Phase IIIb/IV, Randomized, Double Blinded, Study of Nivolumab 3 mg/kg in Combination with Ipilimumab 1 mg/kg vs Nivolumab 1 mg/kg in Combination with Ipilimumab 3 mg/kg in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma

Published: 04-04-2016
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Primary Objective:The primary objective is to compare the incidence of drug-related Grade 3 - 5 AEs of N3I1 to N1I3 in subjects with previously untreated, unresectable or metastatic melanoma.Secondary Objective:• To evaluate the ORR, as determined...

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

Summary

ID

NL-OMON47433

Source
ToetsingOnline

Brief title
CA209-511

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: Ipilimumab, Metastatic melanoma, Nivolumab, PET tracer

Outcome measures

Primary outcome

The primary endpoint of the study is the incidence of drug-related Grade 3 - 5 AE*s.

Secondary outcome

The first secondary endpoint is objective response rate (ORR) as determined by investigators. The ORR is defined as the number of subjects with a Best overall response (BOR) of complete response (CR) or Partial response (PR) divided by the number of treated subjects for each treatment group.

The second secondary endpoint is Progression free survival (PFS) defined as the time between the date of randomization and the first date of documented progression, as determined by the investigator, or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death.

The third secondary endpoint is Overall survival (OS) defined as the time between the date of randomization and the date of death due to any cause.

The fourth secondary objective (to evaluate HRQoL) will be measured by mean changes from baseline in the EORTC-QLQ-30 global health status/QoL composite scale and by mean changes from baseline in the remaining EORTC QLQ-30 scales.

Study description

Background summary

Considerable progress in the treatment of metastatic melanoma has been made in the past 5 years, with the approval of immune checkpoint-blocking antibodies. The safety and efficacy of individual checkpoint inhibition was first established with ipilimumab, a CTLA-4 blocker, in advanced melanoma. Subsequently, nivolumab, an anti-PD-1 antibody was shown to be safe and effective in multiple advanced tumor types including advanced melanoma. To determine if dual checkpoint blockage combining these 2 distinct agents could improve outcome, multiple trials were initiated in various advanced cancers. The most mature of these trials are in advanced melanoma patients. Published Phase 3 trials in advanced melanoma utilizing the combination of ipilimumab and nivolumab have reported an acceptable safety profile with improved efficacy over either monotherapy alone. However, the combination doses tested, specifically nivolumab 1 mg/kg + ipilimumab 3 mg/kg, did have increased toxicity compared to either single agent. Hence, if modifying the doses of the combination compares favorably, it may offer clinicians another option and patients the potential of improved outcome.
This study is the first double-blind randomized study to evaluate adverse events of nivolumab 3 mg/kg + ipilimumab 1 mg/kg (N3I1) vs nivolumab 1 mg/kg + ipilimumab 3 mg/kg (N1I3) combination therapy in patients with previously untreated, unresectable, or metastatic melanoma.

Study objective

Primary Objective:
The primary objective is to compare the incidence of drug-related Grade 3 - 5 AEs of N3I1 to N1I3 in subjects with previously untreated, unresectable or metastatic melanoma.
Secondary Objective:
• To evaluate the ORR, as determined by investigators, of N3I1 and N1I3 in subjects with untreated, unresectable or metastatic melanoma.
• To evaluate PFS of N3I1 and N1I3 in subjects with untreated, unresectable or metastatic melanoma.
• To assess OS of N3I1 and N1I3 in subjects with untreated, unresectable or metastatic melanoma.

• To evaluate Health Related Quality of Life (HRQoL) as assessed by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-30.

Exploratory Objectives:
• To evaluate duration of and time to objective response of nivolumab combined with ipilimumab in both N3I1 and N1I3 arms
• To assess the overall safety and tolerability of nivolumab combined with ipilimumab in both N3I1 and N1I3 arms
• To characterize the immunogenicity of nivolumab and ipilimumab when combined in both N3I1 and N1I3 arms
• To characterize the overall safety, tolerability, PK, immunogenicity of nivolumab combined with ipilimumab administered sequentially in both N3I1 and N1I3 arms.
• To analyze biomarkers, such as serum inflammatory factors and circulating T cell subsets, that are modulated by nivolumab+ipilimumab combination treatment and may be associated with clinical efficacy or incidence of adverse events in N3I1 and N1I3 arms
• To explore potential biomarkers associated with clinical efficacy (ORR, PFS and OS) by analyzing biomarker measures within the tumor microenvironment and periphery (eg, blood, serum, PBMCs) in comparison to clinical outcomes in both N3I1 and N1I3 arms
• To assess the effects of natural genetic variation (SNPs) in select genes including, but not limited to, PD-1, PD-L1, PD-L2, and CTLA-4 on clinical endpoints and/or on the incidence of adverse events in both N3I1 and N1I3 arms.
• To assess changes in health status using the EuroQoL EQ-5D.

Study design

This is a Phase IIIb/IV, randomized, double blinded, study of nivolumab 3 mg/kg in combination with ipilimumab
1 mg/kg versus nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in adult subjects with previously untreated, unresectable or metastatic melanoma.

Approximately 346 subjects will be randomized 1:1 in both arms and stratified by programmed cell death receptor-ligand 1 (PD-L1) expression and AJCC M stage. Record of BRAF V600 status must be provided (by local institutional standard), but will not be used for stratification.
The study will consist of 3 phases: screening, treatment, and follow-up.

On-treatment phase consists of Parts 1 and 2:
During Part 1, subjects will be treated every 3 weeks with the combination of nivolumab and ipilimumab for
4 cycles. A cycle will be defined as 3 weeks during Part 1.
During Part 2, subjects will be treated by nivolumab, flat dose 480 mg every four weeks, beginning 6 weeks after the last combination dose. A cycle will be defined as 4 weeks during Part 2.

Treatment will continue until progression or unacceptable toxicity in both arms.

The follow-Up Phase begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy). Patients will be followed for efficacy and overall survival. After completion of the first two follow-up visits, subjects will be followed every 3 months for survival.

Treatment with Nivolumab will be limited to 2 years maximum duration.

Intervention

The medicinal interventions include nivolumab/ipilimumab combination therapy. All of these compounds will be supplied by the sponsor. In part 1, Nivolumab/ipilimumab combination therapy (Arm A and B) will be given every 3 weeks for 4 doses. 6 weeks after the last combination dose subjects will enter the Part 2 phase of the study and will receive a flat dose 480 mg nivolumab IV every 4 weeks, until progression or unacceptable toxicity.

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, blood tests for safety assessment, pregnancy testing (for females of child bearing potential), and monitoring for adverse events. In addition patients will undergo radiographic assessment of their tumours (by CT or MRI) at the following times: 12 weeks following randomization, then every 8 weeks for the first 12 months from randomization. From the second year from randomization, tumor assessments should occur every 12 weeks until disease progression. Subjects will have pre-treatment and optional 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

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

-Adult subjects (>=18 years) with histologically confirmed unresectable Stage III or Stage IV Melanoma as per AJCC staging system.;-Eastern Cooperative Oncology Group (ECOG) performance status of 0-1;-No prior systemic anticancer therapy for unresectable or metastatic melanoma. Prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 6 weeks prior to date of first dose, and all related adverse events have either returned to baseline or stabilized.;-Measurable disease as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST) criteria;-Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. In order to be randomized, a subject must be classified as PD-L1 positive, PD-L1 negative, or PD-L1 indeterminate. If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase, subjects must consent to allow the acquisition of additional tumor tissue for performance of biomarker analyses.;-Known BRAF V600 mutation status as determined by local institutional standard or subject to consent to BRAF V600 mutation testing per local institutional standards during the Screening Period, the results of which must be reported within 3 months of randomization. All BRAF statuses (BRAF wild-type or BRAF 600 mutation positive) are eligible.

Exclusion criteria

- Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no evidence of progression via magnetic resonance imaging (MRI, except where contraindicated in which CT scan is acceptable) for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for high doses of systemic corticosteroids that could result in immunosuppression (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.;-Ocular melanoma;-Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enrol;ADDITIONAL FOR PET TRACER SUB STUDY:
Additional exclusion criteria for PET imaging. Subjects with the following condition(s) may be considered for participation in the study but will not undergo the PD-L1 PET imaging:
- Subjects who cannot tolerate an imaging procedure.
- Subjects who have received therapeutic radiopharmaceutical within 7 days prior to participation in
this study.
- Subjects with history of IV drug use which would prevent venous access for PET tracer injection.

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):	25-10-2017

Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	[18F]-BMS-986192
Generic name:	[18F]-BMS-986192
Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Yervoy
Generic name:	Ipilimumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	04-04-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	03-08-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	31-08-2016
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:	16-06-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	03-11-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-11-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-02-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	01-05-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-06-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	27-09-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-11-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-12-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-05-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-05-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	28-11-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-12-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-04-2020
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-05-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-02-2021
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-05-2021
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	08-04-2022
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	EUCTR2015-004920-67-NL
CCMO	NL56261.031.16

Study results

Date completed: 01-01-2022

Results posted: 25-05-2022

First publication
01-01-1900