris Life Sciences between 2009 thru 2013 from 50 states and 59 countries were evaluated; diagnoses were collected from referring physicians and classified at intake based on pathology and clinical history. Specific testing was performed per physician request and included a combination of sequencing (Sanger NGS), protein expression (immunohistochemistry), gene amplification (CISH or FISH), promoter methylation (pyrosequencing) and/or RNA fragment analysis. Biomarker associations were calculated by two-tailed Fisher Exact tests.

Results

*** Full analysis includes additional metastases and further investigation of the biomarker data since the abstract submission.*

Figure 1: Biomarkers that are significantly different in the metastases compared to the primary CRC tumors. Biomarkers including protein expression (IHC), gene amplification (ISH) and mutation (mut) were examined in various metastatic tumors and compared to those of 2510 tumor samples taken from the colon. Odds ratios of the comparisons are shown on the left. The associated therapeutic implications are in the tables on the right, with the left column showing agents that are potentially more beneficial in the metastasis considered than the primary CRC tumors, and the right column showing agents that are potentially less beneficial than the primary CRC tumors.

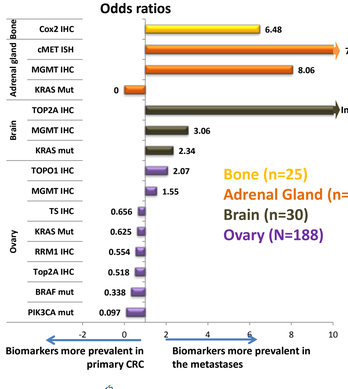
Figure 1A: Biomarker comparisons in common metastases (liver, peritoneal and lung) compared to primary CRC tumors.



	p value	Metastatic sites are more responsive to	Metastatic sites are less responsive to
Her2 IHC	0.028	trastuzumab	
TOPO1 IHC	<0.0001	Irinotecan*, topotecan	
MGMT IHC	<0.0001		temozolomide
KRAS mut	<0.0001		cetuximab*, panitumumab*
ckit IHC	0.037	imatinib	
BRAF mut	<0.0001		BRAF inhibitors
TOPO1 IHC	<0.0001	Irinotecan*, topotecan	
Cox2 IHC	<0.0001	Cox2 inhibitors	
ERCC1 IHC	<0.0001		Oxaliplatin*
ckit IHC	0.008	imatinib	
SPARC IHC	<0.0001	nab-paclitaxel	
MGMT IHC	0.0053		temozolomide
TS IHC	0.0004	fluorouracil*, capecitabine*	
RRM1 IHC	<0.0001	gemcitabine	
BRAF mut	<0.0001		BRAF inhibitors
Top2A IHC	<0.0001		Anthracyclines
TOP2A ISH	0.013	Anthracyclines	
TOPO1 IHC	<0.0001	Irinotecan*, topotecan	
TUBB3 IHC	<0.0001		paclitaxel, docetaxel
ckit IHC	<0.0001	imatinib	
cMET IHC	0.023	cMET inhibitors	
TS IHC	<0.0001	fluorouracil*, capecitabine*	
PDGFR IHC	0.003		PDGFR inhibitors
BRAF mut	<0.0001		BRAF inhibitors

*Agents that are on NCCN compendium

Figure 1B: Biomarker comparisons in rarer metastases (ovary, brain, adrenal gland and bone) compared to primary CRC tumors. Bladder metastasis was also investigated, however no significant differences in biomarker distribution was found when compared to primary CRC tumors.



p value	Metastatic sites are more responsive to	Metastatic sites are less responsive to
0.047	Cox2 inhibitors	
0.029	cMET inhibitors	
0.0282		temozolomide
0.006	Cetuximab*, panitumumab*	
0.0349	Etoposide	
0.022		temozolomide
0.0458		Cetux*, panitum*
<0.0001	Irinotecan*, topotecan	
0.009		temozolomide
0.023	Fluorouracil*, capecitabine*	
0.0044	Cetuximab*, panitumumab*	
0.001	gemcitabine	
0.0008		anthracyclines
0.0006		BRAF inhibitors
0.0023		PAM inhibitors

*Agents that are on NCCN compendium

Figure 2A

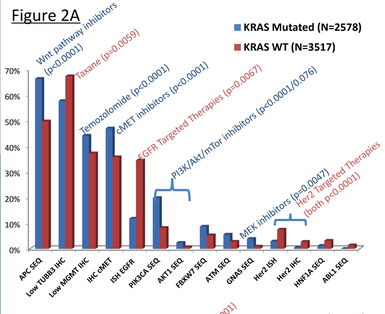
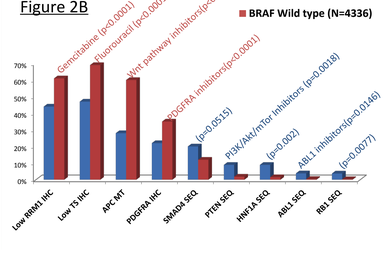


Figure 2B



In addition to the difficulties in treating metastatic CRCs, presence of KRAS and BRAF mutations present another difficult-to-treat subgroups of CRC.

Figure 2: Frequencies of biomarkers that are significantly different in KRAS mutated and wild type CRC (Figure 2A) and in BRAF mutated and wild type CRC (Figure 2B). Agents shown in blue are potentially more likely to benefit KRAS mutated (2A) or BRAF mutated (2B) patients; agents in red are potentially more likely to benefit KRAS wild type (2A) or BRAF wild type (2B) patients.

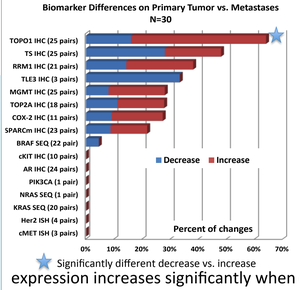


Figure 3: Frequencies of biomarker differences observed in paired samples. 120 paired samples were analyzed for biomarker differences. The intervals between the tissue collections were > 6 months. Out of the 120, 30 had the primary tumor sample and a metastasis profiled (shown) while 90 had two metastatic tumors profiled (data not shown). TOPO1 expression increases significantly when comparing the metastases with the primary tumor ($p=0.03$). Within all 120 pairs, only 11 showed no biomarker differences while the rest of 109 cases had 1-7 biomarker changes per case, averaging at 3.1 per case. Differences in the mutational status was seen in 4/89 pairs for KRAS, and 1/81 pairs for BRAF. PIK3CA and NRAS have concordant results in all pairs considered.

Conclusions

- Significant biomarker differences are seen in 7 sites of metastases from a large cohort of metastatic CRC patients, suggesting potential differences in response to associated treatments.
- When compared to the primary CRC, significantly higher Her2 overexpression, TOPO2A amplification, Cox2 overexpression, cMET amplification and TOP2A overexpression were observed for metastases to lung, liver, bone, adrenal gland and brain, respectively. The associated agents include trastuzumab for lung, anthracyclines for liver, Cox2 inhibitors for bone, cMET inhibitors for adrenal gland and etoposide for brain metastases. The molecular heterogeneity of the various metastases highlight the need for a comprehensive molecular profiling for individual patients in order to identify the most effective treatments.
- Mutations in KRAS and BRAF are associated with significant differences in predictive biomarkers, suggesting that potential effective therapies could be identified for KRAS or BRAF mutated tumors based on actionable targets revealed by MP.
- Biomarker differences were frequently observed in paired serial tumor samples from individual patient, highlighting the importance of timely profiling to direct the next line of therapy.

References

1. Cancer Genome Atlas Network, 2012, Nature, 2012 487(7407):330-7
2. NCCN Clinical Practice Guidelines in Oncology Version 2, 2013