A Randomized Double-Blind Phase III Study of Ipilimumab Administered at 3 mg/kg vs at 10 mg/kg in Subjects with Previously Treated or Untreated Unresectable or Metastatic Melanoma

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To compare the overall survival of ipilimumab monotherapy at doses of 3 mg/kg versus 10 mg/kg in subjects with previously treated or untreated unresectable Stage III or Stage IV melanoma

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

Summary

ID

NL-OMON37618

Source
ToetsingOnline

Brief title
Ipilimumab dose comparison study in Metastatic Melanoma

Condition

- Skin neoplasms malignant and unspecified

Synonym
Melanoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Ipilimumab, metastatic melanoma, Phase III

Outcome measures

Primary outcome

Study Assessments and Primary Endpoint: Safety Assessments: All subjects who receive at least one dose of study treatment (ipilimumab) will be evaluated for safety parameters.

Primary Endpoint: All randomized subjects will be evaluated for efficacy analyses. Overall survival (OS) will be defined as the time from the date of randomization until the date of death. For those subjects who have not died, OS will be censored on the last date the subject was known to be alive.

Secondary outcome

Secondary Objectives:

Efficacy:

* To compare progression-free survival between doses of 3 mg/kg and 10 mg/kg by mWHO criteria

* To compare best overall response rate between doses of 3 mg/kg and 10 mg/kg by mWHO criteria

* To compare disease control rate between doses of 3 mg/kg and 10 mg/kg by mWHO criteria

* To evaluate duration of response and stable disease for the of 3 mg/kg and 10

mg/kg dose groups by mWHO criteria

* To evaluate the OS in each of the two dosing groups in the subset of subjects

with brain metastases

Study description

Background summary

Ipilimumab is approved for use in the US (metastatic melanoma) and in the EU (for previously treated metastatic melanoma). The currently approved dose is 3 mg/kg every 3 weeks for up to 4 doses. A dose effect was observed in Phase 2 with an acceptable safety profile for 10 mg/kg, suggesting that the higher dose may be more appropriate. However, 2 randomized Phase 3 studies demonstrated comparable increments in overall survival (OS) relative to their respective controls. The first Phase 3 study, MDX010-20, examined ipilimumab (3 mg/kg monotherapy) vs a melanoma vaccine in previously treated subjects. The second Phase 3 study, CA184024, compared ipilimumab + DTIC to DTIC alone in treatment-naïve subjects. In light of the meaningful differences in Phase 3 study designs, a cross-study comparison of the 2 doses is difficult to interpret. The current study offers direct comparison of 3 vs 10 mg/kg monotherapy in a well-sized, randomized Phase 3 study in order to more clearly define the relative risk:benefit of each dose.

Study objective

To compare the overall survival of ipilimumab monotherapy at doses of 3 mg/kg versus 10 mg/kg in subjects with previously treated or untreated unresectable Stage III or Stage IV melanoma

Study design

Study Design: This is a randomized, multicenter, double-blind Phase 3 study. Subjects aged * 18 years of age with untreated or previously treated unresectable Stage III or Stage IV (metastatic) melanoma who have not received a B-Raf inhibitor or prior immune checkpoint modulatory therapy (see eligibility criteria) will be randomly assigned to be treated with ipilimumab at a dose of either 3 mg/kg or 10 mg/kg by intravenous infusion every 3 weeks x 4 doses. After initial response (or stable disease for at least 3 months) followed by subsequent progression and in the absence of intolerable toxicity, subjects are eligible to receive re-induction therapy using the same dose and

schedule as used for induction. Re-induction may be provided at the discretion of the investigator using the same criteria.

When the analysis for the primary endpoint of overall survival has been conducted, all subjects, including subjects in the Re-induction phase, will no longer be treated on this study and will revert to commercial supplies of ipilimumab where available as per local labels. Subjects will continue to be followed for long term survival.The study will be double-blinded and subjects will be randomized in a 1:1 ratio between the two treatment arms. Randomization will be stratified by:
1) M substage: M0+M1a+M1b versus M1c without brain metastases versus M1c with brain metastases
2) Prior treatment for metastatic melanoma: yes versus no
3) ECOG Performance Status: 0 versus 1
This study is divided into the following phases: Screening, Induction, Re-induction, Progression Follow-up, and Survival Follow-up.

Intervention

Study Population: Men and women, * 18 years of age, with previously treated or untreated unresectable Stage III or IV histologically or cytologically confirmed melanoma, ECOG Performance Status 0 or 1, and who have not received a B-Raf inhibitor or prior CTLA-4 or PD-1antagonists, or PD-L1 or CD137 agonists are eligible. Subjects with brain metastases who are free of neurologic symptoms related to metastatic brain lesions and who do not require or receive systemic corticosteroid therapy in the 10 days prior to beginning ipilimumab therapy are eligible. Subjects with a history of or current active autoimmune diseases (see eligibility criteria) or current uncontrolled infectious disease will be excluded. Subjects must provide a baseline blood sample for biomarker testing.

Study burden and risks

This trial can cause the following side effects,
A). Common Side Effects Considered to be Related to the Infusion: hypotension (low blood pressure), fever,chills, nausea and/or vomiting, flushing, fatigue diarrhea, skin rash, skin itchiness, abdominal pain, loss of appetite , local reaction at the site of injection, headache.
B). Immune*related side effects associated with administration of ipilimumab:
* The most common stomach/intestinal side effect is diarrhoea, constipation, blood in stool and abdominal pain.
* Rash: Rashes on the skin and or together with itching.
* Inflammation in the various parts of the eye or with pigment (colour) changes in the retina (back wall of the eye). In rare cases, double vision occurred as a result of muscle weakness.
* Serious problems with particular glands (a gland is a group of cells or an

organ that secretes a substance) such as the pituitary gland, the thyroid or the adrenal gland. Symptoms that may be associated with problems of the pituitary gland or adrenal gland include tiredness, confusion, weight loss, impotence (inability to perform sexually) and headache.
* Inflammation of the liver which can be life threatening.
C). Risks Associated with Study Procedures:
* Risks associated with taking blood or putting a needle in a vein might include pain from the puncture, bruising, bleeding, infection, or fainting.
* During a CT and MRI scan it is know that there are rare occurrences of allergic reactions to the contrast dyes injected into a vein during the scan. Such allergic reactions can involve itching, rash, or in severe cases, difficulty in breathing and dangerous lowering of blood pressure or other general symptoms.
D). Men, pregnant women and women that are breastfeeding are at risk because it not known if the study medication can cause potential damage to the sperm, foetus and baby.

E). In rare occasions there are side effects that occur in patients who use Ipilimumab such as
* In more than one organ alike such as the liver, kidney, heart, lungs and cardiovascular system (body system consisting of the heart, blood vessels and blood circulation)
* Meningitis (inflammation of the membrane surrounding the spinal cord and brain). This can cause headache, feeling sick and vomiting, stiff neck and sensitivity of your eyes to light.
* Inflammation of the nerves that control muscles
* Inflammation of the kidneys (Nephritis).
* Vitiligo, a condition where the skin loses pigment and turns white. Blistering and peeling of the top layer of skin resembling that of a severe burn have been rarely reported.
* Symptoms associated with immune-based reactions against other parts of the body such as joints

Contacts

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Scientific
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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion Criteria
1) Signed Written Informed Consent
a) Willing and able to give written informed consent;
2) Target Population
a) Histologically or cytologically confirmed diagnosis of malignant melanoma;
b) Previously-treated or untreated unresectable Stage III or Stage IV melanoma (AJCC 2010) (regardless of B-Raf mutation status or HLA type);
c) Prior adjuvant melanoma therapy is permitted; any number of previous treatments for melanoma are permitted except for prior B-Raf inhibitors, CTLA-4 antagonists or PD-1 antagonists, or PD-L1 or CD137 agonists;
d) Measurable/evaluable disease, within 28 days of first dose of study drug;
e) Subjects with brain metastases who are free of neurologic symptoms related to metastatic brain lesions and who do not require or receive systemic corticosteroid therapy in the 10 days prior to beginning ipilimumab therapy are eligible;
f) ECOG performance status of 0 or 1;
g) Subjects must have the complete set of baseline (ie, screening) digital radiographic images of lesions and anatomic regions limited to brain, chest, and abdomen within 28 days of first dose of study drug;
h) Provision of baseline DNA samples from peripheral blood for testing of:
* CD86 and CTLA-4 polymorphisms, and
* genome-wide association analysis to identify genetic determinants of immune-related adverse events;
i) Adequate hematologic, renal and hepatic function, specifically:
* WBC * 2500/uL, ANC * 1000/uL,

* Platelets * 75 x 10^3/uL,
* Hemoglobin * 9 g/dL,
* Creatinine * 2.5 x ULN,
* AST/ALT * 3 x ULN for subjects without liver metastasis; * 5 x ULN for subjects with liver metastasis,
* Total bilirubin * 3 x ULN, (except subjects with Gilbert*s Syndrome, who must have a total bilirubin less than 3.0 mg/dL);
j) Accessible for treatment and Follow-up;
3) Age and Reproductive Status
a) Men and women * 18 years of age
b) Women of childbearing potential (WOCBP) and men must be using an acceptable method of contraception to avoid pregnancy throughout the study and for up to 12 weeks after the last dose of investigational product] in such a manner that the risk of pregnancy is minimized. See Section 3.3.4 for the definition of WOCBP.
c) WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of investigational product.
d) Women must not be breastfeeding
e) Sexually active fertile men must use effective birth control if their partners are WOCBP.

Exclusion criteria

Exclusion Criteria
1) Target Disease Exceptions
a) Primary ocular melanoma;
b) Active brain metastases with symptoms or requiring corticosteroid treatment;
2) Medical History and Concurrent Diseases
a) Any other malignancy from which the subject has been disease-free for less than 2 years, with the exception of adequately treated and cured basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix;
b) History of or current active autoimmune diseases, including but not limited to inflammatory bowel diseases, rheumatoid arthritis, autoimmune thyroiditis, autoimmune hepatitis, systemic sclerosis (scleroderma and variants), systemic lupus erythematosus, autoimmune vasculitis, autoimmune neuropathies (eg, Guillain-Barre syndrome). Vitiligo is NOT excluded;
c) Uncontrolled infectious diseases * requires negative tests for clinically suspected HIV, HBV and HCV. If positive results are not indicative of true active or chronic infection, the subject may enter the study after discussion and agreement between the Investigator and the Medical Monitor;
d) History of or current immunodeficiency disease, splenectomy or splenic irradiation;
e) Prior allogeneic stem cell transplantation;
f) Any underlying medical or psychiatric condition, which in the opinion of the Investigator, will make the administration of study drug hazardous or obscure the interpretation of AEs, such as a condition associated with frequent diarrhea;
3) Physical and Laboratory Test Findings
a) Not applicable; defined in Inclusion criteria

4) Prohibited Therapies and/or Medications
a) Prior therapy with a B-Raf inhibitor, CTLA-4 or PD-1 antagonists, or PD-L1 or CD137 agonists;
b) Concomitant therapy with any anti-cancer agent, potent immunosuppressive agents, surgery or radiotherapy or other investigational anti-cancer therapies or chronic use of systemic corticosteroids (used in the management of cancer or non-cancer-related illnesses);
c) Prior anti-cancer therapy < 4 weeks prior to randomization;
d) Prior therapies with systemic immunosuppressive agents within prior 2 years (excluding episodic low dose corticosteroids, eg, for treatment of allergic dermatologic conditions); prior therapies with cytotoxic or investigational drugs within 4 weeks of randomization;
e) Any non-oncology vaccine therapy used for prevention of infectious diseases (for up to 4 weeks prior to or after any dose of ipilimumab);
f) Treatment with any other investigational products within 4 weeks prior to randomization into this study;
g) Any psychological or medical condition which may interfere with the ability to provide informed consent;
h) Any psychological, familial, cultural/sociological or geographical condition which could potentially hamper compliance with study schedule, procedures and testing;
5) Allergies and Adverse Drug Reaction
a) History of allergic reaction to parenteral administered recombinant protein product;
6) Sex and Reproductive Status
a) Sexually active fertile men not using effective birth control if their partners are WOCBP
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

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-06-2012
Enrollment:	28
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	27-02-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-05-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-08-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	04-02-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2011-0044029-2-NL
ClinicalTrials.gov	NCT01515189
CCMO	NL39470.029.12