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ORIGINAL ARTICLE

A chemotherapy-free, pathological response-adapted strategy using trastuzumab—pertuzumab and T-DM1 in HER2-positive early breast cancer: the PHERGain-2 study☆

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Background: PHERGain-2 is a multicenter, single-arm, phase II study evaluating a pathologic complete response (pCR)-guided de-escalation strategy to omit chemotherapy in selected patients with HER2-positive early breast cancer (EBC).

Patients and methods: Eligible patients were adults, treatment-naive, centrally confirmed HER2-positive (immunohistochemistry 3+), node-negative EBC, with tumors 5-30 mm by magnetic resonance imaging. Patients received eight cycles of neoadjuvant trastuzumab—pertuzumab (HP) (600 mg H + 1200 mg P loading dose, followed by 600 mg H + 600 mg P maintenance dose) every 3 weeks. Patients with hormone receptor (HR)-positive tumors also received endocrine therapy. After surgery, patients received 10 cycles of adjuvant therapy guided by the pathological response: HP for patients with pCR (ypT0/is ypN0) (cohort A), trastuzumab emtansine (T-DM1; 3.6 mg/kg) for patients with residual invasive breast tumors and/or ypN0(i+/mol+), ypN1mi (cohort B), and optional chemotherapy followed by T-DM1 for patients with ypN1-3 (cohort C). Co-primary endpoints were 1-year health-related quality of life (HRQoL) decline (based on the European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire) and 3-year recurrence-free interval (based on the Standardized Definitions for Efficacy End Points). Key secondary endpoints included overall and HR-specific pCR rates and safety.

Results: From August 2021 to March 2024, 396 patients initiated neoadjuvant treatment, 391 (98.7%) underwent surgery. A total of 236 patients (59.6%) achieved pCR (cohort A). Among those with residual disease, 148 (37.8%) entered cohort B and 7 (1.8%) cohort C. One year after initiation of neoadjuvant treatment, ≥10% decline rate in global HRQoL was 42.8% [95% confidence interval (CI) 36.9% to 48.8%]; 37.3% (95% CI 30.1% to 44.9%) in patients with pCR and 51.9% (95% CI 41.9% to 61.7%) in those with residual disease. Treatment-related adverse events occurred in 86.6% of patients (5.6% grade ≥3). Serious adverse events occurred in 6.1% of patients. One death (0.3%) due to pneumonitis was attributed to T-DM1.

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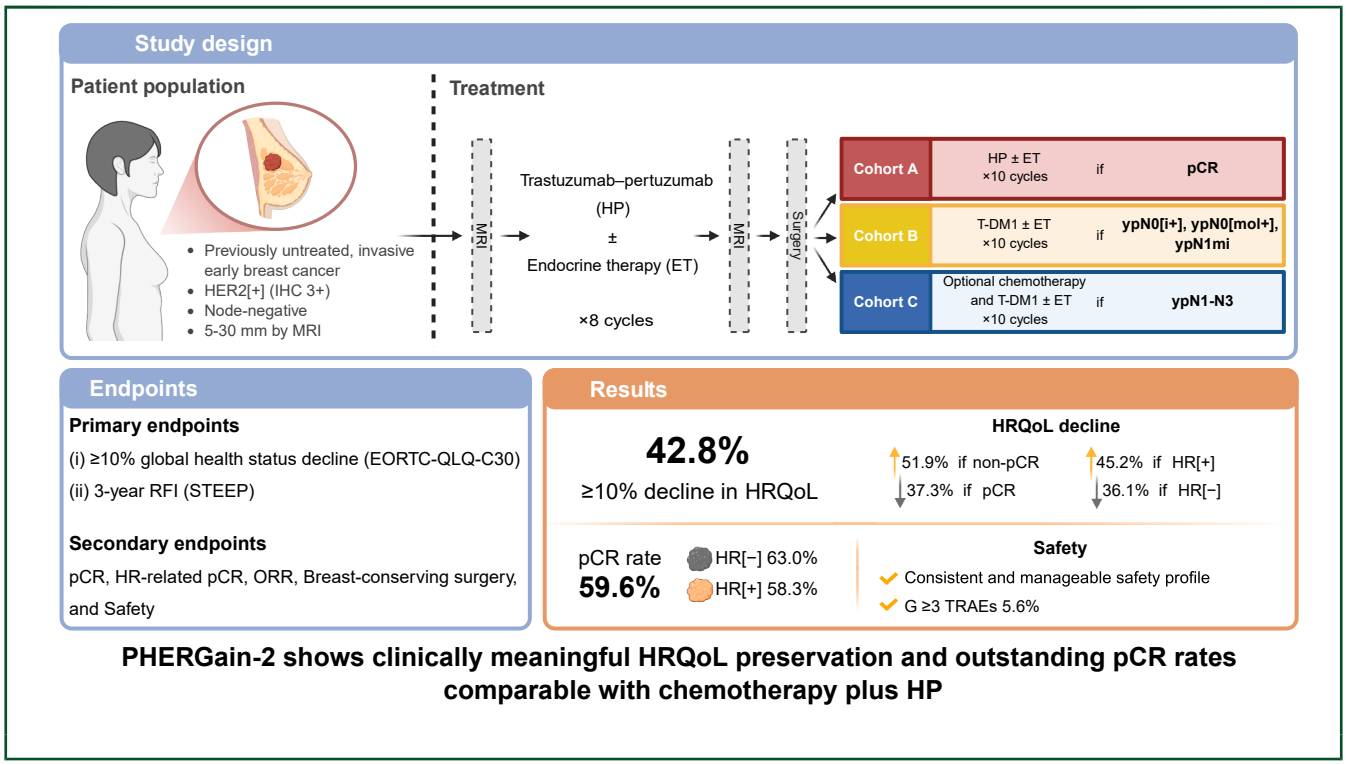
☆Note: This study was presented at ESMO Breast Cancer 2026, 6-8 May 2026, Berlin, Germany.

Conclusions: PHERGain-2 shows meaningful HRQoL preservation, expected HP/T-DM1 toxicity, and an outstanding pCR rate comparable with standard chemotherapy plus HP regimens in this patient population.

Key words: trastuzumab—pertuzumab, trastuzumab emtansine (T-DM1), de-escalation, pathological complete response, HER2-positive, early breast cancer

GRAPHICAL ABSTRACT



A chemotherapy-free, pathological complete response-adapted strategy using trastuzumab—pertuzumab and T-DM1 in HER2-positive early breast cancer: the PHERGain-2 study. EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HRQoL, health-related quality of life; IHC, immunohistochemistry; MRI, magnetic resonance imaging; ORR, objective response rate; pCR, pathologic complete response; RFI, recurrence-free interval; STEEP, Standardized Definitions for Efficacy End Points; T-DM1, trastuzumab emtansine; TRAE, treatment-related adverse event.

INTRODUCTION

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer accounts for ∼15%-20% of all breast cancer cases. This tumor subtype, which is historically correlated with high risk of recurrence and poor prognosis,[1] has seen markedly improved outcomes with the introduction of HER2-targeted therapies.[2-4] These advances have also enabled the development of chemotherapy de-escalation strategies for selected subgroups of patients with HER2-positive early breast cancer (EBC). The neoadjuvant setting offers an optimal framework for such de-escalation, as pathologic complete response (pCR) is a validated surrogate marker for long-term outcomes, including disease-free survival (DFS) and overall survival (OS).[5-7]

The PHERGain study (NCT03161353) demonstrated the feasibility of a ^{18}F-fluorodeoxyglucose-positron emission tomography ([^{18}F]FDG-PET)-guided, pathological response-adapted strategy to safely omit chemotherapy in patients with HER2-positive EBC undergoing neoadjuvant dual HER2 blockade with trastuzumab and pertuzumab.[8,9] The first primary endpoint, pCR, showed that 37.9% of patients in the adaptive treatment group (group B), who were identified as [^{18}F]FDG-PET responders after 2 initial cycles of trastuzumab and pertuzumab and treated with 6 additional cycles of the same chemotherapy-free regimen, achieved pCR at surgery. Interestingly, pCR rate was higher in patients with an HER2 immunohistochemistry (IHC) score 3+ tumors (40.8%) than in patients with HER2 IHC score 2+ tumors (25.6%).[8] At a median follow-up of 3 years, the second primary endpoint, 3-year invasive DFS (iDFS), showed that 94.8% of patients who followed this strategy remained cancer-free, despite approximately one-third of

them having omitted chemotherapy.[9] Notably, patients from group B who were [^{18}F]FDG-PET responders and achieved a pCR with trastuzumab and pertuzumab alone, and therefore did not receive chemotherapy as part of their (neo)adjuvant treatment, also demonstrated excellent 3-year outcomes, with no cases of metastatic relapse. An exploratory analysis of the PHERGain trial including only patients from group B with cT1c-T2 N0 tumors showed a pCR rate of 42.9% and a 3-year iDFS of 98.3%.[10]

At the time that PHERGain trial was designed and conducted, trastuzumab emtansine (T-DM1) was not yet approved for patients not achieving pCR after neoadjuvant treatment. The subsequent KATHERINE study demonstrated improved iDFS and OS with T-DM1 in this population, establishing it as the standard adjuvant treatment.[11,12] These findings support the development of novel de-escalation strategies incorporating trastuzumab, pertuzumab, and T-DM1, with the goal of further increasing the number of patients who can be cured without traditional cytotoxic chemotherapy.

The PHERGain-2 trial aims to evaluate the feasibility of a complete chemotherapy de-escalation in patients with operable, node-negative, HER2-positive EBC by using a pCR-guided strategy that involves neoadjuvant trastuzumab and pertuzumab, followed by adjuvant treatment with either trastuzumab and pertuzumab or T-DM1 based on the pathological response.

PATIENTS AND METHODS

Study design and participants

PHERGain-2 is a multicenter, single-arm, open-label phase II study conducted across Spain, Italy, Denmark, Hungary, Poland, and Bulgaria. The trial protocol is available in the Supplementary Information, available at https://doi.org/10.1016/j.annonc.2026.01.013.

Patients aged ≥18 years who had previously untreated, invasive, centrally confirmed HER2-positive (defined as IHC score 3+ according to the 2018 American Society of Clinical Oncology/College of American Pathologists criteria[13]) operable EBC with a tumor size between 5 and 30 mm, as determined by central assessment using magnetic resonance imaging (MRI), were enrolled. Patients with lymph node involvement, bilateral breast cancer, and metastatic disease were not eligible. Patients were enrolled regardless of sex, which was collected according to the identity information each patient provided. Complete inclusion and exclusion criteria are provided in Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2026.01.013.

This study complied with International Conference on Harmonization guidelines and the Declaration of Helsinki and was approved by the institutional review boards or independent ethics committees at each site. All participants provided written informed consent before enrollment. The study was registered with ClinicalTrials.gov (NCT04733118) and EuCT (2023-508738-32-00).

Procedures

An overview of the study design is provided in Figure 1.

At screening, core biopsies of the primary tumor were obtained for histopathological diagnosis, including local evaluation of estrogen and progesterone receptor, as well as central assessment of HER2 status. Tumors exhibiting estrogen receptor or progesterone receptor expression of ≥1% were defined as hormone receptor (HR)-positive.[14] Extended procedures are detailed in the Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2026.01.013.

Health-related quality of life (HRQoL) was evaluated using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the breast cancer module QLQ-BR23 questionnaires. Extended definitions, as well as detailed information on the HRQoL assessment schedule, are provided in the Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2026.01.013. Breast MRI was required at screening and within 2 weeks before surgery. Radiological response was evaluated exclusively by MRI using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[15]

Detailed procedures during the follow-up phase of the study, which is ongoing and ranges from each patient's surgery to up to 5 years from the last patient's completed surgery, can be found in Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2026.01.013.

Safety assessments consisted of monitoring and recording adverse events (AEs), including treatment-emergent AEs (TEAEs) and serious AEs (SAEs) according to the Common Terminology Criteria for Adverse Events version 5.0.[16]

Study treatment

All patients received eight cycles of neoadjuvant fixed-dose subcutaneous trastuzumab—pertuzumab every 3 weeks (600 mg trastuzumab plus 1200 mg pertuzumab loading dose, then 600 mg trastuzumab plus 600 mg pertuzumab maintenance). Patients with HR-positive tumors also received sex- and menopausal status-based endocrine therapy. It was highly recommended that premenopausal and perimenopausal women receive ovarian function suppression plus tamoxifen (20 mg/day orally) or letrozole (2.5 mg/day orally); postmenopausal women receive letrozole (2.5 mg/day orally); and men receive tamoxifen (20 mg/day orally). Patients with MRI-confirmed disease progression while receiving neoadjuvant treatment could continue the study with alternative neoadjuvant treatment at the investigator's discretion.

Surgery (breast-conserving or mastectomy with sentinel lymph node evaluation or axillary dissection) was carried out within 4 weeks after completion of neoadjuvant treatment. Adjuvant anti-HER2 therapy was initiated within 4 weeks thereafter. Based on pathological findings, patients were assigned to 3 cohorts:

- **Cohort A** [pCR in breast and axilla (ypT0/is ypN0)] received 10 additional cycles of fixed-dose subcutaneous trastuzumab—pertuzumab (maintenance dose) every 3 weeks.

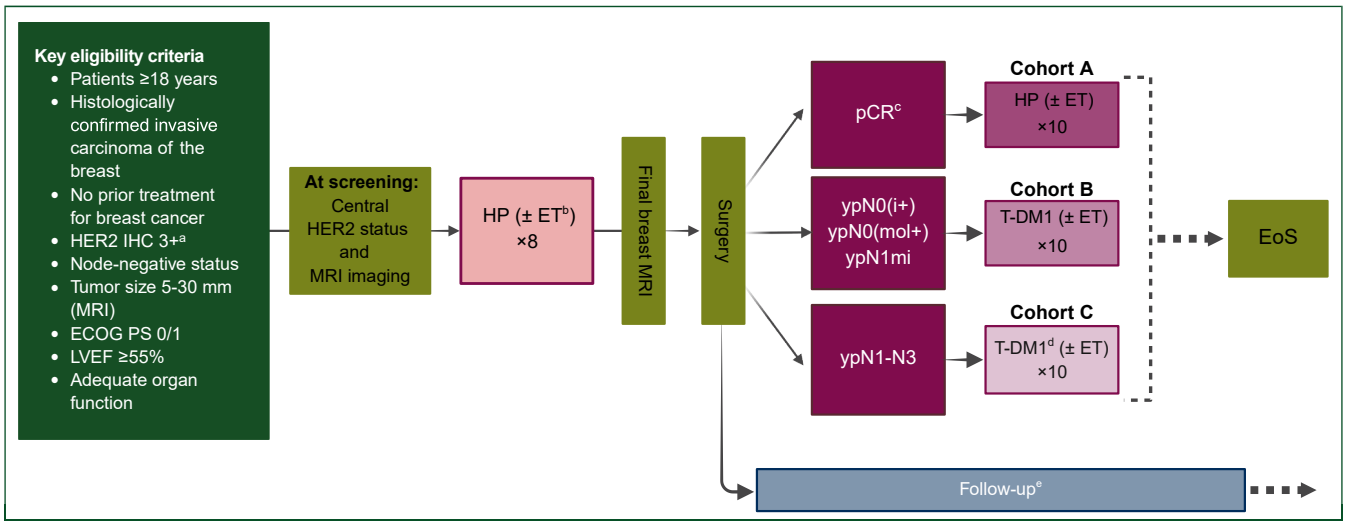


Figure 1. Study design.
ECOG PS, Eastern Cooperative Oncology Group performance status; EoS, end of study; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HP, trastuzumab and pertuzumab; IHC, immunohistochemistry; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; pCR pathologic complete response.
[a]According to the 2018 American Society of Clinical Oncology/College of American Pathologists criteria.
[b]All patients who were hormonal receptor-positive received ET concomitantly with HP or T-DM1.
[c]pCR was defined as ypT0/is, ypN0.
[d]Physician's choice chemotherapy was allowed before adjuvant T-DM1.
[e]All patients must be followed up for 5 years from when the last patient has completed surgery (EoS), even if the assigned treatment is discontinued permanently.

- **Cohort B** [residual invasive breast tumor and/or ypN0(i+), ypN0(mol+), ypN1mi] received 10 additional cycles of intravenous T-DM1 (3.6 mg/kg of body weight) every 3 weeks.
- **Cohort C** [locoregional nodal progression (ypN1-N3)] received 10 additional cycles of intravenous T-DM1 (3.6 mg/kg of body weight) every 3 weeks. Standard chemotherapy could be administered before adjuvant T-DM1 at the physician's discretion, with taxane-based regimens recommended.

According to the American Joint Committee on Cancer classification,[17] pT0/is was defined as no evidence of residual primary tumor in the breast, with or without the presence of ductal carcinoma *in situ*; pN0(i+) was defined as the absence of lymph node metastases on hematoxylin and eosin staining, with isolated tumor cells $\leq$0.2 mm detected by immunohistochemistry (typically cytokeratin staining); pN0(mol+) was defined as the absence of lymph node metastases on hematoxylin and eosin and cytokeratin staining, with positive molecular findings; pN1mi was defined as histologically confirmed micrometastases measuring $>$0.2 mm and $\leq$2.0 mm; and pN1–pN3 were defined as the presence of macrometastatic nodal disease ($>$2.0 mm), according to the number and location of involved lymph nodes.

Patients also received adjuvant endocrine therapy ($\geq$5 years) and radiotherapy as per HR status and institutional practices, respectively. Adjuvant treatment continued until disease progression, unacceptable toxicity, withdrawal, or investigator decision.

T-DM1 dose reductions were permitted per protocol, whereas trastuzumab and pertuzumab allowed dose interruptions only.

Outcomes

The primary endpoints were (i) global health status decline, defined as the rate of patients with a $\geq$10% global health status decline at 1 year from start of neoadjuvant treatment assessed by the EORTC QLQ-C30 Global Health Status scale; and (ii) 3-year recurrence-free interval (RFI), defined as time from start of treatment in the adjuvant setting until recurrence, new invasive disease, or breast cancer-related death, per Standardized Definitions for Efficacy End Points criteria.[18] The 3-year RFI analysis is ongoing and not included here.

Secondary endpoints included local assessment of breast and axillary pCR rates (ypT0/is ypN0), pCR rates according to HR status and tumor stage, objective response rate (ORR) assessed by MRI, rate of breast-conserving surgery (BCS), and safety. Other secondary endpoints are still under analysis and not reported here: 5-year RFI and 3- and 5-year event-free survival, relapse-free survival, DFS, iDFS, and OS.

Statistical analysis

One-year global health status decline was assessed in the HRQoL analysis set, including all patients with baseline quality-of-life (QoL) questionnaire who received neoadjuvant treatment and either completed a QoL questionnaire at 1 year ($\pm$3 months) or discontinued treatment due

to toxicity or death. Analyses were descriptive, with no formal hypothesis testing. Patients without a ≥10% decline at 1 year who discontinued due to toxicity or died within the first year after starting neoadjuvant treatment were considered events. Completion rate was defined as the proportion of patients included in the HRQoL analysis set.

Safety was assessed in all patients who received at least one dose of study treatment. Efficacy was assessed in the full analysis set, which included all patients who had surgical excision of the primary tumor. Rates of pCR, BCS, and ORR are reported with 95% Pearson—Clopper confidence interval (CI). The trial was not designed to test between-cohorts comparisons; subgroup analyses are only descriptive.

RESULTS

Between 5 August 2021 and 28 March 2024, a total of 693 patients with operable HER2-positive EBC were screened across 47 sites in 6 countries, of whom 396 (57.1%) met eligibility criteria and received at least one dose of study treatment. Screening failure occurred in 297 (42.9%) patients, primarily due to lack of central confirmation of HER2-positive status (185, 62.3%) or tumor size criteria not met according to centralized breast MRI assessment (59, 19.9%) (Figure 2).

At data cut-off (28 March 2025), the median duration of follow-up was 15.1 months (range, 0.49-36.1 months). The median age of patients in the study was 55 years (range, 24-85 years). Most patients had HR-positive tumors (72.7%) and T1 disease (61.6%). Median tumor size centrally assessed by MRI was 18 mm (range, 7-30 mm) (Table 1).

Of the 396 patients who initiated study treatment, 391 (98.7%) proceeded to surgery after completing the neoadjuvant phase. A total of 5 (1.3%) patients discontinued neoadjuvant treatment before surgery due to investigator decision (3, 0.8%) and disease progression (2, 0.5%). Following surgery, 236 (60.4%), 148 (37.8%), and 7 (1.8%) patients were assigned to cohorts A, B, and C, respectively, based on the pathological response. Among patients who underwent surgery ($n = 391$), 10 (2.6%) did not start adjuvant treatment due to withdrawal of consent (3, 0.8%), disease recurrence (2, 0.5%), patient's decision to discontinue treatment (3, 0.8%), protocol violation (1, 0.25%), or investigator's decision (1, 0.25%) (Figure 2).

Of the 381 patients who started adjuvant therapy, 24 (6.3%) did not complete the treatment regimen; 16 (4.2%)

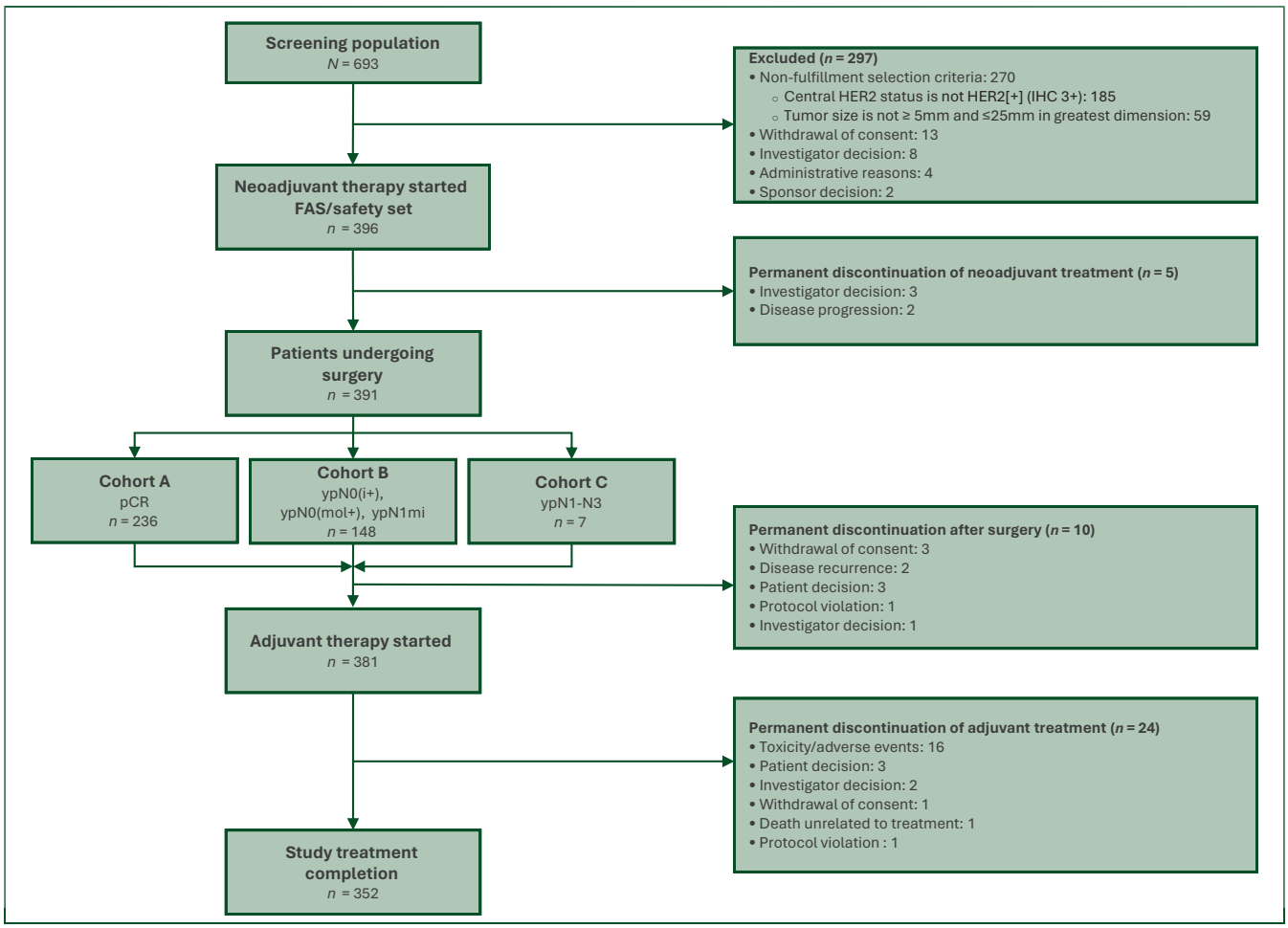


Figure 2. Trial profile. At data cutoff, five patients continued receiving adjuvant treatment. Tumor staging was defined according to the American Joint Committee on Cancer classification (AJCC 8th edition).
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; pCR, pathologic complete response.

Table 1. Patient baseline characteristics

Baseline characteristics, *N* = 396	
Age, years, median (range)	55 (24-85)
Sex, *n* (%)	
Female	394 (99.5)
Menopausal status, *n* (%)	
Postmenopausal	235 (59.3)
Premenopausal	159 (40.2)
Not available	2 (0.5)
Ethnicity, *n* (%)	
White	380 (95.9)
Hispanic or Latino	8 (2.0)
Black	3 (0.8)
Arabic or North African	2 (0.5)
Asian	2 (0.5)
Mixed ethnicity	1 (0.3)
Multifocal or multicentric breast cancer, *n* (%)	15 (3.8)
Primary tumor size, *n* (%)	
T1	244 (61.6)
T2	152 (38.4)
Primary tumor size (mm), median (min/max)	18 (7/30)
Regional node, *n* (%)	
N0	395 (99.7)
N1	1 (0.3)
Stage, *n* (%)	
IA	252 (63.6)
IIA	144 (36.4)
Histologic grade, *n* (%)	
Gx[a]	52 (13.1)
G1	21 (5.3)
G2	185 (46.7)
G3	133 (33.6)
Hormonal receptor status, *n* (%)	
Negative	108 (27.3)
Positive	288 (72.7)
ECOG performance status, *n* (%)	
0	252 (96.2)
1	15 (3.8)

ECOG, Eastern Cooperative Oncology Group; G, grade.
[a]Differentiation status could not be assessed.

due to toxicity, 3 (0.8%) due to patient's decision, 2 (0.5%) due to investigator's decision, 1 (0.3%) withdrew consent, 1 (0.3%) due to death unrelated to treatment, and 1 (0.3%) due to protocol violation. Two out of 7 patients (28.6%) in cohort C received optional adjuvant chemotherapy before T-DM1 treatment. Endocrine treatment administered to patients with HR-positive tumors is detailed in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2026.01.013. Overall, a total of 352 out of 396 (88.9%) patients completed all study treatment. At data cut-off, 5 patients (1.3%) continued receiving adjuvant treatment (Figure 2).

At 1-year following neoadjuvant treatment (primary analysis time point), the completion rate for QoL assessments was 90.9% (360/396). Baseline mean score for global HRQoL was 78.6 (95% CI 76.8-80.5). The rate of patients with a $\geq$10% global health status decline at 1 year from the start of neoadjuvant treatment was 42.8% (154/360; 95% CI 36.9% to 48.8%) (Table 2). Patients with HR-positive tumors treated with endocrine therapy had a greater deterioration of global health status [45.2% (119/263; 95% CI 38.3% to 52.3%)] compared with those with HR-negative tumors [36.1% (35/97; 95% CI 25.4% to 47.9%)] (Table 2). Detailed data on HRQoL according to the EORTC QLQ-C30 Global Health Status scale and the EORTC QLQ-BR23 scale are shown in Supplementary Tables S2 and S3, available at https://doi.org/10.1016/j.annonc.2026.01.013.

Overall, 236 (59.6%) of 396 patients achieved a pCR in both the breast and axilla. No significant differences in pCR rates were observed between patients with HR-negative and HR-positive tumors (63.0% versus 58.3%), or between patients with T1 and T2 tumors (59.6% versus 59.6%) (Figure 3). Patients who achieved a pCR experienced a smaller numerical decline in HRQoL at 1 year [37.3% (84/225; 95% CI 30.1% to 44.9%)] compared with those without a pCR [51.9% (70/135; 95% CI 41.9% to 61.7%)], who systematically received T-DM1 as adjuvant therapy (Table 2).

ORR evaluated by MRI within 2 weeks before surgery was 78.3% (95% CI 73.9% to 82.1%), with 246 (62.1%) complete responses (CR) and 64 (16.2%) partial responses (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2026.01.013). In patients showing a radiological CR, the pCR rate was higher compared with those without radiological response (71.1% versus 40.7%, respectively) (Supplementary Table S5A, available at https://doi.org/10.1016/j.annonc.2026.01.013). Among patients with HR-negative tumors, 51 (80.9%) who achieved a radiological CR also attained a pCR; whereas among patients with HR-positive tumors with radiological CR (n = 183), 124 (67.8%) achieved a pCR (Supplementary Table S5B, available at https://doi.org/10.1016/j.annonc.2026.01.013). Breast-conserving surgery was carried out in 328 patients (83.9%; 95% CI 79.3% to 87.8%) out of the 391 undergoing surgery.

Overall, TEAEs of any grade were reported in 97.2% of patients, with grade $\geq$3 events in 9.3%. Treatment-related AEs occurred in 86.6% of patients (5.6%; grade $\geq$3). SAEs occurred in 6.1% of patients. Of all TEAEs, 86.6% were related to study treatment, including 5.6% of grade $\geq$3 events. Treatment-related SAEs were observed in 1.0% of patients (Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2026.01.013). TEAEs leading to discontinuation of any study drug occurred in 4.5% of patients (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2026.01.013). Two TEAEs resulted in death; 1 (0.3%) unrelated to study treatment (respiratory tract infection) and 1 (0.3%) related to T-DM1 (pneumonitis) in cohort B.

The most common hematologic TEAEs of any grade were anemia (10.0%; grade 3, 0.3%), thrombocytopenia (4.5%; grade 3, 0.3%), and neutropenia (4.3%; grade 3, 0.5%). The most frequent non-hematologic TEAEs of any grade ($\geq$20% of patients) were diarrhea (59.0%; grade 3, 0.8%), fatigue (53.0%; grade 3, 0.3%), arthralgia (31.0%; grade 3, 0.0%), nausea (24.0%; grade 3, 0.5%), and rash (20.0%; grade 3, 0.0%) (Table 3).

The safety profile during the neoadjuvant phase is presented in Supplementary Tables S8 and S9, available at https://doi.org/10.1016/j.annonc.2026.01.013. The safety profiles during the adjuvant phase by cohort are provided in Supplementary Tables S10-S15, available at https://doi.org/10.1016/j.annonc.2026.01.013.

Table 2. Patient-reported outcomes assessed by EORTC QLQ-C3

Patient-reported outcomes $N = 396$	
Completion rate at baseline, *n* (%)	391 (98.7)
Baseline HRQoL score, mean (95% CI)	78.6 (76.8% to 80.5%)
Completion rate at 1 year, *n* (%)	360 (90.9)
1-year HRQoL score, mean (95% CI)	69.6 (67.5% to 71.8%)
Global health status decline (≥10% decline) *n* = 360[a]	
At 1 year, *n* (%)	
Yes	154 (42.8)
95% CI	36.9% to 48.8%
No	206 (57.2)
At 1 year by HR status, *n* (%)	
HR negative ($n = 97$)	35 (36.1)
95% CI	25.4% to 47.9%
HR positive ($n = 263$)	119 (45.2)
95% CI	38.3% to 52.3%
At 1 year by pCR	
Yes ($n = 225$)	84 (37.3)
95% CI	30.1% to 44.9%
No ($n = 125$)	70 (51.9)
95% CI	41.9% to 61.7%

CI, confidence interval; HR, hormone receptor; HRQoL, health-related quality of life; pCR, pathologic complete response.

[a]Patient-reported outcomes were analyzed on patients who received at least one dose of study treatment and completed baseline and at least one follow-up questionnaire at 1-year post-neoadjuvant treatment, including those patients that discontinued the study treatment due to adverse events.

DISCUSSION

The interest in de-escalation strategies in HER2-positive EBC has increased in recent years, aiming to minimize treatment-related toxicity without compromising long-term efficacy. PHERGain-2 is the second study following a two-step, strategy-based de-escalation approach in the neoadjuvant/adjuvant setting, using a pathological response-adapted design in operable, node-negative, HER2-positive EBC.

This trial differs from the preceding PHERGain study in several aspects, beyond the use of adjuvant T-DM1 in patients without pCR. Firstly, the neoadjuvant treatment was not guided by radiological response. Secondly, only patients with HER2 IHC 3+ tumors up to 30 mm and negative axillary nodes were included. Thirdly, the study lacked a control arm. Finally, adjuvant chemotherapy was reserved for patients without pCR and macrometastatic axillary lymph node involvement, according to investigators' criteria.

The PHERGain-2 trial showed meaningful results for one of its co-primary endpoints, with 42.8% (95% CI 36.9% to 48.8%) of patients experiencing a ≥10% decline in global health status. Notably, patients without pCR (cohorts B and C), who therefore received adjuvant T-DM1 (± chemotherapy), showed greater deterioration than those who achieved pCR (cohort A) (51.9% versus 37.3%, respectively). Additionally, HRQoL outcomes were worse among patients with HR-positive tumors receiving endocrine therapy, likely reflecting cumulative treatment burden. The safety profile reported in this study was consistent with known toxicities of trastuzumab, pertuzumab, and T-DM1, largely attributable to the low chemotherapy exposure (only 2 patients out of 396 received chemotherapy).

These outcomes compare favorably with those in group A of the PHERGain trial, where 65.0% (95% CI 46.5% to 72.4%) of patients receiving neoadjuvant chemotherapy plus trastuzumab and pertuzumab experienced a ≥10% HRQoL decline, and are similar to those observed in the response-adapted group B (35.5%; 95% CI 29.7% to 41.7%).[8] In line with these studies, the ATEMPT trial demonstrated excellent long-term disease control with adjuvant T-DM1 in patients with stage I HER2-positive breast cancer and improved HRQoL compared with paclitaxel plus trastuzumab, despite comparable toxicities

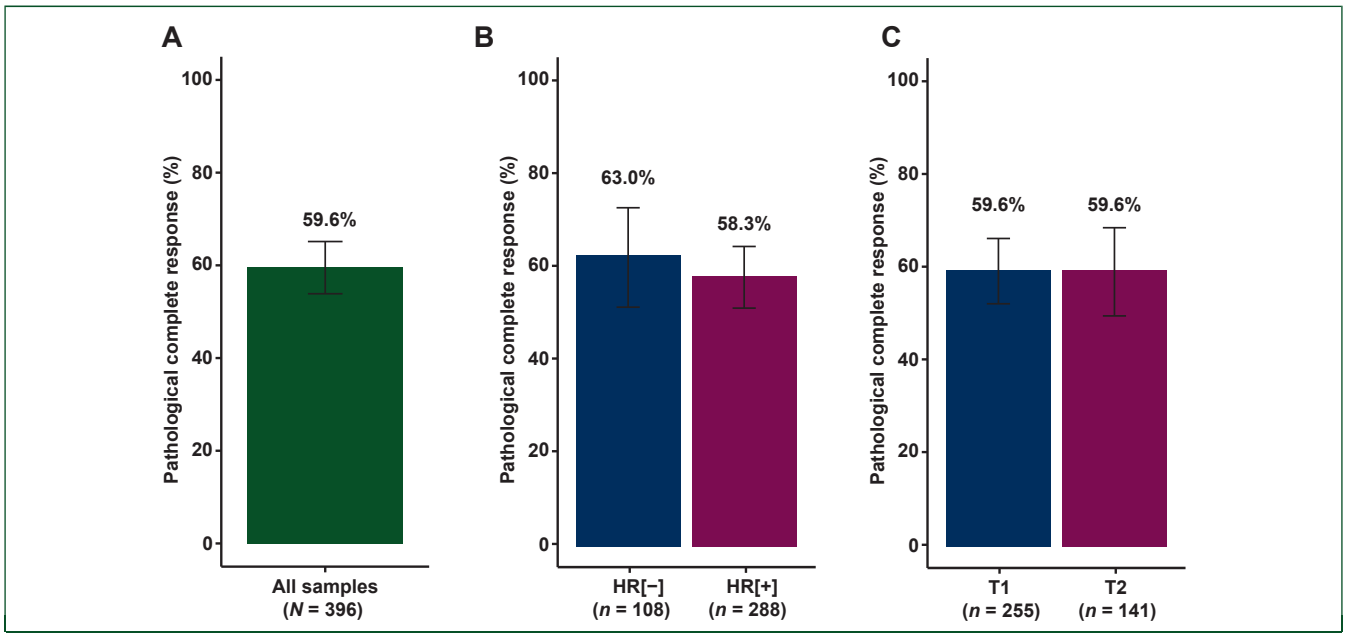


Figure 3. Pathological complete response. (A) Overall, (B) by hormone status, (C) by tumor stage.
HR, hormone receptor; T, tumor stage.

Table 3. Treatment-emergent adverse events affecting at least 10% of patients or of grade ≥3

Adverse events *N* = 396	TEAE, *n* (%)		Related TEAE, *n* (%)	
	Any grade	Grade ≥3[a]	Any grade	Grade ≥3[a]
Any	385 (97)	35 (8.8)	343 (87)	21 (5.3)
Hematologic	69 (17)	4 (1.0)	44 (11)	3 (0.8)
Anemia	41 (10)	1 (0.3)	27 (6.8)	0 (0.0)
Thrombocytopenia	18 (4.5)	1 (0.3)	13 (3.3)	1 (0.3)
Neutropenia	17 (4.3)	2 (0.5)	13 (3.3)	2 (0.5)
Non-hematologic	384 (97)	32 (8.1)	342 (86)	18 (4.5)
Diarrhea	235 (59)	3 (0.8)	193 (49)	2 (0.5)
Fatigue	210 (53)	1 (0.3)	156 (39)	1 (0.3)
Arthralgia	121 (31)	0 (0.0)	103 (26)	0 (0.0)
Nausea	97 (24)	2 (0.5)	69 (17)	1 (0.3)
Rash	80 (20)	0 (0.0)	53 (13)	0 (0.0)
Hot flush	75 (19)	1 (0.3)	65 (16)	1 (0.3)
Headache	57 (14)	0 (0.0)	28 (7.1)	0 (0.0)
COVID-19	54 (14)	0 (0.0)	0 (0.0)	0 (0.0)
Alanine aminotransferase increased	50 (13)	3 (0.8)	40 (10)	3 (0.8)
Pruritus	50 (13)	1 (0.3)	31 (7.8)	1 (0.3)
Pyrexia	50 (13)	0 (0.0)	27 (6.8)	0 (0.0)
Stomatitis	49 (12)	0 (0.0)	35 (8.8)	0 (0.0)
Aspartate aminotransferase increased	47 (12)	0 (0.0)	40 (10)	0 (0.0)
Insomnia	43 (11)	0 (0.0)	15 (3.8)	0 (0.0)
Radiation skin injury	43 (11)	1 (0.3)	2 (0.5)	1 (0.3)
Breast pain	42 (11)	0 (0.0)	2 (0.5)	0 (0.0)
Gamma-glutamyltransferase increased	27 (6.8)	1 (0.3)	20 (5.1)	1 (0.3)
Musculoskeletal pain	27 (6.8)	1 (0.3)	24 (6.1)	1 (0.3)
Myalgia	27 (6.8)	1 (0.3)	22 (5.6)	1 (0.3)
Hypertension	18 (4.5)	1 (0.3)	2 (0.5)	1 (0.3)
Transaminases increased	16 (4.0)	1 (0.3)	11 (2.8)	0 (0.0)
Neurotoxicity	12 (3.0)	1 (0.3)	9 (2.3)	1 (0.3)
Respiratory tract infection	10 (2.5)	1 (0.3)[b]	2 (0.5)	0 (0.0)
Dyspnea	8 (2.0)	1 (0.3)	2 (0.5)	1 (0.3)
Gastroenteritis	8 (2.0)	1 (0.3)	0 (0.0)	0 (0.0)
Chest pain	6 (1.5)	1 (0.3)	0 (0.0)	0 (0.0)
Ejection fraction decreased	6 (1.5)	2 (0.5)	4 (1.0)	2 (0.5)
Pneumonitis	3 (0.8)	1 (0.3)[c]	2 (0.5)	1 (0.3)[c]
Seroma	3 (0.8)	1 (0.3)	0 (0.0)	0 (0.0)
Left ventricular dysfunction	2 (0.5)	1 (0.3)	2 (0.5)	1 (0.3)
Polyneuropathy	2 (0.5)	1 (0.3)	2 (0.5)	1 (0.3)
Cardiac failure congestive	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Hypertensive crisis	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Interstitial lung disease	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Pneumonia bacterial	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)

TEAE, treatment-emergent adverse event.
[a]No grade 4 adverse events were reported; two grade 5 were reported.
[b]Grade 5 respiratory tract infection unrelated to the study treatment.
[c]Grade 5 pneumonitis and hospitalization related to trastuzumab emtansine.

rates.[19] Evidence from PHERGain-2 highlights the clinical relevance of response-adapted de-escalation strategies within the prevailing standard-of-care for stage I HER2-positive EBC: upfront surgery followed by adjuvant therapy based on the APT (Adjuvant Paclitaxel and Trastuzumab) regimen of:12 weekly infusions of paclitaxel plus trastuzumab, followed by 9 months of trastuzumab monotherapy.[3]

The observed pCR rate of 59.6% is remarkably high, especially considering the inclusion of a significant proportion of patients with HR-positive tumors (72.7%). These results demonstrate that a carefully selected subset of patients with small (median tumor size by MRI, 18 mm), HER2 IHC score 3+, node-negative tumors can achieve excellent pCR rates with 8 cycles of dual HER2 blockade alone, without conventional chemotherapy. This rate is within the expected range of standard regimens combining chemotherapy with trastuzumab and pertuzumab, and surpass that achieved with other chemotherapy-free regimens.[5,8,20-24] For instance, in the PHERGain study, only 37.9% of patients who had a [^{18}F]FDG-PET response after 2 initial cycles of trastuzumab and pertuzumab, and subsequently completed 8 cycles of the same chemotherapy-free regimen, achieved a breast and axillary pCR. This rate was higher (40.8%) among patients with HER2 IHC 3+ tumors, yet still lower than in PHERGain-2 trial. Similarly, the NeoSphere trial reported a modest breast pCR of 16.8% with 4 cycles of trastuzumab and pertuzumab alone, which was only slightly improved by adding endocrine therapy.[5] However, it should be acknowledged that both the PHERGain and NeoSphere trials enrolled patients with more advanced-stage tumors and HER2-positive disease defined as IHC 2+. Whether the high pCR rates reported in our study are attributable to patient selection, neoadjuvant

treatment duration, the addition of endocrine therapy, or their combination remains unclear. Future studies integrating additional molecular biomarkers may help further contextualize these findings and refine prediction of pCR.

Disease progression during neoadjuvant therapy of HER2-positive EBC is rare. Here, despite the absence of early imaging assessments to identify non-responders and without chemotherapy intensification options, only 2 of 396 patients (0.5%) experienced disease progression. This supports the feasibility of omitting interim imaging in low-risk patients following this strategy, although it should be considered in higher-risk subsets, particularly those with larger tumors and/or lymph node involvement. Moreover, chemotherapy omission did not lead to higher mastectomy rates compared with historical controls, although this may be influenced by the small tumor size and the initially low rate of planned mastectomies in the study population.

Taken together, these findings contribute to the growing evidence supporting treatment de-escalation, including chemotherapy omission, in highly selected patients with HER2-positive EBC. In the PHERGain-2 trial, the proportion of patients completely avoiding chemotherapy (394 out of 396, 99.5%) exceeded that of the PHERGain trial (86 of 285, 30.2%). However, this does not imply that our de-escalation strategy should be limited to patients with small, node-negative, HER2 IHC 3+ tumors, although they currently appear to benefit the most from this approach.

The PHERGain trial reported excellent 3-year outcomes in patients achieving pCR with trastuzumab and pertuzumab alone, without neoadjuvant or adjuvant chemotherapy.[9] Likewise, the TRAIN-3 trial used MRI to tailor neoadjuvant treatment duration with chemotherapy and dual HER2 blockade in patients with HER2-positive EBC, showing that reducing the number of treatment cycles was both safe and effective in patients who achieved a rapid radiological complete response.[25] However, interpretation and implementation of such de-escalating strategies require caution. In the curative EBC setting, complete disease eradication and the achievement of complete and durable clinical remission remain the goal. Although pCR is an established surrogate marker, its prognostic significance irrespective of treatment modality is still under evaluation. Therefore, solid long-term efficacy data remain essential before broadly adopting de-escalation strategies in clinical practice. In PHERGain-2, follow-up is ongoing to assess its co-primary 3-year RFI endpoint. Beyond response-adapted neoadjuvant strategies, de-escalation approaches are also being explored in the adjuvant setting for patients with stage I HER2-positive EBC. In this context, the phase II ADEPT trial (NCT04569747) investigates the feasibility of omitting chemotherapy in patients with HR-positive, HER2-positive stage I disease using dual HER2 blockade with trastuzumab and pertuzumab plus endocrine therapy, with 3-year iDFS as the primary endpoint.

Trastuzumab deruxtecan (T-DXd) is expected to reshape the treatment landscape of HER2-positive EBC. In the neoadjuvant setting, DESTINY-Breast11 (NCT05113251) is evaluating T-DXd alone or followed by paclitaxel, trastuzumab, and pertuzumab (THP) in high-risk patients. Initial results showed significantly higher pCR rates with T-DXd-THP compared with standard therapy, with mature outcomes pending.[26] In the adjuvant setting, DESTINY-Breast05 (NCT04622319) demonstrated a significant improvement in 3-year iDFS with T-DXd compared with T-DM1 in patents with high-risk and residual disease after neoadjuvant therapy.[27] Despite these advances, T-DXd has limited likelihood of being incorporated into the management of stage I HER2-positive breast cancer, where treatment de-escalation is the prevailing strategy. Only if the ongoing 3-year outcomes from PHERGain-2 fail to confirm the efficacy of its de-escalation strategy, could adjuvant T-DXd be considered as an alternative to T-DM1 for the small subset of patients with residual disease after surgery.

Limitations of PHERGain-2 include the absence of a control arm, which prevents direct comparisons with standard regimens and limits the ability to draw definitive conclusions. In addition, assessment of pCR was not centralized, which may introduce inter-observer variability and affect the consistency of the results. Key strengths include a robust sample size for a single-arm phase II trial, which enhances the statistical power and generalization of the findings, the central confirmation of HER2 status, and the MRI-based tumor size evaluations, both providing an accurate patient selection and increasing the internal validity of the trial.

In conclusion, PHERGain-2 showed a meaningful HRQoL preservation at 1 year of treatment and reinforces the feasibility of response-guided, chemotherapy-free strategies in highly selected patients with HER2-positive EBC. Pending 3-year RFI outcomes, this approach may offer a less toxic yet effective alternative for patients with small, node-negative, HER2 IHC 3+ tumors. Nevertheless, caution is warranted before broadly implementing these de-escalation strategies in routine clinical practice. Although reducing treatment burden is a meaningful goal, it must be carefully balanced to avoid compromising patient outcomes. Any shift in standard care should be supported by robust long-term efficacy data to ensure that therapeutic effectiveness is maintained despite reduced treatment intensity.

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DISCLOSURE

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DATA SHARING

Data from this study will be available upon request to the corresponding author and subject to revision and approval by the PHERGain-2 trial management group, including qualified statisticians. Access to data will require a detailed proposal and a data-sharing agreement with the study sponsor, beginning at 1 month and ending 5 years after article publication. All data will be anonymized in accordance with applicable laws and regulations. Responses will be provided within 30 days.

REFERENCES

1. Hudis CA. Trastuzumab — mechanism of action and use in clinical practice. *N Engl J Med*. 2007;357(1):39-51.
2. Harbeck N, Gluz O, Christgen M, et al. De-escalation strategies in human epidermal growth factor receptor 2 (HER2)—positive early breast cancer (BC): final analysis of the West German Study Group Adjuvant Dynamic Marker-Adjusted Personalized Therapy Trial Optimizing Risk Assessment and Therapy Response Prediction in Early BC HER2- and hormone receptor—positive phase II randomized trial—efficacy, safety, and predictive markers for 12 weeks of neoadjuvant trastuzumab emtansine with or without endocrine therapy (ET) versus trastuzumab plus ET. *J Clin Oncol*. 2017;35(26):3046-3054.
3. Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med*. 2015;372(2):134-141.
4. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med*. 2017;377(2):122-131.
5. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13(1):25-32.

6. Gluz O, Nitz UA, Christgen M, et al. LBA17 Survival outcome of neoadjuvant endocrine therapy + trastuzumab and pertuzumab (ET+T+P) vs. de-escalated chemotherapy (CT)+T+P in hormone receptor positive (HR+)/HER2+ early breast cancer (EBC): WSG-TP-II trial. *Ann Oncol*. 2024;35:S1210.
7. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014;384(9938):164-172.
8. Pérez-García JM, Gebhart G, Borrego MR, Stradella A, Bermejo B. Chemotherapy de-escalation using an ^{18}F-FDG-PET-based pathological response-adapted strategy in patients with HER2-positive early breast cancer (PHERGain): a multicentre, randomised, open-label, non-comparative, phase 2 trial. *Lancet Oncol*. 2021;22(6):858-871.
9. Pérez-García JM, Cortés J, Ruiz-Borrego M, et al. 3-year invasive disease-free survival with chemotherapy de-escalation using an 18F-FDG-PET-based, pathological complete response-adapted strategy in HER2-positive early breast cancer (PHERGain): a randomised, open-label, phase 2 trial. *Lancet*. 2024;403(10437):1649-1659.
10. Garcia JMP, Cortés J, Borrego MR, et al. 197P Clinical outcomes in patients (pts) with stage cT1/T2cN0 HER2[+] breast cancer (BC) treated with neoadjuvant trastuzumab and pertuzumab (HP): an exploratory analysis from the PHERGain trial. *ESMO Open*. 2025;10:104751.
11. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med*. 2019;380(7):617-628.
12. Geyer CE, Untch M, Huang CS, et al. Survival with trastuzumab emtansine in residual HER2-positive breast cancer. *N Engl J Med*. 2025;392(3):249-257.
13. Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice guideline focused update. *J Clin Oncol*. 2018;36(20):2105-2122.
14. Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Guideline update. *Arch Pathol Lab Med*. 2020;144(5):545-563.
15. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.
16. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2017.
17. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin*. 2017;67(2):93-99.
18. Tolaney SM, Garrett-Mayer E, White J, et al. Updated standardized definitions for efficacy end points (STEEP) in adjuvant breast cancer clinical trials: STEEP version 2.0. *J Clin Oncol*. 2021;39(24):2720-2731.
19. Tolaney SM, Tayob N, Dang C, et al. Adjuvant trastuzumab emtansine versus paclitaxel in combination with trastuzumab for stage I HER2-positive breast cancer (ATEMPT): a randomized clinical trial. *J Clin Oncol*. 2021;39(21):2375-2385.
20. Gluz O, Nitz UA, Christgen M, et al. Efficacy of endocrine therapy plus trastuzumab and pertuzumab vs de-escalated chemotherapy in patients with hormone receptor-positive/*ERBB2* -positive early breast cancer: the neoadjuvant WSG-TP-II randomized clinical trial. *JAMA Oncol*. 2023;9(7):946.
21. Gianni L, Bisagni G, Colleoni M, et al. Neoadjuvant treatment with trastuzumab and pertuzumab plus palbociclib and fulvestrant in HER2-positive, ER-positive breast cancer (NA-PHER2): an exploratory, open-label, phase 2 study. *Lancet Oncol*. 2018;19(2):249-256.
22. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol*. 2013;24(9):2278-2284.
23. González-Santiago S, Saura C, Ciruelos E, et al. Real-world effectiveness of dual HER2 blockade with pertuzumab and trastuzumab for neoadjuvant treatment of HER2-positive early breast cancer (The NEOPETRA Study). *Breast Cancer Res Treat*. 2020;184(2):469-479.
24. Nitz UA, Gluz O, Christgen M, et al. De-escalation strategies in HER2-positive early breast cancer (EBC): final analysis of the WSG-ADAPT HER2+/HR− phase II trial: efficacy, safety, and predictive markers for 12 weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab ± weekly paclitaxel. *Ann Oncol*. 2017;28(11):2768-2772.
25. Van Der Voort A, Louis FM, Van Ramshorst MS, et al. MRI-guided optimisation of neoadjuvant chemotherapy duration in stage II-III HER2-positive breast cancer (TRAIN-3): a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2024;25(5):603-613.
26. Harbeck N, Modi S, Pusztai L, et al. Neoadjuvant trastuzumab deruxtecan alone or followed by paclitaxel, trastuzumab, and pertuzumab for high-risk HER2-positive early breast cancer (DESTINY-Breast11): a randomised, open-label, multicentre, phase III trial. *Ann Oncol*. 2026;37(2):166-179.
27. Geyer CE, Park YH, Shao Z-M, et al. LBA1 Trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients (pts) with high-risk human epidermal growth factor receptor 2−positive (HER2+) primary breast cancer (BC) with residual invasive disease after neoadjuvant therapy (tx): Interim analysis of DESTINY-Breast05. *Ann Oncol*. 2025;36(suppl 2):S1556-S1557.

APPENDIX 1

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