Independent validation of the HER2DX assay in HER2-positive (HER2+) breast cancer treated with neoadjuvant paclitaxel, trastuzumab and pertuzumab (THP): a correlative analysis from the BiOnHER study

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ESMO Breast Cancer 2023

BACKGROUND

- HER2DX is a 27-gene prognostic (risk-score) and predictive (pathological complete response [pCR]-score) assay in early-stage HER2+ breast cancer (BC) based on clinical data and the expression of 4 gene signatures (immune, proliferation, luminal differentiation and HER2 amplicon) *(Prat A et al EBioMedicine 2022 ; Prat A et al Lancet Oncol 2020).*
- Tumor transcriptome shortly after treatment initiation may serve a superior predictor of pCR than pre-treatment evaluation, as observed in the phase II trial (NCT01796197) in HER2+ inflammatory BC *(Pernas S Ther Adv Med Oncol 2022).*The BiOnHER study (N=60) is a prospective study of paired tumor samples from patients with newly diagnosed HER2+ BC eligible for neoadjuvant treatment to evaluate whether early on-treatment biomarkers can improve the accuracy of predicting pCR over pre-treatment samples alone.
- Patients with stage I-III HER2+ BC undergo a tumor biopsy pre-treatment (D1) and 8 days later (D8), following the loading-dose of trastuzumab and pertuzumab (HP), prior to adding paclitaxel (T); patients are treated with neoadjuvant THP x 16 weeks.
- Here, we aim to further validate the ability of HER2DX to predict pCR in the BiOnHER study.

OBJECTIVES

- To assess the ability of the HER2DX pCR score to predict pCR (ypT0/is pN0) in D1 FFPE samples.
- To evaluate the ability of HER2DX pCR score to predict pCR independently of hormone receptor (HR) status
- To assess differences in HER2DX 4 gene expression between D1 and D8

METHODS

- All patients enrolled on the BionHER trial underwent a pre-treatment (D1) and an early on-treatment (D8) tumor biopsies. Standarized HER2DX was evaluated centrally on FFPE tumor biopsies.
- Descriptive and receiver-operator curve (ROC) analysis were performed. Logistic regression analyses identified associations with pCR. T-tests determined significant changes between D1 and D8.

STUDY DESIGN

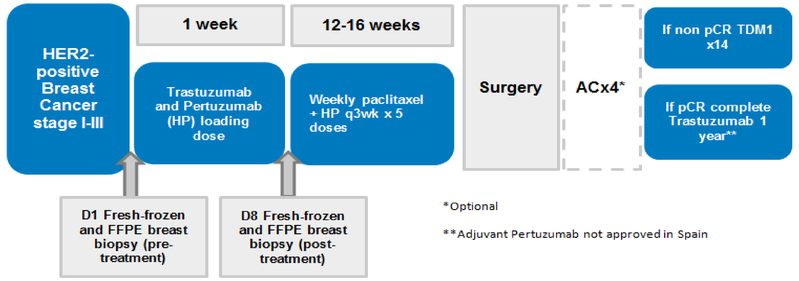


Fig. 1: BiOnHER study design

RESULTS

Table 1. Patient baseline characteristics

	N (%)
N	49 (100)
Age, (mean and range)	59 (35-83)
Hormonal receptor status	
Positive	33 (67.3)
Negative	16 (32.6)
Clinical stage	
IA	11 (22.4)
IIA	20 (40.8)
IIB	11 (22.4)
IIIA	1 (2.0)
IIIB	5 (10.2)
IIIC	1 (2.0)
Pathological response	
pCR	26 (53.1)
RCB I	6 (12.2)
RCB II	11 (22.5)
RCB III	6 (12.2)

HER2DX pCR score groups

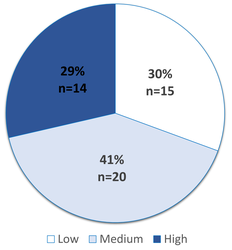


Fig. 2: Distribution of HER2DX pCR score

HER2DX pCR score distribution

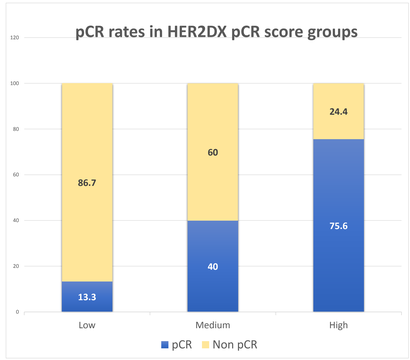


Fig. 3: Responders and non-responders between HER2DX pCR score groups

Keypoints:

- HER2DX pCR-score (as a continuous variable [CV]) was significantly associated with pCR (odds ratio[OR]=4.25, p=0.001) and as categorical variable (HER2DX pCR-high vs pCR-low OR=18.33, p=0.004)
- HR status was significantly associated with pCR score (OR=0.43, p=0.008).
- HER2DX pCR score was significantly associated with pCR independently of HR status (OR=3.89, p=0.010), which lost its statistically significance in the presence of HER2DX pCR-score (OR=0.87), p=0.756).
- The AUC ROC of HER2DX pCR score (as a CV) and pCR status was 0.813.

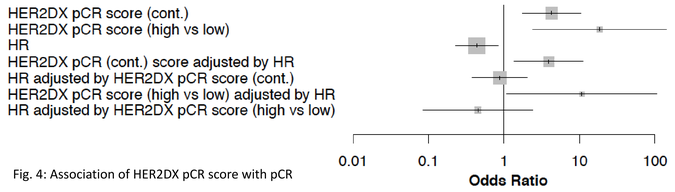
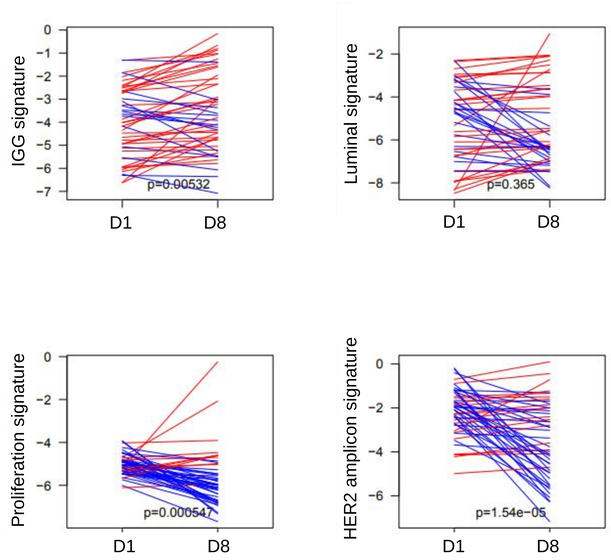


Fig. 4: Association of HER2DX pCR score with pCR

Changes in HER2DX gene expression signatures between D1 and D8



Keypoints:

- Early variations in the four gene expression signatures in the HER2DX pCR score were assessed at D1 and at D8, only one dose after starting HP, without chemotherapy
- Differences between pre-treatment and post-treatment biopsies were statistically significant in the immune, proliferative and HER2 amplicon signatures; changes in the luminal were not significant.

Fig. 5: Differences in the HER2DX IGG, luminal, proliferation, and HER2 amplicon gene expression signatures between D1 and D8

KEY FINDINGS AND CONCLUSIONS

- HER2DX pCR score was predictive of pCR in patients with HER2+ BC treated with neoadjuvant THP.
- HER2DX pCR score predicted pCR with high accuracy in the overall population, independently of HR status subgroup.
- Immune infiltration, tumor cell proliferation and HER amplicon gene expression signatures varied significantly between D1 and D8 analysis.

These findings validate HER2DX as a predictive assay for pCR in the early setting of HER2+ BC treated with neoadjuvant therapy, regardless of HR status; also evidence substantial early changes in gene expression just one week after the loading dose of the dual HER2-blockade.

The author has no conflicts of interest to declare.