**Overall Study Goal**

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 Schema**

<table>
<thead>
<tr>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
<th>Arm D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Treatment Immunotherapy Induction</strong></td>
<td><strong>Initial Treatment Immunotherapy Induction</strong></td>
<td><strong>Initial Treatment Immunotherapy Induction</strong></td>
<td><strong>Initial Treatment Immunotherapy Induction</strong></td>
</tr>
<tr>
<td>Regimen 1: Nivolumab</td>
<td>Regimen 1: Dabrafenib</td>
<td>Regimen 1: Nivolumab</td>
<td>Regimen 1: Nivolumab</td>
</tr>
<tr>
<td>• 1 mg/kg, iv, d 1 and 22 of cycles 1 and 2</td>
<td>• 150 mg, po, bid, d 1-42 of each 6-wk cycle</td>
<td>• 1 mg/kg, iv, d 1 and 22 of cycles 1 and 2</td>
<td>• 1 mg/kg, iv, d 1 and 22 of cycles 1 and 2</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Trametinib</td>
<td>Ipilimumab</td>
<td>Ipilimumab</td>
</tr>
<tr>
<td>• 3 mg/kg, iv, d 1 and 22 of cycles 1 and 2</td>
<td>• 2 mg, po, qd 1-42 of each 6-wk cycle</td>
<td>• 3 mg/kg, iv, d 1 and 22 of cycles 1 and 2</td>
<td>• 3 mg/kg, iv, d 1 and 22 of cycles 1 and 2</td>
</tr>
<tr>
<td><strong>Immunotherapy Maintenance</strong></td>
<td><strong>Immunotherapy Maintenance</strong></td>
<td><strong>Immunotherapy Maintenance</strong></td>
<td><strong>Immunotherapy Maintenance</strong></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Nivolumab</td>
<td>Nivolumab</td>
<td>Nivolumab</td>
</tr>
<tr>
<td>• 3 mg/kg, iv, d 1, 15 and 29 of cycles 3-14</td>
<td>• 3 mg/kg, iv, d 1, 15 and 29 of cycles 3-14</td>
<td>(max 72 wk of maintenance)</td>
<td>(max 72 wk of maintenance)</td>
</tr>
</tbody>
</table>

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

**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 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
- 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.
How Your Site Can Participate

- Before recruitment, investigators must be registered members of an NCTN network group
- All individuals contributing to NCI-sponsored trials must register and renew annually
- Registrants must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam)
- Investigator (IVR), Non-physician Investigator (NPIVR), or Associate Plus (AP) must complete annual registration using CTEP’s Web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr)
- Required documentation for IVR, NPIVR, and AP includes FDA Form 1572 (IVR and NPIVR only), Financial Disclosure Form, NCI Biosketch, HSP/GCP training, Agent Shipment Form (IVR only), and CV (optional)
- IVRs and NPIVRs must list clinical practice sites and IRBs covering their practice sites on FDA Form 1572 in RCR to allow the following: added to site roster; assigned treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN; acting as site-protocol Principal Investigator (PI) on IRB approval; assigned Clinical Investigator (CI) role on Delegation of Tasks Log (DTL)
- For questions, please contact RCR Help Desk via e-mail: RCRHelpDesk@nih.gov
- Sites participating on the NCI CIRB initiative and CIRB-approved need not submit IRB approval documentation to CTSU. Their CIRB approval is applied to RSS in an automated process. Signatory institutions must submit a Study Specific Worksheet for Local Context to the CIRB via IRBManager, indicating intent to open locally

Requirements for EA6134 (DREAMseq) trial site registration:
- IRB approval (for sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- Submit all required regulatory documents to:
  - The CTSU Regulatory Office via the Regulatory Submission Portal; documentation will be entered and tracked in the CTSU RSS
  - Regulatory Submission Portal: www.ctsu.org (members’ area) → Regulatory Tab → Regulatory Submission

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Required regulatory documentation:
- Copy of IRB Informed Consent Document
- CTSU IRB Certification Form or signed HHS OMB No. 0990-0263 (replaced Form 310) or IRB Approval Letter
Note: Submission includes all sites approved for the protocol under an assurance number; OHRP assurance number of reviewing IRB; full protocol title and number; version date; type of review (full board vs expedited); date of review; signature of IRB official.
- Check registration status at https://www.ctsu.org
- Once documentation has been submitted and approved:
  - Protocol treatment should start within 7 working days after registration (must not start before)
  - Ipilimumab, nivolumab, dabrafenib, and trametinib are considered investigational for this study and will be distributed free of charge by the NCI. Address questions to PMB via phone (240) 276-6575 or e-mail PMBAfterHours@mail.nih.gov
  - Patient enrollment is via OPEN, accessed at https://open.ctsu.org. Data collection is exclusively through Medidata Rave. Address OPEN and Rave questions to the CTSU Help Desk at 1-888-823-5923 or ctsucolor@westat.com
  - Pathologic samples must be submitted for central diagnostic review (mandatory) and for defined laboratory research studies (per patient consent), and biologic samples submitted for defined laboratory research studies (per patient consent), per protocol (Section 10)
  - Each investigator must take the training course “EA6134 Ipilimumab and Nivolumab Immune Related Adverse Events: Summary and Recommended Management,” prior to first patient enrollment by accessing: http://ecog.mindflash.com/PublicCoursePage.aspx?c=1232832108. OPEN will block enrollment if the enrolling investigator has not completed the training. E-mail EATraining@ecog-acrin.org when a patient is waiting, or for additional questions

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For Further Study Information

- For more information about the EA6134 study, please visit the following:
  - Cancer.gov; search EA6134
  - Clinicaltrials.gov; search NCT02224781
- For more information about ECOG-ACRIN, visit ecog-acrin.org