Prevalence and prognosis of ER-loss in advanced invasive lobular carcinoma

Whitney L Hensing[1,2], Joanne Xiu[3], W. Michael Korn[3], Stephanie L Graff[4], Irene Kang[5], Evanthia Roussos Torres[5], Arielle L Heeke[6], Andrew A. Davis[1], Nusayba A. Bagegni[1], Katherine Clifton[1], Ron Bose[1], Cynthia Ma[1], Foluso O. Ademuyiwa[1]

[1]Washington University School of Medicine, St. Louis, MO. [2]St. Luke's Cancer Institute, Kansas City, MO. [3]Caris Life Sciences, Phoenix, AZ. [4]Lifespan Cancer Institute, Brown University, Providence, RI. [5]Keck School of Medicine, University of Southern California, Los Angeles, CA. [6]Atrium Health Levine Cancer Institute, Charlotte, NC.

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Background

- Estrogen receptor (ER) loss occurs in about 20% of recurrent breast cancers (BC) and is associated with unresponsiveness to endocrine therapy (ET) and poor prognosis[1].
- ILC is the second most common histologic type, accounting for 10-15% of breast cancers and is typically ER-positive[2].
- ILC differs from invasive ductal carcinoma (IDC) in terms of clinicopathologic characteristics, molecular alterations and response to treatment, with studies showing less response to chemotherapy[3-4].
- Prior studies evaluating ER-loss included predominately patients with IDC, and therefore the impact of ER-loss in ILC is unknown[1,5].
- In this retrospective analysis, using real-world data, we aimed to determine the prevalence and clinical significance of ER-loss in ILC.

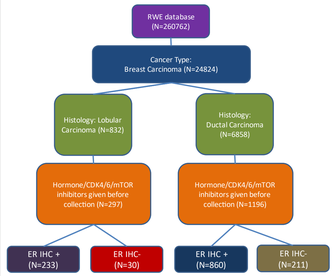
Methods

- Advanced breast cancers were molecularly profiled at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing of DNA (592-gene panel or whole-exome sequencing), RNA (whole transcriptome sequencing, WTS) and immunohistochemistry (IHC) of select markers.
- A large real-world evidence (RWE) database combining Caris' molecular data with clinical information obtained from insurance claims data (CODEai) was interrogated and overall survival (OS) was calculated from time of tissue collection to last patient contact. We assumed that any patient without a claim for more than 100 days had died, which holds true for more than 95% of patients with a recorded death in the NDI[6].
- **Definition of ER-loss:** A tumor was considered to have ER-loss if therapies approved only for ER-positive breast cancer (ET, CDK4/6, mTOR inhibitors) were prescribed prior to obtaining a negative ER IHC result (IHC 0).
- Median overall survival (time from tissue collection to last day of contact) was used to determine "responders" vs. "non-responders".
- OS was compared using Kaplan-Meier estimates for defined patient cohorts with significance defined as p value <0.05. For molecular analyses, Fisher-Exact or Chi-Square tests were used to determine p values. Correction for multiple comparisons was performed using Benjamin-Hochberg to calculate q values.

Results

Patient Characteristics

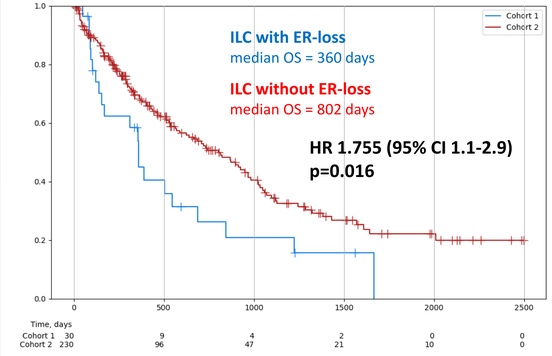
- RWE database included 24,824 patients with advanced BC, with the majority classified as breast carcinoma NOS
- The final analytical cohort included 1,338 patients who had previously been treated with therapies approved only for ER-positive BC, were classified as ductal or lobular histology and had data available for ER IHC
- ER-loss was identified in 11.4% of ILC (N=30/263) compared to 19.6% of IDC (N=210/1075) (p=0.0017)



Specimen Sites	ER+ lobular	ER- lobular	ER+ ductal	ER- ductal
Abdomen			1	
Axilla	2	1	46	19
Bladder	2			
Bone	24	3	39	4
Bone Marrow	1	1	2	
Brain	1		8	
Breast	56	5	423	107
Central Nervous System			1	
Chest or Chest Wall	9		51	21
Colon	0	2	0	0
Colon, Left-sided	3			
Colon, NOS	1			
Colon, Right-sided	4			
Connective Tissue	1	1	26	7
Eye			1	
Female Genital Tract	19	1	2	
Gallbladder and Bile Duct	3			
Head and Neck	2		3	1
Liver	31	1	102	11
Lung	3		18	7
Lymph Node	19	5	72	23
Muscle			1	
Nipple			1	
Omentum	10	1	4	
Pelvis or Pelvic wall			1	
Pericardium	2		1	
Peritoneal Cavity	1			
Peritoneum or Retroperitoneum	5	3	1	1
Skin	23	4	58	18
Small Intestine	5	1	3	1
Stomach	9		1	
Unclear Specimen Site	5	4	26	4

Overall Survival for ILC with or without ER loss*

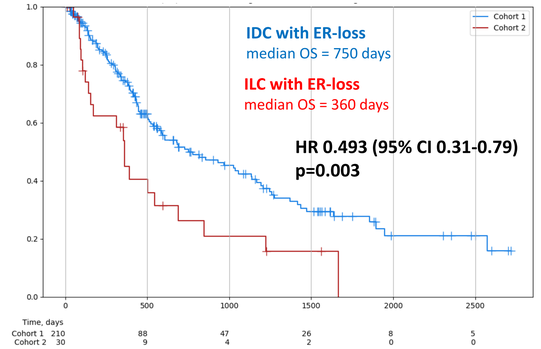
Time of tissue collection to last patient contact



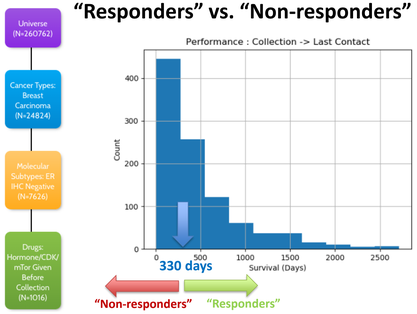
*ER-loss defined by prior therapies as described in methods

Overall Survival for ER-loss* by histologic type (IDC vs ILC)

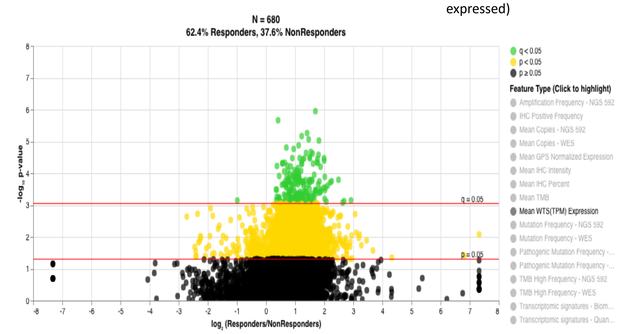
Time of tissue collection to last patient contact



"Responders" vs. "Non-responders" in ER-Loss*

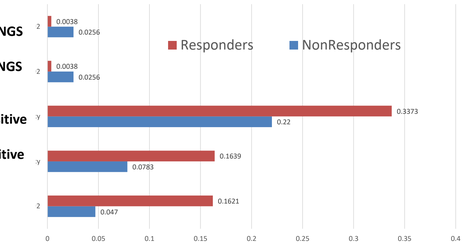


- All patients with ER-loss* regardless of histology (N=1016)
- In the breast cancer cohort investigated, median OS (collection time to last day of contact) was 330 days.
- "Non-responders" defined by OS less than 330 days (N=256)
- Volcano plot shows differentially expressed genes between "responders" vs "non-responders"
- Most genes were enriched in responders (total = 197 genes significantly differentially expressed)



Genomic differences in "Responders" and "Non-Responders"

Shown are the proportion of molecular alteration in the two cohorts



Feature	Unit	q-value	p-value	-Log10 p-value	Statistic used	Fold Change	Log2 Fold Change	N (%) Non-Responders	N (%) Responders
ERBB2 (Her2/Neu)	Amplification Frequency – NGS 592	**0.0421**	**6.00E-04**	3.2298	chi-square	3.4495	1.7864	149 (4.7%)	253 (16.2%)
ERBB2 (Her2/Neu)	IHC Positive Frequency	0.0776	**0.0032**	2.4886	chi-square	2.092	1.0649	217 (7.8%)	360 (16.2%)
PD-L1 (SP142) IC	IHC Positive Frequency	0.22	**0.0412**	1.3846	chi-square	1.5331	0.6164	100 (22%)	169 (33.7%)
MYB	Amplification Frequency - NGS 592	0.2328	**0.0466**	1.3319	chi-square	0.1483	-2.7535	156 (2.6%)	263 (3.8%)
TFEB	Amplification Frequency - NGS 592	0.2328	**0.0466**	1.3319	chi-square	0.1483	-2.7535	156 (2.6%)	263 (3.8%)

Conclusions

- In this large real-word dataset, ER-loss likely occurred in 11.4% of ILC and was associated with worse OS compared to IDC with ER-loss and ILC without ER-loss
- Genomic analysis identified significant differences between treatment "responders" and "non-responders" in patients with ER-loss
- Our analysis had several limitations: Definition of ER-loss was based on prior treatment, could not distinguish between *de novo* and recurrent metastatic disease and time of tissue collection was not standardized
- This study does suggest that ER-loss occurs in a subset of patients with ILC and has poor prognostic implications
- Future work is needed to confirm these findings and to identify new therapeutic targets for patients ILC and ER-loss

References

1. Kuukasjarvi, et al., Loss of estrogen receptor in recurrence breast cancer is associated with poor response to endocrine therapy. J Clin Oncol. 1996 Sep;14(9):2584-9.
2. McCart Reed AE, Kalinowski L, Simpson PT, Lakhani SR. Invasive lobular carcinoma of the breast: the increasing importance of this special subtype. Breast Cancer Res 2021; 23: 6
3. Cristofanilli, et al. Invasive lobular carcinoma classic type: response to primary chemotherapy and survival outcomes. J Clin Oncol 2005; 23:41-48.
4. Cocquyt, et al. Different responses to preoperative chemotherapy for invasive lobular and invasive ductal breast carcinoma. Eur J Surg Oncol 2003; 29:361-367
5. Shiino, et al., Prognostic significance of receptor-expression discordance between primary and recurrent breast cancers: a meta-analysis. Breast Cancer Res Treat. 2022 Jan;191(1):1-14.
6. Abraham, et al., Clinical Validation of a Machine-learning–derived Signature Predictive of Outcomes from First-line Oxaliplatin-based Chemotherapy in Advanced Colorectal Cancer. Clin Cancer Res 2021;27:1174–83

San Antonio Breast Cancer Symposium. December 6-10, 2022.

Correspondence: Whitney Hensing (whensing@saint-lukes.org) and Foluso Ademuyiwa (bisiademuyiwa@wustl.edu)