A Phase 2b, Randomized, Double-blind Study Comparing Tremelimumab to Placebo in Second- or Third-line Treatment of Subjects with Unresectable Pleural or Peritoneal Malignant Mesothelioma

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

Summary

ID

NL-OMON41613

Source
ToetsingOnline

Brief title
MedImmune Protocol D4880C00003 Tremelimumab

Condition

- Other condition

Synonym
Pleural or Peritoneal Mesothelioma

Health condition

inoperabel maligne mesothelioom

Research involving
Human

Sponsors and support

Primary sponsor: Medimmune LLC, subsidiary of AstraZeneca
Source(s) of monetary or material Support: Medimmune

Intervention

Keyword: mesothelioma, overall survival, Phase-2b, Tremelimumab

Outcome measures

Primary outcome

The primary endpoint is OS which is defined as the time from randomization

until death due to any cause.

Secondary outcome

The secondary efficacy endpoints include OS rate at 18 months, durable DCR,

PFS, PROs, ORR, and duration of response, based on modified Response Evaluation

Criteria in Solid Tumors (RECIST) for pleural mesothelioma and RECIST criteria

v1.1 for peritoneal mesothelioma.

The safety endpoints include adverse events (AEs) and serious adverse events

(SAEs) changes from baseline in clinical laboratory evaluations,

electrocardiograms (ECGs), and vital signs. Adverse events and SAEs will be

assessed for severity and relationship to investigational product.

The immunogenic potential of tremelimumab will be analyzed and the

pharmacokinetics of tremelimumab will be assessed.

Study description

Background summary

Patients with pleural or peritoneal malignant mesothelioma who fail first-line treatment have a significant unmet medical need given their poor prognosis, lack of any approved agent in this disease setting, and absence of a clinically meaningful OS benefit with existing salvage regimens. Mesothelioma resulting from asbestos exposure may have an immune-mediated component and so an agent such as tremelimumab that blocks CTLA-4 may lead to enhanced T cell immune function and antitumor activity.

The research hypothesis is that in subjects with unresectable pleural or peritoneal malignant mesothelioma receiving best supportive care, tremelimumab will reduce the risk of death by approximately 29% (hazard ratio = 0.71) over placebo while maintaining an acceptable safety profile. A reduction in the risk of death by 29% will be both statistically significant and clinically meaningful, as there are no available therapies that offer an OS benefit in second- or third-line pleural or peritoneal malignant mesothelioma.

Study objective

The primary objective is to compare the overall survival (OS) between the 2 treatment arms (tremelimumab and placebo) in subjects with unresectable malignant mesothelioma.

Secondary objectives are:
- to estimate and compare OS rate at 18 months between the 2 treatment arms;
- to estimate and compare durable disease-control rate (DCR) , progression-free survival (PFS), overall response rate (ORR) and duration of response between the 2 treatment arms,
- to evaluate the effect of tremelimumab on patient-reported outcomes (PROs),including disease-related symptoms, pain symptoms, and time to deteriorationof diseae-related symptoms
- to describe the safety and tolerability of tremelimumab in treated subjects,
- to evaluate the immunogenicity of tremelimumab in treated subjects;
- and to describe the pharmacokinetics (PK) of tremelimumab in treated subjects.

Exploratory objectives are:
* To estimate and compare durable DCR, PFS, ORR, and duration of response based on immune related response criteria (irRC) between the 2 treatment arms;
* To examine health-related QoL, disease-related symptoms, pain, and health status in subjects with durable clinical activity;
* To examine biomarkers and their association with tremelimumab treatment and

clinical outcome.

Study design

This is a Phase 2b, randomized, double-blind, placebo-controlled study in adults with unresectable pleural or peritoneal malignant mesothelioma who have progressed after previous receipt of 1 or 2 prior systemic treatment regimens that included pemetrexed (or other anti-folate) in combination with a platinum agent. For subjects in whom pemetrexed was contraindicated or not tolerated or not an approved therapy (eg, peritoneal mesothelioma), prior therapy with a first-line platinum-based regimen is required. Though the number of subjects not receiving prior pemetrexed is expected to be small, the proportion of such subjects enrolled in the study will be capped at 20%. Subjects will be randomized in a 2:1 ratio to receive either tremelimumab or placebo. Randomization will be stratified by the European Organization for Research and Treatment of Cancer (EORTC) status (low-risk vs high-risk), line of therapy (second vs third), and anatomical site (pleural vs peritoneal). Approximately 564subjects will be enrolled at approximately 180 study centers in multiple countries.

If at the time of the second interim analysis or at the time of final analysis, the study demonstrates evidence of clinical benefit with a favorable benefit-risk profile, subjects receiving placebo will be given the option to *cross-in* to receive tremelimumab treatment (subject to a decision by the Sponsor in discussion with the IDMC). See Appendix 8 in the protocol for details. Additionally, subjects on the tremelimumab arm who are receiving clinical benefit at the time of the interim or final analyses can continue to receive treatment with tremelimumab.

Intervention

Tremelimumab is to be administered as an intravenous (IV) solution of 10 mg/kg at a rate of 250 mL/hr. Subjects will receive one dose of investigational product every 4 weeks (Q4W) for 6 doses, followed by doses every 12 weeks (Q12W) unless permanent discontinuation criteria are met.

Study burden and risks

During the trial the patient performs 18 visits to the hospital. During these visits physical examination, vital signs will be measured and blood will be collected, no more than 50 mL per visit. Questionnaires for pain, lung disease (LCSS) and general health (EQ-5D) will be completed as well as ECGs . CT or MRI is done at screening and visit 5 and every 3 months or earlier if clinically indicated by the investigator. Also pulse oximetry will be measured at each visit
The study medication may cause some side effects. Some of these side effects

could be inflammatory events. These events are caused by the activation of the body*s immune system by tremelimumab and cause inflammation in different body organs. The most commonly affected organs are gastrointestinal tract, skin, liver, and endocrine system.

The most frequently reported adverse events (all grades of severity: mild to severe) in subjects receiving tremelimumab as a single agent/monotherapy included the following in decreasing order of frequency: diarrhea (in approx 1 out of 2 subjects), fatigue, nausea, rash in approx 1 out of 3 subjects), itchiness, decreased appetite, vomiting (in approx 1 out of 4 subjects), fever,cough, constipation, abdominal pain, headache, difficulty of breathing (in approx 1 out of 3-8 subjects), and decreased weight (in approx 1 out of 10 subjects). Of these events, diarrhea, rash and itchiness) have an established association with the administration of tremelimumab.
Approximately half of the subjects experienced adverse events that were severe .The most frequent of these severe adverse events reported were (in decreasing order of frequency): diarrhea (in approx 1 out of 8 subjects), fatigue (in approx 1 out of 20 subjects), inflammation of the large intestine (colitis), disease progression, difficulty of breathing, dehydration/nausea/vomiting, abdominal pain, decreased appetite, and body weakness (in approx 1 out of 30-50 subjects).
The most frequent treatment-related adverse events (in more than 1 out of 20 subjects) were diarrhea, rash, itchiness, fatigue, nausea, vomiting, decreased appetite, headache, fever, abdominal pain and inflammation of the large intestine (colitis).

In addition you may experience:
- Decreased blood platelet count with symptoms such as unexpected bruising, bleeding from the nose or gums, blood in vomit or stools, or red spots under the skin
- Inflammation of the pancreas (also known as pancreatitis) with symptoms such as abdominal pain, nausea, vomiting and tenderness when touching the abdomen or laboratory abnormality
- Inflammation of the liver with symptoms such as abdominal swelling, distention or bloating, diarrhea, discolored urine and stool, loss of appetite, tiredness and lethargy, nausea with or without vomiting, yellowing of the skin and whites of the eyes (jaundice)
- Hormonal secreting glands: symptoms can be non-specific and vary depending on cause, and can include, but not limited to, headaches, nausea, vomiting, fatigue, dizziness, weakness, tiredness, mood alterations, poor appetite, weight fluctuations and possibly sexual dysfunction.

Intravenous administration can cause slight discomfort or bruising at the site where the needle is inserted and may also cause lightheadedness and fainting, infection, and excessive bleeding. Obtaining blood may sometimes cause pain at the site where the blood is drawn, bruising, occasional lightheadedness and, rarely, fainting. Repeated blood draws may lead to anemia.

The risks from a CT (or CAT) and/or MRI x-rays include exposure to radiation and possible reaction to the dye used in the procedure.

Contacts

Public
Medimmune LLC, subsidiary of AstraZeneca

One MedImmune Way
Gaithersburg MD 20878
US
Scientific
Medimmune LLC, subsidiary of AstraZeneca

One MedImmune Way
Gaithersburg MD 20878
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects must meet all of the following criteria:
- Histologically and/or cytologically confirmed pleural or peritoneal malignant mesothelioma. ;- Disease not amenable to curative surgery;;- Age 18 and over at the time of consent;;- ECOG Performance status 0-1;;- Progressed after receipt of 1-2 prior systemic treatments for advanced disease that include a first-line pemetrexed (or anti-folate)-based regimen in combination with platinum agent;;- Recovered from all toxicities associated with prior treatment;- Measurable disease;- Adequate bone marrow, hepatic, and renal function ;- Negative screening test results for human immunodeficiency virus (HIV), hepatitis A, B and C.

;- Written informed consent and any locally required authorization (eg, HIPAA in the USA, EU Data Privacy Directive authorization in the EU) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations;;- Females of childbearing potential who are sexually active with a nonsterilized male partner must use a highly effective method of contraception for 28 days prior to the first dose of investigational product, and must agree to continue using such precautions for 6 months after the final dose of investigational product;;- Nonsterilized males who are sexually active with a female partner of childbearing potential must use a highly effective method of contraception from Day 1 through 90 post last dose.

Exclusion criteria

Any of the following would exclude the subject from participation in the study:
- Subjects who failed more than 2 prior systemic treatment regimens for advanced malignant mesothelioma;
- Received any prior monoclonal antibody against CTLA-4, programmed cell death 1 (PD1) or programmed cell death 1 ligand 1 (PD-L1);
- History of chronic inflammatory or autoimmune disease;
- Active, untreated central nervous system (CNS) metastasis;
- Any serious uncontrolled medical disorder or active infection that would impair the subject's ability to receive investigational product, such as conditions associated with frequent diarrhea
- History of other malignancy unless the subject has been disease-free for at least 3 years. Non-invasive cancer history (such as carcinoma in situ [CIS] that has been resected) is allowed;
- Pregnant or breast feeding at time of consent;
- Any condition that would prohibit the understanding or rendering of information and consent and compliance with the requirements of this protocol;
- Active or history of diverticulitis. Note that diverticulosis is permitted;
- Active or history of inflammatory bowel disease (eg, colitis,
Crohn's), irritable bowel disease, celiac disease or other serious gastrointestinal chronic conditions associated with diarrhea. Active or history of systemic lupus erythematosis or Wegener's granulomatosis;
- History of sarcoidosis syndrome;
- Currently receiving systemic corticosteroids or other
immunosuppressive medications;
- Subjects should not be vaccinated with live attenuated vaccines within one month prior to starting tremelimumab treatment;
- The last dose of prior chemotherapy or radiation therapy (with the exception of palliative radiotherapy) was received less than 2 weeks prior to randomization;
- Any unresolved toxicity NCI CTCAE Grade >- 2from previous anticancer therapy, with the exception of vitiligo and alopecia;
- Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results;
- Concurrent enrollment in another clinical study or receipt of an investigational product

within the last 4 weeks (participation in the survival follow-up period of a study is not an exclusion criterion);
- Employees of the study site directly involved with the conduct of the study, or immediate family members of any such individuals.
- Subjects with a history of hypersensitivity to compounds of similar biologic composition to tremelimumab or any constituent of the product.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-11-2013
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	tremelimumab

Ethics review

Approved WMO

Date:	11-07-2013
Application type:	First submission

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-08-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-11-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-12-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-02-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-04-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	01-09-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-03-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-03-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-09-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2012-003524-21-NL
ClinicalTrials.gov	NCT01843374
CCMO	NL44425.060.13