An open-label, single-arm, phase II, multicenter study to evaluate the efficacy of nivolumab in metastatic melanoma patients with symptomatic brain metastases.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON42782

Source
ToetsingOnline

Brief title
Nivolumab in symptomatic brain metastases of melanoma origin

Condition

- Metastases

Synonym
advanced melanoma, Metastatic melanoma

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Bristol-Myers Squibb

Intervention

Keyword: Brain metastases, Nivolumab

Outcome measures

Primary outcome

Main endpoint of this study is the best overall response rate (BORR) of all previously determined target lesions in the brain, which will be determined according to the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria.

Secondary outcome

Secondary efficacy endpoints that will be determined are: duration of response (DOR), time to development of new brain metastases in responding patients, progression-free survival, and overall survival.

Study description

Background summary

All previous clinical trials concerning anti-PD-1 or -PD-L1 treatment have excluded patients with symptomatic brain metastases. As a consequence the effect of nivolumab on symptomatic brain metastases is currently unknown and this treatment could therefore not be administered to these patients, which is a substantial part of the metastatic melanoma population. This phase 2 clinical trial will be the first to evaluate this intracranial effect in humans, with the aim to give these patients the possibility to be treated with anti-PD-1. Besides the objective response rate, long term benefits in this patient category will be evaluated by measuring survival in terms of progression free survival and overall survival. Furthermore safety and tolerability of administration of this drug in patients with symptomatic brain metastases will

be studied, as this is the first study for nivolumab in this specific patient category. As nivolumab shows response rates ~30% with a median time to response of 2.1 months this might be a very important treatment option in this target population with only very limited therapeutic options.

Study objective

Main objective of this phase 2 trial is to evaluate efficacy of nivolumab in symptomatic brain metastases of metastatic melanoma patients. In addition, the efficacy will be compared between patients with previously locally treated (e.g. surgery, stereotactic radiotherapy) and untreated brain metastases. Furthermore, difference in response between intra- and extra cranial metastases will be evaluated. Secondary efficacy parameters will be assessed in addition, including survival. Safety and tolerability of nivolumab will be assessed, because this is the first time nivolumab is administrated to patients with symptomatic brain metastases.

Study design

This study is an open label, single arm, phase II clinical trial of prospectively collected data evaluating efficacy and safety of nivolumab in metastatic melanoma patients with symptomatic brain metastases. It will be conducted in several WIN-O (Werkgroep Immunotherapie Nederland voor Oncologie) study centers in the Netherlands.

Intervention

All patients in this phase 2 trial will receive treatment with nivolumab, a monoclonal antibody against the PD1-receptor on T cells. Dosing will be based on patients* weight (3 mg/kg). It will be administered in an intravenous infusion every 2 weeks and for a maximum of 2 years.

Study burden and risks

Patients can benefit from participation in this study, by receiving a treatment which is possibly able to produce an intracranial effect and which could lead to a durable response. Nivolumab is currently not available outside of this trial.
Risks of participation in this trial and treatment with nivolumab are the appearance of known adverse events of this drug. Especially, pneumonitis, hepatitis, and thyroiditis are regularly occurring immune-related adverse events with substantial morbidity. In addition, intracranial side effects of nivolumab could occur like intracranial hemorrhage and responses could be accompanied by pseudoprogression of the tumor, most likely by immune cell invasion, which can raise the intracranial pressure and eventually could lead

to cerebral incarceration.

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

1.Subjects must sign informed consent prior to inclusion in this trial.
2.Subjects must be *18 years of age and competent to give informed consent.
3.Subjects must have a histologically confirmed diagnosis of stage IV melanoma.
4.Subjects must have clinical symptoms that are relatable to the intracranial lesions as assessed by a neurologist.
5.At least one new cerebral lesion on MRI, measurable by RANO-BM criteria (longest diameter * 10 mm and perpendicular diameter * 5 mm), must be present. Lesions with prior local treatment (i.e., SRT or surgical resection) are considered measurable if progression since the time of local treatment has been demonstrated. Leptomeningeal metastases are allowed, but

will not be labeled target lesions.
6.Treatment with BRAF-inhibitors during a maximum of eight weeks is allowed for patients with a positive BRAF-mutational status.
7.Subjects must be treatment-naive to nivolumab.
8.Subjects must score 0 * 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status.
9.Subjects must have adequate organ function as defined by the following laboratory values (determined within 28 days prior to randomization and registration):
*White blood cells (WBC) * 2000 /µL
*Absolute neutrophil count (ANC) * 1500 /µL
*Platelets * 100 x103 /µL
*Hemoglobin * 9 g/dL or * 5.6 mmol/L
*Serum creatinine * 1.5 times upper limit of normal (ULN) or creatinine clearance > 40 ml/min (using the Cockcroft-Gault formula)
*Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) * 3 times ULN
*Bilirubin * 1.5 times ULN (Except patient with Gilbert Syndrome, who can have total bilirubin * 3.0 mg/dL)
*LDH < 2 times ULN
10.Women of childbearing potential (WOCBP) should have a negative urine or serum pregnancy test within 24 hours prior to receiving the first administration of nivolumab. Women with non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for * 1 year.
11.WOCBP and men who are sexually active with WOCBP must agree to use appropriate method(s) of contraception.

Exclusion criteria

1.Subjects who have been treated with an anti-PD-1, anti-PD-L1, anti-PD-L2 antibody previously.
2.Subjects who have not recovered to Common Terminology Criteria for Adverse Events (CTCAE) v4.0 grade 1 or better from adverse events due to previous cancer therapy.
3.Evidence for an active autoimmune disease, known or suspected. Potential subjects diagnosed 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 enroll.
4.Subjects treated with corticosteroids in an increasing dosage 7 days prior to the first administration of nivolumab. (A stable or decreasing dosage of * 4 mg dexamethasone or equivalent is allowed. In addition, inhaled or topical steroids and adrenal replacement doses are permitted in the absence of active autoimmune disease.)
5.Known history of other (non-melanoma) malignancies, with the exception of non-melanoma skin cancers, in situ bladder cancer, gastric or colon cancers andcervical cancers/dysplasia or breast carcinoma in situ or patients in whom a complete remission was achieved at least 1 year prior to study entry and no additional therapy is required nor anticipated during the study period.
6.Known history of severe hypersensitivity reaction to treatment with monoclonal antibodies,

or known hypersensitivity to study drug components.
7.Acute or chronic hepatitis B or C infection, indicated by a positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody).
8.Known history of human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS).
9.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 impairs the ability of the patient to receive protocol therapy.
10.A known psychiatric or substance abuse disorder that could interfere with cancer therapy.
11.Women of childbearing potential with a positive serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of nivolumab.
12.Breastfeeding women.
13.Inability to comply with other requirements of the protocol.

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):	01-08-2016
Enrollment:	70
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:	16-09-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-01-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-05-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	23-05-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	29-08-2017
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	EUCTR2015-003199-56-NL
ClinicalTrials.gov	NCT02621515
CCMO	NL54395.042.15