Ipilimumab and Nivolumab in the Treatment of malignant Pleural Mesothelioma: a Phase II study

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

Summary

ID

NL-OMON46045

Source
ToetsingOnline

Brief title
Ipilimumab and Nivolumab in malignant Pleural Mesothelioma: INITIATE

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: Ipilimumab, malignant Pleural Mesothelioma, Nivolumab

Outcome measures

Primary outcome

The primary outcome of this study is the DCR

Secondary outcome

Secondary outcomes include PFS, OS, ORR, safety

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 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

The primary objective of the study is the disease control rate (DCR) at 12 weeks of the combination treatment of Nivolumab and Ipilimumab in patients with progressive MPM.
The secondary objectives are:
- to determine the safety profile of the combination treatment of Nivolumab plus Ipilimumab in patients with advanced MPM
- to determine DCR at 6 months, PFS and OS in the study population
- to determine objective response rate (ORR) as defined by modified RECIST criteria

- to determine the immunological changes of tumors before and after 6 weeks of treatment. This research will include PD-L1 status and other possible biomarkers.

Study design

This is a prospective, monocenter, single arm, phase II trial in 33 patients with unresectable MPM, who experience disease progression or recurrence after at least one previous line of platinum-based systemic treatment.

Intervention

Nivolumab will be administered at a fixed dose of 240 mg every 2 week. Nivolumab will be given in combination with ipilimumab on week 1, 7, 13 and 19 and will be administered prior to the infusion of ipilimumab. Ipilimumab will be administered at the dose of 1 mg/Kg.The patients will receive nivolumab monotherapy on week 3, 5, 9, 11, 15 and 17. From week 21 thereafter, Nivolumab will be then administered every 2 weeks for a maximum period of 2 year or until disease progression or unacceptable toxicity occurs.

Study burden and risks

An ECG will be done at screening. A pulmonary function test will be performed during screening, at 6 weeks and 12 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 according 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 Ipilimumab and may experience specific side effects of Nivolumab and Ipilimumab.

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

* Signed informed consent form
* Age * 18 years
* WHO-ECOG performance status 0 or 1
* Able to comply with the study protocol, in the investigator*s judgment
* Patients with histologically confirmed diagnosis of the recurrence of MPM. Any pleural MPM subtype is permitted for inclusion in the study
* Progressive disease after at least one prior systemic treatment with a platinum-based doublet (both cisplatin and carboplatin are allowed) for unresectable MPM. All prior cytotoxic toxicities must have resolved to grade * 1 prior to registration
* Measurable disease on CT scan, according to modified RECIST Criteria for Mesothelioma
* Life expectancy * 12 weeks
* Adequate hematologic and organ function, defined by the following laboratory results, obtained within 14 days prior to the first study treatment:
- Absolute neutrophil count (ANC) * 1500 cells/µL (without granulocyte colony-stimulating factor support within 2 weeks prior to Cycle 1, Day 1)
- WBC count * 3000 cells/µL
- Lymphocyte count * 250 cells/µL
- Platelet count * 100.000/µL (without transfusion within 2 weeks prior to Cycle 1, Day 1)
- Hemoglobin * 5.6 mmol/L
- Serum albumin * 25 gr/L

- AST, ALT and alkaline phosphatase * 2.5 x ULN, with the following exceptions: patients with documented liver or bone metastases: alkaline phosphatase * 5 x ULN
- Serum bilirubin * 1.5 x ULN
Patients with known Gilbert disease who have serum bilirubin level * 3 x ULN may be enrolled
- INR and aPTT * 1.5 x ULN
Patients receiving therapeutic anticoagulation should be on a stable dose
- Creatinine clearance * 45 mL/min
Cockcroft-Gault, Chronic Kidney Disease Epidemiology Collaboration or Modification of Diet in Renal Disease formulae may be used; 24-hour urine collection is not required
* Women who are not postmenopausal (* 12 months of non-therapy*induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus) and men with partners of childbearing potential, must agree to use adequate contraception (double barrier birth control) for the whole duration of study treatment and for 3 months after the last dose of therapy
* Women of childbearing potential must have a negative serum or urine pregnancy test within 48 hours prior the first dose of treatment

Exclusion criteria

* Medical or psychological impediment to comply with the protocol
* Patients with only peritoneal MPM
* Prior malignancy except adequately treated basal cell or squamous cell skin cancer, superficial or in-situ cancer of the bladder or other cancer for which the patient has been disease-free for at least five years
* Concomitant participation in another clinical trial (by the investigator*s judgement)
* Uncontrolled pleural/peritoneal effusion, pericardial effusion or ascites requiring recurrent drainage procedures (once monthly or more frequently)
* Uncontrolled tumor-related pain
Patients requiring pain medication must be on a stable regimen at study entry.
Symptomatic lesions amenable to palliative radiotherapy should be treated prior to enrolment.
* Previous treatment with any checkpoint inhibitor
* Pregnant or lactating women
* Patients with brain metastases
* History of or active autoimmune disease (e.g. pneumonitis; rheumatoid arthritis; severe form of psoriasis; uncontrolled type I diabetes or hypothyroidism)
* History of idiopathic pulmonary fibrosis (including pneumonitis) or unresolved drug-induced pneumonitis, organizing pneumonia, or active pneumonitis on screening chest CT scan
* History of relevant gastrointestinal disease, including, but not limited to, Crohn*s disease, ulcerative colitis, recurrent diverticulitis
* Prior allogenic bone marrow transplantation or prior solid organ transplantation
* History of HIV
* Patients with history of HBV infection are eligible if serological profile is compatible with past/resolved infection (defined as negative HBsAg test and positive antibody to HBV core antigen [anti-HBc] antibody test) and HBsAg test and HBV-DNA are both negative prior to Cycle 1, Day 1

* Patients with history of HCV infection must be screened for HCV-RNA PCR test prior to Cycle 1, Day 1, and are eligible if the test turns negative
* Other serious concomitant disease, including:
- Active tuberculosis
- Severe infections within 4 weeks prior to Cycle 1, Day 1
- Significant cardiovascular disease (NYHA class III or IV), myocardial infarction within the previous 6 months, unstable angina, or unstable arrhythmias
- Significant pulmonary (asthma or COPD) or hepatic disease or other illness considered by the investigator to constitute an unwarranted high risk for investigational treatment
* Major surgical procedures within 28 days prior to Cycle 1, Day 1
* Concurrent medications:
- Treatment with systemic immunosuppressive medications, including but not limited to prednisone (with specific exceptions; see below), cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti*tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1.
- The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.
- The use of systemic prednisone at the dosage of 10 mg/day or lower (or equivalent) is allowed.
* Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1

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):	15-12-2016
Enrollment:	33
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	22-08-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-08-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-01-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-01-2018
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	EUCTR2016-001599-31-NL
CCMO	NL57471.031.16