GeparPiPPa - A randomized, open-label, phase II trial comparing neoadjuvant trastuzumab, pertuzumab and endocrine therapy +/- the PI3K inhibitor inavolisib in patients (pts) with HER2+/HR+, *PIK3CA* mutant early breast cancer (BC)

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Background

Neoadjuvant treatment has become the standard of care for HER2-positive (+) breast cancer. HER2+/hormone receptor-negative and HER2+/hormone receptor-positive (HR+) breast cancers are biologically distinct, with less aggressive characteristics and less chemosensitivity of HER2+/HR+ subgroup.[1]

Several attempts have been made to use a more targeted approach in HER2+/HR+ breast cancer by investigating different anti-HER2 therapies with or without endocrine therapies in pre-and postmenopausal women.

The PI3K/AKT/mTOR pathway was found to be a key survival mechanism responsible for endocrine resistance, and crosstalk between HR and the PI3K/AKT/mTOR pathways has been described. In addition, inhibition of PI3K signaling results in activation of HER2-pathway.[2,3,4,5,6,7]

PIK3CA mutations can be found in about 20%-30% of HER2+ breast cancer patients and indicate a lower response to chemotherapy and anti-HER2 therapy, especially in HER2+/HR+ tumors.[8,9,10]

The phase III Solar-1 study demonstrated a significant improvement in progression-free survival with the addition of alpelisib to fulvestrant in *PIK3CA*-mutant metastatic breast cancer.[11]

GeparPiPPa investigates - in the neoadjuvant setting - the potential incremental efficacy and safety of inavolisib, an oral pure PI3Kα inhibitor, in addition to endocrine and anti-HER2 therapy, in patients with early HER2+/HR+ and *PIK3CA*-mutant breast cancer.

Study Overview

GeparPiPPa (GBG 105/EUDRA-CT 2021-002323-38) is a multicenter, randomized, open-label, parallel-group, phase II study. Approximately 170 patients with early-stage HER2+/HR+, *PIK3CA*-mutant breast cancer will be randomized in a 1:1 ratio to receive neoadjuvant endocrine therapy in combination with dual anti-HER2 blockade consisting of ready-to-use fixed-dose combination of pertuzumab and trastuzumab as subcutaneous (PH-FDC SC) formulation q3w for 6 cycles (18 weeks) with or without inavolisib (9mg 1x1/d orally, day 1-21 q3w). Endocrine therapy consists of either tamoxifen 20mg or an aromatase inhibitor (1x1/d orally, day 1-21 q3w). Premenopausal women and men receive a gonadotropin-releasing hormone (GnRH) analogue in addition to an aromatase inhibitor. After end of therapy, patients will undergo a core biopsy and/or surgery. In case of tumor residuals in the biopsy, additional neoadjuvant treatment may be given. In case of ycT0 and no tumor residuals in the biopsy, it is recommended to undergo surgery. Further (neo)adjuvant systemic treatment and radiotherapy will be administered at the discretion of the investigator and according to standard of care.

Primary objective:

- To compare pathological complete response (pCR=ypT0/is ypN0) rates between the two treatment arms

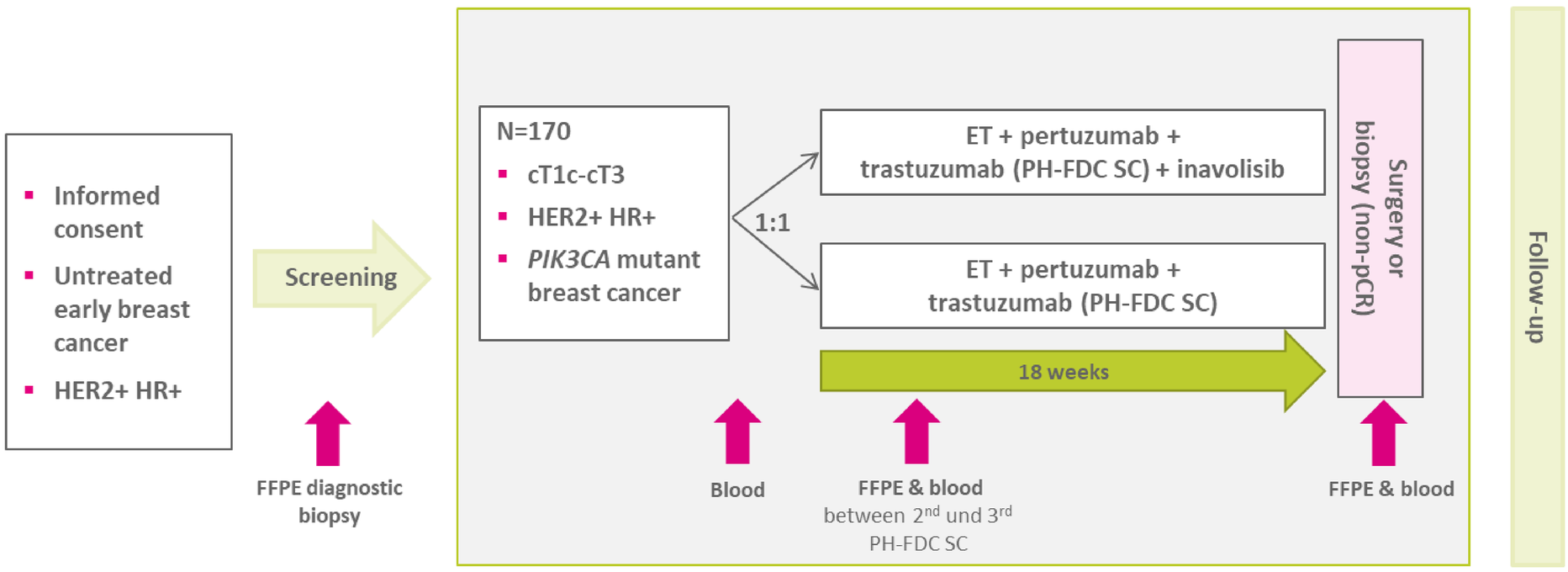
Secondary objectives (selection):

- To assess other pCR definitions
- To assess invasive disease-free survival and overall survival
- To assess breast conservation rate
- To assess safety, tolerability and compliance

Correlative objectives (selection):

- To examine molecular/pathway markers in core biopsies and residual disease
- To assess the predictive/prognostic effect of different *PIK3CA* hot spot mutations
- To explore potential novel biomarkers through the use of baseline and on-therapy specimens

Figure 1. GeparPiPPa Study Design



Study Treatment:

- Endocrine Therapy (ET): tamoxifen or an aromatase inhibitor (1x1/d orally, day 1-21 q3w) +/- GnRH analogue
- Pertuzumab/trastuzumab as subcutaneous formulation on d1, q3w:
  - Loading dose 1st cycle: 1200 mg/600 mg
  - 2nd-6th cycles: 600 mg/600 mg
- Inavolisib 9mg 1x1/d orally, day 1-21 q3w

Supportive Treatment:

- Strategies for prevention of stomatitis, hyperglycemia (including home glucose monitoring), and diarrhea are provided in the protocol

Key Inclusion Criteria

- Age ≥ 18 years
- Females or males
- Diagnosis of a unilateral primary carcinoma of the breast by core needle biopsy
- Central testing must confirm HER2 positivity and HR positivity (according to ASCO/CAP guidelines) as well as *PIK3CA* mutation(s) (tumor)
- Primary tumor must be cT1c – cT3
- Normal cardiac function must be confirmed by ECG and cardiac ultrasound (LVEF ≥55%)
- Complete staging work-up prior to randomization

Key Exclusion Criteria

- Excisional biopsy or lumpectomy and/or surgical axillary staging procedure prior to randomization
- Patients with definitive clinical or radiologic evidence of Stage IV BC
- Need of immediate neoadjuvant chemotherapy, e.g. inflammatory BC
- Body-Mass Index >30
- Patients with diabetes mellitus type I or uncontrolled type II
- Patients with currently documented pneumonitis/interstitial lung disease
- Patients with active uveitis or vitritis, history of uveitis, or active infectious process in the eye

Collection of Biomaterial

Study requirements	Screening	Pre-treatment	After 2nd/ before 3rd dose of PH-FDC SC	At end of treatment
FFPE tissue breast tumor	X[1]		X	X
Whole blood		X		
Plasma collection ctDNA		X	X	X

1. Central testing of *PIK3CA* mutation status

Follow-Up

Information on the health status of German patients will be collected within the GBG's patient self-reporting registry (Patientenselbstauskunft) and of patients from other countries within the GBG's long-term registry of previous study participants (Eternity[B]).

Recruitment

- The study will be conducted in approximately 50 GBG and IBCSG sites.
- First patient in Q IV/2022.

References

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