Adjuvant immunotherapy with anti-CTLA-4 monoclonal antibody (ipilimumab) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 trial of the EORTC Melanoma Group

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

Summary

ID

NL-OMON47131

Source
ToetsingOnline

Brief title
EORTC protocol 18071

Condition

- Skin neoplasms malignant and unspecified

Synonym
Cancer, melanoma

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Adjuvant immunotherapie, anti-CTLA-4 monoclonal antibody (ipilimumab), Placebo, Stage III melanoma

Outcome measures

Primary outcome

The primary efficacy endpoint is Recurrence-free survival (RFS). The primary

outcome measure of recurrence*free survival will be determined based on the

disease recurrence date provided by the IRC (Independent Review Committee).

Secondary outcome

Secondary endpoints:

. Overall survival (OS)

. Distant metastases-free survival (DMFS)

. Adverse event profile

. Quality of life

. Quality-adjusted survival

The secondary outcome measure of distant metastasis*free survival (DMFS) will

be determined based on the 1st date of

distant metastasis provided by the Independent Review Committee. The secondary

outcome measure of overall survival (OS) is defined as the time from the date

of randomisation to the date of death.

Study description

Background summary

Malignant melanoma is a type of skin cancer and is an aggressive disease with a 46% 5-year survival rate. Due to the limited efficacy (how well the treatment works) together with frequent side effects experienced with existing treatment (such as interferon), there is a need for new drugs for patients who have had their melanoma cells removed during an operation (surgically resected melanoma) but who remain at high risk of their melanoma coming back (recurrence). Immunotherapies may improve the survival outcome for these patients.
This study is funded by Bristol-Myers Squibb, and is being conducted in Europe, North America, Canada and Australia. Enrolment starts in North America in summer 2008 and will continue until late 2010.

Study objective

The purpose of this study is to determine the safety and efficacy of post-surgery treatment with the monoclonal antibody ipilimumab, to see whether treatment improves recurrence-free survival (RFS), overall survival and distant metastases-free survival (DMSF) as compared todummy treatment (placebo) in high-risk patients with complete resection of Stage IIIA (>1mm metastasis), IIIB and IIIC (no in-transit metastases) melanoma. This will be done in patients who are currently free of the disease but remain at high risk of melanoma recurrence.

Study design

This study is a double-blinded phase III trial.

The study will enrol 950 patients with Stage III melanoma, assigned 1:1 to either ipilimumab 10 mg/kg treatment or placebo.

By signing the informed consent, patients will enter the screening phase to assess the eligibility within a time window of 4 weeks but no later than 6 weeks after complete resection of stage III melanoma (AJCC 2002). Patients will be randomized within a time window of 6 weeks, but not longer then 12 weeks after complete lymph node dissection. Treatment will start after surgical removal of the primary melanoma and additional sites of disease (nodes). Ipilimumab is given via a 90 minute infusion every 3 weeks for a total of 4 infusions, then every 12 weeks for a maximum of 3 years or until recurrence, unacceptable toxicity or early withdrawal from the study by patient or

physician. During the study, patients will undergo physical examinations and have blood samples taken at all study visits. Patients will have urine taken, weight and vital signs measured at some visits, and will undergo one electrocardiogram (ECG) and 2 eye (opthalmological) examinations

Intervention

Initial dose and schedule

Each patient will receive ipilimumab (10 mg/kg) or placebo as a single dose via a 90 minute IV infusion (not as bolus or IV push)

Induction Phase

Ipilimumab/Placebo at a dose of 10 mg/kg, administered as tolerated by IV infusion as one single dose during Day 1, 22, 43 and 64 for a total of four separate doses, until un-resectable local recurrence or distant progression, unacceptable toxicity or withdrawal of consent

Maintenance Phase

Ipilimumab/Placebo at a dose of 10 mg/kg, administered as tolerated by IV infusion every 12 weeks (3 months),
beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent with a maximum of 3 years from randomization

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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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

ELIGIBILITY CRITERIA
To be eligbile to participate in this study, patients must be/ have
* At least 18 years of age
* No mucosal or ocular (eye) melanoma, or melanoma with unknown origin of the primary
* Complete surgical removal (resection) of Stage III melanoma with cutaneous melanoma spread to lymph node,confirmed by microscopy and classified by the American Joint Committee on Cancer (AJCC, 2002) as: Stage IIIA with metastasis greater than 1mm thick; any Stage IIIB or IIIC (no in*transit spread)
* Adequate removal of Stage III lymph nodes per Criteria for adequate surgical procedures for complete lymph node dissection (CLND) as documented on the operating report and pathology report. (Patients without documentation of adequate resection are not eligible).
* General recommendations for surgical and pathological procedures are given in Appendix J of the protocol; a data quality check will be done based on the surgical and pathological reports
* Recommendations for management of the lymph nodes are given in Appendix J of the protocol and should include the following:
Head and Neck
* Minimum of 15 pathologically investigated nodes
* Face, ear and anterior scalp: parotidectomy plus modified radical neck dissection
* Posterior scalp: modified radical neck dissection plus suboccipital nodes
Upper Extremity
* Minimum of 10 pathologically investigated nodes
* Axillary node dissection included at least 10 nodes taken from Levels I and II
* Level III nodes dissected if they were clinically involved
* Pectoralis minor muscle was divided or sacrificed

Lower Extremity
* Minimum of 5 pathologically investigated nodes
* Superficial inguinal node dissection was performed for non*palpable nodal involvement
* If Cloquet*s node was positive, a deep inguinal node dissection was performed Lymph Node Dissection for Nodal Recurrence
* Regional node recurrence was treated using the appropriate lymphadenectomy as above
* Diagnosis of regional node recurrence was made by fine needle aspiration technique to avoid contaminating the region with tumour, followed by Cloquet's Lymph Node Dissection as above
* Full lymphadenectomy must be performed within 12 weeks (84 days) prior to randomisation
* Disease status for the post*surgery baseline assessment must be documented by full Chest/ Abdomen/ Pelvis CT and/or MRI with Neck CT and/or MRI (for Head and Neck primary tumours) and complete clinical examination after the informed consent and prior to randomisation
* The complete set of baseline radiographical images must be available before randomisation and all images must be of adequate quality
* Disease*free (no loco*regional relapse or distant metastasis); no clinical evidence for brain metastases
* No radiation therapy to the lymph node dissection field after surgery
* No prior therapy for melanoma except surgery for primary melanoma lesions; patients who have previously received interferon (IFN) are not eligible
* No prior or concomitant therapy with any anti*cancer agents, immunosuppressive agents; other investigational anti*cancer therapies, or chronic use of systemic corticosteroids (used in the management of cancer or non*cancer*related illnesses)
* No non*cancer vaccine therapy can be used for prevention of infectious diseases (up*to) 4 weeks prior and after any dose of ipilimumab or placebo
* No prior treatment with a CD137 agonist or CTLA*4 inhibitor or agonist
* No previous participation in another ipilimumab (MDX*010) clinical trial
* No treatment with other investigational products within the last 4 weeks prior to randomisation into this study
* ECOG performance status of 0 or 1 (see Appendix B of the protocol)
* Adequate heart function (less or equal to NYHA II, see Appendix C)
* Adequate blood, kidney and liver function as defined by laboratory values performed within 4*6 weeks from enrolment
* White blood count (WBC) greater than or equal to 2.5x 10 to the power 9 per litre
* Absolute neutrophil count (ANC) greater than or equal to 1x 10 to the power 9 per litre
* Platelet count greater than or equal to 75x10 to the power 9 per L
* Haemoglobin greater than or equal to 9 grammes per decilitre (5.6 millimoles per litre)
* Serum creatinine less or equal to 2.5 times upper limit of laboratory normal range (ULN) Total serum bilirubin, AST, ALT, alkaline phosphatase and LDH less or equal to 2 times ULN
* No uncontrolled infectious disease including negative testing for HIV, HBV, HCV
* No autoimmune disease: patients with a documented history of inflammatory bowel disease, including ulcerative colitis and Crohne*s disease are excluded from this study as are patients with a history of symptomatic disease (e.g., rheumatoid arthritis, autoimmune thyroiditis (e.g. Hashimoto*s disease),

autoimmune hepatitis, systemic progressive sclerosis (scleroderma), Systemic Lupus Erythematosus, autoimmune vasculitis (e.g. Wegener*s Granulomatosis)
* Patients must not present immunodeficiency or previous splenectomy or radiation therapy to the spleen
* No second malignancies in the past 5 years with the exception of surgically cured cancer of the cervix and basal or squamous cell carcinoma of the skin
* Women of child*bearing potential (WOCBP) include any female who has experienced menarche and who has not undergone successful surgical sterilisation (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhoea for more than 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level greater than 35 international units per litre].
Women who are using oral implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device (IUD; coil) or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g. vasectomy), are considered to be of child bearing potential
* WOCBP must have a negative serum pregnancy test (minimum sensitivity 25 international units per litre or equivalent units of human chorionic gonadotropin * HCG) before randomisation and within 72 hours prior to the start of study medication. It is the investigator's responsibility to repeat the pregnancy test should start of treatment be delayed.
* Not eligible for this study are WOCBP unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for up to 8 weeks after the last administration of the infusion, women who are pregnant or breastfeeding, women with a positive pregnancy test on enrolment or prior to study drug administration, and sexually active fertile men whose partners are WOCBP, unless using an adequate method of birth control.
* Patients must have absence of 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 or efficacy, such as a condition associated with frequent diarrhoea
* No prisoners or patients who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g. infectious disease) illness must be randomised into this study
* Patients must have absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow*up schedule; those conditions should be discussed with the patient before registration in the trial
* Written informed consent required prior to clinical trial participation, including informed consent for any screening procedures conducted to establish subject eligibility for the trial registration, according to ICH/EU GCP, and national/local regulations

Exclusion criteria

This is mentioned in the Eligibility criteria

Study design

Design

Study phase:	3
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):	14-12-2010
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ipilimumab
Generic name:	Ipilimumab (BMS-73016, MDX-010) human Anti-human CTL4(CD152) mAb

Ethics review

Approved WMO

Date:	22-07-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	22-07-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-10-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-12-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-02-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-03-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-03-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-10-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-12-2010
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-04-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-04-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-07-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-07-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-11-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-12-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-04-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-07-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-09-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-10-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-10-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-07-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-08-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-11-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-01-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-08-2017

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2007-001974-10-NL
CCMO	NL24415.078.09