A single arm phase II study of Nivolumab in patients with progressive malignant pleural mesothelioma: interim biopsy analysis to determine efficacy. Acronym: NivoMes Study

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Primary Objective* To determine the DCR (disease control rate) at 12 weeks of nivolumab monotherapy in patients with progressive MPM.Secondary Objectives* To determine the safety of nivolumab monotherapy in patients with progressive MPM* To...

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

Summary

ID

NL-OMON41970

Source
ToetsingOnline

Brief title
Nivolumab in patients with progressive MPM: NivoMes

Condition

- Mesotheliomas

Synonym
pleural mesothelioma

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Bristol-Myers Squibb,firma BMS

Intervention

Keyword: interim biopsy analysis, malignant pleural mesothelioma, Nivolumab, progressive

Outcome measures

Primary outcome

Primairy outcome: DCR at 12 weeks.

Secondary outcome

Secondary outcome: safety, DCR at 6 months, PFS, OS, TTP and ORR.

Exploratory outcome: the (immune) effects on tissue samples after exposure to

nivolumab.

Study description

Background summary

Malignant Pleural Mesothelioma (MPM) accounts for over 5000 deaths each year in Europe and is expected to increase to more than 9000 by the year 2018. The standard treatment for patients in good condition is combination chemotherapy including cisplatin and an anti-folate like pemetrexed or raltitrexed.
Although the disease is responsive in one third of the cases with this approach, most patients die from recurrent disease within 24 months. Other treatment combinations of neo-adjuvant chemotherapy followed by surgery and radiotherapy are under investigation but can only be offered to very fit patients.
No studies in second line or as maintenance have resulted in an improvement of overall survival. Many patients are referred to phase I units for experimental therapies. Therefore there is an unmet need to find new, promising treatments. Since immunological aspects play an important role in MPM it is a logical step to test the effects of the immune checkpoint inhibitors in this disease.

Study objective

Primary Objective
* To determine the DCR (disease control rate) at 12 weeks of nivolumab monotherapy in patients with progressive MPM.

Secondary Objectives
* To determine the safety of nivolumab monotherapy in patients with progressive MPM
* To determine the DCR at 6 months, PFS, OS and TTP of nivolumab monotherapy
* To determine the objective response rate (ORR) as defined by the modified RECIST criteria

Exploratory Objectives
* To determine the effects of nivolumab on tissue samples with respect to influx of immuno-modulating cells.
* To determine the PD-L1 status of tumors and other possible biomarkers and explore correlations between biomarkers and anti-tumor activity.

Study design

This is a prospective, single arm, phase II trial in previously treated patients with MPM who are considered candidates for immunotherapy and repeat thoracoscopies/transthoracic biopsies.

Intervention

Nivolumab will be administered 3 mg/kg q2 weeks by intravenous injection. Patients will undergo pre- and post-treatment thoracoscopies/biopsies.

Study burden and risks

An ECG and lung function test will be done at screening and 6 weeks. Nivolumab is given every 2 weeks, so physical examination and lab. tests will also be done every 2 weeks (this is more frequently than the standard care). Tumor assessment by CT-scan will be done every 6 weeks, so this is acoording to the standaard.
The risk of participation in this study is that there will be more blood taken than normally. There will also be 2 tumor biopsies done at the patient, what possibly may cause a bleeding, low blood pressure, redness, bruising, swelling and/or infection at the site of biopsy or other discomfort, such as fair feeling. The anesthetic can possibly give an allergic reaction. On the place where the biopsy has been done, a scar can arise. If a tumor in the lung is punctured a pneumothorax can occur. All the patients get Nivolumab and may experience specific side effects of Nivolumab.

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

* Patients with proven malignant pleural mesothelioma, who have progressive disease after chemotherapy in first or second line.
* Patients with histological or cytological diagnosed malignant pleural mesothelioma and age > 18 years.
* Progressive disease after at least one course of chemotherapy.
* Previous chemotherapy or experimental therapy * 4 weeks ago
* Medically suitable for limited surgical intervention (pleural biopsies up to limited pleurectomy).
* Not considered candidates for trimodality treatment (as part of a study).
* Measurable or evaluable disease (see tumor response assessment).
* Ability to understand the study and give signed informed consent prior to beginning of protocol specific procedures including the approval of a second thoracoscopy or transthoracic

pleural biopsy after the third course.
* Radiotherapy is allowed when this is given for palliation of painful sites, the interval is > 12 weeks and not all tumor is within the irradiation field.
* WHO performance status 0 or 1 (see appendix 1).
* Adequate organ function as evidenced by the following peripheral blood counts or serum chemistries at study entry:
* Hematology: Neutrophil count * 1.5 x 109/l, Platelets * 150 x 109/l, Hemoglobin * 6,0 mmol/l.
* Chemistry: Total serum bilirubin * 1.5 times within the upper limits of normal (ULN); ASAT and ALAT * 2.5 x ULN, AP (alkaline phosphatases) < 5x ULN (unless bone metastases are present in the absence of any liver disease).
* Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception to avoid pregnancy during treatment and for 23 weeks after the last dose of investigational drug.
* Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the first startdose of nivolumab.
* Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year during treatment and for a period of 31 weeks after the last dose of investigational drug.
* Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile) as well as azoospermic men do not require contraception.

Exclusion criteria

* Active uncontrolled infection, severe cardiac dysfunction or uncorrectable bleeding tendency.
* Inability to perform biopsies of the pleural lesions.
* Symptomatic peripheral neuropathy * grade 2 according to NCI CTC, version 4.0.
* Presence of symptomatic CNS metastases.
* Unstable peptic ulcer, unstable diabetes mellitus or other serious disabling condition.
* Impaired renal function: creatinine clearance less than 50ml/min.
* Concomitant administration to any other experimental drugs under investigation.
* Patients are excluded if they have an active, known or suspected autoimmune disease. Subjects are permitted to enroll if they have 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
* Patients are excluded if they have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immuno-suppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses < 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
* Patients are excluded if they have had prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-

stimulation or immune checkpoint pathways.

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):	16-07-2015
Enrollment:	33
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nivolumab
Generic name:	BMS-936558

Ethics review

Approved WMO Date:	15-01-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-07-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO Date:	16-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	27-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2014-003935-20-NL
CCMO	NL50577.031.14