

# 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



## Study Schema

- Stratification
- BRAF mutational status of tumor (WT or mutated)
  - Stage (AJCC v7) (III/M1a, M1b, M1c)
  - Prior anti-PD1/PD-L1 therapy (yes or no)

Accrual goal = 600 patients.

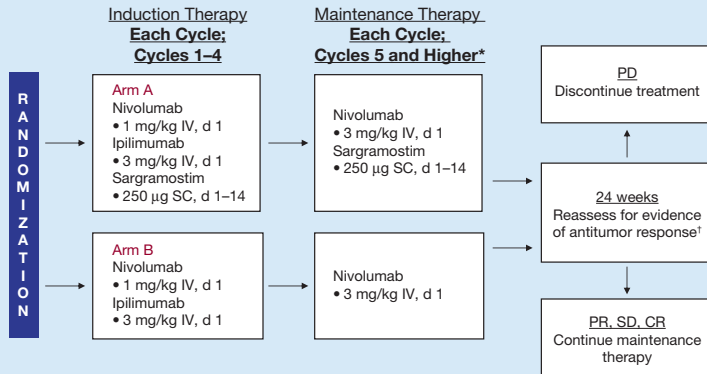
Cycle = 21 days.

Doses are based on actual body weight.

Nivolumab is infused over 30 minutes, followed by a saline flush. Ipilimumab is then infused over 30 minutes. Separate infusion bags and filters must be used for each infusion.

\*Patients will receive protocol therapy until progressive disease, nonprotocol therapy, or up to 2 years, whichever comes first.

†Scans will be done at week 12, but treatment should continue until week 24, regardless of progression, unless treatment is contraindicated by Section 5.4. CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease; WT = wild type.



## Overall EA6141 Study Objectives

To determine whether the addition of sargramostim (granulocyte-macrophage colony-stimulating factor; GM-CSF) to the combination of nivolumab and ipilimumab improves efficacy of the agents, therefore providing a prolonged survival benefit, and whether it improves tolerability by decreasing high-grade adverse events

## Study Objectives

### *Primary Objective*

- Compare the overall survival of patients treated with nivolumab/ipilimumab/GM-CSF versus nivolumab/ipilimumab

### *Secondary Objectives*

- Evaluate progression-free survival of patients treated with nivolumab/ipilimumab/GM-CSF versus nivolumab/ipilimumab
- Assess for differences in tolerability, specifically the rate of grade 3 or higher adverse events, between nivolumab/ipilimumab/GM-CSF versus nivolumab/ipilimumab
- Evaluate and compare immune-related response rate (based on immune-related response criteria) and response rate (RECIST criteria)

### *Exploratory Tobacco Use Objectives*

Refer to protocol Section 2.1.3 for a list of objectives.

## Eligibility Criteria\*

### *Main Inclusion Criteria*

- $\geq 18$  years of age
- ECOG performance status 0–1
- Unresectable stage III or IV melanoma (AJCC v7); histologic or cytologic confirmation of melanoma that is metastatic or unresectable and clearly progressive
- Known BRAF mutational tumor status; wild-type or mutated, prior to randomization
- Measurable disease per RECIST 1.1 criteria; all sites of disease must be evaluated within 4 weeks prior to randomization
- May have had:
  - Prior systemic therapy in the adjuvant setting (eg, interferon, BRAF, or MEK agents)

\*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.

- Prior anti-CTLA-4 or prior anti-PD-1/PD-L1 agent in the adjuvant setting, if at least one year from the last dose has passed before beginning treatment
- Discontinued chemotherapy, immunotherapy, or other investigational agents used in the adjuvant setting  $\geq 4$  weeks prior to randomization and recovered from adverse events due to those agents
  - Mitomycin and nitrosoureas must be discontinued  $\geq 6$  weeks, and radiation therapy  $\geq 2$  weeks, prior to study entry with recovery from adverse events due to treatment
  - Prior surgery must be  $\geq 4$  weeks from randomization with full recovery from postsurgical complications
- Adequate hematologic, hepatic, and renal function within 4 weeks prior to randomization

### ***Main Exclusion Criteria***

- Prior ipilimumab or PD-1/PD-L1 agent in the metastatic setting
- Receiving other investigational agents while on study or within 4 weeks prior to randomization
- Receiving any live vaccine within 30 days prior to randomization, while participating on study, and for 28 days after the last dose of protocol treatment
- Active central nervous system (CNS) metastases
- Other known current malignancies, other than basal cell skin cancer, squamous cell skin cancer, in situ cervical cancer, or ductal or lobular carcinoma in situ of the breast

- Any serious or unstable preexisting medical conditions, including but not limited to, ongoing or active infection requiring parenteral antibiotics on day 1, history of bleeding diathesis or need for concurrent anticoagulation, or psychiatric illness/social situations that would limit compliance with study requirements or interfere with patient's safety or obtaining informed consent
- Active hepatitis B or C viral infection
- HIV positivity
- Autoimmune disorders or conditions of immunosuppression that require current ongoing treatment with systemic corticosteroids (or other systemic immunosuppressants), including oral steroids or continuous use of topical steroid creams or ointments or ophthalmologic steroids

***(Continued)***

## **Main Exclusion Criteria (cont)**

- History of symptomatic autoimmune disease (eg, rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [eg, Wegener's granulomatosis]); motor neuropathy considered of autoimmune origin (eg, Guillian-Barré syndrome and myasthenia gravis); or other CNS autoimmune disease (eg, multiple sclerosis)
- History of inflammatory bowel disease or diverticulitis (history of diverticulosis is allowed)
- Significant medical, surgical, or psychiatric conditions requiring medication or treatment that in the opinion of the investigator may interfere with compliance, make the administration of the study drugs hazardous, or obscure the interpretations of adverse events
- Pregnancy or breast-feeding

