Addition of PD-L1 Antibody MEDI4736 to a Taxane-anthracycline Chemotherapy in Triple Negative Breast Cancer (GeparNuevo)

This study is not yet open for participant recruitment. (see Contacts and Locations)

Verified January 2016 by German Breast Group

Sponsor:
German Breast Group

Collaborators:
AstraZeneca
Celgene Corporation

Information provided by (Responsible Party):
German Breast Group

ClinicalTrials.gov Identifier:
NCT02685059

First received: January 14, 2016
Last updated: February 12, 2016
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History of Changes

Purpose

To date no targeted agents are available to treat TNBC. Therefore chemotherapy is the only treatment option. TNBC often has a high amount of tumour infiltrating lymphocytes. Stimulating the immune cells of TNBC might therefore be an option for these patients to increase the pathological complete response. pCR is highly correlated with outcome in TNBC.

Therefore the addition of a checkpoint inhibitor in addition to chemotherapy might be an additional option for these patients.

Condition	Intervention	Phase
Breast Cancer	Drug: MEDI4736 (Anti PD-L1) Drug: Placebo Drug: nab-Paclitaxel Drug: Epirubicin Drug: Cyclophosphamide	Phase 2

Study Type: Interventional
Study Design: Allocation: Randomized
Intervention Model: Parallel Assignment
Masking: Double Blind (Participant, Investigator)
Primary Purpose: Treatment

Official Title: A Randomized Phase II Study to Investigate the Addition of PD-L1 Antibody MEDI4736 to a Taxane-anthracycline Containing Chemotherapy in Triple Negative Breast Cancer (GeparNuevo)

Resource links provided by NLM:

Genetics Home Reference related topics: breast cancer

MedlinePlus related topics: Breast Cancer

U.S. FDA Resources

Further study details as provided by German Breast Group:

Primary Outcome Measures:

- pathological complete response (pCR= ypT0 ypN0) [Time Frame: 22 weeks]

To compare the pathological complete response (pCR= ypT0 ypN0) rates of neoadjuvant treatment of sequential, nab-Paclitaxel followed by EC +/- the PD-L1 antibody MEDI4736 in patients with early triple negative breast cancer.

Secondary Outcome Measures:

- pCR rates per arm [Time Frame: 22 weeks]

  To assess the pCR rates per arm separately for the stratified subpopulations.

- Rates of ypT0/is ypN0 [Time Frame: 22 weeks]

  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 different arms.

- Rates of ypT0/is ypN0/+ [Time Frame: 22 weeks]

  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 different arms.

- Rates of ypT(any) ypN0 [Time Frame: 22 weeks]

  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 different arms.

- Rates of ypT0 ypN0/+ [Time Frame: 22 weeks]

  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 different arms.

- Clinical response [Time Frame: 22 weeks]

  To assess clinical response rate after taxane in both groups.

- Breast conservation rate [Time Frame: 22 weeks]

  To determine the breast conservation rate after each treatment.

- Toxicity and compliance as measured by number of participants with treatment-related [Time Frame: 22 weeks]

  Number of participants with treatment-related adverse events CTCAE v4.0

- Molecular markers and gene expression [Time Frame: 22 weeks]

  To examine and compare pre-specified molecular markers and gene expression signatures such as tumor infiltrating lymphocytes, PD-1, PD-L1, Ki-67, etc. on core biopsies before chemotherapy, after the window phase and surgical tissue after end of chemotherapy (in %)

- Survival [Time Frame: 22 weeks]

  To determine loco-regional invasive recurrence free survival (LRRFS), distant-disease-free survival (DDFS), invasive disease-free survival (IDFS), event free survival (EFS per FDA definition) and overall survival (OS) in different arms and according to stratified subpopulations (in months)

Estimated Enrollment:	174
Study Start Date:	March 2016
Estimated Study Completion Date:	March 2018
Estimated Primary Completion Date:	March 2018 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: MEDI4736 part 1: MEDI4736 (with half dose as monotherapy for the first two weeks) part 2: MEDI4736 1.5 g total for 20 weeks	Drug: MEDI4736 (Anti PD-L1) MEDI4736 1.5g total i.v. every 4 weeks As monotherapy for the first two weeks (0.75g absolute) (part 1) followed by: MEDI4736 in combination with nab-paclitaxel 125 mg/m² every week for 12 weeks (part 2) followed by MEDI4736 in combination with epirubicin 90mg/m² plus cyclophosphamide 600 mg/m² every 2 weeks for 4 cycles (part 3). Other Name: Antibody against cell death ligand 1 (PD-L1)
Placebo Comparator: Placebo	Drug: Placebo Placebo i.v. every 4 weeks

part 1: Placebo (for the first two weeks) part 2: Placebo for 20 weeks	As monotherapy for the first two weeks (0.75g absolute) (part 1) followed by: Placebo in combination with nab-paclitaxel 125 mg/m² every week for 12 weeks (part 2) followed by MEDI4736/Placebo in combination with epirubicin 90mg/m² plus cyclophosphamide 600 mg/m² every 2 weeks for 4 cycles (part 3).
Active Comparator: Taxane Nab-Paclitaxel 125 mg/m² weekly for 12 weeks	Drug: nab-Paclitaxel nab-Paclitaxel 125 mg/m² weekly for 12 weeks Other Name: non-solvent based taxane
Active Comparator: Epirubicin Epirubicin 90 mg/m² 2-weekly for 8 weeks	Drug: Epirubicin Epirubicin 90 mg/m² 2-weekly for 8 weeks Other Name: Farmorubicin
Active Comparator: Cyclophosphamide Cyclophosphamide 600 mg/m² 2-weekly for 8 weeks	Drug: Cyclophosphamide Cyclophosphamide 600 mg/m² 2-weekly for 8 weeks Other Name: Endoxan

Detailed Description:

To date no targeted agents are available to treat TNBC. Therefore chemotherapy is the only treatment option. TNBC often has a high amount of tumour infiltrating lymphocytes. Stimulating the immune cells of TNBC might therefore be an option for these patients to increase the pathological complete response. pCR is highly correlated with outcome in TNBC.

Therefore the addition of a checkpoint inhibitor in addition to chemotherapy might be an additional option for these patients.

The primary objective therefore is to compare the pathological complete response (pCR= ypT0 ypN0) rates of neoadjuvant treatment of sequential, nab-Paclitaxel followed by EC +/- the PD-L1 antibody MEDI4736 in patients with early triple negative breast cancer.

Eligibility

Ages Eligible for Study: 18 Years and older (Adult, Senior)
Sexes Eligible for Study: Female
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Written informed consent for all study according to local regulatory requirements prior to beginning specific protocol procedures.
- Complete baseline documentation must be sent to GBG Forschungs GmbH.
- Unilateral or bilateral primary carcinoma of the breast, confirmed histologically by core biopsy. Fine-needle aspiration alone is not sufficient. Incisional biopsy 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 be in the following stages of disease: cT1b - cT4a-d irrespective of nodal involvement.

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

- Triple negative disease with centrally confirmed ER negative/PR negative/HER-2 negative, and centrally confirmed Ki-67 value. ER/PR negative is defined as <1% stained cells and HER2-negative is defined as either IHC 0/1+ or IHC 2+ and in-situ hybridisation (ISH) of either ratio <2.0 or less than 6 copies of HER2 per tumor cell. Stromal TILs will be evaluated in three groups: no immune infiltrate (0-10% stromal TILs) intermediate immune infiltrate (11-59% stromal TILs), LPBC 60-100% stromal TILs. PD-L1 status and other predefined markers will be prospectively assessed during the study. 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.
- ECOG Performance status 0-1.
- Normal cardiac function must be confirmed by ECG and cardiac ultrasound (LVEF or shortening fraction) within 3 months prior to randomization. Results must be above the normal limit of the institution.
- Negative pregnancy test (urine or serum) within 14 days prior to randomization for all women of childbearing potential. Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: >=60 years old and no menses for >=1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.
- Complete staging work-up within 3 months prior to randomization. All patients must have had 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 done. In case of positive bone scan, bone X-ray is mandatory. Other tests may be performed as clinically indicated.
- Patients must be available and compliant for central diagnostics, treatment and follow-up.
- Laboratory requirements: Hematology, Hepatic function, Renal Function, Thyroid function

Exclusion Criteria:

- 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.
- Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Bazett's Correction
- Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
- History of primary immunodeficiency
- History of allogeneic organ transplant
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV).
- Known history of previous clinical diagnosis of tuberculosis
- Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving MEDI4736
- Autoimmune disease and conditions (i.e. inflammatory bowel disease)
- History of significant neurological or psychiatric disorders including psychotic disorders, dementia or seizures that would prohibit the understanding and giving of informed consent
- Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results
- Pre-existing motor or sensory neuropathy of a severity >= grade 2 by NCI-CTC criteria v 4.0.
- Currently active infection.
- Incomplete wound healing or unhealed bone fracture.
- 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 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.
- other immunosuppressive medication (e.g. low dose MTX)
- sex hormones (including hormonal contraception) 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.
- Any previous treatment with a PD1 or PD-L1 inhibitor, including MEDI4736
- Male patients.

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: NCT02685059

Contacts

Contact: Konstantin Reißmüller +49 (0) 6102 / 7480 ext 0 geparnuevo@gbg.de

Locations

Germany

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Sponsors and Collaborators

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AstraZeneca

Celgene Corporation

Investigators

Principal Investigator: Sibylle Loibl, Prof. Dr. Sana Klinikum Offenbach

More Information

Responsible Party:	German Breast Group
ClinicalTrials.gov Identifier:	NCT02685059 History of Changes
Other Study ID Numbers:	GBG89
Study First Received:	January 14, 2016
Last Updated:	February 12, 2016
Individual Participant Data Plan to Share IPD:	No

Keywords provided by German Breast Group:

breast cancer	Nab-Paclitaxel
Medi4736	Placebo
Anti PD-L1	triple negative

Additional relevant MeSH terms:

Breast Neoplasms	Antineoplastic Agents
Triple Negative Breast Neoplasms	Tubulin Modulators
Neoplasms by Site	Antimitotic Agents
Neoplasms	Mitosis Modulators
Breast Diseases	Molecular Mechanisms of Pharmacological Action
Skin Diseases	Immunosuppressive Agents
Paclitaxel	Immunologic Factors
Taxane	Physiological Effects of Drugs
Albumin-Bound Paclitaxel	Antirheumatic Agents
Cyclophosphamide	Antineoplastic Agents, Alkylating
Epirubicin	Alkylating Agents
Antibodies	Myeloablative Agonists
Immunoglobulins	Antibiotics, Antineoplastic
Antibodies, Monoclonal	Topoisomerase II Inhibitors
Antineoplastic Agents, Phytogenic	Topoisomerase Inhibitors

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