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A phase 2 study of chemotherapy de-escalation using a pathological response-guided strategy in patients with HER2-positive, low-risk early breast cancer: PHERGain-2

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BACKGROUND

- The introduction of trastuzumab (H) and pertuzumab (P) with ado-trastuzumab emtansine (T-DM1) has drastically improved clinical outcomes in patients (pts) with HER2-positive early-stage breast cancer (EBC), allowing to explore chemotherapy-sparing approaches in this population [1].
- PHERGain trial is evaluating the efficacy of dual HER2-blockade with H plus P as both neoadjuvant and adjuvant treatment using an ^{18}F-fluorodeoxyglucose-PET-based and a pathological response-adapted strategy. Among PET-responder pts who received exclusively neoadjuvant H plus P ± endocrine therapy (ET) as per hormone receptor (HR) status, 37.9% (95% CI 31.6-44.5%) achieved a pathological complete response (pCR) [2].
- As reported in previous studies [3,4], PHERGain obtained a higher pCR rate in pts with HER2 immunohistochemistry score 3+ tumors than in those with HER2 immunohistochemistry score 2+ and *in situ* hybridization-positive tumors [2]. The relationship between HER2 protein expression and pCR with H and P in EBC seems extremely relevant for future de-escalating strategies [3].
- PHERGain-2 study is an additional step forward and was designed to assess the feasibility of chemotherapy de-escalation with neoadjuvant H and P followed by adjuvant treatment with either H and P or T-DM1 using a pathological response-adapted strategy in low-risk HER2-positive EBC pts.

STUDY DESIGN

- PHERGain-2 is a response-adapted, multicenter, open-label, non-comparative, investigator-initiated phase 2 study (NCT04733118).
- Neoadjuvant treatment will consist of 8 cycles of fixed-dose combination of H and P along with ET as per HR status.
- Surgery will be performed within 4 weeks from the last dose of the neoadjuvant treatment.
- Adjuvant treatment will be started within 4 weeks after surgery and pts will be assigned to one of the following three groups according to their pathological response:
  - **Group A**: Pts who achieve a pCR in the breast and axilla (ypT0/is, ypN0) will receive an additional 10 cycles of fixed-dose combination of H and P along with ET as per HR status.
  - **Group B**: Pts who do not achieve a pCR (residual invasive breast tumor and/or ypN0(i+), ypN0(mol+), ypN1mi) will receive 10 cycles of T-DM1 along with ET as per HR status.
  - **Group C**: Pts with macro-metastatic lymph node involvement (ypN1–3) will receive 10 cycles of T-DM1 along with ET as per HR status. Chemotherapy of physician's choice may be administered before adjuvant T-DM1.
- An overview of the study design is shown in **Figure 1**.

STUDY OBJECTIVES

Primary Objective Of Efficacy

- To assess 3-year recurrence-free interval (3y-RFI) –defined as time from registration until invasive recurrence in the ipsilateral breast or locoregionally, at a distant site, or death from breast cancer as per Standardized Definitions for Efficacy End Points (STEEP) criteria in adjuvant breast cancer clinical trials.

Primary Objective Of Safety

- To assess 1-year health-related quality of life (HRQoL) deterioration –defined as the proportion of pts with a ≥10% global health status decline from start of neoadjuvant treatment by the EORTC QLQ-C30 and QLQ-BR23 questionnaires– in the overall population.

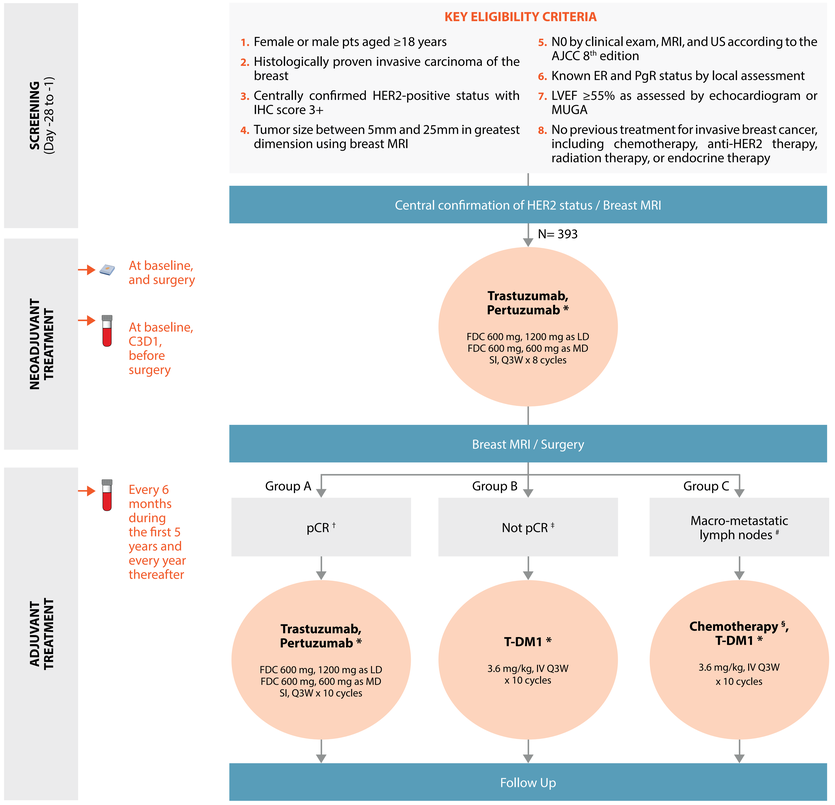
Secondary Objectives

- To determine 5-year RFI, 3-year and 5-year event-free survival, relapse-free survival, distant relapse-free survival, disease-free survival, invasive disease-free survival, overall survival, and breast cancer-specific survival (BCSS) in the overall population.
- To assess the proportion of pts with pCR in breast and axilla (ypT0/is, ypN0) and breast (ypT0/is) as determined by a local pathologist in the overall population, and according to HR status.
- To assess residual cancer burden (RCB) index as determined by a local pathologist in the overall population and according to HR status.
- To determine objective response rate (ORR) per RECIST 1.1 as measured by breast magnetic resonance imaging in the overall population.
- To determine the correlation of pCR in breast and axilla (ypT0/is, ypN0) and breast with ORR per RECIST 1.1, RCB index, and BCSS in the overall population.
- To determine the ratio of pts who received adjuvant chemotherapy in the overall population.
- To assess the overall safety and tolerability profile of neoadjuvant and adjuvant treatments as per NCI-CTCAE 5.0, and cardiac toxicity profile after 1 year of adjuvant treatment.
- To determine HRQoL as assessed by the EORTC-QLC-C30 and QLQ-BR23 questionnaires in the overall population.

Exploratory Objectives

- To determine the correlation between pCR rates and intrinsic molecular subtypes as determined by PAM50 assay.
- To monitor pharmacodynamic levels of miRNA and circulating tumor DNA and determine their predictive value.
- To evaluate the predictive value of tumor infiltrating lymphocytes and additional biomarkers.
- To determine the correlation between molecular factors with early relapse rates.

FIGURE 1. STUDY DESIGN



* Pts with hormone receptor-positive early breast cancer will receive endocrine therapy concomitantly (except when on chemotherapy).
† Pts who obtained a pathological complete response (ypT0/is, ypN0) after neoadjuvant regimen.
‡ Pts who have residual invasive breast tumor and/or ypN0(i+), ypN0(mol+), ypN1mi after neoadjuvant regimen.
# Pts who have macro-metastasis in the axillary lymph nodes (ypN1–3) after neoadjuvant regimen.
§ Chemotherapy of physician's choice may be administered before adjuvant T-DM1.

AJCC, American Joint Committee on Cancer; ER, estrogen receptor; FDC, fixed-dose combination; IHC, immunohistochemistry; IV: Intravenously; LD, loading dose; LVEF, left ventricular function; MD, maintenance dose; MRI, Magnetic resonance imaging; MUGA, multiple-gated acquisition scan; PD: Progressive disease; Pts: Patients; PgR, progesterone receptor; Q3W, once every 3 weeks; SI, subcutaneous injection; US, ultrasound.

STATISTICAL METHODS

Primary Objective Of Efficacy

- 3y-RFI will be analyzed on full analysis set.
- Accrual period of 18 months and an additional 42 months of follow-up for primary analysis (maximum follow-up of 6 to 7 years).

Statistical Assumptions

- Sample size based on the one sample non-parametric survival confidence interval based on the log-minus-log Kaplan–Meier estimator.
- Decisions will be based on the 95% confidence interval calculated with Kaplan-Meier method (Null hypothesis: 3y-RFI ≤94%).
- This analysis was designed to attain an 80% power (Alternative hypothesis: 3y-RFI ≥ 98%) at α=5% two-sided level.
- We considered a 20% dropout rate.

TRIAL ENROLLMENT

- PHERGain-2 study was opened to accrual in May 2021 and currently recruiting in 21 institutions from Spain.
- An additional 5 countries (Germany, Italy, Hungary, Bulgaria, and Poland) are participating.

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