A Phase 3, Randomized, Double-Blind Study of Adjuvant Immunotherapy with Nivolumab versus Placebo after Complete Resection of Stage IIB/C Melanoma (CA209-76K)

Published: 14-10-2019
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This study has been transitioned to CTIS with ID 2022-502354-14-00 check the CTIS register for the current data. Primary Objective:To measure the efficacy provided by nivolumab therapy on its own compared to placebo in participants who have had...

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

Summary

ID

NL-OMON52620

Source
ToetsingOnline

Brief title
CA209-76K

Condition

- Skin neoplasms malignant and unspecified
- Skin neoplasms malignant and unspecified

Synonym
melanoma, skin cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Melanoma, Nivolumab

Outcome measures

Primary outcome

Recurrence-free survival provided by nivolumab monotherapy versus placebo in participants with completely resected stage IIB/C melanoma with no evidence of disease who are at high risk for recurrence.

Secondary outcome

Overall survival (OS) provided by nivolumab monotherapy versus placebo in participants with completely resected stage IIB/C melanoma with no evidence of disease, who are at high risk for recurrence.

Adverse events, clinical laboratory values, vital signs, ECGs, or other safety biomarkers of of nivolumab monotherapy in participants with completely resected stage IIB/C melanoma with no evidence of disease.

Distant-metastases free survival (DFMS)

* Objective response rates

* Duration of treatment on next-line therapies

* Progression-free survival through next-line therapy (PFS2) is defined as the

time from randomization to recurrence/objective disease progression after the start of the next-line of systemic anti-cancer therapy, or to the start of a second next-line systemic therapy, or to death from any cause, whichever occurs first.

* End-of-next-line-treatment: To be used for situations where PFS2 cannot be reliably determined. Event defined as end or discontinuation of next-line treatment, second objective disease progression, or death from any cause, whichever occurs first.

Study description

Background summary

This is a multicentre, phase 3 study to test the effectiveness (how well the drug works), safety, and tolerability of an investigational drug called nivolumab. The study is for patients with early stage (IIB/C) melanoma (a type of skin cancer) who have had their tumours completely removed via surgery, but could possibly have their cancer return in the future.

Around 1000 participants over the age of 12 will be enrolled in this study, with approximately 30 patients participating from the Netherlands. Participants will be randomly assigned to one of two treatment arms to receive either nivolumab (66% chance) or placebo (33% chance). A placebo is a *dummy treatment* that looks like the real one but contains no active study drug.

Participants will receive study treatment for a maximum of 12 months, and will then enter an initial follow up phase of up to approximately 100 days, then an additional follow up period of up to approximately 5 years. The treatment will be blinded, i.e., neither the participants, nor the study doctor will know which treatment the participant is receiving. Participants who have their cancer return and meet certain criteria, may be able to receive nivolumab as part of this study.

Participants will undergo the following procedures during the study: imaging assessments (CT/MRI scans), physical examinations, provide urine blood samples for routine safety and study-specific testing and complete questionnaires relating to their health/quality of life. Participants will also need to have

adequate tumour sample from previous surgery or biopsy.

Nivolumab is a type of immunotherapy drug that is designed to boost the body*s own immune system to fight cancer cells. Nivolumab is approved for the treatment of certain types of cancer including the skin, kidney, blood, and lung, in multiple countries including the United States, the European Union, and Japan. Nivolumab is also approved for use in patients after complete surgical removal of melanoma that has spread to either the local/regional lymph nodes or other distant areas of the body. As nivolumab is not yet approved in early stage IIB/C melanoma, positive results from this research study may help to gain approval in the future.

This study is sponsored by Bristol-Myers Squibb.

Study objective

This study has been transitioned to CTIS with ID 2022-502354-14-00 check the CTIS register for the current data.

Primary Objective:
To measure the efficacy provided by nivolumab therapy on its own compared to placebo in participants who have had their stage IIB/C cancer completely removed, and have no evidence of disease, but are at high risk of recurrence.

Efficacy will be measured by recurrence-free survival (RFS). RFS is the length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer. In a clinical trial, measuring the RFS is one way to see how well a new treatment works.

Secondary and exploratory objectives:
To compare the overall survival (OS) provided by nivolumab monotherapy versus placebo in participants with completely resected stage IIB/C melanoma with no evidence of disease, who are at high risk for recurrence.

To assess safety and toxicity of nivolumab monotherapy in participants with completely resected stage IIB/C melanoma with no evidence of disease.

To evaluate distant metastases-free survival (DMFS).

To evaluate investigator-assessed outcomes on next-line therapies.

To evaluate freedom from relapse (FFR) defined asthe time from randomization to recurrence, with censoring of data for participants who had died from causes other than melanoma or treatment-related toxic effects.

To evaluate treatment-free interval (TFI) defined as the time from last dose of study treatment to the start of subsequent systemic therapy or the last known

date alive (for those who never received subsequent cancer therapy).

- To assess the participant*s cancer-related Quality of Life (QoL) using the EORTC QLQ-C30.
- To characterise participant perceptions of the bothersomeness of symptomatic AEs based on FACIT GP5 item.
- To assess the participant*s quality of life and overall health status using the EQ-5D-5L utility index and visual analog scale, respectively.

To explore potential association of biomarkers (e.g., PD-L1 expression) with clinical efficacy (RFS, DMFS, and OS) and/or incidence of adverse events of nivolumab by analyzing biomarker measures within the tumor microenvironment and periphery (eg, blood, serum, plasma, tumour tissue, and PBMCs) in comparison to clinical outcomes.
- To assess tumor mutational burden (TMB).
- To explore the role of circulating tumour DNA (ctDNA) to understand minimal residual disease (MRD) and disease recurrence predictability.

To characterise the pharmacokinetics (PK) and explore exposure-response relationships with respect to safety and efficacy.

- To characterise the immunogenicity of nivolumab.

- To assess the impact of SARS-CoV-2 serologic status on subjects receiving nivolumab and to support heath authority requests.

Study design

This is a phase 3, randomised, double-blind study of Adjuvant Immunotherapy with Nivolumab compared to placebo after complete resection of stage IIB/C melanoma in adults and paediatric participants over the age of 12.

Around 1000 participants over the age of 12 will be enrolled in this study. Participants will be randomly assigned to one of two treatment arms A and B to receive either nivolumab or placebo. A placebo is a *dummy treatment* that looks like the real one but contains no active study drug.

Arm A:
Adult dose:
Nivolumab 480 mg flat dose over approximately 30 minutes every 4 weeks (Q4W).

Paediatric dose:
• 12-17 years of age and weighing >=40 kgs: Nivolumab 480 mg IV Q4W.
• 12-17 years of age and weighing < 40 kgs: 6 mg/kg Q4W up to a maximum of 240 mg.
• For sites that do not prefer to use flat dosing: 6 mg/kg Q4W (maximum of 240

mg for weight < 40 kgs; maximum of 480 mg for weight >=40 kgs).
• All nivolumab infusions to be administered over approximately 30 minutes.

Arm B: Adult and paediatric dose
Nivolumab matched placebo (0.9% Sodium Chloride for Injection / 5% Dextrose for Injection) over approximately 30 minutes Q4W.

Participants have a 66% chance of being assigned to arm A to receive nivolumab, and a 33% of being assigned to arm B to receive placebo. Nivolumab or placebo are administered by intravenous (IV) infusion, meaning the drug is a solution given through a vein. The infusions can take about 30 minutes.

There are three parts to this study: screening period (about 1 month), a blinded treatment period (up to 1 year) and follow-up period (up to 5 years). During the blinded treatment period, neither the participant nor the study doctor will know which treatment the participant is receiving. In an emergency, it will be possible for the study doctor to know which treatment the participant is receiving.
In addition, participants who experience disease recurrence during study participation, either during study treatment or during follow-up, may be qualified to participate in an optional Open-Label (OL) treatment. *Open-label* means that both the participant and the study doctor will know which treatment the participant is receiving at all times.
The optional OL treatment will consist of nivolumab and will not have a placebo arm.

Treatment will continue until recurrence, unacceptability toxicity, withdrawal of consent, or a maximum of 12 months from the first dose of study treatment, whichever occurs first. Participants will continue to be followed for survival status for up to 5 years from the first dose of study treatment (either blinded or open-label treatment).

A Data Monitoring Committee (DMC) will be established and meet regularly during the study to ensure that subject safety is carefully monitored and to provide oversight regarding safety and efficacy considerations.

Intervention

Participants will be randomly assigned to one of two treatment arms A and B to receive either nivolumab or placebo. Allocation of study treatment will be via an interactive response technology, and will be double-blinded.

Arm A:
Adult dose:
Nivolumab 480 mg flat dose over approximately 30 minutes every 4 weeks (Q4W).

Paediatric dose:
• 12-17 years of age and weighing >=40 kgs: Nivolumab 480 mg IV Q4W.
• 12-17 years of age and weighing < 40 kgs: 6 mg/kg Q4W up to a maximum of 240 mg.
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Participants have a 66% chance of being assigned to arm A to receive nivolumab, and a 33% of being assigned to arm B to receive placebo. Nivolumab or placebo are administered by intravenous (IV) infusion, meaning the drug is a solution given through a vein. The infusions can take about 30 minutes.

Everyone taking part in this study will receive either the active treatment or placebo treatment for up to 12 months (1 year). Patients will have 13 visits during the treatment period. At each visit, patients will receive study medication (nivolumab or placebo). The first treatment will occur on Day 1 and subsequent visits will be every 4 weeks after that day.

At the end of the study treatment period, patients will enter the follow-up phase, which includes includes an initial follow up period with two visits in the first year and an additional follow up period with visits every 3 months for up to 5 years.

Study burden and risks

As part of the trial, patients will be asked to attend the hospital for frequent visits for the study procedures to be performed, where they will undergo physical examinations, vital sign measurements, blood tests for safety assessment, pregnancy testing (for females of child-bearing potential), and monitoring for adverse events. Timings of these visits will be based on the protocol schedule but will be mutually agreed with both the hospital staff and the patient to avoid patient and/or staff attending hospital at unsocial hours, and to minimise any inconvenience to the patient. Patients will be reimbursed for reasonable travel expenses incurred for attending study visits.

Patients will undergo radiographic surveillance assessments (CT and/or MRI scans) at screening (within 28 days of randomisation). Following randomisation, tumour assessments will be carried out every 26 weeks during the treatment period. In the open-label part of the study, the frequency of imaging assessments will be from every 12 weeks to every 26 weeks, depending on the status of disease.
The frequency of CT/MRI scans might be higher than the normal standard of care.

CT scans expose patients to radiation. MRI scans are not thought to be associated with any adverse effects on health.

Blood will also be collected at certain visits for research purposes (PK, immunogenicity and biomarker studies) as well as optional stool samples for microbiome analysis. 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.

A Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy considerations in Protocol CA20976K. Additionally, the DMC will provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of participants enrolled in the study. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab in both blinded treatment, and in the optional open-label nivolumab treatment after first recurrence portion of the trial. The DMC will act in an advisory capacity to BMS and will monitor participant safety and evaluate the available efficacy data for the study. The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study.

Contacts

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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

Participants must have been diagnosed with stage IIB/C cutaneous melanoma (AJCC Cancer Staging, 8th edition) and have histologically confirmed melanoma that is completely surgically resected with documented negative margins (per local standard) for disease on resected specimens.

All melanomas, except ocular and mucosal melanoma, regardless of primary site of disease will be allowed.

Complete resection must be performed within 12 weeks prior to randomization.

Participants must have had a negative sentinel lymph node biopsy.

Participants in whom a sentinel lymph node biopsy procedure could not be done or a sentinel lymph node was not detected are not eligible.

Participants must have disease-free status documented by a complete physical examination (within 14 days) and imaging studies within 4 weeks (28 days) prior to randomization.

Imaging studies must include CT scans of the chest/abdomen/pelvis or CT scan of the chest and MRI scans of the abdomen and pelvis, and all known sites of resected disease (lymph nodes >= 15 mm in short axis).

Participants with signs and symptoms consistent with brain metastases should have imaging studies done to rule out the presence of brain metastases.

Has not been previously treated for melanoma beyond complete surgical resection of the melanoma lesion.

Has recovered adequately from toxicity and/or complications from surgery prior to study start.

ECOG performance status of 0 or 1 at the time of enrollment.

Tumor tissue (minimum of 15 unstained slides or 1 FFPE block) from the resected

site of disease must be provided to the central lab prior to randomization.

Exclusion criteria

History of ocular and mucosal melanoma.

Participants with active, known, or suspected autoimmune disease.
Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

Prior malignancy active within the previous 3 years.
Except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization.
Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

Women who are pregnant or breastfeeding.

Participants with serious or uncontrolled medical disorders.

Use of an investigational agent or an investigational device within 28 days before administration of first dose of study drug

Treatment directed against the resected melanoma (e.g., chemotherapy, targeted agents, biotherapy, or limb perfusion) that is administered after the complete resection.

Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA-4 antibody, or agents that target IL-2 pathway any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

Treatment with botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended for general health support or to
treat the disease under study within 2 weeks prior to randomization/treatment.
Such medications are
permitted if they are used as supportive care.

Participants who have received a live/attenuated vaccine within 30 days of first treatment.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-03-2020
Enrollment:	25
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	14-10-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	12-02-2020
Application type:	First submission
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:	07-04-2020
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:	04-11-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-03-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-05-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-06-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-07-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	01-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-12-2022
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
EU-CTR	CTIS2022-502354-14-00
EudraCT	EUCTR2019-001230-34-NL
ClinicalTrials.gov	NCT04099251
CCMO	NL71182.042.19