# #10P; HER2 loss and PAM50 dynamics after neoadjuvant therapy in HER2 positive early breast cancer

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## Background and objectives

- HER2 loss at time of residual disease (RD) is frequent after neoadjuvant therapy (NAT) for HER2-positive (HER2+) early breast cancer[1-5]
- Subtype switch is also frequent, with HER2-Enriched (HER2E) tumors often converting to non-HER2E[6-8].
- The association between HER2 status by immunohistochemistry (IHC) and intrinsic subtype (IS) has never been described.

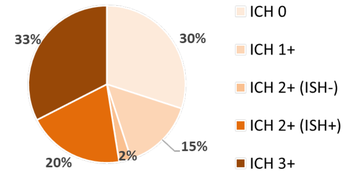
## Methods

- Between Feb/08 and Mar/22, 82 patients (pts) with HER2+ breast cancer underwent NAT at Hospital Clinic of Barcelona and had RD with matched IHC data.
- HER2 loss was defined as HER2 IHC 0/1+ or 2+/ISH not amplified on RD. Research-based PAM50 subtyping was performed with the nCounter platform.
- Associations between HER2 loss, IS dynamics, clinicopathological characteristics and event-free survival (EFS) were assessed.

## Results

- At baseline, 61% (n=50) of tumors were HER2 3+ and 83% (n=68) were hormone receptor (HR) positive. All pts received NAT with trastuzumab, 98% with chemotherapy and 52% with pertuzumab. Twenty-five pts (30%) received adjuvant T-DM1 (**Table 1**).
- HER2 loss was identified in 46% (n=38) of BC (24 IHC 0, 12 IHC 1+, 2 IHC 2+/ISH-) (**Figure 1 and table 1**).

**Figure 1. HER2 IHC at surgery.**




N = 82

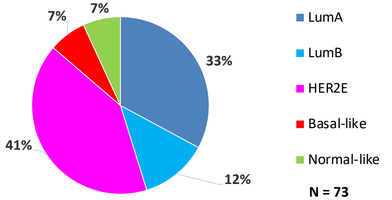
## Results

**Table 1. Baseline characteristics.**

| | Overall | HER2 status on RD | |
|---|---|---|---|
| | N=82 | HER2- N=38 | HER2+ N=44 |
| **Age** Median (range) yr | 57 (30 - 88) | 57 (36-88) | 56 (30-80) |
| **Histology** – no. (%) | | | |
| Ductal | 70 (85%) | 37 (97%) | 33 (75%) |
| Lobular | 2 (2%) | 1 (3%) | 1 (2%) |
| Other | 3 (4%) | 0 | 3 (7%) |
| Unknown | 7 (9%) | 0 | 7 (16%) |
| **Grade** – no. (%) | | | |
| 1 | 6 (7%) | 4 (11%) | 2 (5%) |
| 2 | 47 (57%) | 20 (53%) | 27 (61%) |
| 3 | 19 (23%) | 6 (16%) | 13 (30%) |
| Unknown | 10 (12%) | 8 (21%) | 2 (5%) |
| **HR** – no. (%) | | | |
| Positive | 68 (83%) | 33 (87%) | 35 (80%) |
| Negative | 13 (16%) | 4 (11%) | 9 (20%) |
| Unknown | 1 (1%) | 1 (3%) | 0 |
| **Baseline HER2 ICH** – no. (%) | | | |
| 2+ (ISH positive) | 32 (39%) | 25 (66%) | 7 (16%) |
| 3+ | 50 (61%) | 13 (34%) | 37 (84%) |
| **TILs** – no. (%) | | | |
| <10 | 33 (40%) | 8 (21%) | 25 (57%) |
| 10-50 | 13 (16%) | 7 (18%) | 6 (14%) |
| >50 | 3 (4%) | 1 (3%) | 2 (5%) |
| Unknown | 33 (40%) | 22 (58%) | 11 (25%) |
| **Ki67** – no. (%) | | | |
| Median (range) | 25 (5 - 90) | 24 (5 - 90) | 30 (7 - 60) |
| **cT** – no. (%) | | | |
| T1 | 31 (38%) | 13 (34%) | 18 (41%) |
| T2 | 31 (38%) | 16 (42%) | 15 (34%) |
| T3 | 9 (11%) | 7 (18%) | 2 (5%) |
| T4 | 2 (2%) | 0 | 2 (5%) |
| Unknown | 9 (11%) | 2 (5%) | 7 (16%) |
| **cN** – no. (%) | | | |
| N0 | 52 (63%) | 26 (68%) | 26 (59%) |
| N1 | 21 (26%) | 10 (26%) | 11 (25%) |
| N2 | 1 (1%) | 1 (3%) | 0 |
| N3 | 1 (1%) | 1 (3%) | 0 |
| Unknown | 7 (9%) | 0 | 7 (16%) |
| **Time from NAT to surgery** Median (range) | 28 (4 – 66) | 28 (4 - 66) | 26 (5 – 54) |
| **Adjuvant T-DM1** – no. (%) | 25 (30%) | 7 (18%) | 18 (41%) |

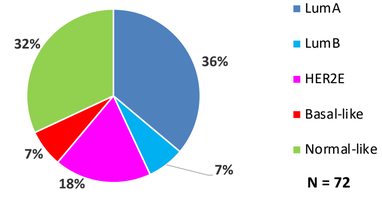
- IS was assessed on 73 baseline and 72 RD samples (67 paired).
- At baseline, distribution of IS was: HER2E 41%, Luminal A (LumA) 33%, Luminal B (LumB) 12%, normal-like 7%, basal-like 7% (**Figure 2**).
- On RD, distribution of IS was: HER2E 18%, LumA 36%, LumB 7%, normal-like 32%, basal-like 7% (**Figure 3**).
- *ERBB2* mRNA levels significantly decreased after NAT (p=0.001). An IS switch was observed in 40% (n=27) of samples (**Figure 5**) and was not associated with HER2 loss (p=0.455). However, HER2 loss was numerically more frequent among BC that switched from HER2E to non-HER2E (58%) than in BC that remained HER2E (23%) (p=0.082).

**Figure 2. Baseline IS distribution.**




N = 73

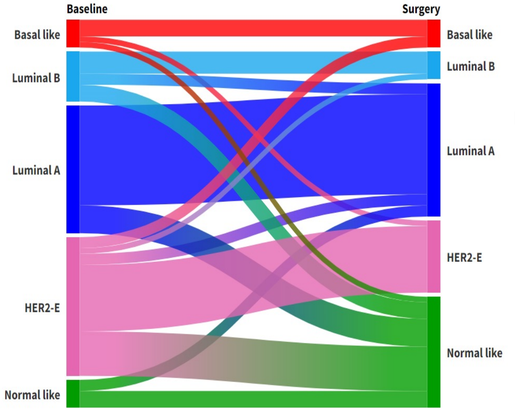
**Figure 3. IS distribution on RD at surgery.**




N = 72

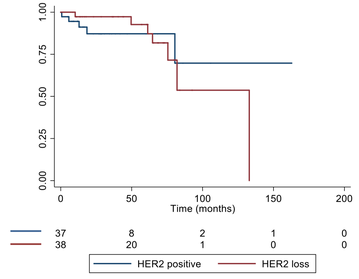
- In a multivariate regression analysis including baseline IHC, *ERBB2* mRNA, IS, HR status, time from NAT to surgery and administration of dual HER2 blockade, only *ERBB2* mRNA was associated with HER2 loss (p=0.003).

**Figure 5. Sankey plot with subtype switch (n = 67).**




- At a median follow up of 61.0 months, 12 EFS events were recorded.
- After adjusting for T-DM1 use, none of the variables assessed, including HER2 loss, was associated with EFS.

**Figure 6. EFS in pts with and without HER2 loss.**




## Conclusions

- **HER2 loss on RD after NAT is associated with decrease in ERBB2 mRNA levels and is more frequent in tumors switching from HER2E to non-HER2E subtype.**
- **EFS is similar between pts with HER2+ and HER2- RD after trastuzumab-based NAT.**
- **Further validation on large cohorts is warranted.**

**References and Acknowledgements**

1. Guarneri et al., Ann Oncol 2013; 2. Mittendorf et al., CCR 2009; 3. Niikura et al., Ann Oncol 2016; 4. Yoshida et al., J Surg Oncol 2017; 5. Morganti S., SABCS 2021; 6. Bianchini et al., Ann Oncol 2018; 7. Carey et al., J Clin Oncol 2016; 8. Braso-Maristany et al., Nat Comm 2020.

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