Pre-operative phase II trial for breast cancer with nivolumab in combination with novel IO (BELLINI trial)

Published: 18-02-2019
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This study has been transitioned to CTIS with ID 2024-515080-54-00 check the CTIS register for the current data. Primary objectiveTo determine the pathological complete response rate per cohort

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

Summary

ID

NL-OMON54814

Source
ToetsingOnline

Brief title
BELLINI

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer, pre-operative

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut
Source(s) of monetary or material Support: Bristol-Myers Squibb,door farmaceutische industrie

Intervention

Keyword: neoadjuvant therapy allowed, pre-operative, resectable stage I-III, TN or Luminal-B-like

Outcome measures

Primary outcome

Primary objective

To determine the pathological complete response rate per cohort

Secondary outcome

Secondary objectives

• To establish whether short-term pre-operative nivolumab either as monotherapy or in combination with ipilimumab or novel IO combinations is safe in early BC patients

• To assess the proportion of clinical and radiological responses as measured by imaging

• To assess the proportion of pathological responses (pCR, residual cancer burden)

• To correlate parameters of systemic immune suppression in early BC with intratumoral immune landscape and with responses seen in patients

• To correlate changes in tumor fragments (ex vivo model system, developed by Daniela Thommen) upon nivolumab either as monotherapy or in combination with ipilimumab or novel IO combinations with changes in the on-treatment biopsy

• To explore the putative predictive value of upcoming biomarkers such as but not limited to: CD8, IFNy gene signature, mutational load, homologous recombination deficiency (HRD)

• To evaluate 3-year, 5-year and 10-year overall and event free survival rate

Study description

Background summary

The absolute benefit in terms of overall survival of adjuvant chemotherapy in early breast cancer (BC) is relatively low (±10%), at the cost of substantial toxicity. Therefore, the identification of BC patients who could benefit from more targeted treatment approaches that improve outcome, thereby preventing the toxicity of chemotherapy, is of high priority for breast cancer management.
Data in lung cancer has now revealed that PD1-blockade is in general less toxic compared to chemotherapy. Promising activity of anti-PD(L)1 treatment has been observed in patients with metastatic BC, leading to the motivation of this study to investigate which patients with primary breast cancer might benefit from anti-PD1. In order to improve quality of life for BC patients, de-escalating or omitting chemotherapy might be an attractive future strategy for those tumors responding to immunotherapy.

Study objective

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Primary objective
To determine the pathological complete response rate per cohort

Study design

This trial has an adaptive design (Simon*s two stage) and therefore the number of patients is defined for stage I and stage II. 90 patients in stage I (6 cohorts with 15 patients each). Depending on the results in stage I, in stage II 31 additional patients will be needed per cohort, so if all cohorts show promising results in stage I a total of (6*(15+31)) 276 patients will be included (funding for full stage I available).

Intervention

This study is a pre-operative window of opportunity phase II multiple-cohort trial in TNBC and luminal B-like early BC
Separate cohorts will be opened in this trial, LumB and TNBC tumors will be divided in separate cohorts.
The following cohorts will start in this trial:
• Cohort IA (n=15, LumB) and 1B (n=15, TNBC) will be treated pre-surgically for

4 weeks (in waiting time for surgery) with nivolumab (2 courses 240mg flat dose day 1 and day 15).
• Cohort 2A (n=15, LumB) and 2B (n=15, TNBC) will be treated pre-surgically for 4 weeks (in waiting time for surgery) with nivolumab (2 courses 240 mg flat dose day 1 and day 15) and one single dose ipilimumab 1 mg/kg day 1.
• Cohort 2B (n=15, TN, high TIL) will be treated pre-surgically for 6 weeks (in waiting time for surgery) with nivolumab (2 courses 240 mg flat dose day 1 and day 21) and 2 courses ipilimumab 1 mg/kg day 1 en 21

New cohorts with novel IO in combination with nivolumab can be added if safety data are available and signals for efficacy are convincing in breast cancer or other cold tumors, e.g. resulting in cohort 3A (n=15, LumB) and 3B(n=15, TNBC), and an addition of 30 patients in total in stage I.

• Cohort 3B (n=15, TNBC) will include only TIL-high breast tumors of patients with cT1c-T2N0 disease and patients will be treated pre-surgically for 6 weeks with nivolumab (240 mg flat dose) and ipilimumab (1mg/kg) at day 1 and day 21. Each therapy cycle will be 3 weeks and after 6 weeks patients will be scheduled for surgery.
• Cohort 4B (n=15, TNBC cT1b-cT2N0, TIL upper-intermediate 30-49%) will be treated pre-surgically for 8 weeks with nivolumab (480mg)/relatlimab (480mg) at day 1 and day 29. Each cycle will be 4 weeks and after 8 weeks patients will be scheduled for surgery.
• Cohort 5B (n=15, TNBC cT1b-cT2N0, TIL high >=50%) will be treated pre-surgically for 8 weeks with nivolumab (480mg)/relatlimab (480mg) at day 1 and 29. Each cycle will be 4 weeks and after 8 weeks patients will be scheduled for surgery.

Study burden and risks

The subjects' load will consist of taking an extra biopsy, extra blood tests, physical examination and the possibility of side effects of the therapy. The reported side effects for Nivolumab in pre-operative clinical trials are low (see page 9 protocol) and the specific combination of Nivolumab combined with a broad knowledge of side effects in patients, leads to a low chance of side effects for patients in the BELLINI study. In order to be able to give better, personalized, therapy to patients with a primary breast tumor in the future, where we try to prevent over-treatment with chemotherapy and additional side effects, participation of the subjects and the additional burden is justified.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Resectable primary breast cancer stage I-III. Nodal status must be examined by ultrasound, fine needle aspiration, sentinel node biopsy, or FDG-PET scan (cohort 3B, 4B and 5B4: PET-CT mandatory).
- Patients indicated for neoadjuvant chemotherapy will also be eligible, whereby a new dedicated biopsy is performed before the beginning of the chemotherapy. Adjuvant systemic treatment is allowed if indicated according to local guidelines.
• Tumor size at least 5 mm (minimum cT1b) as determined by MRI
• TNBC defined as ER<10%, HER2-negative OR luminal B defined as ER>=10%, HER2-negative with either Ki67>=20% or PR <=20% OR grade 3. HER2 negative is defined as an IHC score of <2 or 2+ with a negative ISH.
- For TNBC patients: TIL>=5%
- For LumB breast cancer patients: TIL>=1%
- For cohort 3B: N0 status, TNBC and TIL >=1%
- For cohort 4B: N0 status, TNBC and TIL >=30-49%
- For cohort 5B: N0 status, TNBC and TIL >=50%
• Age >=18

• WHO performance status <=1

Exclusion criteria

• evidence or suspicion of metastatic disease. Evaluation of the presence of distant metastases may include chest X-ray, liver ultrasound, isotope bone-scan, CT-scan of chest and abdomen and/or FDG-PET scan, according to local procedures;
• other prior invasive malignancy 1) in the breast or 2) localized in the near proximity of the breast, that was treated with radiotherapy at the localization of the new breast tumor;
• Concurrent ipsilateral or contralateral disease of the primary or a secondary tumor is allowed, as long as the other lesions is not a distant metastasis.
• Locoregional recurrences are not allowed. Second primary tumors are allowed in the study;
• occult breast cancer;
• previous anti-cancer hormone therapy or chemotherapy;
• prior treatment with checkpoint inhibitors (including anti- PD1, -PD-L1, -CTLA-4 - LAG3);
• concurrent anti-cancer treatment, neoadjuvant therapy or another investigational drug;

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):	04-10-2019
Enrollment:	90
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ipilimumab
Generic name:	ipilimumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	NA
Generic name:	relatlimab
Product type:	Medicine
Brand name:	nivolumab
Generic name:	nivolumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	18-02-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	15-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-04-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	14-11-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-11-2019
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	24-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-08-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-02-2022
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	15-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-06-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	27-02-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-03-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	CTIS2024-515080-54-00
EudraCT	EUCTR2018-004188-30-NL
ClinicalTrials.gov	NCT03815890
CCMO	NL67890.031.18