Cancer Research Consortium of West Michigan
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FAST FACTS

EA6192 - A Phase II Study of Biomarker Driven Early Discontinuation of Anti-PD-1 Therapy in Patients with Advanced Melanoma (PET-Stop)

Eligibility criteria

Step 0 Pre-registration Eligibility Criteria

1. Patient must be ≥ 18 years of age.
2. Patient must have active advanced melanoma, defined as unresectable stage IIIB-IV by AJCC 8th edition. Patients with mucosal melanoma defined as unresectable stage III or regional/distant metastatic disease are eligible.
3. Patient must have melanoma originating from cutaneous, acral-lentiginous, or mucosal primary sites. Patients with melanoma of unknown primary site are eligible. Patients must not have melanoma from an ocular primary site.
4. Patient must have had measurable disease by imRECIST prior to start of initial anti-PD-1 therapy as defined in Section 6.1.
5. Patient must be actively receiving standard of care anti-PD-1 therapy, currently be 52 weeks (+/- 2 weeks) from start of anti-PD-1 therapy, and have not experienced a toxicity that prevents them from continuing on therapy. Patients are not required to complete all four induction doses of nivolumab/ipilimumab or pembrolizumab/ipilimumab if they continued to receive anti-PD-1 monotherapy. Weight based anti-PD-1 dosing is permited in place of flat dosing. Permitted systemic anti-PD-1 therapy regimens include:
    a. Nivolumab 240mg IV Q2weeks or 480mg IV Q4weeks
    b. Pembrolizumab 200mg IV Q3weeks or 400mg IV Q6weeks
    c. Nivolumab 1mg/kg plus Ipilimumab 3mg/kg IV Q3weeks induction x 4 doses, followed by Nivolumab 240mg IV Q2weeks or 480mg IV Q4weeks maintenance
    d. Nivolumab 3mg/kg plus Ipilimumab 1mg/kg IV Q3weeks induction x 4 doses, followed by Nivolumab 240mg IV Q2weeks or 480mg IV Q4weeks maintenance
    e. Pembrolizumab 2mg/kg (or 200mg flat dose) plus Ipilimumab 1mg/kg IV Q3weeks induction x 4 doses, followed by Pembrolizumab 200mg IV Q3weeks or 400mg IV Q6weeks maintenance
    f. Nivolumab 480mg / Relatlimab 160mg FDC IV Q4weeks
6. Patient must not be receiving concurrent anti-tumor therapies in addition to the standard of care anti-PD-1 regimens. Patients who are receiving bisphosphonates and RANKL inhibitors for management of bone metastases are eligible.
7. Patient must have an ECOG performance status of 0-2.
8. Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial. Patients with detectable viral loads are excluded as it is unclear if these patients have a low risk of melanoma progression off anti-PD-1 treatment.
9. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

10. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.
11. Patients with baseline brain metastases must have been treated with surgery and/or stereotactic radiosurgery and demonstrate disease control or response. Alternatively, patients with baseline brain metastases primarily treated with systemic therapy must demonstrate ongoing response/disease control. Patients with emergent or progressive brain metastases after start of systemic therapy are not eligible. Brain imaging (MRI with IV contrast preferred; non-contrast MRI contrast enhanced CT scan are acceptable) at week 48 (+/- 6 weeks) to confirm disease control/response is required in patients withknown brain metastasis history.
12. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
13. Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.
14. Patient must have experienced complete response, partial response, or stable disease on restaging scans by imRECIST that is maintained on the PET/CT scan at week 52 (+/- 2 weeks) from start of initial anti-PD-1 therapy as defined in Section 6.1.
15. Patient must have completed an FDG-PET/CT scan at week 52 (+/- 2 weeks) from start of initial anti-PD-1 therapy
    a. Patients with FDG - PET/CT positive for hypermetabolic lesions: If a core needle, punch or excisional biopsy and pathological review of a representative lesion was not performed prior to pre-registration (Step 0) must either:
        i. Be amenable to undergo a biopsy. Patient must not be on anticoagulation therapy or, if on anti-coagulation therapy, patient must be able to hold treatment for a biopsy procedure (core needle, punch or excisional biopsy). Anti-coagulation therapy is defined as low molecular weight heparin, warfarin, factor Xa inhibitor, or direct thrombin inhibitor.
        ii. Have documentation of inability to perform the biopsy due to feasibility or safety concerns.
16. Patients must not be pregnant or breast-feeding due to potential harm to an unborn fetus and possible risk for adverse events in nursing infants with the anti-PD-1 regimens being used.
    All patients of childbearing potential must have a blood test or urine study within 28 days prior to Step 0 pre-registration to rule out pregnancy. A second pregnancy test for patients registered to Arm A may be done as clinically indicated.
    A patient of childbearing potential is defined as anyone, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
    Patient of childbearing potential? _____ (Yes or No)
    Date of blood test or urine study: _____
17. Patients must not conceive or father children by using accepted and effective method(s) of contraception or by abstaining from sexual intercourse from the time of study registration and continuing (for patients of childbearing potential) until at least 5 months after the last dose of

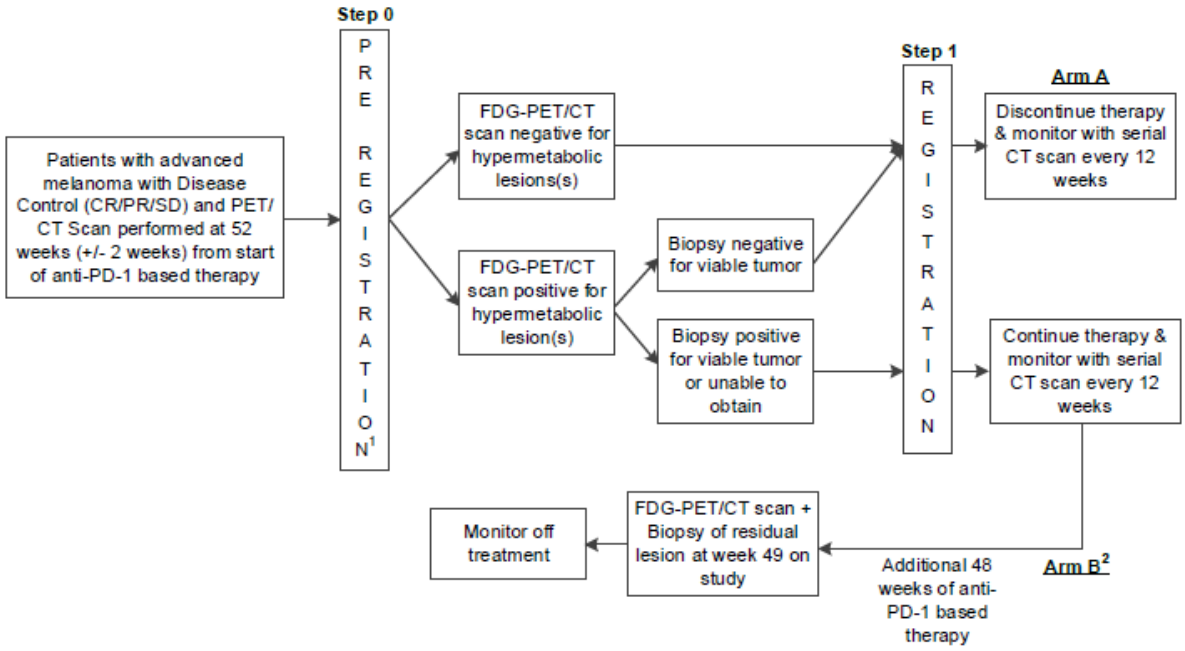
anti-PD-1 treatment. Patients of childbearing potential must also not donate eggs during this same time period.

18. Patient must have adequate organ and marrow function as defined below: (these labs must be obtained ≤ 4 weeks prior to protocol registration)
    Leukocytes ≥ 3,000/mcL
    Leukocytes:_____ Date of Test:_____
    Absolute neutrophil count ≥ 1,500/mcL
    ANC:_____ Date of Test:_____
    Platelets ≥ 100,000/mcL
    Platelet:_____ Date of Test:_____
    Total bilirubin ≤ institutional upper limit of normal (ULN) (patients with history of Gilbert's syndrome are permitted to have a total bilirubin > 1.5 x institutional ULN)
    Bilirubin:_____ Institutional ULN:_____
    Date of Test:_____
    History of Gilbert's syndrome _____(Yes or No)
    AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional ULN
    ALT:_____ Institutional ULN:_____
    Date of Test:_____
    AST:_____ Institutional ULN:_____
    Creatinine ≤ 1.5 x institutional ULN
    Creatinine _____Date of Test:_____

Step 1 Registration Eligibility Criteria

1. Patient met all eligibility criteria outlined in Section 3.1
2. Patient must register to Step 1 within 4 weeks of registration to Step 0.
3. Patients must meet one of the following criteria:
    a. Patient had no positive hypermetabolic lesions on the week 52 FDG-PET/CT.
    b. Patients with positive hypermetabolic lesion(s) on the week 52 FDG-PET/CT (positive hypermetabolic = SUV > pooled mediastinal blood), one of the following must have occurred:
        i. representative lesion was biopsied (core needle, punch or excisional biopsy) and subsequent pathology review performed to determine the presence or absence of viable tumor within 28 days of registration to Step 0.
        ii. Documentation is present that the patient is not able to undergo biopsy of a hypermetabolic lesion due to feasibility or safety concerns, i.e., the lesion location that is not amenable to biopsy

Schema



1. Patient must be actively receiving standard of care anti-PD-1 based therapy and currently be 52 weeks (+/- 2 weeks) from start of anti-PD-1 therapy at the time of step 0 pre-registration.
2. Patients assigned to Arm B will continue the same anti-PD-1 based therapy (Nivolumab, Pembrolizumab, or Nivolumab/Relatlimab FDC).