A randomized phase III trial comparing two dose-dense, dose-intensified approaches (ETC and PM(Cb)) for neoadjuvant treatment of patients with high-risk early breast cancer (GeparOcto)

GBG 84
EudraCT No.: 2014-000619-14

Protocol Amendment 1 (Version 15.11.2015)

- Protocol Synopsis -

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A randomized phase III trial comparing two dose-dense, dose-intensified approaches (ETC and PM(Cb)) for neoadjuvant treatment of high-risk early breast cancer (GeparOcto)

**Study Title**

A randomized phase III trial comparing two dose-dense, dose-intensified approaches (ETC and PM(Cb)) for neoadjuvant treatment of high-risk early breast cancer (GeparOcto)

**Study Code**

GBG 84

**EudraCT Number**

2014-000619-14

**Sponsor**

GBG Forschungs GmbH, Neu-Isenburg

**Development Phase**

Randomized phase III

**Rationale**

Several recent strategies have improved efficacy of systemic treatment for patients with high-risk early stage breast cancer: the addition of a dual HER2-blockade for HER2-positive; the implementation of carboplatin for TNBC and the use of dose-dense or dose-dense, dose escalated chemotherapy in all high-risk subtypes of breast cancer. Two regimen are currently considered to be among the treatments with highest efficacy: sequential treatment of high dose epirubicin, taxane, and cyclophosphamide (ETC) concomitantly with or without a dual HER2-blockade mainly based on the AGO ETC adjuvant study, and weekly treatment with paclitaxel/non-pegylated liposomal doxorubicin with dual HER2-blockade or carboplatin (PM(Cb)) based on the GeparSixto study. The aim of the GeparOcto study is to compare those two regimen/strategies.

Both regimens are myelosuppressive with a significant incidence of chemotherapy induced anaemia. Anemia is often associated with impaired physical and cognitive function and consequently the patients suffer from a reduced quality of life. Surgical complications are higher in anemic patients. The second aim of the GeparOcto study is therefore to compare the use of parental ferric carboxymaltose versus physician’s choice for the treatment of chemotherapy-induced anemia in patients with iron deficiency.

**Primary Objectives**

To compare the pathological complete response (pCR= ypT0/is ypN0) rates of neoadjuvant treatment with sequential, dose-dense, dose-intensified ETC(+HP) vs. weekly PM(Cb)(+HP) in patients with high-risk operable or locally advanced breast cancer.

**Secondary Objectives**

- To assess the pCR rates per arm separately for the stratified subpopulations.
- To determine the rates of ypT0 ypN0; ypT0 ypN0/++; ypT0/is ypN0/++; ypT(any) ypN0; and the residual cancer burden (RCB) score.
- To determine the response rates of the breast tumor and
| **Correlative Science Objectives** | • To examine and compare pre-specified molecular and histological markers such as Ki67, stromal TILs, immunologically relevant genes (e.g. CXCL9, CCL5, CD8A, CD80, CXCL13, IGKC, CD21, IDO1, PD-1, PDL1, CTLA4, FOXP3, and combinations of these genes) as well as e.g. CD138, CD47, MET and other markers on core biopsies before chemotherapy and on surgical tissue after end of chemotherapy.
• To examine PIK3CA mutation in patients with HER2-positive tumor on core biopsies.
• To validate standardized image analysis systems for Ki67 as well as tumor-infiltrating lymphocytes (TILs). |
| **Supportive Anaemia Treatment Objectives** | Only for those patients randomized for the supportive anemia treatment:
Primary:
• To compare the frequency of patients reaching hemoglobin (Hb) levels ≥ 11g/dl 6 weeks after treatment start of a first episode of anemia grade ≥2 (Hb < 10g/dl) between patients receiving supportive treatment for iron deficiency with parental ferric carboxymaltose versus physician’s choice (no supportive treatment, oral iron substitution, erythropoiesis-stimulating agent (ESA), or both). |
Secondary:

- To compare the median time to achieve a hemoglobin level ≥11g/dl between the supportive treatment arms.
- To compare the frequency of patients with hemoglobin level ≥11g/dl in the week after the end of the last chemotherapy cycle between the supportive treatment arms.
- To compare the median time to achieve an increase in Hb levels by 1g/dl between the supportive treatment arms.
- To compare the change in Hb versus baseline (=randomization in anemia study) and weeks 4, 8, 12, 16, and EOT (i.e. day of surgery).
- To compare the transfusion rate (total number and per patient) and hospital admissions during the first episode of anemia between the supportive treatment arms.
- To compare toxicity and compliance in the two arms.
- To describe use of subsequent supportive anemia treatments in both arms.
- To compare the rate of subsequent episodes after successful treatment of the first anemic episode.
- To compare the change in iron parameters from baseline (=randomization in anemia study) and weeks 4, 8, 12, 16, and EOT (i.e. day of surgery).
- To compare quality of life using the FACT-An anemia and fatigue questionnaire between the supportive treatment arms.

Objectives of Substudies:

- To demonstrate that PET-CT before surgery in addition to conventional presurgical staging methods can decrease the mastectomy rate in patients receiving neoadjuvant chemotherapy for breast cancer (GeparPET substudy).
- To evaluate genome wide single nucleotide polymorphisms (SNPs) to detect genes possibly associated with toxicity and efficacy (Pharmacogenetic substudy).
- To assess ovarian function measured by amenorrhea rate in correlation with changes in E2, FSH, LH, Anti-Müller Hormone, ultrasound-follicle count in patients aged <45 years.

Study Design and Treatment

This is a multicenter, prospective, randomized, open-label phase III study with two different dose-intensified approaches as neoadjuvant therapy in patients with untreated high-risk early breast cancer.

Patients will be randomized to one of the following two treatments:

ETC:

epirubicin 150mg/m² every 2 weeks for 3 cycles followed by paclitaxel 225 mg/m² every 2 weeks for 3 cycles followed
**cyclophosphamide 2000 mg/m² every 2 weeks for 3 cycles.**

or

**PM(Cb):**

- paclitaxel 80mg/m² 18 times weekly simultaneously with
  - NPLD (Myocet®)20mg/m² 18 times weekly simultaneously with
    - carboplatin AUC 1.5 18 times weekly (only in patients with TNBC)

Patients with HER2-positive disease will receive trastuzumab 6 (8) mg/kg every 3 weeks and pertuzumab 420 (840) mg every 3 weeks simultaneously to all T and C cycles in the ETC arm and to all PM (Cb) cycles in the PM(Cb) arm.

**Stratification factors for the chemotherapy randomization will be:**

- breast cancer subtype (HER2+/HR+/ vs. HER2-/HR+ vs. HER2-/HR-) based on central testing
- Ki 67 at baseline (≤20% vs. >20%)
- LPBC at baseline (no vs. yes)

In both study arms, treatment will be given until surgery, disease progression, unacceptable toxicity, withdrawal of consent of the patient or termination by the Sponsor.

Patients who develop an iron-deficient anemia grade ≥2 will be randomized to receive immediately after randomization:

- Physician’s choice (no treatment, oral iron substitution, erythropoiesis-stimulating agents or both)
  or
- Ferric carboxymaltose (Ferinject®) i.v. 1000 mg at week 1 and 500 mg (if body weight is <70 kg) or 1000 mg (if body weight is ≥70 kg) at week 2. In case body weight is <50 kg, both dosages will be reduced to 500 mg each.

Subsequent treatment of persisting or recurrent anemia is open to physician’s choice including red blood cell transfusion. In case, additional treatment is required within 6 weeks after randomization, this will be counted as not having reached the primary endpoint. Information on required further supportive treatment will be collected.

Randomization for the supportive anemia question will be stratified by chemotherapy arm and planned physician’s choice.

### Inclusion Criteria

Patients will be eligible for study participation only if they comply with the following criteria:

- Written informed consent according to local regulatory
requirements prior to beginning specific protocol procedures.

- Complete baseline documentation must be submitted via MedCODES to GBG Forschungs GmbH.
- Unilateral or bilateral primary carcinoma of the breast, confirmed histologically by core biopsy. Fine-needle aspiration from the breast lesion alone is not sufficient. Incisional biopsy or axillary clearance is not allowed. In case of bilateral cancer, the investigator has to decide prospectively which side will be evaluated for the primary endpoint.
- Tumor lesion in the breast with a palpable size of $\geq 2$ cm or a sonographical size of $\geq 1$ cm in maximum diameter. The lesion has to be measurable in two dimensions, preferably by sonography. In case of inflammatory disease, the extent of inflammation can be used as measurable lesion.
- Patients must have stage cT1c - cT4a-d disease. Patients with HER2-positive or TNBC are eligible irrespective of nodal status (cN0-CN3). Patients with luminal B-like tumors (defined here as ER and/or PgR $>1\%$ stained cells, HER2 negative, Ki-67 $>20\%$) only with histologically (sentinel-node biopsy, core- or fine-needle biopsy) involved lymph nodes (pN1-3).
- In patients with multifocal or multicentric breast cancer, the largest lesion should be measured.
- Centrally confirmed ER, PR and HER2 status. Central pathology includes also assessment of Ki-67 and LPBC status on core biopsy. ER/PR negative is defined as $\leq 1\%$ stained cells and HER2-positive is defined as IHC 3+ or in-situ hybridization (ISH) and according to ASCO-CAP guidelines as of 2013). Formalin-fixed, paraffin-embedded (FFPE) breast tissue from core biopsy has therefore to be sent to the GBG central pathology laboratory prior to randomization.
- Age $\geq 18$ years.
- Karnofsky Performance status index $\geq 90\%$.
- Confirmed normal cardiac function by ECG and cardiac ultrasound (LVEF or shortening fraction) within 4 weeks prior to randomization. LVEF must be above 55%.
- Laboratory requirements:
  - Hematology
    - Absolute neutrophil count (ANC) $\geq 2.0 \times 10^9$ / L and
    - Platelets $\geq 100 \times 10^9$ / L and
    - Hemoglobin $\geq 10$ g/dL ($\geq 6.2$ mmol/L)
  - Hepatic function
    - Total bilirubin $\leq 1.5x$ UNL and
    - ASAT (SGOT) and ALAT (SGPT) $\leq 1.5x$ UNL and
    - Alkaline phosphatase $\leq 2.5x$ UNL.
- Negative serum pregnancy test within 7 days prior to randomization for all women of childbearing potential with the
result available before dosing.

- Complete staging work-up within 3 months prior to randomization. All patients must have bilateral mammography, breast ultrasound (≤ 21 days), breast MRI (optional). Chest X-ray (PA and lateral), abdominal ultrasound or CT scan or MRI, and bone scan in case of high risk for primary metastasis. In case of a positive bone scan, bone X-ray or CT scan is mandatory. Other tests may be performed as clinically indicated.

- Patients must agree with central pathology testing of core biopsy specimen and final pathology specimen and be available and compliant for treatment and follow-up.

- In addition for patients to be randomized to the two supportive anemia treatment arms:
  - Hemoglobin level <10g/dl
  - Body weight ≥ 40 kg
  - No need for immediate red blood cell transfusion
  - Transferrin saturation (TSAT) ≤20% and serum ferritin <600ng/ml.*

  * Serum ferritin levels of the first 100 patients with hemoglobin drop below 10g/dl will be reviewed. In case less than 25 of these patients have levels <300 ng/ml, the Protocol Board will decide to
    - either increase the threshold of serum ferritin to reach an incidence of 40% of patients eligible for randomization to the supportive anemia treatments or
    - to close the randomization if it will be non-realistic to recruit a sufficient number of patients or
    - to modify and amend the current statistical design to a lower target sample size that can be reached with the expected number of eligible patients.

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### Exclusion Criteria

- Patients with ER- and/or PR-positive, HER2-negative breast cancer and Ki-67 <= 20% (any luminal A-like subtype) or luminal B-like (Ki67>20%) subtype without nodal involvement.
- Patients with stages cT1a, cT1b, or any M1.
- Patients with pure lobular invasive breast cancer.
- Prior chemotherapy for any malignancy.
- Prior radiation therapy for breast cancer.
- Pregnant or lactating patients. Patients of childbearing potential must agree to use one highly effective or two effective forms of non-hormonal contraceptive measures during study treatment and 7 months following the last dose of mAbs.
- Inadequate general condition (not fit for dose-dense, dose-intensified anthracycline-taxane-targeted agents-based chemotherapy).
- Previous malignant disease being disease-free for less than 5 years (except CIS of the cervix and non-melanomatosus skin cancer).
- 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 >140 / 90 mm Hg under treatment with two antihypertensive drugs), rhythm abnormalities requiring permanent treatment, clinically significant valvular heart disease.
- History of significant neurological or psychiatric disorders including psychotic disorders, dementia or seizures that would prohibit the understanding and giving of informed consent.
- Pre-existing motor or sensory neuropathy of a severity $\geq$ grade 2 by NCI-CTC criteria v 4.0.
- Currently active infection.
- Incomplete wound healing.
- Definite contraindications for the use of corticosteroids.
- Known hypersensitivity reaction to one of the compounds or incorporated substances used in this protocol.
- 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 study entry.
  - other experimental drugs or any other anti-cancer therapy.
- Participation in another clinical trial with any investigational, not marketed drug within 30 days prior to study entry.
- Male patients.

In addition for patients to be randomized to the two supportive anemia treatment arms:

- Iron substitution (oral or i.v.) or blood transfusions or treatment with r-HuEPO with the last 4 weeks prior to study start.
- Known hypersensitivity or contraindication against ferric carboxymaltose.

### Investigational products and formulation

- **NPLD (Myocet®):** 20 mg/m² weekly on day 1 q day 8 for 18 weeks.

Patients with HER2-positive disease:

- Pertuzumab 840 mg loading dose i.v. followed by 420 mg i.v. every 3 weeks simultaneously to all T and C cycles in the ETC.
arm and to all PM(Cb) cycles in the PM(Cb) arm.

- Trastuzumab loading dose: 8 mg/kg, maintenance dose: 6 mg/kg, every three weeks (concomitantly with pertuzumab) simultaneously to all T and C cycles in the ETC arm and to all PM(Cb) cycles in the PM(Cb) arm.

Only for Patients with TNBC (PM(Cb)):

- Carboplatin: AUC 1.5 i.v. weekly on day 1 q day 8 for 18 weeks.

For patients randomized to the supportive anemia question:

- Ferric carboxymaltose i.v. 1000, 1500 or 2000 mg, depending on body weight in accordance with the SPC, over a two week period after a first episode of anemia grade ≥2.

The protocol will provide procedures for specific adverse events requesting dose modifications or delays.

ETC:

- Epirubicin 150 mg/m² i.v. on day 1 q day 15 for 3 cycles.
- Paclitaxel 225 mg/m² i.v. on day 1 q day 15 for 3 cycles.
- Cyclophosphamide 2000 mg/m² i.v. on day 1 q day 15 for 3 cycles.

PM(Cb):

- Paclitaxel 80 mg/m² i.v. weekly on day 1 q day 8 for 18 weeks.

These agents are used according to marketed formulation via normal procedures at each site and applied according to recommendations of the manufacturers.

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<th>Non-investigational product and formulation</th>
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**Supportive treatment**

Pegylated filgrastim 6mg s.c. on day 2 as primary prophylaxis will be given in the ETC arm. G-CSF s.c. will be given as secondary prophylaxis on days 2-4 with PM(Cb).
Ciprofloxacin will be given on days 5-12 during C in the ETC arm. Anemia in the ETC should be treated with ESA and/or iron supplementation as recommended by AGO or EORTC guidelines in case patients are not eligible for randomization to the supportive treatment arms.

**Primary endpoint**

Primary efficacy endpoint:

Pathological complete response of breast and lymph nodes (ypT0/is ypN0; primary endpoint)

No microscopic evidence of residual invasive viable tumor cells in all
Pathological response will be assessed considering all removed breast and lymphatic tissues from all surgeries.

Patients with negative sentinel node biopsy prior to treatment start and no axilla surgery after neoadjuvant chemotherapy will be counted as pCR if no invasive residual tumor is detected in the removed breast tissue. Patients with histologically/cytologically positive nodes prior to treatment start and no axilla surgery after chemotherapy will be counted as no pCR (preferably axillary dissection instead of sentinel node biopsy is strongly recommended in this situation). Patients with positive sentinel node biopsy prior to treatment start and no invasive residual tumor detected in the removed breast tissue and lymph nodes after chemotherapy will be counted as pCR.

The primary endpoint will be summarized as pathological complete remission rate for each treatment group. Two-sided 95% confidence intervals will be calculated according to Pearson and Clopper.

The difference in the rates of pathological complete remissions will be evaluated as rate difference (PM(Cb) arm minus ETC arm) with 95% confidence interval. Additionally, an odds ratio with the 95% confidence interval will be reported. The significance will be tested with the two-sided continuity corrected $\chi^2$-test with significance level of $\alpha = 0.05$. The sample size of the study was calculated for this test of superiority.

If the superiority test fails to detect a significant difference, the non-inferiority will be tested. The non-inferiority margin for pCR-rate difference is set to 5%, the non-inferiority will be claimed, if the lower limit of the 2-sided 95% interval for pCR rate difference (PM(Cb) arm minus ETC arm) is greater than -5%.

The significance level for all other tests is set to 2-sided $\alpha = 0.05$. There will be no adjustment for multiple comparisons in the analyses for the stratified subpopulations. A secondary logistic regression analysis correcting for the stratification factors will be conducted for the primary endpoint.

Uni- and multivariate logistic regression will be performed for pCR to adjust for the known factors (treatment group, age, tumor size, nodal status, grade, histological type, ER/PgR receptor, LPBC), based on the ITT population.

<table>
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<tr>
<th>Secondary endpoints</th>
<th>Secondary Endpoints</th>
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<tr>
<td><strong>Secondary short-time efficacy endpoints</strong> (ypT0 ypN0; ypT0 ypN0/++; ypT0/is ypN0/++; ypT_{(any)} ypN0, the residual cancer burden (RCB) score, response by physical examination, imaging response, breast conservation) will also be summarized as rates in each treatment</td>
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</table>
group, two-sided 95% confidence intervals will be calculated according to Pearson and Clopper, and the continuity corrected Pearson $\chi^2$ test will be performed to evaluate the difference of rates in treatment arms; these tests are considered explorative.

Clinical (c) and imaging (i) response will be assessed every 2\textsuperscript{nd} 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 or mammography will be considered with decreasing priority. The same imaging method should be considered for the measurement before, during and after treatment.

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.

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 affect the success rate in the same way as treatment failures. The clinical tumor response by palpation prior to surgery will also be presented, if applicable.

**LRRFS, RRFS, LRFS, DDFS, IDFS and OS** 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 patient's registry. Progression during neoadjuvant treatment are not considered as events. Curves will be estimated using the Kaplan-Meier method, based on the ITT population. The median survival times (and 95\%CIs) will be estimated. Univariate and multivariate Cox-proportional hazards model will be used to adjust hazard ratios for stratification factor and the above defined covariates.

**Tolerability and Safety:** Descriptive statistics for the 5 treatments (ETC +/- anti-HER2-treatment, PM +/- anti-HER2-treatment, PM(Cb) will be given on the number of patients whose treatment had to be reduced, delayed or permanently stopped. The reason for termination includes aspects of efficacy (e.g. termination due to tumor progression), safety (e.g. termination due to adverse events) and compliance (e.g. 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. Safety by toxicity grades including febrile neutropenia and cardiac dysfunction / failure is defined by the NCI-CTCAE version 4.0.

**Correlative science research:** Exploratory analyses will be performed to identify possible relationships between biomarkers and drug activity. The aim is to identify potential prognostic/predictive biomarkers of short and long term outcome parameters (pCR, no treatment effect (according to regression score 0-1), DFS, and OS).
<table>
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<tr>
<th>Statistical Methods</th>
<th>Missing data on response evaluation will be set to no response.</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>An 'intent-to-treat' (ITT) 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. The sample size calculation is based on the following assumptions:</td>
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<td></td>
<td>• pCR rate in the ETC arm is expected to be 50%</td>
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<td>• pCR rate in the PM(Cb) arm is expected to be 60%</td>
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<td>If 463 patients are enrolled into each arm and started therapy, a one-sided continuity corrected χ²-test will have an 85% power to the two-sided significance level of alpha = 0.05 to show the superiority of the PM(Cb) arm. Computation was performed with nQuery Advisor 6.02.</td>
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<td>It is planned to recruit 950 subjects (including 2.5% randomized patients not starting treatment) into this study. It will be aimed to recruit an equal proportion of patients with HER2-positive, triple-negative and luminal B-like tumors.</td>
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<td>Assumptions for the supportive anemia treatment question:</td>
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<td>It is expected that 50% of patients will achieve an Hb level ≥ 11 g/dl after 6 weeks with physicians choice and 65% with ferric carboxymaltose. Using a 2-sided Fisher test at an alpha level of 0.05 with a power of 80%, 184 patients per group are needed. Considering a 10% drop-out rate, 400 patients in total will have to be randomized.</td>
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<td>Number of sites</td>
<td>It is planned to conduct the study within approximately 80-100 sites in Germany.</td>
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<td>Enrollment Period</td>
<td>Approximately 18 months (Q-IV 2014 – Q-I 2016).</td>
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<td>Study duration</td>
<td>Approximately 2 years (18 months recruitment + 4.5 months treatment duration + maximum 1.5 months time to surgery).</td>
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<td>Follow-up Period</td>
<td>As no study specific treatment or investigation is planned after end of systemic treatment, surgery and follow up are not part of this study. However, information on subsequent cancer specific treatments and the health status of the patients is collected either based on yearly chart reviews at the sites or based on information deriving from the GBG registry of previous study participants.</td>
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**GeparOcto**

\[ N=950 \]

**Triple neg.** or **Her2-pos.** or **High risk** HR+/HER2-

R

- Paclitaxel 80 mg/m², q1w or 225 mg/m² q2w
- NPLD 20 mg/m², q1w
- Epirubicin 150 mg/m², q2w
- **Triple-neg:** Carboplatin AUC 1.5, q1w
- Cyclophosphamide 2 g/m², q2w

**Her2-pos:** Trastuzumab (8), 6 mg/kg q3w (for 1y)
- Pertuzumab (840), 420 mg absolute dose q3 w

Surgery