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Assessing ER+HER2+ Lobular Breast Carcinoma: Molecular Response to Perioperative Endocrine Therapy and Clinical Outcomes in the POETIC Trial

Milana A Bergamino Sirvén[1], Xixuan Zhu[1], Elena López-Knowles[1], Holly Tovey[1], Lucy S Kilburn[1], Chris Holcombe[2], Anthony Skene[3], Alistair Ring[4], Ian Smith[4], John Robertson[5], Judith M Bliss[1], Eugene F Schuster[1], Mitch Dowsett[1], Maggie CU Cheang[1], on behalf of POETIC investigators.
[1]The Institute of Cancer Research, London; [2] Liverpool University Hospitals, Liverpool; [3]Birmingham's women and children, Birmingham; [4] Royal Marsden Hospital, London, [5] The University of Nottingham, Nottingham, UK

AIMS

- To report the biological responsiveness of Estrogen Receptor Positive (ER+) HER2+ Invasive Lobular Carcinoma (ILC) to perioperative aromatase inhibitors (POAI).
- To assess clinical outcome amongst ILC within the POETIC trial, one of the most comprehensive studies of the ER+HER2+ breast cancer (BC).

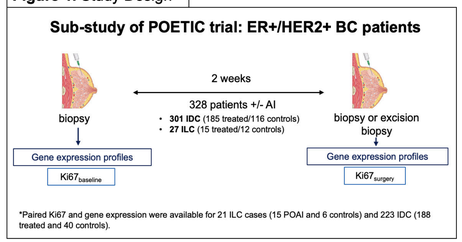
BACKGROUND

- ILC represents approximately 15% of all invasive BC.
- ILC seldom exhibits overexpression of human epidermal growth factor 2 (HER2+), prompting the majority of research to focus on ER+ HER2-negative phenotypes.
- There is limited empirical data of the response of ER+HER2+ ILC to endocrine therapy and the therapeutic efficacy of combined chemotherapy and anti-HER2 treatments (C+T).

MATERIALS & METHODS

- POETIC is a phase III trial of post-menopausal women with ER+ early BC randomized 2:1 to 2-weeks of peri-surgical AI vs control, followed by standard-of-care.

Figure 1. Study Design



Ki67 endpoints:

Ki67 levels were assessed at baseline (B) and on-treatment (2wk) (low ≤10%; high >10%) categorizing tumors based on the biological response to AI:

- Low_B -Low_{2wK} (LL)
- $High_B$ –Low_{2wk} (HL)
- $High_B$–$High_{2wk}$ (HH)

- Baseline RNA extracted from formalin-fixed paraffin-embedded samples was gene expression profiled with BC360™ panel, which includes the intrinsic subtypes and 46 key biological pathway signatures in BC.
- T-tests were used to compare gene expression between ILC and IDC. P-values were adjusted using false discovery rate (FDR; 5%).
- Time to recurrence (TTR) was estimated using Kaplan-Meier method.

RESULTS

Table 1. Comparison of baseline characteristics of ILC and IDC (IQR = interquartile range).

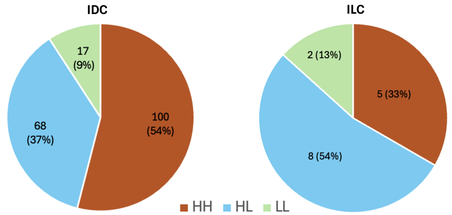
	Median age (IQR)	Grade 1	Grade 2	Grade 3	Median tumor size cm (IQR)	Nodal status N0	N1-3	N4+
IDC (n=301)	66.1 (11.8)	14 (5%)	132 (44%)	**155 (51%)**	2.25 (1.2)	157 (52%)	89 (30%)	55 (18%)
ILC (n=27)	**69.4 (12.5)**	0 (0%)	21 (63%)	6 (37%)	2.5 (1.85)	13 (48%)	9 (33%)	5 (19%)

	Adjuvant C+T YES	NO	Baseline IS LumA	LumB	HER2-E	Basal-like
IDC (n=301)	183 (61%)	118 (39%)	51 (17%)	112 (37%)	133 (44%)	5 (2%)
ILC (n=27)	14 (52%)	13 (48%)	6 (22%)	10 (37%)	11 (41%)	0 (0%)

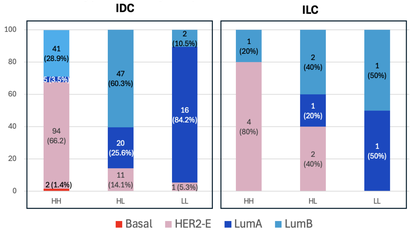
- Patients with ILC were older on average and had lower frequency of G3 tumors. Other baseline characteristics were similar between ILC and IDC.
- Fewer patients with ILC received adjuvant chemotherapy with trastuzumab (C+T).
- The distribution of baseline IS was also comparable between ILC and IDC.

Figure 2. Response to AI in POAI according to changes in Ki67 and baseline IS by histology.

a. Response to AI according to Ki67 levels (HH, HL and LL)

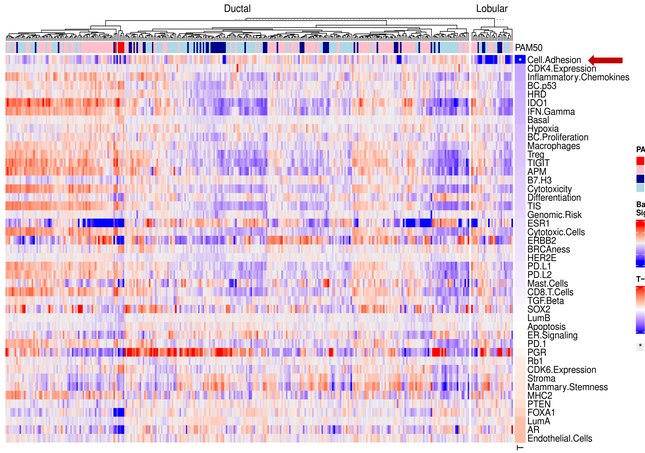


b. Baseline subtype by early response to AI in ILC



- The proportion of HL tumors was higher in ILC compared to IDC, probably due to higher early sensitivity to AI.
- There is a poor anti-proliferative effect conferred by HER2-E subtype in both ILC and IDC.

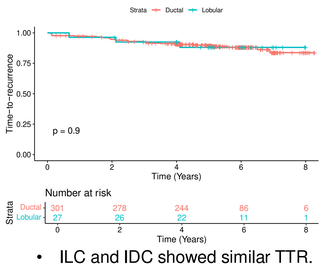
Figure 3. Supervised hierarchical clustering of baseline gene signature expression in IDC and ILC.



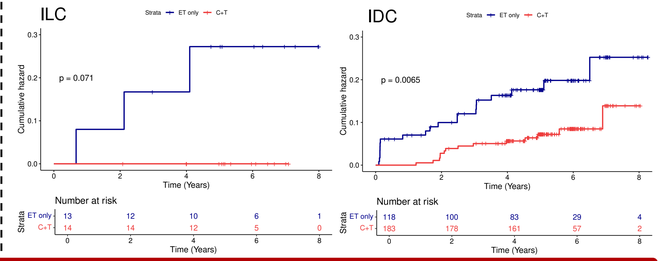
- At baseline, cell adhesion signature was differentially expressed between ILC and IDC, with ILC having significantly lower expressions of the signature (T-test FDR < 0.001).

Figure 4. Survival analysis for Time To Recurrence (TTR).

a. TTR for IDC vs ILC



b. Cumulative Hazard (TTR) according to histology and adjuvant treatment (ET = endocrine therapy, C+T = chemotherapy and trastuzumab)



- ILC and IDC showed similar TTR.

CONCLUSIONS

- This study provides a comprehensive picture of molecular features of ER+HER2+ ILC.
- Our findings show no differences between ILC and IDC in ER+HER2+ BC based on molecular profiles – except lower cell adhesion signature expression in ILC at baseline. Instead, the molecular characteristics and response to POAI are driven by IS.
- While there is a higher proportion of early sensitive tumors to POAI in ILC, it does not translate into different survival.
- However, the small sample size precludes definitive conclusions.

ACKNOWLEDGEMENTS

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