A 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)

Purpose

Two regimen are currently considered to have highest efficacy for patients with high-risk early stage breast cancer: sequential treatment of high dose epirubicin, taxane, and cyclophosphamide concomitantly with a dual HER2-blockade, and weekly treatment with paclitaxel/non-pegylated liposomal doxorubicin with dual HER2-blockade or carboplatin. The aim of the GeparOcto study is to compare those two regimen/stategies.

Both regimens are myelosuppressive with a significant incidence of chemotherapy induced anaemia.

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 anaemia in patients with iron deficiency.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
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</thead>
<tbody>
<tr>
<td>Tubular Breast Cancer Stage II</td>
<td>Drug: non-pegylated liposomal doxorubicin</td>
<td>Phase 3</td>
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<tr>
<td>Tubular Breast Cancer Stage III</td>
<td>Drug: Carboplatin</td>
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<tr>
<td>Mucinous Breast Cancer Stage II</td>
<td>Drug: Paclitaxel</td>
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<tr>
<td>Breast Cancer Female NOS</td>
<td>Drug: Epirubicin</td>
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<tr>
<td>Invasive Ductal Breast Cancer</td>
<td>Drug: Cyclophosphamide</td>
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<tr>
<td>HER2 Positive Breast Cancer</td>
<td>Drug: Pertuzumab</td>
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<tr>
<td>Inflammatory Breast Cancer</td>
<td>Drug: Trastuzumab</td>
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<tr>
<td></td>
<td>Drug: Ferric carboxymaltose</td>
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</tbody>
</table>

Study Type: Interventional
Study Design:
Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: 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)
Further study details as provided by German Breast Group:

**Primary Outcome Measures:**

- Pathological complete response (pCR= ypT0/is ypN0) [Time Frame: 18 weeks (time window + 3 weeks)]
  - [Designated as safety issue: No]
  - 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. Masked role for assessor.

  - Only for those patients randomized for the supportive anemia treatment: frequency of patients reaching hemoglobin (Hb) levels ≥ 11g/dl 6 weeks after treatment start of a first episode of anemia grade ≥2 [Time Frame: 18 weeks (time window + 3 weeks)]
    - [Designated as safety issue: Yes]
    - Only for those patients randomized for the supportive anemia treatment: 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 Outcome Measures:**

- pCR rates per arm [Time Frame: 18 weeks (time frame + 3 weeks)] [Designated as safety issue: No]
  - To assess the pCR rates per arm separately for the stratified subpopulations.

- Clinical and imaging response [Time Frame: 18 weeks (time window + 3 weeks)] [Designated as safety issue: No]
  - To determine the response rates of the breast tumor and axillary nodes based on physical examination and imaging tests (sonography, mammography, or MRI) after treatment in both arms.

- Rates of ypT0 ypN0; ypT0 ypN0/+; ypT0/is ypN0/+; ypT(any) ypN0; and the residual cancer burden (RCB) score. [Time Frame: 18 weeks (time frame + 3 weeks)] [Designated as safety issue: No]
  - Response (by physical examination, imaging response, breast conservation) will also be summarized as rates in each treatment group.

- Toxicity and Compliance including incidence of febrile neutropenia [Time Frame: 18 weeks (time frame + 3 weeks)] [Designated as safety issue: Yes]
  - Descriptive statistics for the 5 treatments (ETC +/- anti-HER2-treatment, PM +/- anti-HER2-treatment, PMCb) will be given on the number of patients whose treatment had to be reduced, delayed or permanently stopped.

- Breast conservation rate [Time Frame: 18 weeks (time frame: + 3 weeks)] [Designated as safety issue: No]
  - To determine the breast conservation rate after each treatment.

- Loco-regional invasive recurrence free survival (LRRFS) in both arms and according to stratified subpopulations [Time Frame: 5 years] [Designated as safety issue: No]
  - LRRFS is 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.

- Distant-disease-free survival (DDFS) in both arms and according to stratified subpopulations [Time Frame: 5 years] [Designated as safety issue: No]
  - DDFS is 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.
- Invasive disease-free survival (IDFS) in both arms and according to stratified subpopulations. [Time Frame: 5 years] [Designated as safety issue: No]
  IDFS is 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.

- Overall survival (OS) in both arms and according to stratified subpopulations. [Time Frame: 5 years] [Designated as safety issue: No]
  OS is 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.

- Regional recurrence free survival (RRFS) in patients with initial node-positive axilla [Time Frame: until event occurs - no event for cured patients] [Designated as safety issue: No]
  To assess regional recurrence free survival (RRFS) in patients with initial node-positive axilla converted to negative (ypN0) at surgery and treated with sentinel node biopsy alone.

- pCR rate and local recurrence free survival (LRFS) in patients with a clinical complete response (cCR) and a negative core biopsy [Time Frame: 5 years] [Designated as safety issue: No]
  To determine the pCR rate and local recurrence free survival (LRFS) in patients with a clinical complete response (cCR) and a negative core biopsy before surgery.

- Correlation of response [Time Frame: 18 weeks (time frame + 3 weeks)] [Designated as safety issue: No]
  To correlate response (complete vs. partial vs. no change) measured by best appropriate imaging method after 6 weeks of treatment with pCR.

- Examination and comparison of molecular markers [Time Frame: Baseline and 18 weeks (time frame + 3 weeks)] [Designated as safety issue: No]
  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 and eventually also on surgical tissue after end of chemotherapy. The aim is to identify potential predictive short and long term parameters.

- Examination of PIK3CA mutation [Time Frame: Baseline and 18 weeks (time frame + 3 weeks)] [Designated as safety issue: No]
  To examine PIK3CA mutation in patients with HER2-positive tumor on core biopsies.

- Only for those patients randomized for the supportive anemia treatment: Quality of life [Time Frame: up to 18 weeks] [Designated as safety issue: No]
  To compare quality of life using the FACT-An anemia and fatigue questionnaire between the supportive treatment arms.

- Only for those patients randomized for the supportive anemia treatment: median time to achieve a hemoglobin level ≥11g/dl [Time Frame: up to 18 weeks] [Designated as safety issue: Yes]
  To compare the median time to achieve a hemoglobin level ≥11g/dl between the supportive treatment arms.

- Only for those patients randomized for the supportive anemia treatment: frequency of patients with a hemoglobin level ≥11g/dl [Time Frame: up to 18 weeks] [Designated as safety issue: Yes]
  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.

- Pharmacogenetic substudy [Time Frame: 18 weeks (time frame + 3 weeks)] [Designated as safety issue: No]
  To correlate Single Nucleotide Polymorphisms (SNPs) of genes with the associated toxicity and histologically assessed treatment effect.

- GeparPET substudy [Time Frame: 18 weeks (time frame + 3 weeks)] [Designated as safety issue: No]
  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.

- Ovarian function [Time Frame: Baseline until 2 years after EOS] [Designated as safety issue: No]
  To assess ovarian function measured by amenorrhea rate in correlation with changes in E2, FSH, LH, Anti-Müller Hormone, ultrasounds-
Follicle count in patients aged <45 years.

Estimated Enrollment: 950
Study Start Date: December 2014
Estimated Study Completion Date: July 2016
Estimated Primary Completion Date: July 2016 (Final data collection date for primary outcome measure)

<table>
<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
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<tbody>
<tr>
<td><strong>Experimental: PM(Cb)</strong></td>
<td>Drug: non-pegylated liposomal doxorubicin</td>
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<tr>
<td>PM(Cb):</td>
<td>20 mg/m², i.V. 18 times weekly</td>
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<td></td>
<td>Other Name: Myocet</td>
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<td></td>
<td>Drug: Carboplatin</td>
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<td></td>
<td>Carboplatin AUC 1.5 18 times weekly (only in patients with triple-negative breast cancer).</td>
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<td></td>
<td>Other Name: Carbomedac</td>
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<td></td>
<td>Drug: Paclitaxel</td>
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<td></td>
<td>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 cycles.</td>
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<td></td>
<td>Other Name: var.</td>
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<td></td>
<td>Drug: Pertuzumab</td>
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<td></td>
<td>420 (840) mg every 3 weeks simultaneously to all T and C cycles in the ETC arm and to all cycles in the PM(Cb) arm.</td>
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<td>Other Name: Perjeta</td>
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<td></td>
<td>Drug: Trastuzumab</td>
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<tr>
<td></td>
<td>Trastuzumab 6 (8) mg/kg every 3 weeks simultaneously to all T and C cycles in the ETC arm and to all cycles in the PM(Cb) arm.</td>
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<td>Other Name: Herceptin</td>
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<td>Drug: Ferric carboxymaltose</td>
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<td>after first anemia grade ≥2 and in case of randomisation: Ferric carboxymaltose i.V. 1000 mg followed 1 week later by an injection of ferric carboxymaltose i.V. 500 mg (if body weight is &lt;70 kg) or 1000 mg (if body weight is ≥70 kg). In case body weight is &lt;50 kg, both dosages will be reduced to 500 mg each.</td>
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<tr>
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<td>Other Name: Ferinject</td>
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<td><strong>Active Comparator: ETC</strong></td>
<td>Drug: Paclitaxel</td>
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<td>ETC:</td>
<td>paclitaxel 80mg/m² 18 times weekly</td>
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<td>Other Name: var.</td>
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<td></td>
<td>Drug: Epirubicin</td>
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<td>150mg/m² every 2 weeks for 3 cycles.</td>
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<td>Other Name: Farmorubicin</td>
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<td></td>
<td>Drug: Cyclophosphamide</td>
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<td>2000 mg/m² every 2 weeks for 3 cycles.</td>
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<td></td>
<td>Other Name: Endoxan</td>
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<td></td>
<td>Drug: Pertuzumab</td>
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<td></td>
<td>420 (840) mg every 3 weeks simultaneously to all T and C cycles in the ETC arm and to all cycles in the PM(Cb) arm.</td>
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<td>Other Name: Ferinject</td>
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Detailed Description:
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 regimens are currently considered to have highest efficacy: sequential treatment of high dose epirubicin, taxane, and cyclophosphamide (ETC) concomitantly with 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 parenteral ferric carboxymaltose versus physician's choice for the treatment of chemotherapy-induced anemia in patients with iron deficiency.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Female
Accepts Healthy Volunteers: No

Criteria

Inclusion 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 2 cm or a sonographical size of 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 <=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 >=18 years.
- Karnofsky Performance status index 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%.
- Negative pregnancy test (urine or serum) within 14 days prior to randomization for all women of childbearing potential.
- 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 <300ng/ml.

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 implement adequate non-hormonal contraceptive measures (barrier methods, intrauterine contraceptive devices, sterilization) during study treatment.
- 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-melanomatous 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 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 IV) or blood transfusions or treatment with r-HuEPO with the last 4 weeks prior to study start.
- Known hypersensitivity or contraindication against ferric carboxymaltose.

**Contacts and Locations**

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT02125344

**Contacts**

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Contact: Mathias Uhlig, MD  + 49 (0)6102/7480 ext 414  mathias.uhlig@germanbreastgroup.de

**Locations**

Germany

NTC  Recruiting
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Contact: Andreas Schneeweiß, MD, Prof.  +49 (0)6221-56 ext 7980  andreas.schneeweiss@med.uni-heidelberg.de
Principal Investigator: Andreas Schneeweiß, MD, Prof.

**Sponsors and Collaborators**

German Breast Group
Amgen
Roche Pharma AG
TEVA
Vifor Pharma
Principal Investigator: Andreas Schneeweiß, MD, Prof. NTC Heidelberg

Additional Information:

Sponsor study homepage

No publications provided

Responsible Party: German Breast Group
ClinicalTrials.gov identifier: NCT02125344
Other Study ID Numbers: GBG 84
Study First Received: April 22, 2014
Last Updated: March 30, 2015
Health Authority: Germany: Federal Institute for Drugs and Medical Devices

Additional relevant MeSH terms:
Breast Neoplasms
Carcinoma, Ductal, Breast
Inflammatory Breast Neoplasms
Adenocarcinoma
Breast Diseases
Carcinoma
Carcinoma, Ductal
Neoplasms
Neoplasms by Histologic Type
Neoplasms by Site
Neoplasms, Ductal, Lobular, and Medullary
Neoplasms, Glandular and Epithelial
Skin Diseases
Carboplatin
Cyclophosphamide

ClinicalTrials.gov processed this record on April 13, 2015