

TYPE OF CANCER: Stage III/Stage IV Melanoma
TYPE OF TRIAL: Phase II
TRIAL SPONSOR: Bristol-Myers Squibb

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STUDY SUMMARY

A Multicenter Treatment Protocol for Compassionate Use of Ipilimumab (BMS-734016) Monotherapy in Subjects with Unresectable Stage III or Stage IV Melanoma

TREATMENT OVERVIEW

The primary objective of the study is to provide treatment with ipilimumab to subjects who have serious or immediately life-threatening unresectable Stage III or Stage IV melanoma, who have no alternative treatment options, and whose physicians believe, based upon available data on benefit and risk, that it is appropriate to administer ipilimumab at a dose of 10 mg/kg induction/maintenance.

PRETREATMENT ASSESMENT

- Informed consent
- Inclusion/exclusion criteria
- Medical history
- Signs and symptoms
- Physical Examination
- Vital signs
- ECOG Performance status
- Electrocardiogram
- Laboratory tests
- Chest Radiography
- Pregnancy test
- Diagnostic imaging (Tumor Assessment)
- Adverse events

ENTRANCE CRITERIA FOR PARTICIPATION IN TRIAL

Inclusion Criteria

1) Signed Written Informed Consent

a) Before any study procedures are performed, subjects (or their legally acceptable representatives) will have the details of the study described to them, and they will be given a written informed consent document to read. Then, if subjects consent to participate in the study, they will indicate that consent by signing and dating the informed consent document in the presence of study personnel.

2) Target Population

Subjects receiving ipilimumab on single-patient INDs are eligible for this study provided that the single-patient IND is closed and the subject meets all other eligibility requirements for this study. If a subject is eligible for a treatment study, he or she is not eligible for this study.

a) Histologically confirmed Stage III (unresectable) or Stage IV melanoma.

b) Must have failed at least one systemic therapy for malignant melanoma or be intolerant to at least one prior systemic treatment. Note: Enrollees must not be eligible for a clinical study with ipilimumab.

c) Subjects with brain metastases are allowed. (Systemic steroids should be avoided if possible, or the subject should be stable on the lowest clinically effective dose, as steroids may interfere with the activity of ipilimumab if administered at the time of the first ipilimumab dose.)

d) Primary ocular and mucosal melanomas are allowed.

e) Must be at least 28 days since treatment with chemotherapy, biochemotherapy, surgery, radiation, or immunotherapy, and recovered from any clinically significant toxicity experienced during treatment. Palliative radiation therapy outside of the brain or therapeutic radiation to the brain after the subject's condition is stabilized and steroid decreased to the lowest fixed dose possible does not require the 28-day waiting period. Consult with the Medical Monitor for individual subjects.

f) Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

g) Life expectancy of \geq 16 weeks.

h) Subjects must have the complete set of baseline (screening/baseline) radiographic images, including but not limited to brain, chest, abdomen, pelvis, and bone scans. The images can be accepted if obtained 6 weeks before initiation of ipilimumab.

i) Required values for initial laboratory tests:

- WBC: $\geq 2000/\mu\text{L}$ ($\geq 2 \times 10^9/\text{L}$)
- ANC: $\geq 1000/\mu\text{L}$ ($\geq 1 \times 10^9/\text{L}$)
- Platelets: $\geq 75 \times 10^3/\mu\text{L}$ ($\geq 75 \times 10^9/\text{L}$)
- Hemoglobin: $\geq 9 \text{ g/dL}$ ($\geq 80 \text{ g/L}$; may be transfused)
- Creatinine: $\leq 2 \times \text{ULN}$
- AST/ALT: $\leq 2.5 \times \text{ULN}$ for subjects without liver metastasis ≤ 5 times for liver metastases
- Bilirubin: $\leq 2.0 \times \text{ULN}$ (except for subjects with Gilbert's Syndrome, who must have a total bilirubin of less than 3.0 mg/dL)

j) No active or chronic infection with HIV, Hepatitis B, or Hepatitis C.

k) Prior treatment with an anti-CTLA-4 drug is allowed.

3) Age and Sex

a) Men and women, at least 16 years of age.

Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 8 weeks after the last dose of investigational product in such a manner that the risk of pregnancy is minimized. 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 $> 35 \text{ mIU/mL}$). Even women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (eg. vasectomy) should be considered to be of childbearing potential. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours before the start of investigational product.

Exclusion Criteria

1) Sex and Reproductive Status

- a) WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study and for up to 8 weeks after the last dose of investigational product.
- b) WOCBP using a prohibited contraceptive method.
- c) Women who are pregnant or breastfeeding.
- d) Women with a positive pregnancy test on enrollment or before investigational product administration.

2) Target Disease Exceptions

- a) Subjects on any other systemic therapy for cancer, including any other experimental treatment.
- b) Prior treatment with an anti-CTLA-4 antibody if treatment failure was due to irAEs. If a subject was discontinued from the prior anti-CTLA-4 treatment due to an AE or SAE, regardless of the type of event, that discontinuation constitutes an exclusion criterion. If irAEs were serious enough to require a subject's withdrawal from prior treatment, the subject should be excluded from this study.
- c) Any subject enrolled in a registrational study (i.e. CA184-020, CA184-024) that has a survival endpoint should not be enrolled in CA184-045. Also, if a subject is eligible for a treatment study, he or she is not eligible for this study.
- d) A history of AEs with prior IL-2 or Interferon will not preclude subjects from entering the current study.

3) Medical History and Concurrent Diseases

- a) Presence of active autoimmune disease (eg, lupus, rheumatoid arthritis, inflammatory bowel disease, including ulcerative colitis and Crohn's disease, inflammatory renal or lung disease or other vasculitis (e.g., Wegener's granulomatosis), autoimmune neurologic disease, or autoimmune hepatitis) or related disease such as scleroderma, active psoriasis, allergic asthma, and atopic dermatitis.
- b) Presence of known hepatitis B or hepatitis C (active) infection, regardless of control on antiviral therapy.

c) Subjects with melanoma who have another active, concurrent, malignant disease are not eligible for the CA184 045 study, with the exception of adequately treated basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix.

4) 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.

c) Any underlying medical or psychiatric condition that, in the opinion of the investigator, could make the administration of ipilimumab hazardous or could obscure the interpretation of adverse events.

d) Any non-oncology vaccine therapy used for prevention of infectious diseases for up to 4 weeks before or after any dose of ipilimumab, with the exceptions of amantadine and flumadine.