3 PROTOCOL SYNOPSIS

Study Title	**Phase II study evaluating the addition of elacestrant, an oral selective estrogen receptor degrader (SERD), to standard-of-care olaparib in patients with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with g*BRCA1/2* mutations - ELEMENT**
Study Code	**ELEMENT GBG-114**
EU-CT Number	**2023-504925-38-00**
Sponsor	GBG Forschungs GmbH, Neu-Isenburg
Phase	Phase II
Rationale	Approximately 75% of all breast cancers are hormone receptor (HR)-positive and human epidermal growth factor-2 (HER2)-negative (Huang J Clin Pathol 2005). In patients with HR-positive locally advanced or metastatic breast cancer (BC), endocrine therapy (ET) remains the cornerstone of treatment, unless there is a visceral crisis (Cardoso Ann Oncol 2020). Available endocrine agents include aromatase inhibitors (AIs; letrozole, anastrozole and exemestane), selective estrogen receptor (ER) modulators (SERMs; tamoxifen and toremifene) and selective ER degraders (SERDs; fulvestrant and elacestrant). AIs decrease peripheral estrogen synthesis through inhibition of aromatase, which catalyzes the conversion of androgens to estrogens (Santen Endocr Rev 2009). SERMs and SERDs directly target the ER; while SERMs reduce ER activity through competitive ER blockade and other effects on ER transcriptional machinery (Liu Mol Pharmacol 2013), SERDs inhibit ER by creating an unstable SERD–ER protein complex eliminated via proteasome degradation pathways (Wu Molec Cell 2005; Wittmann Cancer Res 2007). Until 2023, fulvestrant was the only SERD approved for postmenopausal patients with HR-positive advanced BC and disease progression after ET. Premenopausal patients would additionally receive a gonadotropin-releasing hormone (GnRH) agonist. The initially approved dose of fulvestrant 250 mg intramuscular (Howell J Clin Oncol 2002; Obsborne J Clin Oncol 2002) was modified based on the results of the CONFIRM study (Di Leo J Clin Oncol 2010), which demonstrated a statistically significant increase in progression-free survival (PFS) of fulvestrant 500 mg vs. 250 mg (hazard ratio (HR)=0.80, [95% CI 0.68-0.94]; p=0.006), without increased toxicity. The phase II FIRST study showed that first-line fulvestrant was at least as effective as anastrozole for clinical benefit rate (CBR) and objective response rate and was associated with significantly longer time to progression (HR=0.63, [0.39-1.00]; p=0.0496) (Robertson J Clin Oncol 2009). The phase III FALCON study demonstrated a superior efficacy of fulvestrant compared to anastrozole as first line treatment in postmenopausal patients with HR-positive locally advanced or metastatic BC who had not received previous ET (Robertson Lancet 2016). Median PFS was significantly longer in the fulvestrant group than

	in the anastrozole group (16.6 months [13.83-20.99] vs. 13.8 months [11.99-16.59], HR=0.797 [0.637-0.999]; p=0.0486). Fulvestrant also demonstrated its efficacy and safety in the advanced setting when administered together with novel agents such as cyclin-dependent kinase 4/6 (CDK4/6) inhibitors (Sledge JAMA Oncol 2020; Cristofanilli J Clin Oncol 2021; Slamon Ann Oncol 2021). However, fulvestrant requires two intramuscular administrations of 250 mg each, which limits dose, exposure, and receptor binding, as well as patient selection. Resistance has also been demonstrated (O´Leary Cancer Discov 2018). Therefore, there has been an urgent unmet need for alternative SERDs that are effective against HR-positive metastatic BC, including those with *ESR1* mutations. Moreover, to improve patient compliance, more manageable SERDs with a better safety profile and tolerability need to be investigated. As a result, several SERDs have been under clinical investigation or have demonstrated efficacy, such as amcenestrant, camizestrant, and elacestrant. Elacestrant is a novel, nonsteroidal, orally bioavailable ER antagonist SERD that has demonstrated single-agent activity in phase I (RAD1901-005) study in heavily pretreated patients with HR-positive, HER2-negative BC previously treated with ET including fulvestrant and/or CDK 4/6 inhibitor therapy, and in those with *ESR1* mutations known to confer endocrine resistance (Bardia J Clin Oncol 2021). In this study, patients treated with elacestrant had an overall PFS of 4.5 months. Patients with *ESR1* mutation derived the greatest benefit compared to patients without an *ESR1* mutation (PFS 7.4 vs. 2.8 months, with CBR of 56.5% vs. 29.2%, respectively). In addition, the phase III EMERALD study has shown a statistically significant improvement in PFS with elacestrant compared to standard of care (SOC) ET (fulvestrant or an AI) in patients with HR-positive, HER2-negative advanced BC in second or third line post-CDK4/6 inhibitor treatment (HR=0.70 [0.55-0.88]; p=0.002), even in patients harboring an *ESR1* mutation (HR=0.55 [0.39-0.77]; p=0.0005) with manageable safety (Bidard J Clin Oncol 2022). Given these results, elacestrant was approved by the Food and Drugs Administration (FDA) in January 2023 for postmenopausal women or adult men with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy. It was later approved by the European Medicines Agency (EMA) in September 2023 for postmenopausal women and men with ER-positive, HER2-negative, locally advanced, or metastatic breast cancer with an activating *ESR1* mutation who have disease progression following at least one line of endocrine therapy including a CDK4/6 inhibitor. In addition, patients with HR-positive, HER2-negative advanced or metastatic BC and germline (g)*BRCA1/2* mutations have an unmet need. Further treatment options should be explored to improve patient outcomes.

	The poly-adenosine diphosphate ribose polymerase inhibitor (PARPi) olaparib has been approved by the FDA and the EMA for deleterious or suspected deleterious g*BRCA*-mutated, HER2-negative metastatic BC. The approval was based on positive outcomes in the phase III OlympiAD trial, which showed improved median PFS, response rates, and less toxicity with olaparib monotherapy compared to SOC (Robson N Engl J Med 2017). Recently, it has also been shown that olaparib administered with ET in the Olympia study is safe and effective in patients with early HR-positive BC and g*BRCA1/2* mutation (Tutt N Engl J Med 2021). Patients with HR-positive, HER2-negative advanced or metastatic BC and g*BRCA1/2* mutations have low PFS and represent a patient population with a high unmet need, hence further treatment options should be explored to improve patient outcomes (Robson N Engl J Med 2017, Litton N Engl J Med 2018, Gelmon J Clin Oncol 2020). The purpose of the proposed study is to investigate if the addition of elacestrant to standard-of-care olaparib could potentially lead to an improvement in PFS compared to olaparib alone in patients with HR-positive, HER2-negative locally advanced or metastatic BC with a g*BRCA1/2* mutation.
Study Overview	Phase II, prospective, multi-center, randomized, open label, parallel group study in patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer with g*BRCA1/2* mutation, with 2:1 randomization. **Arm A**: elacestrant* + olaparib **Arm B:** olaparib Olaparib in both arms will be given as SOC background therapy. Treatment in either arm will be given until disease progression, unacceptable toxicity, withdrawal of patient´s consent to study participation, or EOS. * Together with GnRH analogue in pre- and perimenopausal women, and in men, at least two weeks prior to treatment.
Investigational Product	• Elacestrant 400 mg orally once daily The protocol provides procedures for specific adverse events requiring dose modifications or delays (see 10.2).
Non-investigational Product	• Olaparib 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg.
Primary Objective and Endpoint	**Progression free survival (PFS, investigator-assessed)** Objective: To evaluate the impact on PFS of elacestrant with olaparib compared to olaparib alone in patients with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with g*BRCA1/2* mutations. Endpoint:

	PFS is defined as the time from randomization to first progression as assessed by the investigator, or death, whichever occurs first. Patients lost to follow up or progression-free at the end of the study will be censored at the date of last contact.
Secondary Objectives and Endpoints	**1. Time-to-treatment failure (TTF)** Objective: To compare TTF between treatment arms (i.e., elacestrant + olaparib vs. olaparib). Endpoint: TTF is defined as time from randomization to discontinuation of treatment due to disease progression, treatment toxicity, patient´s preference, or death. Patients lost to follow up or still under treatment at the end of the study will be censored at the date of last contact. **2. Overall survival (OS)** Objective: To compare OS between treatment arms. Endpoint: OS is defined as the time from randomization to death due to any reason. Patients lost to follow up or alive at the end of the study will be censored at the date of last contact. **3. Patient reported outcome (PRO) and quality of life (QoL)** Objective: To assess and compare PRO and QoL between treatment arms. Endpoint: Patient reported BC-specific QoL as measured by FACT–ES. **4. PFS, TTF and OS in the minimization subgroups** Objective: To compare PFS, TTF and OS in the minimization subgroups • Pre-treatment chemotherapy in the metastatic setting yes vs. no **5. PFS, TTF and OS in exploratory subgroups** Objective: To compare PFS, TTF and OS in exploratory subgroups: • Prior fulvestrant therapy • *ESR1* wild type (or not done) vs. mutant **6. Overall response rate (ORR)** Objective: To compare ORR between treatment arms. Endpoint:

	ORR is defined as the percentage of patients who have achieved either a confirmed complete response or partial response. **7. Clinical benefit rate (CBR)** Objective: To compare CBR between treatment arms. Endpoint: CBR is defined as the percentage of patients who have achieved either a confirmed complete response or partial response, or stable disease for at least 24 weeks from randomization. **8. Safety** Objective: To assess and compare safety between treatment arms. Endpoint: Frequency and severity of AEs graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. **9. Compliance** Objective: To assess and compare compliance between treatment arms. Endpoint: Dose reductions, dose delays, treatment interruptions, and treatment discontinuation rates.
Translational Research Objectives	• To assess *BRCA1/2* and *ESR1* mutation status via liquid biopsy. • To assess ctDNA at baseline, during treatment, and at disease progression. • To explore ctDNA dynamics as early predictors of disease progression in ctDNA positive patients. • To explore the predictive value of markers for elacestrant treatment. • To explore markers for resistance to elacestrant therapy.
Inclusion Criteria	Patients will be eligible for study participation only if they comply with the following criteria: 1. Written informed consent prior to beginning specific protocol procedures, including expected cooperation of the patients for scheduled visit, the treatment and follow-up, must be obtained and documented according to the local regulatory requirements. 2. Female or male patients. 3. Age at study entry of at least 18 years. 4. Locally advanced or metastatic breast cancer that is HR-positive (ER and/or PgR ≥ 10% of stained cells at IHC) and HER2-negative (IHC 0 or 1+, or 2+ and ISH negative according to ASCO/CAP guidelines).

	5. Patients with deleterious or suspected deleterious g*BRCA1/2* mutation detected upon local testing. 6. Willingness and ability to provide archived formalin fixed paraffin embedded tissue (FFPE) block or a partial block from archived tumor or metastasis. 7. Indication for standard-of-care PARP inhibitor therapy and planned treatment with olaparib. 8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2. 9. Resolution of all acute toxic effects of prior anti-cancer therapy including endocrine therapy or surgical procedures to NCI CTCAE version 5.0 grade ≤ 1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion). 10. Life-expectancy > 6 months. 11. For female patients: patients of childbearing potential (defined as not post-menopausal and not permanently sterile [latter defined as having undergone hysterectomy, bilateral salpingectomy, or bilateral oophorectomy]) require a negative serum or urinary pregnancy test within 72 hours before starting treatment in this study (in this case, patients need to use highly effective non-hormonal contraceptive methods as specified in the protocol). For male patients: during the intervention period and for at least 120 days after the last dose of elacestrant, patients should refrain from heterosexual intercourse or use a condom (and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak), and they should refrain from donating sperm.
Exclusion Criteria	Patients will be ineligible for study participation if they fulfill any of the following criteria: 1. Known hypersensitivity reaction to one of the compounds, excipients, or substances used in this protocol. 2. Active or newly diagnosed CNS metastases, including leptomeningeal carcinomatosis, carcinomatous meningitis, or radiographic signs of CNS hemorrhage. Note: Patients with stable brain metastases are allowed. Radiotherapeutic treatment must be completed 1 week before planned day 1 of study therapy. 3. Presence of symptomatic metastatic visceral disease that are at risk of life-threatening complications in the short term, including but not confined to massive uncontrolled effusions (peritoneal, pleural, pericardial), pulmonary lymphangitis, or fulminant liver involvement. 4. Inadequate organ function prior to enrolment including: ○ Hemoglobin < 9 g/dL (< 5.6 mmol/L) ○ Absolute neutrophil count (ANC) < 1500/mm³ (< 1.5 x 10^9/L) ○ Platelets < 100,000/mm³ (< 100 x 10^9/L)

	○ Alanine aminotransferase (ALT/SGPT) and/or aspartate aminotransferase (AST/SGOT) > 3 x upper normal limits (ULN). If the patient has liver metastases, ALT and AST should not be ≥ 5 x ULN. ○ Alkaline phosphatase (ALP) > 2.5 x ULN ○ Total serum bilirubin > 1.5 x ULN (exception: patients with Gilbert's syndrome permitted up to ≤ 3 x ULN) ○ Serum creatinine > 1.5 x ULN or estimated creatinine clearance < 50 mL/min as calculated using the standard method for the institution. 5. Existing contraindication against the use of the elacestrant or olaparib. 6. Prior treatment with PARP inhibitors. 7. Female patients: pregnancy or lactation at the time of randomization or intention to become pregnant during the study and for a predefined period after the end of treatment (as described in protocol). Male patients: intention to get a child during the study and for a predefined period after the end of treatment (as described in protocol). According to the treatment received during the study, required contraception timelines for female and male patients are described in the study protocol. 8. Any of the following within 6 months prior to enrolment: myocardial infarction, severe/unstable angina, ongoing grade ≥ 2 cardiac dysrhythmias, prolonged QT corrected by Fridericia's formula (QTcF) grade ≥ 2, uncontrolled atrial fibrillation of any grade, coronary/peripheral artery bypass graft, heart failure of New York Heart Association (NYHA) Class II or greater, or cerebrovascular accident including transient ischemic attack. 9. Uncontrolled hypertension at the time of screening (systolic BP > 140 mmHg or diastolic BP > 90 mmHg that has not been adequately treated or controlled). 10. Active and current anticoagulation for treatment purposes of thrombotic events occurring < 6 months before enrolment is not allowed (prophylactic anticoagulation, however, is acceptable). Treatment with an anticoagulant for a thrombotic event occurring > 6 months before enrolment, or for an otherwise stable and allowed medical condition (e.g., well controlled atrial fibrillation) is acceptable, provided dose and coagulation parameters (as defined by local standard of care) are stable for at least 28 days prior to the first dose of study drug. 11. Known difficulty in tolerating oral medications or conditions which would impair absorption of oral medications such as: uncontrolled nausea or vomiting (i.e., CTCAE ≥ grade 3 despite antiemetic therapy), ongoing gastrointestinal obstruction/motility disorder, malabsorption syndrome, or prior gastric bypass. 12. History of endometrial intraepithelial neoplasia in patients who have not undergone a hysterectomy.

	13. Malignant disease other than breast cancer, active or being disease-free for less than 5 years (except carcinoma in situ of the cervix, DCIS, and non-melanomatous skin cancer adequately treated). 14. Uncontrolled significant active infections including HBV, HCV, and/or HIV. Patients with a positive hepatitis B surface antigen result or a positive hepatitis C antibody test result at screening or within 3 months before first dose of study treatment are excluded, except for the following: ▪ Participants with positive anti-HBs antibody titer and confirmatory negative hepatitis B DNA polymerase chain reaction. ▪ Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled only if they have both completed curative therapy and have a hepatitis C viral load < quantifiable limit. 15. Any severe, acute, uncontrolled, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational or non-investigational products administration, or may interfere with the interpretation of study results, and, in the judgment of the investigator, would make the patient inappropriate for entry into this study. Moreover, patients who, by virtue of an order issued by judicial or administrative authorities, are committed to an institution or those who cannot take part in clinical trials are excluded from this study. 16. History of significant neurological or psychiatric disorders including psychotic disorders, dementia, or seizures that would prohibit the understanding and giving of informed consent. 17. Unable or unwilling to avoid medications, supplements (e.g., St. John's wort), or foods (e.g., grapefruit, pomegranate, pomelos, star fruit, Seville oranges and their juices) that are moderate/strong inhibitors or inducers of CYP3A4 activity. Participation will be allowed if the medication, supplements, or foods are discontinued for at least 14 days prior to study entry and for the duration of the study. 18. Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational not marketed drug within 30 days prior to study entry. 19. Receipt of live attenuated vaccination within 30 days prior to study entry. COVID-19 vaccines that do not contain live viruses are allowed (at least one week prior to study entry).
Sample Size Determination	The sample size determination was based on the following assumptions: • Median PFS in control arm of 8 months • HR of 0.68 (corresponding to median PFS of 11.8 months in the elacestrant arm • Randomization ratio elacestrant vs. control is 2:1

<table>
<tr><td></td><td>Assuming 3 years of recruitment with ramp-up and 6 patients per month at peak and one additional year of follow-up, median PFS in control arm of 8 months, an exponential drop-out rate of 10% in 3 years and HR of 0.68 (corresponding to median PFS of 11.8 months in the elacestrant arm), 137 events and 176 patients (118 in the elacestrant arm, 58 in the control arm) are necessary for the log-rank test to have 80% power for the significance level of α=0.2 (Cannistra J Clin Oncol 2009).

<table>
<tr><th>Study</th><th>Ref.</th><th>Collective</th><th>Arm</th><th>N</th><th>Median PFS (months)</th></tr>
<tr><td>OlympiAD</td><td>Robson N Engl J Med 2017</td><td>Phase III, HER2-negative ABC, gBRCA1/2, ≤2 previous treatment lines for ABC</td><td>Olaparib</td><td>205</td><td>7.0</td></tr>
<tr><td>EMBRACA</td><td>Litton N Engl J Med 2018</td><td>Phase III, HER2-negative ABC, gBRCA1/2, ≤3 previous treatment lines for ABC</td><td>Talazoparib</td><td>287</td><td>8.6</td></tr>
<tr><td>LUCY</td><td>Gelmon Eur J Cancer 2021</td><td>Phase IIIb, HER2-negative ABC, gBRCA1/2, treatment ≤2 lines for ABC</td><td>Olaparib</td><td>252</td><td>8.1</td></tr>
<tr><td>BRAVO</td><td>Turner Clin Cancer Res 2021</td><td>Phase III, HER2-negative ABC, gBRCA1/2, treatment ≤2 lines for ABC</td><td>Niraparib</td><td>141</td><td>4.1 (central)
5.0 (local)</td></tr>
<tr><td rowspan="2">Olaparib Expanded</td><td rowspan="2">Tung J Clin Oncol 2020</td><td>ABC with gPALB2</td><td>Olaparib</td><td>11</td><td>13.3</td></tr>
<tr><td>ABC with tBRCA1/2</td><td>Olaparib</td><td>16</td><td>6.2</td></tr>
<tr><td>California Cancer Consortium Trial</td><td>Somlo Clin Cancer Res 2017</td><td>Phase II, HER2-negative ABC, gBRCA1/2, treatment ≥1 line for ABC</td><td>Veliparib</td><td>44*</td><td>5.2</td></tr>
<tr><td rowspan="2">ABRAZO</td><td rowspan="2">Turner Clin Cancer Res 2019</td><td>HER2-negative ABC gBRCA1/2, CR/PR on prior platinum-based CT</td><td>Talazoparib</td><td>49*</td><td>4.0</td></tr>
<tr><td>HER2-negative ABC, gBRCA1/2, ≥3 previous CT lines (not platinum-based)</td><td>Talazoparib</td><td>35**</td><td>5.6</td></tr>
</table>
*Inclusive 1 patient with HER2-positive disease; **Inclusive 5 patients with HER2-positive disease.
Abbreviations: ABC, advanced breast cancer; CR, complete response; CT, chemotherapy; m, mutation; PFS, progression-free survival; PR, partial response.</td></tr>
<tr><td>Randomization</td><td>As this is an open label study, the treatment assignments will not be blinded. Patients will be randomized in 2:1 ratio by Pocock-Simon minimization.</td></tr>
<tr><td>Minimization Factor</td><td>The minimization (stratification) factor for the randomization will be:
• Pre-treatment chemotherapy in the metastatic setting yes vs no</td></tr>
<tr><td>Statistical Methods – Primary Endpoint</td><td>Primary Analysis
An ‘intent-to-treat' (ITT) analysis will be conducted for all patients who are randomized. Patients will be analyzed according to the group to which they were randomized.</td></tr>
</table>

	PFS curves will be compared between the treatment arms with the stratified log-rank test (stratification factor = minimization factor as randomized). The significance level for this analysis is set to a two-sided $\alpha = 0.2$. **Further Analyses of the Primary Endpoint** PFS curves will be estimated using the Kaplan – Meyer method. Median PFS and 3, 6, 12, and 18-months-PFS rates with 80% and 95% confidence intervals (CIs) will be calculated. Univariate and multivariate Cox proportional hazards models (full models without variables selection) will be used to adjust hazard ratios for the given minimization factor and for age, tumor size, nodal status, grade, and histological type. Other potential factors will be defined in the SAP. Hazard ratios will be reported together with the 80% and the 95% CIs. A sensitivity analysis for intercurrent events like starting another treatment for another reason as disease progression will be described in the SAP. The significance level for these analyses is also set to a two-sided $\alpha = 0.2$.
Statistical Methods – Secondary Endpoints	Analysis of the secondary efficacy endpoints will be based on the ITT set. As the subsequent analyses are more likely to be understood as explorative or descriptive (in case of safety and compliance), no correction for multiple testing will be performed, e.g., for subgroups, and no formal alpha level is given. **Time to treatment failure and overall survival (overall and in subgroups, ITT set); PFS (in subgroups, ITT set)**: PFS, TTF, and OS curves will be estimated using the Kaplan – Meyer method and compared using a stratified two-sided log-rank test (stratification factor = minimization factor as randomized). Median survival rates as well as 3, 6, 12, and 18-months-rates with 80% and 95% CIs will be calculated. Univariate and multivariate Cox proportional hazards models (full models, without variables selection, factors are the same as those for the primary analysis) will be used to adjust hazard ratios. Hazard ratios will be reported together with the 80% and 95% confidence intervals. **Overall response rate and clinical benefit rate (overall and in subgroups, ITT set):** The ORR and CBR and the associated two-sided 95% Pearson-Clopper-confidence intervals will be reported for both treatment arms. ORR and CBR rates will be compared between arms using a stratified $\chi 2$-test (Cochran–Mantel–Haenszel) (stratification factor = minimization factor as randomized). Uni- and multivariate logistic regression will be performed (as full models, without variables selection, factors are the same as those for the primary analysis) for ORR and CBR to report odds ratios (OR) with 95% CI and to adjust for the given factors.

	Patients in whom response cannot be determined will be included in the denominator, i.e., these patients will be treated as treatment failures. This applies both for ORR and CBR. **Safety and compliance (overall, safety set):** Frequencies of patients whose treatment had to be reduced, delayed, interrupted, or prematurely discontinued will be reported for both arms, together with reasons for such modifications. Comparisons between the two arms will be conducted with the χ2-test with continuity correction. The reason for termination includes aspects of efficacy (i.e., termination due to tumor relapse), safety (i.e., termination due to adverse events), and compliance (i.e., termination due to patient's withdrawal of consent). Reasons for premature termination will be categorized according to the main reason and will be presented in frequency tables. Incidence of adverse events and serious adverse events will be descriptively displayed for both treatment arms. 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. **Quality of life (overall, ITT set):** The patient reported BC-specific QoL as measured by FACT–ES incorporates various scales which will be computed and analyzed according to the scoring manuals. Details will be given in the statistical analysis plan. The longitudinal analyses and comparisons between the two arms will be conducted via a linear-mixed-effects regression approach.
Interim Analyses	• An interim safety analysis will be performed in the study after the first 15 patients per arm have completed 2 cycles (or 2 months) of treatment. • No efficacy interim analysis is planned.
Biomaterials	The following biomaterials will be collected: • Collection of FFPE from the locally advanced/metastatic lesion of the current site of progression sampled within routine patient care. In case such a biopsy was not performed, an FFPE tumor tissue of the metastatic lesion from an earlier timepoint is acceptable. If not available, then a sample from the primary tumor is also possible. The availability of at least one sample is mandatory, with the aforementioned order of preference. • If disease progression occurs and the investigator decides to biopsy the metastatic lesion according to standard of care (e.g., for assessment of treatment options), FFPE from this biopsy will be collected. • Plasma samples (20 mL) of each patient for liquid biopsy (ctDNA) will be collected before study treatment, at predefined timepoints during

	treatment (as specified in protocol), at disease progression, and at the end of treatment, independent of the reason. • One whole blood sample (10 mL) of each patient will be collected before start of study treatment for pharmacogenetics analysis.
Enrollment period	Approximately 36 months.
Follow-up	Patients who discontinue randomized study treatment will enter the long-term follow-up phase. In this phase, additional data will be collected including first new anti-cancer therapy, subsequent disease progression data, and death. These data will be collected every three months until progression or end of study, whatever occurs first. After progression, data will be collected every six months until end of study. For patients who experience progression during the treatment phase, data will also be collected every six months from the date of progression until the end of study. Information collected in medical records or via telephone contact is acceptable. The follow-up phase will be discontinued early due to study closure, patient death, withdrawal of consent, or loss to follow-up.
Number of sites	Approximately 40 sites in Germany are necessary to recruit approximately 6 patients per month at full speed recruitment.
Timelines	FPI Q4/2024 LPI Q4/2027 Final analysis Q4/2028

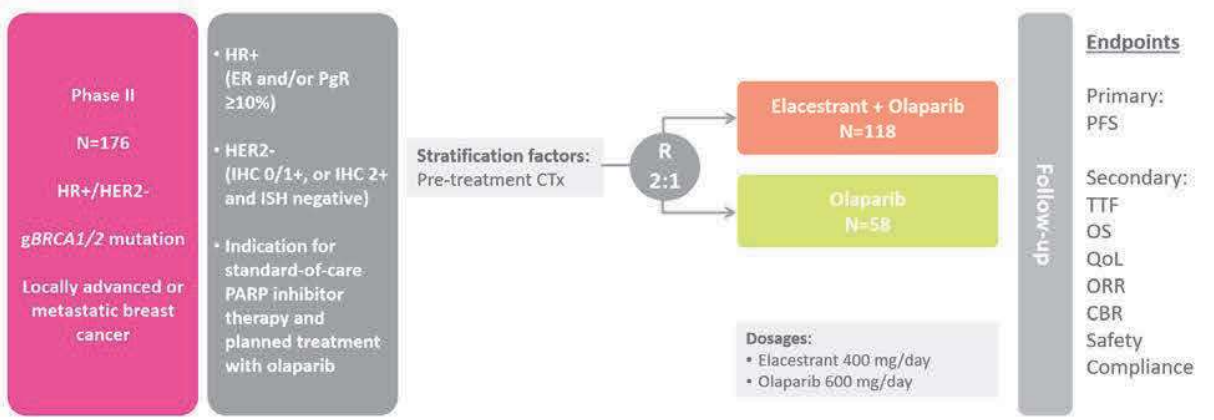

Figure 1: Study Design