A Randomized Phase III Trial of Dabrafenib + Trametinib Followed by Ipilimumab + Nivolumab at Progression vs Ipilimumab + Nivolumab Followed by Dabrafenib + Trametinib at Progression in Patients With Advanced BRAFV600 Melanoma

Overall EA6134 Study Objective

To investigate whether the initial combination treatment of ipilimumab + nivolumab (followed by dabrafenib + trametinib) will provide a greater therapeutic benefit and more durable complete response compared with initial treatment with dabrafenib + trametinib (followed by ipilimumab + nivolumab) in patients with BRAFV600-mutant melanoma.

Accrual goal = 300 patients.
Cycle = 42 days.

Doses based on actual body weight.

Step 1: patients will be randomized to either arm A or B. Step 2: patients progressing on either arm A or B will re-register and cross over to step 2. Arm A patients will re-register and cross over to arm C. Arm B patients will re-register and cross over to arm D.

1Elevated serum LDH is defined as above upper limit of normal for institution.
†Progressive disease will be determined by RECIST criteria for all arms (in protocol, Section 6). Crossover should proceed no sooner than 2 and no longer than 12 weeks following RECIST-defined PD on either arm.
‡Must meet eligibility criteria found in protocol (Section 3.2).

LDH = lactate dehydrogenase; PD = disease progression.
Study Objectives

Primary Objective
• Determine whether initial treatment with either the combination ipilimumab + nivolumab (followed by dabrafenib + trametinib) or dabrafenib + trametinib (followed by ipilimumab + nivolumab) significantly improves 2-year overall survival (OS) in patients with unresectable stage III or IV BRAFV600-mutant melanoma

Secondary Clinical Objectives
• Evaluate OS and hazard ratio for death
• Determine 3-year OS
• Evaluate antitumor activities (RECIST-defined response rate, median progression-free survival, and safety profiles) of each study arm
• Assess feasibility of crossover to the alternative treatment strategy (percentage of patients able to cross over from one arm to the other and complete at least an initial treatment course (12 wk) after crossover without intervening symptomatic disease progression or treatment-limiting toxicity)

Secondary Laboratory Objectives
• Determine the association of inherited variation with immune-mediated adverse events and response to ipilimumab + nivolumab
• Determine the utility of circulating BRAF levels in determining response and resistance to either BRAF/MEK directed and/or combination immunotherapy in patients with BRAF-mutant melanoma

Secondary Patient-Reported Outcomes Objectives
• Evaluate differences in overall health between initial treatment arms at 2 years, accounting for toxicities and OS (primary)
• Assess differences in overall function over 2 years between initial treatments (secondary)
• Document effects of treatment crossover and treatment administration sequence on symptom burden and overall function (secondary)

Eligibility Criteria*

Step 1: Main Inclusion Criteria
• ≥ 18 years of age
• ECOG performance status 0-1
• Unresectable stage III or stage IV disease
• Measurable disease; all sites must be evaluated within 4 weeks prior to randomization

*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.
Histologic or cytologic confirmation of melanoma that is metastatic or unresectable and clearly progressive

Note: Patients with BRAFV600 E or K mutant melanoma (whether cutaneous, acral, or mucosal primary) are eligible; patients with uveal melanoma are ineligible

BRAFV600E or BRAF600K mutations, identified by an FDA-approved test at a CLIA-certified lab

Discontinuation of chemotherapy, immunotherapy, or other investigational agents used in the adjuvant setting ≥ 4 weeks prior to entering study and recovered from adverse events due to those agents. Mitomycin and nitrosoureas must have been discontinued ≥ 6 weeks prior to entering study; discontinuation of radiation therapy ≥ 2 weeks prior to entering study and recovery from treatment-associated adverse effects. Prior surgery must be ≥ 4 weeks from registration with full recovery from postsurgical complications

Adequate hematologic, hepatic, and renal function within 4 weeks prior to randomization

Use of effective contraception or abstinence

**Step 1: Main Exclusion Criteria**

- Prior systemic therapy in adjuvant setting that included CTLA4 or PD1 pathway blocking antibody or BRAF/MEK inhibitor
- Prior systemic treatment for advanced (measurable metastatic) disease
- Use of other investigational agents while on study or within 4 weeks prior to registration
- Active CNS metastases
- Current malignancies, other than basal cell skin cancer, squamous cell skin cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of breast; other malignancies are eligible if continuously disease-free for > 3 years before registration
- History of RAS mutation–positive tumors. Note: prospective RAS testing not required
- Serious or unstable preexisting medical conditions (besides malignancy exceptions), including ongoing or active infection requiring parenteral antibiotics on day 1, history of bleeding diathesis or need for concurrent anticoagulation, or psychiatric illness/social situations limiting compliance with study requirements or interfering with patient’s safety or obtaining informed consent
- History or evidence of cardiovascular risks
- HIV positivity; active hepatitis B or C
- Active or history of autoimmune disease that might recur, which may affect vital organ function or require immune-suppressive treatment including systemic corticosteroids
- Use of other anticancer or investigational therapies; medications or substances that are strong inhibitors or inducers of CYP3A or CYP2C8
Step 1: Main Exclusion Criteria (cont)
- History of retinal vein occlusion
- Evidence of interstitial lung disease or pneumonitis
- Malabsorption, swallowing difficulty, or other conditions that would interfere with the ingestion or absorption
- Pregnancy or breast-feeding

Step 2 (Crossover): Main Inclusion Criteria
- No restriction on serum lactate dehydrogenase
- Melanoma that is metastatic and clearly progressive on prior therapy
- At least 2 weeks and within 12 weeks from documented disease progression on study step 1. All disease sites must be evaluated within 4 weeks prior to registration
- Recovery from adverse events (resolved to grade 1 or less) of prior therapy. Patients with immune-related toxicities from ipilimumab + nivolumab may continue to study step 2, even if still on steroids to control side effects, if toxicity resolved to grade 1 or less
- Discontinuation of radiation therapy ≥ 2 weeks prior to registering to study step 2 and recovery from treatment-associated adverse events. Prior surgery must be ≥ 2 weeks from registration to step 2 with full recovery from postsurgical complications

Step 2 (Crossover): Main Exclusion Criteria
- Active CNS metastases
- Concurrent malignancies, other than basal cell skin cancer, squamous cell skin cancer, in situ cervical cancer, and ductal or lobular carcinoma in situ of the breast