CARIS® | MOLECULAR TUMOR BOARD

Caris Molecular Tumor Board: Case Study

Metastatic extrahepatic bile duct cancer

Background

While the diagnosis of metastatic cholangiocarcinoma 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 by a multidisciplinary expert group.

Presented Case

- 57-year-old female
- Diagnosed with metastatic extrahepatic bile duct cancer with a proven liver metastasis.
- Family history of breast cancer. Father has a known pathogenic variant of *PALB2* gene.

Treatment and Molecular Profiling

- Initial Caris molecular profiling revealed the same pathogenic *PALB2* mutation (c.3549C>A) found in her father's germline testing and a tumor mutational burden (TMB) of 15 mutations/Megabase (Mb).
- Patient received FOLFIRINOX then olaparib.
- As tumor markers were rising, she resumed FOLFIRINOX and then switched to Abraxane®, Gemzar®, and Cisplatin.
- CT scan showed metastatic disease in the liver, right lobe with enlarging lesions. Lesion was biopsied and submitted to Caris for molecular profiling.
- Caris molecular profiling revealed TMB high (TMB-H) disease. While there was no *ERBB2* amplification and limited HER2 expression, the tumor contained two mutations in *ERBB2* (pathogenic: c.929C>A; likely pathogenic: c.2305G>C).
- The patient has started on Keytruda®.

CMTB Recommendation

In this case of metastatic extrahepatic bile duct cancer with TMB-H and *ERBB2* mutations, the CMTB agreed that *ERBB2*/HER2 is a valuable target given the mutational mechanism leads to hyperactive HER2. The S310Y mutation is at the pertuzumab binding site in the extracellular domain of HER2 and may be associated with benefit from a combination of trastuzumab/pertuzumab. Whereas the protein detection of HER2 by immunohistochemistry (IHC) resulted in a negative score, presence of these mutations warrants a consideration of targeting HER2 using either trastuzumab or ERBB/EGFR family member kinase inhibitors (afatinib, neratinib, poziotinib, tarloxotinib). The CMTB also suggested exploring clinical trials with antibody-drug conjugates targeting genes with high expression levels in the patient's tumor, including *TACSTD2* (TROP2) and *MSLN* (mesothelin).

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® | MOLECULAR TUMOR BOARD

TMB-H

- TMB is a measure of the frequency of mutations in a tumor's DNA per megabase of DNA.
- In the summer of 2020, the FDA approved pembrolizumab (Keytruda®) for the treatment of patients with unresectable or metastatic TMB-H (≥10 mutations/ Mb) solid tumors that progressed on treatment and which have no satisfactory alternative treatments.[1]
- This approval was based on a retrospective analysis of the KEYNOTE-158 study, in which objective responses to pembrolizumab were observed in 29% of TMB-H patients versus 6% of non-TMB-H patients.[2]

PALB2 and Homologous Recombination Deficiency (HRD)

- Pathogenic mutations in homologous recombination (HR) genes occur in 28.9% of biliary tract cancers, with 1.2% of tumors harboring pathogenic mutations in *PALB2*.[3]
- Based on the family history, it is likely that the pathogenic *PALB2* variant detected in the tumor originated in the germline.
- The mutation resulting in mutant PALB2 Y1183* observed in this patient was previously reported as a germline mutation in another patient who developed intrahepatic cholangiocarcinoma.[4]
- This germline mutation is also associated with an increased risk for hereditary breast[5] and pancreatic tumors.[6]
- The *PALB2* mutation also explains the high HRD score found in this patient's tumor, as *PALB2* plays a critical role in homologous recombination as a BRCA2 binding partner (reviewed in[7]).
- From a therapeutic perspective, clinical trials are currently evaluating whether pathogenic *PALB2* mutations are associated with increased benefit from platinum-based chemotherapy and PARP inhibitors.

ERBB2/HER2 Mutations

- *ERBB2* point mutations and amplifications are found in 9.7% of extrahepatic cholangiocarcinomas.[8]
- Caris molecular profiling revealed two mutations in *ERBB2* that result in mutant HER2 (S310Y and D769H).
- S310Y and D769H are activating mutations with demonstrated sensitivity to neratinib and trastuzumab/ pertuzumab in HER2+ breast cancer patients (reviewed in [9]).
- Even though the expression of HER2 by IHC did not meet the criteria for a positive test (tumor score: intensity 1+ and 2% of cells stained; threshold for positivity: intensity ≥3+ and >10% of cells stained), the CMTB felt the presence of two activating mutations was an indicator of the tumor's dependence on HER2, thus represented a possible therapeutic option for this fifth line treatment.

Author: *Magda Grabowska, PhD*

References:

1. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-adults-and-children-tmb-h-solid-tumors
2. Marabelle A, et al. "Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study." *Lancet Oncology*. 2020
3. Heeke AL, et al. "Prevalence of Homologous Recombination–Related Gene Mutations Across Multiple Cancer Types". *JCO Precision Oncology*. 2018
4. Maynard H, et al. "Germline Alterations in Patients with Biliary Tract Cancers: A Spectrum of Significant and Previously Under Appreciated Findings". *Cancer*. 2021
5. Antoniou AC, et al. "Breast-Cancer Risk in Families with Mutations in PALB2". *New England Journal of Medicine*. 2014
6. Jones S, et al. "Exomic Sequencing Identifies PALB2 as a Pancreatic Cancer Susceptibility Gene". *Science*. 2009
7. Wu S. et al. "Molecular Mechanisms of PALB2 Function and Its Role in Breast Cancer Management". *Frontiers in Oncology*. 2020
8. Jacobi O, et al. "ERBB2 Pathway in Biliary Tract Carcinoma: Clinical Implications of a Targetable Pathway". *Oncology Research and Treatment*. 2021
9. Gaibar M, et al. "Somatic Mutations in HER2 and Implications for Current Treatment Paradigms in HER2-Positive Breast Cancer". *Journal of Oncology*. 2020

To order or learn more, visit **www.CarisLifeSciences.com.**
US: 888.979.8669 | CustomerSupport@CarisLS.com
Intl: 00 41 21 533 53 00 | InternationalSupport@CarisLS.com

Where Molecular Science Meets Artificial Intelligence.

CARIS® LIFE SCIENCES