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 metastatic NUT carcinoma, presenting as a squamous cell carcinoma of the trachea.

Background

While the diagnosis of a metastatic NUT carcinoma can be devastating, discovery of the tumor's molecular vulnerabilities can offer effective therapeutic interventions and identify optimal treatments. This requires a 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 CMTB can leverage broad expertise to identify potential therapeutic approaches.

Presented Case

- A 36-year-old female patient presented with shortness of breath and chest pain and underwent tumor and stent placement.
- Pathology showed poorly differentiated carcinoma with squamous and undifferentiated components.
- A brain MRI showed foci of cortical enhancement in both right parietal and left occipital lobes, concerning for metastatic disease. Additional imaging revealed a lytic lesion within the superior endplate of the T2 vertebral body, concerning for a focus of osseus metastasis.
- Prior to initiating treatment, tumor was staged as T4 N3 M1c, Stage IVB
- Treatment and molecular profiling:
  - The patient received radiation therapy and started on carboplatin, paclitaxel, and pembrolizumab.
  - A tumor sample was sent to Caris for comprehensive molecular profiling to aid in clinical decision-making.
  - Whole exome sequencing (WES), whole transcriptome sequencing (WTS), and immunohistochemistry (IHC) did not yield any biomarker results with a level of clinical evidence sufficient to provide an association with a particular therapy.
  - However, WTS revealed a *BRD4-NUTM1* gene fusion, which is diagnostic for NUT carcinoma. NUT protein expression was confirmed via IHC.
  - WES also identified pathogenic mutations in *KMT2D* and *RAD51C*.
- Question: what therapeutic options does the CMTB recommend for this patient?

CMTB Recommendation

- There are no accepted treatment guidelines for NUT carcinomas.
- Combination chemotherapy including anthracyclines, topoisomerase inhibitors, microtubule antagonists, alkylating agents and aromatase inhibitors may be considered.
- The physician could also consider more aggressive chemotherapy with vincristine-doxorubicin-cyclophosphamide/ifosfamide-etoposide, but performance status may be limiting.

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.

- Clinical trials for BET inhibitors (NCT05019716, NCT05488548) would be ideal given the BRD4-NUTM1 fusion.
- While the tumor is PD-L1 negative, there is a case report suggesting PD-L1 inhibitors may work in the absence of PD-L1 positive status due to a hypothesized mechanism of predicted high affinity of the *BRD4-NUTM1* fusion peptide to MHC complexes.[1]
- Based on pathogenic mutation in *RAD51C*, PARP inhibitors or ATM inhibitors in clinical trials could be considered.

NUT Carcinomas

- NUT carcinomas are a rare subtype of carcinoma, sometimes with squamous differentiation, that typically arises in the midline of the body such as the head, neck, or mediastinum (NUT midline carcinomas), but can occur elsewhere.[2,3]
- NUT carcinomas are characterized by rearrangements of the gene *NUTM1* (NUT Midline Carcinoma Family Member 1, also known as *NUT*).[2]
- In a cohort study, 78% (99/127) NUT carcinomas had a *BRD4-NUTM1* gene fusion,[4] which was also observed in this patient.
- NUT carcinomas have poor clinical outcomes, but anatomic site and *NUTM1* fusion partner can be used to group patients into prognostic groups.[4]

The BRD4-NUT Fusion Protein

- *BRD4* encodes BRD4, a member of the BET (Bromodomain and Extra Terminal) family, whose bromodomains bind acetylated lysine residues on histones, promoting initiation and elongation steps of gene transcription.[5]
- *NUTM1* encodes NUTM1 (or NUT), which recruits the p300 histone acetyltransferase (HAT) to activate transcription of target genes.[6]
- The BRD4-NUT fusion protein maintains the transcriptional properties of BRD4 with the addition of NUT-mediated p300 recruitment, likely resulting in increased levels of target gene expression.[6]
- BRD4-NUT drives expression of cancer-associated transcription factors *MYC*, *SOX2*, and *TP63*.[6]

Targeting the BRD4-NUT Fusion Protein via BET Inhibitors

- Numerous BET inhibitors have been developed and evaluated in clinical trials.[7]
- In NUT carcinoma, BET inhibitors have shown some clinical efficacy.[8,9]
- Ongoing clinical trials (NCT05019716 [ZEN003694, cisplatin, and etoposide] and NCT05488548 [EP31670, a dual BET and CBP/p300 inhibitor]) are evaluating BET inhibitors in NUT carcinomas.

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