Clinical and pharmacological feasibility study with 2B3-101 in patients with breast cancer and leptomeningeal metastases

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Primary: To determine the response of 2B3-101 treatment as single agent or in combination with trastuzumab in patients with LM from breast cancer using the LM response scoreSecundary: - To determine the safety profile in patients with LM treated…

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

Summary

ID

NL-OMON39893

Source
ToetsingOnline

Brief title
N12LMB: Clinical study with 2B3-101 in patients with breast cancer and LM

Condition

- Breast neoplasms malignant and unspecified (incl nipple)
- Spinal cord and nerve root disorders

Synonym
leptomeningeal metastases from breast cancer, metastases in brain membranes from breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: To-BBB, Leiden,To-BBB;Leiden

Intervention

Keyword: 2B3-101, breast cancer, leptomeningeal metastase, liposomal doxorubicin

Outcome measures

Primary outcome

LM response score

Secondary outcome

- safety profile in patients with LM from breast cancer treated with 2B3-101

as single agent or in combination with trastuzumab

- CNS progression free survival

- correlation of the clinical and radiological findings (MRI) and CSF cytology

with free doxorubicin levels in CSF and in plasma

- systemic progression free survival

- overall survival

- change in number of CTCs in CSF and blood and its correlion with the LM

response score

- change in number of CTCs in CSF and blood and its correlation with free

doxorubicine CSF and plasma levels

Study description

Background summary

Leptomeningeal metastases (LM) develop when tumor cells reach the cerebrospinal

fluid (CSF) and infiltrate the leptomeninges. Clinically symptomatic LM affects approximately 5 percent of patients with metastatic cancer. Among patients with LM caused by solid tumors, the most common tumor types are breast cancer (12-35%), lung cancer (10-26%), melanoma (5-25%) and gastrointestinal malignancies (4-14%). The median survival of untreated patients with LM derived from solid tumors is only 6-8 weeks. Chemotherapy and radiotherapy of symptomatic central nervous system (CNS) sites extends the median survival up to 2-4 months. The median survival of patient with breast cancer and LM is even longer (4-6 months) with up to 25% long-term survivors. Many potentially highly efficacious intravenous chemotherapies are currently not effective to treat LM because they do not adequately cross the blood-CSF barrier. The effectiveness of intrathecal (IT) chemotherapy is thought to be limited due to rapid cerebrospinal fluid (CSF) clearance of the drug and/or insufficient penetration into larger (>1mm) tumor deposits in the subarachnoid space. Besides, only a few cytostatic drugs can be administrated intrathecally because of neurotoxicity.
Doxorubicin, the anthracycline chemotherapeutic agent, has a well-established antineoplastic activity in breast cancer. It has triple action mechanisms, viz. binding to the DNA strands by intercalation, blocking the enzyme topoisomerase II, necessary for DNA replication and formation of free radicals. The treatment of breast cancer patients with anthracycline containing adjuvant chemotherapy reduces the relative risk (RR) of mortality in breast cancer patients with ± 38% per year in patients younger than 50 years and with ± 20% in patients between 50 and 69 years. To optimally enhance the delivery of liposomal doxorubicin to the brain, to-BBB technologies B.V. has designed a glutathione (GSH) pegylated liposomal doxorubicin hydrochloride formulation (2B3-101). Coating of liposomes with PEG ensures the prolonged circulation time in plasma, whilst conjugation of GSH to the tips of the PEG molecules targets the liposomes towards the active GSH transporters on the BBB to enhance the delivery of doxorubicin to the brain.
In the ongoing Phase IIa study (M11TBB, the Phase I, dosis-escalation is completed) the safety and preliminary efficacy of 2B3-101 is being determined in patients with brain metastases of solid tumours and patients with recurrent malignant glioma in 10 hospitals in the Netherlands, Belgium, France and USA.

To examine the enhanced delivery of 2B3-101 in the central nervous system (brain and CSF), measurements of free doxorubicin in the brain interstitial space or CSF is indicated. Technically, doxorubicin measurement in the brain interstitial space is difficult, as invasive probes (microdialysis or open probe) should be positioned in the brain tissue. Measurement of free doxorubicine in the CSF is easier as CSF can be obtained by a lumbar puncture in patients with LM treated with 2B3-101. Free doxorubicine CSF levels will be compared with free doxorubicine plasma levels.

To measure the anti-tumor response of 2B3-101 on leptomeningeal metastases we plan to explore enumeration of circulating tumor cells (CTC) prior to and during 2B3-101 therapy, using a fluorescence-activated cell sorting (FACS) flow

cytometry method that is currently validated in the ongoing study N12CLM study (NKI/AvL). The CTC method can determine single cell change in epithelial cell adhesion molecule (EpCAM) positive tumors, like breast cancer.

This a feasibility study that aims to determine preliminary efficacy of treatment with 2B3-101 as single agent or in combination with trastuzumab in patients with leptomeningeal metastases of breast cancer using the LM response score.

Study objective

Primary: To determine the response of 2B3-101 treatment as single agent or in combination with trastuzumab in patients with LM from breast cancer using the LM response score
Secundary:
- To determine the safety profile in patients with LM treated with 2B3-101 as single agent or in combination with trastuzumab
- To determine CNS progression free survival in patients with LM from breast cancer treated with 2B3-101 as single agent or in combination with trastuzumab
- To correlate the clinical and radiological findings (MRI) and CSF cytology with free doxorubicin levels in CSF and in plasma during the treatment of patients with LM from breast cancer with 2B3-101 as single agent or in combination with trastuzumab
- To determine systemic progression free survival in patients treated with LM from breast cancer with 2B3-101 as single agent or in combination with trastuzumab
- To determine overall survival in patients treated with LM from breast cancer with 2B3-101 as single agent or in combination with trastuzumab
- To explore the change in number of CTCs in CSF and blood and correlate this with the LM response score
- To explore the change in number of CTCs in CSF and blood and correlate this with free doxorubicine CSF and plasma levels
- To determine efficacy of 2B3-101 in patients with breast cancer and LM with the individual components of the LM response score.

Study design

Clinical study with 2B3-101 as single agent or in combination with trastuzumab in patients with LM from breast cancer, given in a dose and frequency determined in M11TBB study.

This Phase II study will use the recommended dose (50 mg/m2) and frequency (every 21 days) from the Phase I study (M11TBB) in patients with solid tumors with brain metastases or recurrent malignant glioma, in which the MTD was determined. A single dose of 2B3-101 will be administered IV on day 1 of cycle

1. To minimize the risk of infusion reactions, 5% of the total dose of 2B3-101 (in mg) will be administrated over the first 30 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes.

Patients with HER2+ breast cancer will receive trastuzumab 30 minutes after the completion of the 2B3-101 infusion. The trastuzumab dose at day 1 will be given as a loading dose of 8 mg/kg at day 1 (if the patient is not already being treated
with trastuzumab) and thereafter a continued dose of 6 mg/kg will be given every 3 weeks at the subsequent cycles.

Safety will be assessed by means of physical examination, neurological examination, cognitive screening tests, weight, vital signs, performance status, laboratory evaluations (haematology, biochemistry, urinalysis and N-terminal Pro-Brain Natriuretic Peptide (NT-ProBNP) and cardiac Troponin T (cTnT)), electrocardiograms (ECG), LVEF (MUGA/ECHO), and recording of concurrent illness/therapy and adverse events according to The National Cancer Institute*s Common Terminology Criteria for Adverse Events (NCI-CTCAE version 4.0).

Patients that will receive 2B3-101 in combination with trastuzumab are required to enter in an intensified cardiac program including ECG and LVEF measurements before the start of every treatment cycle.

Preliminary clinical efficacy of 2B3-101 as single agent or in combination with trastuzumab will be determined using the LM response score (see protocl Table 2) based on neurological signs by neurological examination, MRI-scans of brains and spinal cord and CSF cytology (semi-quantitative score for tumor cell number, see protocol Table 3). This score will be determined every six weeks. Furthermore, CT thorax/abdomen will be performed every six weeks (in the last week of every even 2B3-101 cycle) to determine the respons of systemic metastases. A bone scan should only be obtained if clinically indicated and should be performed during the study, if the patient develops symptoms or signs of bone disease. Enumeration of CTCs in plasma and CSF will be exploratory biomarkers.

Patients will remain on treatment until they have no longer clinical benefit from treatment or when toxicity leads to patient withdrawal. Patients will be followed up until death.

Intervention

Plasma and CSF are closely monitored during the first cycle, according to the following schedule:
• CSF samples for cytology (Cycle 1 (within 1 week prior to start 2B3-101, Cycle 1 Day 2 and Cycle 1 Day 8 and every 6 weeks, before the start of uneven

cycles (cycle 3, 5, 7 etc at Day 1 predose) (5 ml).
• CSF and blood samples for chemistry: at the same time as cytology sampling (2 ml CSF and 8 ml blood)
• Total doxorubicin in plasma and in CSF both encapsulated in liposomes and free): at the same time as cytology sampling up to and including cycle 5 day 1 predose (2.5 ml CSF and 4 ml blood)
• Enumeration of CTCs in blood and CSF: at the same time as cytology sampling (5 ml CSF and 3 x 8 blood)
Cytological CSF samples will be stored and archived as cytospins at the Department of Pathology at the NKI-AvL. Blood and CSF chemistry samples will be stored in the CSF bank, Department of Clinical Chemistry, NKI-AVL. The rest of the samples (for CTC assay) will be destructed after analysis.

Archival tumor tissue:
If not already done, an analysis of the EPCAM, Her-2/neu, ER and PR status of the primary tumor will be performed by immunohistochemistry (IHC). IHC will be performed at the Department of Molecular Pathology, according to specific guidelines provided by the NKI.

Study burden and risks

Risks/adverse events
Doxorubicin, in its free (Adriamycin®), non-pegylated liposomal (Myocet®) and pegylated liposomal (Caelyx®) forms, is an established anti-cancer drug and its toxicological profile is well known.

The important (dose-limiting) clinical adverse events at patients with breast cancer in clinical studies with Caelyx ® are the following systemic adverse event:
palmo-plantar erytrodysesthesis PPE, stomatitis / mucositis en hematological toxitities (leukopenia / neutropenia). There were no neurotoxicities seen during the treatment with Caelyx ® or other forms of doxorubicin. It is possibly related to poor BBB penetration of those substancies.

2B3-101 is till now been administrated to 28 persons in the completed phase I study with patients with brain tumors.the most comon adverse events were nausea (57%), neutropenia (46%), PPE (32%), abdominal pain (32%), headache (18%) and infusion reactions (25)

in the combination cohort the safety, tolerability and maximal tolerated dose of 2B3-101 in combination with standard trastuzumab dose in patient with HER2+ breast cancer has been investigated. At this moment 2 out of 9 patients are still ongoing and so far in total 38 cycles are being administered (range 1-10 and average of 4.2 cycles).

The most frequent reported grade 1-4 2B3-101 related adverse events were: fatigue (77%), palmo-plantar erythrodysesthesia (77%), neutropenia (56%),

anorexia (56%), (oral) mucositis (44%), leucopenia (33%), thrombocytepenia (33%), anemia (33%), infusion reactions (33%), alopecia (33%) diarrhoea (22%) and rash (22%). No 2B3-101-related CNS or cardiac toxicity was reported

Burden
Patients participating are hospitalized for 1 day in the first week of the first cycle.
During the first three weeks, a lumbar puncture will be performed at baseline (within 1 week prior to 2B3-101), and at Day 2 and Day 8 after 2B3-101 infusion. Thereafter patients will undergo a lumbar puncture every 6 weeks. Blood sampling occurs on the same time-points as CSF sampling.
The burden of sampling includes lumbar puncture and vena-puncture. During a lumbar puncture procedure, patients can experience transient back pain and parasthesiaes of the legs. Post dural puncture headache with nausea occurs in 5.6% of the patients undergoing a lumbar puncture.
The most common complications of a veni-puncture consist of slight discomfort, bruising, hematoma and occasionally local infection
The patient will undergo a neurological and physical examination every three weeks (on the last day of every 2B3-101 cycle) and MRI scan of the brains and spinal cord and cognitive screening tests every 6 weeks.

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

1. Age >= 18 years.
2. Radiological or cytological evidence of clinically symptomatic leptomeningeal metastases of pathologically confirmed breast cancer.
3. Concomitant brain metastases are allowed
4. ECOG Performance Status <= 2.
5. Estimated life expectancy of at least 8 weeks.
6. Stable or decreasing dosage of steroids (e.g.dexamethason) for 7 days prior to baseline MRI 7. Use of non-enzyme inducing anti-epileptic drugs is allowed
8. Toxicities incurred as a result of previous anticancer therapy (radiation therapy, chemotherapy, or surgery) must be resolved to <= grade 2 (as defined by CTCAE version 4.0).
9. Written informed consent according to local guidelines.
10. Local radiation of CNS symptomatic sites more than four weeks prior to start of the study is allowed.
11. Previous trastuzumab treatment will be allowed to continue without interruption in patients with histologically-confirmed HER2-positive (IHC 3+ or fluorescence in situ hybridization [FISH] amplified; by
clinical assay on either primary or metastatic tumor) adenocarcinoma of the breast

Exclusion criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist:
Prior Treatment:
1. Less than 1 week since the last treatment of lapatinib, dabrafenib, everolimus, capecitabine, anastrazole, letrozole and exemestane; less than 2 weeks since the last treatment of vemurafenib; less than 4 weeks from the last treatment of trametinib, chemotherapy, biological therapy, immunotherapy and systemic radiotherapy (except palliative radiation delivered to <20% of bone marrow); less than 6 weeks for nitrosoureas and mitomycin C Previous trastuzumab treatment will be allowed to continue without interruption in patients with HER2+ breast
2. Radiotherapy of the brain or spinal cord/cauda equine or symptomatic bone metastases is

allowed before or during 2B3-101 treatment both as single agent and in combination with trastuzumab but radiated localizations will not be used for response evaluation.
3. Patients that have received a maximum cumulative dose of free (i.e., non-liposomal) or liposomal doxorubicin > 360mg/m2 or free epirubicin > 600mg/m2
4. Current or recent (less than 4 weeks before first 2B3-101 treatment) treatment with another investigational drug.
5. Any other current anticancer therapy
Haematology, coagulation and biochemistry:
6. Inadequate bone marrow function, defined as: Absolute Neutrophil Count (ANC): < 1.5 x 109/L, or platelet count < 100 x 109/L or haemoglobin < 6 mmol/L.
7. Inadequate liver function, defined as:
• Serum (total) bilirubin > 1.5 x the Upper Limit of Normal (ULN) for the institution in absence of liver metastases (> 2 x ULN in patients with liver metastases);
• Aspartate Amino Transferase (ASAT) or Alanine Amino Transferase (ALAT) > 3 x ULN if no liver metastases (> 5x ULN in patients with liver metastases);
• Alkaline phosphatase levels > 2.5 x ULN if no liver metastases (> 5 x ULN in patients with liver metastases, or > 10 x ULN in patients with bone metastases).
8. Inadequate renal function, defined as:
• Serum creatinine clearance < 50 ml/min ;Other:
9. Pregnancy or lactation. A serum pregnancy test needs to be performed within 7 days prior to study treatment start in case of childbearing potential, or within 14 days followed by a confirmatory urine pregnancy test within 7 days prior to study treatment start.
10. For female subjects of childbearing potential (defined as < 2 years after last menstruation and not surgically sterile) and male subjects who are not surgically sterile and with female partners of childbearing potential: absence of effective, non-hormonal means of contraception (intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal gel).
11. Major surgical procedure (including open biopsy, excluding central line IV and Port-a-cath) within 4 weeks prior to the first study treatment, or anticipation of the need for major surgery during the course of the study treatment.
12. Grade 3 or 4 motor, sensory, or cranial neuropathy symptoms (as defined by CTCAE version 4.0) caused by previous chemotherapy.
13. Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic >100mm Hg).
14. Clinically significant (i.e. active) cardiovascular disease defined as:
• Stroke within 6 months prior to treatment with 2B3-101 (day 1);
• Transient Ischaemic Attack (TIA) within 6 months prior to day 1;
• Myocardial infarction (MI) within <= 6 months prior to day 1;
• Unstable angina pectoris (AP);
• New York Heart Association (NYHA) Grade II or greater Congestive Heart Failure (CHF);
• Cardiac arrhythmia, except stable atrium fibrillations;
15. Left Ventricle Ejection Fraction (LVEF) by MUGA or ECHO < 50%. and < 55% for patients receiving 2B3-101 in combination with
trastuzumab.
16. Known hypersensitivity to any of the study drug components or its excipients (doxorubicin, PEG or GSH).
17. Evidence of any other medical conditions (such as psychiatric illness, infectious disease, and physical examination or laboratory findings) that may interfere with the planned

treatment, affect patient compliance or place the patient at high risk from treatment-related complications.
18. Contra-indications for lumbar punctures:
- blood clotting disorders (INR>1.5, platelets <20x109 /l, aPTT > 1.5 ULN). Lumbar puncture after platelets transfusion resulting into platelets > 20x109 /l after transfusion is allowed.
- therapeutic anticoagulant treatment that cannot be interrupted for 24 hours. Low dose prophylactic treatment with low molecular weight heparins is allowed.
- cerebral space-occupying lesions with a risk of cerebral herniation.
- spinal space-occupying lesions with a risk of myelum compression or conus/cauda compression.
19. Active systemic or CNS infection.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-08-2013
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Herceptin
Generic name:	trastuzumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-11-2012
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-08-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-02-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	28-02-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-11-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-11-2014
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
EudraCT	EUCTR2012-005096-13-NL
CCMO	NL42727.031.12