A Phase 3, Randomized, Double-blind Study of Adjuvant Immunotherapy with Nivolumab versus Ipilimumab after Complete Resection of Stage IIIb/c or Stage IV Melanoma in Subjects who are at High Risk for Recurrence.

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The purpose of this study is to find out if treatment with Nivolumab monotherapy will improve recurrence-free survival (RFS) when compared to Ipilimumab monotherapy in subjects with high risk for recurrence, completely resected Stage III and Stage...

Ethical review	Approved WMO
Status	Completed
Health condition type	Skin neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON55473

Source
ToetsingOnline

Brief title
CA209-238

Condition

- Skin neoplasms malignant and unspecified

Synonym
Fully resected (Stage IIIb/c or Stage IV) melanoma & Adjuvant therapy

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Fully Resected, Ipilimumab, Melanoma, Nivolumab

Outcome measures

Primary outcome

Primary:

•To compare the efficacy, as measured by recurrence free survival (RFS), provided by nivolumab versus ipilimumab in subjects with completely resected Stage IIIb/c or Stage IV NED melanoma who are at high-risk for recurrence.

The Primary purpose of Revised Protocol 06 is to extend the collection of Overall Survival (OS) data for approximatively 5 additional years. In addition, data associated with the primary, secondary, and exploratory efficacy outcomes (eg. melanoma recurrence data, data on development of new primary melanomas and non-melanoma cancers, subsequent anti-cancer therapies) will continue to be collected on Case Report Forms. Study-drug-related serious adverse events (SAEs) will continue to be collected, whereas follow-up surveillance imaging assessments, plasma biomarker samples, and the EQ-5D questionnaire will no longer be required during extended follow-up.

Secondary outcome

Secondary:

•To compare the overall survival of nivolumab vs ipilimumab in subjects with completely resected Stage IIIb/c or Stage IV NED melanoma who are at high risk for recurrence;

•To assess the overall safety and tolerability of nivolumab and ipilimumab in subjects with completely resected Stage IIIb/c or Stage IV NED melanoma who are at high risk for recurrence;

•To evaluate whether PD-L1 expression is a predictive biomarker for RFS;

•To evaluate the Health Related Quality of Life (HRQoL) as assessed by European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30.

Study description

Background summary

CA209238 (CheckMate 238: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation
238) is a Phase 3 randomized, double-blind study of nivolumab versus ipilimumab in subjects with high risk for recurrence, completely resected Stage IIIb/c or Stage IV no evidence of disease (NED) melanoma.
Currently, there is no standard of care or no available treatment for this patient population following complete resection of their lesion(s) and who are at the highest risk of recurrence.
Furthermore, available clinical trials for various anti-cancer agents for later stage melanoma usually require measurable disease as an eligibility criteria. Thus, there is a remaining need to improve the outcome for fully resected Stage IV patients, and a willingness to improve on the benefit/risk ratio for Stage IIIb/c melanoma patients.
Interferon, pegylated interferon therapy or observation alone are the typical options for the Stage III patients who achieve a complete resection. Both interferon and peg-interferon are Food and Drug Administration (FDA) approved. Interferon is indicated for patients with malignant melanoma who are free of disease but at high risk for systemic recurrence, within 56 days of surgery. Peg-interferon is indicated for the adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy. In a meta-analysis of interferon trials, it was shown that interferon has an extremely modest survival benefit

with a toxicity profile that is significant.Given the unexceptional benefit and high toxicity profile in a patient population that is free of disease, it is controversial whether interferon can be considered standard of care for Stage III melanoma.
Ipilimumab 10 mg/kg has shown a recurrence-free survival (RFS) benefit in the adjuvant melanoma setting, and has proven a survival benefit in two Phase 3 randomized clinical trials in the advanced melanoma setting.
Nivolumab has shown a survival benefit in treatment naive patients with BRAF Wild Type
(WT), metastatic melanoma in a Phase 3, randomized clinical trial.
This study will allow for direct comparison of the clinical benefit, as measured by recurrence-free survival and overall survival, provided by ipilimumab and nivolumab.

Study objective

The purpose of this study is to find out if treatment with Nivolumab monotherapy will improve recurrence-free survival (RFS) when compared to Ipilimumab monotherapy in subjects with high risk for recurrence, completely resected Stage III and Stage IV NED melanoma. Ipilimumab is a drug which is approved for use in Europe for people with advanced Melanoma.

Study design

This is a Phase 3, randomized, double-blinded study of nivolumab versus ipilimumab in subjects (* 15 years) with complete resection Stage IIIb/c or Stage IV NED melanoma at high risk for recurrence.
Approximately 800 subjects will be randomized 1:1 and stratified by PD-L1 status (positive vs negative/indeterminate) and American Joint Committee on Cancer (AJCC) stage.
Dose reductions will not be allowed.
Subjects will be treated with one of the following:
Arm A: ipilimumab: 10 mg/kg IV q3 weeks for 4 doses, then q12 weeks starting at Week 24 with nivolumab placebo IV q2 weeks
Arm B: nivolumab 3mg/kg IV q2 weeks with ipilimumab placebo IV q3weeks for 4 doses, then q12 weeks starting at Week 24
All subjects will be treated until recurrence of disease, unacceptable toxicity, or subject withdrawal of consent with a maximum of 1 year of treatment.

Intervention

The medical interventions for this trial include both Nivolumab and Ipilimumab. All compounds will be supplied by the Sponsor Company with exception of the placebo. (Should be sourced by investigative sites if available and permitted by local regulations)

Solutions used as diluent or placebo (ie, 0.9% Sodium Chloride Injection or 5% Dextrose Injection)

Subjects will be treated with one of the following:
- Arm A: Ipilimumab 10 mg/kg IV every 3 weeks for 4 doses and then every 12 weeks starting at week 24+ Nivolumab placebo IV every 2 weeks

- Arm B: Nivolumab 3 mg/kg IV every 2 weeks + Ipilimumab placebo IV every 3 weeks for 4 doses then every 12 weeks starting at week 24

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. Subjects will be evaluated for presence or continued lack of tumor until distant recurrence beginning 12 weeks relative to the first dose of study treatment, and will continue to have surveillance assessment every 12 weeks for the first 12 months. From > 12 months to 24 months after randomization, efficacy assessments should be every 12 weeks. From > 24 months until year 5 after randomization, efficacy assessments should be performed every 6 months.

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. The procedures are carried out by trained medical 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. An independent Data
Monitoring Committee (DMC) will be utilised in this trial to ensure that the safety data is reviewed during the study.
New Immune system targeted therapy (immunotherapies) such as Nivolumab and Ipilimumab could potentially provide clinical benefit and improvement in the outcome for patients with this disease (disease improvement and improvement in survival).However, with all experimental drugs and clinical trials, there are known and unknown risks. Study medication and procedure related risks are outlined in the patient information sheet in detail to ensure the patients are fully informed before agreeing to take part in the study.

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

Key Inclusion Criteria:
• At least 15 years of age
Except: where local regulations and/or institutional policies do not allow for subjects < 18 years of age (pediatric population) to participate. For those sites, the eligible subject population is >= 18 years of age.
• All subjects must be either Stage IIIb/c or Stage IV American Joint Committee on Cancer (AJCC) Melanoma Staging (7th edition) and have histologically confirmed melanoma that is completely surgically resected in order to be eligible. Subjects must have been surgically rendered free of disease with negative margins on resected specimens. Please refer to Appendix 1 for description of AJCC 7th editions of TNM and staging.
If Stage III melanoma (whether Stage IIIb or IIIc) the subjects usually have clinically detectable lymph nodes that are confirmed as malignant on the pathology report and/or ulcerated primary lesions.
Subjects who are *N2c* classification with 2-3 metastatic nodes and in transit metastases/satellites without metastatic nodes, or, *N3*classification with any *T* and 4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes are eligible. The pathology report

for both Stage IIIb and IIIc must be reviewed, signed and dated by the investigator; this process will be confirmed during the IVRS randomization call. Clinically detectable lymph nodes are defined as:
(1) a palpable node (confirmed as malignant by pathology)
(2) a non-palpable but enlarged lymph node by CT scan (at least 15 mm in short axis) and confirmed as malignant by pathology., (3) a PET scan positive lymph node of any size confirmed by pathology
(4) evidence of pathologically macrometastatic disease in one or more lymph nodes defined by one or more foci of melanoma at least 1cm in diameter, If Stage IV melanoma, the pathology report confirming negative margins must be reviewed, dated, and signed by the investigator prior to randomization.
• Complete resection of Stage III disease that is documented on the surgical and pathology reports or complete resection of Stage IV disease with margins negative for disease that is documented on the pathology report.
• Complete resection must be performed within 12 weeks prior to randomization
• All subjects must have disease-free status documented by a complete physical examination and imaging studies
within 4 weeks prior to randomization. Imaging studies must include a CT scan of the neck, chest, abdomen, pelvis and all known sites of resected disease in the setting of Stage IIIb/c or Stage IV disease and brain magnetic resonance (MRI) or CT (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions).
• Tumor tissue from the resected site of disease must be provided for biomarker analyses. In order to be randomized, a subject must have a PD-L1 expression classification (positive, negative/or indeterminate) as determined by a central lab.

Exclusion criteria

Key Exclusion Criteria:
• History of ocular/uveal melanoma
• Subjects with active, known, or suspected autoimmune disease. Subjects with type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll.
• Subjects with previous non-melanoma malignancies are excluded unless a complete remission was achieved at least 3 years prior to study entry and no additional therapy is required or anticipated to be required during the study period (exceptions include but are not limited to, non-melanoma skin cancers; in situ bladder cancer, in situ gastric cancer, in situ colon cancers; in situ cervical cancers/dysplasia; or breast carcinoma in situ)
• Subjects with a condition requiring systemic treatment with either corticosteroids (>= 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of randomizationstudy drug

administration. Inhaled or topical steroids are permitted in the absence of active autoimmune disease.
• Prior therapy for melanoma except surgery for the melanoma lesion(s) and/or except for adjuvant radiation therapy (RT) after neurosurgical resection for central nervous system (CNS) lesions. and except for prior adjuvant interferon (see qualifier below). Specifically subjects who received prior therapy with interferon, anti- PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways) are not eligible.
i) Prior treatment with adjuvant interferon is allowed if completed >= 6 months prior to randomization.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	21-05-2015
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ipilimumab
Generic name:	Ipilimumab
Registration:	Yes - NL outside intended use

Product type:	Medicine
Brand name:	Nivolumab
Generic name:	Nivolumab

Ethics review

Approved WMO Date:	27-03-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-05-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-07-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-10-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-03-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-06-2016

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-08-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-12-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-01-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-04-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-05-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-05-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-10-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-10-2017

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-01-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-03-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-05-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-09-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-06-2019

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-07-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-10-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-11-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-04-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-05-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-09-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-09-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-02-2021

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-07-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-07-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-09-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-10-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-11-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-06-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-07-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-09-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-10-2022

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-11-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-01-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-08-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-10-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-11-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-05-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-07-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
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Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-10-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2014-002351-26-NL
CCMO	NL51400.042.15