A Randomized, Multicenter, Double-blind, Placebo-controlled Phase 3 Study of Nivolumab Versus Placebo in Combination With Neoadjuvant Chemotherapy and Adjuvant Endocrine Therapy in Patients With High-risk, Estrogen Receptor-Positive (ER+), Human Epidermal Growth Factor Receptor 2-Negative (HER2-) Primary Breast Cancer

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Ethical review	Approved WMO
Status	Completed
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON52593

Source
ToetsingOnline

Brief title
CA209-7FL

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast Cancer, Breast Ductal Carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Breast Cancer, Immunotherapy, Nivolumab

Outcome measures

Primary outcome

Event Free Survival (EFS) means the length of time a patient lives with their cancer from the point of diagnosis or start of treatment without it getting worse. It is a good indicator of how well the treatment is working and is often used as a standard measure in clinical trials. EFS will be defined as the time from randomization to disease progression that: precludes definitive surgery, results in a local or distant recurrence, results in a second primary malignancy, or results in death due to any cause, whichever occurs first.

Pathological Complete Response (pCR) is defined as no invasive residual disease in breast and lymph nodes, this will be determined by a local pathologist.

Secondary outcome

The secondary objectives of the study are:

- to compare Overall Survival (OS) for Arm B vs Arm C participants

- to compare Progression Free Survival (PFS) for Arm B vs Arm C

- to assess Objective Response Rate (ORR) and Complete Response Rate

- to assess Duration of Response (DOR)

- to assess Time to Response (TTR)

- to assess Time to Death or Distant Metastases (TTDM)

All of the above assessments will be performed per RECIST 1.1 using a blinded independent committee review (BICR)

Definitions:

Progression free survival or PFS is defined as the length of time a patient lives with their cancer from the point of diagnosis or start of treatment without it getting worse.

Overall survival or OS is defined as the length of time a patient lives with their cancer from the point of diagnosis or start of treatment.

Objective response rate or ORR refers to a proportion of patients with reduction in tumour burden of a predefined amount

Duration of response or DOR is defined as the time from documentation of tumour response to disease progression

Time to response (TTR) Time to response is defined as the time, in months, from randomisation to the first objective documentation of partial response (PR- at least a 30% reduction in measurable tumour size) or better assessed per BICR.

TTDM is defined as the time from the date of randomisation until the first date of distant metastasis or death in the absence of distant metastasis. Distant metastasis is defined as any new lesion that is outside of the radiation field according to RECIST 1.1

Study description

Background summary

CA209-7FL is a multicentre, phase 3, double-blind study involving adult patients with newly diagnosed, untreated breast cancer. The study will compare treatment with either nivolumab given at the same time as chemotherapy or chemotherapy given alone before breast cancer surgery (neoadjuvant setting), followed by nivolumab given at the same time as endocrine treatment or endocrine treatment given alone after breast cancer surgery (adjuvant setting). Approximately 1200 patients will take part in this study, approximately 20 of these will be from the Netherlands.

Breast cancer is the second leading cause of cancer-death in women after lung cancer. Patients with localised (stage 0) disease have a five year survival rate of about 99%. Approximately 80% of breast cancers express the estrogen receptor (ER+), which is generally associated with a lower recurrence rate. However, despite the availability of chemotherapy and endocrine treatment options, this risk of recurrence seen with this breast cancer subtype persists over time in patients, which presents an unmet need for additional treatment strategies.

Cancer immunotherapy is based on the knowledge that tumours can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. Nivolumab is a type of immunotherapy drug called a monoclonal antibody that works by blocking inhibitory signalling pathways in the immune response. This results in stimulation of the body*s own immune system to help attack the cancer cells. Nivolumab has demonstrated clinical activity and been

approved for the treatment of several tumour types, including melanoma, advanced renal cell cancer and advanced non-small cell lung cancer.

This phase 3 study will evaluate clinical efficacy. Specifically, this study will compare the pathological complete response (pCR) rate and event free survival (EFS) rate among participants with localised invasive ER+, human epidermal growth factor receptor 2 negative (HER2-) Breast Cancer, treated with a combination of noeadjuvant nivolumab and chemotherapy, before surgery, followed by adjuvant nivolumab and endocrine therapy. The pCR and EFS rate will be compared to that among participants treated with neoadjuvant chemotherapy, followed by surgery and adjuvant endocrine therapy, alone.

Study objective

The purpose of this study is to compare the effectiveness of treatment Arm A and Arm B by measuring the event free survival (EFS) and pathological complete response (pCR).

EFS is defined as the time from the first treatment dose that the patient receives until the cancer gets worse, prevents the patient from undergoing surgery, or results in death.

pCR is defined as the absence of disease remaining in breast and lymph node tissues.

Study design

This is a double-blind, randomised phase 3 clinical trial of nivolumab given in combination with chemotherapy before breast cancer surgery (neoadjuvant setting), followed by nivolumab given in combination with endocrine treatment given after breast cancer surgery (adjuvant setting). Subjects will undergo screening tests and assessments to determine eligibility, and those eligible for the study will be randomised to a treatment arm in a 2:1 ratio:

Arm A:
Nivolumab 360mg + paclitaxel for 4 treatment cycles, followed by
Nivolumab 360mg every 3 weeks + anthracycline and cyclophosphamide for a maximum of 4 treatment cycles

Or
Nivolumab 360mg + paclitaxel for 4 treatment cycles, followed by
Nivolumab 240mg every 2 weeks + anthracycline and cyclophosphamide for a maximum of 4 treatment cycles

Arm B:

Nivolumab Placebo + paclitaxel for 4 treatment cycles, followed by Nivolumab Placebo every 3 weeks + anthracycline and cyclophosphamide for a maximum of 4 treatment cycles

Or

Nivolumab Placebo + paclitaxel for 4 treatment cycles, followed by Nivolumab Placebo every 2 weeks + anthracycline and cyclophosphamide for a maximum of 4 treatment cycles

Patients in both treatment arms will undergo breast surgery after completing pre-surgery treatment.
After surgery patients assigned to Arm A will receive Nivolumab 480 mg + endocrine treatment for 7 treatment cycles (1 treatment cycle is equal to 4 weeks). Patients assigned to Arm B will receive Nivolumab placebo + endocrine treatment for 7 treatment cycles (1 treatment cycle is equal to 4 weeks).

Randomization will be done by an automated sorting process through IVRS (a telephone based computer system) which will assign subjects to a treatment based on their PD-L1 status (>/ 1% or < 1%) Tumour Grade (2 or 3), Axillary Nodal Status (+or-), Chemotherapy Anthracycline Cyclophosphamide (AC) dosing frequency (Q3W or Q2W). This ensures that both Arms are equally balanced with subject numbers for comparison at time of analysis, while maintaining the integrity of the randomization itself.

A Data Monitoring Committee (DMC) will be established and meet regularly during the study to ensure that subject safety is carefully monitored and to provide oversight regarding safety and efficacy considerations.

Subjects will be evaluated for Event Free Survival (EFS) throughout the study. EFS is defined as the time from randomization to disease progression that: precludes definitive surgery, results in a local or distant recurrence, results in a second primary malignancy, or results in death due to any cause, whichever occurs first. Pathological Complete Response (pCR) will be performed by the local pathologist following examination of breast and lymph node tissue removed at the time of surgery.

Treatment will be discontinued if the subject withdraws consent, if their cancer gets worse or if it is no longer safe for the subject to continue in the trial.

Survival follow-up will continue for up to 10 years after the subject is randomised.

Intervention

Subjects will undergo screening tests and assessments to determine eligibility,

and those eligible for the study will be randomised to a treatment arm in a 2:1 ratio:

Arm A:

Nivolumab 360mg + paclitaxel for 4 treatment cycles, followed by
Nivolumab 360mg every 3 weeks + anthracycline and cyclophosphamide for a maximum of 4 treatment cycles

Or
Nivolumab 360mg + paclitaxel for 4 treatment cycles, followed by
Nivolumab 240mg every 2 weeks + anthracycline and cyclophosphamide for a maximum of 4 treatment cycles

Arm B:

Nivolumab Placebo + paclitaxel for 4 treatment cycles, followed by
Nivolumab Placebo every 3 weeks + anthracycline and cyclophosphamide for a maximum of 4 treatment cycles

Or

Nivolumab Placebo + paclitaxel for 4 treatment cycles, followed by
Nivolumab Placebo every 2 weeks + anthracycline and cyclophosphamide for a maximum of 4 treatment cycles

Patients in both treatment arms will undergo breast surgery within 2-4 weeks, after completing pre-surgery treatment.

Post-operative radiotherapy treatment is required if breast-conserving surgery (BCS) is performed, per international guidelines. In the event of mastectomy, administration of adjuvant RT will follow local clinical practice.

For patients not receiving radiotherapy, the post-surgery treatment (adjuvant phase) will begin within 4 weeks following surgery. For patients receiving radiotherapy, adjuvant treatment will start no later than 1 week after the completion of radiotherapy.

Participants will return to the clinic within 7-14 days following surgery to begin the adjuvant treatment phase. In the adjuvant phase patients assigned to Arm A will receive Nivolumab 480 mg + endocrine treatment for 7 treatment cycles (1 treatment cycle is equal to 4 weeks). Patients assigned to Arm B will receive Nivolumab placebo + endocrine treatment for 7 treatment cycles (1 treatment cycle is equal to 4 weeks).

Study burden and risks

As part of the trial, patients will be expected to attend multiple clinic visits where they will undergo physical examinations, vital sign measurements, blood tests for safety assessment, pregnancy testing (for females of child bearing potential) and monitoring for adverse events. Blood will also be collected at certain visits for research purposes (PK, immunogenicity and biomarker studies). Patients will be asked to complete questionnaires (EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-BR23, FACIT GP5, HCRU) about their quality of life throughout the treatment and follow-up study periods.

A breast tumour tissue sample will be collected at screening if there is no archival tissue, or if the sample was taken too long ago (more than 60 days prior to enrolment). Patients will be required to have a biopsy in order to participate. An axillary lymph node biopsy will also be required if at screening, except if there is there is no suspicion for positive axillary lymph node(s) radiographically, or if a pathological report of suspicious lymph nodes from the results of a fine needle biopsy or core biopsy is available. A tumour tissue biopsy will also be performed at the time of surgery. A tumour tissue biopsy is optional at cycle 2 day 1 and upon disease progression / recurrence.

Surgery will be performed on patients post completion of neo-adjuvant therapy. Surgery may be either Breast Conserving Surgery or mastectomy.

Patients will undergo imaging assessment of the breast and axilla by ultrasound and mammogram at screening, prior to surgery and annually during the follow-up phase of the study. X-ray, CT, MRI and PET assessments will only be performed as clinically indicated.

The frequency of visits and number of procedures carried out during this trial would typically be considered over and above standard of care. The procedures are carried out by trained medical professionals and every effort will be made to minimise any risks or discomfort to the patient.

Treatment for cancer often has side effects, including some that are life threatening. To assure an ongoing favourable risk/benefit assessment for participants enrolled onto the study, an independent Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy considerations.

New Immune system targeted therapy (immunotherapies) such as Nivolumab potentially provide clinical benefit and improvements in the outcomes for patients with this disease (improvement in progression free and overall survival). However, with all experimental drugs and clinical trials, there are known and unknown risks. Study medication and procedure related risks are outlined in the patient information sheet in detail to ensure the patients are

fully informed before agreeing to take part in the study.

Contacts

Public
Bristol-Myers Squibb

Orteliuslaan 1000
Urecht 3528 BD
NL
Scientific
Bristol-Myers Squibb

Orteliuslaan 1000
Urecht 3528 BD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Participants must have histologically confirmed unilateral invasive breast carcinoma, with the following characteristics (i, ii, iii):
i) Localized invasive breast ductal carcinoma, confirmed by the local pathologist, that includes T1c-T2, clinical node stage (cN)1-cN2, or T3 T4, cN0-cN2. Inflammatory breast cancer is allowed.
ii) Participants must have ER+, HER2- BC meeting below characteristics (1,2):
(1)ER+ breast cancer and with or without progesterone-receptor (determined by central laboratory as defined in the relevant American Society of Clinical Oncology [ASCO]-College of American Pathologists [CAP] Guidelines).

(2)HER2- breast cancer tested in a local laboratory defined as a negative in situ hybridization test or an immunohistochemistry (IHC) status of 0, 1+, or 2+ (determined by local laboratory as defined in the relevant ASCO- CAP Guidelines).
iii)Participant must have Protocol-specified disease grade 2 or 3 according to the most recent ASCO-CAP guidelines.
• Participant must have an Eastern Cooperative Oncology Group (ECOG) scale performance status of 0 or 1.
• Participants provide tumor tissue at baseline (collected <= 60 days prior to enrollment) and at surgery.
• Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within 24 hours prior to the start of study treatment.
• Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written ICF, in accordance with regulatory and institutional guidelines

Exclusion criteria

• Women who are breastfeeding

• Participants who are pregnant or expecting to conceive or father children during the study, starting with the screening visit through 12 months for patients who receive cyclophosphamide, or 7 months for patients who do not receive cyclophosphamide, after the last dose of study treatment.

• The following Breast Cancer (BC) characteristics:
- Ipsilateral invasive BC, Inoperable BC, Multicentric BC, Bilateral invasive BC, ipsilateral ductal carcinoma in situ treated with radiation, or contralateral invasive BC, at any time.
- Definitive clinical or radiologic evidence of metastatic disease.
- Any of the following clinical lymph node staging: cN3, cN3a, cN3b, or cN3c
- History of ductal carcinoma in situ
- History of pleomorphic lobular carcinoma in situ
- Evidence of ER- BC
- Undergone excisional biopsy of the primary tumour and/or axillary lymph nodes or has undergone sentinel lymph node biopsy

• Patients with >= Grade 1 peripheral neuropathy.

• Patients with an active, known, or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

• Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) within 14 days or other immunosuppressive medications within 30 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

• Known human immunodeficiency virus (HIV) positive with an acquired immunodeficiency syndrome (AIDS).

• Prior malignancy active within the previous 3 years, except for locally curable cancers that have been apparently cured.

• Participants with serious or uncontrolled medical disorders.

• Other non-malignant systemic disease that would preclude the participant from receiving study treatment or would prevent required follow-up.

• Active infection or chronic infection requiring chronic suppressive antibiotics.

• Malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, resection of the stomach or small bowel, or other disease or condition significantly affecting gastrointestinal function.

• Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

• Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

• Any treatment, local or systemic, including prior chemotherapy, Endocrine Therapy (ET), targeted therapy, and/or radiation therapy for the currently diagnosed BC prior to enrollment.

• Concurrent use of hormone replacement therapy, hormonal contraception or any other estrogen-containing medication.

• Surgical axillary staging procedure prior to enrollment (with the exception of fine-needle aspiration or core biopsy).

• Surgical excisional biopsy of primary tumour.

• Participants for whom upfront ET alone is judged clinically appropriate as optimal neoadjuvant therapy.

• Treatment with botanical preparations (eg, herbal supplements, traditional Chinese medicines).

• Participants who have received a live/attenuated vaccine within 30 days before the first treatment.

• Significant cardiovascular disease, interstitial lung disease, active pneumonitis, myocarditis, or a history of myocarditis.
• Serologic evidence of chronic HBV infection with an HBV viral load above the limit of quantification.
• Serologic evidence of current HCV infection with an HCV viral load above the limit of quantification.

• History of allergy or severe hypersensitivity to study drug components
• Prisoners or participants who are involuntarily incarcerated.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	12-03-2021
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Adrimedac
Generic name:	Doxorubicin Hydrochloride
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Epimedac
Generic name:	Epirubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Opdivo (100 mg/10 ml)
Generic name:	Nivolumab 10ml vial
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Opdivo (40 mg/4 ml)
Generic name:	Nivolumab-4 ml vial
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Taxol
Generic name:	Paclitaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-12-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-01-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-07-2020
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-08-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-02-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-02-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-02-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	24-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-01-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-002469-37-NL
ClinicalTrials.gov	NCT04109066
CCMO	NL71322.056.19

Study results

Date completed:	05-06-2023
Results posted:	18-12-2024

First publication
01-01-1900