# An open-label, phase II, single-arm study of everolimus in combination with letrozole in the treatment of postmenopausal women with estrogen receptor positive metastatic breast cancer (CRAD001Y24135)

Published: 17-07-2013
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Primary: to estimate progression-free survival in patients treated with everolimus + letrozole in the first line setting.Secondary: overall response rate, clinical benefit rate, overall survival in the first line setting, progression free survival...

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

## Summary

### ID

NL-OMON41506

**Source**
ToetsingOnline

**Brief title**
CRAD001Y24135 (Bolero-4)

### 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:** breast cancer, everolimus, exemestane, letrozole

## Outcome measures

### Primary outcome

Progression free survival in the 1st line.

### Secondary outcome

Overall response rate, clinical benefit rate, overall survival in the 1st line setting, progression free survival and clinical benefit rate in the 2nd line setting, safety and tolerability. Severity and duration of stomatitis after therapeutic intervention.

# Study description

### Background summary

Preclinical studies suggest that in breast cancer cells with upregulated AKT signaling, sensitivity to hormonal therapy may be restored by treatment with everolimus or other mTOR inhibitors. mTOR inhibitors given in combination with aromatase inhibitors (AIs) in preclinical models result in synergistic inhibition of proliferation and induction of apoptosis. This preclinical work suggests that co-targeting the mTOR pathway and ER signaling may improve the effectiveness of endocrine therapy. In addition, endocrine-resistant breast cancer cells demonstrate hyperactivation of the PI3K/mTOR pathway, and treatment with mTOR inhibitors reverses this resistance.
Results from recent clinical studies support these findings. Combining everolimus with letrozole in the neoadjuvant setting induced higher response rates than with letrozole alone in postmenopausal women with ER-positive breast cancer. The combination of everolimus with tamoxifen was also associated with

prolonged PFS and improved overall survival (OS) in a phase II randomized study in patients progressing after prior AI treatment compared with tamoxifen alone. In a recent pivotal phase III, randomized, double-blind, placebo-controlled trial of everolimus plus exemestane versus exemestane plus placebo in ER positive postmenopausal women with locally advanced or metastatic disease refractory to letrozole or anastrozole, the addition of everolimus to exemestane prolonged median progression free survival from 3.2 to 7.8 months based on local assessment and 4.1 to 11 months based on central radiology review.
The above data support the activity of everolimus both in patients progressing after initial endocrine treatment and in patients who have not received prior treatment in the neoadjuvant setting. However, to date the efficacy of everolimus plus endocrine therapy has not been explored for first line therapy of patients with metastatic disease. Preclinical studies have shown that inhibition of the PI3K/mTOR pathway can prevent the emergence of hormone-independent cells, suggesting that early intervention with combined endocrine therapy and mTOR inhibition may prevent or delay endocrine resistance. It is also of interest to investigate whether continued mTOR inhibition with sequential endocrine therapy may provide clinical benefit. The proposed trial will assess the efficacy of everolimus plus letrozole in the first line treatment of patients with metastatic breast cancer and explore the efficacy of continued treatment with everolimus plus exemestane after initial progression.

**Study objective**

Primary: to estimate progression-free survival in patients treated with everolimus + letrozole in the first line setting.
Secondary: overall response rate, clinical benefit rate, overall survival in the first line setting, progression free survival and clinical benefit rate in the second line setting, safety and tolerability. Severity and duration of stomatitis after therapeutic intervention.

**Study design**

Multicenter open label non-comparative phase II study.
Study treatment: everolimus + letrozole until progression as first line therapy; option to continue with everolimus + exemestane as second line therapy until progression.
Follow-up for survival.
Patients developing stomatitis be randomized to take a 5% dexamethasone mouth rinse (3 times/day) or the best supportive care normally used at each participating center.
200 patients.

**Intervention**

Treatment with everolimus + letrozole and everolimus + exemestane. In case of stomatitis: treatment with dexamethasone mouth rinse or best supportive care.

### Study burden and risks

Risk: Adverse events of study medication.
Burden: Study duration in principle until disease progression (1st or 2nd line). Thereafter optional follow-up for survival. Visits every 4 weeks.
Physical examination every visit.
Blood draws every visit, 20-30 mL/occasion (screening 40 mL).
Urine analysis at screening.
ECG at screening.
Tumor evaluations as during regular treatment every 8 weeks
Questionnaire for stomatitis symptoms.

## Contacts

**Public**
Novartis

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**Scientific**
Novartis

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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

### Age

Adults (18-64 years)

Elderly (65 years and older)

### Inclusion criteria

• Postmenopausal (>= 18 years) women with locally advanced or metastatic breast cancer not amenable to curative treatment. Postmenopausal status definition: see protocol page 27 for details
• No prior treatment for metastatic breast cancer.
• Must have measurable disease (see protocol page 27) or non-measurable lytic or mixed (lytic + sclerotic) bone lesions.
• ECOG performance status 0-2.

### Exclusion criteria

• Prior hormonal or any other systemic therapy for metastatic breast cancer. Prior neoadjuvant or adjuvant NSAI (letrozole/anastrozole) therapy patients must have completed therapy at least 1 year prior to study enrollment.
• Previous treatment with mTOR inhibitors.
• HRT unless discontinued prior to enrollment.
• Evidence of CNS metastases.
• Chronic treatment with systemic immunosuppressive agents.
• Bilateral diffuse lymphangitic carcinomatosis.

## Study design

### Design

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

### Recruitment

NL
Recruitment status: Recruitment stopped

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|---|---|
| Start date (anticipated): | 16-06-2014 |
| Enrollment: | 4 |
| Type: | Actual |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Afinitor |
| Generic name: | everolimus |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | Aromasin |
| Generic name: | exemestane |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | dexamethasone 5% mouth rinse |
| Generic name: | dexamethasone 5% mouth rinse |
| Product type: | Medicine |
| Brand name: | Femara |
| Generic name: | letrozole |
| Registration: | Yes - NL intended use |

## Ethics review

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|---|---|
| Approved WMO Date: | 17-07-2013 |
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 09-09-2013 |
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 18-12-2013 |

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| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 06-01-2014 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 20-06-2014 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 09-07-2014 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 15-09-2014 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 19-09-2014 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 05-11-2015 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 12-11-2015 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

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| Approved WMO Date: | 09-12-2015 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 15-08-2016 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 04-10-2016 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 08-06-2017 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 12-07-2017 |
| 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 | EUCTR2012-003065-17-NL |
| ClinicalTrials.gov | NCT01698918 |
| CCMO | NL42199.068.13 |