CARIS | MOLECULAR TUMOR BOARD

Caris Molecular Tumor Board: Case Study

TNBC tumors tested by DNA and RNA sequencing

Case Background

- 61-year-old female
- Originally diagnosed with localized triple-negative breast cancer (TNBC) in 2001
- Over the 20 years since the initial diagnosis, developed suspected de novo breast cancers and numerous metastases
- Went on various clinical trials and recently enrolled in the All4Cure research study
- Received Caris molecular profiling as part of the trial

Changes of molecular findings over time

- At least seven tumor specimens profiled, using tissue from punch biopsies, mastectomies and metastatic mass resections.
- Subsequent biopsies taken from both breasts in 2017 revealed ER-positive/HER2-positive disease and a different genetic makeup from the original TNBC, suggesting the presence of *de novo* cancers.
- Hormone and Her2-targeted therapies administered in addition to chemotherapy.
- Mutations observed in older samples were conserved in later profiles; however, *PIK3CA* and *NF1* mutations were only detected in samples profiled after 2017.
- *PIK3CA* H1047R mutation was only seen in a sample from the right-sided mastectomy and not from the left-mastectomy.
- Most recent profile from neck specimen revealed a triple-negative breast cancer with *EGFR* amplification, *PIK3CA* and *NF1* mutations, and *TROP2* expression.

Molecular findings and considerations: *EGFR amplification*

- Masses taken from the right neck in 2021 were submitted for Caris molecular profiling.
- Compared against tumors from 2019, a large molecular resemblance was seen along with a high level of *EGFR* amplification.
- Electronic-karyotyping map was provided as part of an expanded "Quantum Report" offering by Caris Life Sciences, showing unequivocal amplification at the pericenter region of the short arm of chromosome 17.
- Since EGFR-targeted monoclonal antibodies (e.g. cetuximab) have shown efficacy in similar TNBCs based on case reports, a combination of EGFR-targeted therapy plus chemotherapy was considered.

PIK3CA mutation

- A *PIK3CA* mutation was detected in the patient's tumor in 2017 and subsequently in the right neck mass in 2021.
- PI3K inhibitor, alpelisib, is an FDA approved agent for HR-positive, Her2-negative, PIK3CA-mutant advanced/metastatic breast cancer and is being investigated in TNBC clinical trials.
- Currently, patient is tolerating everolimus-based regimens nicely, and an ongoing phase 3 trial in TNBC studying alpelisib in combination with nab-paclitaxel (Abraxane) is recommended.

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NF1 mutation

- Presence of an inactivating *NF1* mutation suggests activation of the RAS/MAPK pathway, suggesting various combination strategies, including encorafenib/binimetinib combinations which are well-tolerated in the clinic.
- Co-targeting MEK/PIK3CA has demonstrated marked anti-tumor activity in metaplastic PDX models.
- MEKi and anti-PD-1/PD-L1 combination was also brought up based on data suggesting RAS-MAPK activity can suppress expression of MHC.

Pathology and RNA expression

- Recurrent tumor carries the morphological and genetic characteristics of TNBC with sarcomatoid variant and spindle-shaped histology.
- Whole transcriptome sequencing allows for evaluation of expressions and patterns of 22,000 genes.
- Important drug targets like TACSTD2 (TROP2) showed expression at almost 100 percentile among reported TNBCs, suggesting sacituzumab govitecan-hziy, now FDA approved for TNBC patients regardless of biomarker status, as a promising agent for treatment.
- Despite the somewhat elevated expression level of androgen receptor, further evaluation of expression patterns of key biomarkers suggest the tumor is likely mesenchymal, instead of the LAR subtype; therefore, androgen receptor-targeted therapies are deprioritized in the recommendations.

Further comments

The presence of multiple molecular alterations in the patient's tumor present several treatment opportunities but may also suggest escape mechanisms if the alterations are targeted individually; a combinatorial approach may be necessary. Comprehensive molecular characterization along with interpretations from clinicians and biomarker translational researchers provides several options for subsequent treatment. It is also suggested that it may be worthwhile to determine the molecular profiles of the lung, bone or other visceral metastases, as systemic therapy may be appropriate if similar profiles are seen, but if different, local radiation therapy post-excision can be an option.

The Caris Molecular Tumor Board

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 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.

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