A randomized pre-surgical pharmacodynamics study to assess the biological activity of LEE011 plus letrozole versus single agent letrozole in primary breast cancer (CLEE011A 2201)

Published: 30-08-2013
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Primary objective: To estimate the difference in anti-proliferative activity of LEE011 600 mg QD and LEE011 400 mg QD in combination with letrozole 2.5 mg QD vs single agent letrozole 2.5 mg QD as measured by changes in Ki-67 levels from baseline to...

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

Summary

ID

NL-OMON40407

Source
ToetsingOnline

Brief title
MONALEESA-1

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast 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, LEE011, letrozole, resectable

Outcome measures

Primary outcome

Changes in Ki-67 levels from baseline to day 15

Secondary outcome

ECG parameters (e.g. QTc), pharmacodynamic markers (e.g. pRB, p-pR and Cyclin

D1), pharmacokinetics.

Study description

Background summary

The purpose of this study is to characterize the difference in anti-proliferative activity of LEE011 600 mg QD and LEE011 400 mg QD in combination with letrozole 2.5 mg QD versus (vs) single agent letrozole 2.5 mg QD in postmenopausal women with HR+, HER2-negative, newly diagnosed, resectable breast cancer who received no prior antineoplastic therapy. The collection of data from the two experimental arms will help to better evaluate the safety and biological activity of treatment with LEE011 plus letrozole.
Hormone dependence is a fundamental hallmark of the majority of breast cancers, and tumor growth can be inhibited either by deprivation of circulating estrogens or by antagonising the effect of these hormones on their receptors. For postmenopausal women with breast cancer, aromatase inhibitors are an important treatment option. Letrozole is an aromatase inhibitor and several trials have demonstrated that in terms of cell cycle response, the main biologic effect occurs as early as two weeks after starting therapy. In breast cancer, genetic alterations such as amplifications and deletions occur at high frequencies, and are closely related to poor clinical outcome. One such region of amplification is with Cyclin D1, which plays a crucial role as a cell cycle regulator, promoting progression through the G1-S phase, following complex formation with CDK4/6 and phosphorylation of the retinoblastoma (rb) protein.

LEE011 is a highly soluble, potent, selective inhibitor of CDK4/6 kinases. LEE011 inhibits CDK4/6 specific phosphorylation of pRb, thereby halting cell cycle progression in the G1 phase. The preoperative setting is increasingly used to assess new drugs in shorter-term window-of-opportunity studies for early evidence of clinical efficacy. The establishment of Ki67 as an intermediate marker of treatment benefit and of long-term outcome, with endocrine drugs, provides the opportunity for new trial designs with Ki67 as the primary endpoint. Also, change in proliferation early on in the treatment was reported to mirror the recurrence-free survival in the adjuvant setting. The effects of letrozole treatment could be improved by combining it with a targeted therapy.
Recent clinical data indicate that inhibitors of CDK4/6 are active in advanced ER+ breast cancer. PD0332991 is a selective inhibitor of CDK4/6 that, when used in combination with letrozole, significantly prolonged progression free survival in postmenopausal women with ER+, Her2- advanced breast cancer in a randomized phase II trial.

Study objective

Primary objective: To estimate the difference in anti-proliferative activity of LEE011 600 mg QD and LEE011 400 mg QD in combination with letrozole 2.5 mg QD vs single agent letrozole 2.5 mg QD as measured by changes in Ki-67 levels from baseline to time day 15 as determined by cell cycle response rate. See protocol for further details.
Secondary objectives: Safety and tolerability, ECG effects, pharmacodynamic markers, pharmacokinetics.

Study design

Open-label randomized pre-surgical pharmacodynamics study. Approximately 120 patients.
Randomization (1:1:1) to treatment with
• LEE011 600 mg QD plus letrozole 2.5 mg QD
• LEE011 400 mg QD plus letrozole 2.5 mg QD
• letrozole 2.5 mg QD.
Treatment duration 14 days.
Surgery from day 15.

Intervention

Treatment with letrozole with or without LEE.

Study burden and risks

Risk: Adverse events of study medication.
Burden:

6 visits. Duration 2-8 h.
Fasting blood draws during 6 visits (max. 20 mL/visit). During 3 visits 4 blood draws for PK during 6 h.
ECG monitoring during 4 visits. During 3 visits 3-4 ECGs during 8 h.
2 times 24 h Holter monitoring.
2 times tumor biopsy (during screening and on day 15). In case there is tumor tissue available from prior biopsy or surgery, no biopsy is required during screening. On the day 15 a biopsy is required.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Female >= 18 years old, with newly diagnosed resectable grade II or grade III invasive breast cancer. No prior therapy for breast cancer.

• Postmenopausal. See protocol page 30 for details.
• Confirmed diagnosis of estrogen-receptor positive and/or progesterone receptor positive HER2 negative breast cancer.
• Patient has a grade II or grade III invasive breast cancer
• Adequate bone marrow and organ function as defined by laboratory values (See protocol page 30 for details.
• At least one breast lesion with a diameter of >=1.0 cm by ultrasound, mammography, CT-scan, or MRI.
• ECOG performance status 0 or 1.

Exclusion criteria

• Any prior therapy for breast cancer.
• Known history of HIV infection (testing not mandatory).
• Active cardiac disease or a history of cardiac dysfunction. See protocol page 31 for details.
• Systemic corticosteroids within 1 week prior to starting study drug. See protocol page 31 for exceptions.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	17-01-2014
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Femara
Generic name:	letrozole
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	LEE011
Generic name:	LEE011

Ethics review

Approved WMO Date:	30-08-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-12-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-06-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-06-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	17-07-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-08-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-10-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2013-002588-24-NL
ClinicalTrials.gov	NCT01919229
CCMO	NL45905.078.13