A phase Ib/II, multi-center, open-label study to evaluate the efficacy of AUY922 in combination with Trastuzumab in patients with locally advanced or metastatic HER2-positive breast cancer, that has progressed after or during at least one Trastuzumab-containing regimen.

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Primary objective(s)Phase Ib:-Define the maximum tolerated dose (MTD) and/or recommended phase two dose (RPTD) of AUY922 in combination with Trastuzumab in patients with advanced or metastatic HER2-positive breast cancers.Phase II:-Evaluate...

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

Summary

ID

NL-OMON36445

Source
ToetsingOnline

Brief title
Phase Ib/II study of AUY922 plus trastuzumab in HER-2+ breastcancer

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
advanced HER-2 positiv breastcancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: AUY922, Breastcancer, HER-2 positive, HSP90

Outcome measures

Primary outcome

Phase Ib:

- Incidence rate of Dose Limiting Toxicities (DLT)

Phase II:

- Overall response rate (ORR)

Secondary outcome

Phase Ib and II

- Safety: Adverse drug reactions , changes in hematology and chemistry values,

specifically those associated with hepatic and renal function; assessment of

physical examinations, neurological exams, vital signs and electrocardiograms.

- Pharmacokinetics: Cmax, Tmax, AUC0-tlast and AUC(0-infinity)

Phase Ib:

- Preliminary efficacy: Tumor response assessment using CT/MRI.

- Pre vs. serial post-treatment intracellular protein measurement of HSP70 in

PBMCs

Phase II:

- -PFS/OS as defined in RECIST guidelines.

-Temporal and magnitude changes in blood and tissue marker levels comparing

pre- vs. post-treatment.

Study description

Background summary

Breast cancer is the most common form of malignancy occurring in women. In the US, approximately 182.460 new cases of invasive breast cancer have been diagnosed in 2008. In the same year about 40.480 women have died from their disease. In Europe approximately 13% (370.100) of all new cases of cancer that were diagnosed were breast cancer. Approximately 40% of diagnosed patients will eventually develop metastatic breast cancer. Treatment for metastatic breast cancer is palliative and median life expectancy after recurrence is between 24 to 30 months.
HER-2 neu positive breast cancer accounts for approximately 20-25% of all cases of breast cancer. This breast cancer type is characterized by high levels of HER2 protein expression. These proteins and their associated signal transduction pathways play a dominant role in cell growth and survival. These HER-2 positive patients will have an aggressive form of breast cancer and therefore a worse prognosis.

Study objective

Primary objective(s)
Phase Ib:
-Define the maximum tolerated dose (MTD) and/or recommended phase two dose (RPTD) of AUY922 in combination with Trastuzumab in patients with advanced or metastatic HER2-positive breast cancers.
Phase II:
-Evaluate preliminary anti-tumor activity of AUY922 in combination with Trastuzumab in patients with advanced or metastatic HER2-positive breast cancers.

Secondary objective(s)

- Safety and tolerability of AUY922 when administered in combination with Trastuzumab.
- Pharmacokinetic profile of AUY922 and its metabolite BJP762 when given in combination with Trastuzumab.
- Evaluate preliminary anti-tumor activity
- Assess the pharmacodynamic (PD) effect of AUY922 in combination with Trastuzumab
- Characterize the relationship between PK and PD of the combination.
- Investigate the pharmaco dynamic effect of AUY922 in combination with Trastuzumab on HSP90 client proteins in pre- and post-therapy tumor tissue pairs and blood

Study design

Open-label, multicenter Phase Ib/II trial with a dose-escalation part with AUY922 administered in combination with Trastuzumab (Phase Ib), followed by a dose expansion part (Phase II).
The dose escalation will use an adaptive Bayesian logistic regression model to find the MTD and/or the recommended phase II dose.
The phase II part will use a Bayesian design to estimate the overall response rate (ORR).
One cycle is defined as 28 days.
Treatment should be continued as long as the patient does not have disease progression and tolerates the treatment.
Tumor assessments using CT or MRI will be performed every 8 weeks, for 24 weeks, then every 12 weeks until progression or until a new anticancer therapy is initiated. During the study, bone scans are to be performed only if clinically indicated.
Follow-up: After the End of Treatment visit all patients will have their follow-up visit 1 (FUP1) visit performed, 28 days after the last dose. Patients who discontinued for any reason other than disease progression will continue to have tumor assessments every 12 weeks until progression, death or until a new anticancer therapy is initiated. All patients who have progressed during study treatment will be followed every 3 months for survival. The follow-up period will stop, in any case, 2 years after the last patient is enrolled in the study.

Intervention

AUY922 - startdose 55mg/m2 - weekly infusion
Trastuzumab - 2mg/kg - weekly infusion

Study burden and risks

Side effects of AUY922 (especially vision toxicity, diarrhea, cardiac toxicity

and changes in adrenal glands) and side effects of trastuzumab.
The risks of taking blood and an intravenous catheter.
Risks of a tumor biopsy depend on the area of the biopsy.
Radiation exposure of CT-scan). The exposure to radiation in these scans is within the standard limits in this country.

Contacts

Public
Novartis

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Confirmed HER2-positive, non-operable locally advanced or metastatic breast cancer
- Tumor samples must demonstrate HER2 over-expression based on either:
- Immunohistochemistry (IHC) 3+ or IHC 2+ confirmed by fluorescence in-situ hybridization (FISH).
- At least 1 but no more than 2 prior anti-HER2 based regimens including at least 1 regimen

containing Trastuzumab.
- At least one measurable lesion as defined by RECIST.
-ECOG Performance Status of <= 1
• Patients must have the following laboratory values:
Absolute Neutrophil Count >=1.5x109/L
Hemoglobin >= 9 g/dl = 5.58 mmol/l
Platelets >=100x109/L
Potassium, total calcium and phosphorus within normal limits
Magnesium above LLN
Adequate liver function defined as:
AST/SGOT and ALT/SGPT <= 1.5 x Upper Limit of Normal or
AST/SGOT and ALT/SGPT <= 2.5 x Upper Limit of Normal (ULN) if <= 5.0 x ULN if liver metastases are present
Serum bilirubin <= 1.5 x ULN
Serum albumin > 2.5 g/dl
Serum creatinine <= 1.5 x ULN or 24-hour clearance >= 50 ml/min.
• Negative serum pregnancy test.

Exclusion criteria

• Patients with known CNS metastasis which are symptomatic or require treatment for symptom control and/or growing.
• Prior treatment with any HSP90 or HDAC inhibitor.
• Systemic anti-cancer treatment prior to the first dose of AUY922 within the following time frames:
- Palliative radiotherapy: within 2 weeks
- Nitrosoureas, mitomycin: within 6 weeks
• Unresolved diarrhea >= CTCAE grade 1
• Reversible side effects of previous systemic anticancer therapy (except for alopecia) to less than CTCAE grade 2 prior to the first dose.
• Therapeutic doses of sodium warfarin (Coumadin).
• Acute or chronic liver or renal disease.
• Patients with other concurrent severe and/or uncontrolled medical conditions that could cause unacceptable safety risks or compromise compliance with the protocol.
• Known hypersensitivity to any study medication.
• Impaired cardiac function, including any one of the following:
- History (or family history) of long QT syndrome.
- Mean QTcF >= 450 msec on screening ECG.
- History of clinically manifested ischemic heart disease <= 6 months prior to study start.
- (LVEF <= 45%) by MUGA or ECHO.
- Clinically significant ECG abnormalities
- History or presence of atrial fibrillation, atrial flutter or ventricular arrhythmias including ventricular tachycardia or Torsades de Pointes.
- Other clinically significant heart disease (e.g. congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an

antihypertensive regimen).
- Clinically significant resting bradycardia (< 50 beats per minute).
- Current treatment with any medication which has a relative risk of prolonging the QTcF interval or inducing Torsades de Pointes
- Obligate use of a cardiac pacemaker.
• Another primary malignancy that is currently clinically significant or currently requires active intervention.

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):	28-02-2011
Enrollment:	3
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	29-11-2010
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-01-2011
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-07-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-08-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-09-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-09-2011
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	EUCTR2009-015628-27-NL
CCMO	NL34231.031.10