# Phase I/II study with the combination of dacomitinib and PD-0325901 in metastatic KRAS mutation positive non-small cell lung cancer

Published: 27-09-2013
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Primary objectivesPhase I:To determine the recommended phase 2 dose (RP2D) of the dacomitinib-PD-0325901 combination in patients with KRASm NSCLC Phase II:To determine the progression free survival of the dacomitinib/PD-0325901 combination compared...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Metastases |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON47225

**Source**
ToetsingOnline

**Brief title**
Phase I/II study with dacomitinib + PD-0325901 in KRASm NSCLC

### Condition

- Metastases

**Synonym**
non-small cell lung cancer

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Antoni van Leeuwenhoek Ziekenhuis

**Source(s) of monetary or material Support:** Farmaceutische industrie,Pfizer

## Intervention

**Keyword:** cancer, Dacomitinib, KRAS, PD-0325901

## Outcome measures

### Primary outcome

Incidence of dose-limiting toxicities (DLTs)

Progression free survival (PFS) per RECIST version 1.1

### Secondary outcome

Incidence and severity of adverse events

Overall response rate, duration of response, time to response and overall

survival (phase II only)

Plasma concentrations of dacomitinib, PD-0325901 and relevant metabolites

Baseline molecular status of potential predictive markers of tumor response

(BRAF, HRAS, KRAS, NRAS, PTEN, PIK3CA, MAPK1, MAPK2, ARAF, c-MET, EGFR etc.)

Gene alteration (baseline, relapse) in tumor tissue

# Study description

### Background summary

In a pre-clinical study, treatment of KRAS mutant (KRASm) colorectal cancer (CRC) cell lines with a dual inhibitor of the human epidermal growth factor receptor 2 (ErbB2) and epidermal growth factor receptor (EGFR) kinases, in combination with a MEK-inhibitor resulted in synthetic lethality. MEK inhibition alone in these cells resulted in a strong feedback activation of ErbB receptors, causing primary resistance via subsequent activation of the phosphoinositide 3-kinase (PI3K) pathway. Concomitant treatment with a MEK inhibitor and a dual EGFR/ErbB2 inhibitor completely suppressed this feedback activation and resulted in cell death. Subsequently, the anti-tumor activity of this combination was confirmed in cell lines derived from KRASm non-small cell lung cancer (NSCLC) and pancreatic cancer. Because of the histology-independent activity of this concept and the similarities at a molecular level, it is plausible that this combination has the same effect on KRASm driven CRC, NSCLC and pancreatic cancer in patients. Hence, there is a strong rationale for combining dacomitinib, an EGFR/ErbB2/ErbB4 inhibitor, and PD-0325901, a MEK inhibitor, in patients with KRASm NSCLC.

**Study objective**

Primary objectives
Phase I:
To determine the recommended phase 2 dose (RP2D) of the dacomitinib-PD-0325901 combination in patients with KRASm NSCLC

Phase II:
To determine the progression free survival of the dacomitinib/PD-0325901 combination compared to standard of care therapy in patients with KRASm NSCLC

Secondary objectives
- To characterize the safety and tolerability of dacomitinib in combination with PD-0325901.

- To asses anti-tumor activity of dacomitinib in combination with PD-0325901.

- To determine the pharmacokinetic profile of dacomitinib and PD-0325901 in this combination.

- To explore genetic determinants of response to the dacomitinib-PD-0325901 combination

- To evaluate pharmacodynamic biomarkers

- To explore the potential mechanism of resistance to dacomitinib in combination with PD-0325901, as measured by gene alterations/expression profiles (baseline, relapse) in tumor tissue upon progression

## Study design

This is a phase I/II multi-center open-label proof of concept study, consisting of a two parts. Part A of this study is a pharmacological dose-finding study, designed to identify the recommended phase 2 dose (RP2D) of the combination regimen of dacomitinib plus PD-0325901 in patients with advanced KRASm NSCLC. Part B is randomized cross-over study to perform a randomized comparison of the combination of dacomitinib and PD-0325901 versus standard of care therapy in patients with advanced KRASm NSCLC

## Intervention

In phase I, all patients will be treated with dacomitinib + PD-0325901. Start doses are dacomitinib 30 mg once daily and PD-0325901 2 mg twice daily during the first 21 days of every 28 day cycle. Guided by toxicity of this treatment, the doses of both compounds can be escalated in new cohorts of patients to be able to determine the recommended phase II dose.

In phase II, patiens will be randomized to be treated with the recommended phase II dose of dacomitinib + PD-0325901 or with the standard of care second line treatment for NSCLC (docetaxel,). Upon progression after dacomitinib + PD-0325901, patients will cross-over to the comparator arm with standard of care therapy and vice versa.

## Study burden and risks

Possible risks with venapunctions is the development of a heamatoma at the place of venapunction. Possible risks of tumor biopsies are mild pain during anasthesia and the place where the biopsy is taken can become sensitive an mildly painful during a few days. With biopsies from pulmonary tissue, there is a slight risk of a pneumothorax.

Dacomitinib and PD-0325901 are non-registered drugs. Frequently occurring adverse events with monotherapy of these compounds include: diarrhea, nausea, fatigue and skin related adverse events.

Docetaxel is registered for the treatment of NSCLC. Frequently occurring adverse events are: stomatitis, diarrhea, nausea, cmiting, alopecia, skin related toxicities and hematological aberrations (anemia, leucopenia, thrombocytopenia)

# 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

1. Histological or cytological proof of metastatic NSCLC
2. Written documentation of a known pathogenic KRAS (exon 2, 3 or 4) mutation and PIK3CA wildtype (exon 9 and 20).
3. Age >< = 18 years.
4. Able and willing to give written informed consent.
5. WHO performance status of 0 or 1.
6. Able and willing to undergo blood sampling for PK and PD analysis.
7. Able and willing to undergo tumor biopsies prior to start, while on study treatment and upon progression of disease
8. All toxicities related to prior treatment should have resolved to CTCAE grade 1 or less (excluding alopecia)
9. Life expectancy >< = 3 months allowing adequate follow up of toxicity evaluation and

antitumor activity.
10. Measurable disease according to RECIST 1.1 criteria
11. Adequate organ system function

### Exclusion criteria

1. Any treatment with investigational drugs within 30 days prior to receiving the first dose of investigational treatment.
2. History of additional prior malignancies.
3. Symptomatic or untreated leptomeningeal disease.
4. Symptomatic brain metastasis.
5. Patients previously treated with any targeted drug combination known to interfere with EGFR, HER-2, HER-3, HER-4 or MAPK- and PI3K-pathway components, including inhibitors of PTEN, PI3K, AKT, mTOR, BRAF, MEK and ERK.
6. History of interstitial lung disease or pneumonitis
7. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral dacomitinib/PD-0325901 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).
8. Woman who are pregnant or breast feeding.
9. Unreliable contraceptive methods.
10. Radio-, immuno- or chemotherapy within the last 4 weeks prior to receiving the first dose of investigational treatment. Palliative radiation (1x 8Gy) is allowed.
11. Patients who have undergone any major surgery within the last 2 weeks prior to starting study drug or who would not have fully recovered from previous surgery.
12. Uncontrolled infectious disease or known Human Immunodeficiency Virus HIV-1 or HIV-2 type patients.
13. Patients with a known history of hepatitis B or C.

## Study design

### Design

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

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 02-04-2014 |
| Enrollment: | 132 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | niet van toepassing |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | niet van toepassing |
| Generic name: | dacomitinib |
| Product type: | Medicine |
| Brand name: | niet van toepassing |
| Generic name: | docetaxel |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | niet van toepassing |
| Generic name: | niet van toepassing |

# Ethics review

Approved WMO

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|---|---|
| Date: | 27-09-2013 |
| Application type: | First submission |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |

Approved WMO

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|---|---|
| Date: | 14-01-2014 |
| Application type: | First submission |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |

Approved WMO

| | |
|---|---|
| Date: | 14-03-2014 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |

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|---|---|
| Approved WMO Date: | 24-03-2014 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |

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|---|---|
| Approved WMO Date: | 02-04-2014 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |

| | |
|---|---|
| Approved WMO Date: | 24-04-2014 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |

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|---|---|
| Approved WMO Date: | 30-04-2014 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |

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|---|---|
| Approved WMO Date: | 15-07-2014 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |

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|---|---|
| Approved WMO Date: | 12-08-2014 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |

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|---|---|
| Approved WMO Date: | 09-10-2014 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van |

| | |
|---|---|
| | Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 13-10-2014 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 09-01-2015 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 15-01-2015 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 02-10-2015 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 06-10-2015 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 15-10-2015 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 19-10-2015 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 15-01-2016 |

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| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 27-01-2016 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 29-12-2016 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 11-01-2017 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 23-08-2017 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 27-10-2017 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 16-08-2018 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 21-08-2018 |
| 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 | EUCTR2013-003299-10-NL |
| CCMO | NL45985.031.13 |