San Antonio Breast Cancer Symp - In 05-09 December 2017

Abstract: #66

CHEMOTHERAPY-FREE TRASTUZUMAB AND PERTUZUMAB(PH) IN HER2[+] BREAST CANCER(BC): FDG-PET RESPONSE-ADAPTED STRATEGY. THE PHERGAIN STUDY.

Antoni Llombart[1,10], Giuseppe Curigliano[2], Geraldine Gebhart[3], Joseph Gligorov[4], Kerrou Khaldoun[4], Frederik Marmé[5], Aleix Prat[6], Peter Schmid[7], Javier Cortes[8,10] and José Perez[9,10].

[1]Hospital Arnau de Vilanova, Valencia, Spain [2]Istituto Europeo di Oncologia Milano, Italy [3]Institute Jules Bordet, Brussels, Belgium [4]Hôpital Tenon AP-HP, Paris, France [5]National Center for Tumor Disease (NCT), Heidelberg, Germany [6]Hospital Clínic i Provincial de Barcelona, Spain [7]Barts Cancer Institute, London, United Kingdom [8]Hospital Ramón y Cajal, Madrid, Spain [9]Instituto Oncológico Baselga, Hospital Quirón, Barcelona, Spain [10]Medica Scientia Innovation Research (MedSIR), Barcelona, Spain

BACKGROUND:

- Several studies have confirmed that a significant subset of patients (pts) with HER2 [+] BC achieve pathological complete response (pCR) with a dual HER2 blockade without chemotherapy [1,2].
- Early metabolic evaluation using 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) might help to recognize those pts with a higher likelihood of obtaining a pCR and an excellent outcome [3].
- It is mandatory to design a strategy-based study to de-escalate systemic therapy for HER2-positive pts using the neodajuvant setting.

INCLUSION CRITERIA:

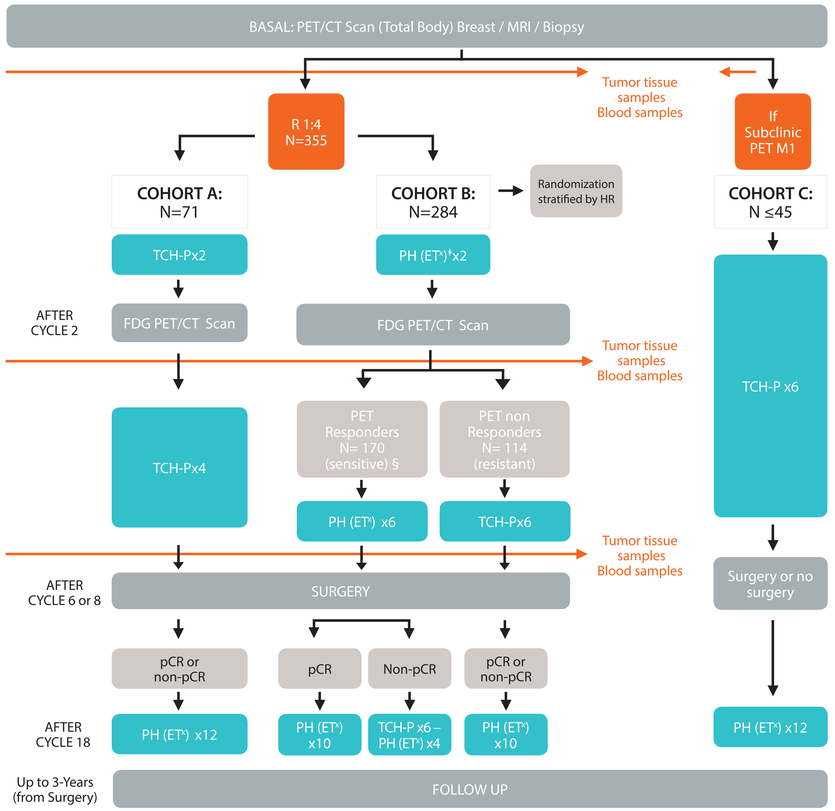
1. Pts age ≥ 18 years.
2. Operable breast cancer (cT1-3 and/or cN0-2 tumors).
3. Centrally-confirmed HER2 [+] by ASCO/CAP criteria.
4. Known estrogen receptor (ER) and progesterone receptor (PR) status locally determined.
5. Tumor size:
   - Diameter larger ≥ 1.5 cm by magnetic resonance imaging (MRI) or ultrasound.
   - Maximum standardized uptake value (SUVmax) ≥1.5 x SUVmean liver + 2 SD in FDG PET/CT.
   - Multicentric/multifocal allowed if ≥2 HER2 [+] lesions with a diameter larger ≥ 1.5 cm by MRI or ultrasound.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
7. Adequate bone marrow and organ function.

EXCLUSION CRITERIA:

1. Bilateral breast cancer or cT4 and/or cN3 tumors.
2. Evidence of metastatic disease by routine clinical assessment. Patients with subclinic metastases (M1) according with FDG PET/CT will be included into Cohort C.
3. Other malignancy ≤ 5 years.
4. Clinically significant cardiovascular disease.
5. Prohibited treatments:
   - Previous chemotherapy, anti-HER2, radiotherapy, or endocrine therapy for invasive breast cancer.
   - Currently receiving anti-coagulant therapy, chronic treatment with corticosteroids, or another immunosuppressive agent.
   - Receiving any investigational treatment within 28 days prior to randomization.
6. Uncontrolled infection or current infection with HIV, hepatitis B virus, or hepatitis C virus.
7. Severe and/or uncontrolled medical condition that contraindicate patient participation.

TRIAL DESIGN

This is a randomized, multicenter, non-comparative phase II trial.



H, Herceptin SC; P, Perjeta IV; C, Carboplatin; T, Docetaxel; ETᵡ, endocrine therapy (letrozole – post-menopausal / tamoxifen – pre-menopausal), PH(ETᵡ), trastuzumab and pertuzumab + endocrine therapy; TCH-P, trastuzumab and pertuzumab + docetaxel and carboplatin.

ǂ All ER+ patients will receive ETᵡ concomitantly with PH (except on chemotherapy)

§ PET RESPONDERS - sensitive: RECIST responders with SUV reduction >=40%

PRIMARY OBJECTIVES:

- **1st co-primary endpoint: the rate of pCR as defined by the absence of invasive disease in the breast and axilla (ypT0/isN0) at the time of surgery achieved with PH ± endocrine therapy in PET responders pts (cohort B/PET responders).**
- **2nd co-primary endpoint: 3-year (3-y) invasive disease-free survival (iDFS) rate defined as time from the first date of no disease to invasive recurrence, new invasive disease, or death by any cause in cohort B.**

SAMPLE SIZE:

- Total accrual will be 400 pts, with 71, 170, 114, and 45 pts included in cohorts A, B (PET-responders), B (PET non-responders), and C, respectively.
  - Considering a 10% and 25% of drop-out rates at the time of 1st and 2th co-primary analysis, the study will be positive if ≥41 pts achieved a pCR in cohort B/PET responders; or if we observe ≤14 events of 3-y iDFS in cohort B.
  - Decisions will be based on one-sided, exact binomial test. With a 2.5% type I error rate (H0: pCR ≤20% and 3-y iDFS ≤89%) and 80% power (HA: pCR ≥30% and 3-y iDFS ≥95%).

SECONDARY OBJECTIVES:

- Other definitions of pCR
- Rates of breast-conserving surgery
- Tumor response by MRI
- Optimal FDG PET cut-off for pCR and other
- FDG PET/CT quantification parameters beside SUVmax for pCR
- DFS
- Distant-DFS
- Overall survival
- Progression-free survival
- Health-related quality of life
- Translational sub-studies will analyze biomarkers that may be predictive of response to dual HER2 blockade with PH:
  - PAM50 intrinsic subtypes
  - mRNA HER2 expression
  - Tumor-infiltrating lymphocytes
  - ctDNA
  - PIK3CA mutations
  - p53 mutations
  - Immune-related genes expression
  - Other genes expression included in the 72 gene RNA-based CodeSet)

BIBLIOGRAPHY

(1) Llombart-Cussac A et al. HER2-enriched subtype as a predictor (…), single-group,multicentre, phase 2 trial. Lancet Oncol.2017 Apr;18 (4):545-554.

(2) Gianni L et al. Efficacy and safety (…) (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012 Jan;13 (1):25-32.

(3) Coudert B et al. Use of [(18)F]-FDG PET to Predict Response (…) Randomised Phase 2 Trial». The Lancet. Oncology 15 (13): 1493-1502.

ACKNOWLEDGEMENT

We thank all participating patients and study team involved in PHERGAIN trial as well as ROCHE for their outstanding collaboration and support.

TRIAL REGISTRATION: NCT03161353. Date: May 15, 2017. 1st patient included: June 26, 2017.