A Randomized Phase 3 Double-Blinded Study Comparing the Efficacy and Safety of Niraparib to Placebo in Participants with Either HER2-Negative BRCA-Mutated or Triple-Negative Breast Cancer with Molecular Disease Based on Presence of Circulating Tumor DNA After Definitive Therapy (ZEST)

Published: 21-04-2021
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This study has been transitioned to CTIS with ID 2023-504454-35-00 check the CTIS register for the current data. Primary objective:Evaulation of safety and tolerability of niraparibExploratory:Evaluation of the efficacy of niraparib relative to...

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

Summary

ID

NL-OMON52131

Source
ToetsingOnline

Brief title
213831 - ZEST

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
HER2 Negative Breast Cancer; Breast Cancer

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline
Source(s) of monetary or material Support: GlaxoSmithKline B.V.

Intervention

Keyword: Breast Cancer, circulating tumor DNA, Niraparib

Outcome measures

Primary outcome

DFS is defined as the time until disease recurrence, measured from the time of randomization to the earliest date of assessment of disease recurrence or death by any cause, as assessed by Investigator using RECIST v1.1.

Secondary outcome

Exploratory

DFS is defined as the time until disease recurrence, measured from the time of randomization to the earliest date of assessment of disease recurrence or death by any cause, as assessed by Investigator using RECIST v1.1.

DRFS is defined as the time from randomization to the first detection of distant metastasis or death by any cause as assessed by Investigator using RECIST v1.1.

TFST is defined as the time from randomization to the date of the first

anticancer therapy used subsequent to the date of the primary endpoint DFS or death by any cause.

Time to first subsequent chemotherapy is defined as the time from randomization to the date of the first systemic chemotherapy used subsequent to the date of the primary endpoint DFS or death by any cause.

Time to symptomatic progression is defined as the time from randomization to the date of symptomatic progression, which either coincides with or is subsequent to the date of the primary endpoint DFS. Symptomatic progression includes any of the following:

• Development of a skeletal-related event: pathologic fracture, spinal cord compression, or need for surgical intervention or radiation therapy (including palliative radiotherapy) to the bone

• Initiation of a new systemic anticancer therapy for cancer pain progression or worsening of disease-related symptoms

• Development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy.

IDFS will be assessed as per definition included in STEEP 2.0 (see Section 8.3.7 in the protocol).

IBCFS will be assessed as per definition included in STEEP 2.0 (see Section 8.3.8 in the protocol).

TTP in the brain is defined as the time from the date of randomization until

the earliest date of documented PD involving brain metastasis, based on

Investigator assessment using RECIST v.1.1 criteria.

Specific ctDNA analyses to be performed include, but are not limited to, change

in ctDNA levels and association with study outcomes and other clinical metrics.

Endpoints will be further defined in the SAP.

Tumor and blood samples for the evaluation of biomarkers will be obtained at

the time points specified in the SOA table in the protocol.

Study description

Background summary

Breast cancer is the most common cancer in women globally and makes up approximately 15% to 24% of all new cancer cases in women.
The incidence of breast cancer in men is approximately 70- to 100-fold lower than the incidence in women According to GLOBOCAN, the estimated number of new cases worldwide in women and men combined was 2,088,849 in 2018 In the European Union-28, the estimated number of new cases in women that year was 404,920.
There are 4 main breast cancer subtypes characterized by the expression status of the estrogen and progesterone receptors (also called hormone receptor [HR] status) and the lack or presence of overexpression of the human epidermal growth factor 2 (HER2).:
• HR positive, HER2 negative (HR+/HER2*)
• HR negative, HER2 negative (HR*/HER2*; *triple negative*)
• HR positive, HER2 positive (HR+/HER2+)
• HR negative, HER2 positive (HR*/HER2+)
Studies show that the prevalence of the 4 main breast cancer subtypes is dependent on factors such as sex, age, and ethnicity.
For approximately 5% to 10% of patients with breast cancer, the breast cancer is hereditary Up to 25% of hereditary breast cancers have been linked to specific germline mutations, with mutations in BRCA1 and BRCA2 making up approximately 20% BRCAmut breast cancer is

characterized by a more aggressive phenotype than sporadic breast cancer: BRCAmut
breast cancer is often of higher histological grade and is frequently triple negative
Although the prevalence of tBRCAmut in TNBC varies depending on factors such as age, ethnicity, and region, based on data from The Cancer Genome Atlas, the prevalence of tBRCAmut in TNBC is up to 25% Survival and recurrence are dependent on tumor stage and tumor subtype, as follows:
• Patients with metastatic TNBC have a 5-year survival rate of only 11.5%; 30.4% for patients with metastatic HR+/HER2* breast cancer; 36.8% for patients with metastatic HR*/HER2+ breast cancer; and 43.5% for patients with metastatic HR+/HER2+ breast cancer
• Patients with early stage TNBC have a very high 5-year recurrence rate (30% to 50%) compared to patients with other breast cancer subtypes
• Patients with TNBC demonstrate a peak in the risk of recurrence 1 to 3 years after last intervention, while the risk of recurrence in patients with other types of breast cancer, including HR+/HER2* breast cancer, seems to be steady for at least 15 years
• Patients with TNBC have a higher risk of distant recurrence than those with other breast cancer subtypes
• Peak of recurrence is 12 months postsurgery in patients with TNBC and 36 months postsurgery in patients with HR+/HER2* breast cancer

The population selected for this study are participants with TNBC (HER2*/HR*) and
HR+/HER2* breast cancer. Treatment of HER2+ breast cancer has evolved such that targeted therapies are the backbone for treatment in both the neoadjuvant/adjuvant and
metastatic setting, regardless of BRCA status. There are also limited data on the use of
PARP inhibitors and their effectiveness in BRCAmut HER2+ patients, and available data
suggest that the proportion of patients with BRCAmut amongst patients with HER2+ breast cancer is low (1.5% to 3.3%) Thus, patients with HER2+ breast cancer have been excluded from this study.

Study objective

This study has been transitioned to CTIS with ID 2023-504454-35-00 check the CTIS register for the current data.

Primary objective:
Evaulation of safety and tolerability of niraparib

Exploratory:
Evaluation of the efficacy of niraparib relative to placebo as measured by disease-free survival (DFS)

Evaluation of distant recurrence-free survival (DRFS)
Time to first subsequent therapy (TFST)
Time to first subsequent chemotherapy
Time to symptomatic progression
Evaluation of the efficacy of niraparib relative to placebo as measured by invasive disease-free survival (IDFS)
Evaluation of the efficacy of niraparib relative to placebo as measured by invasive breast cancer-free survival (IBCFS)
To evaluate and compare the time to progression (TTP) involving metastasis to the brain as assessed by the Investigator using RECIST v1.1 criteria in the protocol
Assessment of ctDNA dynamics
Exploration of biomarkers in tumor and/or blood that may be predictive of response and to evaluate mechanisms of resistance

Study design

The study will include 2 separate cohorts: a tBRCAmut HER2* breast cancer (including TNBC) cohort (Cohort 1) and a tBRCAwt TNBC cohort (Cohort 2).

Participants will initially enter a Prescreening Period for confirmation of detectable ctDNA. For participants with detectable ctDNA, the Prescreening Period is followed by the Screening Period (Day -28 to Day -1) for completion of the remaining Screening assessments. The Screening Period will start no more than 14 days after a participant has detectable ctDNA confirmed.
Eligible participants in Cohorts 1 and 2 are then randomized to either niraparib or placebo.

For Cohort 1, a Safety Run-in as well as a PK substudy will be performed. The Safety Run-in will include the first 40 randomized participants receiving concomitant endocrine therapy.
The PK substudy will include at least the first 40 randomized participants receiving endocrine therapy at sites participating in the PK substudy. Additional participants may be included in the PK substudy so that 6 participants per endocrine therapy are included, if feasible.
The Niraparib/Placebo Treatment Period is followed by an End of Treatment (EOT) Visit occurring within 7 days of last dose, a Safety Follow-up Visit 30 (+7) days after last dose, and Post-treatment Follow-up with assessments every 90 (±14) days for 2 years after the last dose and every 180 (±14) days thereafter.

Intervention

Niraparib/placebo will be administered orally once a day, continuously throughout each 28-day cycle starting on Cycle 1/Day 1. Two tablets of 100-mg strength or 3 tablets of 100-mg strength, based on baseline body weight and/or platelet count and hepatic function.

Study burden and risks

Preselection:
* Taking part in the pre-selection can cause extra stress. If ctDNA is found, the participant knows that there is a highly increased risk of the breast cancer returning.
* The tumor tissue is tested for the presence of a BRCA mutation. This test does not differentiate between BRCA mutations that are only present in the tumor and those that can be found in every cell of the body. The outcome of this research therefore does not say whether the participant is hereditary.
* Signatera Test: this test has not yet been registered. One risk of an experimental test is that the test results may not be correct. In such a case, this may lead to the decision to use study medication without this being of benefit, but with a risk of side effects.
Blood collection, see main study.

Main study:

Side effects: very common (may affect more than 1 in 10 people):

• thrombocytopenia
• anaemia
• leukopenia
• neutropenia
• hypertension
• palpitations
• urinary tract infection
• dyspnoea
• nose or upper throat infection
• Cough
• Headache
• Dizziness
• asthenia
• fatigue
• insomnia
• arthralgia
• Back pain
• abdominal pain
• heartburn
• nausea
• Vomiting
• diarrhoea
• constipation
• Decreased appetite (anorexia)

side effects: common (may affect up to 1 in 10 people):
• neutropenic infection
• bronchitis
• tachycardia
• peripheral edema
• myalgia
• Rash
• Decrease in weight
• depression
• anxiety
• conjunctivitis
• epistaxis
• stomatitis
• mucosal inflammation/mucositis
• dysgeusia
• xerostomia
• photosensitivity
• hypokalemia
• blood creatinine increase
• increased liver enzymes AST, ALT, and/or GGT in the blood
• liver function test, ALP increased in the blood

Side effects: uncommon (may affect up to 1 in 100 people):
• febrile neutropenia
• pancytopenia

Side effects: rare (may affect up to 1 in 1000 people):
• neutropenic sepsis
• hypertensive crisis
• posterior reversible encephalopathy syndrome [PRES]

In addition to the above, the side effects below were reported by patients who were prescribed niraparib by their doctors:
• Allergic reaction (hypersensitivity, including severe allergic reaction anaphylaxis).
o Life-threatening allergic reaction (such as difficulty breathing, rash, localized swelling, such as tongue, throat or lips) (anaphylaxis)
• Confusion (confusional state)
• Disorientation
• hallucination
• cognitive impairment
• non-infectious inflamed lung tissue, pneumonitis

Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML):
o PARP inhibitors may cause blood cancers known as MDS and acute myeloid leukemia (AML) in less than one percent of patients taking a PARP inhibitor.
o In 2 studies comparing niraparib to placebo, the likelihood of getting

MDS/AML was similar between the patients who took niraparib and those who took placebo.
o MDS/AML, including cases with a fatal outcome, have been reported in a small number of patients who took PARP inhibitors.

Secondary Primary Malignancy:
o PARP inhibitors may also cause a new primary cancer (.
* In 2 studies comparing niraparib to placebo, the likelihood of getting a new primary cancer was similar between the patients who took niraparib and those who took placebo.

Risks associated with study procedures/tests are listed below:
• Blood draws: When giving blood, the patient may feel faint or experience mild pain, bruising, irritation or redness from the needle.
• CT scans and bone scans: The cumulative radiation exposure from these tests is considered small and is not likely to adversely affect the patient or the patient*s disease. However, the effects of radiation add up over a lifetime. It is possible that having several of these tests may add to the patients risk of injury or disease.
• MRI: Some people cannot have an MRI because they have some type of metal in their body. Some patients are scared or anxious in small places (claustrophobic). The MRI scanner makes loud banging noises while scanning, ear plugs or specially designed headphones will be used to reduce the noise.

Contacts

Public
GlaxoSmithKline

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Scientific
GlaxoSmithKline

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Amersfoort 3811 LP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Pre-screening:
Stage I to III breast cancer, with surgical resection of the primary tumor that is confirmed to be either:
- TNBC, irrespective of BRCA status
- HR+/HER2* breast cancer with a known and documented deleterious or suspected deleterious tBRCA mutation
Completed prior standard therapy for curative intent
An archival tumor tissue specimen of the primary tumor sufficient in quality and quantity for ctDNA assay design and tBRCA and HRD testing
Have a significant risk of disease recurrence
Have no known or suspected locally recurrent metastatic disease

Main study:
Stage I to III breast cancer, with surgical resection of the primary tumor that is confirmed to be either:
• TNBC, irrespective of BRCA status
• HR+/HER2* breast cancer with a known and documented deleterious or suspected deleterious mutation
Completed prior standard therapy for curative intent.
Participants with HR+ breast cancer must be on a stable regimen of endocrine therapy
Detectable ctDNA
An archival tumor tissue specimen of the primary tumor sufficient in quality and quantity for ctDNA assay design and tBRCA and HRD
An ECOG performance status of 0 or 1
Must be >=18 years of age.
Must have adequate organ and bone marrow function
Participants with toxicity from prior cancer therapy must have recovered to Grade 1.
Must be able to swallow and retain orally administered study treatment.
A female participant is eligible if she is not pregnant or breastfeeding, and is not a woman of childbearing potential or is a WOCBP and using a

contraceptive method that is highly effective
Male participants are eligible if they agree to the following during the Treatment Period and for at least 90 days after the last dose of study treatment
Be abstinent from heterosexual intercourse or must agree to use contraception/barrier
Male participants must refrain from donating sperm for at least 90 days after the last dose of study treatment

Exclusion criteria

Prior treatment with a PARP inhibitor.
Current treatment with a CDK4/6 inhibitor or endocrine therapy other than anastrozole, letrozole, exemestane, and tamoxifen.
Participants have any sign of metastasis or local recurrence
Participants have shown no definitive response to preoperative chemotherapy
Participants have systolic BP >140 mmHg or diastolic BP >90 mmHg, that has not been adequately treated or controlled,
Participants have any clinically significant gastrointestinal abnormalities
Participants have received colony-stimulating factors within 4 weeks prior to the first dose of study treatment.
Participants have previously or are currently participating in a treatment study of an investigational agent within 4 weeks of the first dose of therapy preceding the study.
Participants have received live vaccine within 30 days of planned start of study randomization.
Participants have known hypersensitivity to the components of niraparib, placebo, or their formulation excipients.
Participants have undergone major surgery within 4 weeks of starting the first dose of study treatment or have not recovered from any effects of any major surgery.
Participants have a second primary malignancy.
Participants have current active pneumonitis or any history of pneumonitis requiring steroids or immunomodulatory treatment within 90 days of planned start of the study.
Participants have any clinically significant concomitant disease or condition
Participants have high medical risk due to a serious, uncontrolled medical disorder; nonmalignant systemic disease; or active, uncontrolled infection
Participant is pregnant, breastfeeding, or expecting to conceive children while receiving study treatment and/or for up to 180 days after the last dose of study treatment.
Participants have presence of hepatitis B surface antigen or a positive hepatitis C antibody test result at Screening or within 3 months prior to first dose of study treatment.
Participants is immunocompromised. Participants with splenecometry and

participants with known HIV are allowed.
Participants have a known history of MDS or AML.

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:	Recruiting
Start date (anticipated):	06-08-2021
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Zejula
Generic name:	Niraparib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	21-04-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	25-06-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-08-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-08-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-12-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-01-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-02-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-06-2022

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-07-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-08-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-08-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-11-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-11-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-07-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	29-01-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-02-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	CTIS2023-504454-35-00
EudraCT	EUCTR2020-003973-23-NL
CCMO	NL76762.100.21
Other	www.trialsummaries.com; 213831