A phase III randomized, double blind placebo controlled study of BKM120 with fulvestrant, in postmenopausal women with hormone receptor-positive HER2-negative locally advanced or metastatic breast cancer which progressed on or after aromatase inhibitor treatment (CBKM120F2302)

Published: 07-08-2012
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Primary: To determine whether treatment with BKM120 plus fulvestrant prolongs PFS based on local investigator assessment compared to treatment with placebo plus fulvestrant for all patients regardless of PI3K pathway activation status (full...

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

Summary

ID

NL-OMON39514

Source
ToetsingOnline

Brief title
BKM120+Fulvestrant in HR+/Her- breast cancer patients

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: BKM120, breast cancer, fulvestrant, metastatic

Outcome measures

Primary outcome

Progression free survival.

Secondary outcome

Overall survival, Overall response rate, Clinical benefit rate, Safety, PK,

Quality of life.

Time to deterioration ECOG performance

Study description

Background summary

Therapies which interfere with the estrogen receptor (ER) functions such as tamoxifen have significantly contributed to mortality reduction in advanced breast cancer, but at best 50-60% of hormone receptor positive patients have a benefit from this therapy. Consequently, a number of other therapeutic options have been developed for the treatment of locally advanced or metastatic breast cancer (MBC) including aromatase inhibitors (AIs) that reduce peripheral estrogen synthesis and fulvestrant which is an ER antagonist.
There are currently no treatments specifically approved after recurrence or progression on an AI. Current clinical practice and treatment guidelines include fulvestrant and exemestane as available options.
A significant number of ER-positive HER2-negative breast cancer patients are

expected to have an activated PI3K pathway, and this pathway can play a critical role in inducing resistance to endocrine therapies. The PI3K signaling regulates diverse cellular functions, including cell proliferation, survival, translational regulation of protein synthesis, glucose metabolism, cell migration, and angiogenesis. PI3K signaling also serves a central role in the pathogenesis of numerous forms of neoplasia. Evidence suggests that the PI3K pathway may play a role in primary and/or acquired resistance to systemic antineoplastic therapy in MBC.
Evidence suggestes that PI3K pathway could be a critical therapeutic target for the treatment of patients with ER positive metastatic breast cancer. Hence, the pan-PI3K inhibitor BKM120 as a treatment option potentially addresses an unmet medical need in such patients. BKM120 is a potent and highly specific oral PI3K inhibitor.
A pan PI3K inhibitor in combination with an endocrine agent might present a benefit in advanced breast cancer patient population who is ER-positive, HER2-negative and refractory to AI. Promising pre-clinical and clinical activity has been observed with single agent BKM120 in breast cancer together with the combined effect with fulvestrant in the pre-clinical setting. The concept of combining a PI3K/AKT/mTOR pathway inhibitor treatment with an AI has also been supported in the clinical setting: promising improvements in terms of PFS have been observed recently with the combination of everolimus (mTORi) and exemestane compared to exemestane alone in MBC patients after prior endocrine therapy. Therefore the addition of BKM120 to fulvestrant may be an effective treatment in ER-positive HER2-negative MBC patients.
The purpose of this study is to determine whether treatment with BKM120 plus fulvestrant prolongs PFS compared to treatment with placebo plus fulvestrant in postmenopausal women with hormone receptor-positive HER2-negative locally advanced or MBC whose disease has progressed on or after AI for all patients regardless of PI3K pathway activation status and PI3K pathway activated sub-population.

Study objective

Primary: To determine whether treatment with BKM120 plus fulvestrant prolongs PFS based on local investigator assessment compared to treatment with placebo plus fulvestrant for all patients regardless of PI3K pathway activation status (full population) and for PI3K pathway activated sub-population.
Secondary: Overall survival, Overall response rate, Clinical benefit rate, Safety, PK, Quality of life.
Time to deterioration ECOG performance

Study design

Multicenter randomized double blind placebo controlled parallel group phase III study.
Essay of existing or fresh tumor tissue for PI3K activation status.

Randomization (1:1) to treatment with:
* Fulvestrant 500 mg intramuscularly every 4 weeks (plus after 1st 2 weeks) + BKM120 daily 100 mg orally.
* Fulvestrant 500 mg intramuscularly every 4 weeks (plus after 1st 2 weeks) + Placebo.
Until disease progression.
Follow-up for survival.
Interim-analysis planned (see protocol section 10.7, protocol page 127).
Independent DMC.
~842 patients (at least 334 with PI3K activation).

Intervention

Treatment with BKM120 or placebo in combination with fulvestrant.

Study burden and risks

Risk: Adverse events of study medication.
Burden: Study duration in principle until disease progression. Bi-weekly visits during 1st 3 courses of 4 weeks; 4-weekly thereafter. Follow-up for survival every 3 weeks.
Physical examination every 4 weeks.
Blood draws mostly 30-40 ml/week during treatment period.
PK blood sampling (2 ml/sample):
1st 68 patients:
* Day 1 course 2: 9 samples in 9 h.
* Next morning: 1 sample.
* Day 1 course 3: 1 sample.
Next 132 patients:
* Day 15 course 1: 3 samples in 6 uur. Optional after 9 h.
* Day 15 course 2 and day 1 course 3: 1 sample.
1st 200 patients:
* Day 1 course 1-5: 1 sample.

Urine sample during screening.
ECG every 4 weeks.
Echocardiography or MUGA-scan every 16 weeks.
Tumor evaluations as during regular treatment, every 8 weeks.
Questionnaires (2 on mood changes, 2 on quality of life) (nearly) every visit.
Tumor biopsy during screening (PI3K activation), only in case no tissue from prior biopsy available.
Optional tumor biopsy 1x for biomarker research.

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

* Women (* 18 years) with histologically confirmed ER-positive and/or PgR-positive and HER2-negative inoperable locally advanced or metastatic breast cancer.
* Known PI3K pathway status (Novartis central lab).
* Postmenopausal (see protocol page 47 for details).
* Refractory to aromatase inhibitors (see protocol page 47 for details).
* (Non) measurable disease as per RECIST 1.1 criteria.
* Patient has adequate bone marrow and organ function
* Fasting plasma glucose * 6.7 mmol/L, HbA1c * 8%.
* ECOG performance status 0-2.

Exclusion criteria

* Previous treatment with a PI3K inhibitor
* More than one chemotherapy line for metastatic disease (see protocol page 48 for details).
* Symptomatic CNS metastases.
* Wide field radiotherapy * 4 weeks or limited field radiation for palliation * 2 weeks prior to starting study drug.
* Chronic treatment (> 5 days) with corticosteroids or another immunosuppressive agent, as chronic administration of corticosteroids (> 5 days) can induce CYP3A4. Exceptions see protocol page 49.
* Coumarin derived anti-coagulant. Therapy with heparin, LMWH, or fondaparinux is allowed
* Drugs known to be moderate or strong inhibitors or inducers of isoenzyme CYP3A.
* Score * 12 on the PHQ-9 questionnaire.
* Response of *1, 2 or 3* to question number 9 on the PHQ-9 questionnaire regarding potential for suicidal thoughts or ideation (independent of the total score of the PHQ-9).
* GAD-7 mood scale score * 15.
* Documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of or current risk of doing harm to self or others.
* * CTCAE grade 3 anxiety.
* Active cardiac disease or a history of cardiac dysfunction. See protocol page 49-50 for details.

Study design

Design

Study phase:	3
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):	30-01-2013

Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BKM120
Generic name:	Unknown
Product type:	Medicine
Brand name:	Faslodex
Generic name:	fulvestrant
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-08-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-11-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-12-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-04-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	29-07-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-08-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-06-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-11-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-12-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-01-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-10-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	21-10-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-08-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-08-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-02-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-12-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2011-005524-17-NL
ClinicalTrials.gov	NCT01610284
CCMO	NL40888.091.12