Adaptive phase II randomized non-comparative trial of nivolumab after induction treatment in triple-negative breast cancer (TNBC) patients: TONIC-trial

Published: 17-08-2015
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This study has been transitioned to CTIS with ID 2025-520487-18-00 check the CTIS register for the current data. To determine the activity of nivolumab after four different immune response induction treatments in TNBC patients with metastatic...

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

Summary

ID

NL-OMON47543

Source
ToetsingOnline

Brief title
TONIC

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast cancer, triple negative

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut
Source(s) of monetary or material Support: Medicatie via BMS

Intervention

Keyword: Breast cancer, ER and HER2 negative, Max three lines prior chemotherapy, Metastatic

Outcome measures

Primary outcome

• Progression-free survival (PFS1, time from randomization to tumor progression

or death) Progression as defined by RECIST 1.1 will be used.

• For the first stage of the trial, proportion of patients with PFS of at least

12 weeks in each treatment arm. Treatment arms with >30% of patients with PFS

of at least 12 weeks will continue to stage II of the study. Progression as

defined by RECIST 1.1 will be used.

Secondary outcome

• Progression-free survival (PFS1, time from randomization to tumor progression

or death). Progression as defined by modified RECIST 1.1 for immune-based

therapeutics (iRECIST) will be used

Progression-free survival (PFS2, time from nivolumab treatment initiation to

tumor progression) Progression as defined by RECIST 1.1 and iRECIST will be

used.

• Overall response rate ORR (complete response CR or partial response PR) at 12

weeks, and at 6 months according to RECIST 1.1 and iRECIST will be used

• Clinical benefit rate (CR+PR+stable disease >= 6 months and CR+PR+stable

disease >= 3 months) according to RECIST 1.1 and iRECIST will be used

• Overall survival (OS, time from start nivolumab to death from any cause)

• Percentage of patients with toxicity (classified according to CTCAE v4.0 and

immune-related toxicity

Study description

Background summary

Triple negative breast cancer (TNBC) patients have a relatively high relapse rate and upon relapse the median overall survival is less than a year. No targeted therapies are currently available for this subgroup. Compared to other breast cancer subtypes, the percentage of tumor-infiltrating lymphocytes (TILs) is significantly higher in TNBC. Given the durable responses induced by the immune checkpoint inhibitor nivolumab in other advanced solid cancers, immunotherapeutic approaches, such as blockade of PD-1 by nivolumab may be the key to treat TNBC. Moreover, since classical anticancer agents can stimulate immune effector cells, we hypothesize that short-term induction treatment with radiation, doxorubicin, cyclophosphamide or cisplatin induces an anticancer immune response resulting in synergistic activity with nivolumab.

Study objective

This study has been transitioned to CTIS with ID 2025-520487-18-00 check the CTIS register for the current data.

To determine the activity of nivolumab after four different immune response induction treatments in TNBC patients with metastatic disease. We hypothesize that short-term induction treatment induces an anticancer immune response resulting in increased activity of nivolumab as compared to unprimed, single agent nivolumab.

Study design

This is a single center non-blinded randomized non-comparative phase II trial with a Simon two-stage design.The first stage of the trial consists of five arms (4 with induction treatment followed by nivolumab, 1 with no induction treatment before nivolumab), all with a Simon two-stage design. For the second stage, the number of arms will be reduced based on the results obtained in the first stage.

Protocol version 4.0 dd 07 march 2018;
In stage II of the trial, doxorubicin and the no induction treatment cohorts

will be expanded. In both cohorts, an additional 17 evaluable patients will be accrued. In the no induction treatment cohort, a two-week waiting period with an additional biopsy before the start of anti-PD1 (nivolumab) will be optional.

protocol version 5.0 dd 04 july 2018;
Two week waiting period in the no induction cohort is removed, additional biopsy after 1 cycle of nivolumab in this cohort

Protocol version 6.0 dd 19aug2019;
Disease Free Interval (defined as time between first diagnosis or local recurrence and first metastasis) longer than 1 year added to inclusion criteria
After 26 weeks, nivolumab will be administered every 4 weeks.

Intervention

Treatment arms part I;
1. Radiation therapy, followed by nivolumab 3 mg/kg one week later, every 2 weeks
2. Low dose doxorubicin 15mg flat dose, once weekly for 2 weeks, after 2 weeks followed by nivolumab 3 mg/kg, every 2 weeks
3. Cyclophosphamide, metronomic schedule, 50mg daily orally, after 2 weeks followed by nivolumab 3 mg/kg, every 2 weeks
4. Cisplatin 40mg/m2, weekly, after 2 weeks followed by nivolumab 3 mg/kg, every 2 weeks
5. No induction treatment, nivolumab 3 mg/kg, every 2 weeks

For the second stage, the number of arms will be reduced based on the results obtain in the first stage.

Protocol version 4.0 dd 07 march 2018;
In stage II of the trial, doxorubicin and the no induction treatment cohorts will be expanded. In both cohorts, an additional 17 evaluable patients will be accrued. In the no induction treatment cohort, a two-week waiting period with an additional biopsy before the start of anti-PD1 (nivolumab) will be optional.

Protocol version 6.0 dd 19aug2019;
After 26 weeks, nivolumab will be administered every 4 weeks.

Study burden and risks

The risks involved in treatment with nivolumab are low. There is a lot of experience with this agent in patients with melanoma, lung cancer, Hodgkin's disease and other cancers. There is a small chance (<5%) of pneumonia by the nivolumab but that can often be treated. Serious side effects are rare. In a Phase 1 study with anti-PDL1 in breast cancer patients was shown that 11% of the patients have moderate or sometimes serious side effect, which are often

treatable or resolve after cessation of anti-PDL1. As the patient population that will participate in the TONIC study do not have a good anti-cancer treatment option more and we expect that we will see an anti-tumor effect in 1/3 of the participants, thus creating an extended lifetime, we consider the risk / burden acceptable compared to the potential profits of the treatment with nivolumab.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- metastatic ER and HER2 negative breast cancer
- 18 years or older
- metastatic lesions accessible for histological biopsy
- maximum of three lines of chemotherapy for metastatic disease

- measurable or evaluable disease according to RECIST 1.1
- disease free interval (defined as time between first diagnosis or local recurrence and first metastasis) longer than 1 year
- WHO performance status 0 or 1
- Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 4 weeks after treatment is completed and prior to first dose of study drug administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration
- Signed written informed consent

Exclusion criteria

- known leptomenigeal disease localization- history of having recceived other anticancer therapies within 2 weeks of start of the study drug
- history of immunodeficiency, autoimmune disease, conditions requiring immunosuppression (>10 mgl daily prednisone equivalents) or chronic infections
- prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody
- current pregnancy or breastfeeding

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-09-2016
Enrollment:	84
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nivolumab
Generic name:	nivolumab

Ethics review

Approved WMO Date:	17-08-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	03-09-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-08-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-08-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	03-07-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-07-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	15-03-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-03-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-07-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-07-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-04-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-08-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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
EU-CTR	CTIS2025-520487-18-00
EudraCT	EUCTR2015-001969-49-NL
ClinicalTrials.gov	NCT02499367
CCMO	NL53438.031.15