PROTOCOL SYNOPSIS

Study Title	A randomized, open-label, phase II trial comparing neoadjuvant endocrine therapy in combination with trastuzumab, pertuzumab +/- the PI3K inhibitor inavolisib in patients with HER2-positive, HR-positive, PIK3CA mutant early breast cancer- GeparPiPPa
Study Code	GBG 105
EUCT Number	2022-501152-28-00
Sponsor	GBG Forschungs GmbH, Neu-Isenburg
Phase	Randomized phase II trial
Rationale	• *PIK3CA* mutations can be found in about 20%-30% of HER2+ breast cancer patients. • *PIK3CA* mutations indicate a lower response to chemotherapy + anti-HER2 therapy, especially in HR+ breast cancer (pathological complete response, pCR <10%). • Low PTEN and *PIK3CA* mutation predict response to anti-HER2 therapy without chemotherapy in HER2+ early breast cancer.[i] • Crosstalk exists between ER pathway and PI3K pathway as well as ER pathway and HER2 pathway and HER2 and PI3K pathway. • Inhibition of PI3K signaling results in activation of HER2.[ii] • Inavolisib is an oral pure PI3K alpha inhibitor comparable with alpelisib but with an expected improved efficacy and tolerability profile. • Phase III data from SOLAR-1 in *PIK3CA* mutant metastatic breast cancer demonstrated a significant improvement in progression-free survival.[iii] • The addition of palbociclib to endocrine therapy and the dual blockade demonstrated a pCR rate of 27% (95% CI 12-46%) in triple positive early breast cancer[iv], demonstrating that a chemotherapy-free regimen with targeted agents only is feasible. • Based on animal and clinical data a further development of a chemotherapy-free therapy with dual HER2 blockade is warranted. • Escape mechanisms might be less common by blocking ER, HER2 and PI3K pathway.
Study Overview	This is a multicenter, prospective, randomized, open-label, parallel-group, phase II study to evaluate the potential incremental efficacy and safety of inavolisib in the neoadjuvant treatment of early-stage HER2-positive, HR-positive, *PIK3CA* mutant breast cancer. 170 patients with confirmed eligibility criteria and *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** inavolisib (6 cycles) or • **without** inavolisib. Endocrine therapy consists of either tamoxifen 20 mg or an aromatase inhibitor +/- GnRH analogue. In both study arms, treatment will be given until surgery/core-biopsy, disease progression, unacceptable toxicity, or withdrawal of consent of the patient. All patients will undergo surgery or biopsy after completing study therapy to assess pCR rate. In case of ycT0 and no tumor residuals in the biopsy, it is recommended to undergo surgery; in case of tumor residuals in the biopsy further neoadjuvant treatment may be given (the patient will be considered no pCR for the study regardless of the response to the further neoadjuvant treatment). Pseudonymized histology and surgery reports will be collected. Further neoadjuvant or adjuvant treatment including chemotherapy, radiotherapy, endocrine therapy and HER2-therapy will be administered at the discretion of the investigator and according to standard of care. Information on those additional adjuvant treatments will be captured within a registry. Biomaterial collection is planned and includes: • Screening: Formalin-fixed, paraffin-embedded (FFPE) tissue from core biopsy of primary breast tumor (central baseline confirmation and translational research). • FFPE tissue from breast tumor core biopsy between 2nd and 3rd PH-FDC SC administration • 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) • Plasma collection for ctDNA pre-treatment (after randomization accepted), between 2nd and 3rd PH-FDC SC administration and at EOT • Whole blood collection pre-treatment (after randomization accepted) Planned enrollment period is approximately 36 months. As no study specific treatment or investigations are planned after end of neoadjuvant treatment, surgery and subsequent treatment after surgery are not part of this study. Long-term follow up will be collected beyond this protocol.
Investigational Products and Formulations	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: Pertuzumab and trastuzumab, fixed-dose combination of pertuzumab and trastuzumab with hyaluronidase s.c. (PH-FDC SC) q3w beginning on day 1 of cycle 1 for 6 cycles • PH-FDC SC loading dose: pertuzumab 1200 mg/ trastuzumab 600 mg

	• PH-FDC SC maintenance dose: pertuzumab 600 mg/ trastuzumab 600 mg The protocol provides information about supportive treatment as well as procedures for specific adverse events requesting dose modifications or delays (see 10.5.3 and 10.6). Inavolisib and PH-FDC SC will be supplied by F. Hoffmann-La Roche Ltd.
Non-investigational Products and Formulations	Endocrine therapy per physician´s choice with either tamoxifen 20 mg or an aromatase inhibitor +/- GnRH analogue. If medically indicated, initiation of endocrine therapy is allowed up to 28 days prior to randomization. Agents are used according to marketed formulation via normal procedures at each site and applied according to recommendations of the manufacturers and local guidelines. **Post-surgery:** Further adjuvant treatment with systemic therapy and HER2-therapy is not part of the study and will be administered at the discretion of the investigator and according to standard of care. Up to a total duration of 1-year anti-HER2 therapy according to current guidelines is recommended.
Primary Objectives and Endpoints	**Pathologic complete response in the breast and axillary lymph nodes (ypT0/is ypN0):** Objective: To compare pathological complete response (pCR=ypT0/is ypN0) rates between HER2-positive, HR-positive, *PIK3CA* mutant early breast cancer treated with inavolisib concurrently given to endocrine therapy, pertuzumab and trastuzumab vs. endocrine therapy, pertuzumab and trastuzumab alone. Endpoint: Pathological complete response (ypT0/is ypN0) is defined as no microscopic evidence of residual invasive tumor cells in all resected specimens of the breast and axilla. Pathological response will be assessed considering all removed breast and lymphatic tissues from all surgeries. Biopsy alone is not sufficient to confirm pCR, patients without residual tumor in the biopsy should undergo surgery (otherwise they will be considered as no pCR, as well as all other patients in whom pCR cannot be determined); patients with additional treatment after biopsy or additional treatment without biopsy will be considered as no pCR for the study regardless of the response to the further neoadjuvant treatment. It should be avoided to give additional neoadjuvant treatment without definitive pCR assessment by surgery after the end of the study treatment. Since such cases, if they occur, could decrease the pCR rate of the study, their number will be monitored during the study. In order not to compromise the power of the study additional patients will be recruited if this scenario affects more than 10% of the patients.

Secondary Objectives and Endpoints	• 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 and axillary nodes based on physical examination and imaging tests (sonography, mammography, or MRI) after study treatment in both arms • To determine the percentage of patients receiving additional neoadjuvant chemotherapy after residual disease was confirmed by core biopsy at the end of study treatment • To determine the breast conservation rate after each treatment • To assess early safety and tolerability after the first 20 and the first 40 patients who started therapy and have completed two cycles of therapy • To assess the overall safety and tolerability and treatment compliance in the two arms • Invasive disease-free survival (IDFS) and overall survival (OS) in both arms and according to stratified subpopulations (data collected within a registry). The timing for the time-to-event endpoints analysis will be defined in the statistical analysis plan. **Endpoints:** • ypT0 ypN0 is defined as no microscopic evidence of residual invasive or non-invasive viable tumor cells in all resected specimens of the breast and axilla; ypT0 ypN0/+ is defined as no microscopic evidence of residual invasive or non-invasive viable tumor cells in all resected specimens of the breast; ypT0/Tis ypN0/+ is defined as no microscopic evidence of residual invasive viable tumor cells in all resected specimens of the breast; • Clinical (c) and imaging (i) response will be assessed every 2nd cycle and before surgery by physical examination and imaging tests. Sonography is the preferred examination, however, if sonography appears not to provide valid results or is not performed, MRI, mammography or palpation will be considered with decreasing priority. The same imaging method should be considered for the measurement before, during and after treatment. The response categories of the breast are: o Complete response (CR): complete disappearance of all tumor signs in the breast as assessed by all available imaging test and palpation. The response of the axillary nodes is not to be considered o Partial response (PR): reduction in the product of the two largest perpendicular diameters of the primary tumor size by 50% or more assessed by imaging test or palpation. In patients with multifocal or multicentric disease, the lesion with the largest diameters should be chosen for follow-up. The response of the axillary nodes is not to be considered

	○ Stable disease (NC): no significant change in tumor size during treatment which means an estimated reduction of the tumor area by less than 50%, or an estimated increase in the size of the tumor area lesions of less than 25% ○ Progressive disease (PD): development of new, previously undetected lesions, or an estimated increase in the size of pre-existing lesions by 25% or more after at least two cycles of therapy • Breast conservation is defined as tumorectomy, segmentectomy or quadrantectomy as a most radical surgery Patients in whom success cannot be determined (e.g. patients in whom histology is not evaluable) will be included in the denominator, i.e. these patients will be considered to be treatment failures. • Tolerability and safety analyses include assessment of patients whose treatment had to be dose reduced, delayed or permanently stopped. The reason for treatment discontinuation includes aspects of efficacy (e.g. discontinuation due to tumor progression), safety (e.g. discontinuation due to adverse events) and compliance (e.g. discontinuation due to withdrawal of consent). Safety by toxicity grades is defined by the NCI-CTCAE version 5.0. • Survival endpoints are defined as the time period between randomization and first event and will be analyzed after the end of the study by referring to data from GBG ´s registries.
Translational Research Objectives	• To examine and compare pre-specified molecular markers such as Ki-67, tumor infiltrating lymphocytes, and other pathway markers e.g. AKT, PTEN on core biopsies and if applicable residual disease • To assess the predictive and prognostic effect of different *PIK3CA* hot spot mutations • To use baseline and on therapy specimens, such as plasma ctDNA and germline DNA to explore potential new biomarkers of responses and resistance to administration of inavolisib • To evaluate potential new biomarkers for HER2+/HR+ breast cancer and its association with responses and resistance to neoadjuvant administration of endocrine and dual HER2-therapy +/- inavolisib
Inclusion Criteria	Patients will be eligible for study participation only if they comply with the following criteria: 1. Written informed consent for all study procedures according to local regulatory requirements prior to beginning specific protocol procedures. 2. Untreated, unilateral primary carcinoma of the breast, confirmed histologically by core biopsy. Fine-needle aspiration alone is not sufficient. Incisional biopsy is not allowed.

	3. Tumor lesion in the breast must be measurable in two dimensions, preferably by sonography. 4. Patients must be in the following stages of disease: • cT1b – cT3 regardless of nodal status In patients with multifocal or multicentric breast cancer the largest lesion (target lesion) should be measured. 5. HR+/HER2+ disease with centrally confirmed ER-status, PR-status, HER2-status, *PIK3CA* mutation (tumor), Ki-67 value and TILs on core biopsy (target lesion). ER/PgR positive and HER2-positive is defined according to current ASCO/CAP guidelines. Formalin-fixed, paraffin-embedded (FFPE) breast tissue from core biopsy of target lesion has therefore to be sent to the GBG central pathology laboratory prior to randomization. In patients with multifocal or multicentric breast cancer, all non-target lesions must also be HR+/HER2+, as confirmed by local testing. 6. Age ≥ 18 years, female and male. 7. ECOG Performance status 0-1. 8. Normal cardiac function must be confirmed by ECG and cardiac ultrasound (LVEF or shortening fraction) within 3 months prior to randomization. Results for LVEF must be above 55%. 9. Laboratory requirements: **Hematology** • Absolute neutrophil count (ANC) ≥ 1.5/ nL • Platelets ≥ 100/ nL and • Hemoglobin ≥ 10 g/dL (≥ 6.2 mmol/L) **Hepatic function** • Total bilirubin < ULN except for patients with Gilbert's syndrome who may only be included if the total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN • AST and ALT ≤ 1.5x ULN and • Alkaline phosphatase ≤ 2.5x ULN **Glucose Metabolism:** • Glycosylated hemoglobin (HbA1c) < 6.5% 10. Negative pregnancy test (urine or serum) within 14 days prior to randomization for all women of childbearing potential. A woman is considered to be of childbearing potential if she is not hysterectomized or not postmenopausal. Postmenopausal is defined as: • ≥12 continuous months of amenorrhea with no identified cause other than menopause. • Having undergone bilateral oophorectomy. 11. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for least 7 months after the last dose of PH-FDC SC. Examples of non-

	hormonal contraceptive methods with a failure rate of < 1% per year include: bilateral tubal ligation; male partner sterilization; intrauterine devices. For men: men must remain abstinent or use a condom with a spermicidal product during the treatment period and for 7 months after the last dose of PH-FDC therapy to avoid exposing the embryo. Men and women must refrain from donating sperm/eggs during this same period. 12. Staging work-up according to country guidelines prior to randomization including: • Bilateral mammography and/or breast MRI in combination with a breast ultrasound. Exception: In men where MRI is medically not indicated breast ultrasound is sufficient. 13. Patient must be willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.
Exclusion Criteria	Patients will be ineligible for study participation if they comply with the following criteria: 1. Patients with HER2-negative breast cancer and/or HER2-positive, HR-negative breast cancer. 2. Need of immediate neoadjuvant chemotherapy, e.g. inflammatory breast cancer. 3. Patients with definitive clinical or radiologic evidence of Stage IV cancer. 4. Excisional biopsy or lumpectomy and /or axillary lymph node dissection and/or sentinel lymph node biopsy performed prior to study entry (biopsy of clinical involved LN is warranted). 5. Prior chemotherapy or endocrine therapy or radiation therapy prior to study entry with the following exceptions: • If medically indicated, initiation of endocrine therapy up to 28 days prior to randomization and use of established fertility preservation methods in young patients interested in subsequent pregnancies is allowed. 6. Patients with a history of breast cancer are ineligible with the following exceptions: • Patient has been disease-free for more than 5 years and is at low risk for recurrence (at the investigator's discretion). 7. Patients with a history of any treated malignancy are ineligible in case of high risk of recurrence (at the investigator's discretion) and/or ongoing oncological treatment. This also applies to patients who are at high risk that oncological treatment is indicated during study therapy. 8. Patients with BMI>30 can be included at the investigator's discretion. 9. Known hypersensitivity reaction to one of the compounds or substances, and/or murine proteins, and/or recombinant human hyaluronidase used in this protocol. 10. Patients with an established diagnosis of diabetes mellitus type I or uncontrolled type II based on FPG and HbA1c.

	11. Patients who are immunocompromised as the result of HIV or receiving immunosuppressive therapies. 12. Clinically significant and active liver disease, for example, sclerosing cholangitis, active viral hepatitis B or C infection, or autoimmune hepatic disorders. 13. Patients with inflammatory bowel disease, such as Crohn's disease or ulcerative colitis, and active bowel inflammation (e.g., diverticulitis). 14. Patients with any concurrent ocular or intraocular condition, excluding baseline cataracts, that would require medical or surgical intervention during the study period to prevent or treat vision loss. In addition, patients with active uveitis or vitritis, history of uveitis, or active infectious process in the eye. 15. Patients with currently documented pneumonitis/interstitial lung disease. 16. Known or suspected congestive heart failure (>NYHA I) and / or coronary heart disease, angina pectoris requiring antianginal medication, previous history of myocardial infarction, evidence of transmural infarction on ECG, uncontrolled or poorly controlled arterial hypertension (i.e. BP >160 / 90 mm Hg under treatment with three antihypertensive drugs), rhythm abnormalities requiring permanent treatment, clinically significant valvular heart disease. 17. Damaged skin at planned site of subcutaneous (SC) injections (thigh). 18. Patients who may have had a recent episode of thromboembolism and are still trying to optimize the anticoagulation dose and/or have not normalized their INR. 19. Concurrent treatment with: • Chronic corticosteroids unless initiated > 6 months prior to study entry and at low dose (10 mg or less methylprednisolone or equivalent). • Sex hormones. Prior treatment must be stopped before randomization (GnRH a is allowed). • Other experimental drugs or any other anti-cancer therapy. 20. Participation in another clinical trial with any investigational, not marketed drug within 30 days prior to study entry. 21. Female patients: pregnancy or lactation at the time of randomization. 22. History of significant neurological or psychiatric disorders including psychotic disorders, dementia or seizures that would prohibit the understanding and giving of informed consent. 23. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.
Sample Size Determination	The sample size calculation is based on the following assumptions[, iv, v, vi, vii, viii, ix]: • pCR rate in the control arm is expected to be 20%

	• pCR rate in the inavolisib arm will be 38.5% (odds ratio (OR) of 2.5, corresponding to the absolute difference of 18.5%) ET + trastuzumab + pertuzumab + inavolisib arm will be compared with ET + trastuzumab + pertuzumab alone. With 170 patients a two-sided continuity corrected chi-square test with α=0.1 will have 80% power to reject the null hypothesis of no difference in pCR rates, if the true pCR rates are 20% and 38.5% in control and inavolisib arm correspondingly. If more than 10% of patients receive additional neoadjuvant therapy after the end of study treatment without a definite assessment of pCR, additional patients will be recruited to compensate the loss of power.
Randomization	Once eligibility has been established, the patient with *PIK3CA* mutant breast cancer may be randomized. The site will obtain the patient`s treatment assignment. As this is an open label study, treatment assignments will not be blinded. Patients with *PIK3CA* mutant breast cancer enrolled but not randomized have to be registered as screen failures with a reason documented. Patients will be randomly assigned in a 1:1 ratio to treatment arms. Assignment will be stratified by the predetermined factors using Pocock minimization.
Stratification (minimization)	Stratification (minimization) factors for randomization will be: • study group (GBG vs. non-GBG) • N0 vs. N+
Statistical Methods	A modified 'intent-to-treat' (mITT) analysis will be conducted for all patients who started therapy. In addition, a 'per-protocol' analysis will be conducted; the detailed definition of the per-protocol analysis set will be given in the statistical analysis plan. **Primary Endpoint** The primary endpoint will be summarized as pathological complete remission rate for each treatment group and compared between treatment groups using stratified chi-square test (Cochran–Mantel–Haenszel). Stratification factors are study group (GBG vs. non-GBG) and nodal status (N0 vs. N+). Two-sided 90% confidence intervals per arm will be calculated according to Pearson and Clopper; 90% CI for the difference will also be reported. Patients in whom success cannot be determined (e.g. patients in whom histology is not evaluable) will be included in the denominator, i.e. these patients will be treated as treatment failures. This applies both for primary and secondary efficacy endpoints. The significance level is set to 2-sided p=0.1 for all efficacy endpoints and p= 0.05 for all other analyses. There will be no adjustment for multiple comparisons in the analyses for the stratified subpopulations. A secondary logistic regression analysis correcting for the stratification (minimization) factors (study group and nodal status as defined above) will be conducted for the primary endpoint. Sensitivity analysis based on the per protocol set will be performed a similar way.

	Secondary endpoints The Cochran–Mantel–Haenszel test will be performed for all secondary short-term efficacy endpoints to evaluate the difference of rates in treatment arms; these tests are considered exploratory. • Secondary short-time efficacy endpoints (ypT0 ypN0; ypT0 ypN0/+; ypT0/is ypN0/+; ypT(any) ypN0, response by physical examination, imaging response, breast conservation) will also be summarized as rates in each treatment group, two-sided 90% confidence intervals will be calculated according to Pearson and Clopper, 90% CI for the difference will also be reported. • Clinical (c) and imaging (i) response: For defined categories of efficacy (complete, partial, stable, or progression), the proportion of patients with success will be determined and appropriate confidence intervals will be calculated. The clinical tumor response by palpation prior to surgery will also be presented, if applicable. • IDFS and OS will be collected and are defined as the time period between registration and first event and will be analyzed after the end of the study by referring to data from GBG's registry. Progressions during neoadjuvant treatment are not considered as events. Long-term endpoints e.g. IDFS and OS will be analyzed using the Kaplan-Meier method and compared between treatment arms using the stratified log-rank test. • Tolerability and Safety: Descriptive statistics for the 2 treatment arms will be given on the number of patients whose treatment had to be dose reduced, delayed or permanently stopped. Reasons for premature discontinuation will be categorized according to the main reason and will be presented in frequency tables. Safety by toxicity grades is defined by the NCI-CTCAE version 5.0, laboratory parameters will be converted in CTC-grades and reported together with other adverse events. • Translational research: Exploratory analyses will be performed to identify possible relationships between biomarkers and drug activity. The aim is to identify potential predictive short and long-term parameters (pCR, no treatment effect (according to regression score 0-1), IDFS, and OS), based on the mITT population. The 3-year survival rates (and 95%CIs) will be estimated. Univariate and multivariate Cox-proportional hazards model will be used to adjust hazard ratios for stratification (minimization) factor and the above defined covariates.
Interim Analyses	• Two safety interim analyses will be performed after 20 and 40 patients completed two cycles of treatment. • No efficacy interim analysis is planned
Biomaterial	• Screening: Formalin-fixed, paraffin-embedded (FFPE) tissue from core biopsy of primary breast tumor (central baseline confirmation and translational research)

	• FFPE tissue from breast tumor core biopsy between 2nd and 3rd PH-FDC SC administration • 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) • Plasma collection for ctDNA pre-treatment (after randomization accepted), between 2nd and 3rd PH-FDC SC administration, and at EOT • Whole blood collection pre-treatment (after randomization accepted)
Enrollment period	Approximately 36 months
Follow-up	As no study specific treatment or investigation is planned after end of neoadjuvant treatment, surgery and subsequent treatment after surgery are not part of this study. However, information on the health status of the patients will be collected within in the patient self-reporting registry (Patientenselbstauskunft; German patients) or the GBG long-term registry of previous study participants (Eternity[B]).
Observational Cohort	For patients who are not enrolled in the study because they do not meet the study requirements (screen failures), observation and data collection of systemic and locoregional breast cancer treatment according to local standard of care and surgery details will be performed in case of patient´s consent. Data collection includes amongst others: • Systemic breast cancer treatment • Surgery details • Histologic response (pCR) after neoadjuvant systemic breast cancer treatment No safety assessment and reporting (including AE/SAE/SUSAR) will be performed for patients treated according to standard of care within the observational cohort. **Objectives:** • In patients with neoadjuvant therapy: to assess the pCR rate • In all patients: to assess long-term outcome overall and in subgroups by approach (examples: adjuvant vs neoadjuvant; pCR vs no pCR; further details will be stated in the statistical analysis plan). • To determine systemic and locoregional breast cancer treatment according to local standard of care • To use baseline specimen to explore potential new biomarkers of resistance and response to systemic therapy **Follow-up:** Information on the health status and further treatment of the patients will be collected as in the clinical trial population. **Statistical Methods:**

	Descriptive tables will be used to report breast cancer treatment. pCR rate will be reported together with the 95% CI according to Pearson and Clopper. Invasive disease-free survival (IDFS) and overall survival (OS) (data collected within a registry) will be estimated using Kaplan-Meier method. Further details will be described in the corresponding statistical analysis plan.
Number of sites	It is planned to conduct the study within approximately 50 sites.
Timelines	FPI Q1/2023 LPI Q1/2026 LP EOT Q3/2026 pCR Publication Q1/2027

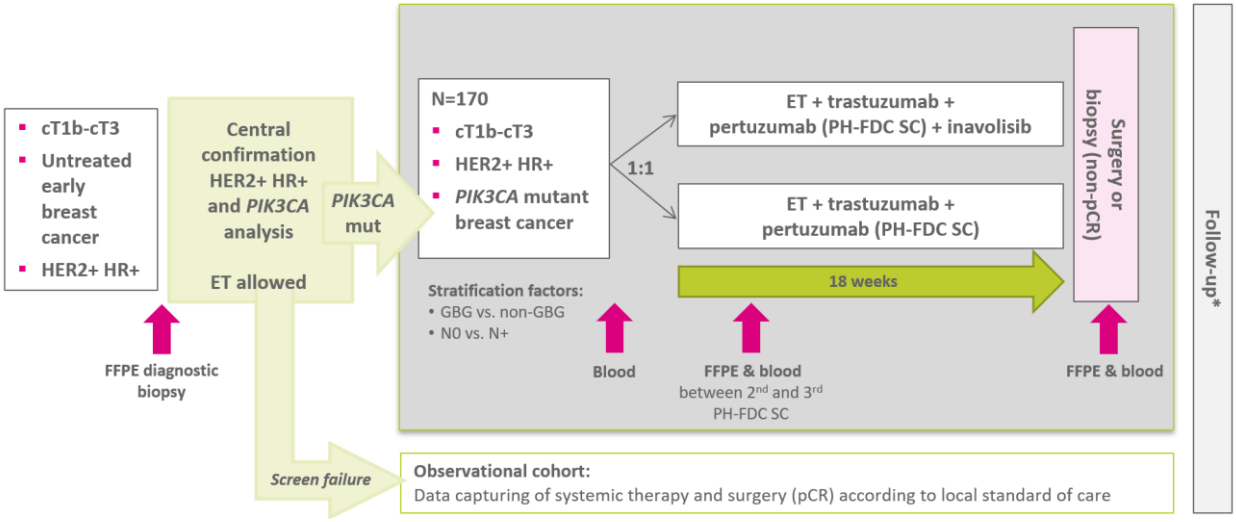

Figure 1: GeparPiPPa Study Design

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