**DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing) a Phase III Trial**

**Study Schema**

**Arm A**
- **Initial Treatment Immunotherapy Induction**
  - Regimens (1 or 2)
    - Regimen 1: Nivolumab
      - 1 mg/kg, IV, d 1 and 22 of cycles 1 and 2
    - Regimen 2: Nivolumab
      - 3 mg/kg, IV, d 1 and 22 of cycles 1 and 2

**Arm B**
- **Dabrafenib**
  - 150 mg, PO, bid, d 1-42 of each 6-wk cycle
- **Trametinib**
  - 2 mg, PO, qd d 1-42 of each 6-wk cycle

**Arm C**
- **Dabrafenib**
  - 150 mg, PO, bid, d 1-42 of each 6-wk cycle
- **Trametinib**
  - 2 mg, PO, qd d 1-42 of each 6-wk cycle

**Arm D**
- **Initial Treatment Immunotherapy Induction**
  - Regimens (1 or 2)
    - Regimen 1: Nivolumab
      - 1 mg/kg, IV, d 1 and 22 of cycles 1 and 2
    - Regimen 2: Nivolumab
      - 3 mg/kg, IV, d 1 and 22 of cycles 1 and 2

**Immunotherapy Maintenance**
- Nivolumab
  - 3 mg/kg, IV, d 1, 15 and 29 of cycles 3-14 (max 72 wk of maintenance)

**Stratification Factors**
- ECOG PS (0 vs 1)
- Serum LDH
  - (normal vs elevated)

**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.

**Elevated serum LDH** is defined as above upper limit of normal for institution.

**1Progressive disease** will be determined by RECIST criteria for all arms (in protocol, Section 6). Crossover should proceed no sooner than 2 weeks following RECIST-defined PD on either arm.

**Must meet eligibility criteria found in protocol (Section 3.2).**

LDH = lactate dehydrogenase; PD = disease progression.
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.

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.
- Identify tumor-related predictive markers of response to either BRAF/MEK directed and/or combination immunotherapy
- Identify blood-based correlates of specific immune-related adverse events and the impact of immunosuppressive therapy on these and tumor biomarkers

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)

Exploratory Tobacco Use Objectives
Refer to Protocol Section 2.5 for list of objectives.
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
• Histologic or cytologic confirmation of melanoma that is metastatic or unresectable and clearly progressive
  Note: Patients with BRAFV600 mutant melanoma (whether cutaneous, acral, or mucosal primary) are eligible; patients with uveal melanoma are ineligible
• BRAFV600 mutation, 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 ≥ 1 week prior to entering study and recovery from treatment-associated adverse effects. Prior surgery must be ≥ 2 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
• Known active and definitive CNS metastases (patients with treated brain metastases may be eligible per protocol)
• 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 > 2 years before registration
• Serious or unstable preexisting medical conditions (besides malignancy exceptions), including ongoing or active infection requiring parenteral antibiotics on day 1, 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

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

Step 1: Main Exclusion Criteria (cont)
- 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
- History of retinal vein occlusion
- Evidence of interstitial lung disease or pneumonitis
- Malabsorption, swallowing difficulty, or other conditions that would interfere with 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

Step 2 (Crossover): Main Exclusion Criteria
- Active and definitive CNS metastases (patients with treated brain metastases may be eligible per protocol)
- Other current malignancies
- Pregnancy or breastfeeding

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