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# Validation of the HER2DX genomic test in first-line advanced HER2-positive breast cancer treated with trastuzumab, pertuzumab, and taxane



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Trastuzumab, pertuzumab, and a taxane (THP) has been the standard first-line therapy for HER2+ advanced breast cancer for over a decade. With new regimens emerging, genomic tools like HER2DX may help identify patients who benefit durably from THP versus those requiring intensification. Here, baseline tumor tissue from 122 patients with HER2+ treated with THP in Poland was tested with HER2DX. A previously published Spanish real-world cohort ($n = 93$) was added to generate a combined cohort ($n = 215$). Univariable analyses were performed in the Polish cohort, and multivariable Cox and logistic regression models were applied to the combined cohort. A HER2DX metastatic prognostic score was trained on overall survival (OS) in the Spanish cohort and validated in the Polish cohort. In the Polish cohort, high ERBB2 mRNA scores were associated with significantly longer real-world progression-free survival (rwPFS) (33.8 vs. 17.9 months; hazard ratio [HR] 0.57; $p = 0.022$) and real-world overall survival (rwOS) (75.1 vs. 40.2; HR 0.48; $p = 0.009$). In the combined cohort, ERBB2 high-score tumors showed prolonged rwPFS (33.8 vs. 12.5; HR 0.50; $p < 0.001$) and rwOS (not reached vs. 37.1; HR 0.36; $p < 0.001$), and higher rwORR (84.4% vs. 52.0%; $p < 0.001$). Prognostic value was independent of clinical variables, including number of metastatic sites. Subgroup analyses showed particularly favorable outcomes in patients with <3 sites (median rwPFS 51.7 vs. 20.3 months). The HER2DX metastatic prognostic score outperformed ERBB2 alone in the validation cohort. In conclusion, the HER2DX ERBB2 mRNA score provides independent prognostic information in HER2+ advanced breast cancer treated with THP. The HER2DX metastatic prognostic score further improves prognostic accuracy.

The treatment of advanced HER2-positive (HER2 + ) breast cancer has been transformed by HER2-targeted therapies[1–3]. The CLEOPATRA trial established trastuzumab, pertuzumab, and a taxane (THP) as the first-line standard, significantly improving progression-free survival (PFS) and overall survival (OS)[1]. Median outcomes with THP remain ~18–21 months for PFS and 57–65 months for OS[1]. Long-term follow-up also showed that nearly one-third of patients were progression-free at 3-years and one in six remained without progression at 8 years[1], underscoring that while a subset of patients derive durable benefit, many still experience early progression or limited benefit.

The therapeutic landscape in first-line is now evolving[3–5]. In the pre-specified interim analysis of the DESTINY-Breast09 trial (NCT04784715), trastuzumab deruxtecan (TDXd) plus pertuzumab reduced the risk of progression or death by 44% compared with THP, with median PFS

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extended from 26.9 to 40.7 months[4]. Similarly, the PATINA trial (NCT02947685) demonstrated that adding the CDK4/6 inhibitor palbociclib to maintenance endocrine therapy (ET) and dual HER2 blockade prolonged PFS by more than 15 months in hormone receptor-positive disease[5]. Other maintenance strategies are also being investigated, including selective estrogen receptor degraders such as giredestrant (heredERA BC, NCT05296798), the CNS-active HER2 tyrosine kinase inhibitor tucatinib (HER2CLIMB-05, NCT05132582), and the PI3Kα inhibitor inavolisib for PIK3CA-mutant tumors (INAVO122, NCT05646862). Together, these developments highlight the shift toward more personalized treatment strategies.

To date, efforts to identify prognostic factors in patients treated with THP have focused mainly on clinical features such as performance status, disease burden, and metastatic distribution, but these are insufficient to guide therapeutic decisions[6,7]. There is a critical need for biologically based biomarkers that can identify patients likely to derive durable benefit from THP and those who may require treatment intensification.

HER2DX is a clinically validated genomic assay initially developed in early-stage HER2+ breast cancer[8–19]. It integrates clinical features with a 27-gene panel encompassing four biological signatures: immune response, proliferation, luminal differentiation, and HER2 amplicon expression (including ERBB2 mRNA). The assay provides three outputs: a recurrence risk score, a pathological complete response (pCR) score, and an ERBB2 mRNA score, the latter offering a continuous measure of ERBB2 expression across breast cancer linked to HER2 protein levels. HER2DX scores have shown prognostic and predictive value in multiple (neo)adjuvant trials and have been validated in two large patient-level meta-analysis[10,11].

Building on this evidence, a Spanish real-world study of more than 90 patients treated with first-line THP showed that the HER2DX ERBB2 mRNA standardized score was strongly associated with clinical outcomes[20]. Patients with ERBB2-high scores had significantly longer real-world PFS (rwPFS) (33.9 vs. 10.6 months) and real-world OS (rwOS) (not reached vs. 30.8 months) compared with those in the ERBB2-low group, with hazard ratios of 0.40 and 0.26, respectively[20]. These findings underscored the potential of the HER2DX ERBB2 score as a clinically relevant prognostic biomarker in advanced HER2+ breast cancer.

Here, we extend this work by validating the score in an independent Polish cohort, assessing its performance in a combined Spanish–Polish dataset, and introducing an enhanced HER2DX metastatic prognostic score, trained on rwOS and designed to improve risk stratification in this setting.

## Results

### Patient characteristics

In the Polish cohort ($n = 122$, all females), the mean age was 59.2 years (range 36–85.7), 72.1% of patients presented with de novo metastatic disease, and 59% had hormone receptor-positive tumors. The real-world ORR (rwORR) was 68.9%. The median rwPFS was 28.4 months (95% CI 17.9–42.9), and the median rwOS was 51.1 months (95% CI 43.8–87.6). The median follow-up was 36.25 months (inter-quartile range [IQR] 22.4–51.0) in the Polish cohort and 34.23 months (IQR 19.5–52.2) in the combined cohort. Among the combined dataset ($n = 215$), 65.1% of tumor samples were obtained from metastatic sites ($n = 140$) and 34.9% from primary tumors ($n = 75$). The type of biopsy analyzed (metastatic vs. primary) was not associated with rwPFS (HR 0.86, 95% CI 0.59–1.26; $p = 0.429$) or rwOS (HR 0.94, 95% CI 0.61–1.46; $p = 0.797$). Baseline characteristics of the Polish, Spanish, and combined cohorts are summarized in Table 1. The median number of cycles of taxane chemotherapy was 7 (range 2–16), 6 (range 1–30) and 7 (range 1–30) in the Polish, Spain and combined cohorts, respectively. No significant differences were observed between the Polish and Spanish datasets in terms of HER2DX ERBB2 score distribution ($p = 0.573$), rwORR ($p = 0.168$), rwPFS ($p = 0.540$), or rwOS ($p = 0.950$) (Supplementary Figure 1), confirming consistency across cohorts.

### Validation of the HER2DX ERBB2 score in the Polish cohort

When stratifying patients into three ERBB2 mRNA groups, those in the high group showed significantly improved outcomes compared with the low group: median rwPFS 33.8 vs. 17.9 months (HR 0.53; 95% CI 0.30–0.94; $p = 0.030$) and median rwOS 75.1 vs. 40.2 months (HR 0.51; 95% CI 0.26–0.98; $p = 0.044$) (Fig. 1A, B). No statistical significance was found for rwPFS and rwOS between the low and medium group (HR 0.84; 95% CI 0.40–1.79; $p = 0.655$ for rwPFS and HR 1.10; 95% CI 0.50–2.42; $p = 0.807$ for rwOS), justifying their combination in further analyses. Therefore, when patients in the medium and low ERBB2 groups were combined, the high ERBB2 group continued to demonstrate longer survival: median rwPFS 33.8 vs. 17.9 months (HR 0.57; 95% CI 0.35–0.92; $p = 0.022$) and median rwOS 75.1 vs. 40.2 months (HR 0.48; 95% CI 0.28–0.83; $p = 0.009$) (Fig. 1C, D).

### Validation of the HER2DX ERBB2 Score in the combined cohort

In the combined cohort ($n = 215$), the prognostic value of the ERBB2 score was confirmed. Patients in the high ERBB2 group had significantly longer rwPFS (median 33.8 months, 95% CI 26.9–52.9) and rwOS (median not reached) compared with those in the medium/low group (median rwPFS 12.5 months, 95% CI 10.3–29.1; median rwOS 37.1 months, 95% CI 29.8–48.3), with HRs of 0.50 (95% CI 0.35–0.71; $p < 0.001$) for rwPFS and 0.36 (95% CI 0.23–0.54; $p < 0.001$) for rwOS (Fig. 2A–D).

In multivariable Cox analyses (Fig. 3A, B), the HER2DX ERBB2 score remained independently prognostic for both rwPFS (HR 0.78; 95% CI 0.65–0.95; $p = 0.011$) and rwOS (HR 0.78; 95% CI 0.64–0.96; $p = 0.020$). The number of metastatic sites was also independently associated with outcomes, with patients presenting with ≥3 sites showing worse rwPFS (HR 2.18; 95% CI 1.36–3.50; $p = 0.001$) and rwOS (HR 1.81; 95% CI 1.04–3.15; $p = 0.040$). In addition, the presence of brain metastases at baseline was independently associated with shorter rwOS (HR 2.27; 95% CI 1.11–4.65; $p = 0.02$). No other clinical covariates retained independent prognostic value, including HER2 IHC.

Finally, the rwORR was also significantly higher in the high ERBB2 group (84.4%) compared with the medium/low group (52.0%; $p < 0.001$). In multivariable analysis, the HER2DX ERBB2 score remained independently associated with rwORR, with the high group showing an odds ratio of 6.60 (95% CI 1.87–25.38; $p = 0.004$) compared with the low group (Supplemental Fig. 2).

### Association of HER2DX ERBB2 score with disease burden and clinical response

We next evaluated whether the prognostic effect of the HER2DX ERBB2 score was consistent across clinically relevant subgroups in the combined cohort. The ERBB2 score retained prognostic significance in patients with <3 metastatic sites (HR 0.44; 95% CI 0.27–0.72; $p < 0.001$), with a median rwPFS of 51.7 months in the high group compared with 20.3 months in the low/medium group (Fig. 4A). Similar results were obtained for rwOS (Fig. 4B).

Similarly, the HER2DX ERBB2 score was prognostic regardless of best overall response after THP. Among patients achieving partial or complete response, the high HER2DX ERBB2 group had improved rwPFS compared with the medium/low group (HR 0.56; 95% CI 0.35–0.89; $p = 0.015$), with a median rwPFS of 29.2 months versus 16.6 months, respectively (Fig. 4C). Similar results were obtained for rwOS (Fig. 4D).

### Validation of the HER2DX metastatic prognostic score

The HER2DX metastatic prognostic score was developed in the Spanish cohort by integrating three biological signatures, proliferation, luminal differentiation, and ERBB2 expression, while excluding the immune/IGG signature, which did not provide independent prognostic information (Fig. 5A). In the Polish dataset, the HER2DX ERBB2 score and the HER2DX metastatic prognostic score were moderately correlated (Fig. 5B), providing complementary, not fully overlapping, information and reflecting the

**Table 1 | Baseline Clinical and Pathological Characteristics of Patients in the Polish, Spanish, and Combined Cohorts**

| Median age (range) | Polish cohort (*n* = 122) | | Spanish cohort (*n* = 93) | | Combined cohort (*n* = 215) | |
|---|---|---|---|---|---|---|
| | 59.2 (36.0–85.7) | | 57.0 (30.0–87.0) | | 58.0 (30.0–87.0) | |
| Sex (*n*, %) | | | | | | |
| Female | 122 | 100 | 92 | 98.9 | 214 | 99.5 |
| Male | 0 | 0 | 1 | 1.1 | 1 | 0.5 |
| Menopausal status (*n*, %) | | | | | | |
| Premenopausal | 35 | 28.7 | 19 | 21.3 | 54 | 25.1 |
| Postmenopausal | 87 | 71.3 | 70 | 78.7 | 157 | 73.0 |
| Metastatic pattern (*n*, %) | | | | | | |
| Visceral disease | 52 | 42.6 | 68 | 73.1 | 120 | 55.8 |
| Brain metastasis | 1 | 0.8 | 12 | 12.9 | 13 | 6.0 |
| Bone-only disease | 26 | 21.3 | 15 | 16.1 | 41 | 19.1 |
| Metastatic burden (*n*, %) | | | | | | |
| <3 metastatic sites | 87 | 71.3 | 60 | 64.5 | 147 | 68.4 |
| ≥3 metastatic sites | 35 | 28.7 | 33 | 35.5 | 68 | 31.6 |
| Type of biopsy analyzed (*n*, %) | | | | | | |
| Primary | 14 | 11.5 | 61 | 65.6 | 75 | 34.9 |
| Metastatic | 108 | 88.5 | 32 | 34.4 | 140 | 65.1 |
| HER2 IHC status (*n*, %) | | | | | | |
| 3+ | 88 | 73.3 | 62 | 68.1 | 150 | 69.8 |
| other | 32 | 26.7 | 29 | 31.9 | 61 | 28.4 |
| Hormone receptor status (*n*, %) | | | | | | |
| Negative | 48 | 41 | 35 | 37.6 | 83 | 38.6 |
| Positive | 69 | 59 | 58 | 62.4 | 127 | 59.1 |
| Type of advanced disease (*n*, %) | | | | | | |
| De novo | 88 | 72.1 | 49 | 52.7 | 137 | 63.7 |
| Relapse | 34 | 27.9 | 44 | 47.3 | 78 | 36.3 |

biological contributions of the proliferation and luminal differentiation signatures. Among patients with HER2DX ERBB2-high tumors, 54% (75/138) were classified as HER2DX low metastatic risk, identifying a subgroup with particularly favorable prognosis. In contrast, nearly all patients with HER2DX ERBB2-low/medium tumors (94%, 72/77) fell into the HER2DX medium/high metastatic risk category.

When applied to the Polish cohort, the HER2DX metastatic prognostic score stratified patients into three groups with distinct survival outcomes. Median rwPFS was 42.9 months in the low-risk group, 38.3 months in the medium-risk group, and 11.6 months in the high-risk group. Median rwOS was not reached in the low-risk group, 75.1 months in the medium-risk group, and 36.8 months in the high-risk group (Fig. 5C, D). Compared with the low-risk group, patients in the high-risk group had significantly worse outcomes for both rwPFS (HR 2.58; 95% CI 1.46–4.55; $p = 0.001$) and rwOS (HR 3.77; 95% CI 1.95–7.30; $p < 0.001$).

In a bivariate Cox model including both the HER2DX ERBB2 score and the HER2DX metastatic prognostic score, the HER2DX metastatic prognostic score retained independent prognostic significance, while the ERBB2 score lost statistical significance for both rwPFS and rwOS. Likelihood ratio testing confirmed that HER2DX metastatic score added significant prognostic information beyond ERBB2 for rwOS ($\chi^2$=10.944, $p = 0.004$) and showed a trend for rwPFS ($\chi^2$=5.673, $p = 0.059$). In contrast, ERBB2 did not add prognostic value beyond HER2DX metastatic prognostic score for either rwOS ($\chi^2$=0.051, $p = 0.820$) or rwPFS ($\chi^2$=0.093, $p = 0.760$).

## Discussion

This study confirms and extends the prognostic relevance of HER2DX-derived genomic scores in HER2+ advanced breast cancer[8,10,20]. In an independent real-world Polish cohort, we validated the prognostic value of the HER2DX ERBB2 mRNA score previously observed in Spain[20]. In the combined dataset, the ERBB2 score retained independent prognostic significance for rwPFS, rwOS, and rwORR, even after adjusting for clinical variables. In addition, the HER2DX metastatic prognostic score, integrating *ERBB2* expression with luminal and proliferation signatures, provided superior risk discrimination and remained significant when ERBB2 alone did not.

The prognostic value of the HER2DX ERBB2 score in the metastatic setting has now been validated not only in two independent real-world cohorts but also in the pivotal CLEOPATRA phase III trial. In an exploratory analysis of 214 patients (53% of those randomized to first-line THP), presented at the 2024 SABCS annual meeting[21], ERBB2-high tumors were associated with significantly longer PFS (median 20.3 months) and OS (median 72.7 months) compared with ERBB2-low tumors (median PFS 10.4 months; median OS 40.3 months). Taken together, across the Spanish real-world cohort ($n = 93$), the Polish real-world cohort ($n = 122$), and the CLEOPATRA trial correlative analysis ($n = 214$), the HER2DX ERBB2 score has been consistently validated in a total of 429 patients treated with THP, reinforcing its robustness as a biomarker across both clinical trial and real-world settings.

Biologically, the interpretation of the ERBB2 mRNA score differs between early and metastatic disease. In early-stage HER2+ breast cancer, *ERBB2* expression is not prognostic and is not part of the HER2DX risk score[8], as outcomes are mainly determined by tumor stage, proliferation, immune activity, and luminal differentiation. In the metastatic setting, however, the ERBB2 score appears to capture a different signal. Indeed, the improved outcomes observed in the ERBB2-high group (longer rwPFS and rwOS and higher rwORR) likely reflect heightened therapeutic sensitivity to HER2 blockade rather than intrinsic favorable tumor biology. In contrast, the HER2DX metastatic prognostic score, although also developed in the context of THP, incorporates proliferation and luminal differentiation in addition *to ERBB2* expression, thereby providing a more balanced measure of intrinsic aggressiveness beyond HER2 dependence. Importantly, given that more than half of ERBB2-high tumors were classified as low HER2DX metastatic prognostic score, the latter score may be particularly valuable within the ERBB2-high subgroup to identify patients with exceptionally favorable long-term outcomes. Thus, while the ERBB2 score may primarily serve as a correlate of treatment sensitivity, HER2DX metastatic prognostic score offers complementary prognostic information rooted in tumor biology. Together, these scores highlight both treatment-linked and biologically driven determinants of outcome in metastatic HER2+ disease.

Beyond molecular biology, tumor burden remains a potent prognostic marker in our study. In particular, the number of metastatic sites independently predicted both rwPFS and rwOS, consisitent with reported data[22,23]. Within the subgroup of patients with fewer than three metastatic sites, *ERBB2* status further stratified long-term outcomes, although these results are exploratory and should be interpreted with caution due to small sample size. Patients with ERBB2-high tumors had excellent survival, with a median rwPFS of 52.7 months and rwOS not reached. Landmark outcomes were also favorable, with rwPFS rates of 88.9% at 1 year, 58.3% at 3 years, and 40.4% at 7 years, and rwOS rates of 96.7%, 82.5%, and 62.7% at the same timepoints. These findings highlight the complementary prognostic value of tumor burden and ERBB2 expression, underscoring their potential utility in refining expectations for long-term disease control. Of note, hormone receptor status was not prognostic, even in univariable analysis, consistent with previous findings from the CLEOPATRA trial[1] and highlighting that hormone receptor status expression alone by IHC offers limited prognostic information. Instead, the HER2DX luminal signature was prognostic, again demonstrating that genomic profiling better captures the endocrine sensitivity of a tumor than receptor status alone. Integrating genomic metrics

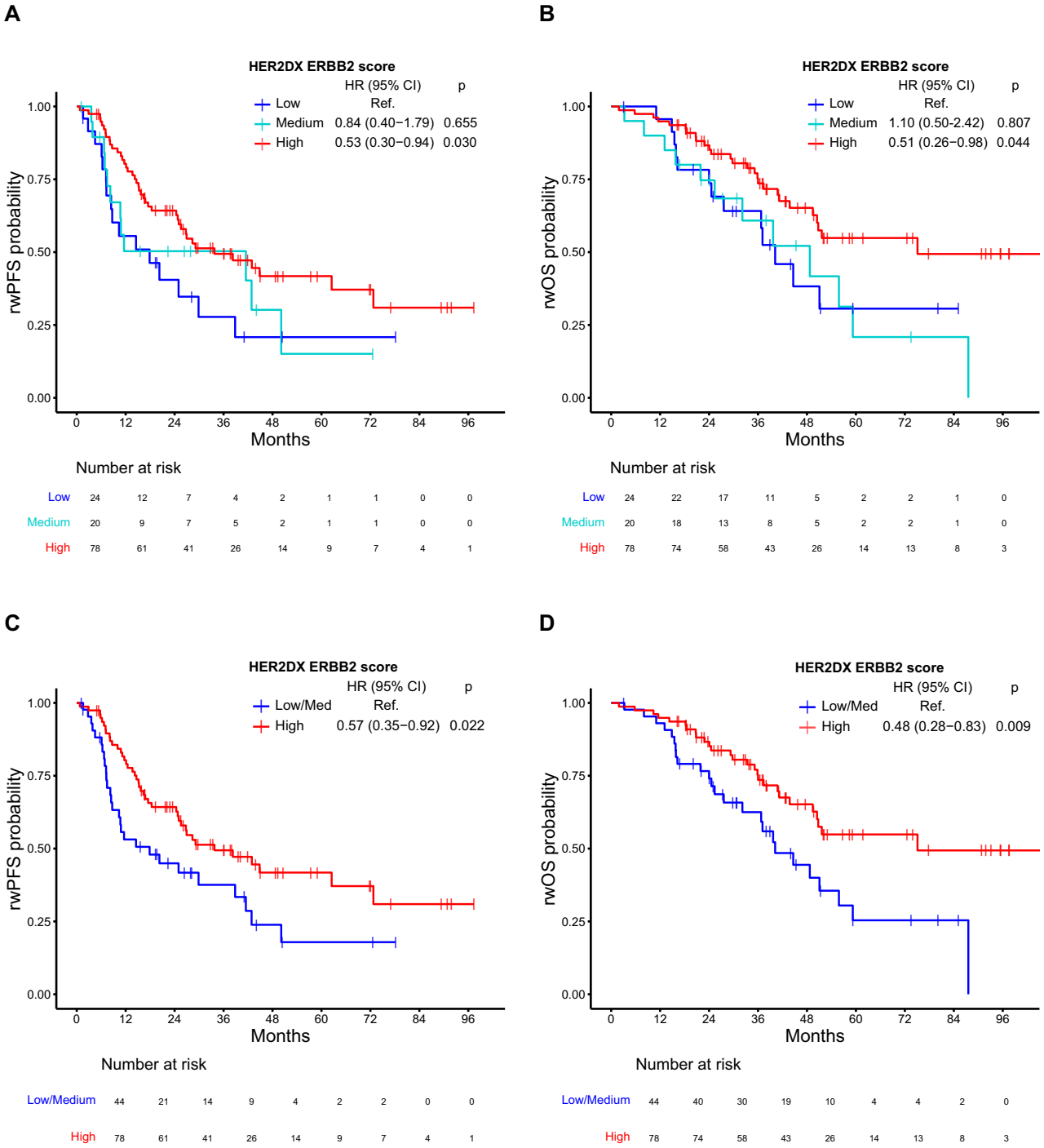


**Fig. 1 | Association of HER2DX ERBB2 mRNA score and outcomes in the Polish cohort. A** rwPFS by HER2DX ERBB2 mRNA score (low, medium, high). **B** rwOS by HER2DX ERBB2 mRNA score (low, medium, high). **C** rwPFS comparing HER2DX ERBB2-high versus low/medium groups. **D** rwOS comparing HER2DX ERBB2-high versus low/medium groups.

with disease burden therefore provides a more nuanced and clinically actionable risk framework.

The therapeutic landscape of HER2+ advanced breast cancer is evolving rapidly. Although THP has remained the backbone of first-line therapy for over a decade, TDXd combined with pertuzumab has recently demonstrated superior efficacy in the interim analysis of DESTINY-Breast09[4], including patients with hormone receptor-positive, who seemed to benefit from T-DXd[4]. However, follow-up remains relatively short, and OS results are still immature. In addition, results from the TDXd monotherapy arm have not yet been reported, and these will be essential to fully understand the incremental benefit of adding pertuzumab. For patients with fewer metastases and high ERBB2, the excellent survival observed with THP supports de-escalation approaches. This patient subgroup may be ideal candidates for standard THP or for novel sequences such as THP induction followed by maintenance with palbociclib, endocrine therapy, and continued HER2 blockade. If palbociclib becomes available for HER2 + /HR+ maintenance based on the PATINA trial results[5], a patient with HER2DX ERBB2-high and HER2DX metastatic prognostic low scores may also lean

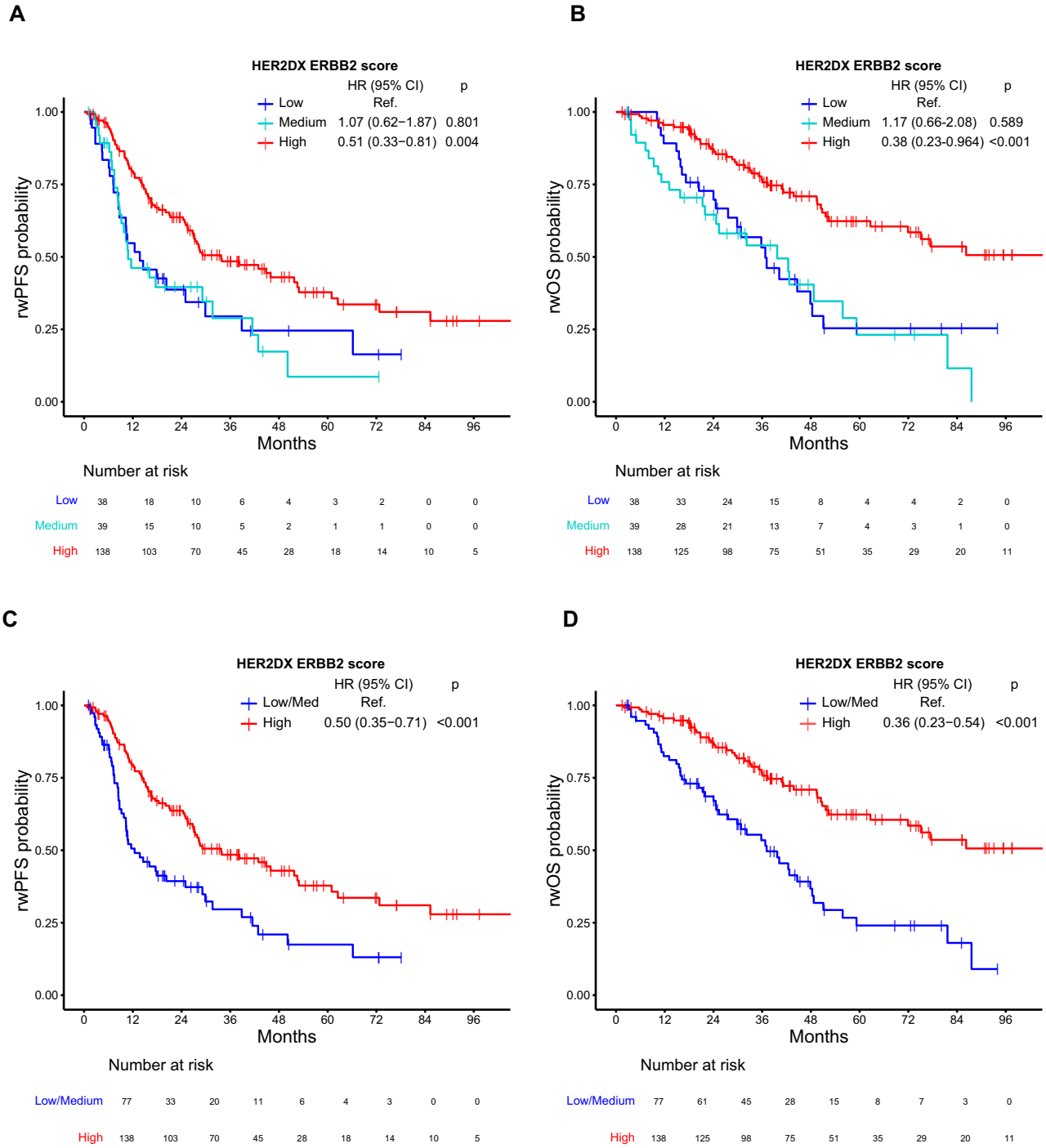


**Fig. 2 | Association of HER2DX ERBB2 mRNA score and outcomes in the combined cohort (Polish and Spanish). A** rwPFS by HER2DX ERBB2 mRNA score (low, medium, high). **B** rwOS by HER2DX ERBB2 mRNA score (low, medium, high). **C** rwPFS comparing HER2DX ERBB2-high versus low/medium groups. **D** rwOS comparing HER2DX ERBB2-high versus low/medium groups.

toward this maintenance strategy rather than upfront TDXd, balancing efficacy with long-term tolerability. Other options in ERBB2-high disease could be starting with short induction of TDXd followed by maintenance with trastuzumab and pertuzumab, potentially preserving effectiveness while mitigating toxicity. This approach is being explored in the ongoing Phase II DEMETHER trial (NCT06172127), which investigates six cycles of TDXd induction followed by maintenance with subcutaneous trastuzumab plus pertuzumab in HER2+ metastatic breast cancer. The trial aims to assess 1-year PFS and 3-year OS, offering a de-escalation strategy that aligns with our subgroup findings of durable outcomes under THP-based regimens.

Several limitations should be acknowledged. First, the retrospective nature of the analyses introduces potential sources of bias, and variability in clinical practice across centers may have influenced outcome assessments. While HER2DX testing was centralized and blinded, pathology evaluation was not uniformly standardized, which could have contributed to heterogeneity in baseline tumor characterization. The relatively limited number of patients in certain subgroups, such as those with brain metastases, also constrains the generalizability of subgroup analyses. Moreover, data on PIK3CA mutational status were not available, despite its recognized impact on

**A**

rwPFS

| Variable | | N | Hazard ratio | Univariate | p | Multivariable | p | | p |
|---|---|---|---|---|---|---|---|---|---|
| **HER2DX ERBB2 score (cont.)** | | 215 | | 0.83 (0.74, 0.92) | <0.001 | 0.78 (0.65, 0.95) | 0.011 | | |
| **HER2DX ERBB2 score (cat.)** | Low | 38 | | Reference | | | | Reference | |
| | Med | 39 | | 1.07 (0.62, 1.87) | 0.800 | | | 0.94 (0.48, 1.86) | |
| | High | 138 | | 0.51 (0.33, 0.81) | 0.004 | | | 0.44 (0.21, 0.90) | 0.02 |
| **HER2 IHC status** | 0/1+/2+ | 61 | | Reference | | Reference | | Reference | |
| | 3+ | 150 | | 0.67 (0.45, 0.99) | 0.044 | 1.56 (0.81, 2.99) | 0.183 | 1.45 (0.79, 2.68) | 0.23 |
| **HR status** | negative | 83 | | Reference | | | | | |
| | positive | 127 | | 0.95 (0.66, 1.36) | 0.776 | | | | |
| **Metastasis de novo** | 0 | 78 | | Reference | | | | | |
| | 1 | 137 | | 0.81 (0.56, 1.16) | 0.251 | | | | |
| **Bone only disease** | 0 | 135 | | Reference | | Reference | | Reference | |
| | 1 | 41 | | 0.45 (0.27, 0.77) | 0.003 | 0.52 (0.21, 1.26) | 0.146 | 0.52 (0.21, 1.27) | 0.15 |
| **Viseral disease** | 0 | 56 | | Reference | | Reference | | Reference | |
| | 1 | 120 | | 1.92 (1.22, 3.04) | 0.005 | 0.77 (0.34, 1.75) | 0.525 | 0.70 (0.31, 1.60) | 0.40 |
| **Brain metastasis** | 0 | 202 | | Reference | | Reference | | Reference | |
| | 1 | 13 | | 2.34 (1.28, 4.26) | 0.005 | 1.79 (0.94, 3.40) | 0.075 | 1.82 (0.96, 3.44) | 0.07 |
| **Number of metastatic sites** | <3 | 147 | | Reference | | Reference | | Reference | |
| | ≥3 | 68 | | 2.36 (1.65, 3.38) | <0.001 | 2.18 (1.36, 3.50) | 0.001 | 2.26 (1.41, 3.60) | <0.001 |
| **Number of taxane cycles** | | 209 | | 0.98 (0.95, 1.02) | 0.330 | | | | |

0.5 1 2

**B**

rwOS

| Variable | | N | Hazard ratio | Univariate | p | Multivariable | p | | p |
|---|---|---|---|---|---|---|---|---|---|
| **HER2DX ERBB2 score (cont.)** | | 215 | | 0.77 (0.68, 0.87) | <0.001 | 0.78 (0.64, 0.96) | 0.02 | | |
| **HER2DX ERBB2 score (cat.)** | Low | 38 | | Reference | | | | Reference | |
| | Med | 39 | | 1.17 (0.66, 2.07) | 0.59 | | | 1.23 (0.62, 2.44) | |
| | High | 138 | | 0.38 (0.23, 0.64) | <0.001 | | | 0.42 (0.19, 0.91) | 0.03 |
| **HER2 IHC status** | 0/1+/2+ | 61 | | Reference | | Reference | | Reference | |
| | 3+ | 150 | | 0.47 (0.31, 0.73) | <0.001 | 1.06 (0.52, 2.15) | 0.88 | 1.03 (0.54, 1.96) | 0.93 |
| **HR status** | negative | 83 | | Reference | | | | | |
| | positive | 127 | | 1.22 (0.78, 1.90) | 0.38 | | | | |
| **Metastasis de novo** | 0 | 78 | | Reference | | | | | |
| | 1 | 137 | | 0.78 (0.51, 1.19) | 0.25 | | | | |
| **Bone only disease** | 0 | 135 | | Reference | | | | | |
| | 1 | 41 | | 0.57 (0.31, 1.04) | 0.07 | | | | |
| **Viseral disease** | 0 | 56 | | Reference | | Reference | | Reference | |
| | 1 | 120 | | 1.78 (1.04, 3.07) | 0.04 | 1.19 (0.62, 2.26) | 0.60 | 1.11 (0.59, 2.11) | 0.74 |
| **Brain metastasis** | 0 | 202 | | Reference | | Reference | | Reference | |
| | 1 | 13 | | 2.32 (1.20, 4.49) | 0.01 | 2.27 (1.11, 4.65) | 0.02 | 2.33 (1.14, 4.76) | 0.02 |
| **Number of metastatic sites** | <3 | 147 | | Reference | | Reference | | Reference | |
| | ≥3 | 68 | | 2.10 (1.38, 3.18) | <0.001 | 1.81 (1.04, 3.15) | 0.04 | 1.92 (1.11, 3.31) | 0.02 |
| **Number of taxane cycles** | | 209 | | 0.99 (0.95, 1.03) | 0.53 | | | | |

0.5 1 2

**Fig. 3 | Univariable and multivariable analyses of rwPFS and rwOS in the combined cohort.** Forest plot of hazard ratios from Cox proportional hazards analyses for (**A**) PFS and (**B**) OS, including HER2DX ERBB2 mRNA score (continuous and categorical), HER2 IHC status, hormone receptor status, de novo versus relapsed disease, visceral involvement, bone-only disease, brain metastases, and number of metastatic sites.

outcomes in HER2+ metastatic disease[24], and subsequent lines of therapy were not consistently recorded, potentially confounding OS. Importantly, these results reflect historical treatment patterns, and it remains unknown how outcomes would evolve in the current standard-of-care sequence where TDXd follows THP in the second-line setting. It is reasonable to hypothesize, however, that patients with ERBB2-high tumors, already showing the best long-term outcomes with THP, would likely derive even greater OS benefit in this modern treatment paradigm. Additionally, the cohorts explored were not racially diverse. Finally, limitations regarding the reporting of rwORR are that scans timepoints were not standardized, and heterogeneity in terms of how local investigators assess response to therapy may exist. Despite these caveats, the reproducibility of the findings across three independent cohorts, coupled with the use of predefined HER2DX cutoffs, underscores the robustness of the test and its clinical relevance in THP-treated HER2+ advanced breast cancer.

Looking ahead, the next steps should focus on embedding HER2DX ERBB2 and HER2DX metastatic prognostic scores into ongoing and future prospective trials, particularly pivotal studies that are evaluating new HER2+ treatment strategies. These include regimens based on TDXd (with or without pertuzumab), CDK4/6 inhibitors such as palbociclib, ribociclib, and abemaciclib, novel SERDs, the PI3Kα inhibitor inavolisib, as well as emerging HER2 TKIs and next-generation ADCs. In this setting, HER2DX could serve as a stratification tool or exploratory biomarker to better define patient subgroups and refine risk-adapted therapeutic strategies.

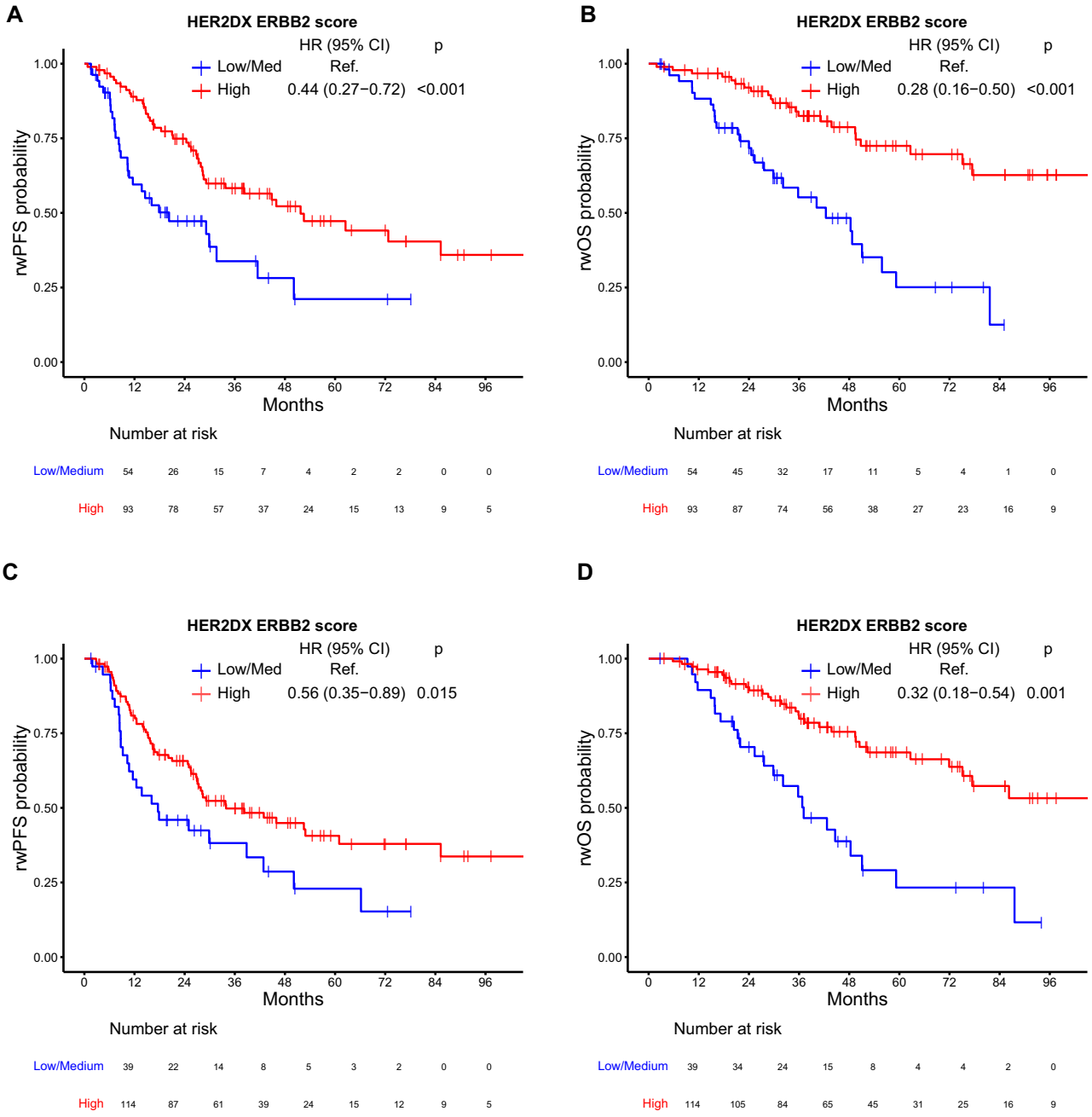


**Fig. 4 | Association of HER2DX ERBB2 mRNA score with outcomes by metastatic burden and treatment response in the combined cohort. A** rwPFS in patients with fewer than 3 metastatic sites. **B** rwOS in patients with fewer than 3 metastatic sites. **C** rwPFS in patients achieving partial or complete response as best response after THP, comparing HER2DX ERBB2-high versus low/medium groups. **D** rwOS in patients achieving partial or complete response after THP, comparing HER2DX ERBB2-high versus low/medium groups.

In conclusion, this study independently validates the prognostic role of the HER2DX ERBB2 mRNA score in advanced HER2+ breast cancer treated with first-line THP and introduces the HER2DX metastatic prognostic score as a potential enhanced model that provides superior risk stratification. These results extend the clinical utility of HER2DX into the metastatic setting and highlight its potential role in supporting treatment personalization in an era of rapidly expanding therapeutic options.

## Methods

### Study populations

We conducted a retrospective, two-cohort observational study of patients with advanced HER2+ breast cancer who received first-line treatment with trastuzumab, pertuzumab, and paclitaxel or docetaxel (THP). The Polish cohort comprised 122 consecutive patients treated between 2016 and 2025 at the Maria Sklodowska-Curie National Research Institute of Oncology (Gliwice, Poland). The Spanish cohort included 93 consecutive patients treated between 2010 and 2024 at the Clínic Barcelona Comprehensive Cancer Center and Hospital Universitario 12 de Octubre (Madrid, Spain). This cohort was previously published[20] and has been updated here with extended follow-up. The difference in the total number of patients compared with the previously published report (94 vs 93) was due to an updated normalization procedure. While the original analysis used only housekeeping genes, the new approach incorporates both negative and positive controls, which resulted in the exclusion of 3 cases but allowed the inclusion

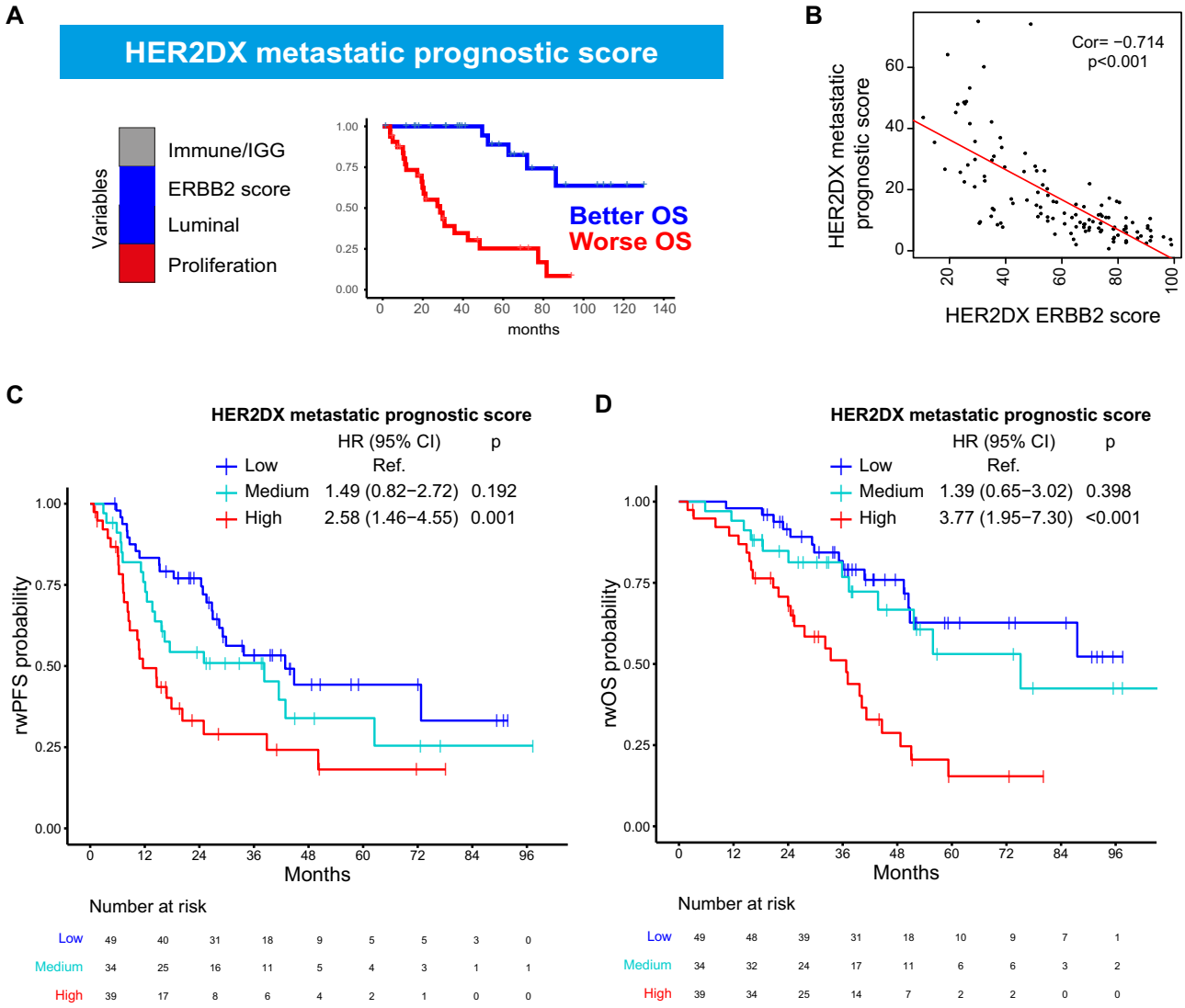


**Fig. 5 | Association of HER2DX metastatic prognostic score and outcomes in the combined cohort. A** Identification of biological drivers of the HER2DX metastatic prognostic score in the Spanish cohort using rwOS as the endpoint. The type of association between each variable and outcome is represented in colors: red = higher variable score associated with worse survival; blue = higher variable score associated with better survival; grey = no association. **B** Correlation between HER2DX metastatic prognostic score and HER2DX ERBB2 score in the Polish cohort. **C** Kaplan–Meier curve for rwPFS according to HER2DX metastatic prognostic score tertiles (low, medium, high; cutoffs derived from the Spanish cohort). **D** Kaplan–Meier curve for rwOS according to HER2DX metastatic prognostic score tertiles.

of 2 additional cases, yielding a final total of 93 patients. Both cohorts included patients with de novo or recurrent metastatic disease, locally advanced non-curable disease, and histologically confirmed HER2+ tumors, defined as IHC 3+ or IHC 2+ with confirmed ISH amplification. For both cohorts, demographic and clinicopathological data were extracted from electronic medical records.

### Clinical trial registry

Clinical trial number: not applicable

### HER2DX testing

Standardized HER2DX testing was performed in a central laboratory (Reveal Genomics) in Barcelona, Spain, under applicable In Vitro Diagnostic Regulation standards, and in all cases, blinded to clinical data. One formalin-fixed paraffin-embedded tumor sample per patient was analyzed; when available, a biopsy from the metastatic site obtained nearest in time to THP initiation was preferred. The HER2DX assay quantifies mRNA expression levels of 27 target genes and 5 housekeeping genes[8]. These 27 target genes are grouped into 4 distinct gene signatures: immune infiltration (*CD27, CD79A, HLA-C, IGJ, IGKC, IGL, IGLV3-25, IL2RG, CXCL8, LAX1, NTN3, PIM2, POU2AF1*, and *TNFRSF17*), tumor cell proliferation (*EXO1, ASPM, NEK2*, and *KIF23*), luminal differentiation (*BCL2, DNAJC12, AGR3, AFF3*, and *ESR1*), and HER2 amplicon expression (*ERBB2, GRB7, STARD3*, and *TCAP*)[8]. HER2DX has demonstrated high analytical reproducibility and stability across laboratories, sample types, and protocol variations, with strong concordance between nCounter and RNA-seq platforms[14]. Although validated in early-stage HER2-positive breast cancer, it has also shown consistent performance in metastatic and previously treated samples[20,25].

### HER2DX ERBB2 score

The HER2DX ERBB2 score was calculated based on ERBB2 mRNA levels[8,9]. Predefined cutoffs, established in prior validation studies, were used to

classify the scores as low(1–32), medium (33–50), or high (51–99). The assay quantifies ERBB2 mRNA expression as a continuous score ranging from 1 to 99. These categories were designed to align with clinical HER2 status, as defined by ASCO/CAP guidelines, and reflect progressively higher levels of HER2 protein expression. The cut-off at 33, which distinguishes HER2DX ERBB2-low from ERBB2-medium/high, is associated with clinical HER2-negative versus HER2-positive status[8,9]. The cut-off that distinguishes ERBB2-med from ERBB2-high (i.e. 51) corresponds to the upper 33% of HER2DX ERBB2 expression levels in HER2-positive breast cancer[8,9]. In this study, these thresholds were applied for stratification.

### HER2DX metastatic prognostic score

An new prognostic model, the HER2DX metastatic prognostic score, was developed to enhance prognostic assessment in metastatic breast cancer. This score integrates the HER2DX ERBB2 score with additional molecular features, including luminal and proliferation gene expression signatures. The model was trained exclusively on data from the Spanish cohort, with the objective of evaluating its association with OS. Based on the coefficients derived from the trained survival model, a continuous prognostic score was calculated and normalized using min–max scaling. A categorical version of the score was then created by dividing the distribution into tertiles within the Spanish cohort. These tertile-based cutoffs were subsequently applied to the Polish cohort to test generalizability. For the continuous score, normalization in the Polish cohort used the minimum and maximum values from the Spanish cohort, ensuring a fixed range from 1 to 99.

To assess the stability of the model coefficients, the Spanish cohort was randomly split into two subsets (66.7% training and 33.3% testing). In each iteration, the model was fitted to the training set and the coefficients were recorded; the same procedure was then applied to the testing set. This process was repeated 10,000 times, and coefficients from both training and testing sets were compared using Cliff's delta to evaluate effect size and absolute difference to quantify discrepancies.

HER2DX scores are represented in Supplementary Fig. 3 for clarity.

### Study objectives

The primary objective of the study was to validate the prognostic value of the HER2DX ERBB2 score for real-world PFS (rwPFS) and real-world OS (rwOS) in the Polish cohort. The secondary objective was to evaluate the prognostic impact of the ERBB2 score in the combined Spanish + Polish cohort ($n = 215$), using multivariable analyses. A third exploratory objective was to develop and test the HER2DX metastatic prognostic score trained in the Spanish cohort and validated in the Polish cohort.

### Endpoints

rwPFS was defined as the time from initiation of THP to disease progression or death, whichever occurred first. rwOS was defined as the time from initiation of THP to death from any cause. Best overall response (BOR), assessed by investigators according to local practice, was recorded as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). For the purpose of this analysis, real-world objective response rate (rwORR) was defined as the proportion of patients achieving CR or PR, while SD and PD were considered non-response. Of note, these were investigator-assessed endpoints in a real-world setting.

### Statistical analysis

In the Polish cohort, univariable Cox proportional hazards models were used to test the association of the HER2DX ERBB2 score with rwPFS and rwOS. In the combined cohort, multivariable Cox models were applied for rwPFS and rwOS, adjusting for baseline covariates including HER2 IHC status (3+ vs other), HR status (positive vs negative), de novo versus recurrent disease, bone-only disease (yes vs no), visceral disease (yes vs no), brain metastasis (yes vs no), and number of metastatic sites ( < 3 vs ≥3). Logistic regression models were used to assess associations with rwORR. Both the ERBB2 score and the HER2DX metastatic prognostic score were evaluated as continuous and categorical variables. Analyses were performed in R software environment (version 4.2.2), with two-sided $p$ values < 0.05 considered significant.

### Ethics approval

The study was performed according to the Declaration of Helsinki and relevant national regulations. The study was approved by the ethics committee at Hospital Clinic of Barcelona (HCB/2022/0269). Informed written consent was obtained from each subject. All patient data were pseudonymized at the source in compliance with applicable data protection regulations. HER2DX testing was conducted under formal data-sharing agreements between institutions and Reveal Genomics.

## Data availability

The datasets analyzed during the current study are not publicly available as participants of this study did not agree for their data to be shared publicly. However, data can be made available from the corresponding author on reasonable request under a data transfer agreement and upon Ethics Committee approval.

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## Author contributions

M.K., A.P. and F.B-M. designed the study. M.K., S.C., R.S-B., B.P, J.S., E.Ch., E.S., M.R., F.P., A.A., O.C., A.L., M.O-W., E.Ca., B.A., M.V., M.B., J.M., G.V., L.P., P.V., E.Ci., M.J., A.P. and F.B-M. contributed to data collection and assembly, wrote and reviewed the article, and approved the final version for submission.

## Competing interests

Potential conflicts of interest are the following: M.K. reports advisory board for Novartis; speaker's honoraria from Novartis, Roche, MSD, Pfizer, Lilly, Teva, Amgen, Swixx Biopharma, Gilead, and AstraZeneca; clinical trials for Roche, MSD, Novartis, Seagen, and Gilead; conference fees for Pfizer, Roche, Novartis, Teva, Amgen, Gilead, MSD, Swixx Biopharma, and AstraZeneca; all outside the submitted work. M.J. reports conference fees for Gilead, Roche; clinical trials for Roche, MSD, Novartis, Seagen, and Gilead; speaker's honoraria from Novartis, Roche, Lilly, Pfizer, Teva, Exact Sciences, Mammotome, and Gilead; advisory boards for Novartis and Pfizer; all outside the submitted work. A.P. reports advisory and consulting fees from AstraZeneca, Roche, Pfizer, Novartis, Daiichi Sankyo, Ona Therapeutics, and Peptomyc, lecture fees from AstraZeneca, Roche, Novartis, and Daiichi Sankyo, institutional financial interests from AstraZeneca, Novartis, Roche, and Daiichi Sankyo; stockholder and employee of Reveal Genomics; patents filed PCT/EP2016/080056, PCT/EP2022/086493, PCT/EP2023/060810, PCT/EP2024/068197 and EP23383369; editor of NPJ Breast Cancer journal. F.B-M. reports part-time employment from Reveal Genomics and has patents filed: PCT/EP2022/086493, PCT/EP2023/060810,PCT/EP2024/068197, and EP23383369B. MBS declares Advisor o consulting fees from Pfizer, Novartis, Lilly and Astra Zeneca and travel expenses from Pfizer, Lilly, Novartis, Astra Zeneca and Gilead. R.S.-B. reports advisory/consulting/speaker fees from Roche, AstraZeneca, Novartis, Lilly, Daiichi Sankyo, Pfizer, Eisai, GlaxoSmithKline, Reveal Genomics, and Gilead; travel expenses from Pfizer, AstraZeneca, Gilead, Novartis, and Roche. E.S. reports Advisory Board and speaker honoraria of Sysmex and Astra Zenica; and consultant of Reveal Genomics INC. A.L. reports conference fees: Accord, Novartis, clinical studies: Roche, MSD, Novartis; speaker's honorarium: Novartis; all outside the submitted work.

## Additional information

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