3-year invasive disease-free survival with chemotherapy de-escalation using an ^{18}F-FDG-PET-based, pathological complete response-adapted strategy in HER2-positive early breast cancer (PHERGain): a randomised, open-label, phase 2 trial

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Summary

Background PHERGain was designed to assess the feasibility, safety, and efficacy of a chemotherapy-free treatment based on a dual human epidermal growth factor receptor 2 (HER2) blockade with trastuzumab and pertuzumab in patients with HER2-positive early breast cancer (EBC). It used an ^{18}fluorine-fluorodeoxyglucose-PET-based, pathological complete response (pCR)-adapted strategy.

Methods PHERGain was a randomised, open-label, phase 2 trial that took place in 45 hospitals in seven European countries. It randomly allocated patients in a 1:4 ratio with centrally confirmed, HER2-positive, stage I–IIIA invasive, operable breast cancer with at least one PET-evaluable lesion to either group A, where patients received docetaxel (75 mg/m², intravenous), carboplatin (area under the curve 6 mg/mL per min, intravenous), trastuzumab (600 mg fixed dose, subcutaneous), and pertuzumab (840 mg loading dose followed by 420 mg maintenance doses, intravenous; TCHP), or group B, where patients received trastuzumab and pertuzumab with or without endocrine therapy, every 3 weeks. Random allocation was stratified by hormone receptor status. Centrally reviewed PET was conducted at baseline and after two treatment cycles. Patients in group B were treated according to on-treatment PET results. Patients in group B who were PET-responders continued with trastuzumab and pertuzumab with or without endocrine therapy for six cycles, while PET-non-responders were switched to receive six cycles of TCHP. After surgery, patients in group B who were PET-responders who did not achieve a pCR received six cycles of TCHP, and all patients completed up to 18 cycles of trastuzumab and pertuzumab. The primary endpoints were pCR in patients who were group B PET-responders after two treatment cycles (the results for which have been reported previously) and 3-year invasive disease-free survival (iDFS) in patients in group B. The study is registered with ClinicalTrials.gov (NCT03161353) and is ongoing.

Findings Between June 26, 2017, and April 24, 2019, a total of 356 patients were randomly allocated (71 patients in group A and 285 patients in group B), and 63 (89%) and 267 (94%) patients proceeded to surgery in groups A and B, respectively. At this second analysis (data cutoff: Nov 4, 2022), the median duration of follow-up was 43·3 months (range 0·0–63·0). In group B, the 3-year iDFS rate was 94·8% (95% CI 91·4–97·1; p=0·001), meeting the primary endpoint. No new safety signals were identified. Treatment-related adverse events and serious adverse events (SAEs) were numerically higher in patients allocated to group A than to group B (grade ≥3 62% *vs* 33%; SAEs 28% *vs* 14%). Group B PET-responders with pCR presented the lowest incidence of treatment-related grade 3 or higher adverse events (1%) without any SAEs.

Interpretation Among HER2-positive EBC patients, a PET-based, pCR-adapted strategy was associated with an excellent 3-year iDFS. This strategy identified about a third of patients who had HER2-positive EBC who could safely omit chemotherapy.

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Introduction

Human epidermal growth factor receptor 2-positive (HER2-positive) breast cancer is a clinically and biologically heterogeneous disease characterised by the amplification of the *HER2* gene (also known as *ERBB2*), or overexpression of its related kinase receptor protein, or both simultaneously. This tumour subtype accounts for approximately 15–20% of all breast cancers, and it has

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Research in context

Evidence before this study

We performed a comprehensive literature search using PubMed and MEDLINE. We initially searched for research articles published in English from database inception until Dec 1, 2015, and then we regularly updated the search until Sept 30, 2023. The search encompassed three key areas: first, de-escalation strategies in breast cancer management, second, clinical studies investigating trastuzumab and pertuzumab in human epidermal growth factor receptor 2 (HER2)-positive early breast cancer, and third, early metabolic treatment evaluation using ^{18}fluorine-fluorodeoxyglucose (^{18}F-FDG)-PET. We used the search terms "de-escalation", "early breast cancer", "HER2-positive","trastuzumab", "pertuzumab", and "PET".

Multiple clinical studies have confirmed that the pathological complete response (pCR) after neoadjuvant chemotherapy is a reliable surrogate endpoint to predict long-term outcomes in patients with early breast cancer, especially in HER2-positive and triple-negative breast cancers.

Different studies have also demonstrated encouraging antitumour activity in terms of pCR in HER2-positive patients exclusively treated with dual HER2 blockade. In addition, an early metabolic evaluation using ^{18}F-FDG-PET could help to define which patients with HER2-positive tumours have an increased probability of reaching a pCR to chemotherapy-free regimens.

In contrast to the PHERGain study, most patients included in these de-escalation trials received adjuvant chemotherapy and, consequently, the viability of the de-escalation approach could not be established. PHERGain is the first study evaluating an individualised ^{18}F-FDG-PET-based, pCR-adapted strategy that permits patients who are sensitive to exclusive neoadjuvant treatment with trastuzumab and pertuzumab to completely skip chemotherapy.

At the first planned analysis, the study met its first primary endpoint showing that the proportion of ^{18}F-FDG-PET early responder patients who reached a pCR with trastuzumab and pertuzumab was higher than that reported in previous studies assessing the same treatment in unselected patients who were HER2-positive.

Added value of this study

This study shows that the 3-year invasive disease-free survival from surgery with an innovative de-escalating approach was excellent, despite omitting chemotherapy in around one third of the patients. Outstanding 3-year outcomes were also observed in the subgroup of patients who obtained a pCR response with trastuzumab and pertuzumab and therefore never received chemotherapy. This de-escalation approach enables a significant reduction of toxicity for this specific patient population.

Implications of all the available evidence

Our ^{18}F-FDG-PET-based, pCR-adapted strategy represents a unique approach with the potential to affect the way that we design clinical trials, not only for early breast cancer patients, but also for other oncological diseases. Specifically, the PHERGain trial was able to identify a subgroup of HER2-positive early breast cancer patients who could omit chemotherapy and receive exclusive dual HER2 blockade with trastuzumab and pertuzumab without compromising efficacy. This study offers a new potential therapeutic alternative to be carefully discussed in our daily clinical practice.

been historically correlated with a high risk of recurrence and poor prognosis.[1] However, the introduction of HER2–targeted therapies has substantially improved the survival outcome of patients with HER2-positive early breast cancer (EBC) and has opened the door to de-escalate chemotherapy in selected subgroups. The neoadjuvant setting represents the best scenario for chemotherapy de-escalation, considering that pathological complete response (pCR) is a well-defined surrogate marker for long-term disease-free survival and overall survival.[2]

Multiple studies have analysed predictive factors of pCR to neoadjuvant treatment. There is a significant focus on non-invasive imaging tools that monitor the response to preoperative therapy, in particular, the potential role of ^{18}fluorine-fluorodeoxyglucose (^{18}F-FDG)-PET. The relationship between early treatment response on ^{18}F-FDG-PET and efficacy has been assessed in patients with HER2-positive breast cancer in both neoadjuvant and metastatic settings.[3,4] Among patients with HER2-positive EBC, early metabolic evaluation using ^{18}F-FDG-PET selected HER2-positive tumours with high anti-HER2 sensitivity and an increased likelihood of having a pCR to neoadjuvant HER2 blockade.[3,4]

PHERGain is an international, randomised, open-label, phase 2 trial. The study is evaluating the feasibility of a chemotherapy-free strategy based on a dual HER2 blockade with trastuzumab and pertuzumab (plus endocrine therapy for hormone receptor-positive tumours) in patients with HER2-positive EBC through an ^{18}F-FDG-PET-based, pCR-adapted strategy.[5]

At the first planned analysis, the study met its first primary endpoint. A total of 227 (80%) of 285 patients in group B, who were treated exclusively with a dual HER2 blockade of trastuzumab and pertuzumab without chemotherapy, were ^{18}F-FDG-PET responders. From this group of ^{18}F-FDG-PET responders, 86 patients (38% [95% CI 31·6–44·5]; p<0·0001 compared with the historical rate) reached a pCR.[5]

Here, we report the results for the second primary endpoint, 3-year invasive disease-free survival (iDFS) among patients included in group B who underwent surgery according to protocol. Additional efficacy

endpoints and updated safety results from groups A and B are also reported. The objective of the PHERGain study is to assess the viability of a chemotherapy-free approach in patients with HER2-positive EBC.

Methods

Study design and participants

PHERGain is a strategy-based, multicentre, randomised, non-comparative, open-label, phase 2 study in patients with HER2-positive early breast cancer.

As described previously,[5] female patients who were aged 18 years or older, and who had the following characteristics, were enrolled: previously untreated, centrally confirmed HER2-positive, stage I–IIIA, invasive, operable breast cancer (≥1·5 cm tumour size), with at least one breast lesion evaluable by ^{18}F-FDG-PET (maximum standard uptake value [SUV_{max}] ≥1·5×[mean standardised uptake value of the liver plus 2 standard deviations]); an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; a left ventricular ejection fraction (LVEF) of 55% or more; and adequate organ function. The main exclusion criteria were metastatic disease identified by standard staging evaluation (stage IV), bilateral breast cancer, or previous treatment for this invasive breast cancer. Full eligibility criteria are listed in the trial protocol (appendix pp 12–125).

This study was performed in accordance with the guidelines of the International Conference on Harmonization and ethical principles outlined in the Declaration of Helsinki. Written informed consent was required before enrolment, and all participants agreed to study-specific procedures. Approvals from appropriate regulatory authorities and ethics committees were obtained as detailed in the appendix (p 3).

Randomisation and masking

Patients who underwent baseline ^{18}F-FDG-PET were randomly assigned in a 1:4 ratio to groups A or B. A central randomisation procedure was set up with the OpenClinica web-based software. Random allocation was stratified by hormone receptor status (positive or negative). Patients with subclinical metastases detected at baseline ^{18}F-FDG-PET, but not previously detected by routine clinical assessment, were included in an exploratory group C (not reported in this Article). In this open-label study, patients, investigators, and the study team were aware of the group assignment. However, investigators participating in the centralised review of ^{18}F-FDG-PET results were masked to the group assignment.

Procedures

An overview of the study design is provided in figure 1. All study drugs were administered intravenously, except for endocrine therapy, which was given orally, and trastuzumab, which was given subcutaneously at a fixed dose of 600 mg. Chemotherapy and HER2-targeted therapies were administered every 3 weeks. The pertuzumab loading dose was 840 mg, followed by a maintenance dose of 420 mg. Docetaxel was administered at 75 mg/m². Carboplatin was administered at a dose of area under the curve, 6 mg/mL per min (AUC6). Dose modifications were not permitted for trastuzumab and pertuzumab. Dose reductions of docetaxel and carboplatin were allowed as per local prescribing information.

As reported previously,[5] ^{18}F-FDG-PET was performed before random allocation and after two cycles of neoadjuvant therapy in group A (the control group) and group B (the adaptive group). Patients allocated to group A received six cycles of docetaxel and carboplatin concurrently with trastuzumab and pertuzumab, regardless of the on-treatment ^{18}F-FDG-PET results. All patients enrolled in group B initially received two cycles of trastuzumab and pertuzumab. Hormone receptor-positive patients also received letrozole (2·5 mg per day, orally) if they were postmenopausal or tamoxifen (20 mg per day, orally) if they were premenopausal or perimenopausal. Group B patients with a 40% reduction or more of the SUV_{max} from the baseline to on-treatment ^{18}F-FDG-PET (group B ^{18}F-FDG-PET-responders) continued the same treatment for six more cycles (for a total of eight cycles of trastuzumab and pertuzumab, with or without endocrine therapy). Group B patients who did not reach this reduction (group B ^{18}F-FDG-PET-non-responders) switched to neoadjuvant chemotherapy consisting of six cycles of docetaxel and carboplatin plus concurrent trastuzumab and pertuzumab.

Patients who discontinued the neoadjuvant phase of the study treatment could start another neoadjuvant therapy, or undergo surgery outside the clinical trial. Surgery (breast conservation or mastectomy, either with sentinel lymph node biopsy or axillary dissection) according to protocol was done 2–6 weeks after the last treatment cycle of the neoadjuvant phase.

After surgery, group B ^{18}F-FDG-PET-responders who did not reach pCR received an additional six cycles of adjuvant docetaxel and carboplatin plus concurrent trastuzumab and pertuzumab. All patients from groups A and B completed up to 18 cycles of treatment with trastuzumab and pertuzumab in the absence of disease progression or unacceptable toxicity, patient withdrawal, or investigator decision. Adjuvant endocrine therapy and radiotherapy were administered as per hormone receptor status and institutional practices, respectively. Efficacy and safety assessments during the neoadjuvant phase of the study have already been extensively described.[5]

During the adjuvant phase of the study, laboratory assessments were performed every 3 weeks, at the time of study drug administration. Urine pregnancy tests, electrocardiograms, and LVEF values (with their maximum absolute change from baseline by multiple-gated acquisition scanning or echocardiography) were done every four cycles of treatment. Moreover, patients underwent a mammogram at the end of study treatment.

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See **Online** for appendix

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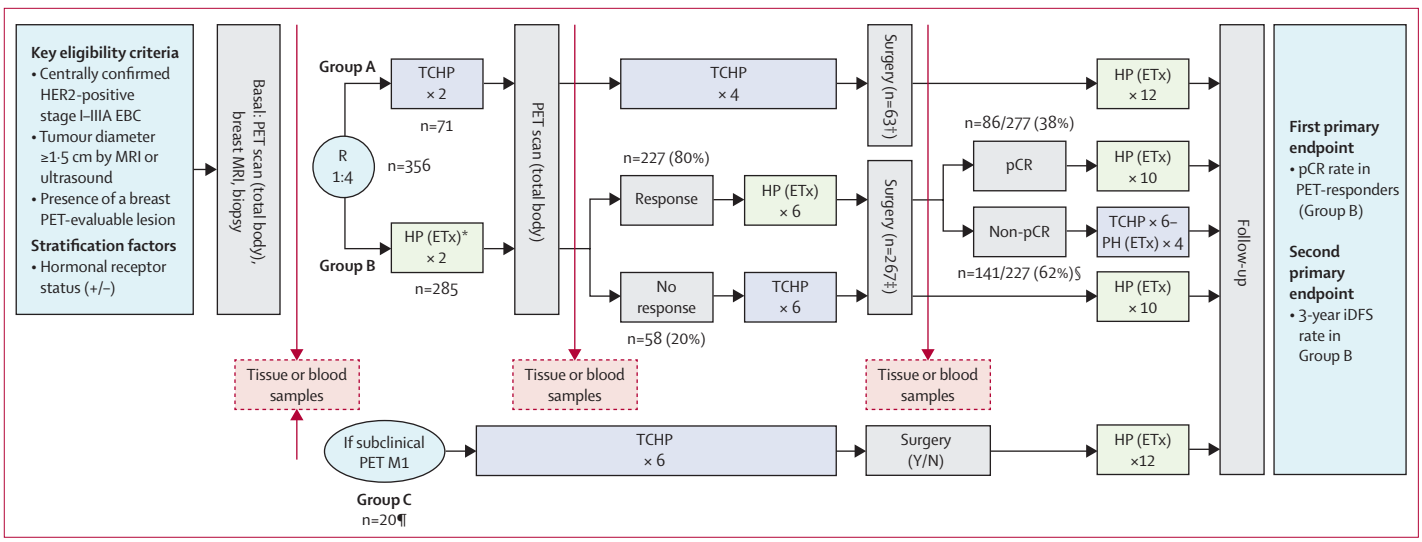

Figure 1: **Study design**

EBC=early breast cancer. ETx=endocrine therapy (letrozole if postmenopausal or tamoxifen if premenopausal). Group A=control group. Group B=adaptive group. Group C=exploratory group. HER2=human epidermal growth factor receptor 2. HP=trastuzumab (subcutaneous) and pertuzumab (intravenous). iDFS=invasive disease-free survival. M1=subclinical metastasis by PET. pCR= pathological complete response (ypT0/isN0). PET=^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography. PET-responders=patients with maximum standard uptake value reduction of 40% or greater after cycle 2. R=random allocation. TCHP=docetaxel, carboplatin, trastuzumab, and pertuzumab. *All patients who were hormonal receptor-positive received ETx concomitantly with PH (except on chemotherapy). †Eight patients in Group A discontinued treatment. Among them, three patients never received the study treatment (one patient due to the investigator's decision, and two patients withdrew informed consent themselves). Additionally, five patients discontinued treatment before surgery, with three patients experiencing toxicity-related issues and two patients withdrawing consent. ‡18 patients discontinued in Group B before surgery. Two patients did not receive study treatment (one owing to a protocol violation and one due to investigator's decision); and 16 patients were discontinued before surgery (seven patients due to progressive disease, five withdrew consent, two had protocol violations, one patient due to investigator's decision, and one patient due to toxicity). §There were ten patients in group B who were PET-responders who did not undergo surgery and were considered as non-pCR. ¶Data for Group C are not reported in this publication.

Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 was used to grade toxicity at each cycle.

During the follow-up phase of the study, which lasted from the end of study treatment until 3 years after the last patient's surgery, a physical examination was performed every 3 months during the first year, and every 6 months during the second and third years of follow-up. A mammogram was done every year. Other radiological assessments, including breast MRI, were performed if clinically indicated and according to institutional practices. All efforts were made by the investigators to rule out an invasive disease event.

Outcomes

The first primary endpoint, pCR rate (defined as disappearance of invasive cancer in the breast and axilla [ypT0/is ypN0]) as per local assessment among group B ^{18}F-FDG-PET-responders, has been reported previously.[5] Here, we report the second primary endpoint, 3-year iDFS in patients allocated to group B who underwent surgical resection according to protocol, as well as additional efficacy endpoints (ie, 3-year iDFS among patients in group A, and 3-year disease-free survival, distant disease-free survival [DDFS], event-free survival, and overall survival in patients assigned to groups A and B), and updated safety results as per CTCAE version 4.0 from groups A and B.

3-year iDFS was defined as the percentage of patients who were alive without ipsilateral invasive breast tumour recurrence, ipsilateral locoregional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, a second non-breast primary cancer, and death from any cause at 3 years after surgery. 3-year disease-free survival was defined as the percentage of patients who were alive without an iDFS event and ipsilateral or contralateral ductal carcinoma in situ at 3 years after surgery. 3-year DDFS was defined as the percentage of patients who were alive without distant disease recurrence and death from any cause at 3 years after surgery. 3-year event-free survival was defined as the percentage of patients who were alive without disease progression that precludes definitive surgery, local or distant recurrence, a second non-breast primary cancer, and death from any cause at 3 years after random allocation. 3-year overall survival was defined as the percentage of patients who were alive at 3 years after random allocation.

We performed subgroup analyses based on hormone receptor status, lymph node status, and HER2 protein expression.

Statistical analysis

Efficacy analyses for 3-year iDFS were performed in the intention-to-treat population, which included all patients who underwent random allocation and had

surgical resection of the primary tumour according to protocol. Safety data were assessed in the safety population, which included all patients who received at least one dose of study drug.

The exact binomial method was used to compare differences between observed and historical rates. Analyses were done in a fixed sequence: first, pCR endpoint, and thereafter, the 3-year iDFS endpoint in group B. It was predetermined that 3-year iDFS would be analysed at a nominal α level of 0·025 if the pCR endpoint was not met, or with a 0·05 nominal α level if the pCR endpoint was met. The statistical analysis plan for pCR has been described previously.[5]

The 3-year iDFS analysis was designed to test the null hypothesis that the true 3-year iDFS rate in patients assigned to group B who underwent surgical excision of the primary tumour was 89% or less.[6,7] The alternative hypothesis was that the true 3-year iDFS rate was greater than or equal to 95%.[6] We estimated that enrolling 284 patients in group B would provide 80% power at a nominal level of one-sided α of 0·025, assuming a 25% dropout rate. This primary objective would be met if at least 93% patients were free of an invasive disease event at 3 years among a minimum of 213 patients who underwent surgical excision of their primary tumour in group B. Thus, we planned to enrol 355 patients and randomly allocate them in a 1:4 ratio, with 71 patients assigned to group A and 284 patients assigned to group B.

The Kaplan–Meier estimator was used to estimate the percentage of patients alive without recurrence of invasive disease at 3 years. Patients who did not have an event or with a missing value at the time of data analysis had their data censored for iDFS at the date on which they were last known to be alive and disease-free. The 95% CIs were based on the log–log method. The same methods were used to estimate 3-year disease-free survival, DDFS, event-free survival, and overall survival in groups A and B. The analysis for event-free survival and overall survival were performed in all patients who underwent random allocation.

The 3-year iDFS rate for those patients who did not receive chemotherapy (group B ^{18}F-FDG-PET-responders who reached a pCR) was described due to its clinical relevance.

The trial was not designed to test a formal comparison between groups. Consequently, the 3-year survival endpoints were estimated in each group, but the treatment differences in terms of hazard ratio or p-value have not been reported. The study is registered with ClinicalTrials.gov (NCT03161353) and is ongoing.

Role of the funding source

The study was conceived and designed by Medica Scientia Innovation Research (MEDSIR) in collaboration with F Hoffmann-La Roche. MEDSIR, as legal sponsor of the study, is responsible for compliance with all clinical and regulatory procedures and adherence to the study protocol. MEDSIR was responsible for the collection, analysis, interpretation of the data, and in writing the report. All authors had full access to the data used to prepare the manuscript and participated in writing, editing, or critically reviewing the manuscript. The funder of the study had no role in data collection, data analysis, data interpretation, or writing of the report.

Results

Patients were recruited from 45 hospitals in seven countries (Spain, France, Belgium, Germany, UK, Italy, and Portugal) between June 26, 2017, and April 24, 2019. Of the 376 patients who were enrolled, 356 did not have subclinical metastases by ^{18}F-FDG-PET, and 71 (19%) were assigned to group A, and 285 (76%) were assigned to group B. 20 patients (5%) who had subclinical metastases identified by ^{18}F-FDG-PET were allocated to an exploratory group C (figure 1), not reported in this Article.

At this second analysis (data cutoff of Nov 4, 2022), the median duration of follow-up was 43·3 months (range 0·0–63·0). Patient baseline characteristics have been described previously (table 1).[5] Hormone receptor

	Docetaxel, carboplatin, trastuzumab, and pertuzumab (n=71; group A)	Adaptive group, initially treated with trastuzumab and pertuzumab (n=285; group B)
Age, years	51 (42–58)	50 (45–59)
Postmenopausal		
No	37 (52%)	146 (51%)
Yes	34 (48%)	139 (49%)
Stage		
I	9 (13%)	24 (8%)
II	50 (70%)	219 (77%)
IIIA	12 (17%)	42 (15%)
Nodal status		
Negative	39 (55%)	145 (51%)
Positive	32 (45%)	140 (49%)
Hormone receptor status		
ER-positive or PgR-positive, or both	44 (62%)	192 (67%)
ER-negative and PgR-negative	27 (38%)	93 (33%)
HER2 immunohistochemistry score and ISH analysis		
2+ and ISH positive	13 (18%)	64 (22%)
3+	58 (82%)	221 (78%)
Tumor grade		
I (well differentiated)	0	6 (2%)
II (moderately differentiated)	29 (41%)	109 (38%)
III (poorly differentiated)	33 (46%)	127 (45%)
Unknown*	9 (13%)	43 (15%)
SUV_{max}	8·7 (5·9–13.3)	10·4 (6·4–16.0)

Data are median (IQR) or n (%). ER=oestrogen receptor. PgR=progesterone receptor progesterone receptor. HER2=human epidermal growth factor receptor 2. ISH=in situ hybridisation. SUVmax=maximum standardised uptake value. *Tumour grade could not be assessed.

Table 1: **Baseline characteristics**

status was positive in 236 (66%) of 356 patients, 172 (48%) of 356 patients had lymph node involvement, and 269 (76%) of 356 patients were clinical stage II.

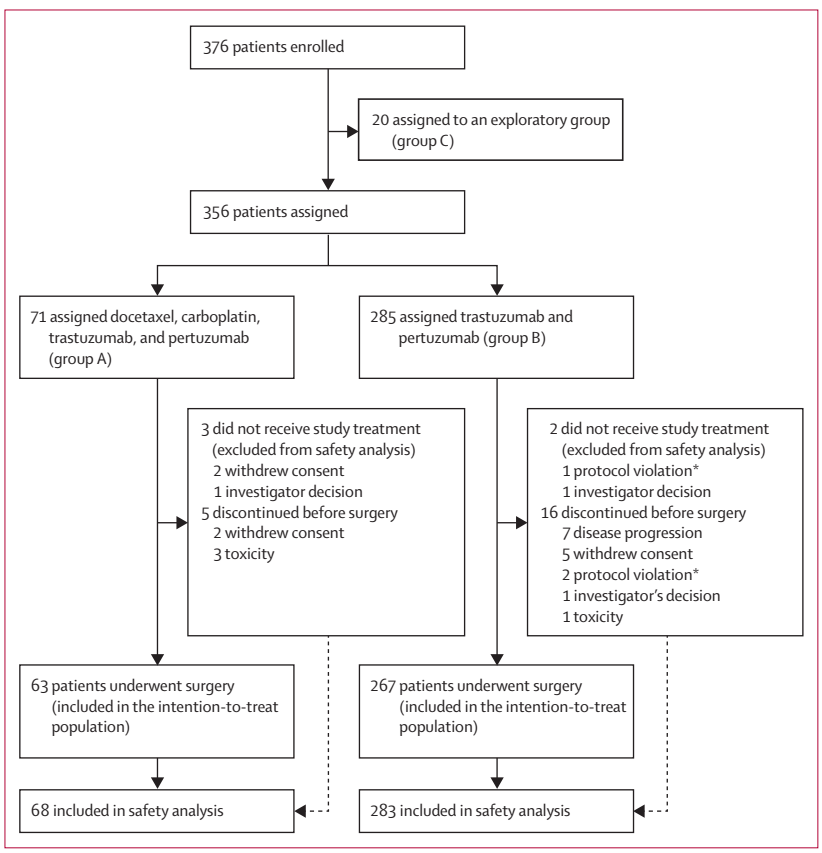

Figure 2: **Trial profile**
*Protocol violations are detailed in the appendix (p 11).

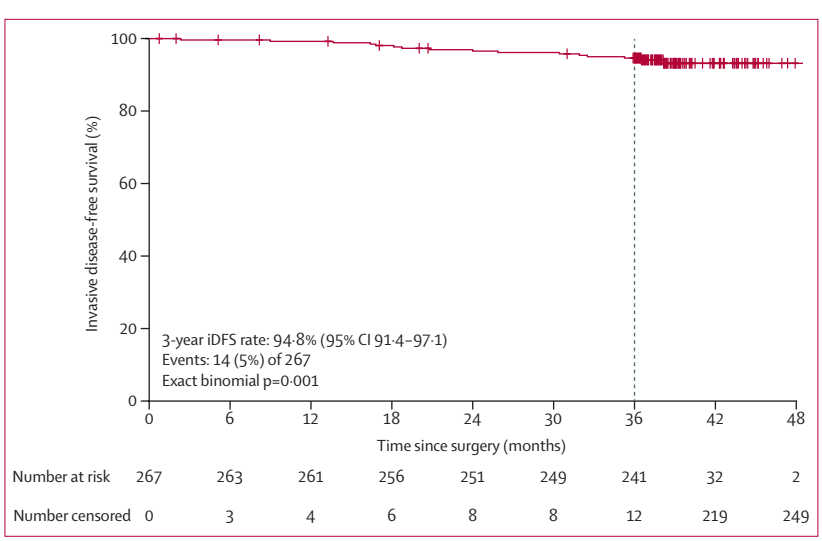

Figure 3: **3-year iDFS survival among patients included in group B**
iDFS=invasive disease-free survival. The 3-year iDFS rate has been defined as a dichotomous measure (N – events/N) to conduct the primary analysis with binomial test. The 95% CI is based on Clopper–Pearson method. Time-to-event estimation with Kaplan–Meier method for 3-year iDFS rate is 94·6% (95% CI 91·9–97·4).

A total of 68 (96%) of the 71 patients in group A and 283 (99%) of the 285 patients in group B received at least one trial drug; no patients are still receiving treatment. Among all randomly allocated patients, 63 (89%) and 267 (94%) patients proceeded to surgery according to protocol in groups A and B, respectively. The reasons for not starting study treatment and not performing surgery according to protocol have already been reported (figure 2).[5] Three group B ^{18}F-FDG-PET–non-responder patients who did not reach a pCR received adjuvant trastuzumab emtansine and 11 group B ^{18}F-FDG-PET–responder patients who did not reach a pCR were not treated with adjuvant chemotherapy as established in the protocol.

A total of 14 (5%) of 267 patients who underwent surgery according to protocol in group B had an invasive event or died. The estimated 3-year iDFS rate for the intention-to-treat population was 94·8% (95% CI, 91·4–97·1), meeting the second primary endpoint (p=0·001; figure 3).

The most common event in the analysis of iDFS was distant recurrence, which occurred in eight (3%) patients. Seven of these patients did not reach a pCR, and five of them were ^{18}F-FDG-PET-responders. A total of six of the eight patients with metastatic recurrence had node-positive disease, and the other two patients had stage II node-negative disease. The remaining iDFS events in group B included three locoregional ipsilateral relapses (1%), two second primary non-breast cancers in the ovary (1%), and one death due to suicide (<1%; table 2). 3-year iDFS was similar regardless of the hormone receptor status, lymph node status, and HER2 protein expression (appendix p 4). For patients assigned to group B, the estimated 3-year disease-free survival was 94·8% (95% CI 91·4–97·1) and DDFS was 96·5% (94·3–98·8; table 2).

The estimated 3-year iDFS in group B ^{18}F-FDG-PET–responder patients who reached a pCR and did not receive chemotherapy during the study treatment (n=86) was 96·4% (95% CI 92·4–100) with a total of three iDFS events: one locoregional ipsilateral relapse and two second, non-breast, primary cancers (both ovarian; figure 4). No distant recurrence events were observed. Consequently, 85 (99%) of these 86 patients were free of breast cancer relapse at 3 years after surgery.

Among the 63 patients included in group A who underwent surgery according to protocol, the estimated 3-year iDFS, disease-free survival, and DDFS were 98·3% (95% CI 95·1–100), 98·3% (95·1–100), and 98·3% (95·1–100), respectively (table 2).

Among all patients who were randomly allocated, the estimated 3-year event-free survival for patients assigned to groups A and B were 98·4% (95% CI 95·3–100) and 93·5% (90·7–96·5), respectively. Data on overall survival were immature at the time of this analysis. Deaths occurred in one (1%) patient in group A (distant recurrence event) and four (1%) patients in group B (three distant recurrences events and one death by suicide). The estimated 3-year overall survival for

	Docetaxel, carboplatin, trastuzumab, and pertuzumab	Adaptive group (initially treated with trastuzumab and pertuzumab)
Population who underwent surgery	n=63; group A	n=267; group B
Invasive disease-free survival		
Invasive disease-free survival events	1 (2%)	14 (5%)
Ipsilateral invasive breast tumour recurrence	0	1 (<1%)
Regional invasive breast cancer recurrence	0	2 (1%)
Contralateral invasive breast cancer	0	0
Distant recurrence	1 (2%)	8 (3%)
Second primary non-breast cancer	0	2 (1%)
Death	0	1 (<1%)
3-year invasive disease-free survival rate, % (95% CI)	98·3% (95·1–100)	94·8% (91·4–97·1)
Disease-free survival		
Disease-free survival events	1 (2%)	14 (5%)
Ipsilateral invasive breast tumour recurrence	0	1 (<1%)
Regional invasive breast cancer recurrence	0	2 (1%)
Contralateral invasive breast cancer	0	0
Distant recurrence	1 (2%)	8 (3%)
Second primary non-breast cancer	0	2 (1%)
New diagnosis of ductal carcinoma in situ	0	0
Death	0	1 (<1%)
3-year disease-free survival rate, % (95% CI)	98·3% (95·1–100)	94·8% (91·4–97·1)
Distant disease-free survival		
Distant disease-free survival events	1 (2%)	9 (3%)
Distant recurrence	1 (2%)	8 (3%)
Death	0	1 (<1%)
3-year distant disease-free survival rate, % (95% CI)	98·3% (95·1–100)	96·5% (94·3–98·8)
All patients who underwent random allocation	n=71; group A	n=285; group B
Event-free survival		
Event-free survival events	1 (1%)	18 (6%)
Disease progression	0	8 (3%)
Ipsilateral invasive breast tumour recurrence	0	1 (<1%)
Regional invasive breast cancer recurrence	0	1 (<1%)
Contralateral invasive breast cancer	0	0
Distant recurrence	1 (1%)	6 (2%)
Second primary non-breast cancer	0	1 (<1%)
New diagnosis of ductal carcinoma in situ	0	0
Death	0	1 (<1%)
3-year event-free survival rate, % (95% CI)	98·4% (95·3–100)	93·5% (90·7–96·5)
Overall survival		
Overall survival events	1 (1%)	4 (1%)
Death	1 (1%)	4 (1%)
3-year overall survival rate, % (95% CI)	98·4% (95·3–100)	98·5% (97·1–100)

Data are n (%) unless otherwise specified.

Table 2: **Time-to-event efficacy endpoints**

groups A and B were 98·4% (95·3–100) and 98·5% (97·1–100), respectively (table 2).

The incidence and severity of adverse events at the time of this analysis was different to those reported previously, mainly in group B ^{18}F-FDG-PET–responder patients who did not reach a pCR and, therefore, received adjuvant chemotherapy.[5]

Of the 351 patients included in the safety analysis, 55 (81%) of 68 patients in group A and 244 (86%) of 283 patients in group B received all the scheduled cycles of study treatment (data not shown). 77 (90%) of 86 were group B ^{18}F-FDG-PET-responders with pCR, 124 (88%) of 141 were group B ^{18}F-FDG-PET-responders without pCR, and 43 (77%) of 56 were group B

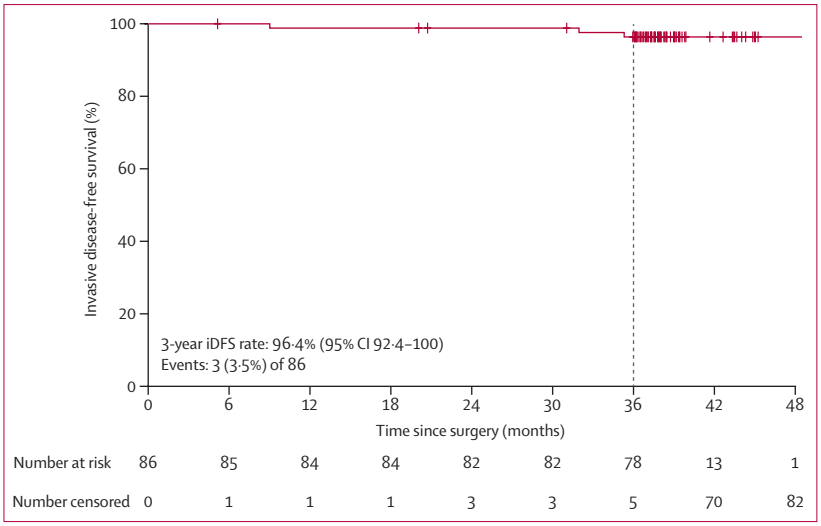

Figure 4: **3-year iDFS rate without chemotherapy in PET responders with pCR (n=86).**
Kaplan–Meier estimation for 3-year iDFS in group B ^{18}F-FDG-PET–responder patients who reached a pCR and did not receive chemotherapy during the study treatment (n=86). No distant recurrence events were observed. A total of three iDFS events were observed (one locoregional ipsilateral relapse and two second, non-breast [ovarian] primary cancers). Consequently, 99% (85 of 86 patients) were free of breast cancer relapse at 3 years after surgery. iDFS=invasive disease-free survival. ^{18}F-FDG-PET=^{18}fluorine-fluorodeoxyglucose-positron emission tomography. pCR=pathological complete response.

	Docetaxel, carboplatin, trastuzumab, and pertuzumab (n=68; group A)		Adaptive group, initially treated with trastuzumab and pertuzumab (n= 283; group B)	
	Grade 1–2	Grade ≥3	Grade 1–2	Grade ≥3
Haematological TEAEs				
Anaemia	22 (32%)	5 (7%)	67 (24%)	21 (7%)
Neutropenia	7 (10%)	19 (28%)	22 (8%)	32 (11%)
Thrombocytopenia	14 (21%)	3 (4%)	35 (12%)	10 (4%)
Febrile neutropenia	0	14 (21%)	0	38 (13%)
Non-haematological TEAEs				
Fatigue	47 (69%)	11 (16%)	169 (60%)	19 (7%)
Diarrhoea	45 (66%)	7 (10%)	177 (63%)	16 (6%)
Nausea	38 (56%)	0	106 (37%)	5 (2%)
Stomatitis	24 (35%)	6 (9%)	83 (29%)	3 (1%)
Alopecia	23 (34%)	1 (1%)	77 (27%)	2 (1%)
Vomiting	21 (31%)	1 (1%)	63 (22%)	5 (2%)
Rash	14 (21%)	1 (1%)	70 (25%)	1 (<1%)
Arthralgia	20 (29%)	0	52 (18%)	0
Dysgeusia	14 (21%)	0	40 (14%)	0

Data are n (%). TEAEs=treatment-emergent adverse effects.

Table 3: **TEAEs occurring in more than 20% of patients by maximum severity**

^{18}F-FDG-PET-non-responders. Reasons for treatment discontinuation are summarised in the appendix (p 5). Study treatment was discontinued because of toxicity in six (9%) of 68 patients in group A and six (2%) of 283 patients in group B.

Fatigue, diarrhoea, nausea, stomatitis, alopecia, anaemia, and neutropenia were the most common adverse events among patients who received chemotherapy in the neoadjuvant or adjuvant setting, whereas diarrhoea and fatigue were the most frequent adverse events identified in those patients who were not treated with chemotherapy as part of study treatment (table 3).

Incidences of treatment-related grade 3–4 toxicities and serious adverse events were higher in patients allocated to group A than to group B (grade ≥3, 42 [62%] of 68 patients *vs* 93 [33%] of 283 patients; serious adverse events, 19 [28%] of 68 patients *vs* 39 [14%] of 283 patients). Group B ^{18}F-FDG-PET–responder patients who reached a pCR presented the lowest incidence of grade 3–4 related treatment-emergent adverse events (one event [1%]) with no related serious adverse events (appendix p 6–9).

Discussion

The combination of neoadjuvant chemotherapy with dual HER2 blockade with trastuzumab and pertuzumab is the treatment of choice for patients with HER2-positive, stage II–IIIA, invasive, operable breast cancer. The PHERGain study explores an individualised ^{18}F-FDG-PET-based, pCR-adapted strategy that allows patients who are sensitive to exclusive neoadjuvant treatment with trastuzumab and pertuzumab to omit chemotherapy. The 3-year iDFS rate from surgery for patients in group B treated with this de-escalating approach was 94·8% despite omitting chemotherapy in around one third of patients. Strong 3-year outcomes were observed among group B ^{18}F-FDG-PET–responder patients who obtained a pCR with trastuzumab and pertuzumab and never received chemotherapy without any metastatic relapse.

While there are limitations of making indirect comparisons between studies, the 3-year iDFS results and the percentage of patients with a metastatic relapse observed in the PHERGain trial are in range with other clinical trials using the combination of neoadjuvant chemotherapy and dual HER2 blockade in HER2-positive EBC. In the NeoSphere and TRYPHAENA studies, the combination of neoadjuvant chemotherapy, trastuzumab, and pertuzumab reached a 3-year disease-free survival of 92% and 88%, respectively.[8,9] The KRISTINE trial also showed a 3-year iDFS of 92%, with 4% of patients developing distant metastases.[10]

Very few studies have evaluated a chemotherapy de-escalation strategy with the intention of reducing toxicities to improve the health-related quality of life of patients with breast cancer. The two largest trials were limited to patients with extremely good prognosis, mostly stage I (T1, N0), and used adjuvant treatment following surgery. The adjuvant paclitaxel and trastuzumab study[6] and ATEMPT study[11] demonstrated 3-year iDFS rates of 98·7% and 97·8% for the combination of adjuvant paclitaxel and trastuzumab and trastuzumab emtansine, respectively,[6,11] with very few distant recurrences (0·49% and 1·75%, respectively). Other trials have assessed different anti-HER2-based

chemotherapy-free combinations in the neoadjuvant setting with the intention of defining the pCR rates as well as correlating the pathological response with different biomarkers. In general, all patients were recommended to receive subsequent standard chemotherapy and, consequently, the feasibility of the de-escalation approach could not be confirmed.[12,13]

In PHERGain, by using an ^{18}F-FDG-PET-based, pCR-adapted strategy, about a third of patients were treated without chemotherapy at any time for HER2-positive EBC without compromising patient outcomes. As expected, this de-escalation approach of skipping chemotherapy was clearly associated with a more favourable toxicity profile.

In this way, PHERGain trial also reinforces that pCR in patients with HER2-positive EBC is associated with very good survival outcomes despite the type of treatment. Of interest, 98·8% of group B ^{18}F-FDG-PET-responder patients who reached a pCR on trastuzumab and pertuzumab and did not receive chemotherapy at any point of their treatment were free of breast cancer relapse at 3 years after surgery, with only one locoregional ipsilateral relapse. No distant recurrences were observed in this subgroup, in which around half of patients had basal node-positive disease. Although further research is needed, these results suggest that a pCR on exclusive trastuzumab and pertuzumab might provide similar outcomes to a pCR gained via chemotherapy with dual HER2 blockade.[8,14,15] We note that the pCR rates on exclusive trastuzumab and pertuzumab were significantly higher among HER2 immunohistochemistry scores of three than HER2 immunohistochemistry scores of two with *HER2* gene amplification.[5]

A small percentage (3%) of patients in group B experienced locoregional progression without metastatic disease during neoadjuvant treatment. All of them were receiving treatment with trastuzumab and pertuzumab. Moreover, a total of eight (3%) patients in group B developed a distant recurrence at 3 years. Metastatic relapse is the most relevant event, as it represents a life-threatening situation with limited options for a curative approach. All distant recurrences accounted for patients who presented with residual disease at the time of surgery regardless of the ^{18}F-FDG-PET initial response. Several biomarker analyses, including circulating tumour DNA and HER2DX, might help to identify patients at a higher risk of recurrence with this response guided, chemotherapy-free therapeutic strategy.[16–18]

Most adjuvant trials evaluating de-escalation approaches (eg, shorter trastuzumab duration) had a non-inferiority design and, despite the high number of patients enrolled and global efforts carried out, 1 year of adjuvant trastuzumab still represents the standard of care of HER2-positive EBC. Therefore, it is also necessary to conduct agile and more efficient strategy-based trials with adaptative designs to bring de-escalation approaches to clinical practice in the shortest amount of time in order to address the most relevant and meaningful issues for improving cancer care, especially in cases where outcomes are expected to be excellent, such as in HER2-positive EBC.[19–22]

The above-mentioned single-group, phase 2 adjuvant paclitaxel and trastuzumab trial[6] is the only practice-changing study that has successfully assessed a de-escalation strategy using a shorter and less toxic chemotherapy regimen in appropriately selected patients with stage I, HER2-positive breast cancer.[6,23] Despite its single-arm design and small sample size, this strategy has been widely accepted as the standard of care for patients with small HER2-positive tumours since the first results reporting 3-year outcomes were published. Based on the adjuvant paclitaxel and trastuzumab trial experience, the results of the PHERGain study[6] could be the basis for a new therapeutic approach to carefully discuss with patients with stage I (≥1·5 cm) and T2N0 HER2-positive breast cancer, as it would allow for a subgroup of low-risk patients to safely avoid chemotherapy. This recommendation is based on the observation that most of the metastatic recurrences in the PHERGain study were in patients with node-positive disease. Despite the growing interest in de-escalation therapeutic strategies in patients with EBC, we urge caution before using these de-escalation approaches in a curative setting. The inclusion of patients with clinical stage I cancer is of special interest, considering that the current standard of care for this patient population is the combination of chemotherapy with trastuzumab.

Although upcoming results from DESTINY-Breast05 (NCT04622319) and DESTINY-Breast11 (NCT05113251) trials will define the role of trastuzumab deruxtecan in HER2-positive EBC, there will still be a place for treatments based on dual HER2 blockade with trastuzumab and pertuzumab. The main challenge will be identifying those patients in which a PHERGain approach is enough, and recognising the patients who will need to escalate to trastuzumab deruxtecan, thus increasing toxicity and reducing the patient's quality of life. The ongoing PHERGain-2 study (NCT04733118) might strengthen the results of the PHERGain trial and help to define which patients are candidates for chemotherapy de-escalation.

The main limitations of PHERGain include its limited sample size and short follow-up. However, to validate this de-escalating strategy with a classic phase 3 non-inferiority design, it would require thousands of patients with a very long follow-up before mature results. Regarding the short follow-up, adjuvant studies conducted in patients with HER2-positive EBC have consistently shown that some recurrences can also occur after the first 3 years of follow-up. Nevertheless, despite more events observed with the longer follow-up in the adjuvant paclitaxel and trastuzumab trial, patient outcomes remain excellent after 10 years of follow-up.[23] Accordingly, extended follow-up of the PHERGain study will permit evaluation of long-term outcomes of this strategy.

Another limitation was the unavailability of trastuzumab emtansine for patients without pCR, considering that this treatment has shown increased iDFS in the KATHERINE study and has become the adjuvant standard approach for patients without pCR.[24] When the PHERGain trial was designed and conducted adjuvant trastuzumab emtansine was not approved, and therefore patients resistant to trastuzumab-based and pertuzumab-based neoadjuvant therapy were treated with the same anti-HER2 agents for 1 year in the course of their treatment before adjuvant trastuzumab emtansine was approved. This fact also reflects the opportunity to work on new chemotherapy de-escalating strategies that could further improve long-term outcomes for patients without pCR.

Third, the use of ^{18}F-FDG-PET to evaluate the treatment response has both positives and negatives. ^{18}F-FDG-PET is an expensive imaging tool with restricted access, requires a learning curve for clinicians, and despite including patients with breast tumours measuring 1·5 cm or larger, around 15% patients did not fulfil the inclusion criterion of at least one breast lesion evaluable by PERCIST criteria.[25] Conversely, cumulative evidence has consistently shown the ability of ^{18}F-FDG-PET to predict pCR during neoadjuvant treatment in patients with breast cancer, and its use at baseline has also allowed for the exclusion of patients with subclinical metastases not detected by routine clinical assessment.[3,4,26] Until additional data with different imaging methods are available, ^{18}F-FDG-PET should be used to implement the PHERGain strategy in clinical practice. It would be valuable to explore the use of breast MRI or ultrasound instead of ^{18}F-FDG-PET as an alternative assessment method of early treatment response in centres without access to ^{18}F-FDG-PET.[27]

Finally, although very few patients experienced loco-regional progression by investigators' criteria during the neoadjuvant period in group B, the study design did not allow these patients to be rescued by the introduction of neoadjuvant chemotherapy. Consequently, all these progressions were considered as a clinical event of the event-free survival endpoint, and these patients continued their treatment outside the clinical trial. There is debate on the optimal surrogate endpoint for neoadjuvant studies. Recently, event-free survival has been considered as the most accurate endpoint for the evaluation of systemic therapies given before definitive surgery. However, there is still insufficient evidence to support for traditional approval in EBC.[28]

In conclusion, this strategy-based, randomised, non-comparative, multicentre, open-label, phase 2 study showed that an ^{18}F-FDG-PET-based, pCR-adapted strategy can identify a group of patients with HER2-positive EBC who can safely omit chemotherapy and receive exclusive dual HER2 blockade with trastuzumab and pertuzumab. Although such a strategy will require further clinical investigation and prolonged follow-up, our study offers a new therapeutic alternative to be considered in our daily clinical practice that enables a significant reduction of toxicity for this patient population without compromising efficacy.

Contributors

JC and AL-C formulate the initial concept of the study. JMP-G, GG, SDC, MS-C, JC, and AL-C contributed to the final study design. MR-B, MC, AS, BB, SE-d-R, LCM, NR, AC, CA, and AP made valuable contributions as investigators. GG, AP, FD, KK, PS, MC, FM, JMP-G, MR-B, SB, JC, and AL-C were members of the trial Steering Committee. CP and ES administrated the study ensuring its successful execution. MS-C, DA-L, and LM analysed the data. JMP-G, MS-C, LM, JC, and AL-C contributed to data interpretation. JMP-G wrote the first draft of the paper. JMP-G, MS-C, DA-L, and PG were responsible for the creation of the tables and figures in the study. All authors were involved in the revision and discussion of the paper. All authors reviewed and approved the final version of the manuscript for submission.

Declaration of interests

JMP-G reports consulting roles for Roche, Lilly, Eisai, Daiichi Sankyo, AstraZeneca, Gilead, MSD, and Seattle Genetics and travel expenses from Roche. JC reports consulting roles for Roche, Celgene, Cellestia, AstraZeneca, Biothera Phgroupaceutical, Merus, Seattle Genetics, Daiichi Sankyo, Erytech, Athenex, Polyphor, Lilly, Servier, MSD, GSK, Leuko, Bioasis, and Clovis Oncology; honoraria from Roche, Novartis, Celgene, Eisai, Pfizer, Samsung Bioepis, Lilly, MSD, and Daiichi Sankyo; research funding to their institution from Roche, Ariad pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer healthcare, Eisai, F Hoffman-La Roche, Guardanth health, MSD, Pfizer, Piqur Therapeutics, Puma C, and Queen Mary University of London; and intellectual property for Medica Scientia Innovation Research (MEDSIR). MR-B reports membership of a speaker bureau and advisory board for Novartis. MC reports a research grant to their institution from Roche and the role of co-chair of the scientific committee of the International Breast Cancer Study Group. AS reports consulting roles for Roche, AstraZeneca, Seagen, Novartis, and Boehringer Ingelheim; to be part of a speaker bureau for Daiichi Sankyo, Roche, and Novartis; and travel expenses from Pfizer, Novartis, and Eisai. BB reports receiving fees for medical education in a consulting or advisory role with MSD, Roche, Pierre Fabre, Novartis, AstraZeneca, and Seagen; participating in a speakers bureau for Pfizer, Roche, MSD, Palex, Eisai, Daichii Sankyo, AstraZeneca, and Seagen. SE-d-R reports consulting roles for Daiichi Sankyo/AstraZeneca, Seagen, and Pierre Fabre; to be part of a speaker bureau for Daiichi Sankyo/AstraZeneca, Pfizer, Novartis, Seagen; to have received research funding from Roche, Synthon, Byondis, MEDSIR, SOLTI, Zymeworks, and Daiichi Sankyo/AstraZeneca; and travel, accommodation, or expenses from Pfizer, Kern Pharma, and Daiichi Sankyo/AstraZeneca. NR reports research funding from Pfizer; and to be part of speaker bureau for Novartis, Pfizer, Gilead, and Daiichi Sankyo/AstraZeneca. FM reports grants from Roche, Novartis, AstraZeneca, GSK, MSD, Clovis, Vaccibody, Gilead Sciences, and Esai; consulting fees from AstraZeneca, GSK, and Roche; honoraria from AstraZeneca, MSD, Lilly, Pfizer, Novartis, GSK, Clovis, Myriad, Daiichi Sankyo, Seagen, Pierre Fabre, and Agendia; travel support from AstraZeneca, GSK, Pfizer, and Roche; and participation in advisory boards for Palleos and Amgen. AC reports consulting or advisory roles for Daiichi Sankyo/AstraZeneca, Seagen, and Pierre Fabre; being part of a speakers bureau for Daiichi Sankyo/AstraZeneca, Pfizer, Novartis, and Seagen; institutional research funding from Roche, Synthon, Byondis, MEDSIR, SOLTI, Zymeworks, and Daiichi Sankyo/AstraZeneca; and expert testimony and travel or accommodations expenses from Pfizer, Kern Pharma, and Daiichi Sankyo/AstraZeneca. AP reports honoraria from Pfizer, Novartis, Roche, MSD Oncology, Lilly, Daiichi Sankyo, and Amgen; to have consulting roles for Roche, AstraZeneca, Peptomyc, Novartis, and Daiichi Sankyo; research funding to their institution from Roche, AstraZeneca, Novartis, and Reveal Genomics; to have intellectual property (ERBB2 and HER2DX patents); travel expenses from Daiichi Sankyo; and a share in ownership at Reveal Genomics. PS reports honoraria from Pfizer, AstraZeneca, Novartis, Roche, Merck, and Boehringer Ingelheim; a consulting role in Pfizer, AstraZeneca, Novartis, Roche, Merck, Boehringer Ingelheim,

Bayer, Eisai, Celgene, and Puma; and grants to their institution from Roche, Genentech, Oncogenex, and Novartis. SB reports a consulting or advisory board role at Daiichi Sankyo, AstraZeneca, Novartis, and Roche; speaker or conference fees from Daiichi Sankyo, AstraZeneca, Novartis, and Roche; and travel fees from Daiichi Sankyo, AstraZeneca, Novartis, and Roche. SDC reports receiving fees for medical education from Novartis, Pierre Fabre, and IQVIA; institutional grant IG 20774 of Fondazione AIRC per la Ricerca sul Cancro; Cancer Can.Heal European EU4 Health Programme 101080009–European Commission; and serving as an ad hoc medical advisor for MEDSIR. MG reports honoraria from Roche, Novartis, Gilead, and AstraZeneca; travel grants and accommodation from Roche, Pfizer, and AstraZeneca; and an advisory role at Gilead. GA reports honoraria from MEDSIR. AL-C reports leadership roles at Eisai, Celgene, Lilly, Pfizer, Roche, Novartis, and MSD; intellectual property for MEDSIR and Initia Research; to have consulting roles for Lilly, Roche, Pfizer, Novartis, Pierre Fabre, GenomicHealth, and GSK; to be part of a speakers bureau for Lilly, AstraZeneca, and MSD; research funding from Roche, Foundation Medicine, Pierre Fabre, and Agendia; and travel expenses from Roche, Lilly, Novartis, Pfizer, and AstraZeneca. CP, ES, DA-L, PG, JR-M, LM, and MS-C are employees of MEDSIR. All other authors declare no competing interests.

Data sharing

Data collected within the PHERGain study will be made available to researchers whose full proposal for their use of the data has been approved by the PHERGain Trial Management Group, which includes a qualified statistician. The data required for the approved specified purposes and the trial protocol will be provided after completion of a data sharing agreement that will be set up by the study sponsor. The data will be made available 2 years after publication. Please address requests for data to the corresponding author.

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