CARIS® | MOLECULAR TUMOR BOARD

Caris Molecular Tumor Board Case Study

The Caris Molecular Tumor Board (CMTB) works one-on-one with oncologists to interpret molecular findings and provide therapeutic guidance on difficult-to-treat cases. Read how the CMTB approached a patient with dual primary cancers presenting as both locally advanced Stage IIIA Duodenal Adenocarcinoma and Stage IV Small Bowel GIST with peritoneal metastases.

Background

A patient was diagnosed with dual primary cancers, including locally advanced (Stage IIIA) Duodenal Adenocarcinoma and Stage IV Small Bowel GIST with peritoneal metastases. Multiple primary tumors occur in approximately 2-17% of cancer cases,[1] presenting challenges in defining a therapy strategy to effectively treat each tumor type while mitigating side effects or drug interactions. Clinical trials often exclude patients with an active secondary malignancy. In addition, the two tumor specimens each showed *KIT* exon 11 p.D579del genetic alterations, suggesting a possible common germline component. Such complex cases can benefit from comprehensive molecular profiling with a multidisciplinary CMTB group applying diverse expertise to identify an effective therapeutic pathway.

Presented Case

- A 70-year-old male patient, a former smoker with hypertension, was initially diagnosed with localized Duodenal Adenocarcinoma (Stage IIIA).
- The patient began FOLFOX neoadjuvant treatment to downstage the Duodenal Adenocarcinoma prior to resection. The tumor did not respond to chemotherapy, so surgery was not possible due to involvement of major vasculature structures.
- Concurrently, a small bowel intussusception developed due to disease progression of an incidentally discovered GIST.
- Strong morphological evidence supported the pathologic diagnosis of dual, distinct primaries.
- The patient began combined therapy of FOLFIRI for Duodenal Adenocarcinoma and low dose imatinib (200 mg) for GIST, with modest treatment response and moderate side effects.

Molecular Profiling Results

- GIST specimen
  - Caris Comprehensive molecular profiling of the GIST tumor specimen reported two notable biomarkers with therapy associations, *KIT* Exon 11|p.D579del and BRCA2 deletion.
  - Caris MI GPSai confirmed the submitted diagnosis, reporting a 100% GIST prevalence score.
  - Whole Exome Sequencing (WES) identified pathogenic deletions in *BRCA2, ERCC5* and *RB1*; plus, a pathogenic *KIT* exon 11 mutation at 48% variant frequency was reported.
  - Microsatellite Instability (MSI) was determined to be stable.
- Duodenal Adenocarcinoma
  - Caris Comprehensive molecular profiling of the duodenal adenocarcinoma tumor specimen reported two notable biomarkers with therapy associations, *KIT* Exon 11|p.D579del and *ERBB2* (Her2/Neu).

The Caris Molecular Tumor Board (CMTB)

The CMTB provides oncologists with the opportunity to interact with leading cancer experts from across the country to obtain interpretation of molecular findings and therapeutic guidance for individual patients. This proprietary virtual tumor board platform is an innovative, real-time approach to deciphering complex data and treatment decisions on difficult-to-treat cases. The efficient access to cutting-edge information provided by the Caris Molecular Tumor Board allows oncologists to focus their efforts on what matters most – developing the most informed personalized treatment strategies for their patients. Please visit **www.CarisLifeSciences.com/CMTB** to register and submit a case for review.

- Caris GPSai was not obtained for this specimen.
- WES identified pathogenic deletions in *B2M*, *KRAS* (G12A) and *PIK3CA*; plus, a pathogenic *KIT* exon 11 mutation at 47% variant frequency was found.
- Microsatellite Instability (MSI) was determined to be stable.

- Despite both tumors having *KIT* Exon 11|p.D579del mutations with similar variant allele frequencies, the presence of additional distinct cancer-relevant biomarkers supports the conclusion that these are indeed two distinct primary tumors.
- Question: What therapeutic options does the CMTB recommend for this patient?

CMTB Recommendation

Germline Testing

- Both duodenal adenocarcinoma and GIST exhibit pathogenic *KIT* exon 11 mutations at similar variant allele frequencies (47-48%). In order to rule out an underlying germline mutation, the CMTB recommends germline peripheral blood testing with a panel that includes *KIT*.
- Although rare, familial GIST-mastocytosis syndrome with germline *KIT* mutation (KIT D579del) has been reported.[2,3]

Tyrosine Kinase Inhibitors

- (GIST) A favorable response to imatinib treatment and surgery has been reported in a GIST harboring the *KIT* D579del mutation; the patient has since had stable disease.[3] Switching to sunitinib upon imatinib resistance may be effective. Likewise, switching to regorafenib upon sunitinib resistance may be effective.
- (Duodenal Adenocarcinoma) Despite imatinib demonstrating activity against other non-GIST tumors,[4] the drug's benefit for treating duodenal adenocarcinoma is unclear. Mechanistically, the tumor's *KIT* and *KRAS* mutations create pathway redundancy, likely preventing significant benefit from KIT blockade (imatinib) alone. Similarly, there is an unclear benefit to sunitinib.

PARP inhibitors

- In the GIST tumor, concomitant deletions in *BRCA2* and tumor suppressor *RB1* suggest there may not be BRCA-driven homologous recombination deficiency (HRD), since a tumor is not likely to endure losses of both HR (BRCA) and NHEJ (RB1) repair pathways. Therefore, the benefit of a PARP inhibitor is uncertain.

PI3K inhibitors

- The adenocarcinoma has a *PIK3CA* alteration in exon 9. Tumors with this hotspot mutation (p.E545K) have been shown to be sensitive to PI3K inhibitors such as alpelisib in preclinical and clinical studies. A clinical trial using a PI3K inhibitor could be considered if the adenocarcinoma were to progress on current therapy.

RAS inhibitors

- Clinical trials of novel RAS inhibitors might be considered at progression of the adenocarcinoma given the *KRAS* G12A mutation.

References:

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2. Ke H, Kazi JU, Zhao H, Sun J. Germline mutations of KIT in gastrointestinal stromal tumor (GIST) and mastocytosis. *Cell Biosci.* 2016 Oct 18;6:55.
3. Jones DH, Caracciolo JT, Hodul PJ, Strosberg JR, Coppola D, Bui MM. Familial gastrointestinal stromal tumor syndrome: report of 2 cases with KIT exon 11 mutation. *Cancer Control.* 2015;22:102–108.
4. Carvajal RD, Antonescu CR, Wolchok JD, Chapman PB, Roman RA, Teitcher J, Panageas KS, Busam KJ, Chmielowski B, Lutzky J, Pavlick AC, Fusco A, Cane L, Takebe N, Vemula S, Bouvier N, Bastian BC, Schwartz GK. KIT as a therapeutic target in metastatic melanoma. *JAMA*. 2011 Jun 8;305(22):2327-34.