

TYPE OF CANCER: Stage III Melanoma
TYPE OF TRIAL: Phase III
TRIAL SPONSOR: Bristol Myers Squibb

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STUDY SUMMARY

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

TREATMENT OVERVIEW

- Patients will be randomized to receive either ipilimumab (10mg/kg) or placebo via IV infusion once every 3 weeks for the first 10 weeks, then once every 12 weeks until disease reoccurrence, toxicity, or withdrawal of consent for up to 3 years
- Patient should be seen by the physician prior to each infusion

PRE-TREATMENT ASSESSMENTS

- Informed consent
- Medical history
- HIV, Hepatitis B and C testing
- Pregnancy test if applicable
- Physical Exam
- Performance status
- Vital signs
- Hematology
- Serum chemistries
- Urinalysis
- ECG
- Ophthalmology exam
- CT or MRI of neck, chest, abdomen, and pelvis

ENTRANCE CRITERIA FOR PARTICIPATION IN TRIAL

Patient selection criteria:

- At least 18 years of age
- No mucosal or ocular melanoma, or melanoma with unknown origin of the primary
- Complete resection of Stage III melanoma (AJCC R0) with histologically confirmed cutaneous melanoma metastatic to lymph node, classified as

(AJCC, 2002): Stage IIIA with metastasis > 1mm; any Stage IIIB or IIIC (no in-transit metastases)

- Adequate resection 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; 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 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 tumor, followed by CLND as above
- Full lymphadenectomy must be performed within 12 weeks (84 days) prior to randomization
- 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 primaries) and complete clinical examination after the informed consent and prior to randomization
- The complete set of baseline radiographic images must be available before randomization 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 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-oncology 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 randomization into this study
- ECOG performance status of 0 or 1 (see Appendix B)
- Adequate cardiac function (less or equal to NYHA II, see Appendix C)
- Adequate hematologic, renal and liver function as defined by laboratory values performed within 4-6 weeks from enrollment
 - White blood count (WBC) greater than or equal to $2.5 \times 10^9/L$
 - Absolute neutrophil count (ANC) greater than or equal to $1 \times 10^9/L$
 - Platelet count greater than or equal to $75 \times 10^9/L$
 - Hemoglobin greater than or equal to 9 g/dL (5.6 mmol/L)
 - 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 Crohn'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 carcinoma in-situ 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 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 > 35 IU/L]. 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), are considered to be of child bearing potential

- WOCBP must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) before randomization and within 72 hours prior to the start of study medication. It is the investigators 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 perfusion, women who are pregnant or breastfeeding, women with a positive pregnancy test on enrollment 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 diarrhea
- 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 randomized 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