A Single-Arm, Open-Label, Multicenter Clinical Trial with Nivolumab (BMS-936558) for Subjects with Histologically Confirmed Stage III (unresectable) or Stage IV Melanoma Progressing After Prior Treatment Containing an Anti-CTLA-4 Monoclonal Antibody

Published: 06-08-2014
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The primary objective of this trial are:- To determine the incidence of high-grade (CTCAE v4.0 Grade 3 orhigher), treatment related, select adverse events in patients withhistologically confirmed stage III (unresectable) or stage IV melanomaand...

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

Summary

ID

NL-OMON47051

Source
ToetsingOnline

Brief title
CA209172

Condition

- Skin neoplasms malignant and unspecified

Synonym
Malignant melanoma, skin cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Melanoma, Nivolumab, Solid Tumor

Outcome measures

Primary outcome

The primary objective of this trial are:

- To determine the incidence of high-grade (CTCAE v4.0 Grade 3 or higher), treatment related, select adverse events in patients with histologically confirmed stage III (unresectable) or stage IV melanoma and progression after prior treatment containing an anti-CTLA-4 monoclonal antibody.

Secondary outcome

The secondary objectives:

- To determine the incidence and to characterize the outcome of all highgrade (CTCAE v4.0 Grade 3 or higher), select adverse events in patients with histologically confirmed stage III (unresectable) or stage IV melanoma and progression after prior treatment containing an anti-CTLA-4 antibody, treated with nivolumab monotherapy.

- To estimate OS in all treated patients

- To estimate Investigator-assessed objective response rate (ORR)

Exploratory objectives: Refer to study protocol

Study description

Background summary

Bristol-Myers Squibb*s ongoing development program of nivolumab investigates the efficacy and safety of anti-PD-1 or nivolumab, a fully human IgG4 (kappa) isotype monoclonal antibody that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 and PD-L2 in advanced (unresectable and metastatic) melanoma patients.
There is currently an unmet medical need in patients with stage III (unresectable) or stage IV
metastatic melanoma who have progressed or recurred after prior treatment containing an anti-CTLA-4
monoclonal antibody.
The current is study is to determine the rate and frequency of high-grade (CTCAE v4.0 Grade 3 or higher), treatment-related, select
adverse events in subjects with histologically confirmed stage III (unresectable) or stage IV melanoma and progression post prior treatment containing an anti-CTLA-4 monoclonal antibody, treated with nivolumabat a dose of 3 mg/kg every two weeks for a maximum of 24 months.

Study objective

The primary objective of this trial are:
- To determine the incidence of high-grade (CTCAE v4.0 Grade 3 or higher), treatment related, select adverse events in patients with histologically confirmed stage III (unresectable) or stage IV melanoma and progression after prior treatment containing an anti-CTLA-4 monoclonal antibody.
The secondary objectives:
- To determine the incidence and to characterize the outcome of all highgrade (CTCAE v4.0 Grade 3 or higher), select adverse events in patients with histologically confirmed stage III (unresectable) or stage IV melanoma and progression after prior treatment containing an anti-CTLA-4 antibody, treated with nivolumab monotherapy.
- To estimate OS in all treated patients
- To estimate Investigator-assessed objective response rate (ORR)
Exploratory objectives: Refer to study protocol

Study design

The study will include subjects with histologically-confirmed stage III (unresecteable) or stage IV
advanced melanoma who have documented progression after treatment containing an anti-CTLA-4 monoclonal
antibody. Patients will be treated with 3 mg/kg of nivolumab IV every 2 weeks for a maximum of 24 months.
Since there is, to date, only limited information about safety of nivolumab in subjects presenting with Performance
Status 2, a separate prospective cohort of a maximum of 300 subjects with Performance Status 2 (Cohort 2) at initial
consultation will be enrolled to assess the safety and tolerability in this specific population. Clinical risk/benefit ratio
will be monitored by the Scientific Steering Committee and evaluated after treatment of n = 50 for at least 2 months
with consecutive decision about further enrollment.
Currently there is only little reliable data describing the percentage of subjects with melanoma progressing after prior
therapy containing treatment with an anti-CTLA-4 antibody, presenting with Performance Status 2 and eligible for
nivolumab treatment. It is estimated that a minimum of 20% to 30% of the potential study population will initially
present with PS2. This estimation of Cohort 2 results in a maximum of 300 subjects.

Intervention

3 mg/kg of nivolumab every 2 weeks

Treat until progression* or unacceptable toxicities. Safety is followed continuously. Subjects followed for ongoing drug-related AEs until resolution, symptoms return to baseline, AE deemed irreversible, lost to follow/death, disease progression,* or withdrawal of consent.
*Subjects may be treated beyond progression under protocol-defined circumstances.

Study burden and risks

Information can be found in section 7 and 8 of the informed consent form: 7) Which Risks / Possible Adverse Drug Reactions can the subject expect? Treatments for cancer often have side effects, including some that are life-threatening. There is the possibility of death occurring as a result of this treatment and its side effects. There may be additional unknown and potentially serious or life-threatening risks that could occur with the study drug. If the subject experiences severe side effects associated with the study drug, the doctor may prescribe medications to treat the side effect(s), future treatments may be delayed, or treatment may be stopped permanently. Any

significant new findings that develop during the course of the research and may relate to the subject*s willingness to continue participation will be provided to the subject. Nivolumab Nivolumab may cause one or more of the side effects listed below. This information is based on data from cancer subjects in other clinical trials with nivolumab. In addition, there may be side effects that are not yet known that may occur. The subject should tell the doctor or nurse right away about any possible side effects the subject experiences. The most common side effects of nivolumab are: • Fatigue • Rash • Itching • Diarrhea Some side effects that have been observed in patients taking Nivolumab are less common or even rare (but potentially serious). The subject can read more about these in addendum VIII of the informed consent form. Lung Inflammation (pneumonitis): It is possible that nivolumab may cause inflammation of the tissues of the lung. This adverse effect has been reported in patients treated with nivolumab. While many patients with x-ray or CT abnormalities have not developed any symptoms, some patients have developed mild to severe symptoms and in rare cases, death has occurred as a result of their lung inflammation. Signs and symptoms of lung inflammation may include difficulty breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, increased rate of breathing, fever, low blood oxygen levels, or fatigue. The study doctor and nurse will watch the subject closely for changes in the ability to breathe and for other signs or symptoms that might show the subject is developing this type of lung inflammation and will perform regular tests including physical exams, measurement of oxygen levels through non-invasive testing (i.e., pulse oximeter), blood tests, chest x-rays and/or CT scans. The subject should inform the study doctor or nurse at once if the subject experiences any of the following: • Any new or increased shortness of breath; • Any new or increased chest pain; • Any new or increased pain/difficulty while breathing; • Any new or increased cough or any significant change in type of cough; for example any new or increased mucous or blood in your cough; • Any change in the amount of oxygen the subject requires; • Any fever, fatigue, or other symptoms that occur at the same time as any changes to breathing or other lung symptoms. If the subject starts to develop symptoms, the study doctor will ask the subject to return to the clinic for additional tests, which could include a physical exam, measurement of oxygen levels, blood tests, chest x-rays, and/or CT scans. The subject will be monitored very closely for changes in your overall lung symptoms, monitoring may require hospitalization. The subject may require specific treatment in order to control pneumonitis. The subject may also be seen by a special doctor called a pulmonologist. Prolonged treatment with medicines that suppress inflammation, sometimes needed to manage the side effects of nivolumab treatment, may lower the body*s ability to fight off certain infections (i.e., opportunistic infections). These infections may require treatment with antibiotic or antifungal medications and may be fatal. Other side effects: Side effects associated with blood draws or use of an IV catheter may include infection, bruising, redness, discomfort, or bleeding at the needle puncture site. Sometimes patients have allergic reactions to the dyes used in CT scans. This is rare. It can involve itching or rash. In severe cases, the subject may have difficulty breathing and dangerous lowering of the

blood pressure. If subject knows that he/she has an allergy to the dye, or to iodine or shellfish, the subject should informthe study doctor and radiologist. These scans are also associated with exposure to varying amounts of radiation. There may be risks or side effects which are unknown at this time. The subject*s condition may not get better or may become worse while he/sheis in this study. Certain drugs may increase the severity of these side effects if taken during the study. The subject should ask his/her study doctor for a full list of prohibited medications. Risks to Reproduction, Unborn Babies and Nursing Infants The subject cannot participate in this study in case she is pregnant or breastfeeding. Participation in the study may have effects for the unborn child. Although the use of nivolumab in pregnant women has not been formally studied in clinical studies, there are indications from an animal study which suggest a potential risk to human pregnancy if there is continued treatment with nivolumab during pregnancy. These abnormal findings [e.g., late stage pregnancy loss in monkeys] occurred at doses that are 9 times greater than the human nivolumab dose of 3 mg/kg every 2 weeks used in this clinical trial. More about reproductive risks and pregnancy prevention can be found in the informed consent form in Addendum VIII. 8) What are the possible benefits and disadvantages of participation in the study Nivolumab may or may not lead to improvement of the subjects Melanoma. By taking part in this study, the result may add to the understanding of the subject*s condition. It may also be helpful for future patients. Disadvantages of participation are that the subject has to make additional visits to the clinic, follow the instructions for participation in the trial (section 3) and may experience side-effects (section 7).

Contacts

Public
Bristol-Myers Squibb

Chaussée de la Hulpe 185
Brussels 1170
BE
Scientific
Bristol-Myers Squibb

Chaussée de la Hulpe 185
Brussels 1170
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Signed Written Informed Consent
a) Patients must have signed and dated an IRB/IEC approved written informed consent
form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.
b) Patients must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, and other requirements of the study.
2. Target Population
a) Patients with progression after prior treatment containing an anti-CTLA-4 monoclonal antibody (Cohorts 1 and 2):
i) Patients with histologically confirmed malignant melanoma
ii) Eastern Cooperative Oncology Group (ECOG) PS:
(1) PS 0 to 1 (Cohort 1)
(2) PS 2 (Cohort 2; a minimum of 50 patients and a maximum of 185; clinical risk benefit ratio of Cohort 2 will be monitored by the Scientific Steering Committee)
iii) Previously treated unresectable stage III or stage IV melanoma as per the American Joint Committee on Cancer 2010 Guidelines36 regardless of BRAF mutation status
iv) Patients must have experienced disease progression or recurrence after prior treatment containing an anti-CTLA-4 monoclonal antibody
v) Prior treatment with chemotherapy, interferon (adjuvant setting), IL-2, BRAF/MEK inhibitors for patients with known BRAF mutations, MEK inhibitors for NRAS mutations, and cKIT inhibitor patients with known cKIT mutations are allowed
vi) Patients with CNS metastases:
(1) Patients are eligible if CNS metastases are treated and patients are

neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. In addition, patients must be either off corticosteroids or on a stable or decreasing dose 10 mg daily prednisone (or equivalent)
OR
(2) Patients are eligible if they have previously untreated CNS metastases and are
neurologically asymptomatic. In addition, patients must be either off corticosteroids or on a stable or decreasing dose of 10 mg daily prednisone (or equivalent)
OR
(3) Patients with additional leptomeningeal metastases are eligible if they are treated and neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment and have a life expectancy of at least 3 months. In addition, patients must be either off corticosteroids or on a stable or decrease dose 10 mg daily prednisone (or equivalent)
vii)Prior chemotherapy or immunotherapy (tumor vaccine, cytokine, or growth factor
given to control the cancer) must have been completed at least 4 weeks before study drug administration, and all adverse events have either returned to baseline or have been stabilized
viii) Prior palliative radiotherapy must have been completed at least 2 weeks prior to study drug administration
ix) Prior targeted therapy must have been completed at least 2 weeks prior to study
drug administration
x) Prior anti-CTLA-4 therapy must have been completed at least 4 weeks before study drug administration
xi) Prior radiotherapy or radiosurgery must have be completed at least 2 weeks prior
to the first dose of study drug
xii)Primary uveal (minimum of 30 patients) and mucosal melanoma are allowed
xiii) Screening laboratory values must meet the following criteria prior to commencement of treatment:
(1) WBCs >= 2000/µL
(2) Neutrophils >=1500/µL
(3) Platelets >= 100 x 10^3/µL
(4) Hemoglobin >= 9.0 g/dL
(5) Serum creatinine of <= 1.5 X ULN or creatinine clearance > 40 mL/minute (using Cockcroft/Gault formula)
(a) Female CrCl= [(140- age in years) x weight in kg x 0.85) ÷(72 x serum creatinine in mg/ dL)]
(b) Male CrCl= [(140- age in years) x weight in kg x 1.00) ÷(72 x serum creatinine in mg/ dL)]
(6) AST <= 3 X ULN

(7) ALT <= 3 X ULN
(8) Total bilirubin <= 1.5x ULN (except patients with Gilbert Syndrome who must have total bilirubin < 3.0 mg/dL)
xiv) Patients with a known history of Grades 3-4 adverse reactions during anti-CTLA-4 therapy will be allowed to participate if all toxicities have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of nivolumab (minimum of 40 patients)
xv) Patients must have evaluable disease by CT or MRI per RECIST 1.1 criteria (radiographic tumor assessment performed within 6 weeks of first dose of study drug)
or clinically apparent disease that the investigator can follow for response.
xvi) Patient Re-enrollment: This study permits the re-enrollment of a subject that has
discontinued the study as a pre-treatment failure (ie, subject has not been treated). If
re-enrolled, the subject must be re-consented.
For Other Inclusion Criteria please refer to Protocol

Exclusion criteria

1. Target Disease Exceptions
a) As of Amendment 02, this criterion is no longer applicable.
b) Patients with untreated, symptomatic CNS metastases are excluded
2. Medical History and Concurrent Diseases
a) As of Amendment 03, this criterion is not applicable.
b) Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.
c) Patients with previous malignancies (except non-melanoma skin cancers, in situ bladder cancer, gastric or colon cancers, cervical cancers/dysplasia or breast carcinoma in situ) 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
d) Any serious or uncontrolled medical disorder or active infection that, in the opinion of
the investigator, may increase the risk associated with study participation, study drug
administration, or would impair the ability of the patient to receive protocol therapy
e) Any treatment in a BMS-sponsored, interventional nivolumab trial or

ipilimumab trial
f) Known drug or alcohol abuse
3. Physical and Laboratory Test Findings
a) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic
infection
b) Positive test for HIV
4. Allergies and Adverse Drug Reaction
a) History of severe hypersensitivity reactions to other monoclonal antibodies
b) History of allergy or intolerance (unacceptable adverse event) to study drug components or Polysorbate-80-containing infusions.
c) As of Amendment 02, this criterion is no longer applicable.
5. Sex and Reproductive Status
a) WOCBP who are pregnant or breastfeeding
b) Women with a positive pregnancy test at enrollment or prior to administration of study medication
c) Women treated with ORAL hormone replacement therapy (HRT) are to be excluded
unless the oral replacement therapy was stopped by investigator's discretion at least 4
weeks prior to screening and was changed to other contraception method.
6. As of Amendment 02, this criterion is no longer applicable
7. Other Exclusion Criteria
a) Prisoners or subjects who are involuntarily incarcerated
b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness
Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-03-2015
Enrollment:	110
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nivolumab
Generic name:	nivolumab

Ethics review

Approved WMO Date:	06-08-2014
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-10-2014
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-12-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-12-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-01-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	22-01-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-07-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-08-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-09-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-09-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-10-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-10-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-05-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	10-10-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-10-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-05-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-05-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-10-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-10-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-02-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-02-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-02-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	14-08-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-12-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-12-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2014-001286-28-NL
ClinicalTrials.gov	NCT02156804
CCMO	NL50000.028.14

Study results