CARIS® | MOLECULAR TUMOR BOARD

Caris Molecular Tumor Board: Case Study

Malignant peripheral nerve sheath tumor

Background

While the diagnosis of a metastatic malignant nerve sheath tumor can be devastating, discovery of the tumor's molecular vulnerabilities can offer effective therapeutic interventions and identify optimal treatments. This requires thorough interrogation of the patient's tumor for a complete landscape of the molecular features and interpretation of the molecular information. In challenging cases, a multidisciplinary expert group like the Caris Molecular Tumor Board (CMTB) can leverage broad expertise to identify potential therapeutic approaches.

Presented Case

- 32-year-old male.
- Former smoker with inherited neurofibromatosis 1 (NF1) syndrome.
- Previously undergone multiple resections for neurofibromas.
- Progressive pain in the distal right thigh with imaging suspicious of a malignant peripheral nerve sheath tumor (MPNST).
- Excisional biopsy and subsequent pathology was consistent with MPNST

Treatment and Molecular Profiling

- Patient underwent a radical resection and pathology showed a high-grade MPNST arising in a background of a plexiform neurofibroma.
- Tumor was microsatellite stable, *NTRK* fusion negative, and negative for PD-L1.
- The patient underwent adjuvant radiation.
- On follow-up, the patient presented with six bilateral pulmonary masses, the biopsy of which confirmed metastatic MPNST. Thoracic surgery considered these metastases to be unresectable.
- A sample of the primary tumor was submitted to Caris for comprehensive molecular profiling to aid in clinical decision making.
- In interim, patient started on anthracycline-based chemotherapy combination, AIM (Adriamycin [doxorubicin], ifosfamide, and mesna).
- Caris comprehensive molecular profiling revealed a likely pathogenic *MET* fusion (*RABGEF1:MET*; splice site exon 1:exon 2) and *MET* amplification, along with the known pathogenic NF1 mutation (c.6855C>A).

CMTB Recommendation

In this case of metastatic MPNST in an NF1 patient with a *MET* fusion and amplification, the CMTB recommended *MET*-targeting therapies like crizotinib, cabozantinib, tepotinib, or capmatinib. While the CMTB felt that crizotinib and cabozantinib were reasonable options, they favored tepotinib and capmatinib as these are more specific *MET* inhibitors. Based on a cross-trial comparison that showed improved clinical efficacy, the CMTB recommended capmatinib over tepotinib.[1] The CMTB also noted that capmatinib has also proven effective in lung cancer with *MET* amplifications,[2] which are seen in this patient's tumor. The CMTB did recognize that cabozantinib has demonstrated benefit in other sarcomas,[3] and it could be considered as well. Of particular interest could be a clinical trial (NCT04551430) evaluating cabozantinib in combination with nivolumab and ipilimumab.

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.

Another option presented by the CMTB were clinical trials that are evaluating MEK inhibition in MPSNTs (for example, SARC031). The CMTB also noted case reports where MPNSTs responded to anti-PD-1 therapy,[4] however these have been PD-L1-positive tumors, and the CMTB noted that the patient's tumor is PD-L1 negative, microsatellite stable, and tumor mutational burden low.

Patient Update

The patient responded well to chemotherapy and is being considered for resection of residual disease. The therapeutic plan is to use cabozantinib in the event of recurrence/progression.

NF1 Syndrome

- NF1 syndrome has several clinical manifestations, including benign cutaneous and plexiform neurofibromas, which are driven by pathogenic mutations in the NF1 gene that encodes the tumor suppressor neurofibromin (reviewed in[5]).
- Source of NF1 mutations is evenly split between inherited autosomal dominant and spontaneous NF1 mutations.[6]
- Approximately 15-20% of NF1 patients will develop optic gliomas,[7] and 4-13% of NF1 patients will develop MPNSTs.[5,8,9]

Malignant Peripheral Nerve Sheath Tumors (MPNSTs)

- MPNSTs are soft tissue sarcomas whose development is closely linked with NF1.
- 85.7% of MPNSTs bear NF1 mutations,[10] and 41% of spontaneous MPNSTs have a somatic NF1 mutation.[11]
- Patients with NF1 syndrome have a higher prevalence MPNSTs versus the general populace (2-5% versus 0.0001%).[9]

MET Amplifications and Fusions

- *MET* is a receptor tyrosine kinase, frequently converted to its oncogenic form via amplification or mutations resulting in exon 14 skipping or gene fusions that encode a constitutively active form.
- 25% of MPNSTs have *MET* amplifications.[12]
- To date, no recurring chromosomal translocations or oncogenic gene fusions have been reported in MPNSTs, but it's plausible that unique fusions could serve as oncogenic drivers in some cases.[13]
- In this case, the presence of a previously unreported but likely pathogenic *MET* fusion (*RABGEF1:MET*) and *MET* amplification, alongside supporting clinical evidence, was compelling evidence to recommend *MET*-targeting agents.

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