EA6141

For Patients with Unresectable Melanoma

Randomized Phase II/III Study of Nivolumab plus Ipilimumab plus Sargramostim versus Nivolumab plus Ipilimumab in Patients with Unresectable Stage III or Stage IV Melanoma

Patient Population
See Section 3.0 for Complete Eligibility Details

- Age ≥ 18, ECOG PS 0-1, and adequate lab values
- Must have known BRAF mutational status of tumor; Wild-type or mutated, prior to randomization
- Must have unresectable stage III/IV melanoma; histological/cytological confirmation of melanoma that is metastatic or unresectable and clearly progressive
- Must have measurable disease (RECIST 1.1)
- Must have had prior systemic therapy in the adjuvant setting (i.e., interferon, BRAF, MEK agents); may have had prior anti-CTLA-4 in the adjuvant setting, if at least 1 year from last dose of treatment; may not have had prior PD-1/PD-L1 in the adjuvant setting
- Must not have had any prior ipilimumab and/or anti-PD-1/PD-L1 agent in the metastatic setting
- Must have discontinued chemotherapy, immunotherapy, or other investigational agents used in the adjuvant setting ≥ 4 weeks prior to randomization; ≥ 6 weeks for mitomycin/nitrosoureas; ≥ 2 weeks for RT; ≥ 4 weeks for surgery
- Must not have had any non-oncology vaccine therapy used for prevention of infectious disease for up to 4 weeks prior to/after any dose of ipilimumab
- Must not have had any autoimmune disorders/conditions of immunosuppression that require current ongoing treatment with systemic corticosteroids (exceptions permitted per protocol); no history of symptomatic autoimmune disease, motor neuropathy of autoimmune origin, or other CNS autoimmune disease
- No history of inflammatory bowel disease; no diverticulitis (history of diverticulosis is allowed)

Treatment Plan
See Section 5.0 for Complete Treatment Details

Cycle = 21 days

Arm A:
- Induction (Cycles 1-4):
  - Nivolumab 1 mg/kg IV, day 1 of each cycle
  - Ipilimumab 3 mg/kg IV, day 1 of each cycle
  - Sargramostim (GM-CSF) 250 ug subQ days 1-14 of each 21 day cycle
- Maintenance (starting with cycle 5; until excessive toxicity, progression, or for 2 years):
  - Nivolumab 3 mg/kg IV, day 1 of each cycle
  - Sargramostim (GM-CSF) 250 ug subQ days 1-14 of each 21 day cycle

Arm B:
- Induction (Cycles 1-4):
  - Nivolumab 1 mg/kg IV, day 1 of each cycle
  - Ipilimumab 3 mg/kg IV, day 1 of each cycle
- Maintenance (starting with cycle 5; until excessive toxicity, progression, or for 2 years):
  - Nivolumab 3 mg/kg IV, day 1 of each cycle

Notes:
- Doses are based on actual body weight. If the patient’s weight on the day of dosing differs by > 10% from the weight used to calculate the previous dose, the dose must be recalculated
- Nivolumab is infused over 60 minutes, followed by a saline flush; Ipilimumab is then infused over 90 minutes
- Separate infusion bags and filters must be used for each infusion

Patient Enrollment
All Sites: Oncology Patient Enrollment Network (OPEN), https://open.ctsu.org

Protocol Information

Please Enroll Your Eligible Patients!
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Schema

**Induction Therapy Cycles**

**Arm A**
- Nivolumab 1mg/kg IV Day 1
- Ipilimumab 3 mg/kg IV Day 1
- Sargramostim 250 ug SubQ days 1-14 of each cycle
- Every cycle for 4 cycles.

**Arm B**
- Nivolumab 1mg/kg IV Day 1
- Ipilimumab 3 mg/kg IV Day 1
- Cycles 1-4
- Every cycle for 4 cycles.

**Maintenance Therapy Cycles 5 and higher**

- Nivolumab 3mg/kg IV Day 1 of each cycle
- Sargramostim 250 ug SubQ days 1-14 of each cycle

- **PD:** Discontinue treatment
- **24 weeks:** Reassess for evidence of anti-tumor response
- **PR, SD, CR:** Continue maintenance therapy

Strat Factors:
- BRAF mutational status of tumor: WT or mutated
- Stage: II/M1a, M1b, M1c

Accrual Goal = 400
1 cycle = 21 days

1. Scans will be done at week 12 but treatment should continue until week 24 regardless of progression unless treatment is contraindicated by Section 5.6.
2. Patients will receive protocol therapy until progressive disease, non-protocol therapy, or up to two years, whichever comes first.