A Multi-Center, Randomized, Double-Blind, Two-Arm, Phase III Study in Patients with Untreated Stage III (Unresectable) or IV Melanoma Receiving Dacarbazine Plus 10 mg/kg of Ipilimumab (MDX-010) vs. Dacarbazine With Placebo

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To compare OS in patients with previously untreated Stage IIIc, N3 (unresectable) or Stage IV melanoma receiving dacarbazine plus 10mg/kg ipilimumab (MDX-010) vs. dacarbazine with placebo.

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

Summary

ID

NL-OMON34151

Source
ToetsingOnline

Brief title
Dacarbazine with Ipilimumab vs. Dacarbazine with placebo

Condition

- Skin neoplasms malignant and unspecified

Synonym
melanosarcoma; skincancer

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Double-Blind, Ipilimumab, Melanoma, Placebo

Outcome measures

Primary outcome

The primary outcome of this study will be the comparison of the overall

survival (OS) between the two treatment arms.

Secondary outcome

The main secondary outcome will be the comparison of progression free survival

(PFS) between the two treatment arms.

Other secondary outcomes will be survival rate at 1 year, PFS at week 12, best

overall response rate (BORR), disease control rate, time to best objective

response and duration of best objective response.

Study description

Background summary

In the last 50 years (i.e., 1950-2001), the incidence of malignant melanoma has risen by 690% while mortality rate increased by 165%. Even with the recent decline in the incidence of several cancer types, the incidence of malignant melanoma is continuing to rise. Despite this, overall survival has improved for early stage tumors because of early detection and improved surgical treatment, the only currently available curative therapy. Recurrent and/or metastatic melanoma remains largely a fatal disease with a median survival of 3-11 months. The US Food and Drug Administration (FDA) currently approve high-dose interferon alfa-2b (IFN-*) for use as adjuvant therapy in patients

with a high risk of relapse. Treatment with high-dose IFN-* is associated with only a 10% improvement in recurrence-free survival, 0-10% improvement in overall survival and very significant toxicities that limit compliance with its use. Dacarbazine is the only FDA-approved chemotherapeutic agent in this setting and provides an objective tumor response in only 5% to 20% of patients but these responses are short-lived (e.g. median duration of response = 6 months) and there is no associated increase in survival. Over the last 30 years many chemotherapeutic drugs, including the aggressive Dartmouth combination regimen (dacarbazine, cisplatin, carmustine, and tamoxifen) and newer drugs such as temozolamide, have been unable to significantly improve survival in comparison to dacarbazine. Fotemustine, with an overall response rate of 15%, 6 months median duration of response and 2 months median time to progression, is approved in parts of Europe for use in metastatic melanoma. Interleukin-2 (IL-2) was approved by the FDA in 1998 for treatment of metastatic melanoma based on data suggesting a 16% overall objective response rate with a 6% complete response. Toxicities of high-dose IL-2 therapy are severe (e.g., capillary leak, sepsis, and hypotension). Additionally, 2% of patients died from such associated AEs. Malignant melanoma continues to be a considerable unmet medical need based on the unsatisfactory efficacy and significant toxicities of the currently available drugs and the rising incidence of the disease throughout the world.

Malignant melanoma is an immune responsive disease. The earliest evidence, provided by epidemiological observations, suggests that immunosuppressed patients have an increased incidence of melanoma and in some (< 1%) immunocompetent patients the primary melanoma lesions spontaneously regressed. Infiltration of melanoma lesions by T lymphocytes has been shown to be associated with a better clinical prognosis.10 Immunologic interventions to treat cancer can potentially be achieved through the induction of an immune response (active immunotherapy), administration of antibodies (passive immunotherapy) and/or stimulation of effector cells with cytokines or antibodies. All of these approaches have been investigated in melanoma and have shown early promise. Immune-modulating agents such as IFN-* and IL-2 have shown efficacy against melanoma and have been approved by the FDA for the treatment of various stages of melanoma. In addition to a direct cytotoxic effect, IFN-* is able to stimulate natural killer (NK) cell activity and to regulate the expression of histocompatibility antigens or tumor-associated antigens to demonstrate a 15% response rate in metastatic melanoma but a less than 5% complete response. The median duration of response ranged from 6-12 months. IFN-* treatment is also associated with significant toxicities. Interleukin-2 modulates the immune system by stimulating the growth and activity of T-lymphocytes, human lymphocyte antigen (HLA)-restricted or non-restricted cytotoxic T cells and induces the production of many cytokines, such as tumor necrosis factor (TNF), IFN-* and IL-1. IL-2 is currently approved for treatment of Stage IV melanoma; however its usage is also limited due to significant toxicities. Various combinations of IL-2, IFN-*, TNF-* and chemotherapy drugs have failed to significantly improve survival or quality of

life.

Ipilimumab (MDX-010) alone or in combination with dacarbazine, induced durable (i.e., > 1 year) objective clinical responses in previously untreated patients with metastatic melanoma. The BORR observed in patients treated with the combination of dacarbazine and ipilimumab (MDX-010) appears higher than reported with dacarbazine alone (6%). Furthermore, it should be noted that the OS survival in the dacarbazine/ipilimumab (MDX-010) combination arm was observed to be 30% higher than the arm that received ipilimumab (MDX-010) alone, suggesting an increased clinical benefit when dacarbazine is added to the anti-CTLA-4 antibody.

Study objective

To compare OS in patients with previously untreated Stage IIIc, N3 (unresectable) or Stage IV melanoma receiving dacarbazine plus 10mg/kg ipilimumab (MDX-010) vs. dacarbazine with placebo.

Study design

This study is divided into four phases: the Screening Phase, the Induction Phase, Maintenance Phase, and the Follow-Up Phase. After informed consent is obtained, patients will enter the Screening Phase to assess eligibility criteria. Upon meeting criteria, eligible patients will be randomized into the Induction Phase to receive placebo or active ipilimumab and dacarbazine treatment (4 separate infusions of either placebo or active 10mg/kg dose of ipilimumab and dacarbazine infusions at 3 week intervals) and tumor assessments. Tumor response and patient tolerability to placebo or active ipilimumab will determine whether, and in what capacity, patients will be allowed to continue in the Maintenance Phase (continued placebo or active ipilimumab dosing in 12 week intervals until PD, drug intolerance, withdrawal of consent or study closure). Patients who show PD or who do not wish to continue in study phase assessments in the Induction Phase or Maintenance Phase, will enter the Follow-Up Phase.

Intervention

Not applicable

Study burden and risks

Significant drug-related immune-mediated phenomena have been observed in some patients, most commonly including rash and pruritus. Some patients with melanoma have developed vitiligo. Colitis, manifesting as diarrhea (including Grade 3 diarrhea and/or bloody diarrhea requiring hospitalization and uncommonly [<2%] requiring colectomy) has been the most clinically significant

drug-related AE. Immune-mediated AEs, or so called IBEs, appear to have an association with anti-tumor activity. The rate of SAEs is significantly less than would be expected with high-dose IL-2 or combination chemotherapy regimes, while the expected response rate is in the 10-15% range. This response rate is comparable to high dose IL-2, but demonstrates improved durability when compared in combination chemotherapy. The overall risk and benefit for patients entering this protocol are therefore at least comparable to, and possibly better than, alternative options.

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

1) Willing and able to give written informed consent;
2) Histologic diagnosis of malignant melanoma;

3) Untreated unresectable Stage III melanoma with N3 macroscopic lymph nodes or in-transit / satellite metasteses or Stage IV melanoma (AJCC 2001) (note that prior adjuvant melanoma therapy is permitted) [i.e., IFN therapy]);
4) Measurable/evaluable disease (as per modified WHO criteria), within 28 days of first dose of study drug;
5) Life expectancy of * 16 weeks;
6) ECOG performance status of 0 or 1;
7) Have the complete set of baseline (i.e. Screening) digital images of lesions and radiographic images, including, but not limited to: brain, chest, abdomen, pelvis and bone scans. All images must be of adequate quality;
8) Required values for initial laboratory tests:
* Platelets * 75 x 103/uL
* Hemoglobin * 9 g/dL
* Creatinine * 2.5 x ULN
* AST * 3 x ULN for patients without liver metastases
* 5 x ULN for patients with liver metastases
* Bilirubin * 3 x ULN, (except patients with Gilbert*s Syndrome, who must have a total bilirubin less than 3.0 mg/dL;
9) Negative Screening tests for HIV, HepB, and HepC. If positive results are not indicative of true active or chronic infection, the patient can enter the study after discussion and agreement between the Investigator and the CRO Medical Monitor;
10) Accessible for treatment and Follow-Up;
11) Men and women > 18 years of age (or, * 16, if allowable per local regulatory authority);WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea * 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35mIU/mL]. Even women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g., vasectomy), should be considered to be of child bearing potential.
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 study medication.

Exclusion criteria

1) WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for up to 8 weeks after the study.
2) Women who are pregnant or breastfeeding
3) Women with a positive pregnancy test on enrollment or prior to study drug administration.
4) Sexually active fertile men whose partners are WOCBP, unless using an adequate method of birth control
5) Evidence of brain metastases on brain imaging (i.e. MRI or contrast CT);
6) Any other malignancy from which the patient has been disease-free for less than 5 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;
7) Primary ocular or mucosal melanoma;
8) Autoimmune disease: Patients with a documented history of inflammatory bowel disease, including ulcerative colitis and Crohn*s disease are excluded from this study as are patients with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], Systemic Lupus Erythematosus, autoimmune vasculitis [e.g., Wegener*s Granulomatosis]);
9) 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;
10) Prior or concomitant therapy with any anti-cancer agent, immunosuppressive agents, surgery or radiotherapy (except as defined in Sections 6.2.8.3 and 6.2.8.4 of the protocol); other investigational anti-cancer therapies, or chronic use of systemic corticosteroids (used in the management of cancer or non-cancer-related illnesses). Prior adjuvant therapy is not exclusionary;
11) Any non-oncology vaccine therapy used for prevention of infectious diseases (for up to 4 weeks prior to or after any dose of ipilimumab or dacarbazine);
12) Prior treatment with a CD137 agonist or CTLA-4 inhibitor or agonist;
13) Previous participation in another ipilimumab (MDX-010) clinical trial;
14) Treatment with other investigational products within the last 4 weeks prior to randomization into this study.
15) Prisoners or patients who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness must not be randomized into this study.

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):	16-06-2007
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	DITC
Generic name:	dacarbazine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	not applicable yet
Generic name:	ipilimumab

Ethics review

Approved WMO Date:	09-10-2006
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-06-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-06-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-07-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-09-2007
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-10-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-11-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-01-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-05-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-09-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-12-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-05-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-07-2009
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-11-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-01-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-05-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-08-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-10-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-11-2012
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	EUCTR2005-006082-14-NL
CCMO	NL13393.029.06