Abstract P05-06-14

Genomic Landscape and Clinical Outcomes of Triple-Negative Invasive Lobular Carcinoma

San Antonio Breast Cancer Symposium®- December 5-9, 2023

Hemali Batra-Sharma MD[1], Smruthy Sivakumar PhD[2], Prashanth Ashok Kumar MBBS[3], Ethan S. Sokol PhD[2], Rebecca A. Shatsky MD[1], Jeffrey S. Ross MD[2,3]

[1]University of California San Diego, San Diego, CA, [2]Foundation Medicine, Inc., Cambridge, MA, [3]SUNY Upstate Medical University, Syracuse, NY

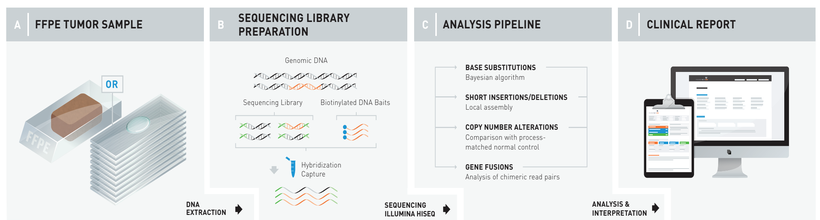
BACKGROUND

- Triple-negative (TN) invasive lobular carcinoma (ILC) of the breast is a rare entity, comprising roughly 2% of primary ILC.
- Clinicopathologic studies have shown that TN ILC is associated with more pleomorphism, higher nuclear grade, older patient age, and worse disease-related outcomes compared to estrogen receptor-positive (ER+) ILC.
- Intrinsic subtyping indicates that TN ILC less frequently expresses basal markers than TN invasive ductal carcinoma (IDC).
- This prompted investigation of the genomic landscape and clinical management of TN ILC to provide insight into potential therapeutic approaches.

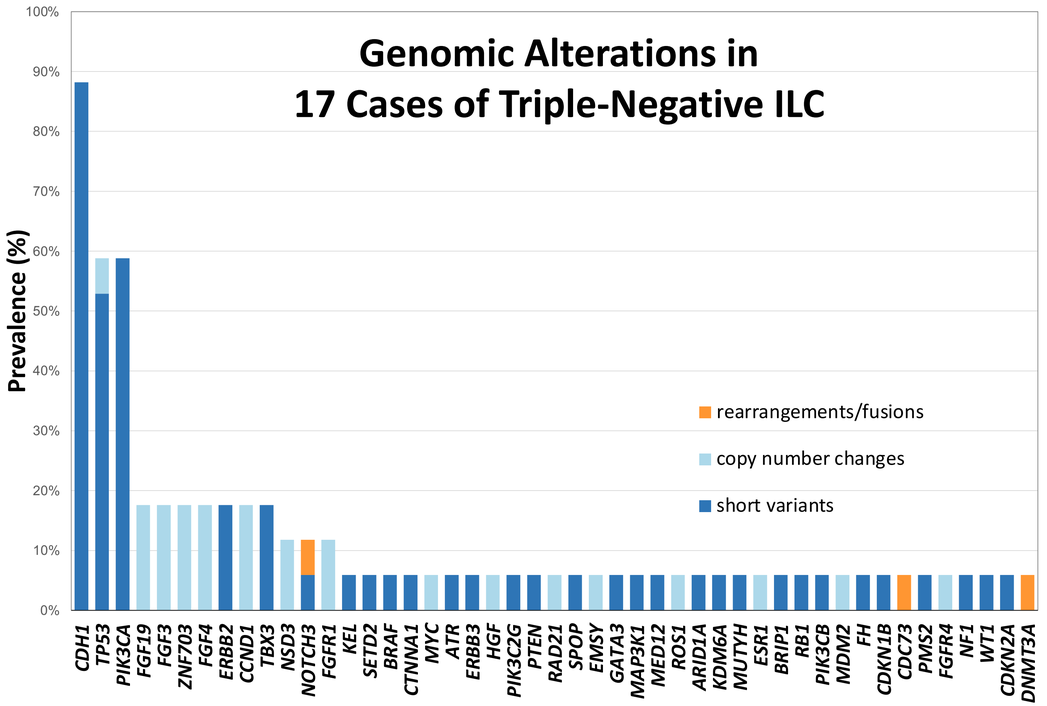
MATERIALS AND METHODS

- Three patients with TN ILC who were treated at a single academic center and underwent comprehensive genomic profiling (CGP) of breast or metastatic tissue were included in this study. Clinicopathologic details were obtained from their electronic health records.
- Seventeen patients with TN ILC were included from the Foundation Medicine, Inc. database, comprising patients who underwent CGP of breast or metastatic tissue as part of routine clinical care.

- ≥50 ng DNA extracted from 40 µm of FFPE sections
- Sequencing performed on exons of ~324 cancer-related genes and introns from additional genes commonly rearranged in cancer
- Hybrid capture-based sequencing using adaptor ligation-based libraries
- Mean coverage depth >600X
- Base substitutions, insertions and deletions (short variants), rearrangements, and copy number changes of known or likely functional significance were assessed
- Tumor mutational burden calculated from 0.80-1.1 Mb sequenced DNA
- PD-L1 expression was measured by IHC (Dako 22C3 or VENTANA SP142)



RESULTS



- In the Foundation Medicine, Inc. database of patients with TN ILC, the most frequent genomic alterations were in *CDH1* (15/17 patients [88.2%]), *TP53* (10/17 patients [58.8%]), and *PIK3CA* (10/17 patients [58.8%]).
- Short variants in *ERBB2* were found in 3/17 patients (17.6%). Fourteen patients (82.3%) were HER2-low (HER2 IHC 1+ or 2+ with non-amplified FISH).
- No cases were MSI high or expressed PD-L1 (8 of 17 cases underwent PD-L1 assessment by VENTANA SP142).
- Median tumor mutational burden (TMB) was 5 muts/Mb.

- Among the three patients with TN ILC treated at a single center, the most common mutations were in *CDH1* and *TP53*, and no cases were MSI high or expressed PD-L1 (by VENTANA SP142 or Dako 22C3).
- All three patients had pleomorphic ILC, histologic grade 2 or 3, and HER2 IHC 0.

This presentation is the intellectual property of the authors. Contact hbatrasharma@ucsd.edu for permission to reprint and/or distribute.

CASE EXAMPLES

A patient with mpT1cN1a(sn) ER+/HER2- ILC of the right breast in 2011 received adjuvant docetaxel + doxorubicin + cyclophosphamide (TAC), breast/axillary radiation, and 10 years of adjuvant endocrine therapy. She was diagnosed with TN pleomorphic ILC of the left supraclavicular nodes in 2022 (PD-L1 neg, with somatic mutations in *CDH1, TP53, CDKN2A*). She did not exhibit a response to docetaxel+ carboplatin+ pembrolizumab. She then received palliative-intent therapy with radiation to the left supraclavicular nodes, followed by ongoing palliative capecitabine.

A patient with locally advanced TN ILC progressed while receiving the KEYNOTE-522 regimen, with ypT3N3a pleomorphic grade 3 disease and 12/14 positive lymph nodes with extranodal extension at the time of mastectomy + axillary lymph node dissection. She immediately developed metastases and had rapid disease progression while receiving palliative-intent therapy with sacituzumab govitecan and subsequently eribulin. She recently transitioned to hospice.

A patient with cT3N1 TN ILC received neoadjuvant therapy (through the I-SPY 2 trial) with oral paclitaxel + encequidar + dostarlimab, followed by dostarlimab + dose-dense doxorubicin and cyclophosphamide (ddAC). She underwent lumpectomy with axillary lymph node dissection, with ypT3N3a pleomorphic grade 3 disease and 13/14 positive lymph nodes with extranodal extension. Due to positive margins, she underwent completion mastectomy, with 10x7 cm of residual tumor. She developed skin metastases on the chest wall within weeks post-operatively. She received comprehensive chest wall and nodal radiation and is currently receiving palliative capecitabine with neratinib given a high variant allele frequency driver somatic *ERBB2* mutation.

CONCLUSIONS

- The most common mutations among TN ILC patients included in this study were in *CDH1*, *TP53*, and *PIK3CA.*
- Currently the management of TN ILC is extrapolated from that of TN IDC, however our patients did not respond to chemoimmunotherapy, suggesting that more research is necessary on the optimal treatment of this rare subtype.
- The presence of HER2-low status or *ERBB2* mutations may provide opportunities for treatment with an anti-HER2 antibody-drug conjugate or tyrosine kinase inhibitor.
- Studies with larger sample sizes of TN ILC are needed for molecular profiling and assessment of outcomes with specific therapeutic approaches.