A phase Ib, open-label, two arm study of i.v. and oral panobinostat (LBH589) in combination with i.v. trastuzumab (HerceptinÂ®) and i.v. paclitaxel as treatment for adult female patients with HER2 overexpressing metastatic breast cancer (MBC)

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Ethical review	Approved WMO
Status	Pending
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON32569

Source
ToetsingOnline

Brief title
Panobinostat (LBH589)

Condition

- Metastases

Synonym
HER2 overexpressing metastatic breast cancer (MBC) / Metastatic Breast Cancer (MBC)

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: NOVARTIS Pharma AG

Intervention

Keyword: - Herceptin, - metastatic breast cancer (MBC)

Outcome measures

Primary outcome

Primary endpoints:

* Determination of maximum tolerated dose (MTD) of i.v. and oral panobinostat

when given in combination with paclitaxel and trastuzumab

Secondary outcome

Secondary endpoints:

* AEs as determined by CTCAE version 3 and SAEs

* ECG parameters

* Pharmacokinetic parameters (for paclitaxel and panobinostat)

* Tumor assessment according to RECIST

Exploratory endpoints (at MTD during expansion phase):

* HER2 ECD and apoptosis markers in serum; cellular and molecular markers in

tumor

Study description

Background summary

HER2-positive breast cancer accounts for approximately 20 to 30% of all cases of breast cancer. In the setting of HER2 gene amplification or high levels of HER2 expression, the HER family of receptors and their associated signal-transduction pathways play a dominant role in cell growth and survival. These tumors have a distinct natural history that, in the absence of HER2-directed therapy, is characterized by short disease-free survival and an aggressive course in the metastatic setting.

Trastuzumab is a monoclonal antibody directed against HER2. Its anti-tumor activity is likely attributable to several different effects including the down regulation of HER2 expression on cell surfaces and activation of p27 and p130. Trastuzumab also sensitizes tumor cells to TNF and inhibits tumor angiogenesis by decreasing the production of VEGF.
Taxanes are among the most active chemotherapy agents used in the management of metastatic breast cancer (Ghersi 2005). Paclitaxel in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress HER2 and who have previously not received chemotherapy for MBC (Herceptin® US PI).
Combining two or more agents has been shown to improve survival in advanced breast cancer (Carrick 2006). Studies indicate that triplet combinations can provide improved survival if over-lapping toxicities can be avoided or adequately managed.

Panobinostat is a multi-targeted agent which inhibits deacetylase (DAC) enzyme activity, activates the p21 tumor suppressor gene and inhibits proliferation of tumor cell lines at nanomolar concentrations. In vivo experiments have demonstrated the single agent anti-tumor activity of panobinostat against both ER positive and HER2 positive tumors. Other pre-clinical data suggests that the anti-tumor effects of panobinostat occur in part through the increased acetylation and consequent loss of HSP90 function. Both ER and HER2 are HSP90 client proteins, and are degraded in cell lines exposed to panobinostat in vitro.

In-vitro data has shown that panobinostat inhibits the function of HSP90 and causes degradation of HER2 and/or ER in molecularly defined breast cancer cell lines
induces highly potent single agent death of all HER2/neu driven breast cancer cell lines tested in vitro.
induces the death of most ER positive cell lines with high potency
causes re-expression of ER in hormone receptor negative breast cancer cell lines and sensitizes them to tamoxifen (receptor antagonist) synergizes with the HER2/neu tyronsine kinase inhibitor lapatinib and AEE788 and has additive activity with the EGFRi Gefitinib.

In-vivo data has shown a profound synergistic anti-tumor effect when panobinostat is combined with trastuzumab or taxotere in the HER2/neu-driven BT474 in vivo model.

Study objective

The purpose of this phase Ib study is to determine the maximum tolerated dose (MTD) of i.v. and oral panobinostat when given in combination with trastuzumab and paclitaxel. Additional patients will be enrolled at the MTD to further evaluate the safety and tolerability of this treatment combination.

Primary objective
* Arm I: to determine the maximum-tolerated dose (MTD) based on dose-limiting toxicities (DLT) of i.v. panobinostat given weekly for two weeks on treatment, one week off treatment (e.g. D1, D8 as part of a 21 day cycle) when given in combination with weekly paclitaxel and weekly trastuzumab in patients with HER2 positive MBC
Arm II: to determine the maximum-tolerated dose (MTD) based on dose-limiting toxicities (DLT) of oral panobinostat given on days 1, 3 and 5 every week as part of a 21 day cycle) when given in combination with weekly paclitaxel and weekly trastuzumab in patients with HER2 positive MBC

Secondary objectives
* To characterize the safety and tolerability of i.v. and oral panobinostat when given in combination with paclitaxel and trastuzumab
* To evaluate the effect on QTc interval in patients receiving i.v. and oral panobinostat when given in combination with paclitaxel and trastuzumab
* To characterize the disposition (pharmacokinetics) of panobinostat following i.v. and oral administration of panobinostat when given at the MTD in combination with paclitaxel and trastuzumab
* To describe the disposition (pharmacokinetics) of paclitaxel alone and following the co-administration of panobinostat at the MTD and trastuzumab
* To explore preliminary antitumor activity of panobinostat when given intravenously (Arm I) and orally (Arm II) in combination with weekly paclitaxel and weekly trastuzumab

Exploratory objectives
* To explore the effect of i.v. and oral panobinostat at the MTD when given in combination with i.v. trastuzumab and i.v. paclitaxel on circulating tumor cells and other biomarkers during treatment

Study design

This is a phase Ib open label, multi-centre, two-arm, international study of i.v. panobinostat and oral panobinostat given in combination with weekly paclitaxel and weekly trastuzumab in women with HER2-positive MBC.

In this study patients screened successfully will be randomly allocated to one of the two arms (i.v. or oral panobinostat) after assignment of a unique patient identification number according to a prearranged sequence provided by Novartis. During the dose escalation phase an arm maybe temporarily *closed* for evaluation. If so then all patients will be enrolled to the *open* arm.

A minimum of 3 patients will be enrolled into a cohort. In each successive cohort patients will receive an increased dose of panobinostat with standard doses of trastuzumab and paclitaxel until the MTD is reached. The starting doses of i.v. and oral panobinostat for this study have been chosen on the basis of their safety in the preceding single-agent phase I trials. The starting dose for i.v. panobinostat (Arm I) will be 10mg/m2 given once a week (e.g. D1 and D8) for two weeks on treatment with one week off treatment as part of a 21 day treatment cycle. The starting dose for oral panobinostat (Arm II) will be 10mg given three times every week (e.g. D1, D3, and D5 weekly) given as part of a 21 day treatment cycle
Data from the ongoing [CLBH589C2204] study combining i.v. and oral panobinostat with trastuzumab will provide supporting dosing and toxicity data.

In arm I, additional panobinostat doses or intermediate panobinostat doses, if needed, may be evaluated to better define the safety, pharmacokinetics and/or pharmacodynamics of the study treatment combination.

During the dose escalation phase, an adaptive Bayesian logistic regression model (Thall, et al 2003) and dose escalation criteria similar to that proposed by Babb (Babb, Rogatki, and Zacks 1998) will be used separately for Arms I and II. The statistical model for the combination treatment will be based on a 6-parameter logistic model with overdose control.
Each cohort will consist of a minimum of 3 newly enrolled evaluable patients. If * 1 patient in the cohort experiences a DLT before the completion of enrollment to that cohort, the model will be re-evaluated and additional patients enrolled as determined necessary.

The patient population used for the determination of MTD will consist of patients who have experienced DLT and/or who have met the minimum safety evaluation requirements for their first cycle of treatment. Once a dose cohort has been identified as the potential MTD, a minimum of 9 patients must be treated at the given dose before it can be declared the MTD. It is anticipated that at least 15 patients from each arm will be required during dose escalation of the study to determine the MTD. This estimate assumes that the third dose level in each arm will be the MTD. Once the MTD is declared an additional 11 patients will be enrolled into each arm during an expansion phase.
After completion of a given dose cohort, the decision to dose escalate and the selection of the next dose to evaluate will depend on a calculated risk of DLT using the Bayesian logistic regression models and the medical review of available clinical and laboratory data by Novartis and the treating investigators.

A DLT is defined as an AE or laboratory abnormality that is considered to be related to the study treatment (see Table 6-6). During the dose escalation phase of the study the MTDs of panobinostat given i.v. and orally will be principally determined from DLTs occurring during the first cycle of therapy. However toxicities occurring in subsequent cycles of treatment may also be considered at the time of dose escalation discussions/decisions. Hypersensitivity or infusion reactions to paclitaxel or to trastuzumab will not be considered DLTs (Section 6.6.1.7). Should a toxicity be considered specifically related to paclitaxel, the paclitaxel dose may be modified and/or interrupted as per the locally approved PI. Toxicities be considered specifically related to trastuzumab the trastuzumab infusion will be interrupted and/or delayed as per the locally approved PI (See Section 6.6.2.1).

Study treatment will be repeated every 21 days unless there is evidence of progression or occurrence of unacceptable toxicities. For a patient to be followed within the context of this study, the patient needs to continue to receive panobinostat treatment.
Pharmacokinetic assessments will be performed in the patients treated at the MTD during the expansion phase.

Intervention

If a patient participates in this study, he/shewill be asked to sign the informed consent before any tests are performed specifically for this study. After the patient sign the informed consent but before starting therapy, the study doctor will ask the patient about his/her health and medical history to determine if the patient is eligible to take part in the study. The patient will undergo a series of tests to evaluate the present state of health and the state of the disease.

If these tests show that the patient is eligible to enter the study, and if the patient chooses to enter the study, he/she will be assigned to one of two groups which will determine whether he/she will receive panobinostat as an intravenous infusion once a week (usually on Mondays) for two weeks out of three weeks or panobinostat as capsule(s) he/she will take by mouth three times a week (usually on Mondays, Wednesdays and Fridays) every week. No matter what group a patient is assigned to, he/she will receive trastuzumab and paclitaxel as intravenous infusions once a week (usually on Mondays). The patient will return to the doctor*s office at regular intervals so that his/her condition can be checked. The study doctor will ask the patient how he/she is feeling. The patient may continue to receive treatment provided that tests show the disease is not getting worse, and the patient is not experiencing unacceptable side effects and the doctor thinks that the patient is benefiting from treatment. The patient will continue to have tests on a regular schedule while he/she is in this study.

All patients in this study will receive the investigational drug panobinostat

with an infusion of trastuzumab and infusion of paclitaxel.

Study burden and risks

Risks are the possible side-effects of the study medication and side-effects of the study procedures, like blood- and urine sampling.

An more extensive description of the risks has been described in Paragraph 1.3 (on page 40) of the study protocol.

Contacts

Public
Novartis

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CH
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Histologically or cytologically confirmed HER2 positive breast cancer
* Female patients * 18 years old
* ECOG performance status of * 1
* Non-measurable or measurable disease (according to RECIST)
* Prior treatment for brain metastases is allowed but patient must be neurologically stable and off corticosteroids and not receiving concurrent radiotherapy for brain metastases
* Prior treatment with trastuzumab and/or lapatinib is permitted.
* If patient has received prior treatment with anthracylines, this must be completed * 24 weeks before the start of study treatment
* Patient must have received at least one prior treatment regimen containing a taxane and up to 2 prior regimens for metastatic disease
* Concurrent bisphosphonates are permitted if initiated prior to study entry
* Patients must meet the specified values in the protocol concerning to haematology parameters and biochemistry parameters
* Patients with elevated alkaline phosphatase due to bone metastasis can be enrolled
* Patient who are clinically euthyroid (patients may be on thyroid hormone replacement)
* Potassium, calcium, and magnesium supplements may be given to correct values that are < LLIN, but must be documented as corrected prior to patients enrolling on the study
* Women of childbearing potential must have a negative serum pregnancy test within 7 days of the first administration of study treatment and must be willing to use adequate methods of contraception during the study and for 3 months after last study drug administration

Exclusion criteria

* Prior HDAC, DAC, HSP90 inhibitors or valproic acid administered for the treatment ofcancer
* Need for valproic acid during the study or within 5 days prior to first panobinostat treatment
* History of hypersensitivity reaction to paclitaxel or other drugs formulated with polysorbate 80 (Tween 80), polyethoxylated castor oil
* Known allergy or severe reactions to paclitaxel and/or trastuzumab or its constituents
* Prior chemotherapy within the last 3 weeks (exceptions: * 6 weeks for nitrosoureas or mitomycin, * 2 weeks for capecitabine or oral cyclophosphamide) before the start of study treatment
* Prior treatment with investigational agents within the last 4 weeks before the start of study treatment
* Surgery or not recovering within the last 2 weeks prior to starting study treatment
* Presence of persistent * grade 2 neuropathy or history of grade 3/4 neuropathy
* Presence of unresolved diarrhea *CTCAE grade 1
* Impaired cardiac function (see more details in the protocol)
* Concomitant use of drugs with a risk of causing torsades de pointes where such treatment cannot be discontinued or switched to a different medication prior to starting study drug
* Other concurrent severe and/or uncontrolled medical conditions that could cause unacceptable safety risks or compromise compliance with the protocol
* Known history of HIV seropositivity
* Active bleeding diathesis or on any treatment with therapeutic doses of sodium warfarin or any other anti-vitamin K drugs

* Requirement of diuretics or draining procedures to manage or drain third space fluid accumulation
* Bone marrow support, stem cell support at study entry
* Pregnant or breast-feeding
* History of non-compliance with medical treatments or with inability to grant a reliable written informed consent

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2008
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Herceptin (werkzame stof: Trastuzumab)
Generic name:	Niet van toepassing
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Paclitaxel
Generic name:	Niet van toepassing
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Panobinostat (vloeistof voor injectie)
Generic name:	Niet van toepassing

Product type:	Medicine
Brand name:	Panobinostat (Capsules, Hard)
Generic name:	Niet van toepassing

Ethics review

Approved WMO Date:	15-09-2008
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	20-01-2009
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	07-04-2009
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-06-2009
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	EUCTR2007-004788-23-NL
CCMO	NL24581.031.08
Other	Zie comm.