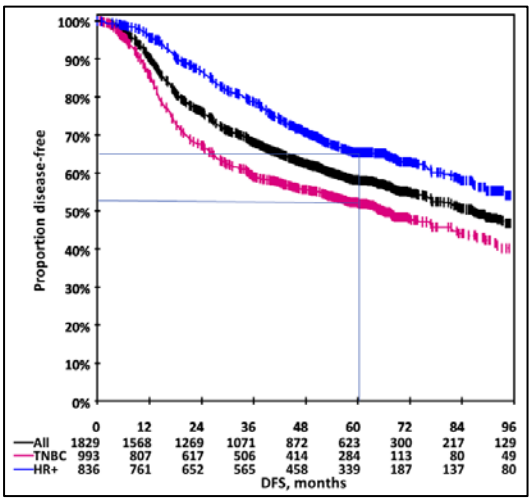
3.0 Protocol Synopsis

Title	**Phase III postneoadjuvant study evaluating Sacituzumab Govitecan, an Antibody Drug Conjugate in primary HER2-negative breast cancer patients with high relapse risk after standard neoadjuvant treatment - SASCIA**
Study Code	GBG 102
EudraCT Number	2019-004100-35
Sponsor	GBG Forschungs GmbH
Phase	III
Study Rationale	Neoadjuvant chemotherapy (NACT) allows monitoring of tumor response to treatment and a pathological complete response (pCR) is associated with superior survival. This association is strongest in the most aggressive subtype, i.e. in patients with triple-negative breast cancer (TNBC). Patients with TNBC not achieving a pCR have a 5-year event free survival rate of about 50%.[1,2,3] The association between pCR and prognosis is less pronounced in HR-positive/HER2-negative patients. However, the CPS+EG scoring system for prognosis after neoadjuvant chemotherapy, taking into account clinical stage, post treatment pathological stage, estrogen receptor status and grade, leads to an improved estimate of prognosis allowing to select patients at high risk of relapse for post-neoadjuvant therapy.[4] Patients with TNBC not achieving a pCR as well as those with HR-positive/HER2-negative tumors and a CPS+EG score of ≥3 or 2/ypN+ are at high risk of relapse (Figure 1), warranting additional experimental therapies after NACT.  **Figure 1 Survival in HER2-negative BC patients without pCR. TNBC without pCR and HR-positive without pCR and CPS+EG ≥3 or CPS+EG 2 and ypN+. Data from 4 prospective, randomized German neoadjuvant trials (n=1829).** There is proof of concept, that post-neoadjuvant therapy can significantly improve survival. First data was provided by the CREATE X trial, randomizing patients with residual tumor after neoadjuvant chemotherapy to either capecitabine or observation.[5] CREATE X included HER2-negative patients and demonstrated a significant improvement in disease-free survival (DFS) and overall survival (OS) in the overall population, which was confined to the TNBC subgroup. Recently, the randomized post-neoadjuvant phase III KATHERINE study demonstrated an improved invasive disease-free survival in HER2-positive patients without pCR after trastuzumab +/- pertuzumab treated postoperatively with T-DM1, an antibody-drug-conjugate compared to trastuzumab.

	This subsequently led to the approval of T-DM1 in this setting.[6] In patients with TNBC, pCR rates with modern platinum containing treatment regimens are about 53%. Therefore, almost 50% of patients with TNBC after NACT remain at high risk of relapse and are candidates for post-neoadjuvant strategies. The post-neoadjuvant approach, in contrast to the adjuvant setting (e.g. ALTTO,[7] Aphinity[8]), avoids overtreatment, limits sample size and limits risk of trial failure from lack of events by selecting a high-risk population. In contrast to neoadjuvant trials, which so far have mainly been powered for pCR rates, post-neoadjuvant trials result in a survival endpoint that is relevant for patients. Post-neoadjuvant trials are probably a more appropriate setting to introduce new therapies into clinical routine for early breast cancer. Sacituzumab govitecan has demonstrated unprecedented activity in heavily pretreated patients with metastatic triple-negative and HR-positive/HER2-negative breast cancer, even after prior immune-checkpoint inhibitors or CDK4/6 and mTOR inhibitors.[9,10] Based on the results of the phase I/II study, sacituzumab govitecan was granted a breakthrough therapy designation for the treatment of patients with advanced or metastatic TNBC who have received at least two previous lines of treatment for metastatic disease.[9] The efficacy of sacituzumab govitecan in advanced TNBC was confirmed in the phase III ASCENT trial.[11] Based on this study, sacituzumab govitecan received regular approval.[12,13] Additionally, the TROPiCS-02 study showed an improvement in progression-free survival and OS over single-agent chemotherapy and a manageable safety profile in patients with heavily pre-treated HR-positive/HER2-negative endocrine-resistant, unresectable locally advanced or metastatic BC.[14,15] Sacituzumab govitecan constitutes a compound with strong activity against highly resistant clones of metastatic breast cancer and an ideal therapy against the resistant residual disease after standard NACT regardless of HR status. The proposed clinical trial evaluates the activity of sacituzumab govitecan in HER2-negative patients at high risk of relapse after NACT.
Study Overview	Phase III, prospective, multi-center, randomized, open label, parallel group, study in patients with HER2-negative breast cancer with residual disease after neoadjuvant chemotherapy with 1:1 allocation to: **Arm A**: Sacituzumab govitecan (days 1, 8 q3w for eight cycles) **Arm B:** Treatment of physician´s choice (TPC, defined as capecitabine or platinum-based chemotherapy for eight cycles or observation). Adjuvant pembrolizumab can be given until the completion of radiotherapy before randomization. Within the study the use of pembrolizumab in patients with TNBC who received pembrolizumab as neoadjuvant therapy is allowed as monotherapy in the TPC arm, according to the approval of pembrolizumab in this setting. In patients with HR-positive breast cancer, endocrine-based therapy, which includes the use of CDK4/6 inhibitors, will be administered according to local guidelines. The start of endocrine therapy will be at the discretion of the investigator; however, it will be encouraged to start after surgery/radiotherapy in patients without additional cytotoxic agents.
Investigational Product	Sacituzumab govitecan 10 mg/kg body weight on days 1, 8 q3w
Non-Investigational Product	Capecitabine 2000 mg/m² day 1-14 q21 day cycle for eight cycles Carboplatin AUC 5 q3w or AUC 1.5 weekly for eight 3 weekly cycles

Primary Objective and Endpoint	1. Invasive disease-free survival Objective: To compare invasive disease-free survival (iDFS) between patients treated with sacituzumab govitecan vs. treatment of physician's choice. Endpoint: iDFS is defined as time from randomization until first iDFS event: local invasive recurrence following mastectomy, local invasive recurrence in the ipsilateral breast following lumpectomy, regional recurrence, distant recurrence, contralateral invasive breast cancer, second non-breast primary cancer (excluding squamous or basal cell carcinoma of the skin), or death from any cause.[16]
Secondary Objectives and Endpoints	1. Overall survival (key secondary endpoint) Objective: To compare overall survival (OS) between both groups. Endpoint: OS is defined as the time from randomization until death from any cause. 2. Distant disease-free survival (DDFS) Objective: To compare distant disease-free survival (DDFS) between both groups. Endpoint: DDFS is defined as the time from randomization until distant recurrence of disease, second primary invasive cancer (non-breast, excluding squamous or basal cell carcinoma of the skin), and death due to any cause. 3. Invasive breast cancer-free survival (iBCFS) Objective: To compare the invasive breast cancer-free survival (iBCFS) between both groups. Endpoint: iBCFS is defined as the time from randomization until first iDFS event excluding any second non-breast primary cancer.[17] 4. Locoregional recurrences-free interval Objective: To compare locoregional recurrences-free interval (LRRFI) between both groups. Endpoint: LRRFI is defined as the time from randomization until any loco-regional (ipsilateral breast (invasive), chest wall, local/regional lymph nodes) recurrence of disease or any invasive contralateral breast cancer whichever occurs first. Distant recurrence, secondary malignancy and death are considered as competing risks and will be accounted for in the analysis. 5. Objective: To compare iDFS and OS in stratified subgroups. • HR-negative vs. HR-positive • ypN+ vs. ypN0. 6. Objective: To compare iDFS and OS in exploratory subgroups. • Prior platinum therapy (TNBC) • Prior immune-checkpoint inhibitor therapy (TNBC) • Experimental arm vs. active TPC in TNBC, overall and in subgroups of different active TPC • low vs. high TROP2-expression (cut off will be defined in the SAP). 7. Safety Objective: To compare safety between both groups. Endpoint: Frequency and severity of adverse events graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. 8. Compliance Objective: To assess and compare compliance on the treatment between both arms. Endpoint: Dose-density, dose reductions, dose delays, treatment interruptions and treatment discontinuation rates. 9. Patient reported outcome and quality of life

	Objective: To assess Patient Reported Outcome (PRO) and Quality of Life (QoL) between both groups. Endpoint: Patient reported breast cancer specific QoL as measured by FACT–B; functional assessment of cognitive function assessed by FACT-Cog; patient reported global QoL assessed by EQ-5D-5L.
Translational Research Objectives	• To explore ctDNA dynamics as early predictors of ctDNA clearance (including time to ctDNA clearance) in ctDNA positive patients. • To explore the predictive value of markers (including immune markers) for sacituzumab govitecan. • To assess UGT1A1 or Dihydropyrimidine Dehydrogenase (DPYD) and additional genotypes (e.g. *gBRCA*). • To explore efficacy and toxicity in variants of UGT1A1 or DPYD. • To assess ctDNA at baseline and during treatment and follow up • To evaluate the microbiome of breast cancer patients and to explore potential new biomarkers, toxicity, immune markers, tumor antigens.
Selection of patients	**Inclusion criteria:** 1. Written informed consent prior to beginning specific protocol procedures, including expected cooperation of the patients for the treatment and follow-up, must be obtained and documented according to the local regulatory requirements. 2. Women or men with age at diagnosis at least 18 years. 3. Willingness and ability to provide archived formalin fixed paraffin embedded tissue (FFPE) block from surgery after neoadjuvant chemotherapy and from biopsy (excluding excisional biopsy or lumpectomy) preferably of the breast, before start of neoadjuvant chemotherapy, which will be used for centralized prospective confirmation of HR status, HER2 status, Ki-67 and tumor-infiltrating lymphocytes (TILs) and for retrospective exploratory correlation between genes, proteins, and mRNAs relevant to sensitivity/resistance to the investigational agents. For patients with bilateral carcinoma, FFPE blocks from both sides have to be provided for central testing. 4. Histologically confirmed unilateral or bilateral primary invasive carcinoma of the breast, confirmed histologically by core biopsy. The lead tumor has to be defined by the investigator based on the inclusion criteria for the respective subtype and on the risk status. 5. Centrally confirmed HER2-negative (IHC score 0-1 or FISH negative according to ASCO/CAP guideline) and either • HR-positive (≥1% positive stained cells) disease or • HR-negative (<1% positive stained cells) assessed preferably on tissue from postneoadjuvant residual invasive disease of the breast, or if not possible, of residual nodal invasion. If not evaluable, core of diagnostic biopsy will be used. In case of bilateral breast cancer, HER2-negative status has to be confirmed for both sides. 6. Patients with residual invasive disease after neoadjuvant chemotherapy at high risk of recurrence defined by either: • For HR-negative: any residual invasive disease > ypT1mi and/or ypN1>1mm

	• For HR-positive disease: a CPS+EG score ≥ 3 or CPS+EG score 2 and ypN+ using local ER and grade assessed on core biopsies taken before start of neoadjuvant treatment. 7. Adequate surgical treatment including resection of clinically evident disease and ipsilateral axillary lymph node dissection. SNB before NACT is discouraged. Axillary dissection before NACT is not permitted. Axillary dissection, including Targeted Axillary Dissection (TAD) should be performed according to guidelines. Histologic complete resection (R0) of all invasive and in situ tumors is required. 8. Patients must have received neoadjuvant taxane-based chemotherapy for 16 weeks (anthracyclines are permitted). This period must include 6 weeks of a taxane containing neoadjuvant chemotherapy (exception: for patients with progressive disease that occurred after at least 6 weeks of taxane-containing neoadjuvant chemotherapy, a total treatment period of less than 16 weeks is also eligible). 9. No clinical evidence for locoregional or distant relapse during or after preoperative chemotherapy. Local progression during chemotherapy is not an exclusion criterion if adequate local control could be obtained. 10. In case of local progression during neoadjuvant therapy, distant metastases must be excluded by adequate imaging (CT/MRI recommend) prior to entering the trial. 11. Immune checkpoint inhibitor / immunotherapy during (neo)adjuvant therapy is allowed until the completion of radiotherapy. 12. Patients with known g*BRCA1/2* mutation without indication to adjuvant olaparib therapy are allowed to participate in the trial. 13. An interval of less than 16 weeks since the date of final surgery or less than 10 weeks from completing radiotherapy (whichever occurs last) and the date of randomization is required. 14. Radiotherapy should be delivered before the start of study treatment. Radiotherapy to the breast is indicated in all patients with breast conserving surgery and to the chest wall and lymph nodes according to local guidelines as well as in all patients with cT3/4 or ypN+ disease treated by mastectomy. 15. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. 16. Resolution of all acute toxic effects of prior anti-cancer therapy or surgical procedure or radiotherapy to NCI CTCAE v 5.0 grade ≤ 1 (except alopecia or other toxicities not considered a safety risk for the patients at the investigator´s discretion). 17. Estimated life expectancy of at least 5 years irrespective of the diagnosis of breast cancer. 18. The patient must be accessible for scheduled visits, treatment and follow-up. 19. Normal cardiac function after neoadjuvant chemotherapy must be confirmed according to local guidelines. Results for LVEF must be above the normal limit of the institution. 20. Laboratory requirements: **Hematology** • Absolute neutrophil count (ANC) ≥1.5 x 10^9 / L • Platelets ≥100 x 10^9 / L • Hemoglobin ≥10 g/dL (≥6.2 mmol/L) **Hepatic function**

- Total bilirubin <1.25x UNL
- AST and ALT ≤1.5x UNL
- Alkaline phosphatase ≤2.5x UNL

Renal Function

- <1.25x ULN creatinine or creatinine clearance ≥30 ml/min (according to Cockroft-Gault, if creatinine is above UNL).

21. 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 postmenopausal or has undergone hysterectomy. Postmenopausal is defined as:
    - Age ≥60 years
    - Age <60 years and ≥12 continuous months of amenorrhea with no identified cause other than menopause
    - Surgical sterilization (bilateral oophorectomy).
22. For women of childbearing potential and males with partners 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 at least 6 months after the last dose of sacituzumab govitecan for female patients and for at least 3 months for male patients; for at least 6 months after the last dose of capecitabine or carboplatin/cisplatin for female patients and for at least 3 months after the last dose of capecitabine or 6 months after the last dose of carboplatin/cisplatin for male patients. Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include: bilateral tubal ligation; male partner sterilization; intrauterine devices.
23. Complete staging work-up prior to the initiation of neoadjuvant chemotherapy. Missing staging investigations must be performed prior to randomization.

<u>Exclusion criteria:</u>

1. Known hypersensitivity reaction to one of the compounds or substances used in this protocol.
2. Patients with definitive clinical or radiologic evidence of stage IV cancer (metastatic disease) are not eligible.
3. Patients with known g*BRCA1/2* mutation and indicated or planned adjuvant olaparib therapy if available.
4. Patients with a history of any malignancy are ineligible with the following exceptions:
    - Patient has been disease-free for at least 5 years and is at low risk for recurrence of that malignancy
    - CIS of the cervix, basal cell and squamous cell carcinomas of the skin.
5. Female patients: pregnancy or lactation at the time of randomization or intention to become pregnant during the study and up to 6 months after sacituzumab govitecan and up to 6 months after treatment with capecitabine or carboplatin/cisplatin.
6. Severe and relevant co-morbidity that would interact with the application of cytotoxic agents or the participation in the study, including Gilbert´s disease, Crigler-Najjar-Syndrom, known hepatitis B, hepatitis C, known HIV positivity, infection requiring intravenous antibiotic use within 1 week of enrolment or known autoimmune disease other than diabetes, stable thyroid disease, vitiligo,

	or other autoimmune skin disease with dermatologic manifestations only are permitted provided all of the following conditions are met: • Rash must cover < 10% of body surface area • Disease is well controlled at baseline and requires only low-potency topical corticosteroids • No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation (PUVA), methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months 7. Any condition that interferes with the safe administration of the treatment of physician´s choice in case the patient is randomized into the TPC arm. 8. 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 prior infarction on ECG, uncontrolled or poorly controlled arterial hypertension (i.e. BP >150/90 mmHg under treatment with at maximum three antihypertensive drugs), rhythm abnormalities requiring permanent treatment (excluding chronic atrial fibrillation not requiring a pacemaker), clinically significant valvular heart disease, supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication; conduction abnormality requiring a pacemaker. 9. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g. bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis or active pneumonitis on chest CT scan. 10. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving chemotherapy. 11. History of significant neurological or psychiatric disorders including psychotic disorders, dementia or seizures that would prohibit the understanding and giving of informed consent. 12. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results. 13. Known allergic reactions to irinotecan. 14. Concurrent treatment with: • Chronic corticosteroids prior to study entry with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or equivalent corticosteroid.
Sample Size Determination	**<u>Total number of patients required: N=1332</u>** The sample size calculation is based on 80% power to detect a 5-year iDFS improvement from 62% to 69.8%, corresponding to a hazard ratio of 0.753 with a 2-sided α=0.05. Assuming 3.25 years of recruitment with 12 months ramp-up and 42 patients per month at peak and 3 years of follow-up after the last patient in, 396 events will be needed, and final analysis is expected 75 months after study start. <u>Sample size rationale:</u> Sample size was determined based on the analysis on the primary endpoint, iDFS. The sample size was calculated based on the following assumptions: • Time to iDFS event follows an approximately exponential distribution. • 5-year iDFS rates for the two arms are assumed below:

5-year iDFS rate for TPC	5-year iDFS rate for SG	Equivalent (HR)
62%	69.8%	0.753

Interim Analyses for primary endpoint:
One interim analysis for overwhelming efficacy will be performed in the study.
O'Brien – Fleming type stopping boundaries based on the Lan-DeMets spending function will be applied.

The interim analysis will take place when 264 events (2/3 of the total events) have occurred. It was estimated that the interim analysis will occur 55 months from study start.

The objectives of the interim analysis will be:

- To assess safety, including any unexpected toxicity. As at the time of the interim efficacy analysis it is expected that all patients will have completed the treatment, this analysis is expected to be the final safety analysis.
- To allow for early stopping of the trial due to overwhelming efficacy.

The following table summarizes the nominal significance level at each analysis when 2/3 and 100% of events are observed at the interim analysis and the final analysis.

Fraction of total events	**Nominal a level**
2/3	0.012
100%	0.046

The actual nominal α levels for the interim analysis and for the final analysis will depend on the fraction of total events occurred at the time of interim analysis.
At this interim analysis statistical hypothesis tests will be performed only for the primary efficacy parameter, iDFS.

Power calculation for the key secondary endpoint:

The testing of the primary and key secondary endpoint is conducted in a hierarchical manner, i.e., only if the primary endpoint is significant to the given α level, the key secondary endpoint OS may be tested to the same overall level of α=0.05.
A 5-year OS improvement from 71.5% to 77.7% is assumed, corresponding to a hazard ratio of 0.753 with a 2-sided α=0.05. Assuming 3.25 years of recruitment 398 events will be needed with a power of 80% and final analysis is expected after 99 months (8.3 years after first patient in, 2 years after final analysis of iDFS).
The power was calculated based on the following assumptions:

- Time to OS event follows an approximately exponential distribution.
- 5-year OS rates for the two arms are assumed below:

5-year OS rate for TPC	5-year OS rate for SG	Equivalent (HR)
71.5%	77.7%	0.753

Interim analysis for the key secondary endpoint:

One interim analysis of OS is planned where O'Brien – Fleming type stopping boundaries based on the Lan-DeMets spending function will be applied.
The interim analysis will take place at the time of the final analysis of iDFS (75 months after study start). It is expected that approximately 302 events (76% of the total events) have occurred.
The actual nominal α levels for the interim analysis and for the final analysis of OS will depend on the fraction of total events occurred at the time of interim analysis.

Randomization	Patients will be randomized in 1:1 ratio by permuted block randomization.
Stratification Factors	• HR-negative vs HR-positive • ypN+ vs ypN0
Efficacy evaluation	An 'intent-to-treat' (ITT) analysis will be conducted for all patients who are randomized (including those who have not started treatment). Patients will be analyzed according to the group they were randomized to. Additionally, a per-protocol analysis will be performed. iDFS will be compared between the treatment arms with the stratified log-rank test.
Interim analyses	• There will be one interim analysis for efficacy after 2/3 of the events to allow for early stopping of the trial due to overwhelming efficacy. • One interim analysis of the key secondary endpoint OS will be performed at the time of the final analysis of the iDFS. • One interim analysis for safety was performed after the first 50 patients completed 4 cycles of treatment.
Biomaterial	The following biomaterial will be collected: • Tumor tissue from breast cores before start of neoadjuvant chemotherapy, breast tissue and nodes from surgery and cores from recurrences. • Full blood for DNA extraction for genomic analysis. • Serum and Plasma for ctDNA (pre-treatment, day 1 cycle 3, day 1 cycle 6, EOT, at relapse). • Stool samples before treatment start and at the end of therapy.
Number of Sites	Approximately 200 sites internationally are necessary to recruit approximately 42 patients per month at full speed recruitment.
Timelines	First patient in: Q4 2020 Last patient in Q1 2024 First interim analysis: Q3 2025 Final iDFS (and interim OS) analysis: Q1 2027 Final OS analysis: Q1 2029
Trial duration	Regular End of Study is defined with the primary objective iDFS (and interim OS). After end of clinical trial, long term follow up continues with no interventional procedures after final iDFS (and interim OS) analysis.
Long Term Follow-up	The protocol GBG 102 (SASCIA) combines an interventional clinical trial part with last patient last visit with the primary efficacy analysis (Primary objective) followed by a non-interventional long term follow up beyond the Study End with the patient self registry established for Germany (GBG 71). This ensures long-term efficacy evaluations beyond the end of the study. Certain sites in other European countries may prefer capturing long term follow up data for SASCIA to use the GBG registry 107 (Eternity). In order to ensure a robust long term follow up post study end, both options will be available for the sites.

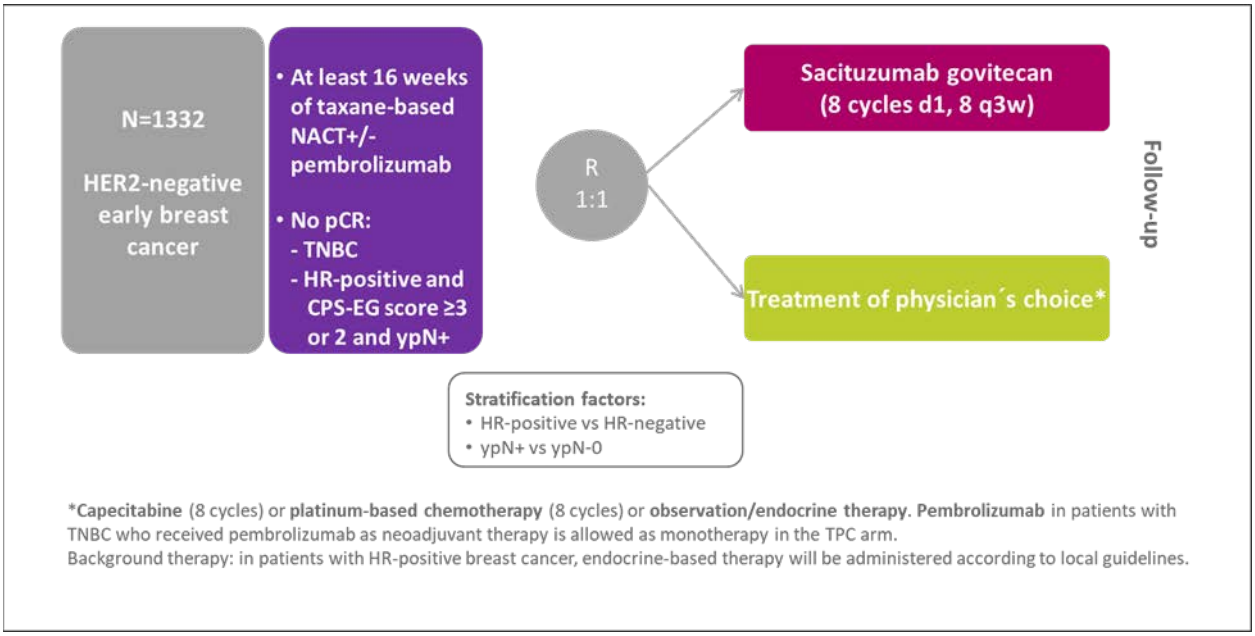


Figure 2 Study Design