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

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Background

PIK3CA mutations, identified in 20%-30% of HER2+ eBC patients, correlate with poorer response to chemotherapy (CT) combined with anti-HER2 therapy, especially in HER2+/HR+ tumours[1]. CT-free regimens (T+P+ET) resulted in a 23.6% pathological complete response (pCR) rate in unselected HER2+/HR+ tumors in the TPII trial[2]. Adding a PI3K inhibitor to ET in *PIK3CA*mut HER2-/HR+ metastatic BC was deemed clinically beneficial in the SOLAR-1 trial[3]. The phase III INAVO120 study showed significant improvement in median progression-free survival with favorable safety profile when inavolisib was added to palbociclib and fulvestrant in patients with *PIK3CA*mut, HER2-/HR+ advanced BC with early resistance to adjuvant endocrine therapy[4]. These results provide rationale for the GeparPiPPa study investigating efficacy and safety of neoadjuvant inavolisib, ET, and dual HER2-blockade in patients with early HER2+/HR+ and *PIK3CA*mut eBC.

Study design

GeparPiPPa (GBG 105; NCT05306041) is a multicenter, randomized, open-label, phase II trial enrolling eBC patients with cT1c – cT3, and centrally confirmed HR+/HER2+ and *PIK3CA*mut tumors. The primary endpoint is pCR (ypT0/is ypN0). 170 patients will be randomised 1:1 to receive 6 cycles of fixed dose subcutaneous T+P (PH-FDC SC) q3w plus ET +/- GnRH analogue with or without inavolisib. Patients with *PIK3CA* wild-type tumors may join the observational cohort outside the trial.

Study overview and objectives

Primary objective:

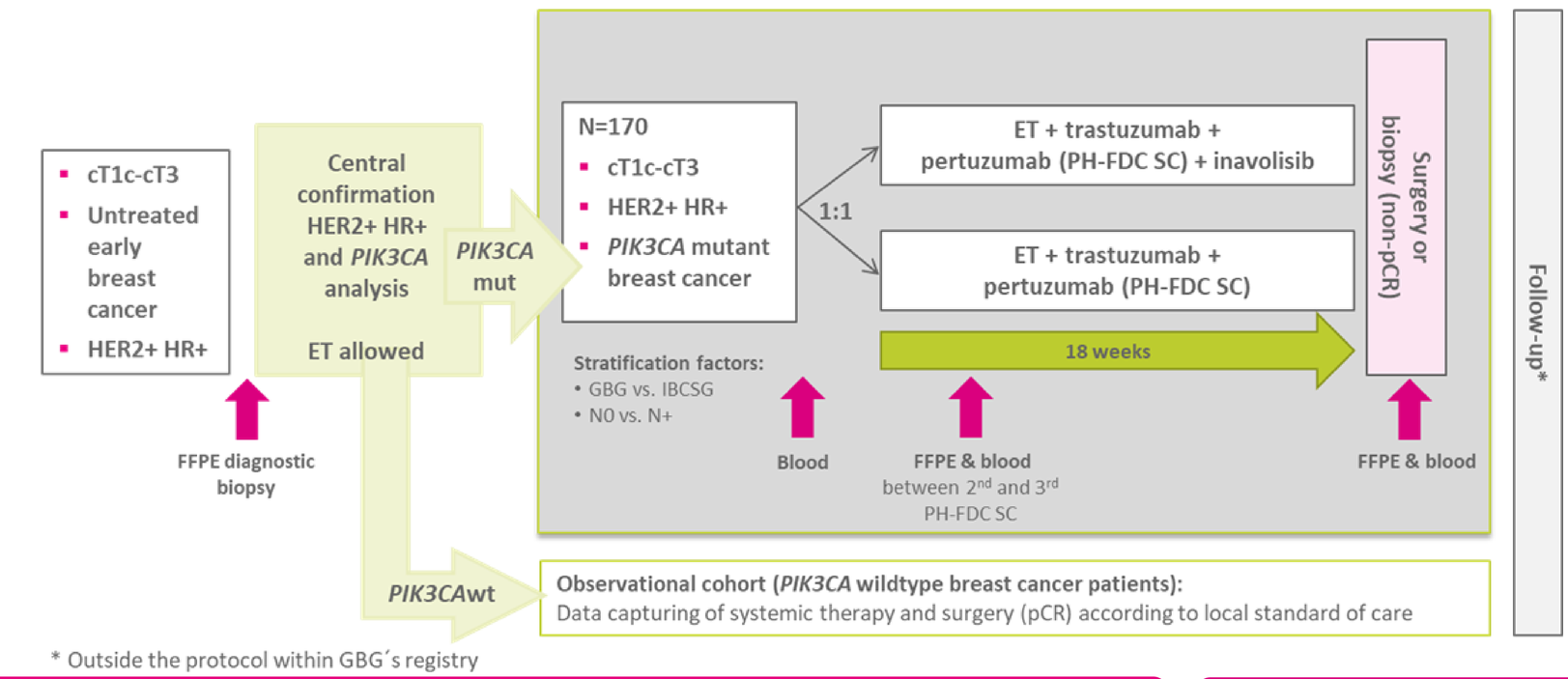
- To compare pCR (ypT0/is ypN0) rates between HER2+, HR+, *PIK3CA*mut eBC treated with inavolisib concurrently given to ET and PH-FDC SC vs. ET and PH-FDC SC alone.

Secondary objectives:

- To determine the rates of ypT0 ypN0; ypT0 ypN0/+; ypT0/is ypN0/+; ypT(any) ypN0
- To assess the pCR rates per arm separately for the stratified subpopulations
- To determine the response rates of the breast tumor in the two arms
- To determine the percentage of patients receiving additional neoadjuvant chemotherapy after residual disease
- To determine the breast conservation rate
- To assess early safety and tolerability after the first 20 and the first 40 patients after two cycles of therapy
- To assess the overall safety and tolerability and treatment compliance in the two arms
- Invasive disease-free survival and overall survival in the two arms

Translational research objectives:

- To examine and compare molecular markers such as Ki67, tumor infiltrating lymphocytes, AKT, PTEN
- To assess the predictive and prognostic effect of different *PIK3CA* hot spot mutations
- To explore potential new biomarkers of responses and resistance to administration of inavolisib
- To evaluate potential new biomarkers for HER2+/HR+ BC and its association with responses and resistance to neoadjuvant administration of study treatment



Study Treatment:

- Inavolisib: 9-mg tablet 1x1/d PO on days 1-21 of each 21-day cycle, beginning on day 1 of cycle 1 for 6 cycles
- Pertuzumab and trastuzumab:, fixed-dose combination of pertuzumab and trastuzumab s.c. (PH-FDC SC) q3w beginning on day 1 of cycle 1 for 6 cycles
  - PH-FDC SC loading dose: pertuzumab 1200mg/trastuzumab 600mg
  - PH-FDC SC maintenance dose: pertuzumab 600mg/trastuzumab 600mg
- Endocrine therapy: per physician's choice with either tamoxifen 20mg or an aromatase inhibitor +/- GnRH analogue for premenopausal women and men

Key Inclusion Criteria

- Age ≥ 18 years, females or males
- Diagnosis of a unilateral primary carcinoma of the breast confirmed histologically
- Central testing of FFPE tumor tissue must confirm HER2 positivity and HR positivity (according to ASCO/CAP guidelines) as well as the presence of (a) *PIK3CA* mutation(s)
- Primary tumor must be cT1c – cT3
- Normal cardiac function must be confirmed by ECG and cardiac ultrasound (LVEF ≥55%)
- Negative pregnancy test (urine or serum) within 14 days prior to randomization
- Fasting plasma glucose (FPG) < 126 mg/dL; glycosylated hemoglobin (HbA1c) < 5.7%
- Complete staging work-up prior to randomization

Key Exclusion Criteria

- Excisional biopsy or lumpectomy and/or surgical axillary staging prior to randomization
- Patients with HER2- and/or HER2+, HR- BC
- Patients with definitive clinical or radiologic evidence of stage IV BC
- Need of immediate neoadjuvant chemotherapy, e.g. inflammatory EBC
- Prior chemotherapy or ET or radiation therapy prior to study entry, initiation of ET up to 21 days prior to randomization allowed
- Patients with: BMI>30; inflammatory bowel disease; type I or uncontrolled type II diabetes mellitus; any concurrent ocular or intraocular condition; clinically significant and active liver disease; currently documented pneumonitis/interstitial lung disease

Collection of Biomaterial

Study requirements	Screening phase	Treatment Phase		
	Before randomization	Pretreatment	During treatment[2]	After EOT[3]
FFPE tissue breast tumor	X[1]		X	X
Plasma liquid biopsy (ctDNA)		X		
Whole blood (Pharmacogen)		X		

[1]tissue from core biopsy of primary breast tumor primary breast tumor (central baseline confirmation and translational research). [2]FFPE tissue from breast tumor core biopsy between 2nd and 3rd PH-FDC SC administration. [3]FFPE tissue of residual breast tumor (core biopsy or surgical tissue) and lymph node (if involved) within 2 weeks after end of study treatment (EOT)

Follow-Up

Information on the health status of German patients will be collected within the GBG's patient self-reporting registry (GBG 071) and of patients from other countries within the GBG's long-term registry of previous study participants (Eternity[B]).

Recruitment

- 10 patients have been enrolled out of 88 screened individuals, with 4 currently in the screening phase across 15 GBG and IBCSG sites. Further trial sites will be activated.
- Recruitment will continue until Q1/2026

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