# An exploratory study of the biologic effects of nivolumab and nivolumab in combination with ipilimumab treatment in subjects with advanced melanoma (unresectable or metastatic).

Published: 02-04-2014
Last updated: 20-04-2024

Primary Objective:To investigate the pharmacodynamic activity of nivolumab, and nivolumab in combination with ipilimumab in the tumor environment and the periphery on biomarker measures such as circulating T cell subsets (activated and memory T...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Skin neoplasms malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON41223

**Source**
ToetsingOnline

**Brief title**
Nivolumab and ipilimumab in advanced melanoma.

### Condition

- Skin neoplasms malignant and unspecified

**Synonym**
Advanced (unresectable or metastatic) melanoma

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Bristol-Myers Squibb
**Source(s) of monetary or material Support:** Pharmaceutical industry

## Intervention

**Keyword:** Advanced melanoma, Ipilimumab, Nivolumab

## Outcome measures

### Primary outcome

The primary objective relating to the pharmacodynamic activity of biomarkers will be measured by changes from baseline in activated and memory T cells, interferon inducible factors, and CD4 and CD8 T cell infiltration.

### Secondary outcome

The secondary objective relates to safety and tolerability of nivolumab and nivolumab in combination of ipilimumab in subjects with advanced melanoma. These will be measured by the following endpoints:

Safety and tolerability of nivolumab and nivolumab in combination with ipilimumab as measured by the incidence of adverse events (AEs), serious AEs, death, laboratory test abnormalities, and changes in vital signs;

Antitumor activity of nivolumab and nivolumab in combination with ipilimumab as measured by the objective response rate (ORR), duration of response, and progression free survival (PFS);

Immunogenicity of nivolumab and nivolumab in combination with ipilimumab as

measured by the frequency of baseline positive subjects and the frequency of

ADA positive subjects

Association between PD-L1 and clinical efficacy will be measured by PDL1

expression levels clinical activity (ORR, PFS)

# Study description

**Background summary**

Currently, the information regarding the mechanism of action of nivolumab in the clinic is limited. Initial data from CA209003 (Phase 1 nivolumab monotherapy) and CA209-006 (Phase 1 study combining nivolumab with a peptide vaccine) have suggested key differences in the action of nivolumab from ipilimumab on peripheral T cells. Specifically, nivolumab treatment does not appear to increase absolute lymphocyte counts, nor increase the frequency of activated CD4 and CD8 T cells. Both agents may be associated with an increase in tumor antigen specific T cells.

This study aims to evaluate the immunomodulatory pharmacodynamic effects of nivolumab and nivolumab in combination with ipilimumab in subjects with melanoma. The goal is to gain an understanding of the how nivolumab and nivolumab in combination with ipilimumab modulate the immune system to affect an anti-tumor response. This will be accomplished through assessments of tumor cells and tumor infiltrating lymphocytes and peripheral immunophenotyping, serum cytokine and antibody measurements, as well as measures of T cell function. The data collected and analyzed in this study will be utilized across the nivolumab program, in order to inform the development of nivolumab for other oncologic indications and for use in determining the best combination therapies.

**Study objective**

Primary Objective:
To investigate the pharmacodynamic activity of nivolumab, and nivolumab in combination with ipilimumab in the tumor environment and the periphery on biomarker measures such as circulating T cell subsets (activated and memory T cells populations by flow cytometry), interferon, interferon inducible factors and T cell (CD4 and CD8) infiltration in tumor biopsy sections from subjects with advanced melanoma.

Secondary Objectives:
• To further describe the safety and tolerability of nivolumab and nivolumab in combination with ipilimumab in subjects with advanced melanoma
• To further describe the preliminary anti-tumor activity of nivolumab and nivolumab in combination with ipilimumab in subjects with advanced melanoma
• To further investigate the immunogenicity of nivolumab and ipilimumab
• To assess the potential association between PD-L1 expression (by IHC) and clinical efficacy measures

Exploratory Objectives:
• To describe the safety, tolerability and efficacy of nivolumab and nivolumab in combination with ipilimumab in patients with brain metastases
• To investigate the potential association between selected biomarker measures in peripheral blood and tumor tissue with safety and clinical efficacy measures including overall survival (OS)
• To investigate the pharmacodynamic activity of nivolumab and nivolumab in combination with ipilimumab in the peripheral blood and tumor tissue as measured by other flow cytometry, immunohistochemistry and soluble factor assays
• To examine the effect of nivolumab and nivolumab in combination with ipilimumab on gene expression as measured by microarray technology and quantitative RT-PCR in peripheral blood and tumors tissue
• To study the effect of nivolumab and nivolumab in combination with ipilimumab on the tumor antigen specific T cell responsiveness in the peripheral blood
• To analyze blood samples for immune-related single nucleotide polymorphisms (SNPs) to support cross study analyses of the association of clinical activity and safety measures with SNPs
• To characterize pharmacokinetics of nivolumab and nivolumab in combination with ipilimumab, and explore the association between pharmacokinetics and selected pharmacodynamic markers in peripheral blood and tumor tissue
• To investigate other potential predictive biomarkers of clinical response to nivolumab or nivolumab in combination with ipilimumab by analyzing tumor specimens for proteins involved in regulating immune responses (e.g. PD-1 and PD-L2) and peripheral blood samples for immune cell populations, such as myeloid derived suppressor cells

**Study design**

This is an exploratory, open-label, multicenter study of nivolumab and nivolumab in combination with ipilimumab to evaluate the effect on cells of the immune system, primarily activated T cells, B cells and monocytes.

Approximately 160 subjects with advanced melanoma (unresectable or metastatic) will be treated in this study in four parts. The first part of this study will have two cohorts consisting of approximately 40 patients each: cohort 1 will consist of anti-CTLA4 therapy naive patients and cohort 2 will consist of patients who have progressed on an anti-CTLA-4 regimen. Cohorts 1 and 2 will be administered nivolumab at the 3mg/kg dose level every 2 weeks. In this part

of the study, patients will go through a screening period of no longer than 28 days and eligible patients will start the treatment period for a maximum of 2 years depending on their response. Nivolumab will be administered by IV infusion every 14 days in 56 day cycles (on days 1, 15, 29 and 43 of each cycle). This part of the study has now been completed and part 2, 3 and 4 will be added per protocol amendment 4.

In the second part of this study, approximately 20 anti-CTLA4 therapy naive patients with matched pre- and on-treatment tumor biopsies will be administered nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg alone every 2 weeks (Arm A). This part of the study is aimed at defining the optimal window for on-treatment biopsy with concurrent nivolumab and ipilimumab therapy. Two groups of approximately 10 patients each will be enrolled sequentially with the first group assigned to an on-treatment biopsy between Days 8 and 15 after the start of therapy and the second group assigned to an on-treatment biopsy between Days 22 and 29 after the start of therapy. Optimal biopsy timing will be defined as the biopsy window with the greatest pharmacodynamic increase in intratumoral activated T cells compared to the pre-treatment biopsy. The defined optimal on-treatment biopsy window will be used in the third part of this study.

In the third part of this study, approximately 30 anti-CTLA4 therapy naive patients will be randomized 2:1:1 and treated with one of the following:
• Arm A: nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W
• Arm B: nivolumab 3 mg/kg IV Q2W

In the fourth part of this study, approximately 20 anti-CTLA4 therapy naive patients with brain metastases will be randomized 1:1 and treated with one of the following:
• Arm D: nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W
• Arm E: nivolumab 3 mg/kg IV Q2W

In parts 2, 3 and 4 of this study, eligible subjects will receive study treatment for a maximum of two years.
Subsequent to a maximum of 2 years of treatment, each patient will continue follow-up consisting of office visits, lab work and tumor assessments for a maximum period of up to 100 days; follow-up office visits 1 and 2 (40-60 days and 101-120 days after the stop of study therapy).

All patients who have not completed 2 years of treatment will be followed for overall survival assessment by telephone contact every 3 months from the last follow-up office visit for the remainder of time left to complete 2 years from the first dose of treatment.

### Intervention

The medicinal interventions include nivolumab and nivolumab/ipilimumab combination therapy. All of these compounds will be supplied by the sponsor.

Nivolumab monotherapy (Arm B and E) is given every 2 weeks for a maximum of 2 years or until disease progression.

Nivolumab/ipilimumab combination therapy (Arm A and D) will be given as 4 doses every 3 weeks followed by nivolumab monotherapy for up to 2 years or until disease progression.
All study drug will be given intravenously.

### Study burden and risks

As part of the trial, patients will be expected to attend multiple clinic visits, where they will undergo physical examinations, vital sign measurements (including oxygen saturation levels), blood tests for safety assessment, pregnancy testing (for females of child bearing potential), and monitoring for adverse events. In addition, every 8 weeks, patients will undergo radiographic assessment of their tumours (by CT or MRI) until disease progression or treatment discontinuation whichever occurs later. Depending on the treatment arm, subjects will have pre-treatment and on-treatment biopsies performed. Blood will also be collected at certain visits for research purposes (PK, immunogenicity and biomarker studies). The frequency of visits and number of procedures carried out during this trial would typically be considered over and above standard of care. These procedures are conducted by medically trained professionals and every effort will be made to minimise any risks or discomfort to the patient. Treatment for cancer often has side effects, including some that are life threatening. Patients will be instructed when to contact their treating physicians if side effects occur and are given a patient card with detailed information.

## Contacts

**Public**
Bristol-Myers Squibb

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**Scientific**
Bristol-Myers Squibb

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NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

• Men and women >= 16 years of age
• Subjects must have ECOG performance status <= 1
• Subjects with advanced melanoma (unresectable or metastatic) who have received and either progressed or discontinued on no more than 3 prior treatment regimens or have refused standard therapy for treatment of metastatic melanoma.
• Subjects enrolled to Arm A, B, D and E (Part 2, 3 and 4) must never received anti-CTLA4 therapy
• Subjects must have histologic confirmation of advanced melanoma
• Subjects must have at least one measurable lesion at baseline by CT or MRI as per RECIST 1.1 criteria
• Subjects must have at least 1 tumor site that can be biopsied at acceptable clinical risk and must consent to pre- and on-treatment tumor biopsies
• Subjects enrolled to Arms D and E (Part 4)
o Must have at least one measurable index brain metastases > 0.5 cm and not larger than 3 cm that has not been previously irradiated
o Index brain lesions must not have sequela of prior therapy that would confound attribution of tumor response including edema or hemorrhage
o Must not have neurologic symptoms secondary to metastatic lesions
o Must not have received systemic corticosteroids within 14 days prior to initiation of study therapy

## Exclusion criteria

• Active brain metastases within 28 days of study enrollment (Arms A and B - Part 2 & 3) within 28 days of study enrollment
• Subjects with known metastases must have a repeat imaging brain scan within 28 days of randomization/registration. If progression in prior lesion(s) or new lesion (s) is/are detected on repeat brain scan, patients are exluded from study (Arms A en B - Part 2 & 3)
• History of carcinomatous meningitis (Arms D and E - Part 4)
• Radiation within 14 days prior to initiation of study therapy, and the radiation field cannot have included the index brain lesion (Arms D and E - Part 4)
• Subjects with other concomitant malignancies, except basal cell or squamous cell skin cancers, superficial bladder cancer, or carcinoma in situ of the cervix or breast, are excluded unless a complete remission was achieved at least 2 years prior to study entry and no additional therapy is required or anticipated to be required during the study period
• Subjects with active autoimmune disease, a history of known or suspected autoimmune disease or a history of a syndrome requiring systemic corticosteroids (> 10 mg daily prednisone equivalent), cytotoxic therapy or immunosuppressive medications with the exception of:
o Isolated vitiligo
o Resolved childhood atopy
o The history of positive ANA titer without associated symptoms or history of symptoms of an autoimmune disorder
o Controlled thyroid disorders
• Positive tests for HIV1/2 antibody or known acquired immunodeficiency syndrome (AIDS)
• History of any hepatitis
• Prior therapy with any antibody/drug that targets the T cell coregulatory proteins, including but not limited to, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40,and anti-CD40 antibodies

# Study design

## Design

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| 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

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 07-07-2014 |
| Enrollment: | 10 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Nivolumab |
| Generic name: | Nivolumab |
| Product type: | Medicine |
| Brand name: | Yervoy |
| Generic name: | Ipilimumab |
| Registration: | Yes - NL intended use |

# Ethics review

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|---|---|
| Approved WMO Date: | 02-04-2014 |
| Application type: | First submission |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 28-05-2014 |
| Application type: | First submission |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 15-07-2014 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 16-07-2014 |

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|---|---|
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 18-09-2014 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 26-09-2014 |
| 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: | 20-01-2015 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 02-04-2015 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 10-04-2015 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 22-05-2015 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |

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|---|---|
| Approved WMO Date: | 29-07-2015 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 13-08-2015 |
| 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: | 20-04-2016 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 22-04-2016 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 25-05-2016 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 23-08-2016 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 29-09-2016 |
| Application type: | Amendment |

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|---|---|
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 04-10-2016 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 27-10-2016 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 01-11-2016 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 16-12-2016 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 06-01-2017 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 10-01-2017 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 12-01-2017 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO | |

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|---|---|
| Date: | 19-04-2017 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 28-04-2017 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 13-09-2017 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 28-09-2017 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 29-11-2017 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 14-12-2017 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 19-01-2018 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 15-02-2018 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van |

# 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 | EUCTR2012-001840-23-NL |
| ClinicalTrials.gov | NCT01621490 |
| CCMO | NL47500.031.14 |

# Study results

Results posted: 02-11-2022

**First publication**
01-01-1900