Monitoring therapy in leptomeningeal carcinomatosis in colorectal cancer using CSF liquid biopsy.- Abstract Code: BIOM40

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GENOMIC TESTING COOPERATIVE

Background

Liquid biopsy (LBx) as performed using CSF is emerging as a reliable tool for the diagnosis and monitoring of patients with LC. Monitoring the levels of LC using CSF LBx and correlating these levels with therapeutic approaches may provide better may help in predicting resistance and implement new therapeutic approach. Toward this goal we present the testing results of 27 consecutive analysis of CSF samples collected through Ommaya reservoir over a period of 13 months.

Methods

Clinical history: 42-year-old male with Stage IV colorectal cancer harboring germline BRCA1 mutation, diagnosed in April 2022 with liver and lung metastases. He was treated with FOLFIRINOX, followed by HIPEC and tumor debulking in May 2022. He subsequently received FOLFOX, BRAF/EGFR/MEK inhibitors (i.e., encorafenib, cetuximab, binimetinib), PARP inhibitors, and underwent Y90 in Sept 2022 and liver resection in Feb 2023 (achieving NED in liver). Brain metastases were first detected on MRI in June 2023 and treated with multiple rounds of SRS (June, Dec 2023; May 2024). Leptomeningeal disease (LMD) was diagnosed in September 2024 via brain MRI and lumbar spine MRI, and progressed by January 2025 brain MRI, prompting treatment with intrathecal nivolumab, methotrexate, and topotecan followed by weekly intrathecal methotrexate. CDH17 CAR-T therapy was initiated in May 2025.

CSF samples were centrifuged to isolate the cells. From the supernatant, cell-free DNA(cfDNA) and cell-free RNA (cfRNA) were extracted. From the cell pellet, cellular RNA (cRNA) was extracted. cfDNA was sequenced by next generation sequencing (NGS) using a targeted DNA panel of 302 genes. The cfRNA and cellular RNA were sequenced independently using a targeted RNA panel of more than 1,600 genes.

Results

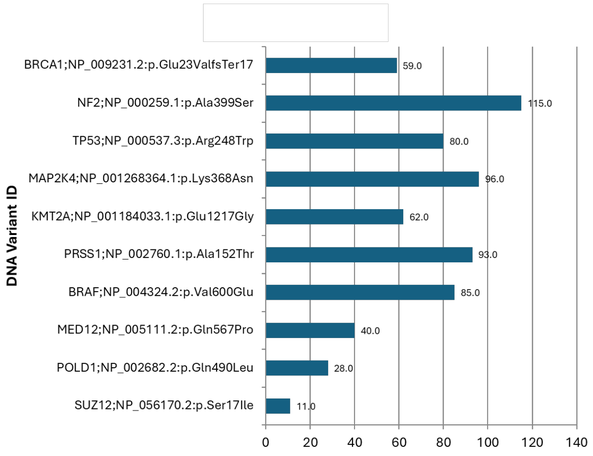
Initial Diagnostic CSF vs Peripheral Blood

CSF

Gene	Alt Variant Freq
BRCA1	54.63
NF2	48.73
TP53	46.24
MAP2K4	42.86
KMT2A	42.46
PRSS1	29.52
BRAF	29.31
MED12	25.16
POLD1	17.18
SUZ12	5.85

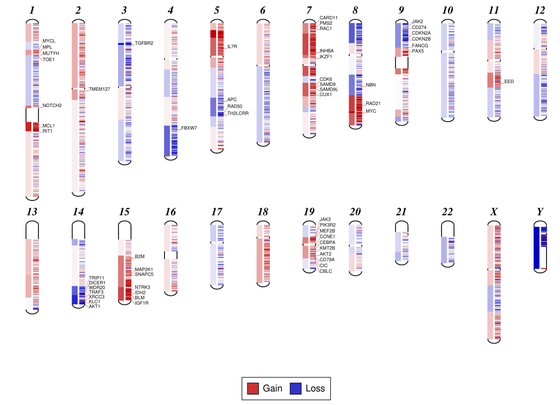
Peripheral Blood

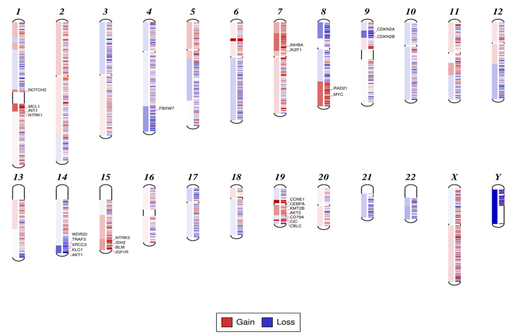
Gene	Alt Variant Freq
BRCA1	46.02
TP53	0.25
KEAP1	0.2
BRAF	0.11
MAP2K4	0.26

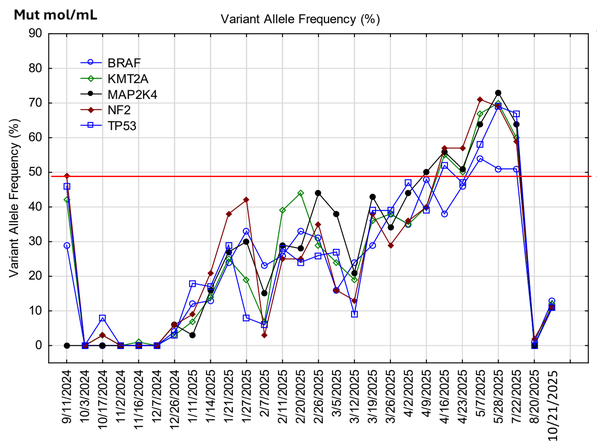


Gene	Alt Variant Freq
BRCA1	81.63
MAP2K4	73.45
KMT2A	69.51
NF2	69.42
TP53	68.57
BRAF	50.71
MED12	39.13
POLD1	31.18
PRSS1	25.73
RET	0.88

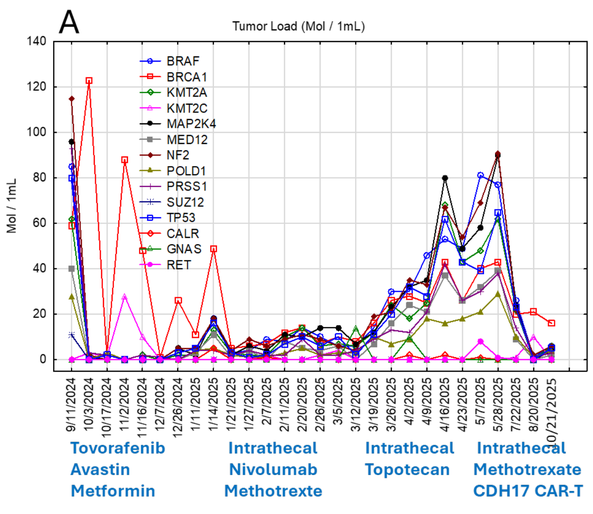
Changes at Resistance

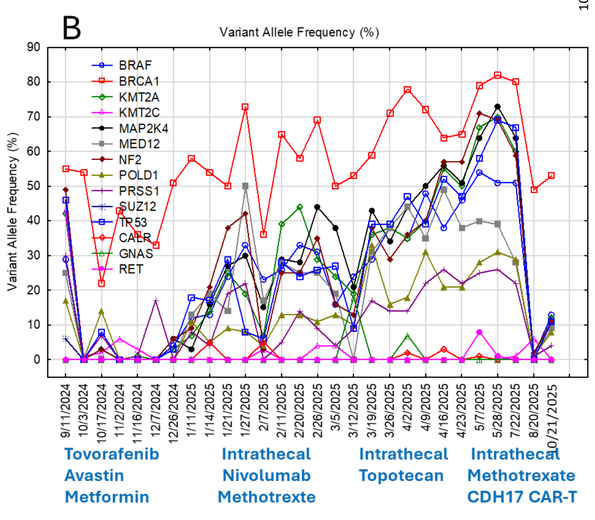






Bi-allelic abnormalities (Mutation of one allele and loss of the second (TP53, MAP2K4, NF2)or gain of extra copy (BRAF and KMT2A)





Conclusions

-CSF testing is reliable for the diagnosis and monitoring for LMD in patients with colorectal cancer.

-CSF quantitative evaluation of tumor load is more accurate than VAF in reflecting response and progression of the disease

-One of the major mechanism of resistance to therapy in LMD is the loss of the wild type allele of the driver mutations or gain of a second mutant allele .