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Clinical characterization, prognostic, and predictive values of HER2-low in patients with early breast cancer in the PALLAS trial (ABCSG-42/AFT-05/BIG-14–13/PrE0109)

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Abstract

Background Bidirectional crosstalk between HER2 and estrogen receptor (ER) pathways may influence outcomes and the efficacy of endocrine therapy (ET). Low HER2 expression levels (HER2-low) have emerged as a predictive biomarker in patients with breast cancer (BC).

Methods PALLAS is an open, international, phase 3 study evaluating the addition of palbociclib for 2 years to adjuvant ET in patients with stage II-III ER-positive/HER2-negative BC. To assess the impact of HER2 expression on patient outcomes in the phase III PALLAS trial, we analyzed (1) the association between rate of HER2-low with demographic and clinicopathological parameters, (2) the prognostic value of HER2-low status on invasive disease-free survival (iDFS), distant relapse-free survival (DRFS), and overall survival (OS) and (3) HER2 expression's value as a predictive biomarker of response to palbociclib. HER2-low was defined as HER2 immunohistochemistry (IHC) 1 + or IHC 2 + with negative in situ hybridization (ISH). All pathologic evaluation was performed locally. Prognostic and predictive power of HER2 were assessed with Cox models.

Results From the original PALLAS intention-to-treat population (N = 5753), 5304 patients (92.2%) were included in this analysis. Among these, 2254 patients (42.5%) were classified as having HER2 IHC 0 (HER2-0), and 3050 (57.5%) as having HER2-low disease (1838 with IHC 1 + and 1212 with IHC 2 +). Median follow-up was 59.8 months. HER2-low prevalence varied significantly across 21 participating countries (range 16.7% to 75.6%; $p < 0.001$) and was more frequent in patients enrolled in North America (63.1%) than in Europe (53.4%) or other regions (53.4%) ($p < 0.001$). HER2

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status was not significantly associated with iDFS in a multivariable Cox model (hazard ratio 0.93, 95% confidence interval 0.81 – 1.06). No significant interaction was observed between treatment arm and HER2 status for iDFS (p = 0.43). Similar results were obtained for DRFS and OS.

Conclusions In this large, prospective, global patient cohort, no differences were observed in clinical parameters, prognosis, or differential benefit from palbociclib between HER2-0 and HER2-low tumors. Significant geographic variability was observed in the prevalence of HER2-low status, suggesting a high degree of variation in pathologic assessment of HER2 expression without impact on outcomes.

Keywords Breast cancer, HER2-low, Palbociclib, Endocrine therapy, Antibody–drug conjugates

Introduction

Endocrine therapy (ET) is the mainstay of adjuvant systemic treatment for patients with estrogen receptor-positive (ER+) and human epidermal growth factor receptor 2-negative (HER2-) early breast cancer. [1] Over the past decades, significant benefits have been demonstrated with the use of tamoxifen, aromatase inhibitors and ovarian function suppression for five to ten years after local treatment. [2] More recently, the addition of a new class of drugs (CDK4/6 inhibitors, CDK4/6i) to ET has led to improvements in progression-free survival and overall survival in the metastatic setting, prompting the investigation of the role of these agents in the early setting. [3–5] In this context, the global phase III PALLAS study assessed whether the addition of 2 years of the CDK4/6i palbociclib to adjuvant ET would reduce the risk of invasive relapse in patients with stage II-III ER+/HER2- breast cancer. [6] Overall, the results of the study showed no difference in disease outcomes with the addition of palbociclib. [6] However, with the results of other adjuvant studies showing benefits from the addition of CDK4/6i [7, 8], the combination of CDK4/6i with ET is now considered a standard treatment approach in both early and advanced settings. [9–11] Although CDK4/6i are associated with toxicities, and primary or secondary resistance to these agents may occur, no predictive biomarkers of response have been validated for clinical use.

Crosstalk between estrogen receptor (ER) and HER2 pathways has been implicated in treatment resistance to both ET and HER2-targeted therapies. [12, 13] HER2 has been shown to promote ligand-independent ER activation through tyrosine kinase domain phosphorylation and both ER and HER2 can activate the MAPK/PI3K/AKT signalling through distinct mechanisms. [12, 14] ER, via its non-genomic signalling pathway, can phosphorylate key components of this pathway, while HER2, through homo- or heterodimerization, leads to phosphorylation of its cytoplasmic tyrosine kinase domain, triggering the MAPK/PI3K/AKT activation. [12, 14] Bidirectional signaling between ER and HER2 can lead to loss of sensitivity to ET via downstream phosphatidylinositol 3-kinase (PI3K) and RAS pathways and/or downregulation of ER expression. [15, 16] Preclinical evidence suggests that combined endocrine and anti-HER2 therapies improve clinical outcomes in patients with ER-positive, HER2-positive disease. [17, 18] Indeed, CDK4/6i have been shown to restore sensitivity to anti-HER2 therapy by suppressing Rb and TSC2 phosphorylation, thus attenuating mTOR complex 1 (mTORC1) activity. [19] In line with these findings, early clinical studies suggest synergistic activity from the addition of CDK4/6i to ET and anti-HER2 therapy. [20–22] This strategy is currently being prospectively tested in a confirmatory randomized trial. [23] The interaction between HER2-targeted therapies and CDK4/6i observed in HER2-positive disease has also been shown to be relevant in cancers with low levels of HER2 expression (HER2-low). In in vitro models derived from ER-positive tumors, the combination of palbociclib, fulvestrant, trastuzumab and pertuzumab demonstrated synergy in both HER2-positive and HER2-low cell lines. [24].

Although the efficacy of anti-HER2 therapies was traditionally restricted to tumors with HER2 amplification / overexpression [25], new generation antibody–drug conjugates (ADCs) have demonstrated activity in patients with HER2-low disease. [26–28] Indeed, trastuzumab deruxtecan (T-DXd), a HER2-targeted ADC, is currently approved for the treatment of patients with advanced HER2-low breast cancer [29, 30] and ongoing studies employ HER2-low status as an inclusion criterion. [31] Interestingly, while in patients with HER2-positive (HER2+) disease the expression of HER2 and ER are inversely related, HER2-low expression has been shown to be positively associated with ER expression. [32, 33] Therefore, in view of the intricate crosstalk between the HER2 and ER pathways, we hypothesized that HER2-low status could influence the response to CDK4/6 blockade in patients with ER+ early breast cancer in the PALLAS trial.

Methods

Study and patients

PALLAS (AFT-05/ABCSG-42/BIG-14–03, PrE0109, ClinicalTrials.gov identifier: NCT02513394, EudraCT

2014–005181-30) is an open-label, international, phase 3 study that enrolled patients with stage II–III ER + / HER2- breast cancer who were randomized to receive adjuvant ET for at least five years either alone, or in combination with palbociclib 125 mg once daily (three weeks on and one week off) for two years. All enrolled patients provided written informed consent, and the trial was approved by institutional review boards and ethics committees and carried out in accordance with the Declaration of Helsinki. Further details regarding study design and results are available in the original publication. [6] Overall, no invasive disease-free survival benefit was observed from the addition of palbociclib to ET. [6].

HER2 assessment was performed locally according to institutional guidelines, in a Clinical Laboratory Improvement Amendments (CLIA)-approved setting in the United States or a certified laboratory in other countries. In patients treated with neoadjuvant systemic therapy, HER2 status was obtained from the baseline core biopsy (prior to neoadjuvant therapy) whenever available. In the case of upfront surgery, the postoperative tissue result was used for HER2 status. HER2-low was defined as HER2 immunohistochemistry (IHC) 1 + or IHC 2 + with negative in situ hybridization. Only patients with HER2-0 and HER2-low breast cancer were included in this analysis; those with HER2 + breast cancer or missing HER2 status were excluded. ER and progesterone receptor (PR) IHC assessments were also performed locally and are reported as the percentage of positive cells.

Objectives and endpoints

The aims of this analysis were [1] to assess the association between low levels of HER2 expression with demographic and clinicopathological parameters, [2] to test the prognostic value of HER2-low status on invasive disease-free survival (IDFS), distant relapse-free survival (DRFS), and overall survival (OS) and [3] to assess the value of HER2 expression as a predictive biomarker of response to palbociclib.

The endpoints were defined as in the original trial and based on the STEEP definitions. [6, 34] IDFS was defined as the time from randomization to the date of the first event: local or regional invasive ipsilateral recurrence, contralateral invasive breast cancer, distant recurrence, second primary invasive cancer of non-breast origin, or death from any cause. DRFS was defined as the time from randomization to the date of the first event, distant recurrence, or death from any cause. OS was defined as the period between randomization and death from any cause.

Statistical considerations

Association of HER2 status with other baseline covariates was tested with Chi-squared tests. Analyses were performed considering two (HER2-0 vs. HER2-low) or three (HER2-0 vs. HER2 1 + vs HER2 2 +) comparison groups. Prognostic power of HER2 was assessed with uni- and multivariable Cox proportional hazards models. Multivariable models included age, T-stage, N-stage, grade, and PR expression. The predictive value of HER2 status for palbociclib benefit was tested with Cox models using an interaction term (hazard ratio is a relative scale measure) as well as on the absolute scale with 5-year Kaplan Meier estimate differences between arms. The proportional hazards assumption was tested using the weighted Schoenfeld residuals. No strong violations were observed. Hazard ratios (HR) and 95% confidence intervals (CI) are reported. For the absolute 5-year differences the 95% CIs were derived via non-parametric bootstrapping (percentile method). Tests with p-values < 0.05 were considered statistically significant. For this PALLAS analysis the 5-year median follow-up data set was used (i.e., all data up to May 30th, 2023). Analyses were performed with SAS 9.4 (SAS Institute Inc, Cary, NC).

Results

From the original PALLAS intention-to-treat population (N = 5753), 5304 patients (92.2%) were included in this analysis. Fourteen patients (0.2%) were excluded due to HER2 positivity (either IHC 3 + or in situ hybridization (ISH) positive/amplified), 435 (7.6%) due to missing/unknown HER2 status. Among the patients included, 2254 (42.5%) were classified as HER2 IHC 0 (HER2-0) and 3050 (57.5%) as HER2-low (1838 with IHC 1 + and 1212 with IHC 2 + with negative in situ hybridization). For this analysis, median follow-up was 59.8 months.

Association of HER2-low status with demographic and clinicopathological characteristics

Compared to HER2-0, patients with HER2-low tumors had minimally higher ER expression levels (mean expression 88.9% vs. 87.9%, p = 0.023), and body mass index (BMI) (mean BMI 27.9 vs. 27.7 kg/m^2, p = 0.047) (Table 1). HER2-low status varied significantly across 21 participating countries, ranging from 16.7% in Mexico to 75.6% in Japan (p < 0.001) and was more frequent in patients enrolled in North America (63.1%) than in Europe (53.4%) and other regions (53.4%) (p < 0.001) (Fig. 1). Among all participating countries, Austria had HER2-low prevalence (57.4%) closest to the overall population (57.5%). We therefore studied the national heterogeneity of HER2 expression in this particular country. Significant heterogeneity in HER2-low expression was

Table 1 Association of HER2-low status with demographic and clinicopathological characteristics

Characteristic	HER2 0N = 2254	HER2 lowN = 3050	p-value
Anatomic stage			0.308
I/IIA	393 (17.4%)	565 (18.5%)	
IIB/III	1861 (82.6%)	2485 (81.5%)	
T-stage			0.926
T0/T1/Tis/TX	424 (18.8%)	561 (18.4%)	
T2	1264 (56.1%)	1717 (56.3%)	
T3/T4	566 (25.1%)	772 (25.3%)	
N-stage			0.318
N0	276 (12.2%)	422 (13.8%)	
N1	1109 (49.2%)	1498 (49.1%)	
N2	554 (24.6%)	731 (24.0%)	
N3	315 (14.0%)	398 (13.0%)	
Missing	0	1 (0.0%)	
Histological grade			0. 890
Grade 1	234 (10.4%)	331 (10.9%)	
Grade 2	1292 (57.3%)	1721 (56.4%)	
Grade 3	627 (27.8%)	854 (28.0%)	
Grade X/Missing	101 (4.5%)	144 (4.7%)	
Age at randomization (years)			0.785
Mean (SD)	53.1 (10.8)	53.0 (11.1)	
Min—Max	26.0 to 90.0	22.0 to 86.0	
Menopausal status at randomization			0.660
Postmenopausal	1209 (53.6%)	1635 (53.6%)	
Pre-/Perimenopausal	1032 (45.8%)	1391 (45.6%)	
Male/Missing	13 (0.6%)	24 (0.8%)	
Baseline ECOG-PS			0.161
0	1917 (85.0%)	2536 (83.1%)	
1/unknown	335 (14.9%)	512 (16.8%)	
Missing	2 (0.1%)	2 (0.1%)	
BMI at randomization			0.047
N	2222	3025	
Mean (SD)	27.7 (6.1)	27.9 (6.1)	
Min—Max	15.6 to 65.6	15.8 to 56.4	
ER positive cells (%)			0.023
N	1987	2726	
Mean (SD)	87.9 (17.3)	88.9 (17.0)	
Min—Max	0.0 to 100.0	0.0 to 100.0	
PR positive cells (%)			0.094
N	2007	2766	
Mean (SD)	59.7 (37.6)	58.3 (37.1)	
Min—Max	0.0 to 100.0	0.0 to 100.0	
Primary surgery type			0.188
Breast-conserving surgery	892 (39.6%)	1138 (37.3%)	
Mastectomy	1359 (60.3%)	1905 (62.5%)	
Both	3 (0.1%)	7 (0.2%)	
Prior radiation			0.552
No	241 (10.7%)	342 (11.2%)	
Yes	2012 (89.3%)	2708 (88.8%)	
Missing	1 (0.0%)	0	
Prior chemotherapy			0.063
No	422 (18.7%)	511 (16.8%)	
Yes	1832 (81.3%)	2539 (83.2%)	

Table 1 (continued)

SD standard deviation, *ECOG-PS* Eastern Cooperative Oncology Group Performance Status, *BMI* body mass index, *ER* estrogen receptor, *PR* progesterone receptor. *P* values are from Chi-square tests excluding the missing category

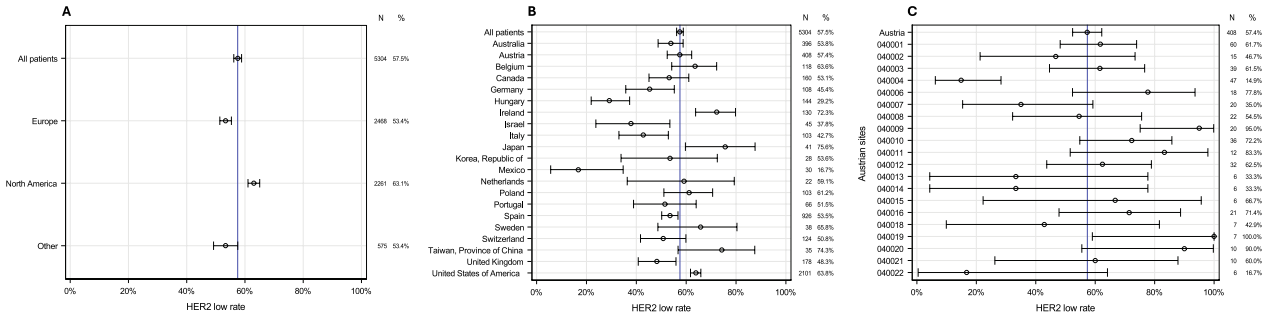

Fig. 1 HER2-low rates by continent (A), by country (B), and by site within a country (Austria, C). Abbreviation: *HER2*, human epidermal growth factor receptor 2

Table 2 Prognostic value of HER2 status (HER2-low vs. HER2-0)

		5-year survival	Unadjusted HR (CI)	Adjusted HR (CI)[a]
IDFS	HER2-0	82.1%	0.92 (0.80 – 1.05)	0.93 (0.81 – 1.06)
	HER2-low	83.5%		
DRFS	HER2-0	85.5%	0.94 (0.81 – 1.10)	0.96 (0.82 – 1.12)
	HER2-low	86.5%		
OS	HER2-0	92.5%	0.94 (0.76 – 1.16)	0.96 (0.78 – 1.18)
	HER2-low	92.9%		

HR hazard ratio, *CI* confidence interval, *IDFS* invasive disease-free survival, *DRFS* distant relapse-free survival, *OS* overall survival. [a]Adjusted for age, T-stage, N-stage, grade, and progesterone receptor status

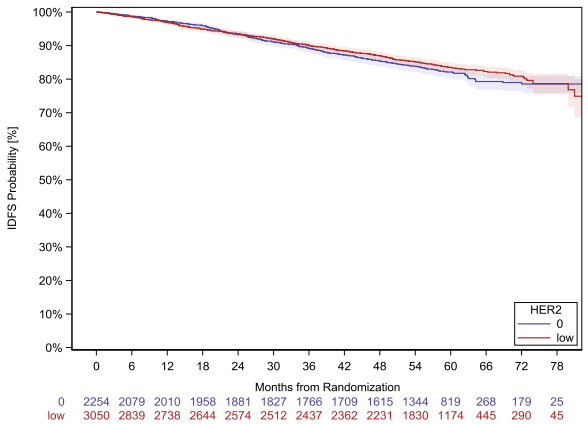

Fig. 2 Invasive disease-free survival according to HER2 status. Abbreviation: *HER2*, human epidermal growth factor receptor 2

demonstrated across 20 Austrian sites, ranging from 14.9% to 100.0% (Fig. 1). No differences in HER2 expression were observed according to age, menopausal status, baseline performance status, anatomic stage, T-stage, N-stage, histological grade, PR, primary surgery type, prior radiation, or prior chemotherapy.

Prognostic value of HER2-low status

Univariable and multivariable models were performed to assess whether HER2 expression was associated with differences in long-term outcomes among patients enrolled in PALLAS. In univariable analyses, HER2-low status was not associated with differences in iDFS (HR 0.92, 95%CI 0.80 – 1.05), DRFS (HR 0.94, 95%CI 0.81 – 1.10), or OS (HR 0.94, 95%CI 0.76 – 1.16) (Table 2**,** Figs. 2**,** Additional File 1**: Supplementary Figs. 1 and 2**).

Consistent with the univariable analysis, in multivariable Cox regression model adjusted for age, T-stage, N-stage, grade and PR, there were no statistically significant differences in iDFS (HR 0.93, 95%CI 0.81 – 1.06), DRFS (HR 0.96, 95%CI 0.82 – 1.12), or OS (HR 0.96, 95%CI 0.78 – 1.18) according to HER2-low status. Similar results were obtained when HER2-0 was compared to HER2 1 + and HER2 2 + separately (Additional File 1**: Supplementary Table 1**).

HER2-low expression as a predictive biomarker of palbociclib benefit

No significant interaction between the HER2 status and the relative benefit to palbociclib was identified for iDFS, DRFS or OS. Similar results were seen for absolute treatment benefit. Absolute effect sizes were similar between HER2-0 and HER2-low patients with mainly overlapping 95% confidence intervals (Fig. 3**; Additional File: Supplementary Table 2 and Supplementary Figs. 3 and 4**). Similar results were obtained when HER2-0 was compared to HER2 1 + and HER2 2 + separately (**Additional File: Supplementary Table 2**).

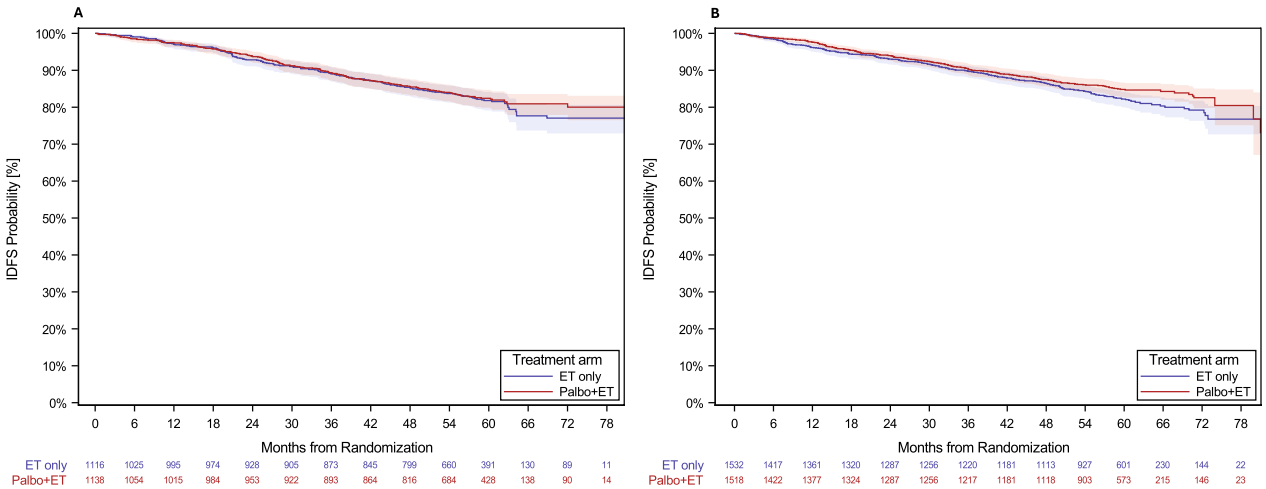

Fig. 3 Invasive disease-free survival probability according to treatment arm in patients with HER2-0 (A) and HER2-low (B) tumor. Abbreviation: *HER2*, human epidermal growth factor receptor 2

Discussion

In this study, we evaluated the distribution and impact of HER2-low expression in patients with ER + early breast cancer enrolled in a large, prospective, randomized, and international trial. Marked regional heterogeneity in the HER2-low rate was demonstrated both across countries and within national sites. HER2-low expression was not associated with significant prognostic impact in this population or with differential benefit from palbociclib.

The significant geographic variability observed in the prevalence of HER2-low status in our analysis was initially identified at the continental level, with patients enrolled in North America having approximately 10% higher HER2-low rates compared to Europe and other regions. To further investigate this finding, we compared the prevalence of HER2-low status among different countries and, subsequently, across different sites within a single country. In all these levels, significant differences in HER2-low rates were observed. This discrepancy is particularly relevant considering that HER2-low status is currently used as an actionable biomarker to select patients for treatment with the ADC trastuzumab deruxtecan (T-DXd) in the metastatic setting. [29, 30] This ADC was approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) based on the results of the DESTINY-Breast04 study, in which T-DXd was superior to investigator's choice therapy in patients with HER2-low metastatic breast cancer. [26, 29, 30] Notably, the recruitment period in PALLAS (2015–2018) preceded the presentation of the results of the pivotal studies demonstrating the benefit of T-DXd in the HER2-low population. [26] Whether the regional discrepancies found were due to a real biological difference in HER2 expression among patients randomized in different regions, differences in HER2 assessment methods, variations in reporting standards across sites, or a spurious finding remains to be determined. Indeed, other studies have shown high inter-observer variability in the assessment of HER2-low status, which likely reflects the original purpose of the available assays to differentiate the presence or absence of HER2 overexpression / amplification, and not to differentiate HER2-low from HER2-0. [35–37] Several assays are currently approved for HER2 assessment, including Pathway 4B5, HercepTest pAb (Autostainer, SK001) and HercepTest mAb pharmDx, and it has been shown that these methodologies differentially identify HER2-low status when directly compared. [35, 36] Geographical differences in the prevalence of HER2 and ER positivity in breast cancer within the same country have been described and were partially attributed to regional variability in racial/ethnic composition. [38, 39] In the specific case of HER2-low, a large retrospective cohort including data from over one million patients in the United States demonstrated significant variations in the prevalence of HER2-low status across participating sites (lower rates were seen at academic centers). [38] In that cohort, variations in the HER2-low rate were also observed according to age, race/ethnicity, ER expression, grade, and histological type. [37] At the individual level, a rapid autopsy study that included patients with HER2-negative primary breast cancer demonstrated that HER2-0 and HER2-low metastases coexisted in approximately 80% of patients. [40] Furthermore, significant intra-organ heterogeneity in HER2-low status was observed among samples obtained from different lesions within the same organ.

[40] Taken together, these findings demonstrate the extreme instability and lack of reproducibility of the current assessment of HER2-low status. The recent results from the DESTINY-Breast06 study, demonstrating the superiority of T-DXd over chemotherapy in patients with HER2-low and HER2-ultralow (HER2 IHC scores greater than 0 but less than 1+), ER+breast cancer, underscore the clinical significance of even minimal HER2 expression and the growing challenges in standardizing scoring methods. [41] Given the current and future relevance of this biomarker, as advised by the ESMO Expert Consensus Statements on HER2-low breast cancer, initiatives aimed at improving the diagnostic accuracy of HER2-low status should be sought, particularly considering that HER2-low status has been adopted as an inclusion criteria for important ongoing trials. [31, 42, 43] Moving forward, evolving investigational approaches could help achieve this goal, including the use of artificial intelligence-assisted pathology tools, HER2-targeted molecular imaging diagnostics, and the use of liquid biopsy for HER2 status determination. [44–46] Other clinicopathological factors with statistically significant differences between HER2-0 and HER2-low groups in the present analysis (i.e., ER, and BMI) were not considered clinically significant due to the small absolute difference observed between the groups. Although the absolute difference in mean ER expression between the HER2-low and HER2-0 groups was small (1.0%), this finding is in line with previous analyses showing a positive correlation between HER2 and ER expression in patients with no HER2 amplification/overexpression. [33, 47].

In our analysis, patients with HER2-low tumors had similar outcomes compared to those with HER2-0 in the entire cohort, regardless of the treatment arm. Interestingly, two large meta-analyses aiming to assess the prognostic value of HER2-low status demonstrated that patients with HER2-low disease have modestly better DFS and OS compared to patients with HER2-0 tumors. [48, 49] Similar results were obtained in sub-analyses including only patients with ER+disease. [48, 49] However, most of the studies included in both systematic reviews were retrospective and with significant methodological heterogeneity. [48, 49] The relatively short follow-up period (approximately five years) and smaller sample in our analysis may also have hindered the detection of a potentially small prognostic effect size. Another aspect to be considered when analyzing the prognostic value of this biomarker is that several initiatives have failed to identify significant different molecular characteristics between tumors categorized according to HER2-low status. [50] Furthermore, the marked regional heterogeneity in HER2-low expression found in our analysis also suggests that studies testing HER2-low as prognostic biomarker or as a separate biological entity may be hampered by the low accuracy of the available diagnostic methods in differentiating HER2-low from HER2-0. Thus, the results observed in our study and the lack of characterization of HER2-low tumors as a distinct biological entity suggest that the prognostic value of this biomarker may be limited or non-existent.

Apart from ER expression, there are no validated biomarkers of response to CDK4/6i incorporated into clinical practice. Considering the crosstalk between the HER2 and ER pathways, we further explored the interaction between HER2-low status with treatment arms. In our analysis, HER2-low status was not shown to predict response to palbociclib. Although HER2-low status was associated with a numerical benefit from palbociclib compared to HER2-0 (absolute IDFS difference at 5 years: 2.6% vs. 0.6%), this difference was not statistically significant. In the metastatic setting, conflicting results were observed in studies evaluating the interaction between HER2-low status and the benefit from CDK4/6i. In a secondary analysis of the PALOMA-2 and PALOMA-3 studies, the addition of palbociclib to ET was associated with PFS improvement only among patients with HER2-low disease in PALOMA-3, while in PALOMA-2 both HER2-0 and HER2-low groups derived similar benefit from CDK4/6i. [51] Large retrospective cohorts also found that the benefit of CDK4/6i was independent of HER2-low status. [52] A protocol-defined analysis assessed the value of genomic subtype (PAM50 intrinsic subtype) from whole-transcriptome RNA sequencing as a predictive biomarker in PALLAS. In this analysis, no significant interaction between PAM50 molecular subtype and palbociclib treatment benefit was identified. [53] Of note, although not statistically significant, the subgroup with the greatest numerical potential for palbociclib benefit was the HER2 enriched (HR 0.25, 95% CI 0.07–0.93). [53] Similarly, biomarker analyses from the monarchE trial demonstrated consistent abemaciclib benefit across breast cancer intrinsic molecular subtypes and the most prevalent genomic alterations, except for MYC amplifications. [54] Interestingly, HER2 / ER crosstalk is an important mechanism underlying MYC upregulation and MYC-mediated glutamine metabolism has been associated with resistance to ET. [55] Overall, these findings demonstrate the lack of accurate biomarkers of response to CDK4/6 inhibition in the early setting and emphasize the need for continued research in the field.

In conclusion, in this large, prospective, international cohort, no differences were observed in clinical characteristics, prognosis, or differential benefit from palbociclib (absolute and relative predictive value) between HER2-0 and HER2-low tumors. Significant geographic variability was observed in the prevalence of HER2-low

status, suggesting a high degree of variation in pathologic assessment of HER2 expression without impact on outcomes.

Abbreviations

HER2	Human epidermal growth factor receptor 2
ER	Estrogen receptor
ET	Endocrine therapy
BC	Breast cancer
iDFS	Invasive disease-free survival
DRFS	Distant relapse-free survival
OS	Overall survival
ISH	In situ hybridization
IHC	Immunohistochemistry
ADC	Antibody–drug conjugate
TDX-d	Trastuzumab deruxtecan
CLIA	Clinical Laboratory Improvement Amendments
PR	Progesterone receptor
CI	Confidence interval
HR	Hazard ratio
FDA	U.S. Food and Drug Administration
EMA	European Medicines Association

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13058-024-01899-2.

Additional file1

Author contributions

Conceptualization: GN-M, CS, PT, GP, ELM and MG; Data curation: GN-M, CS, DH, LS and CF; Formal analysis: DH, LS and CF; Investigation: GN-M, CS, DH, PT, GP, LS and CF; Methodology: GN-M, CS, DH, PT, GP, LS and CF; Project administration: GN-M., CS, DH, AD, ELM and MG; Resources: AD, EdA, ELM and MG; Supervision: DH, AD, EdA, GP, CF, ELM and MG; Writing – original draft: GN-M, CS and DH; Writing—review & editing: AD, PT, EdA., GP, MM, JMB, ZN, MB, AB, AC, PGM, TH, SL, YL, ELM and MG.

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Availability of data and materials

Pseudonymized individual participant data will be made available after completion of the study (i.e., end of the follow-up phase) at the latest; the specific data made available will depend on the data needed to answer the question in the application. Other documents that will be available include the master informed consent form, the study protocol and amendments, and the PALLAS Policy for Access to Study Data or Surplus Samples for Research Projects not related to the Protocol (Policy). We will share data with researchers whose proposed use of the data has been approved according to the PALLAS Policy for Access to Study Data or Surplus Samples for Research Projects not related to the Protocol (Policy), and whose research purpose is in line and approved according to the Policy. Excluded research includes a research project for the benefit of any commercial or for-profit entity to develop (1) any product intended for use in the cure, mitigation, treatment, or prevention of disease in man or other animals (therapeutic product), or (2) any diagnostic product intended for the use in connection with any therapeutic product, whose primary method of action is modulation of the target known as CDK4/6. This restriction does not prevent or preclude development of other diagnostic product development. Proposals should be directed to pallas.proposals@abcsg.at and pallas_aft@alliancefoundationtrials.org to request access. Data will be made available after approval of a research proposal according to the Policy and with a signed Data Transfer Agreement.

Declarations

Ethics approval and consent to participate

The PALLAS trial was approved by institutional review boards and ethics committees. All patients included in this analysis provided written informed consent, and the trial was performed in strict accordance with International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) guidelines.

Consent for publication

Not applicable.

Competing interests

GN-M reports travel support from AstraZeneca. CS has served as a consultant for Novartis and AstraZeneca; and received grant support from Daiichi-Sankyo and Amgen. DH reports research grants from Pfizer to the institution. AD received institutional research support from Novartis, Pfizer, Genentech, and Neogenomics; and reports that her spouse received support from Pfizer DSMB for a non-oncology trial. PT received institutional research support from AstraZeneca; and served in a consultant or advisory role for AstraZeneca, Daiichi Sankyo, Eli Lilly, Gilead, Roche, Genentech, Menarini/Stemline, and Novartis. EdA received honoraria from, and/or served on the advisory boards of, Roche/GNE, Novartis, Seagen, Zodiac, Libbs, Pierre Fabre, Lilly, AstraZeneca, MSD, and Gilead Sciences; received travel grants from Roche/GNE and AstraZeneca; received a research grant to his institution from Roche/GNE, AstraZeneca, GSK/Novartis, and Gilead Sciences; and served as ESMO director of Membership from 2023–2025 and BSMO President from 2023–2026. GP received honoraria and grants from Pfizer, AstraZeneca, Daiichi-Sankyo, Novartis, Amgen, Roche, Seagen, Accord, and MSD. MM received research grants from Roche, PUMA and Novartis; consulting/advisory fees from AstraZeneca, Amgen, Taiho Oncology, Roche/Genentech, Novartis, PharmaMar, Eli Lilly, PUMA, Taiho Oncology, Daiichi Sankyo, Menarini/Stemline, and Pfizer; and speakers' honoraria from AstraZeneca, Lilly, Amgen, Roche/Genentech, Novartis, and Pfizer. JMB receives research support from Genentech/Roche and Incyte Corporation; has received advisory board payments from AstraZeneca and Mallinckrodt; and is an inventor on patents regarding immunotherapy targets and biomarkers in cancer. MB served in a consulting or advisory role for Amgen, AstraZeneca, Daiichi-Sankyo/AstraZeneca, Lilly, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Samsung, Gilead Sciences, and Seagen; served on the Speakers' Bureaus of Amgen, AstraZeneca, Daiichi-Sankyo/AstraZeneca, Lilly, Novartis, Pierre Fabre, Pfizer, Roche, and Seagen; received institutional research funding from Lilly, Novartis, Pfizer, and Pierre Fabre; and received support for travel, accommodations and expenses from MSD. AMB served as a consultant for AstraZeneca, Pfizer, Novartis, Lilly, Genentech/Roche, Seagen, Daiichi-Sankyo, Merck, Agendia, Sanofi, Puma, Myriad, Gilead, Epic Biosciences, Blueprint, Caris, and Tempus. PGM received honoraria from Pfizer, AstraZeneca, Genomic Health, Novartis, Seagen, Gilead Sciences, and Roche; played a consulting or advisory role for Novartis; received research funding from Teva and Genomic Health (to the institution); and received support for travel, accommodations and expenses from Roche/Genentech. TCH received institutional grant funding from Takeda Oncology; and consulting fees to the institution from Puma Biotechnology. SL received grants and other from Abbvie, AstraZeneca, Celgene, Daiichi-Sankyo, Immunomedics/Gilead, Novartis, and Pfizer; other from Amgen, BMS, EirGenix, Eisai Europe Ltd, GSK, Lilly, Merck KG, Relay Therapeutics, Sanofi, and Olema Pharmaceutics (outside the submitted work); grants from Molecular Health; grants, non-financial support and other from Roche; non-financial support and other from Seagen, other from Olema Pharmaceutics, outside the submitted work; and has a patent VM Scope with royalties paid, a patent EP14153692.0 pending, a patent EP21152186.9 pending, and a patent EP15702464.7 pending. YL is a Pfizer employee and owns Pfizer stocks. LS and CF report research grants from Pfizer to the institution. ELM reports a consulting or advisory role for Lilly, Novartis, and AstraZeneca; and is an associate editor for Breast Cancer Research. MG reports personal fees/travel support from Amgen, AstraZeneca, Daiichi-Sankyo, Eli Lilly, EPG Health (IQVIA), Menarini-Stemline, MSD, Novartis, Pierre Fabre, and Veracyte;

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