Purpose

Pharmacologic inhibition of RANKL attenuates the development of mammary carcinoma and inhibits metastatic progression in multiple mouse models.

In a retrospective analysis it could be demonstrated that elevated expression of RANK was found in 14.5% of patients overall, with a significant predominance in patients with hormone-receptor-negative disease. Expression of RANK was associated with a higher pathological complete response rate but with a shorter disease-free and overall survival. The ABCSG-18 study showed that adjuvant denosumab reduces clinical fractures, improves bone health, and can be administered without added toxicity.

It appears therefore reasonable to test denosumab, a clinically available antibody against RANKL in patients with hormone-receptor-negative primary breast cancer as an adjunct to neoadjuvant chemotherapy for its ability to increase pCR rate and improve outcome in relation to the expression of RANK.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer Female NOS</td>
<td>Drug: Denosumab</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Tubular Breast Cancer Stage II</td>
<td>Drug: nab-Paclitaxel</td>
<td></td>
</tr>
<tr>
<td>Mucinous Breast Cancer Stage II</td>
<td>Drug: Epirubicin</td>
<td></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: Carboplatin</td>
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<tr>
<td>Inflammatory Breast Cancer</td>
<td>Drug: Trastuzumab</td>
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</tr>
<tr>
<td>Tubular Breast Cancer Stage III</td>
<td>Drug: Pertuzumab</td>
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</tbody>
</table>

Study Type: Interventional
Study Design:
- Allocation: Randomized
- Intervention Model: Factorial Assignment
- Masking: No masking
- Primary Purpose: Treatment

Official Title: Investigating Denosumab as an add-on Neoadjuvant Treatment for RANK-positive or RANK-negative Primary Breast Cancer and Two Different Nab-Paclitaxel Schedules; 2x2 Factorial Design (GeparX)

Resource links provided by NLM:
- Genetics Home Reference related topics: breast cancer
- MedlinePlus related topics: Breast Cancer
- Drug Information available for: Denosumab
- Genetic and Rare Diseases Information Center resources: Inflammatory Breast Cancer
- U.S. FDA Resources

Further study details as provided by German Breast Group:

Primary Outcome Measures:
- pcR rates of neoadjuvant treatment with or without denosumab in addition to nab-paclitaxel and EC. [ Time Frame: 24 weeks ]
- pcR (ypT0 ypN0) rates of nab-Paclitaxel weekly for 12 weeks or 2 of 3 weeks for 12 weeks [ Time Frame: 12 weeks ]

Secondary Outcome Measures:
- To test for interaction of denosumab treatment with RANK expression. [ Time Frame: 24 weeks ]
- To assess the pCR rates per arm for both randomizations separately for TNBC and HR-/HER2+ tumors. [ Time Frame: 24 weeks ]
### Arms

| Experimental: Denosumab  
Denosumab every 4 weeks for 6 cycles. | Drug: Denosumab  
Denosumab 120 mg every 4 weeks for 6 cycles  
Other Name: Human monoclonal IgG2 antibody |
|-----------------------------------------|---------------------------------------------------------------|
| Experimental: nab-Paclitaxel weekly  
nab-Paclitaxel weekly for 12 weeks. Patients with HER2-positive tumors receive Trastuzumab and Pertuzumab. Patients with triple-negative tumors receive Carboplatin in parallel to nab-paclitaxel. | Drug: nab-Paclitaxel  
nab-paclitaxel 125 mg/m² weekly for 12 weeks or at day 1,8 q22 for 4 cycles (12 weeks)  
Other Name: Abraxane  
Drug: Carboplatin  
Carboplatin AUC 2 weekly in parallel to nab-Paclitaxel  
Other Name: Diamminplatin(II)-cyclobutan-1,1-dicarboxylat  
Drug: Trastuzumab  
Trastuzumab 6 (8) mg/kg every 3 weeks simultaneously to all chemotherapy cycles  
Other Name: Herceptin  
Drug: Pertuzumab  
Pertuzumab 420 (840) mg every 3 weeks simultaneously to all chemotherapy cycles  
Other Name: Perjeta |
| Experimental: nab-paclitaxel 2 of 3 weeks  
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Drug: Trastuzumab |

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**Estimated Enrollment:** 778  
**Actual Study Start Date:** February 13, 2017  
**Estimated Study Completion Date:** December 2018  
**Estimated Primary Completion Date:** December 2018 (Final data collection date for primary outcome measure)
Trastuzumab 6 (8) mg/kg every 3 weeks simultaneously to all chemotherapy cycles
Other Name: Herceptin
Drug: Pertuzumab
Pertuzumab 420 (840) mg every 3 weeks simultaneously to all chemotherapy cycles
Other Name: Perjeta

Experimental: EC every two weeks or every three weeks
Epirubicin and Cyclophosphamide 600mg/m² for 4 times. Patients with HER2-positive tumors receive Trastuzumab and Pertuzumab.

Drug: Epirubicin
Epirubicin 90 mg/m² every 2 or 3 weeks for 4 times
Other Name: Farmorubicin
Drug: Cyclophosphamide
Cyclophosphamide 600 mg/m² every 2 or 3 weeks for 4 times
Other Name: Endoxan
Drug: Trastuzumab
Trastuzumab 6 (8) mg/kg every 3 weeks simultaneously to all chemotherapy cycles
Other Name: Herceptin
Drug: Pertuzumab
Pertuzumab 420 (840) mg every 3 weeks simultaneously to all chemotherapy cycles
Other Name: Perjeta

Detailed Description:
RANK ligand (RANKL), a key factor for bone remodeling and metastasis, is crucial for the development of mouse mammary glands during pregnancy. RANKL functions as a major paracrine effector of the mitogenic action of progesterone in mouse and human mammary epithelium via its receptor RANK and has a role in ovarian hormone-dependent expansion and regenerative potential of mammary stem cells. Pharmacologic inhibition of RANKL attenuates the development of mammary carcinoma and inhibits metastatic progression in multiple mouse models.

In a retrospective analysis of 601 patients treated in the GeparTrio study with chemotherapy (TAC) it could be demonstrated that elevated expression of RANK (immunohistochemical score > 8.5 using the N-1H8 antibody by Amgen) was found in 14.5% of patients overall, with a significant predominance in patients with hormone-receptor-negative disease (33.7% vs 6.4% tumors positive for RANK).

Expression of RANK was associated with a higher pathological complete response rate (pCR) (23.0% vs 12.6%) but with a shorter disease-free and overall survival. The ABCSG-18 study showed that adjuvant denosumab reduces clinical fractures, improves bone health, and can be administered without added toxicity. Moreover denosumab improves disease-free survival in postmenopausal woman with hormone receptor positive breast cancer.

https://clinicaltrials.gov/ct2/show/NCT02682693?term=GeparX&rank=1
It appears therefore reasonable to test denosumab, a clinically available antibody against RANKL in patients with hormone-receptor-negative primary breast cancer as an adjunct to neoadjuvant chemotherapy for its ability to increase pCR rate and improve outcome in relation to the expression of RANK.

**Eligibility**

**Ages Eligible for Study:** 18 Years to 75 Years (Adult, Senior)

**Sexes Eligible for Study:** All

**Accepts Healthy Volunteers:** No

**Criteria**

**Inclusion criteria:**

- 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 tumor isn't measurable by sonography, then MRI or mammography is sufficient. In case of inflammatory disease, the extent of inflammation can be used as measurable lesion.

- Patients must have stage cT1c - cT4a-d disease.

- In patients with multifocal or multicentric breast cancer, the largest lesion should be measured.

- Centrally confirmed ER-negative and PR-negative status. Central pathology includes also assessment of HER2, Ki-67, TIL and RANK 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. LPBC (lymphocyte predominant breast cancer) is defined as more than 50% stromal tumour infiltrating lymphocytes. Formalin-fixed, paraffin-embedded (FFPE) breast tissue from core biopsy has therefore to be sent to the GBG central pathology laboratory prior to randomization.

**Exclusion criteria:**

- Patients with stages cT1a, cT1b, or any M1.

- Prior chemotherapy for any malignancy.

- Prior radiation therapy for breast cancer.

- History of disease with influence on bone metabolism, such as osteoporosis, Paget's disease of bone, primary hyperparathyroidism requiring treatment at the time of randomization or considered likely to become necessary within the subsequent six months.

- Use of bisphosphonates or denosumab within the past 1 year.

- Significant dental/oral disease, including prior history or current evidence of osteonecrosis/osteomyelitis of the jaw, active dental or jaw condition which requires oral surgery, non-healed dental/oral surgery, planned invasive dental procedure for the course of the study.

- Previous malignant disease being disease-free for less than 5 years (except CIS of the cervix and non-melanomatous skin cancer).

https://clinicaltrials.gov/ct2/show/NCT02682693?term=GeparX&rank=1

07.08.2017
• 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.

• Currently active infection.

• Incomplete wound healing.

• Definite contraindications for the use of corticosteroids.

**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: NCT02682693

**Contacts**

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**Locations**

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**Sponsors and Collaborators**

German Breast Group

Amgen

Celgene Corporation

**Investigators**

Principal Investigator: Sherko Kümmel, MD  Kliniken Essen-Mitte

**More Information**

Responsible Party: German Breast Group

ClinicalTrials.gov Identifier: NCT02682693  History of Changes

Other Study ID Numbers: GBG 88

Study First Received: January 27, 2016

Last Updated: July 10, 2017

https://clinicaltrials.gov/ct2/show/NCT02682693?term=GeparX&rank=1  07.08.2017
Individual Participant Data (IPD) Sharing Statement:

Plan to Share IPD: No

Studies a U.S. FDA-regulated Drug Product: No
Studies a U.S. FDA-regulated Device Product: No

Additional relevant MeSH terms:

Breast Neoplasms
Inflammatory Breast Neoplasms
Carcinoma, Ductal, Breast
Neoplasms by Site
Neoplasms
Breast Diseases
Skin Diseases
Carcinoma, Ductal
Adenocarcinoma
Carcinoma
Neoplasms, Glandular and Epithelial
Neoplasms by Histologic Type
Neoplasms, Ductal, Lobular, and Medullary
Paclitaxel
Pertuzumab

ClinicalTrials.gov processed this record on August 04, 2017