# Molecular profiling after short-term preoperative endocrine therapy to identify ER+/HER2+ early breast tumours with favourable prognosis

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# Abstract 560

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## AIMS

We hypothesize that molecular changes (MolC) in Estrogen Receptor positive (ER+)/ Human Epidermal Growth Factor Receptor Positive (HER2+) early Breast Cancer (BC) vary according to response to Aromatase Inhibitors (AI) and predict recurrence outcome.

Our aims are 1. to characterise MolC under short endocrine therapy (ET) and 2. to evaluate their association with response to treatment and survival.

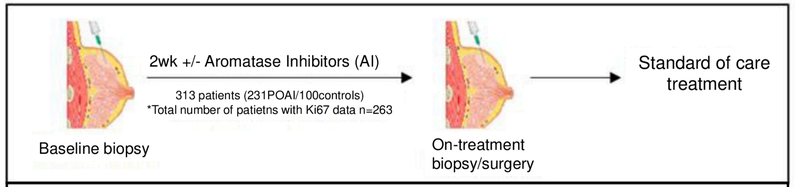
## BACKGROUND

- Twenty per cent of all BC overexpresses HER2+ and 50% of them are also ER+.
- ER+/HER2+ BC is heterogeneous with different behavior and outcome compared to ER-/HER2+ BC.
- The impeded anti-proliferative response of ER+/HER2+ to ET has been considered negated by treatment with anti-HER2 therapies.
- Residual disease after anti-HER2 therapy remains at a higher risk of recurrence.
- Studying the MolC of ER+HER2+ BC in response to ET will provide clinical insights to treatment options.

## MATERIALS & METHODS

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

**Figure 1.** Study design




Trial Endpoints

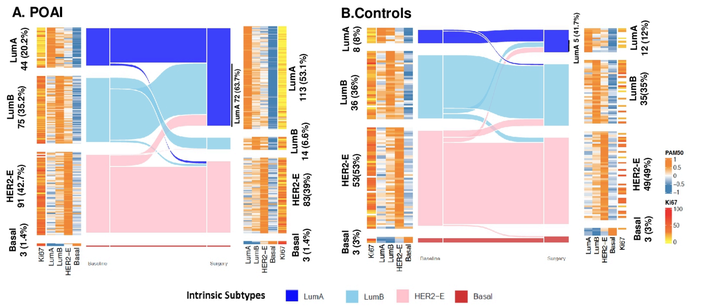
1. Early biological response to AI defined by Ki67
   - Residual Ki67 at 2 weeks ($Ki67_{2wk}$).
   - Ki67 response categories (baseline (B) - on-treatment (2wk): **Low–Low** ($Ki67_B$ and $Ki67_{2wk}$ <10%); **High–Low** ($Ki67_B$ ≥10%, $Ki67_{2wk}$ <10%); **High–High** ($Ki67_B$ and $Ki67_{2wk}$ ≥10%); **Low–High** ($Ki67_B$ <10%, $Ki67_{2wk}$ ≥10%).
2. Patient's survival outcome – Time to recurrence (TTR)

Baseline and on-treatment RNA from formalin-fixed paraffin-embedded samples were gene expression profiled with BC360™ panel, including the intrinsic subtypes (IS) and 46 key biological pathway signatures in BC.

The association of molecular features with Ki67 and TTR were assessed.

## RESULTS

**Figure 2.** Shifts of intrinsic subtype (IS) from baseline to on-treatment timepoints in both groups separately: A. POAI and B. Controls.

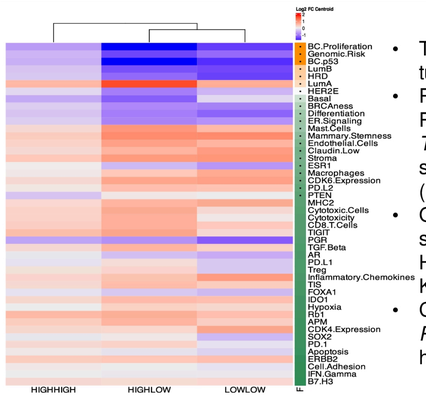



| | On-treatment | | | |
|---|---|---|---|---|
| Baseline | LumA | LumB | HER2-E | Basal |
| LumA | 41 (93.18%) | 0 | 3 (6.82%) | 0 |
| LumB | 59 (78.67%) | 13 (17.33%) | 3 (4%) | 0 |
| HER2-E | 13 (14.29%) | 1 (1.1%) | 77 (84.62%) | 0 |
| Basal | 0 | 0 | 0 | 3 (100%) |

| | On-treatment | | | |
|---|---|---|---|---|
| Baseline | LumA | LumB | HER2-E | Basal |
| LumA | 7 (87.50%) | 1 (12.50%) | 0 | 0 |
| LumB | 3 (8.33%) | 30 (83.33%) | 3 (8.33%) | 0 |
| HER2-E | 2 (3.37%) | 4 (7.54%) | 46 (86.79%) | 1 (1.88%) |
| Basal | 0 | 0 | 0 | 3 (100%) |

- IS shifting was significantly more prevalent in POAI (37%, 79/213) than in controls (14%, 14/100) (p <0.001).
- In POAI most Luminal B (LumB) shifted to Luminal A (LumA; 79%, 59/75).

**Figure 3.** A. BC360 Biological signature expression changes; log2 fold change and changes in PAM50 IS correlation coefficient from baseline to on-treatment samples according to early biological response to AI by $Ki67_{2wk}$.




- There was an overall upregulation of tumor immunity-related signatures.
- Proliferation, Homologous Recombination Deficiency (HRD), *TP53* mutational status and ER-signaling were downregulated (FDR<0.05).
- Gene expression changes were significantly higher in Low-Low and High-Low compared to High-High Ki67 categories.
- Controls showed downregulation of *PDL1* and upregulation of hypoxia (FDR < 0.05).

**Figure 4.** Kaplan Meier curves for Time to Recurrence (TTR) in POAI according to on-treatment IS

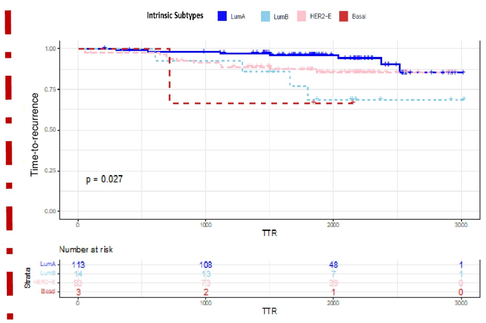



**Table 1**. Multivariable cox regression model for $Ki67_{2wk}$ adjusted by standard clinic-pathological variables

| Variable | Factors | HR (95% CI) | P-value |
|---|---|---|---|
| On-treatment Ki67 | - | 1.03 (1.01 – 1.05) | 0.01 * |
| Age | - | 1.08 (1.02 – 1.14) | 0.0054 ** |
| Tumour size | - | 1.52 (1.21 – 1.91) | 0.0003 *** |
| Nodal status | N0 (ref) (n=111) | - | - |
| | N1-3 (n=62) | 1.52 (0.39 – 3.59) | 0.7563 |
| | N4+ (n=36) | 2.20 (0.84 – 5.77) | 0.1097 |
| Concordance Index = 0.765 (se = 0.057) | | Likelihood Ratio Test = 29.35 (p = 0.00002) | |
| AIC = 205.195 | | | |

- $LumA_{2wk}$ was associated with better outcome compared to $LumB_{2wk}$ as well as $Ki67_{2wk}$ value as continuous variable.

**Table 2.** Multivariable cox regression model for the PAM50 intrinsic subtypes in POAI adjusted by standard clinic-pathological variables (age>70, post-surgery tumour size and nodal status) at A. Baseline and B. On-treatment.

**A. Baseline IS in POAI**

| Variable | Factors | HR (95% CI) | P-value |
|---|---|---|---|
| Baseline PAM50 IS | LumA (ref) (n=43) | - | - |
| | LumB (n=75) | 1.21 (0.30 – 4.80) | 0.7871 |
| | HER2-E (n=89) | 1.72 (0.47 – 6.24) | 0.4091 |
| | Basal (n=3) | 4.84 (0.48 – 49.1) | 0.1823 |
| Age | - | 1.07 (1.01 – 1.12) | 0.0133 * |
| Tumour size | - | 1.50 (1.20 – 1.88) | 0.0004 *** |
| Nodal status | N0 (ref) (n=112) | - | - |
| | N1-3 (n=62) | 1.14 (0.37 – 3.47) | 0.8202 |
| | N4+ (n=36) | 2.41 (0.90 – 6.42) | 0.0791 |
| Concordance Index = 0.742 (se = 0.059) | | Likelihood Ratio Test = 25.61 (p = 0.0006) | |
| AIC = 212.944 | | | |

**B. On-treatment IS in POAI**

| Variable | Factors | HR (95% CI) | P-value |
|---|---|---|---|
| On-treatment PAM50 IS | LumA (ref) (n=110) | - | - |
| | LumB (n=14) | 5.41 (1.50 – 19.5) | 0.0099 ** |
| | HER2-E (n=83) | 2.41 (0.87 – 6.73) | 0.0919 |
| | Basal (n=3) | 6.55 (0.76 – 56.8) | 0.0882 |
| Age | - | 1.07 (1.02 – 1.13) | 0.01125 * |
| Tumour size | - | 1.53 (1.22 – 1.92) | 0.0003 *** |
| Nodal status | N0 (ref) (n=112) | - | - |
| | N1-3 (n=62) | 1.14 (0.38 – 3.46) | 0.8179 |
| | N4+ (n=36) | 2.37 (0.89 – 6.34) | 0.0858 |
| Concordance Index = 0.789 (se = 0.053) | | Likelihood Ratio Test = 31.43 (p = 0.00005) | |
| AIC = 207.1192 | | | |

- On-treatment IS provides more prognostic information than baseline IS.

## CONCLUSIONS

In ER+/HER2+ early BC:

- There is a clinical utility of peri-operative ET, guiding who would have good prognosis for adjuvant ET and who may need additional therapy.
- There is significant upregulation of immune and endocrine-related genes and downregulation of proliferation, HRD and *TP53* mutational status genes in early AI responders.
- Most LumB BC shift to LumA. On-treatment IS provides more prognostic information than baseline IS.
- On-treatment $Ki67_{2wk}$ value as continuous variable was associated with differential outcome in POAI.

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