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 recurrent pancreatic adenocarcinoma.

Background

While the diagnosis of a recurrent pancreatic adenocarcinoma 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

- 65-year-old male patient.
- Presented with weight loss and jaundice and diagnosed with pancreatic adenocarcinoma.
- Underwent a Whipple procedure and completed adjuvant FOLFIRINOX.
- Restaging scans showed no evidence of disease (NED) for 18 months.
- At 21 months, local recurrence was detected and treated with Xeloda and radiation.
- Six months after chemotherapy and radiation, distant lymphadenopathy and new lung nodules were observed.

Treatment and Molecular Profiling

- Patient started on gemcitabine and Abraxane while awaiting results.
- A tumor sample, derived from the Whipple procedure, was sent to Caris Life Sciences 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.
- WES revealed a compound *EGFR* mutation in cis in exon 21 (L858R and A871G) and wildtype *KRAS*.
- The E-karyotype revealed 9p arm loss, and copy number calls were approaching confidence intervals to call biallelic deletions of *CDKN2A, CDKN2B, CREBP, MTAP, SMAD4,* and *TSC2*.

CMTB Recommendation

- Based on established sensitivity of non-small cell lung cancer carrying this mutant EGFR (L858R/A871G), the patient's cancer may be responsive to EGFR tyrosine kinase inhibitors such as erlotinib, afatinib, or osimertinib.
  - As combination of erlotinib and gemcitabine is under the FDA license, such combination can be used immediately.

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 CMTB 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.

- Off-label use of osimertinib alone, or in combination with chemotherapy (gemcitabine), or in combination with the anti-EGFR antibody cetuximab may be considered.

- Loss of *MTAP* in the short arm of chromosome 9 may sensitize this cancer to PRMT5 inhibitors (MRTX1719,[1] AG-270,[2] IDE397[3]).

Patient Update

The patient is currently doing well on gemcitabine/Abraxane. The therapeutic plan is to use targeted therapy for the EGFR mutation in the event of progression/recurrence.

KRAS in Pancreatic Adenocarcinoma

- Mutant *KRAS* is a major oncogenic driver in pancreatic adenocarcinoma, with 89.3% of tumors harboring *KRAS* mutations.[4]
- A recently published study from Caris Life Sciences and partners within the Precision Oncology Alliance demonstrated that in the absence of *KRAS* mutations, pancreatic adenocarcinomas are enriched for other genetic alterations, some of which are linked to FDA-approved therapies in other tumors.[4]
- (Unbranded alternative for the above bullet: Recent studies have shown that in the absence of *KRAS* mutations, pancreatic adenocarcinomas are enriched for other genetic alterations, some of which are linked to FDA-approved therapies in other tumors.[4])

Epidermal Growth Factor Receptor (EGFR) Mutations

- *EGFR* driver mutations are rare in pancreatic adenocarcinoma, occurring in 0.2% of cases.[5]
- Case studies demonstrate a favorable response to erlotinib in patients with pancreatic adenocarcinoma with *EGFR* exon 19 deletions.[6,7]
- In non-small cell lung cancer, *in vitro* data suggests this *EGFR* doublet mutation (L858R/A871G) will be sensitive to gefitinib, erlotinib, afatinib, and osimertinib.[8]
- Two case studies of non-small cell lung cancer with EGFR L858R/A871G reported progressive disease and a partial response on erlotinib and icotinib, respectively.[9,10]

Methylthioadenosine Phosphorylase (MTAP) Deletion and Synthetic Lethality

- *In vitro,* cancer cells with *MTAP* homozygous deletion are sensitive to loss of methionine adenosyltransferase II alpha (MAT2A) or the arginine methyltransferase, PRMT5.[11]
- *In vitro,* inhibition of MAT2A also inhibits PRMT5, resulting in DNA damage.[12]
- Patient-derived xenograft (PDX) preclinical models that are *MTAP* deleted demonstrate synergy with the MAT2A inhibitor AG-270 and taxanes.[12]
- Several clinical trials are currently evaluating this synthetic lethality strategy by inhibiting MAT2A and PRMT5 in *MTAP*-deleted tumors.

References:

1. Smith, C. R. *et al.* Fragment-Based Discovery of MRTX1719, a Synthetic Lethal Inhibitor of the PRMT5•MTA Complex for the Treatment of MTAP-Deleted Cancers. *Journal of Medicinal Chemistry* 65, 1749-1766, doi:10.1021/acs.jmedchem.1c01900 (2022).
2. Konteatis, Z. *et al.* Discovery of AG-270, a First-in-Class Oral MAT2A Inhibitor for the Treatment of Tumors with Homozygous MTAP Deletion. *Journal of Medicinal Chemistry* 64, 4430-4449, doi:10.1021/acs.jmedchem.0c01895 (2021).
3. Fischer, M. M. *et al.* Abstract 1278: MAT2A inhibitor, IDE397, displays broad anti-tumor activity across a panel of MTAP-deleted patient-derived xenografts. *Cancer Research* 81, 1278-1278, doi:10.1158/1538-7445.Am2021-1278 (2021).
4. Philip, P. A. *et al.* Molecular Characterization of KRAS Wild-type Tumors in Patients with Pancreatic Adenocarcinoma. *Clinical Cancer Research* 28, 2704-2714, doi:10.1158/1078-0432.CCR-21-3581 (2022).
5. Chakravarty, D. *et al.* Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion. *Journal of Clinical Oncology* 0, JCO.21.02767, doi:10.1200/jco.21.02767 (2022).
6. Park, R., Al-Jumayli, M., Miller, K., Saeed, A. & Saeed, A. Exceptional response to Erlotinib monotherapy in EGFR Exon 19-deleted, KRAS wild-type, Chemo-refractory advanced pancreatic adenocarcinoma. *Cancer Treatment and Research Communications* 27, 100342, doi:https://doi.org/10.1016/j.ctarc.2021.100342 (2021).
7. Cecchini, M., Sklar, J. & Lacy, J. EGFR Exon 19 Deletion in Pancreatic Adenocarcinoma Responds to Erlotinib, Followed by T790M-Mediated Resistance. *J Natl Compr Canc Netw* 15, 1085-1089, doi:10.6004/jnccn.2017.0151 (2017).
8. Kohsaka, S. *et al.* A method of high-throughput functional evaluation of EGFR gene variants of unknown significance in cancer. *Science Translational Medicine* 9, eaan6566, doi:doi:10.1126/scitranslmed.aan6566 (2017).
9. Kobayashi, S. *et al.* Compound EGFR mutations and response to EGFR tyrosine kinase inhibitors. *J Thorac Oncol* 8, 45-51, doi:10.1097/JTO.0b013e3182781e35 (2013).
10. Jin, L. L. *et al.* Icotinib, an effective treatment option for patients with lung adenocarcinoma harboring compound EGFR L858R and A871G mutation. *Invest New Drugs* 39, 1419-1421, doi:10.1007/s10637-021-01108-3 (2021).
11. Marjon, K. *et al.* MTAP Deletions in Cancer Create Vulnerability to Targeting of the MAT2A/PRMT5/RIOK1 Axis. *Cell Reports* 15, 574-587, doi:10.1016/j.celrep.2016.03.043 (2016).
12. Kalev, P. *et al.* MAT2A Inhibition Blocks the Growth of MTAP-Deleted Cancer Cells by Reducing PRMT5-Dependent mRNA Splicing and Inducing DNA Damage. *Cancer Cell* 39, 209-224.e211, doi:10.1016/j.ccell.2020.12.010 (2021).

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