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 stage II non-small cell lung cancer presenting for consideration of adjuvant therapy.

Background

Though the diagnosis of non-small cell lung cancer (NSCLC) can be devastating, identifying the tumor's molecular weaknesses can guide physicians to optimal treatment strategies that will produce the best patient outcomes. This requires a thorough interrogation of the patient's tumor for a comprehensive landscape of the molecular features and interpretation of the molecular information. In more unique cases, a multidisciplinary expert group, like the Caris Molecular Tumor Board (CMTB), can utilize the experience and knowledge of its members to identify potential therapeutic approaches.

Presented Case

- 78-year-old female patient.
- Remote history of stage IIb breast cancer treated with radical mastectomy and several months of chemotherapy, in remission since the 1990s.
- Diagnosed with stage IIb Non-Small Cell Lung Cancer of left upper lobe without nodal positivity or evidence of metastasis.
- Patient is status post thoracotomy and left upper lobectomy, presenting for consideration of adjuvant therapy.

Molecular Profiling and Interpretation

- Caris Molecular Profiling identified potentially actionable alterations:
  - Tumor exhibits low TMB, is MSI stable, and low LOH.
  - Programmed death ligand 1 (PD-L1) positive via IHC analysis suggesting pembrolizumab or nivolumab/ipilimumab combination therapy (both supported by Level 1 evidence for metastatic disease).
    - 22c3 Positive | TPS: 5%
    - 28-8 Positive | 1+, 5%
    - SP142 Negative | IC: 1%, TC: 0%
  - Likely pathogenic variant of *MET* with mutation at exon 14 (7 residue deletion including Y1003/Y1021 ubiquitin ligase binding site) considered to be analogous to *MET* exon 14 skipping mutations.
  - Amplification of CDK4, HMGA2, and MDM2. No *MET* amplification was observed.

MET and NSCLC

- *MET Exon 14* Mutation
  - *MET*, a proto-oncogene, encodes a receptor tyrosine kinase that binds to hepatocyte growth factor.[1,2]

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.

- *MET* mutations may result in aberrant cell growth, angiogenesis, and metastatic activity through *ERK, JNK, STAT3,* and *mTOR* pathway activation.
- In this patient, DNA sequencing revealed a likely pathogenic variant of *MET*, identifying an in-frame deletion within exon 14 that removed tyrosine residue Y1003 (also known as Y1021)
- This tyrosine residue is involved in ubiquitin ligase binding and, when removed, results in *MET* stability and oncogenic activity. This mutation is proposed to be analogous to the more common *MET* exon 14 skipping mutations, which result in the removal of the entire exon 14 from RNA transcripts.[2]
- *MET* exon 14 skipping mutations are present in up to 3% of NSCLCs and two *MET* tyrosine kinase inhibitors (TKIs), capmatinib and tepotinib, were approved to target this alteration.[3,4]
- Regarding clinical activity for exon 14 non-skipping mutations, the only evidence is for crizotinib. Crizotinib yielded a significant response in a patient with lung adenocarcinoma harboring a *MET* Y1003S mutation, with observational improvement in lung lesion and lymph node size lasting over 10 months.[5]
- Similarly, a patient with recurrent head and neck squamous cell carcinoma with a similar, activating *MET* exon 14 mutation was treated with crizotinib and exhibited rapid response within 1 month of treatment.[6]

PD-L1 and NSCLC

- PD-L1 expression patterns are influenced by interferon gamma (IFN-γ) production via CD8+ T-cells. Elevated PD-L1 expression causes enhanced binding of PD-1 receptors and, subsequently, suppresses immune system activity.[7]
- Caris Molecular Profiling detected expression of PD-L1 using IHC, though two antibodies yielded only slightly positive results, while a third reported a negative result.
- In 2021, the IMpower010 clinical trial provided sufficient evidence for the use of adjuvant atezolizumab as a PD-L1 immune checkpoint inhibitor in NSCLC patients necessary for FDA approval.[8]
- Adjuvant atezolizumab, used after adjuvant platinum-based chemotherapy, improved DFS when compared to patients treated with supportive care only.[8]

CMTB Recommendation

Based on PD-L1 results and adjuvant setting, the patient has been started on atezolizumab. Consideration of *MET* inhibition may be warranted in later lines in the context of a skipping-analogous *MET* exon 14 mutation; however, the CMTB recommends a cautious approach to adjuvant therapy given the paucity of data regarding *MET* TKIs in the adjuvant space and the potential for significant toxicity to the patient. The results of the completed GEOMETRY and VISION trials demonstrate the efficacy of capmatinib, tepotinib, and other *MET* TKIs within the context of *MET* exon 14 skipping and *MET* amplified tumors; however, their efficacy in patients with other exon 14 mutations is unknown. The MET/ALK inhibitor, crizotinib, may also be considered and has demonstrated efficacy in patients with similar *MET* exon 14 mutations (case reports; see below). Holistic approaches and complete evaluation of the clinical characterization must be taken to make an informed decision on adjuvant therapy in this case.

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