Phase II, open label, single arm study to investigate anti-tumor effect of ixabepilone in patients with locally recurrent or metastatic breast cancer (mBC) selected by the ixabepilone Drug Response Prediction (DRP) after failure of an anthracycline and a taxane

Published: 12-05-2023
Last updated: 16-11-2024

Primary:• To evaluate the clinical benefit rate (CBR) of ixabepilone Secondary:• To evaluated progression free survival (PFS)• To evaluate overall survival (OS)• To evaluate objective response rate (ORR) defined as Complete Response (CR) and Partial...

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

Summary

ID

NL-OMON53513

Source
ToetsingOnline

Brief title
Effect of Ixabepilone in Recurrent or Metastatic Breast Cancer

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Recurrent or metastatic breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Allarity Therapeutics Europe ApS
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Ixabepilone, Ixabepilone DRP, Metastatic Breast Cancer, Recurrent Breast Cancer

Outcome measures

Primary outcome

Clinical Benefit Rate (CBR) will be defined as the proportion of patients

having a Complete Response (CR), Partial Response (PR), or Stable Disease (SD)

for at least 24 weeks

Secondary outcome

• Progression Free Survival (PFS) defined as time from first dose until

progressive diseas e(PD) according to RECIST v 1.1 or death, whichever occurs

first

• Overall Survival (OS) defined as the time from first dose until death from

any cause

• Objective Response Rate (ORR) defined as the proportion of patients with

complete response (CR) + partial response (PR) according to RECIST v 1.1

• Duration of response (DOR) defined as time of first documented CR or PR

response until documented tumor progression (RECIST v 1.1)

• Frequency of change in DRP-Ixempra-Breast between archival and fresh biopsies

• An elicited toxicity in target organs based on the Common Terminology

Criteria for Adverse Events (NCI-CTCAE v.5.0)

• A description of the frequency and severity of adverse events based on CTCAE

v.5.0

• Hematology and clinical biochemistry

• Vital signs

Study description

Background summary

Ixabepilone is approved by FDA for use in patients with with metastatic or locally advanced breast cancer. Ixabepilone has documented treatment effect both in combination with capecitabine and as monotherapy (see current SmPC for Ixempra). Since there are few treatment options for patients resistant to anthracylines, taxanes and capecitabine, ixabepilone is an alternative treatment option for these late stage breast cancer patients. Ixabepilone given as monotherapy has a documented ORR that varies between 11.5 to 42% (26). With this relatively low response rate a relatively high amount of patients will be exposed to treatment without having an effect, and thereby also exposed to the side effects of the product. Therefore, a Drug Response Prediction methodology (see below) has been introduced in the current study. Patients expected to respond to treatment will be selected according to a tumor biopsy mRNA expression profiling, leading to a DRP score and only patients having a DRP score > 33% will be considered as possible positive responders and included in the study.

The rationale for using DRP-Ixempra-Breast > 33% was based on retrospective analysis of archival biopsies from the study on neo-adjuvant treatment of breast cancer. Briefly, gene expression was measured in archival biopsies before treatment with 4 series of cyclophosphamide and doxorubicine followed by treatment with Ixabepilone. Based on this archival biopsy, the DRP-Ixempra-Breast was able to correctly predict response to Ixabepilone, and the response above a cutoff of 33 was 31% while the response below cut off 33 was 13%. It is concluded that the DRP-Ixempra-Breast is able to predict response based on an archival biopsy. If the prediction changes during anticancer treatment, the prediction will be even more accurate with a new biopsy.

Between half and two thirds of the patients are expected to have a positive DRP score (above > 33%) and can be offered therapy with ixabepilone.

Study objective

Primary:
• To evaluate the clinical benefit rate (CBR) of ixabepilone

Secondary:
• To evaluated progression free survival (PFS)
• To evaluate overall survival (OS)
• To evaluate objective response rate (ORR) defined as Complete Response (CR) and Partial Response (PR)
• To evaluate the safety profile of ixabepilone in patient with locally recurrent or metastatic breast cancer
• To further establish the clinical validation of the use of the DRP-Ixempra-Breast in selecting patients with locally recurrent or metastatic breast cancer
• Assess difference in prediction based on archival and fresh biopsy from same patient (percent agreement in binary prediction, and difference in primary and secondary endpoints with archival versus fresh biopsies)

Study design

This study is a multi-center, open-label, non-randomized, phase II study of ixabepilone as treatment in patients with locally recurrent or metastatic breast cancer. Previous chemotherapies (neoadjuvant, adjuvant or in the metastatic setting) must have included a taxane and an anthracycline unless anthracycline therapy is not indicated. The patients should have received a maximum of three (3) prior chemotherapies in the metastatic setting. Patients will be screened with the DRP-Ixempra-Breast. If the DRP score is above >33% the patient can be included in the clinical study, if all the other eligibility criteria are fulfilled.

Intervention

Patients will be screened with the DRP-Ixempra-Breast. If the DRP score is above >33% the patient can be included in the clinical study, if all the other eligibility criteria are fulfilled. Archival biopsy is used for determining the DRP-Ixempra-Breast (if obtainable biopsy should be taken after the last anticancer treatment has been stopped for determining any change in DRP-Ixempra-Breast). If such biopsy is not available it has to be done during the screening (first 2 weeks, if possible). The biopsy can be taken from any lesion, and the sample will be used to obtain the DRP score.

The dose of ixabepilone is 40 mg/m2 infused intravenously over 3 hours every 3 weeks.

Study burden and risks

Potential participants will attend a screening visit that will take 2-3 hours to confirm eligibility for the study. This will include taking a biopsy of their tumor if there is not a suitable one already available.

If a participant is enrolled they will remain in on IMP until tumour progression or they have unacceptable side effects. After this they will be followed up every 3 months for for up to 2 years.

IMP is administered every 3 weeks and will be administered as a continuous 3-hour intravenous infusion on Day 1 in each cycle. Before each infusion, participants will also receive pre-medication to reduce the chance of them having a hypersensitivity reaction to the study treatment. During each cycle participants will be asked to attend visits on Day 8 and Day 15.

The following assessments will be carried out during study visits (the full schedule can be found in section 6.2 of the protocol):

• At screening -Tumour biopsy and the DRP analysis; if a biopsy was taken after the last anti-cancer treatment had stopped, this tissue may be used for DRP assessment. However, if a biopsy is not available it may be done during the 4 weeks screening period. The biopsy may be image guided by a CT (Computerized Tomography) scan or by an ultrasound scan to help locate the tumour. This sample will then be used for DRP assessment.
• Medical history,
• Physical examination
• Vital Signs, including height (baseline only), weight, blood pressure, temperature, respiratory rate and heart rate.
• Electrocardiogram
• CT scan or MRI (Magnetic Resonance Imaging) scans. In some cases a chest X-ray may be required.
• Routine blood tests, including Haematology and Chemistry,
• Pregnancy urine or blood test, if you are a woman and can become pregnant
• A neurotoxicity questionnaire

Participants that stop treatment without tumor progression, well receive CT or MRI scans every 9 weeks until week 24 and then every 3 months until progression and thereafter followed every 3 months until death.

Participants that stop treatment due to tumor progression will be followed up every 3 months until death.

Study participants could respond to the study medication (i.e a reduction in tumor size or temporary halt of growth), however it is possible that there will be no direct benefit to participants.

Contacts

Public
Allarity Therapeutics Europe ApS

Venlighedsvej 1
Hørsholm 2970
DK
Scientific
Allarity Therapeutics Europe ApS

Venlighedsvej 1
Hørsholm 2970
DK

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patients with histologically or cytological confirmed adenocarcinoma of the breast and with confirmed locally recurrent or metastatic disease
2. Patients with hormone receptor positive and HER2 negative or triple negative primary tumor.
3. Previous chemotherapies (neoadjuvant, adjuvant or in the metastatic setting) must have included a taxane and an anthracycline unless anthracycline therapy is not indicated.
4. Maximum of three (3) prior chemotherapies in the metastatic setting in addition to any number of prior lines of endocrine therapy
5. Measurable disease by RECIST v 1.1 criteria
6. Performance status of ECOG <= 1
7. DRP-Ixempra-Breast - score of >33% in an archival biopsy or in a more

recent biopsy. If two biopsies are available and disagree the archival biopsy takes precedence.

Exclusion criteria

1. HER2 positive tumor
2. Concurrent chemotherapy, radiotherapy, hormonal therapy, or other investigational drug except non-disease related conditions (e.g. insulin for diabetes) during study period
3. Patients with intracranial disease
4. Other malignancies with exception of curative treated non-melanoma skin cancer or cervical carcinoma in situ within 5 years prior to entering the study
5. Any active infection requiring parenteral or oral antibiotic treatment.
6. Patients with grade 2, in case of diabetes grade 1 or greater neuropathy
7. Clinically significant (i.e. active) cardiovascular disease:
a. Stroke within <= 6 months prior to day 1
b. Transient ischemic attach (TIA) within <= 6 months prior to day 1
c. Myocardial infarction within <= 6 months prior to day 1
d. Unstable angina
e. New York Hart Association (NYHA) Class II or greater congestive heart failure (CHF)
f. Serious cardiac arrhythmia requiring medication
8. Other medications or conditions, including surgery, that in the Investigator*s opinion would contraindicate study participation for safety reasons or interfere with the interpretation of study results
9. Requiring immediate palliative treatment of any kind including surgery and/or radiotherapy
10. Female patients who are pregnant or breast-feeding (pregnancy test with a positive result before study entry)
11. Known prior severe hypersensitivity reactions to agents containing polyoxyethylated castor oil (Cremophor EL)
12. Patients must not continue treatment with the following strong inhibitors of CYP3A4:
Clarithromycin, ketoconazole, itraconazole, ritonavir, amprenavir, indinavir, nelfinavir, delavirdine, saquinavir and voriconazole. These therapies should be discontinued 72 hours prior to initiation of study drug therapy. Similarly, patients must not continue treatment with the following strong inducers of CYP3A4: phenytoin, carbamazepine, rifampin, rifabutin, dexamethasone, and phenobarbital. (20 mg dexamethasone can be used for pre-treatment if required). These therapies should be discontinued 72 hours prior to initiation of study drug therapy
13. Positive HIV and hepatitis B and C status, assessed from medical records only

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	08-08-2023
Enrollment:	5
Type:	Actual

Medical products/devices used

Generic name:	DRP-Ixempra-Breast
Registration:	No
Product type:	Medicine
Brand name:	Ixempra
Generic name:	Ixabepilone

Ethics review

Approved WMO Date:	12-05-2023
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	22-05-2023

Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	30-10-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	06-11-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2020-004610-35-NL
ClinicalTrials.gov	NCT04796324
CCMO	NL83292.000.23