The Genomic, Transcriptomic, and Immune Hallmarks of Metastatic Lobular Breast Cancer

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BACKGROUND

- **Invasive lobular carcinoma (ILC)** is the second most common breast cancer subtype, accounting for up to **15% of all BC cases**, **and its incidence has been steadily increasing** across racial and ethnic groups in recent years.[1]
- Although several biologic differences between ILC and invasive carcinoma of no special type (IBC-NST) have been described, most data are derived from primary tumors. In contrast, the biology of metastatic ILC remains poorly defined.[2,3]
- This study aimed to investigate the unique **genomic, transcriptomic, and immune landscapes of metastatic ILC** using a multi-omic approach.

METHODS

Study Design and Data Source

- Retrospective analysis of de-identified breast cancer samples tested at Caris Life Sciences (Phoenix, AZ), a CLIA/CAP-certified laboratory.

Patient Selection

- Included samples from patients with a **diagnosis of metastatic breast cancer** and either a biopsy of a metastatic lesion, or a biopsy of a primary breast lesion after having received systemic therapy for metastatic disease. Patients were **selected based on tumor histology**, including only those **with IBC-NST or pure ILC** tumors.

Molecular Profiling

- **DNA sequencing (592- or 720-gene panel)** performed on FFPE tumor tissue using Illumina NextSeq or NovaSeq platforms.[4] Variants interpreted per **ACMG** guidelines; pathogenic and likely pathogenic alterations included in analyses.[5]
- **Whole Transcriptome Sequencing (WTS)** performed using RNA extracted from FFPE tissue and sequenced on Illumina NovaSeq.[6] Expression quantification via **Salmon** pipeline.[7]
- Immune cell deconvolution performed using **quanTIseq**.[8]
- **Gene Set Enrichment Analysis (GSEA)** was performed using the **MSigDB Hallmark gene sets**, including Estrogen Response Early/Late signatures originally derived from ER-positive IDC cell-line models.[9,10]
- **Tumor Mutation Burden (TMB)** was calculated as the number of nonsynonymous mutations per megabase after excluding germline variants.[11] High TMB was defined as >10 mutations/Mb.[12]

Statistical Analysis

- Comparisons between ILC and IBC-NST performed using Chi-square tests (categorical variables) and Mann–Whitney U tests (continuous variables**). False discovery rate (FDR)** adjustment applied; FDR<0.25 considered significant.

RESULTS

Baseline Characteristics and PAM50 Subtypes

- A total of **2,645 patients** were included (**605 ILC; 2,040 IBC-NST**). Patients with ILC were older and more often White and HR+ than those with IBC-NST.
- **PAM50 subtypes** differed between groups: **ILC** had a higher proportion of **Luminal A** tumors, whereas **IBC-NST** had more **Basal-like** and **HER2-enriched** disease. Luminal B was similar across subtypes (**Table 1; Figure 1**).

Figure 1. Intrinsic subtype distribution in ILC and IBC-NST

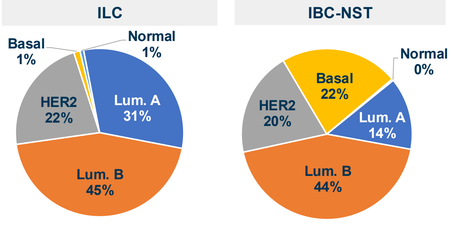


Table 1. Baseline Characteristics and PAM50 Subtypes

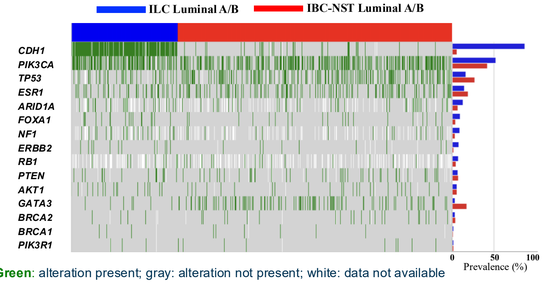
	ILC (N = 605)	IBC-NST (N = 2,040)
Median age (range)	67.0 (26–90+)	63.0 (23–90+)
Race		
White	416 (68.8)	1,168 (57.3)
Black or African American	51 (8.4)	306 (15.0)
Asian or Pacific Islander	15 (2.5)	58 (2.8)
Other	29 (4.8)	67 (3.3)
Unknown	94 (15.5)	441 (21.6)
Ethnicity		
Not Hispanic or Latino	488 (80.7)	1,451 (71.1)
Hispanic or Latino	45 (7.4)	177 (8.7)
Unknown	72 (11.9)	412 (20.2)
Clinical Subtype*		
HR+/HER2−	273 (83.5)	645 (55.8)
TNBC	39 (11.9)	345 (29.8)
HER2+	15 (4.6)	166 (14.4)
PAM50		
Luminal A	188 (31.1)	279 (13.7)
Luminal B	271 (44.8)	893 (43.8)
HER2-enriched	135 (22.3)	405 (19.9)
Basal	7 (1.2)	457 (22.4)
Normal-like	4 (0.7)	6 (0.3)

Clinical subtype based on immunohistochemistry and in situ hybridization. ILC = invasive lobular carcinoma; IBC-NST = invasive breast carcinoma of no special type; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer.

Genomic Alterations in Luminal A/B ILC vs IBC-NST

- **Mutations**: Luminal A/B ILC showed markedly higher frequencies of **CDH1, PIK3CA, ARID1A, FOXA1, NF1**, and **ERBB2** mutations, while **TP53 and GATA3** mutations were more common in IBC-NST (**Table 2; Fig. 2**).
- **PIK3CA enrichment in ILC was driven by the Luminal B** subgroup, whereas Luminal A showed no significant difference.

Figure 2. Mutations in Luminal A/B ILC vs IBC-NST



Green: alteration present; gray: alteration not present; white: data not available

Table 2. Mutation frequency (Luminal A/B)

Gene	ILC (%)	IBC-NST (%)	q-value
CDH1	**87.5**	**5.6**	**<0.0001**
PIK3CA	**52.2**	**42.2**	**0.0039**
TP53	16.3	26.9	0.0003
ARID1A	**12.8**	**6.7**	**0.0033**
FOXA1	**9.6**	**3.6**	**<0.0001**
NF1	**9.0**	**3.3**	**0.0004**
ERBB2	**7.5**	**1.6**	**<0.0001**
GATA3	3.5	17.1	<0.0001
ESR1	14.5	19.3	0.12
RB1	7.0	4.5	0.26
PTEN	6.4	7.3	0.76
AKT1	5.4	5.4	0.99

Bold: significantly higher in ILC

Luminal A vs Luminal B
(Mutation Summary)

- **PIK3CA** difference was driven by **Luminal B** (ILC 50.9% vs NST 39.7%, q=0.018)
- **Luminal A** showed **no significant PIK3CA difference** (ILC 54.2% vs NST 50.8%)
- Other ILC-enriched mutations (CDH1, ARID1A, FOXA1, NF1, ERBB2) were consistent across Luminal A and B

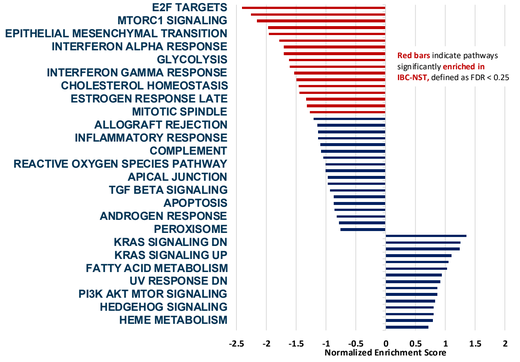
Key amplifications were less frequent in ILC

- **FGFR1**: 6.7% in ILC vs 14.2% in IBC-NST (p=0.0006, q=0.005)
- **MYC**: 0.6% in ILC vs 3.3% in IBC-NST (p=0.01, q=0.05)

Gene Set Enrichment Analysis

- GSEA showed that multiple proliferative, metabolic, and immune-related pathways were significantly enriched in IBC-NST Luminal A/B, whereas none were significantly enriched in ILC (**Fig. 3**).

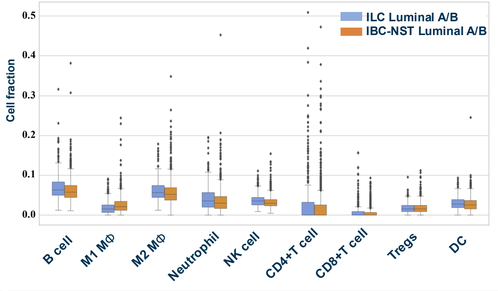
Figure 3. GSEA Pathway Differences in ILC vs IBC-NST (Luminal A/B)



Immune Infiltration

- In the combined Luminal A/B cohort, **ILC** showed modest but significantly higher fractions of several innate immune populations—including **B cells, M2 macrophages, neutrophils, NK cells, and dendritic cells**—compared with IBC-NST (**Fig 5**).
- In subset analyses, Luminal A ILC demonstrated a higher NK-cell fraction versus Luminal A IBC-NST (q < 0.001).

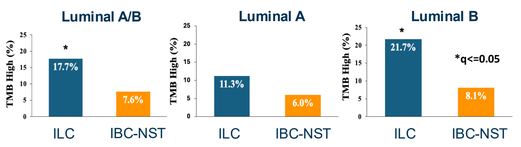
Figure 5. Immune Infiltration Profiles in ILC vs IBC-NST (Luminal A/B)



Tumor Mutational Burden

- **TMB-high** tumors were significantly **more frequent in ILC** than in IBC-NST in the combined Luminal A/B cohort, with this difference driven predominantly by **Luminal B** (**Fig. 4**).

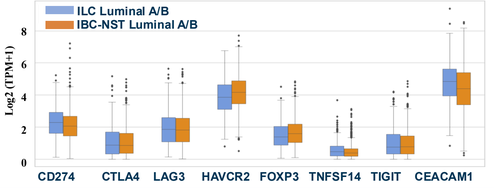
Figure 4. TMB-High Prevalence in ILC vs IBC-NST by Luminal Subtype



Checkpoint Gene Expression

- Checkpoint gene expression was similar between ILC and IBC-NST, with significant differences for selected markers (e.g., **higher CD274/PD-L1 and CEACAM1 in ILC**).

Figure 6. Checkpoint Gene Expression in ILC vs IBC-NST



CONCLUSIONS

- Among Luminal A/B tumors, ILC showed a distinct genomic profile, with higher CDH1, PIK3CA, FOXA1 ARID1A mutations and fewer amplifications than IBC-NST.
- TMB-high tumors were more frequent in ILC, especially within the Luminal B subgroup.
- ILC had higher innate immune cell fractions and higher PD-L1 (CD274) expression.
- GSEA identified several pathways enriched in IBC-NST.

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