BACKGROUND:

- Several studies have confirmed a significant subset of patients (pts) with HER2+ BC achieve pathological complete response (pCR) and an excellent outcome.
- It is mandatory to design a strategy-based study to de-escalate systemic therapy for HER2+ positive pts using the metabolic setting.
- 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 pCR and an excellent outcome.

INCLUSION CRITERIA:

- Pts age ≥ 18 years.
- Operable breast cancer (T1-3 and/or N0-2).
- Centrally-confirmed HER2 [+ ] by ASCO/CAP criteria.
- Adequate bone marrow and organ function.
- Evidence of metastatic disease by routine clinical assessment. Patients with subclinical metastases (M1) according with FDG PET/CT will be included in Cohort C.
- Basal: PET/CT Scan (Total Body) Breast / MRI / Biopsy.
- Tumor response by MRI and PET/CT quantification parameters beside SUVmax for pCR will be included in Cohort C.

EXCLUSION CRITERIA:

- Bilateral breast cancer or CT4 and/or CT3 tumors.
- Other malignancy ≤ 5 years.
- Clinically significant cardiocvascular disease.
- Prohibited treatments: Previous chemotherapy, anti-HER2 radiotherapy, or endocrine therapy for invasive breast cancer.
- Currently receiving anti-coagulant therapy, chronic treatment with corticosteroids, chronic treatment with HIV, hepatitis B virus, or hepatitis C virus.
- Uncontrolled infection or current infection that may be predictive of response to dual therapy.
- Other definitions of pCR may be predictive of response to dual therapy.

TRIAL DESIGN

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

**TRIAL OBJECTIVES:**

- **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 and 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.

- **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.
    - Distal-OFS.
    - 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.
  - miRNA HER2 expression.
  - Tumor infiltrating lymphocytes.
  - ctDNA.
  - PIK3CA mutations.
  - p53 mutations.
  - Immune-related genes expression.
  - Other genes expression included in the 72-gene RNA-based Code5.

- **Sample size:**
  - Total accrual will be 400 pts, with 70, 170, 144, and 45 pts included in cohorts A, B (PET-responders), B (PET-non-responders), and C, respectively.

- **Follow-up:**
  - Up to 5 years after surgery.

- **BIBLIOGRAPHY:**

- **ACKNOWLEDGEMENT:**

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