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Development of a multi-parameter prognostic score to guide systemic therapy in early-stage HER2-positive breast cancer: a retrospective study with an external evaluation

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Contributors

AP and PC had the idea for and designed the study. AP, PC, LP, GG, TP contributed to data collection and assembly. AP, PC, LP and JSP interpreted and analysed data. All authors wrote and reviewed the report and approved the final version for submission.

Data sharing

The data collected for the study will not be made available to others. We encourage investigators interested in data sharing and collaboration to contact the corresponding author.

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Summary

Background: In early-stage HER2-positive (HER2+) breast cancer, escalation or de-escalation of systemic therapy is a controversial topic. As an aid to treatment decisions, we present a prognostic assay that integrates multiple data types for predicting survival outcome in newly diagnosed HER2+ breast cancer.

Methods: Clinicopathological data, stromal tumour infiltrating-lymphocytes (TILs), PAM50 subtypes and expression of 55 genes were obtained from 435 patients (34·7%) who participated in the Short-HER phase III trial, which randomised patients with newly diagnosed node-positive HER2+ breast cancer or, if node negative, with at least one risk factor (tumour size > 2·0 cm, histological grade 3, lympho-vascular invasion, Ki-67>20%, age ≤35 years, or hormone receptor negativity), to adjuvant anthracycline/taxane-based combinations with either 9 weeks or 1 year of trastuzumab. Trastuzumab was administered intravenously every 3 weeks (8 mg/kg loading dose at first cycle, and 6 mg/kg thereafter) for 18 doses or weekly (4 mg/kg loading dose at first week, and 2 mg/kg thereafter) for 9 weeks, starting concomitantly with the first taxane dose. The primary objective of this study was to derive and evaluate a combined score associated with distant metastasis-free survival (DMFS). Patient samples in the training dataset were split into a training set (n=290) and a testing set (n=145), balancing for event and treatment arm. The training set was further stratified into 100 iterations of Monte-Carlo cross validation (MCCV). Cox proportional hazard models were fit to MCCV training samples using Elastic-Net. A maximum of 92 features were evaluated. The final prognostic model was evaluated in an independent combined dataset of 267 patients with early-stage HER2+ breast cancer treated with different neoadjuvant and adjuvant anti-HER2-based combinations and disease-free survival (DFS) outcome data.

Findings: In Short-HER, tumour stage (T1 vs. rest), nodal stage (N0 vs. rest), TILs (continuous variable), subtype (HER2-enriched and Basal-like vs. rest) and 13 genes composed the final model (HER2DX). HER2DX was significantly associated with DMFS as a continuous variable ($p<0·001$). Two cut-offs defined low-risk (50%), med-risk (25%) and high-risk (25%) populations. The 5-year DMFS of the low-, med- and high-risk populations were 98·1% (95% CI 96·3–99·9), 88·9% (83·2–95·0) and 73·9% (66·0–82·7), respectively (hazard ratio [HR] low- vs. high-risk=0·04, 0·0–0·1, $p<0·0001$). In the evaluation cohort, HER2DX was significantly associated with DFS as a continuous variable (HR=2·77, 1·4–5·6, $p=0·0040$) and as group categories (low- vs. high-risk HR=0·27, 0·1–0·7, $p=0·010$). The 5- and 8-year DFS of the HER2DX low-risk group was 93·5% (89·0–98·3%) and 91·7% (86·2–97·6%), respectively.

Interpretation: HER2DX identifies patients with early-stage HER2+ breast cancer candidates for escalated or de-escalated systemic treatment. Future clinical validation of HER2DX seems warranted.

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Introduction

HER2-positive (HER2+) breast cancer is responsible for a substantial proportion of deaths[1]. In early stages, (neo)adjuvant chemotherapy and anti-HER2 therapy (plus endocrine therapy in hormone receptor-positive disease) have consistently shown significant and long-term clinical benefits, in terms of disease-free survival (DFS) and overall survival[1]. However, substantial heterogeneity exists in HER2+ disease regarding tumour biology[2–6], patient's prognosis[7] and treatment benefit[7].

Strategies to either escalate or de-escalate systemic therapy in early-stage HER2+ disease have been explored[8], such as decreasing the amount of chemotherapy[9] and the duration of trastuzumab[10] or increasing HER2 blockade with pertuzumab[11], neratinib[12] or switching the anti-HER2 therapy to T-DM1 in patients who did not achieve a pathological complete response (pCR) following neoadjuvant trastuzumab-based chemotherapy[13]. Despite all these efforts to improve survival outcomes, the crude reality is that the vast majority of patients with early-stage HER2+ disease are cured with chemotherapy and trastuzumab[14].

In early-stage hormone receptor-positive/HER2-negative disease, several prognostic tools allow a better individualization of systemic treatments and are widely available. For example, gene expression-based assays such as OncotypeDX help identify low-risk patients who do not need (neo)adjuvant chemotherapy. Second generation genomic tests, such as PAM50/Prosigna, which include clinical parameters such as tumour size in the final risk assessment, might better discriminate patients who may not need chemotherapy from those who are likely to benefit.

To date, variables beyond the TNM classification have been associated with prognosis in early-stage HER2+ disease. Examples are stromal tumour-infiltrating lymphocytes (TILs)[14–16] and PAM50 subtypes[2,16,17]. Similarly, these biomarkers and PIK3CA mutations[18] have been associated with the probability to achieve a pCR[18,19], which is also associated with long-term outcome[20]. However, decisions today about escalation or de-escalation of systemic therapies are based on nodal status, hormone receptor status and therapy response[21]. Therefore, a multi-parameter prognostic tool that integrates variables already known, as well as additional ones, to help guide systemic therapies in early-stage HER2+ breast cancer is urgently needed. Here, we aimed to develop a prognostic tool based on multiple variables.

Methods

The combined prognostic model was derived using retrospective clinical, pathological and genomic data from a subset of patients who participated in the Short-HER trial. The final

prognostic model was evaluated retrospectively in a combined and independent cohort of patients with early-stage HER2+ breast cancer.

Study designs

Short-HER was a randomized, investigator-driven phase 3 study, aimed to assess the non-inferiority in terms of DFS of 9 weeks versus 1 year of adjuvant trastuzumab combined with chemotherapy[22]. Briefly, women aged 18–75 with surgically resected, HER2+ breast cancer were eligible. Women had to have node positivity, or in case of node-negativity, at least one of the following features: tumour size >2 cm, grade 3, presence of lympho-vascular invasion, Ki67 > 20%, age ≤35 years or hormone receptor negativity. A total of 1,254 patients with a performance status of 0–1 were randomised from 17th December 2007 to 6th October 2013 to arm A or arm B. Chemotherapy in arm A consisted of adriamycin 60 mg/m^2 or epirubicin 90 mg/m^2 plus cyclophosphamide 600 mg/m^2 every 3 weeks for 4 courses followed by paclitaxel 175 mg/m^2 or docetaxel 100 mg/m^2 every 3 weeks for 4 courses. Trastuzumab was administered every 3 weeks for 18 doses, starting with the first taxane dose. Chemotherapy in arm B consisted of docetaxel 100 mg/m^2 every 3 weeks for 3 courses followed by 5-fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 every 3 weeks for 3 courses. Trastuzumab was administered weekly for 9 weeks, starting concomitantly with docetaxel. When indicated, radiation and hormonal therapy were carried out according to local standard. Median follow-up was 91·4 months (IQR 75·1–105·6). In Short-HER, DMFS was an exploratory endpoint.

CHER-LOB[23] was a randomised, noncomparative, investigator-driven phase 2 study from 8th August 2006 to 25th November 2010 of preoperative taxane-anthracycline consisting of paclitaxel (80 mg/m^2) for 12 weeks followed by fluorouracil, epirubicin, and cyclophosphamide for 4 courses every 3 weeks, in combination with trastuzumab, lapatinib (1,500 mg daily) or combined trastuzumab plus lapatinib (1,000 mg daily) for 26 weeks in patients with HER2+, stage II to IIIA operable breast cancer and with a performance status of 0–1. The primary aim was to estimate the pCR rate. Treatment after surgery was left to treating physician discretion. Median follow-up was 60·0 months (IQR 46·9–69·4). In CHER-LOB, DFS was an exploratory endpoint.

PAMELA was a single-group, phase 2 trial from 22nd October 2013 to 30th November 2015 aimed to the ability of the PAM50 HER2-enriched subtype to predict pCR at the time of surgery[19]. Patients with HER2+ disease, stage I–IIIA and a performance status of 0–1 were given lapatinib (1,000 mg per day) and trastuzumab for 18 weeks; hormone receptor-positive patients were additionally given letrozole (2·5 mg per day) or tamoxifen (20 mg per day) according to menopausal status. Treatment after surgery was left to treating physician discretion. Median follow-up was 68·1 months (IQR 57·1–72·3). In PAMELA, DFS was an exploratory endpoint.

The Hospital Clinic and Padova University cohorts are consecutive series of patients with early-stage HER2+ disease and a performance status of 0–1 treated, as per standard practice, from 28th June 2005 to 26th September 2018 (Hospital Clinic) and 23rd February 2009 to 26th May 2016 (Padova University cohort), with neoadjuvant trastuzumab-based chemotherapy for 3–6 months, followed by surgery. Adjuvant treatment was completed with

trastuzumab for up to 1 year. When indicated, radiation and hormonal therapy were carried out according to local standard. Median follow-up of Hospital Clinic and Padova University cohorts were 39·3 (IQR 29·6–55·8) and 38·5 (IQR 30.1–65.7) months, respectively. In both cohorts, DFS was an exploratory endpoint.

The study was performed in accordance with Good Clinical Practice guidelines and the World Medical Association Declaration of Helsinki. Approvals for the study were obtained from independent ethics committees.

Procedures

PAM50 and single gene analyses were performed at IDIBAPS from formalin-fixed paraffin-embedded tumours. Samples analysed from Short-HER were from surgical specimens, whereas samples analysed from the neoadjuvant cohorts were from baseline samples before starting neoadjuvant therapy. A minimum of ~125 ng of total RNA was used to measure the expression of the 50 PAM50 subtype predictor genes and 5 genes (i.e. CD8A, PDL1, PD1, CD4 and AR). Normalization and PAM50 subtyping was performed as previously described[19]. Regarding samples from CHER-LOB, PAM50 gene expression and subtyping was obtained from PAM50-based microarray data as previously described[24]. Genomic analyses were performed blinded from clinical data. Nodal and tumour stages were obtained from clinical report forms. Finally, TILs were assessed according to pre-defined criteria[25].

Outcomes

The primary objective of this study was to derive and evaluate a combined prognostic score, named HER2DX, as a continuous variable. In the training dataset (i.e. Short-HER), the chosen survival endpoint was DMFS, similarly as other gene expression-based prognostic biomarkers such as the PAM50 Risk of Recurrence in hormone receptor-positive/HER2-negative breast cancer. DMFS was defined as the time between randomization and distant recurrence or death before recurrence. In the evaluation dataset, the survival endpoint was DFS due to the availability of the data, calculated as the time between treatment initiation and any of the following events, whichever first: local, regional and distant recurrence; contralateral breast cancer, other second invasive primary cancer, death before recurrence or second primary cancer. For description purposes, 5- and 8-year DMFS and DFS estimates were calculated.

The secondary objectives were: 1) to describe the clinical-pathological and genomic features of the HER2DX risk groups; 2) to explore the association of HER2DX score with DFS in the evaluation dataset according to the type of pathological response; 3) to evaluate the association of HER2DX score, and other individual variables, with pCR in the breast and axilla in the evaluation dataset. We also performed an ad-hoc analysis of the association of HER2DX with DFS in Short-HER.

Statistical analysis

The prognostic model was developed using a training dataset of 435 patients (34·7%) enrolled in the Short-HER trial (webappendix p. 1). The rule to define a patient assessable in Short-HER was availability of gene expression, clinical-pathological and TILs data. Patients

were split into a training set (n=290 [67·0%] patients and 42 events [14·5%]) and a testing set (n=145 [33·0%] patients and 21 events [14·5%]), balancing for distant metastasis-free survival (DMFS) event and treatment arm. The training set was further stratified into 100 iterations of Monte-Carlo cross validation (MCCV). Cox proportional hazard models were fit to MCCV training cases using Elastic-Net (package glmnet). A maximum of 92 features were evaluated. Elastic-Net parameters (alpha and lambda) were selected to reduce partial likelihood deviance and increase Harrell's C-index evaluated in the MCCV test sets. Selected values were then used to fit our final model against the complete training set. A total of 17 variables were selected with the following survival coefficients: nodal stage 1 (0·680), tumour stage 2–4 (0·339), MMP11 (0·200), PAM50 HER2-Enriched or Basal-like (0·156), CDC6 (0·087), CDH3 (0·076), TMEM45B (0·048), EXO1 (0·024), FGFR4 (0·021), RRM2 (0·008), TILs (−0·009), MLPH (−0·022), KRT5 (−0·024), KRT14 (−0·040), MYC (−0·050), PHGDH (−0·050) and BAG1 (−0·168).

Two cut-offs based on quartiles were defined to split patients into low- (quartile 1 and 2), medium- (quartile 3) and high-risk (quartile 4) groups. The final model was tested, as a continuous variable and using the pre-specified cut-offs, in 267 patients from the evaluation dataset (webappendix p. 2). The evaluation dataset was composed of patients from CHER-LOB (n=74 [61·2%] of 121), PAMELA (n=88 [58·3%] of 151), Padova cohort (n=37) and Hospital Clinic cohort (n=68). Missing data were not included in our analyses. This study was not pre-specified in any registry.

Cox proportional hazard regression analyses were used to investigate the association of each variable with survival outcome. Genes associated with HER2DX risk groups were identified using a multi-class Significance Analysis of Microarrays and a false discovery rate <5%. Categorical variables were expressed as number (%) and compared by χ^2 test or Fisher's exact test. Logistic regression analyses were performed to investigate the association of each variable with pCR. The significance level was set to a 2-sided alpha of 0·05. The software used was R code v3.6.2.

Role of the funding source

The study was designed by investigators from Padova University and Hospital Clinic. Funding sources had no role in the design and conduct of this study, and in the analysis and interpretation of data. All authors had full access to all data and had final responsibility for the decision to submit for publication.

Results

To build a prognostic model, clinical-pathological and molecular data were available from 435 patients of the Short-HER trial (Table 1). Briefly, mean age was 55·4 (25–78) and most tumours were ≤2·0 cm (54·0%), node-negative (60·7%), hormone receptor-positive (71·0%), histological grade 3 (71·9%) and had ≤10% TILs (72·6%). Concordant with previous studies[4,26], most tumours (52·9%) were PAM50 HER2-Enriched and the proportion of HER2-Enriched disease was higher in hormone receptor-negative disease (69·8%) compared to hormone receptor-positive disease (46·0%). As expected, most Luminal A/B and Basal-

like subtypes were hormone receptor-positive (99·2%) and hormone receptor-negative (70%), respectively.

Four variables had previously shown to provide independent prognostic information in Short-HER[14,27]: 1) Tumour size, 2) Nodal status, 3) TILs and 4) PAM50 subtype. A multivariable Cox model analysis of DMFS confirmed these findings on the 435 Short-HER patient-dataset (webappendix p. 3). Next, we evaluated the ability of 31 variables to provide additional prognostic information using cross-validated elastic net Cox models. The final score (called HER2DX) included 17 variables: tumour size (i.e. T1 vs. rest), nodal status (N0 vs. rest), TILs (as a continuous variable) and PAM50 subtype (HER2-enriched and Basal-like vs. rest), together with 13 individual genes. Among them, 7 had survival coefficients associated with poor survival outcome and were mostly tracking proliferation-related genes (i.e. CDC6, EXO1 and RRM2), HER2-enriched-related biology (i.e. TMEM45B and FGFR4) and Basal-like-related biology (i.e. CDH3). The other 6 genes had survival coefficients associated with better outcome and were mostly tracking Luminal A-related biology (i.e. BAG1), Normal-like (i.e. KRT5, KRT14, MLPH and MYC) and Basal-like-related biology (i.e. PHGDH). The predictive performance (C-index) of HER2DX in Short-HER was 0·80 (all patients), 0·83 (training set) and 0·72 (testing set).

HER2DX measured as a continuous variable was found significantly ($p<0·0001$) associated with DMFS in the Short-HER 435 patient-dataset. According to HER2DX scoring based on quartiles (webappendix p. 4), the 5-year DMFS of quartile 1 (Q1), Q2, Q3 and Q4 were 97·1% (95% confidence interval [CI] 94·0–100·0), 99·1% (95% CI 97·3–100·0), 88·9% (95% CI 83·2–95·0) and 73·9% (95% CI 66·0–82·7), respectively. No statistically significant difference in DMFS was observed between Q2 vs. Q1 (hazard ratio [HR]=0·92, 95% CI 0·23–3·70, p=0·91). Q3 and Q4 had significant worse DMFS compared to Q1 (Q3: HR=4·57, 95% CI 1·5–13·6, p=0·010; Q4: HR=12·0, 95% CI 4·30–33·5, $p<0·0001$).

Based on these findings, HER2DX median score (i.e. Q1–2) was identified as the cut-off to identify low-risk patients (Fig. 1A). The 5-year DMFS of Q1–2 group was 98·1% (95% CI 96·3–99·9) (Fig. 1B). The HER2DX score that discriminates Q3 from Q4 was identified as the cut-off to distinguish medium- to high-risk patients. The low-risk group (Q1–2) had a significant better DMFS compared to the high-risk (Q4) group (HR=0·04, 95% CI 0·0–0·1, $p<0·0001$) and to the medium/high-risk (Q3-Q4) group (HR=0·10, 95% CI 0·1–0·2, $p<0·0001$). An ad-hoc analysis of HER2DX versus DFS obtained similar results (webappendix p. 4).

Clinical-pathological and molecular features of the HER2DX low-risk patients in Short-HER were compared to med/high-risk patients (Table 1). No clinical-pathological or molecular feature was unique of HER2DX low-risk patients and features previously identified as being associated with poor survival outcome were also represented in the HER2DX low-risk group. Similarly, 7–36% of HER2DX med/high-risk patients had features previously reported to be associated with better survival outcome such as high TILs (>30%), T1 tumours or node-negative disease (Table 1).

Next, we explored the underlying biology of the HER2DX risk groups (low-, med- and high-). A total of 41 (75·0%) genes were found differentially expressed across the three risk groups (webappendix p. 5). Luminal-related genes (e.g. PGR, ESR1 and BCL2) and immune-related gene CD8A were found more expressed in HER2DX low-risk group compared to the other risk-groups. In contrast, HER2-enriched-related genes (e.g. ERBB2 and FGFR4) and proliferation-related genes (e.g. CCNE1 and UBE2T) were more expressed in the high-risk group compared to the other risk-groups. Of note, the medium-risk group had an intermediate gene expression profile, more like the high-risk group than the low-risk group.

A dataset of 267 patients with early-stage HER2+ disease obtained from a combined cohort of 4 neoadjuvant studies was used for an independent evaluation of the HER2DX score, which was determined at baseline before starting neoadjuvant therapy (Table 2). All patients received chemotherapy, 1-year of trastuzumab, 43·4% (116/267) of patients received dual HER2 blockade with lapatinib and trastuzumab for 4·5 to 6·0 months and 7·5% (20/267) received 4 cycles of neoadjuvant pertuzumab. In PAMELA, chemotherapy was administered after surgery. Despite heterogeneity in systemic therapies, no statistically significant differences in DFS were observed across the 4 cohorts (webappendix p. 6).

In the evaluation dataset, HER2DX score as a continuous variable was significantly associated with DFS (HR=2·77, 95% CI 1·4–5·6, p=0·0040) (webappendix p. 7). According to the pre-specified cut-offs, HER2DX low-risk group showed a better DFS compared to the high-risk groups (Fig. 2A and B). The 5-year DFS of the HER2DX low-, high- and med/high- groups were 93·5% (95% CI 89·0–98·3%), 81·1% (95% CI 71·5–92·1%) and 86·7% (95% CI 81·2–92·5%), respectively. The 8-year DFS of the HER2DX low-, high- and med/high- groups were 91·7% (95% CI 86·2–97·6%), 54·1% (95% CI 24·1–100%) and 78·7% (95% CI 62·6–98·9%), respectively.

Concordant with previous studies[2,14–16], TILs as a continuous variable (odds ratio [OR]=1·04, 95% CI 1·0–1·1, p<0·0001) and HER2-enriched subtype (OR=3·25, 95% CI 1·8–5·7, p<0·0001) were associated with pCR. On the contrary, HER2DX score as a continuous variable was not associated with pCR (OR=1·02, 95% CI 0·6–1·6, p=0·93). According to the pre-specified cut-offs, the pCR rates in the HER2DX low-, high- and med/high- groups were 35·8% (42/117), 38·6% (34/88) and 35·5% (22/62). Among 169 patients with residual disease, the distribution of HER2DX low-, med- and high- risk groups was 44·4%, 32·0% and 23·7%, respectively. In this setting, HER2DX low-risk group showed a better DFS compared to the high-risk group (HR=0·34, 95% CI 0·1–0·9, p=0·030) but not to med-risk group (HR=0·63, 95% CI 0·2–1·7, p=0·38) and med/high-risk group (HR=0·47, 95% CI 0·2–1·1, p=0·10) (webappendix p. 7). The 5-year DFS of the HER2DX low- and high- groups were 90·0% (95% CI 83·2–97·4%) and 78·2% (95% CI 65·6–93·2%), respectively. The 8-year DFS of the HER2DX low- and high- groups were 87·6% (95% CI 79·7–96·3%) and 39·1% (95% CI 0·1–100·0%), respectively. Among 98 patients who achieved a pCR, the distribution of HER2DX low-, med- and high- risk groups was 42·9%, 34·7% and 22·4%, respectively. In this setting, 0 and 6 events were observed in the low-risk and med/high-risk groups, respectively.

Discussion

To our knowledge, this is the first study attempting to build a combined prognostic score (called HER2DX) based on 17 clinicopathological and genomic variables in early-stage HER2+ breast cancer using tumour samples from a Phase III trial. Specifically, our results reveal that HER2DX is associated with long-term survival outcome and has the ability to identify groups of patients with different risks of relapsing following standard therapy. In addition, our study provides insights about the relationship between response to therapy in the neoadjuvant setting and long-term prognosis. From a clinical point of view, HER2DX could identify patients with early-stage HER2+ disease candidates for escalated or de-escalated systemic treatment. Future validation of HER2DX seems warranted.

Escalation or de-escalation of systemic therapies in early-stage HER2+ disease is a controversial topic. In stage 1 disease, APT trial[28] demonstrated DFS rates of 93·3% following 3-months of adjuvant paclitaxel plus 1-year of trastuzumab in a single-arm trial of 410 patients. This treatment strategy is now widely adopted[28], although controversy exists in patients with hormone receptor-negative disease[28]. Regarding de-escalation of trastuzumab, several non-inferiority studies, including Short-HER trial[22], have shown a narrow reduction in recurrence risk with 12 months of therapy compared with shorter durations[10,28,29]. This treatment strategy, however, has not been widely adopted worldwide, despite its potential impact in low-income countries where trastuzumab is not reimbursed[21].

In stage 2–3 disease, escalated systemic treatments with pertuzumab, neratinib and T-DM1 are approved by the US Food and Drug Administration and the European Medicines Agency[11–13]. However, the absolute benefit of pertuzumab and neratinib is very low (i.e. <3% in invasive DFS)[11,12]. T-DM1, contrarily, has demonstrated clinically meaningful results with an absolute increase in invasive DFS at 3-years of 11·3% in patients with HER2+ disease who do not achieve a pCR following standard anti-HER2-based chemotherapy[13]. However, 3 of 4 patients in the control arm of the pivotal trial[13] did not present an event at 3-years. Overall, there is an urgent need to better define the populations of patients with early-stage HER2+ disease candidates for escalated or de-escalated systemic therapies.

To our knowledge, our study is the first to report a clinically valuable prognostic biomarker in HER2+ disease. Specifically, the HER2DX score can split the population of early-stage HER2+ breast cancer and identify 2 prognostically distinct groups. To accomplish this, the assay integrates multiple data types and presents a single prognostic score as a continuous variable and proposes specific cut-offs. Importantly, the HER2DX low-risk group cannot be identified by classical clinical-pathological parameters and a substantial proportion of HER2DX low-risk patients have individual features known to be associated with poor survival outcome such as a large tumour size, nodal-positivity, low TILs and residual disease after neoadjuvant therapy. Finally, an intriguing finding is that HER2DX is not associated with the probability to achieve a pCR following anti-HER2-based therapy.

Our study has several limitations. First, the evaluation dataset is a heterogeneous cohort of patients. Second, the survival endpoint from the training dataset (i.e. DMFS) is different

from the evaluation dataset (i.e. DFS). The reason is that PAMELA had DFS data recorded. Third, the confidence intervals of the survival estimates at 5- and 8-years of the different risk-groups overlap. Fourth, a substantial proportion of patients in the evaluation dataset also received dual HER2 blockade with lapatinib and trastuzumab. However, the absolute impact of dual HER2 blockade with these 2 drugs in terms of survival outcomes is small (i.e. absolute increase of 2% at 4-years)[30]. Fifth, HER2DX was developed from primary tumour specimens and staging was based on surgical pathology reports. This is different from the neoadjuvant setting where a core biopsy is the only available tissue and staging is based on imaging. Despite this limitation, HER2DX performed well in the combined neoadjuvant dataset, arguing in favour of its ability to predict outcome at diagnosis before any treatment is initiated using core biopsies. Sixth, the Short-HER cohort was powered for another primary endpoint, which was to compare the DFS between 2 treatment arms. The analysis presented here used all available subjects from this study. Thus, we did not perform a formal power analysis, and focused on statistically significant results. Finally, the HER2DX assay is not standardized and specific cut-offs will need to be defined.

Following our results, it remains the question whether HER2DX will guide the use of systemic therapy in early-stage HER2+ disease. Our opinion is that we are not ready yet to embrace this biomarker and further validation studies should establish its clinical utility in different scenarios with a particular focus in the neoadjuvant setting, where the type of pathological response might be incorporated in the HER2DX algorithm. To accomplish this, the HER2DX assay should be standardised and applied retrospectively in tumour samples from ≥2 large and completed phase III pivotal clinical trials such as APHINITY, NeoALTTO, ExteNET, PERSEPHONE or KATHERINE. For example, patients with HER2DX low-risk disease at diagnosis and who do not achieve a pCR following anti-HER2-based neoadjuvant therapy could be spared 14 cycles of adjuvant T-DM1. Finally, HER2DX should help the design of prospective clinical trials to test novel escalation or de-escalation treatment strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of interest

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Research in context

Evidence before this study

We searched PubMed between Jan 1, 2010 and May 1, 2020, for clinical trials or studies published in English assessing HER2 inhibition in early-stage breast cancer, using the search terms “HER2+”, “early-stage”, “escalation”, “de-escalation”, “biomarker”, “breast cancer” and “anti-HER2 therapy”. To date, several variables associated with survival outcome have been identified in early-stage HER2+ disease such as TNM staging before and after neoadjuvant therapy, hormone receptor status, tumour-infiltrating lymphocytes (TILs), PAM50 intrinsic subtype and PIK3CA mutations. However, validation and clinical utility of these biomarkers, either alone or in combination, remains unknown.

Implementation of clinical decision support tools to help inform decisions regarding the use of systemic therapy in early-stage HER2 breast cancer are urgently needed. International guidelines support the administration of (neo)adjuvant anti-HER2-based chemotherapy in patients with T1b-T4 or lymph-node positive disease. In the last decade, however, many studies have evaluated various strategies to either escalate or de-escalate systemic therapy in early-stage HER2+ disease, such as 1) decreasing the amount of chemotherapy, 2) decreasing the duration of trastuzumab, 3) increasing HER2 blockade with either the addition of 1-year of pertuzumab to trastuzumab or the addition of 1-year neratinib after trastuzumab and 4) switching the type of anti-HER2 therapy to T-DM1 in patients who do not achieve a pathological complete response following neoadjuvant trastuzumab-based chemotherapy. Despite the successes and limitations of these treatment strategies, the reality is that most patients with early-stage HER2+ disease are cured with chemotherapy and trastuzumab.

Added value of this study

To our knowledge, this is the first study attempting to build a combined prognostic score (called HER2DX) based on 17 clinicopathological and genomic variables in early-stage HER2+ breast cancer using tumour samples from a Phase III clinical trial. In addition, the prognostic score was evaluated in a combined neoadjuvant dataset of patients with newly diagnosed HER2+ breast cancer who received anti-HER2-based therapy, providing insights about the relationship between response to therapy in the neoadjuvant setting and long-term survival outcome.

Implications of all the available evidence

The evidence suggests that HER2DX identifies a substantial proportion of patients with early-stage HER2+ breast cancer who might not need additional therapies, such as pertuzumab, neratinib or T-DM1, due to their outstanding survival outcomes with chemotherapy and trastuzumab (plus endocrine therapy if hormonal receptor-positive). Further studies should establish the clinical utility of HER2DX in this context and explore its value to help further de-escalate systemic treatments such as the duration of trastuzumab and/or the amount of chemotherapy. Finally, multi-parameter prognostic models should be explored in other breast cancer subtypes, such as triple-negative disease, as well as other cancer-types.

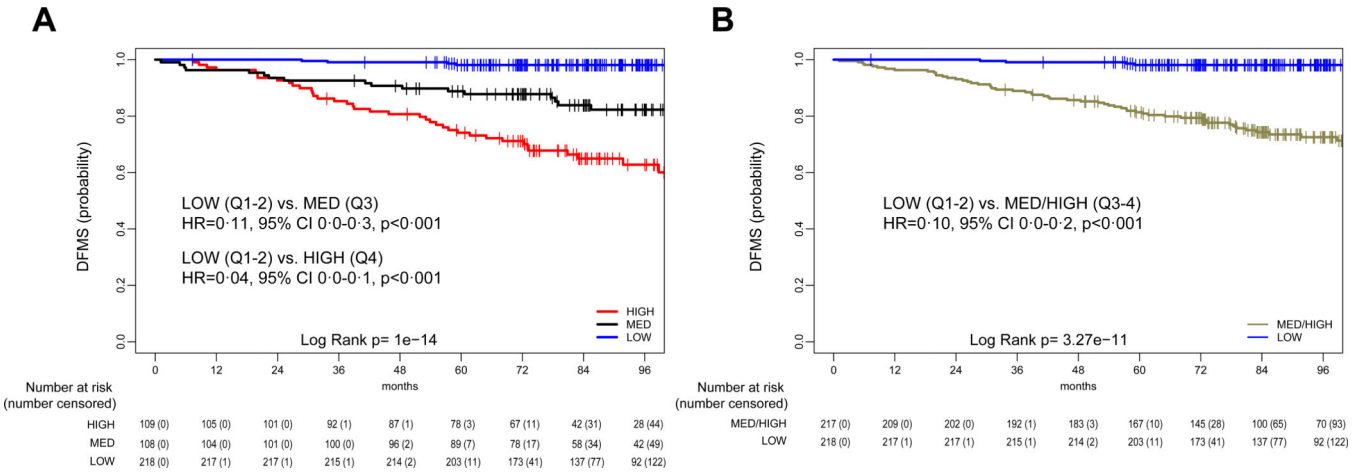

Figure 1. Distant metastasis-free survival (DFMS) outcomes based on HER2DX score in the Short-HER training dataset.

(**A**) DMFS according to low- (quartiles 1 and 2 combined), med- (quartile 3) and high-risk (quartile 4) scores; (**B**) DMFS according to low- (quartiles 1 and 2 combined) and med/high-risk (quartiles 3 and 4 combined) scores. Q, quartile.

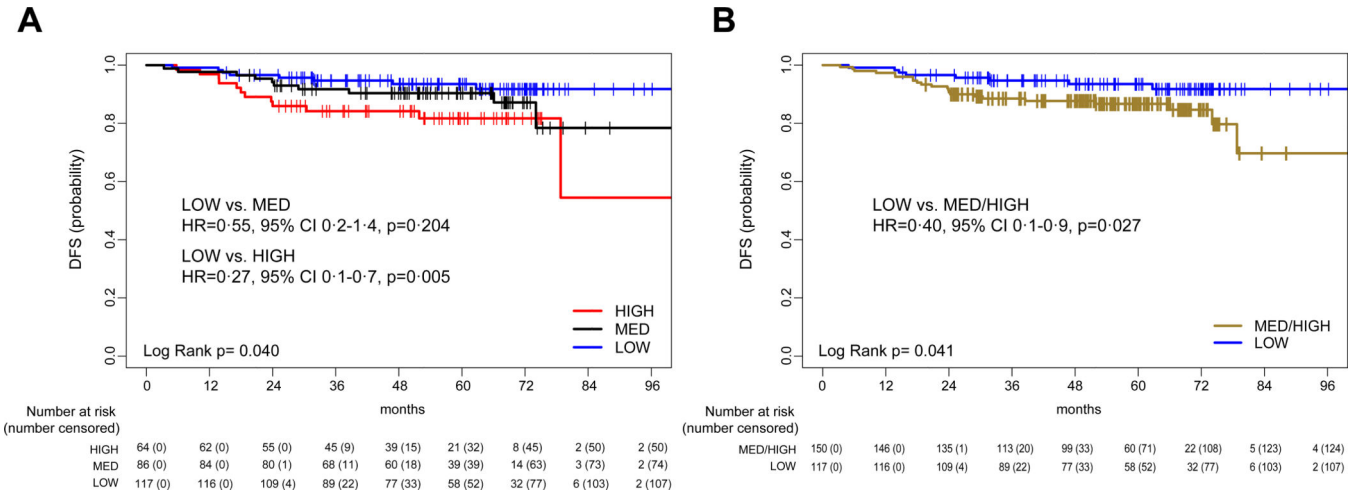

Figure 2. Disease-free survival (DFS) outcomes based on HER2DX score in the combined evaluation dataset.

(**A**) DFS according to low- (quartiles 1 and 2 combined), med- (quartile 3) and high-risk (quartile 4) scores; (**B**) DFS according to low- (quartiles 1 and 2 combined) and med/high-risk (quartiles 3 and 4 combined) scores.

Table 1.

Patient baseline characteristics of the Short-HER dataset.

	All patients		HER2DX Low		HER2DX Med/High		
	N	**%**	**N**	**%**	**N**	**%**	**p-value***
N	435	-	218	50·1%	217	49·9%	-
Age (mean, SD)	55·4 (10·2)		55·0 (10·1)		55·7 (10·4)		0·48
TILs							
TILs 0–29	379	87·1%	176	80·7%	203	93·5%	0·0001
TILs ≥30	56	12·9%	42	19·3%	14	6·5%	
pT							
T1	235	54·0%	157	72·0%	78	35·9%	<0·0001
T2–4	200	46·0%	61	28·0%	139	64·1%	
pN							
N0	264	60·7%	187	85·8%	77	35·5%	<0·0001
N1–3	171	39·3%	31	14·2%	140	64·5%	
PIK3CA mutations							
WT	339	77·9%	169	77·5%	170	78·3%	1·000
MUT	92	21·1%	46	21·1%	46	21·2%	
NA	4	1·0%	3	1·4%	1	0·5%	
Hormone receptor status							
Positive	309	71·0%	163	74·8%	146	67·3%	0·092
Negative	126	29·0%	55	25·2%	71	32·7%	
Treatmet arm							
Arm A (long)	222	51·0%	114	52·3%	108	49·8%	0·63
Arm B (short)	213	49·0%	104	47·7%	109	50·2%	
Grade							
Grade 1	6	1·4%	5	2·3%	1	0·5%	0·25
Grade 2	115	26·7%	58	27·0%	57	26·5%	
Grade 3	309	71·9%	152	70·7%	157	73·0%	
PAM50							
Luminal A	87	20·0%	63	28·9%	24	11·1%	<0·0001
Luminal B	43	9·9%	24	11·0%	19	8·8%	
HER2-enriched	230	52·9%	75	34·4%	155	71·4%	
Basal-like	27	6·2%	17	7·8%	10	4·6%	
Normal-like	48	11·0%	39	17·9%	9	4·1%	

TILs: tumour-infiltrating lymphocytes; MUT: mutated; WT: wild-type

*: p-values represent comparison between HERDX low-risk and med/high-risk groups.

Table 2.

Patient baseline characteristics of the combined evaluation dataset.

	All patients		HER2DX Low		HER2DX Med/High		
	N	%	N	%	N	%	p-value*
N	267	-	117	43·8%	150	56·2%	-
Age (mean, range)	54·5 (11.8)		53·4 (11.8)		55·4 (11.8)		0·48
TILs							
TILs 0–29	220	82·4%	88	75·2%	132	88·0%	0·0090
TILs ≥30	47	17·6%	29	24·8%	18	12·0%	
cT							
T1	57	21·3%	34	29·1%	23	15·3%	0·010
T2–4	210	78·7%	83	70·9%	127	84·7%	
cN							
N0	148	55·4%	101	86·3%	47	31·3%	<0·0001
N1–3	119	44·6%	16	13·7%	103	68·7%	
Pathological response							
pCR	98	36·7%	42	35·9%	56	37·3%	0·90
Residual disease	169	63·3%	75	64·1%	94	62·7%	
Hormone receptor status							
Positive	172	64·4%	91	77·8%	81	54·0%	0·0001
Negative	95	35·6%	26	22·2%	69	46·0%	
Grade							
Grade 1	15	5·9%	5	4·6%	10	6·8%	0·34
Grade 2	71	28·0%	35	32·4%	36	24·7%	
Grade 3	168	66·1%	68	63·0%	100	68·5%	
PAM50							
Luminal A	51	19·1%	38	32·5%	13	8·7%	<0·0001
Luminal B	33	12·4%	20	17·1%	13	8·7%	
HER2-enriched	138	51·7%	35	29·9%	103	68·7%	
Basal-like	21	7·9%	7	6·0%	14	9·3%	
Normal-like	24	9·0%	17	14·5%	7	4·7%	
Study							
PAMELA	88	33·0%	33	28·2%	55	36·7%	0·37
CHER-LOB	74	27·7%	38	32·5%	36	24·0%	
HOSPITAL CLINIC	68	25·5%	30	25·6%	38	25·3%	
PADOVA	37	13·9%	16	13·7%	21	14·0%	

TILs: tumour-infiltrating lymphocytes; pCR: pathological complete response

*p-values represent comparison between HERDX low-risk and med/high-risk groups.