Caris Molecular Tumor Board Case Study

The Caris Molecular Tumor Board (CMTB) works one on one with oncologists to obtain interpretation of molecular findings and therapeutic guidance on difficult-to-treat cases. Read how the CMTB approached a patient diagnosed with stage IV cecal cancer with liver and mesenteric metastases.

**Background**
While the diagnosis of Stage IV colon cancer can be devastating, the revelations of the tumor’s molecular vulnerabilities can offer effective therapeutic opportunities and pave a clear path for the treatment plan to the best outcome. This requires thorough interrogation of the patient’s tumor for a complete landscape of the molecular features and interpretation of the molecular information from a multidisciplinary expert group.

**Presented Case**
- 79-year-old female patient.
- Diagnosed with stage IV cecal cancer with liver and mesenteric metastases.
- Patient received 2 weeks of chemotherapy (capecitabine) prior to CMI testing.
- CMI testing identified the tumor carries two highly actionable alterations:
  - MSI-H/dMMR with a concurrent TPM3-NTRK1 fusion.
  - Two alterations suggests two treatment options both supported by level 1 evidence.
- Tumor displays major microsatellite instability, consistent with observed loss of MLH1 and PMS2 expression.
- Question: how to target alterations sequentially to deliver the most benefit to the patient?

**CMTB Recommendation**
In this case of a newly diagnosed metastatic right-sided colon tumor with dMMR/MSI-H, high TMB and a concurrent TPM3-NTRK1 fusion, the recommendation of the CMTB is to proceed with frontline treatment of an immune checkpoint inhibitor, and to potentially pursue an NTRK inhibitor at progression. Standard options for mCRC, including chemotherapy in combination or singly with bevacizumab, may also be considered.

MSI-H/dMMR
Deficient mismatch repair are caused by either germline or somatic changes in a key DNA repair machinery. The resultant microsatellite instability would lead to a large mutational burden and increased neoantigen production that can be effectively targeted by immune checkpoint inhibitions (ICI).

• Since no deleterious mutations in MLH1 and PMS2 are seen, it’s likely that the MSI is the result of somatically acquired MLH1 deficiency due to promoter hypermethylation. That loss of PMS2 is secondary to MLH1 loss as it becomes unstable in the absence of MLH1.

• As expected, a high tumor mutational burden (25 mt/MB) is also observed.

• In pre-treated MSI-H/dMMR mCRC, the use of ICIs or their combinations have shown very promising activity and have become part of treatment routines.

• In the frontline setting, the practice-changing results of the KEYNOTE-177 trial presented at the 2020 Annual ASCO meeting demonstrated doubling of progression-free survival in MSI-H CRC and a 66% decrease of severe toxicities when pembrolizumab monotherapy was given.

• These results added to the accumulating evidence and led to the FDA approval for pembrolizumab use in first line, making ICI the new standard of care for MSI-H mCRC.

TPM3-NTRK1 fusion
Comprehensive RNA sequencing also detected a TPM3-NTRK1 fusion in this tumor. It’s now evident that RNA based sequencing is the optimal assay for fusion detection as some targetable fusions are products of splicing out of introns and RNAseq simplifies the technical requirements for adequate coverage; additionally, detection of fusions at the RNA level provides direct evidence of functional transcriptions.

• In cancer, fusions that involve the tropomyosin receptor kinase (Trk) receptor family members (NTRK1, 2, or 3) are targetable by two FDA approved agents, larotrectinib and entrectinib.

• NTRK fusions overall are very rare in colorectal cancer; seen in less than 1%. The TPM3-NTRK seen in this tumor, however, is the most frequently observed NTRK fusion in colon cancer.

• The coiled-coil domain of the TPM3 fusion partner is likely responsible for the constitutive dimerization of the Trk A and cause kinase activation.

• Most reported NTRK fusion-positive CRC tumors are MSI-H and KRAS/NRAS/BRAF wild type, similar to the current case.

• The pooled analyses associated with the cancer-agnostic approval of larotrectinib and entrectinib included both small numbers of colorectal tumors (N=8 and 4, respectively) and reported ORRs (50% and 25%). The findings in these previously-treated CRC tumors are lower than what’s observed in the overall populations (79% and 57%).