A multicenter, open-label, dose escalation, Phase I study of LJM716 administered intravenously in combination with trastuzumab in patients with HER2 overexpressing metastatic breast cancer or gastric cancer (CLJM716X2102)

Published: 27-07-2012
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Primary: To estimate the MTD or RDE and preferred dosing schedule of LJM716 when administered in combination with trastuzumab in patients with HER2 overexpressing metastatic breast cancer or gastric cancer.Secondary: Safety and tolerability, PK, PD...

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

Summary

ID

NL-OMON37081

Source
ToetsingOnline

Brief title
CLJM716X2102

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer or gastric cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: breast cancer, HER2, HER3, maagkanker

Outcome measures

Primary outcome

Incidence of dose-limiting toxicities.

Secondary outcome

Adverse events, PK parameters, post-treatment change from baseline in pHER3

levels in tumor and skin, PK/PD, Overall Response Rate, Progression Free

Survival and Duration of Response, antibodies against LJM716.

Study description

Background summary

HER3 plays a major role in ErbB driven tumors and is likely to limit the clinical effectiveness of ErbB targeted therapeutics. The HER2/HER3 signaling complex is a potent activator of PI3K signal transduction in HER2 amplified cancers. Consequently, dual inhibition of both HER2 and HER3 is expected to more effectively inhibit HER2/ HER3 driven signaling in HER2 over -expressing metastatic breast cancer (MBC) or gastric cancer. Furthermore, since inappropriate HER3 signaling is speculated to be a mechanism of trastuzumab resistance, effective HER3 inhibition may restore response to trastuzumab.

LJM716 is a fully-human monoclonal antibody that binds specifically to human HER3. A potential clinical use for LJM716 is in combination with trastuzumab to inhibit growth and/or initiate destruction of HER2 amplified cancer cells dependent upon the HER2/ HER3 signaling pathway. Preclinical in vitro and in vivo data indicates that LJM716 synergizes with trastuzumab in models of HER2

over-expressing cancer, highlighting the potential benefit of combining LJM716 with trastuzumab in the clinic.

The purpose of the dose escalation part of this study is to estimate the maximum tolerable dose (MTD) or a lower recommended dose for expansion (RDE) to use for further testing in patients with HER2 overexpressing MBC or gastic cancer who have progressed after up to 2 (gastric) or 3 (breastcancer) prior anti- HER2 based regimens. The expansion part will further characterize the safety and tolerability profile of the MTD/RDE of LJM716 in combination with trastuzumab.

Study objective

Primary: To estimate the MTD or RDE and preferred dosing schedule of LJM716 when administered in combination with trastuzumab in patients with HER2 overexpressing metastatic breast cancer or gastric cancer.
Secondary: Safety and tolerability, PK, PD in tumor tissue and skin, PK/PD, preliminary anti-tumor activity, anti-LJM716 antibodies.

Study design

Multicenter open-label, dose-escalation phase I study.
LJM716 will be administered weekly intravenously in combination with weekly I.V. trastuzumab 2 mg/kg.
Dose-escalation: at least 15 patients in subsequent cohorts. Starting dose LJM716 3 mg/kg. Until MTD or RDE.
When MTD/RDE has been reached: expansion part with at least 20 Breast cancer patients and 20 gastric cancer patient (LJM716 in MTD/RDE).
Cycle of 28 days. Treatment in principle until disease progression or unacceptable toxicity.

Intervention

Treatment with LJM716 in combination with trastuzumab.

Study burden and risks

Risk: Adverse events of study medication.
Burden: Study duration in principle until disease progression or unacceptable toxicity. Weekly visits for evaluation and I.V. administration of LJM716 and trastuzumab.
Extra visits during cycle 1 and 3: 7x in total.
Physical examination every 4 weeks.
Blood tests 4x during cycle 1 and 2, 2x during the following cycles. Amount: 125-150 mL during cycle 1-3, thereafter 15-25 ml per cycle.
PK blood draws (2 mL): 1 sample 4x during cycle 1 and 3, 1x during other

cycles. On day 1 of cycle 1 and 3: 4-5 samples in 2-8 h.
Urine test during screening and start cycle 1.
Pregnancy test every 4 weeks.
ECG every 4 weeks.
Echocardiography every 12 weeks.
CT/MRI every 8 weeks.
Skin biopsy: day 1 cycle 1-2.
Tumor biopsy day 1 cycle 1.

Optional:
* Remaining blood/tissue stored for 15 years for future testing.
* Skin biopsy at the start of cycle 3.
* Tumor biopsy at the start of cycle 3.

Contacts

Public
Novartis Pharma BV

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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

1. Patients (>18yr) with histologically or cytologically confirmed diagnosis of breast cancer, or patients with documented cytologically or histologically confirmed gastric adenocarcinoma or gastroesophageal junction adenocarcinoma. Patients must have metastatic or locally advanced-unresectable disease.
2. an Eastern Cooperative Oncology Group (ECOG) performance status of * 2.
3. At least one prior trastuzumab-containing regimen.
4. Metastatic breast cancer patients must have received a minimum of 1 and a maximum of 3 prior anti-HER2-based regimens, with documented progression on the most recent regimen which must contain trastuzumab or lapatinib
5. Gastric cancer patients must have received a minimum of 1 and a maximum of 2 prior anti-HER2-based regimens, with documented progression on the most recent regimen which must contain trastuzumab.
During the dose expansion part of the study:
6. Baseline tumor tissue must be obtained by biopsy
7. In dose expansion only, patients must have measurable disease as defined by RECIST v1.1 (at least one lesion * 10 mm in at least one dimension when assessed by CT or MRI, or a cutaneous lesion with clearly defined margins that measures * 10 mm in at least one dimension)

Exclusion criteria

* Untreated and/or symptomatic CNS metastasis (see protocol page 32 for exceptions).
* No archival tumor sample available or tumor sample readily obtainable.
* Prior anti-HER3 treatment.
* Patients who have received systemic antineoplastic therapy or any investigational therapy within 4-6 weeks (see protocol page 32 for details).
* Major surgery within 28 days before study treatment.
* Radiotherapy within 2 weeks prior to the first dose of study treatment except localized radiation therapy for symptomatic bone metastasis.
* Active infection requiring systemic therapy within 10 days before study treatment.
* Known history of HIV or active infection with hepatitis B or C virus.
* Impaired cardiac function (see protocol page 32-33 for details).
* Pregnancy, lactation, inadequate contraception.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-06-2013
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:	LJM716
Generic name:	LJM716

Ethics review

Approved WMO

Date:	27-07-2012
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	23-08-2012
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	19-12-2012
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-02-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-03-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	06-05-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-06-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-07-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-05-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	11-07-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-07-2014
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	EUCTR2011-004881-13-NL
ClinicalTrials.gov	NCT01602406
CCMO	NL40912.031.12