Comprehensive Genomic Landscape of Invasive Lobular Carcinoma Reveals Distinct Molecular Subtypes

Steffi Oesterreich[1], Samuel Rivero-Hinojosa[2], Vasily N. Aushev[2], Sandro Satta[2], Ekaterina Kalashnikova[2], Richard Green[2], Avinash Ramu[2], Angel Rodriguez[2], Minetta C. Liu[2], Julia Foldi[1], Marija Balic[1], Adrian V. Lee[1]

[1]UPMC Hillman Cancer Center, Magee-Womens Research Institute, University of Pittsburgh and UPMC, Pittsburgh, PA; [2]Natera, Inc., Austin, TX, USA

Presentation #: PD9-01

Background

- Invasive lobular carcinoma (ILC) represents a distinct subtype of breast cancer with unique clinical and molecular features compared to invasive ductal carcinoma (IDC).
- A hallmark of ILC is the loss of E-cadherin due to *CDH1* alterations, yet large-scale genomic profiling of this histology, which is predominantly hormone receptor-positive (HR+)/HER2-negative, remains limited.
- Here, we comprehensively characterized the somatic mutational landscape of HR+/HER2-negative ILC and explored associations with clinical outcomes using real-world data.

Methods

- Whole-exome sequencing (WES) was performed as part of the Signatera™ (Natera, Inc.) workflow.
- Somatic variants, from 1,370 patients with HR+/HER2– ILC in Natera's real-world database, representing over 55,000 breast cancer patients, were annotated using the Ensembl Variant Effect Predictor (VEP); only non-synonymous mutations with variant allele frequency ≥ 5% were included in the prevalence analysis.
- Mutational signatures were inferred from 96-trinucleotide mutation contexts with COSMIC SBS signatures (v3.3).
- Clinical events (surgery type, distant relapse, and treatments) were sourced from claims data, with subtype inferred from therapy patterns. Distant relapse-free survival (DRFS) was measured from curative-intent surgery to first distant relapse.
- Associations between gene-level mutation or mutational signatures and DRFS were assessed by Kaplan-Meier estimation and Cox proportional hazards models, with multivariable adjustment for available clinical covariates.

Table 1. Patient age and tumor characteristics

Characteristic (n, %)	N=1,370
Age in years (median (range))	61 (30-93)
Stage	
I	400 (29.20%)
II	277 (20.22%)
III	306 (22.34%)
N/A	387 (28.25%)
Grade	
1	469 (34.23%)
2	544 (39.71%)
3	171 (12.48%)
N/A	186 (13.58%)

Figure 1. *CDH1* alterations are highly prevalent and co-occur with hallmark ILC driver mutations

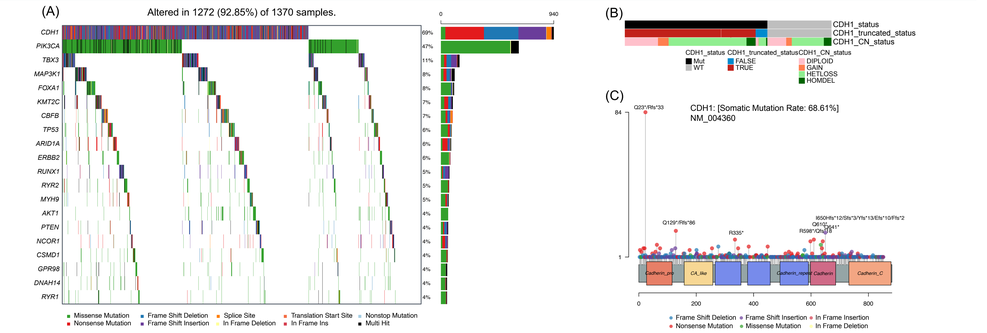


Figure 1. (A) The oncoprint shows the most frequently altered genes in HR+/HER2– invasive lobular carcinoma (n = 1,370). *CDH1* mutations were present in 69% of tumors, consistent with hallmark E-cadherin loss in ILC. Other recurrent alterations included *PIK3CA* (47%), *TBX3* (11%), *FOXA1* (8%), and *MAP3K1* (7%). Each bar represents an individual tumor sample; mutation types are color-coded by functional consequence. **(B)** Bar plots illustrate the frequency of *CDH1* copy-number alterations and *CDH1* mutations, showing that most ILC tumors (91%) harbor alterations in *CDH1* through mutation and/or deletion. **(C)** Lollipop plots map nonsynonymous *CDH1* variants onto the E-cadherin protein structure, highlighting truncating, frameshift, and missense mutations clustered in extracellular and cytoplasmic domains.

Figure 2. Mutational profiles distinguish lobular histology and tumor grade in ILC

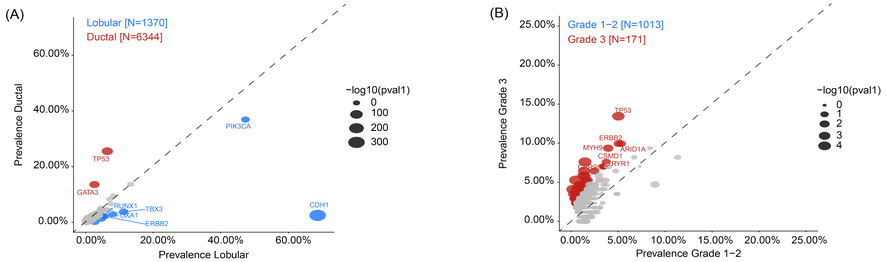


Figure 2. Scatter plots compare mutation prevalence across **(A)** lobular vs ductal carcinomas and **(B)** grade 1–2 vs grade 3 ILCs. Points above the diagonal indicate higher prevalence in the group on the y-axis. *CDH1*, *PIK3CA*, *ERBB2*, and *TBX3* were markedly enriched in ILC compared to IDC. When comparing tumor grades in ILC, mutations in *TP53* and *ERBB2* were more frequent in ILC high-grade tumors.

Figure 3. *TP53* and *ERBB2* mutations are associated with shorter DRFS

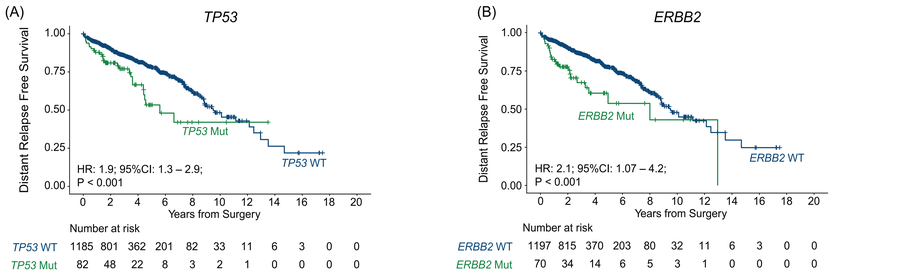


Figure 3. (A) Patients with *TP53* mutations experienced significantly shorter DRFS compared with wild-type (HR = 1.9; 95% CI 1.3–2.9; P < 0.001). **(B)** *ERBB2*-mutated tumors also showed reduced DRFS (HR = 2.1; 95% CI 1.4–2.3; P < 0.001).

Figure 4. Mutational signature defined subgroups exhibit distinct relapse outcomes in ILC

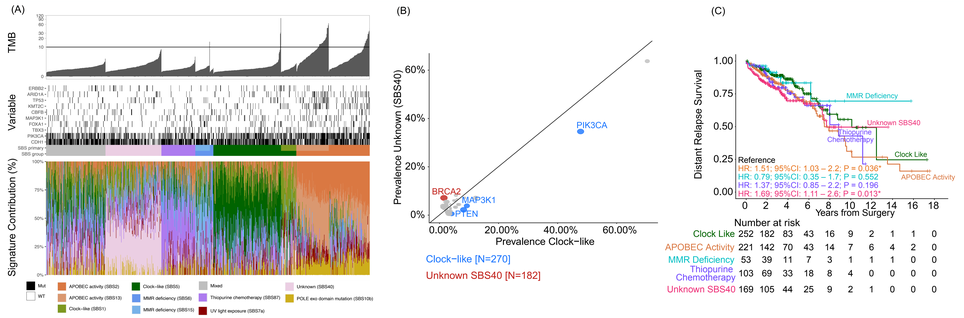


Figure 4. (A) Mutational signature analysis of 1,370 HR+/HER2– ILC tumors identified distinct SBS-defined subgroups dominated by clock-like (SBS1/5), APOBEC (SBS2/13), mismatch repair deficiency (SBS6/15), thiopurine chemotherapy–related (SBS87), and unknown (SBS40) processes. Bar plots show tumor mutational burden (TMB) and co-occurrence of common driver mutations (*PIK3CA*, *CDH1*, *MAP3K1*, *TP53*, *ERBB2*). Each bar represents one tumor, with color-coded signature contributions below. Tumors dominated by APOBEC signature presented the highest TMB, p < 0.001. **(B)** Scatter plot comparing mutation prevalence across tumors with the SBS40 signature and the aging (clock-like) signature. Tumors associated with the SBS40 signature are enriched in *BRCA2* mutations (Fisher's exact test; FDR-corrected). **(C)** Kaplan–Meier curves illustrate distant relapse-free survival by mutational signature group. Tumors dominated by Unknown SBS40 and APOBEC signatures showed significantly poorer outcomes (HR = 1.69 and 1.51, respectively; P < 0.05), whereas MMR-deficiency and thiopurine chemotherapy–associated signatures were not associated with DRFS differences.

Conclusions

- This study provides one of the largest genomic profiling studies of HR+/HER2– ILC, highlighting the central role of *CDH1* loss and its likely function as an early initiating event.
- High-grade ILC were associated with higher rates of *TP53* and *ERBB2* mutations than lower grades; mutations in *TP53* and *ERBB2* were associated with shorter DRFS and may serve as clinically relevant prognostic markers.
- Decomposition of COSMIC SBS signatures stratifies ILC into five dominant signature groups; tumors dominated by SBS40 and APOBEC (SBS2/13) signatures exhibit poorer DRFS, and tumors with SBS40 signature show enrichment for *BRCA2* mutations.
- These insights advance our understanding of ILC biology and may guide future therapeutic stratification and biomarker development in this histologic subtype.

San Antonio Breast Cancer Symposium 2025 | December 9–12, 2025 | San Antonio, Texas | Presentation Number: PD9-01

Disclosures: S.R-H., V.N.A., S.S., A.K., R.G., A.Ramu, A.Rodriguez, M.C.L. are employees of Natera, Inc. and with stock or stock options in the company.