A multicenter, randomized, double blind, placebo controlled, phase II trial evaluating the safety and efficacy of TKI258 combined with fulvestrant, in postmenopausal patients with HER2- and HR+ breast cancer that have evidence of disease progression on or after prior endocrine therapy

Published: 15-03-2012
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Primary: treatment effect of TKI258 in combination with fulvestrant vs. fulvestrant plus placebo on Progression-Free Survival (voor for each of the 2 groups, namely FGF pathway amplified and regardless of FGF pathway amplification status).Secondary...

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

Summary

ID

NL-OMON39886

Source
ToetsingOnline

Brief title
TKI258+fulvestrant in postmenopausal HER2- and HR+ Breast Cancer patients

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
locally advanced breast cancer, metastatic breastcancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: advanced breast cancer, dovitinib, fulvestrant, phase II

Outcome measures

Primary outcome

Progression free survival.

Secondary outcome

Overall response rate (in both groups), duration of response, overall survival,

safety, quality of life, time to deterioration of ECOG performance status, PK.

Study description

Background summary

Although adjuvant endocrine therapy is an effective treatment for HR+ early breast cancer, metastatic relapse is still observed in up to 20% of the patients. The systemic treatment of advanced breast cancer is palliative. Therefore the use of minimally toxic endocrine therapies in HR+ patients is always preferred to the use of chemotherapy whenever reasonable. Several endocrine agents are now available and their sequential use is recommended, although most patients will eventually exhibit resistance to the individual, sequentially administered therapies. Overcoming this endocrine resistance remains thus critical to enhancing further the benefit of available compounds. Fulvestrant is approved for HR+ postmenopausal breast cancer patients after recurrence or progression on anti-estrogen therapy; however there is considerable evidence showing that fulvestrant is effective not only after failure on tamoxifen, but also after failure on aromatase inhibitors. Several

treatment guidelines include fulvestrant as a treatment option for HR+/HER2- patients with bone or soft tissue only or asymptomatic visceral disease.
TKI258, which inhibits FGFR1, may reverse resistance to endocrine therapy related to FGF-pathway amplification, and thus may improve outcomes when combined with fulvestrant. Moreover, TKI258 also has anti-angiogenic effect as it targets VEGF/PDGFR, possibly leading to additional benefits from the fulvestrant + TKI258 combination therapy.
The observed modest efficacy of currently available endocrine therapies with median survival not exceeding two years for 2nd line therapy, emphasizes the fact that treatment of advanced/metastatic HR+ breast cancer is an unmet medical need and new treatment options are needed.
The purpose of this phase II trial is to evaluate the safety and efficacy of treatment with TKI258 in combination with fulvestrant vs. fulvestrant plus placebo in postmenopausal women with HER2- and HR+, LA/mBC that has progressed on or after prior endocrine therapy (either anti-estrogen or aromatase inhibitor). In addition, this study will investigate whether there is a clinical benefit of TKI258 in combination with fulvestrant for patients with FGF-pathway amplification versus those without FGF-pathway amplification.

Study objective

Primary: treatment effect of TKI258 in combination with fulvestrant vs. fulvestrant plus placebo on Progression-Free Survival (voor for each of the 2 groups, namely FGF pathway amplified and regardless of FGF pathway amplification status).
Secondary: Overall response rate (in both groups), duration of response, overall survival, safety, quality of life, time to deterioration of ECOG performance status, PK.

Study design

Multicenter randomized double blind placebo controlled parallel group phase II study.
Essay of existing or fresh tumor tissue for FGF-amplification status.
Randomization (1:1) to treatment with:
* fulvestrant (500 mg i.m. per 4 weeks; 1e 3 injections with 2 weeks in between) + TKI258 (500 mg, 5 days on / 2 days off)
* fulvestrant (500 mg i.m. per 4 weeks; 1e 3 injections with 2 weeks in between) + Placebo (500 mg, 5 days on / 2 days off)
Event-driven.
Follow-up for survival.
Interim-analysis planned (see protocol section 4.2).
Independent DMC.
150 patients (90 FGF amplified, 60 FGF nonamplified).

Intervention

Treatment with TKI258 or placebo in combination with fulvestrant.

Study burden and risks

Risk: Adverse events of study medication.
Burden: Study duration in principle untill disease progression. Therafter optional follow-up for survival. 9 visits until treatment week 9, therafter once every 4 weeks.
I.m. injections 5 ml (2 injections per visit) once evry 4 weeks; 1st 3 injections 2 weeks in between.
Physical examination.
Blood draws 5-15 ml/occasion; in addition approx. 15 ml in total for PK.
Urine analysis.
ECG.
Echocardiography or MUGA-scan.
Tumor evaluations conform regular treatment.
Qustionnaires (QLQ-C30 and BR23).
Optional pharmacogenetic study (blood 6 ml).
Optional tumor biopsy 2x for biomarker study.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Written informed consent obtained prior to any study procedures, including screening assessments;Postmenopausal (* 18 years) women with HER2-, HR+ (ER+ and/or PgR+), (based on most recent analyzed biopsy)locally advanced or metastatic breast cancer not amenable to curative treatment by surgery or radiotherapy. Postmenopausal status is defined either by:;* Age * 55 years and one year or more of amenorrhea, or;* Age < 55 years and one year or more of amenorrhea in the absence of ovarian suppression, with an estradiol assay < 20 pg/mL, or;* Surgical menopause with bilateral oophorectomy. Note that it is not possible to assign menopause status to women who are receiving an LH-RH agonist or antagonist.;Breast cancer that has progressed on or after prior endocrine therapy, with radiological evidence of recurrence or progression as follows:;* While on, or within 12 months of end of adjuvant treatment with any endocrine therapy (e.g., tamoxifen, exemestane, anastrozole, letrozole, etc.);* While on, or within 1 month of end of any endocrine therapy treatment for LA/mBC;Presence of either one of the following:
* Measurable disease as per RECIST v1.1 (Appendix 1).
Notes:
* Measurable lesions include lytic or mixed (lytic + blastic) bone lesions with an identifiable soft tissue component that meets the measurability criteria per RECIST v1.1
* Lesions in previously irradiated areas should not be considered measurable, unless they have clearly progressed since the radiotherapy.
* At least one non-measurable lytic or mixed (lytic + blastic) bone lesion in the absence of measurable disease.
Notes:
* If bone lesions have been previously irradiated, at least one lesion must have clearly progressed since the radiotherapy by CT, MRI or x-ray for trial entry.
* Patients with only non-measurable lesions and no lytic or mixed (lytic and blastic) bone metastases (e.g. pleural effusion, ascites) are not eligible.;Eastern Cooperative Oncology Group (ECOG) performance status that is not greater than 2 (i.e., either 0 or 1 or 2).;Have the following laboratory values:;a. Absolute neutrophil count (ANC) * 1.5 x 109/L;b. Platelets * 100 x 109/L;c. Hemoglobin (Hgb) > 9 g/dL;d. Serum total bilirubin * 1.5 x ULN;e. ALT and AST * 3.0 x ULN (with or without liver metastases);f. Serum creatinine * 1.5 x ULN or Creatinine clearance by 24 hr urine is * 30 mL/min;OR: Serum creatinine >1.5 - 3 x ULN with calculated creatinine clearance (CrCl) is * 30 mL/min using the Cockroft-Gault equation, per the formula provided here: CrCl <= ([140-age (years)] x weight (kg) / [72 x serum Cr (mg/dL)]) x .85;Have completely recovered from major effects of prior radiotherapy and from any drug-related adverse events (AEs) associated with previous treatments, excluding alopecia and grade 1 peripheral neuropathy according to the National Cancer Institute CTCAE, v. 4.03;Provide archival (paraffin embedded tissue or a minimum of 20 unstained slides) or

fresh tumor tissues from which the FGF pathway status can be determined by an Novartis designated laboratory

Exclusion criteria

Current or past evidence of central nervous system (CNS) or leptomeningeal metastases. A brain CT scan or MRI is mandatory at screening prior to study entry;HER2 over expression as depicted by local laboratory IHC 3+ or FISH testing.;Previously treated with fulvestrant as a single agent or in combination with other therapies or FGFR inhibitors;Have any contraindication for being treated with fulvestrant 500 mg as described in the local approved prescribing information;Received more than one line of any prior hormonal therapy for LA/mBC. Any adjuvant/neo adjuvant therapy is allowed;Received any chemotherapy for LA/mBC;Concurrent use of any other approved or investigational anticancer agents, including hormonal agents;Having participated in a prior investigational study within 30 days prior to enrollment or * 5 half-lives of the investigational product, whichever is longer;Received the last administration of anti-cancer targeted small molecule therapy (e.g. sunitinib, sorafenib, pazopanib, axitinib, everolimus, temsirolimus, radaforolimus) * 2 weeks prior to starting study drug, or who have not recovered from the side effects of such therapy;Received the last administration of an anti-cancer monoclonal antibody, immunotherapy or chemotherapy (except nitrosoureas and mitomycin-C) * 4 weeks or last administration of hormonal therapy * 2 weeks prior to starting study drug or who have not recovered from the side effects of such therapy;Received the last administration of nitrosourea or mitomycin-C * 6 weeks prior to starting study drug, or who have not recovered from the side effects of such therapy;Received radiotherapy * 4 weeks prior to starting the study drug or who have not recovered from radiotherapy-related toxicities (palliative radiotherapy for bone lesions * 2 weeks prior to starting study drug is allowed);Undergone major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) * 4 weeks prior to starting study drug or who have not recovered from side effects of such surgery;With a history of pulmonary embolism (PE), or untreated deep venous thrombosis (DVT) * 6 months prior to starting study drug;Impaired cardiac function or clinically significant cardiac diseases, including any of the following:;* History or presence of serious uncontrolled ventricular arrhythmias.;* Clinically significant resting bradycardia (< 50 beats /minute);* LVEF assessed by 2-D echocardiogram (ECHO) < 50% or lower limit of normal (whichever is higher) or multiple gated acquisition scan (MUGA) < 45% or lower limit of normal (whichever is higher);* Any of the following within 6 months prior to starting study drug: myocardial infarction, severe/unstable angina, coronary artery bypass graft, congestive heart failure, cerebrovascular accident, transient ischemic attack;* Uncontrolled hypertension defined by a SBP * 160 mm Hg and/or DBP * 100 mm Hg, with or without anti-hypertensive medication(s). Initiation or adjustment of antihypertensive medication(s) is allowed prior to study entry;Currently receiving anti-platelet therapy of prasugrel or clopidogrel, or full dose anticoagulation treatment with therapeutic doses of warfarin. However, treatment with low doses of warfarin (e.g., * 2 mg/day) or locally accepted low doses of acetylsalicylic acid (up to 100 mg daily) to prevent cardiovascular events or strokes is allowed;Concurrent malignancy or malignancy within 3 years prior to study enrollment, with the exception of adequately treated basal cell carcinoma, squamous cell carcinoma or other non-melanomatous skin cancer, or in-situ carcinoma of the uterine

cervix;Bilateral diffuse lung lymphangitic carcinomatosis or other life-threatening visceral metastases requiring immediate cytotoxic therapy;Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of TKI258 (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or had gastric or small bowel resection);Cirrhosis of the liver, or known hepatitis B or C infection that is either acute or is considered chronic because the virus did not become undetectable (see page 44 protocol excl.criteria 20 voor details);Have Child-Pugh B or worse hepatic impairment;Known history of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory unless required by local regulations);Any concurrent severe and/or uncontrolled medical conditions which could compromise participation in the study or interfere with study results;Unwilling or unable to comply with the protocol

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-10-2012
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	dovitinib
Generic name:	dovitinib
Product type:	Medicine

Brand name:	Faslodex
Generic name:	fulvestrant
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	15-03-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-06-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-09-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-09-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-02-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	27-02-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO	

Date:	16-05-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	26-06-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	10-07-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	31-07-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	15-10-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	24-10-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	29-11-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	03-12-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-12-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-12-2013
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Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-07-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-11-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2011-001230-42-NL
ClinicalTrials.gov	NCT01528345
CCMO	NL39804.068.12