Biomarker discovery randomized phase IIb trial with carboplatin-cyclophosphamide versus paclitaxel with or without Bevacizumab as first-line treatment in advanced triple negative Breast cancer (TRIPLE-B study);Title after protocol amendment August 12, 2017: Biomarker discovery randomized phase IIb trial with carboplatin-cyclophosphamide versus paclitaxel with or without atezolizumaB as first-line treatment in advanced triple negative Breast cancer (TRIPLE-B study)

Published: 18-04-2013
Last updated: 10-01-2025

This study has been transitioned to CTIS with ID 2024-516202-39-00 check the CTIS register for the current data. Modified objectives after implementation of protocol amendment Sept 2024: Primary: 1. Validate the BRCA1-like test* in predicting...

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

Summary

ID

NL-OMON52986

Source
ToetsingOnline

Brief title
TRIPLE-B study

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer; triple negative breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: BOOG Study Center
Source(s) of monetary or material Support: Financiering door de BOOG;die unrestricted grants van farmaceuten krijgt.

Intervention

Keyword: atezolizumab, bevacizumab, breast cancer, triple negative

Outcome measures

Primary outcome

Modified primary variable after implementation of protocol amendment February

2017: Primary Outcome Measures (2x2 factorial design): Interaction test of

BRCA1-like status vs. treatment (CC vs. Paclitaxel (both arms with or without

atezolizumab).

Secondary outcome

Modified secondary variable after implementation of protocol amendment Sept

2024: Secondary Outcome Measures:

• Evaluate whether the addition of atezolizumab to paclitaxel is more favorable

than adding atezolizumab to carboplatin-cyclophosphamide (PFS1).

• Evaluate whether the addition of atezolizumab to paclitaxel is more favorable than adding atezolizumab to carboplatin-cyclophosphamide for patients with PD-L1 positive tumors defined as combined positive score (CPS) 10 or higher (PFS1).

• PFS benefit of the addition of atezolizumab.

• PD-L1 status and PFS • CD8 + TIL abundance and PFS

• Moleculair subtypes and PFS

• Predictive biomarkers for PFS gain.

• PFS of the two first line chemotherapeutic regimens, regardless of bevacizumab yes or no.

• Overall survival.

• Adverse events.

Study description

Background summary

Modified background after implementation of protocol amendment February 2017: Triple negative breast cancer (TNBC) refers to any breast cancer that does not express the genes for estrogen receptor (ER), progesterone receptor (PR) and Her2/neu and is a difficult to treat molecular subtype with a poor survival. Around 40% develops metastatic disease and these patients have a median survival of 1 year. TNBC can be divided into at least two molecular entities; BRStudy design: Klik voor meer iCA-like and non-BRCA-like. There are indications that TNBC that are BRCA-like are more sensitive to bifunctional alkylating and platinum agents than non-BRCA-like TNBCs, and relatively resistant to taxanes. Consequently, because TNBCs in general derive substantial benefit from taxanes, we anticipate that non-BRCA-like TNBCs are exquisitely sensitive to taxanes. TNBCs have a relatively high mutational load resulting in formation of neoantigens making this tumor type an attractive target for immunomodulatory drugs. Atezolizumab, a humanized monoclonal antibody that targets human PD-L1 has shown activity in TNBC.We hypothesize that adding atezolizumab to paclitaxel or carboplatin-cyclophosphamide will increase the

anti-tumor effect of these regimens and possibly can obtain durable responses in a subgroup of patients. It is unknown whether addition of atezolizumab to first line chemotherapy in TNBC is more beneficial than adding this antibody to a second line treatment schedule. Because of this and because of the poor outcome of patients with advanced TNBC experiencing disease progression after first line palliative chemotherapy, patients who were randomized to a chemotherapy only arm in this study will be offered the opportunity to cross over to the other chemotherapy regimen plus atezolizumab at disease progression.

Study objective

This study has been transitioned to CTIS with ID 2024-516202-39-00 check the CTIS register for the current data.

Modified objectives after implementation of protocol amendment Sept 2024:
Primary:
1. Validate the BRCA1-like test* in predicting differential PFS with first line alkylating and platinum agents when compared to paclitaxel in TNBC

Secondary:
1. Evaluate whether the addition of atezolizumab to paclitaxel is more favorable than adding atezolizumab to carboplatin-cyclophosphamide (PFS1)
2. Evaluate whether the addition of atezolizumab to paclitaxel is more favorable than adding atezolizumab to carboplatin-cyclophosphamide for patients with PD-L1 positive tumors defined as combined positive score (CPS) 10 or higher (PFS1)
3. Test whether the addition of atezolizumab to chemotherapy will result in more objective responses and a higher proportion of patients who are free of progression at 6 months and at 12 months
4. Analyze whether PD-L1 (immunohistochemistry) in either tumor cells or tumor infiltrating immune cells predicts for potential PFS benefit of atezolizumab added to first line palliative chemotherapy in TNBC
5. Analyze whether intratumoral CD8 and tumor infiltrating lymphocytes (TIL) predicts for benefit of atezolizumab added to fist line palliative chemotherapy in TNBC
6. Evaluate whether an alkylating-platinum regimen is more effective than paclitaxel as first line chemotherapy regarding progression-free survival in BRCA-like TNBC
7. Evaluate whether paclitaxel is more effective than an alkylating regimen as first line chemotherapy regarding progression-free survival in non-BRCA-like TNBC
8. To define whether different TNBC molecular subtypes- based on RNA - expression analysis - predict for differential PFS benefit of atezolizumab added to first line palliative chemotherapy in TNBC
9. To define whether pretreatment LDH level predicts for benefit of atezolizumab added to first line palliative chemotherapy in TNBC

10. To define biomarkers that can predict for a PFS advantage of carboplatin-cyclophosphamide (CC) as first line palliative chemotherapy in TNBC
11. To define biomarkers that can predict for a PFS advantage of paclitaxel as first line palliative chemotherapy in TNBC
12. To define biomarkers that can predict for a PFS advantage of addition of atezolizumab to first line palliative chemotherapy in TNBC
13. Evaluation of PFS after cross-over to the other chemotherapy regimen with atezolizumab (PFS2)
14. Evaluation of ORR, proportion of patients that is free of progression at 6 months and at 12 months after cross-over to the other chemotherapy regimen with atezolizumab
15. Evaluate whether addition of atezolizumab to chemotherapy in first line is more beneficial than when added in second line (PFS1+PFS2)
16. Evaluation of overall survival (OS) for all (sub)group comparisons as pre-specified for PFS
17. Evaluate clinically relevant toxicity of all study regimens
18. Evaluate preliminary efficacy by PFS and OS in subgroups of patients treated before amendment 3 with carboplatin/cyclophosphamide or paclitaxel with or without bevacizumab
19. Evaluate putative predictive potential of BRCA1-like status in various subgroups defined by treatment regimen received before amendment 3

Study design

Modified study design after implementation of protocol amendment February 2017: Randomized multicenter national fase IIb study. Randomization to A I.v. carboplatin plus cyclofosfamide.on day 1 of each 4 week cycle. At progression paclitaxel + atezolizumab B I.v. carboplatin plus cyclofosfamide.on day 1 of each 4 wek cycle + atezolizumab .on day 1, 15 of each 4 week cycle. At progression: treatment up to the investigator: C I.v. paclitaxel.on day1, 8, 15 of each 4 week cycle. At progression: carboplatin plus cyclofosfamide + atezolizumab D. I.v. paclitaxel.on day 1, 8, 15 of each 4 week cycle + atezolizumab .on day 1, 15 of each 4 week cycle. At progression treatment up to the investigator. 304 subjects.

Intervention

Modified intervention after implementation of protocol amendment February 2017: Trreatment with carboplatin/cyclofosfamide (group A) or paclitaxel (group C) plus atezolizumab (groups B,D); at progression:: paclitaxel plus atezolizumab (group A) or carboplatin/cyclofosfamide plus atezolizumab (group C) or treatment up to the invetigator (groups B,D).

Study burden and risks

Compared to standard first line chemotherapy in metastatic breast cancer there

is hardly any additional burden when participating in this trial.
All treatment regimens, except for those with atezolizumab, are well-known and safe cancer treatment schedules. The first results of studies with regimens with atezolizumab, like a previous phase Ib study performed by the study team to assess carboplatin/cyclofosfamide and atezolizumab, indicate the safety of the combinations.
The BRCA1-test will be performed on archived tissue.
Patients should donate 9 tibes of blood prior to participation to the study, as well as a biopsy. This should be done in an immunohub. Travel v.v. is a consequence..
Optional tests:
1. Blood samples for biomarker study: 6 tubes once during and and after the treatment period..
2. Tumor biopsy once during and after treatment period.
3. Storage for 15 years after the end of the study and use of remaining samples (future research).
4. Genetic councelling: referral to clinical genetics specialist or permission to have access to data on previous councelling.
In case patients are treated in the cross-over, blood samples and a tumor biopsy are mandatory prior to the cross-over treatment for patients treated in an immunohub.

Contacts

Public
BOOG Study Center

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Scientific
BOOG Study Center

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Utrecht 3511 EP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Histologically confirmed triple negative metastasized or locally advanced incurable breast cancer. See protocol section 5.2 for more details.
- Histological confirmation of triple negative breast cancer of a metastatic lesion is
recommended
- Histological or cytological confirmation of metastatic breast cancer is required in case of
normal CA 15.3 levels. Exception: see protocol section 5.2 for details.
- Primary tumor or metastasis tissue sent to NKI-AVL for BRCA1-like testing
- Pretreatment histological biopsy of a metastatic lesion for the translational research
questions (tumor tissue from bone metastases cannot be used). Exception: see protocol section 5.2 for details.
- No previous cytotoxic therapy for metastatic disease
- Disease-free interval of at least 12 months after completion of (meo)adjuvant paclitaxel or (neo)adjuvant platinum compound
- Disease-free interval of at least 6 months after completion of (neo)adjuvant docetaxel
- Measurable or evaluable disease according to RECIST v1.1
- WHO performance status of 0 or 1

Exclusion criteria

- Receptor conversion to hormone receptor positive (defined as >= 10% ER positive tumor cells) or HER2 positive
- Other antitumor therapy within the previous 21 days, with the exception of endocrine therapy. The patient should have stopped any endocrine therapy before start study treatment.
- Radiotherapy with palliative intent within the previous 7 days before start study medication (see protocol 5.3 for details)
- Known CNS disease except for treated brain metastases (see protocol 5.3 for details)
- Pre-existing peripheral neuropathy > grade 1 (NCI-CTC AE (version 4.03) at inclusion)
- Use of denosumab is not allowed. See protocol section 5.3 for details.

- Severe infection in the last 4 weeks.
- Antibiotics in the last 2 weeks.
- History of autoimmune disease. See protocol section 5.3 for details.
- Prior allogeneic stem cell or solid organ transplantation
- History of lung diseases such as idiopathic pulmonary fibrosis, pneumonitis. See protocol section 5.3 for more details
- An infection requiring parenteral antibiotic
- Positive test for hepatitis B, C HIV. See protocol section 5.3 for more details.
- Active tuberculosis.
- Live, attenuated vaccine within 4 weeks prior to randomization.
- Prior treatment with anti cancer vaccins or immune checkpoint blockade therapies, including anti-CTLA-4, CD137 agonist, OX40 agonist, anti-PD-1, or anti-PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents, systemic corticosteroids or other systemic immunosuppressive medications. See protocol section 5.3 for details.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	10-10-2013
Enrollment:	304
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avastin
Generic name:	bevacizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	carboplatin
Generic name:	carboplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Endoxan
Generic name:	cyclophosphamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Taxol
Generic name:	paclitaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tecentriq
Generic name:	atezolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-04-2013
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	24-05-2013
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	12-02-2014

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-03-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-06-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-08-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-08-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-01-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-04-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-04-2015

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-07-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-08-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-09-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-03-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-04-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-06-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-06-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-06-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-06-2016

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-06-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-07-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-09-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-03-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-03-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-07-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-07-2017

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-08-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-08-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-10-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-12-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-06-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-07-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-08-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-08-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-09-2018

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-10-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-01-2021

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-01-2024

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-02-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-03-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-03-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-09-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-10-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-10-2024
Application type:	Amendment
Review commission:	METC NedMec

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
Other	clinicaltrials.gov; NCT01898117.
EU-CTR	CTIS2024-516202-39-00
EudraCT	EUCTR2013-001484-23-NL
CCMO	NL44403.031.13