CTSU E3612: A Randomized Phase II Trial of Ipilimumab with or without Bevacizumab in Patients with Unresectable Stage III or Stage IV Melanoma

Fast Facts

Bevacizumab and Ipilimumab provided.

Patients must receive their first induction dose within seven working days of randomization.
The total dose must be calculated using the most recent subject actual weight (obtained within 3 days of the dosing visit, and prior to the infusion).

Eligibility Criteria

1. Age ≥ 18 years

2. ECOG Performance status: 0 or 1

3. Untreated or previously received one treatment regimen for measurable unresectable Stage III or Stage IV melanoma (AJCC 2010) (for BRAF wild-type, and regardless of HLA type). Untreated or previously received up to two treatment regimens for measurable unresectable Stage III or Stage IV melanoma (AJCC 2010) (for BRAF mutant, and regardless of HLA type; If 2 prior regimens, one should be a BRAF inhibitor). This does not include any therapies given in the adjuvant setting.

4. Prior treatment (chemo, radiation, hormone, and immune therapies) must be completed > 4 weeks prior to randomization (> 6 weeks prior to randomization for nitrosoureas, mitomycin C, and checkpoint inhibitors).

5. Patients who received prior therapy with anthracylines should have a baseline MUGA or echo with a normal ejection fraction within 28 days prior to randomization.

6. Patients must have recovered from any acute toxicity associated with prior therapy by the start of study treatment.

7. Women must not be pregnant or breast-feeding due to the unknown effects on the fetus or infant. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to randomization to rule out pregnancy.

   A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

8. All sites of disease must be evaluated within 4 weeks prior to randomization. Patients must have measurable disease as defined in Section 6.

9. Patients must have the following required values for initial laboratory tests obtained within 4 weeks prior to randomization (ULN: institutional upper limit of normal):
    - WBC ≥ 2000/uL
    - ANC ≥ 1000/uL
    - Platelets ≥ 75 x 103/uL
    - Hemoglobin ≥ 9 g/dL
    - Creatinine ≤ 2.0 x ULN
    - AST/ALT ≤ 2.5 x ULN for patients without liver metastases and ≤ 5 x ULN for patients with liver metastases
    - Serum Bilirubin ≤ 2.0 x ULN (except patients with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL)

10. Patients BRAF mutation status must be known.

11. No Concomitant therapy with any of the following: IL 2, interferon, or other non-study immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; other investigational therapies; or chronic use of systemic corticosteroids; must have been discontinued ≥ 4 weeks prior to randomization.

12. No infection with HIV. Due to the mechanism of action of ipilimumab and bevacizumab, activity and side effects in an immune compromised patient are unknown.

13. No active infection with Hepatitis B.

14. No active or chronic infection with Hepatitis C.

15. Patients are ineligible if they have any history of CNS metastases.

16. Patients are ineligible if they have a history of any other malignancy from which the patient 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.

17. Patients are ineligible if they have a history of autoimmune disease, as follows: Patients with a history of inflammatory bowel 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]). Patients with motor neuropathy considered of autoimmune origin (e.g., Guillain-Barre Syndrome and Myasthenia Gravis) are excluded. Patients with a history of autoimmune thyroiditis are eligible if their current thyroid disorder is treated and stable with replacement or other medical therapy.

18. Patients are ineligible if they have an active infection.

19. Patients are ineligible if they have a history of prior treatment with ipilimumab, bevacizumab, or prior CD137 agonist or CTLA-4 inhibitor or agonist. Patients may be treatment naïve or have had one prior systemic therapy for metastatic disease as outlined in the eligibility criteria. Patients may have received prior anti-PD-1 or anti-PD-L1 as per current protocol eligibility, although they are not currently commercially approved in the front line setting.

20. Patients are ineligible if they have a history of any underlying medical or psychiatric conditions or require any medications or treatment that in the opinion of the principal investigator may interfere with compliance, make the administration of study drug hazardous or obscure the interpretation of adverse events, such as a condition associated with frequent diarrhea.

21. Patients are ineligible if they have any concurrent medical condition requiring the use of systemic steroids. (Use of inhaled or topical steroids is acceptable).

22. Patients are ineligible if they have inadequately controlled hypertension (defined as systolic blood pressure > 150 and/or diastolic blood pressure > 100 mmHg on antihypertensive medications).

23. Patients are excluded if they have any prior history of hypertensive crisis or hypertensive encephalopathy.

24. Patients are excluded if they have New York Heart Association (NYHA) Grade II or greater congestive heart failure.

25. Patients are excluded if they have a history of myocardial infarction or unstable angina within 6 months prior to randomization.

26. Patients are excluded if they have a history of stroke or transient ischemic attack within 6 months prior to randomization.

27. Patients are excluded if they have known significant vascular disease (e.g., aortic aneurysm, aortic dissection).

28. Patients are excluded if they have symptomatic peripheral vascular disease.

29. Patients are excluded if they have evidence of bleeding diathesis or coagulopathy.

30. Patients are excluded if they have had a surgical procedure or a significant traumatic injury within 28 days prior to randomization.

31. Patients are excluded if they have had a biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to randomization.

32. Patients are excluded if they have history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to randomization.

33. Patients are excluded if they have a non-healing wound or ulcer.

34. Patients are excluded if they have proteinuria at screening as demonstrated by either:
    a. Urine dipstick for proteinuria ≥ 2+ (patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis at baseline should undergo a 24 hour urine collection and must demonstrate ≤ 1g of protein in 24 hours to be eligible) **OR**
    b. Urine protein: creatinine (UPC) ratio ≥ 1.0 at screening. For UPC ratio > 1, a 24-hour urine protein should be obtained and the level should be <1000mg.

NOTE: Urine protein should be screened by urine analysis for Urine Protein Creatinine (UPC) ratio. UPC ratio of spot urine is an estimation of the 24 hour urine protein excretion. A UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 g. UPC ratio is calculated using one of the following formulas:

    a. [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
    b. [(urine protein) x 0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

35. Patients must not have known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies.

36. Patients are excluded if they have a history of hemoptysis (bright red blood of 1/2 teaspoon or more per episode) within 3 months prior to randomization.

37. Patients are excluded if they have current, ongoing treatment with full-dose warfarin or its equivalent (i.e., unfractionated and/or low molecular weight heparin). Subjects should have not taken full-dose warfarin or equivalent for at least 2 weeks prior to randomization.

38. Patients are excluded if they have current or recent (within 10 days of enrollment) use of aspirin (> 325 mg/day) or chronic use of other NSAIDs.

39. Patients are excluded if they use medications that inhibit platelet function (e.g., dipryidamolde, epoprostenol, epitfibatide, clopidogrel, cilostazol, abciximab, ticlopidine, and ibuprofen and related compounds) unless subject has been off treatment for at least 2 weeks prior to randomization.

40. Patients are excluded if they have known involvement of melanoma within the gastrointestinal tract.

41. Patients are excluded for any non-oncology vaccine therapy used for prevention of infectious diseases (for up to 1 month before or after any dose of ipilimumab).

42. Women of childbearing potential and sexually active males must agree to practice abstinence or use an accepted and effective method of contraception.

Treatment Plan

Arm A
Induction Therapy: Ipilimumab 3 mg/kg IV Day 1 Cycles 1-4
Maintenance Therapy: Cycles 5 and higher Ipilimumab 3 mg/kg IV Day 1 of every 4th cycle (12 weeks) starting Cycle 8*

Arm B
Induction Therapy: Ipilimumab 3 mg/kg IV Day 1 Cycles 1-4 plus Bevacizumab 15 mg/kg IV
Maintenance Therapy: Cycles 5 and higher
Ipilimumab 3 mg/kg IV Day 1 of every 4th cycle (12 weeks) starting Cycle 8* plus Bevacizumab 15 mg/kg IV Day 1 of each cycle starting Cycle 5*

Maintenance until excessive toxicity, progression or determination that treatment is no longer clinically beneficial.

Pre-Study Parameters

1. Medical History, Physical Exam, ECOG PS, Weight, Vitals
2. Pregnancy Test (serum or urine)
3. Concomitant Medications
4. HIV, HBV, HCV
5. CMP, CBC, LDH, Uric Acid
6. Thyroid function tests
7. Urinalysis
8. CT of Chest/Abdomen/Pelvis
9. CT or MRI of CNS (MRI preferred)
10. BRAF mutation status
11. Mandatory tissue for central review
12. Optional archival tumor and blood specimens