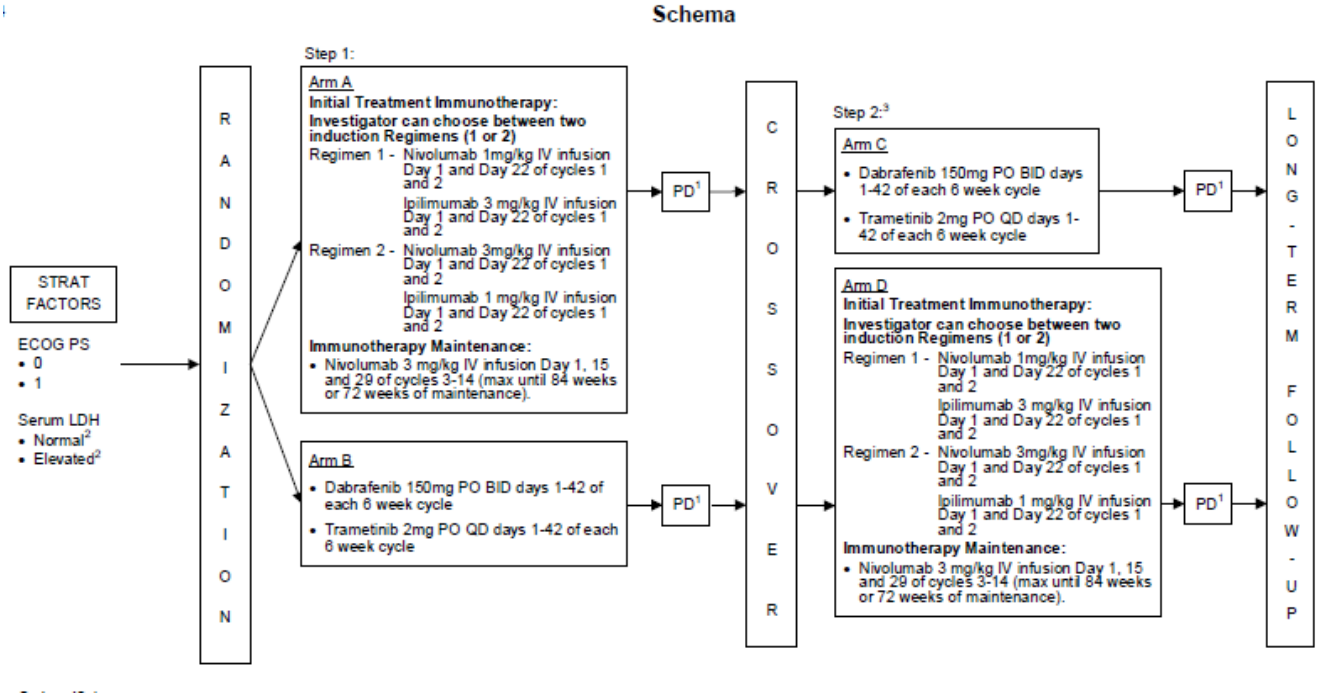
Fast Facts

EA6134: DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing) A Phase III Trial

All drugs are provided by Sponsor – See study schema



Eligibility Criteria Step 1:

1. Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of dabrafenib or dabrafenib + trametinib or nivolumab or nivolumab + ipilimumab therapy in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.
2. ECOG Performance status: 0 or 1
3. Women must not be pregnant or breast-feeding, as the effects of ipilimumab + nivolumab or dabrafenib + trametinib on the developing human fetus are unknown.
   All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy.
   A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

4. The effects of dabrafenib and trametinib or ipilimumab and nivolumab on the developing human fetus are unknown. Furthermore, dabrafenib has been reported to interfere with the effect of hormone based oral contraceptives. For this reason and because other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and sexually active males must agree to use at least two other accepted and effective methods of contraception and/or to abstain from sexual intercourse for the duration of their participation in the study, and for at least 4 weeks after treatment with dabrafenib or for 4 months after dabrafenib in combination with trametinib. Women of child-bearing potential must use at least two other accepted and effective methods of contraception and/or to abstain from sexual intercourse for at least 5 months after the last dose of nivolumab and/or ipilimumab and sexually active males must use at least two other accepted and effective methods of contraception and/or to abstain from sexual intercourse for at least 7 months after the last dose of nivolumab and/or ipilimumab. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.
5. Patients must have unresectable stage III or stage IV disease.
6. Patients must have measurable disease as defined in Section 6.1. All sites of disease must be evaluated within 4 weeks prior to randomization.
7. Patients must have histological or cytological confirmation of melanoma that is metastatic or unresectable and clearly progressive. **NOTE:** Any patient with BRAFV600 mutant melanoma (whether cutaneous, acral or mucosal primary) who meets the eligibility criteria is eligible for participation in this trial. Patients with uveal melanoma are not eligible.
8. Patients must have BRAFV600 mutation, identified by an FDAapproved test at a CLIA-certified lab. If test at CLIA-certified lab used a non-FDA approved method, information about the assay must be provided. (FDA approved tests for BRAF V600 mutations in melanoma include: THxID BRAF Detection Kit and Cobas 4800 BRAF V600 Mutation Test, Foundation Medicine. Prompt information on tumor BRAF mutation status can also be obtained via Novartis "knowNow" Program. See link for details. https://www.knownowbraf.com/melanoma-testing).
9. Patients may have had prior systemic therapy in the adjuvant setting; however this adjuvant treatment must not have included a CTLA4 or PD1 pathway blocking antibody or a BRAF/MEK inhibitor. Also, patients may not have had any prior systemic treatment for advanced (measurable metastatic) disease.
10. Patients must have discontinued chemotherapy, immunotherapy or other investigational agents used in the adjuvant setting ≥ 4 weeks prior to entering the study and recovered from adverse events due to those agents. Mitomycin and nitrosoureas must have been discontinued at least 6 weeks prior to entering the study. Patients must have discontinued radiation therapy ≥ 1 week prior to entering the study and recovered from any adverse events associated with treatment. Prior surgery must be ≥ 2 weeks from registration and patients must be fully recovered from post surgical complications.
11. Patients must not receive any other investigational agents while on study or within four weeks prior to registration.
12. Patients are ineligible if they have any currently known active and definitive CNS metastases. Patients who have treated brain metastases (with either surgical resection or stereotactic radiosurgery (SRS)) could be eligible. Patients must not have taken any steroids ≤ 10 days prior to randomization for the purpose of managing their brain metastases. Repeat imaging after SRS or surgical resection is not required so long as baseline MRI is within 4 weeks of registration. Patients with multiple brain metastases treated with SRS (w or w/o WBRT), are not an exclusion. Patients with definitive CNS metastases treated with only WBRT are ineligible. Patients with potential CNS metastases that are too small for treatment with either SRS or surgery
13. (e.g. 1-2 mm) and/or are of uncertain etiology are potentially eligible, but need to be discussed with and approved by the Study PI.
14. Patients must not have other current malignancies, other than basal cell skin cancer, squamous cell skin cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast. Patients with other

malignancies are eligible if they have been continuously disease-free for > 2 years prior to the time of registration.

15. Patients must have the following values for initial laboratory tests obtained within 4 weeks prior to randomization (ULN: institutional upper limit of normal):
    a) White Blood Count ≥ 3,000/uL
    b) ANC ≥ 1,500/uL
    c) Platelet Count ≥ 100,000/uL
    d) Hemoglobin > 8 g/dL
    e) Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or serum creatinine clearance (CrCl) ≥ 40ml/min. (CrCl= Wt (kg) x (140-age)*/72 x Cr. level, *female x 0.85)
    f) AST and ALT ≤ 3 x ULN (≤ 5 x ULN for patients with documented liver metastases)
    g) Alkaline Phosphatase ≤ 2 x ULN (≤ 5x ULN for patients with known liver involvement and ≤ 7x ULN for patients with known bone involvement)
    h) Total Bilirubin ≤ 1.5 x ULN except subjects with normal direct bilirubin or those with known Gilbert's syndrome
16. Patients must not have any serious or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), including but not limited to, ongoing or active infection requiring parenteral antibiotics on day 1, or psychiatric illness/social situations that would limit compliance with study requirements, interfere with subject's safety, or obtaining informed consent. Therapeutic level dosing of warfarin can be used with close monitoring of PT/INR by the site. Exposure may be decreased due to enzyme induction when on treatment, thus warfarin dosing may need to be adjusted based upon PT/INR. Consequently, when discontinuing dabrafenib, warfarin exposure may be increased and thus close monitoring via PT/INR and warfarin dose adjustments must be made as clinically appropriate. Prophylactic low dose warfarin may be given to maintain central
    catheter patency.
17. Patients must not have a history of or evidence of cardiovascular risks including any of the following:
    a) QT interval corrected for heart rate using the Bazett's formula QTcB ≥ 480 msec.at baseline.
    b) History of acute coronary syndromes (including myocardial infarction or unstable angina), coronary angioplasty, or stenting within the past 24 weeks prior to registration.
    c) History prior to registration or evidence of current ≥ Class II congestive heart failure as defined by the New York Heart Association (NYHA) functional classification system. (See Appendix IX)
    d) LVEF ≤ 45% on cardiac echo or MUGA
    e) Intra-cardiac defibrillator.
18. Individuals who are known to be HIV infected are ineligible (Note: HIV testing is not required for entry into the study).
19. Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, should be excluded. These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease. Patients with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible. Patients with rheumatoid arthritis and other arthropathies, Sjögren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), should be evaluated for

the presence of target organ involvement and potential need for systemic treatment. If no systemic immune suppression is deemed necessary they can be eligible.

20. The following medications or non-drug therapies are also prohibited while on treatment in this study:
    a) Other anti-cancer therapies
    b) Other investigational drugs
    Patients taking any medications or substances that are strong inhibitors or inducers of CYP3A or CYP2C8 are ineligible (appendix XI).
21. Patients must not have history of retinal vein occlusion (RVO).
22. Patients must not have evidence of interstitial lung disease or pneumonitis.
23. Patients must not have malabsorption, swallowing difficulty, or other conditions that would interfere with the ingestion or absorption of dabrafenib or trametinib.

Eligibility Criteria Step 2 (Crossover arm for patients that have progressive disease):

1. The patient must have met all eligibility criteria in Section 3.1 (except as detailed below) at the time of crossover.
    a) RECIST defined measurable disease is not required (see 3.2.3).
    b) Only prior systemic therapy as part of step 1 is allowed. Patients who received allowed systemic therapy in the adjuvant setting prior to Step 1 and were eligible for step 1 are not excluded from proceeding to Step 2 if they meet other eligibility criteria.
    c) malabsorption, swallowing difficulty, or other conditions that would interfere with the ingestion or absorption of dabrafenib or trametinib, or history of retinal vein occlusion are acceptable for patients crossing over to ipilimumab + nivolumab treatment.
    d) history of autoimmune disease, excluding interstitial lung disease or pneumonitis, is allowed in patients crossing over to dabrafenib/trametinib therapy (see 3.2.4).
    e) Patients crossing over from nivolumab/ipilimumab to dabrafenib/trametinib who underwent surgery or SRS to CNS metastases need not be off of steroids to start treatment (see 3.2.6).
    f) There is no restriction on serum LDH at crossover.
    g) Patients with a history of cardiovascular risks that developed during step 1 of therapy should be discussed with study PI at time of crossover.
2. Patients must have melanoma that is metastatic and clearly progressive on prior therapy.
3. Patients must be at least 1 week from documented PD on Step 1 of current study. All sites of disease must be evaluated within 4 weeks prior to registration.
4. Patients must have recovered from adverse events (toxicities resolved to grade 1 or less) of prior therapy. Patients with immune related toxicities from ipilimumab + nivolumab may continue onto Step 2 even if still on steroids to control side effects, so long as toxicity has resolved to grade 1 or less.
5. Patients must have discontinued radiation therapy prior to registering to Step 2 of the study and recovered from any adverse events associated with treatment. Prior surgery must be ≥ 2 weeks from registration to Step 2 and patients must be fully recovered from post-surgical complications.
6. Patients are ineligible if they have any currently active and definitive CNS metastases. Patients who have treated brain metastases (with either surgical resection or stereotactic radiosurgery (SRS)) could be eligible to proceed. Patients crossing over from dabrafenib/trametinib to nivo/ipi must not have taken any steroids ≤ 10 days prior to registration for the purpose of managing their brain metastases. Patients with only Whole Brain irradiation for treatment of CNS metastases are ineligible. Patients with definitive CNS metastases treated with only WBRT are ineligible. Patients with potential CNS metastases that are too small for treatment with either SRS or surgery (e.g. 1-2 mm) and/or are of uncertain etiology are potentially eligible, but need to be discussed with and approved by the Study PI.
7. Patients must not have other current malignancies.

8. Women must not be pregnant or breast-feeding, as the effects of ipilimumab + nivolumab or dabrafenib + trametinib on the developing human fetus are unknown. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to Step 2 crossover to rule out pregnancy.

   A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months.

9. The effects of dabrafenib and trametinib or ipilimumab and nivolumab on the developing human fetus are unknown. Furthermore, dabrafenib has been reported to interfere with the effect of hormone based oral contraceptives. For this reason and because other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and sexually active males must agree to continue to use the same contraception requirements as on Step 1 of this study (ie: use at least two other accepted and effective methods of contraception and/or to abstain from sexual intercourse for the duration of their participation in the study, and for at least 4 weeks after treatment with dabrafenib or for 4 months after dabrafenib in combination with trametinib. Women of child-bearing potential must use at least two other accepted and effective methods of contraception and/or to abstain from sexual intercourse for at least 5 months after the last dose of nivolumab and/or ipilimumab and sexually active males must use at least two other accepted and effective methods of contraception and/or to abstain from sexual intercourse for at least 7 months after the last dose of nivolumab and/or ipilimumab). Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately