Cancer Research Consortium of West Michigan
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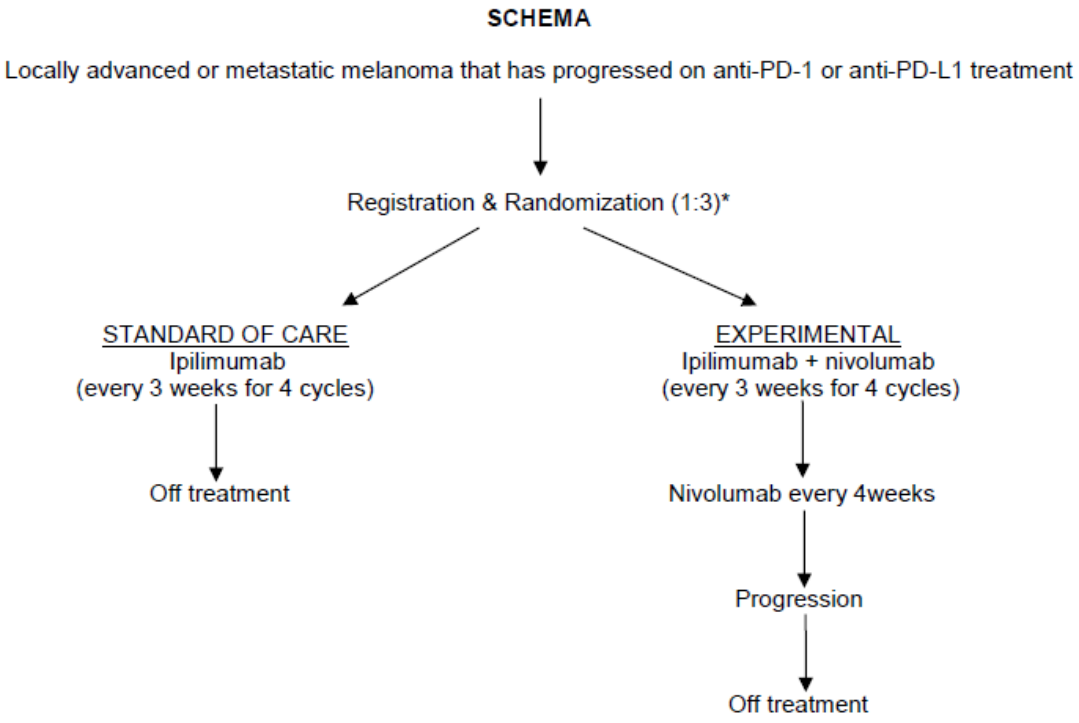
FAST FACTS

S1616, "A Phase II Randomized Study of Nivolumab (NSC-748726) with Ipilimumab (NSC-732442) OR Ipilimumab Alone in Advanced Melanoma Patients Refractory to an Anti-PD-1 or Anti-PD-L1 Agent"



Disease Related Criteria

1. Patients must have pathologically confirmed melanoma that is either Stage IV or unresectable Stage III. Patients may have primaries of cutaneous, mucosal or unknown origin. Patients with uveal (ocular) primary are not eligible.
2. Patients must have measurable disease per RECIST 1.1 (see Section 10.1). All measurable lesions must be assessed by physical examination, CT scans or MRIs within 28 days prior to registration. If the only measurable disease is cutaneous or subcutaneous, lesions must be at least 10 mm in greatest dimension and able to be serially recorded using calipers and photographs. Tests used to assess non-measurable disease must have been performed within 42 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form.
3. Patients with central nervous system (CNS) metastases must have all lesions adequately treated with stereotactic radiation therapy, craniotomy, Gamma Knife® therapy, or whole brain radiotherapy, with no subsequent evidence of CNS progression. Patients must not have required steroids for at least 14 days prior to registration.

Prior/Concurrent Therapy Criteria

1. Patients must have had prior treatment with anti-PD1 or anti-PD-L1 agents and had documented disease progression per the treating physician either while on these agents or after stopping therapy with these agents without intervening therapy. Patients who received adjuvant therapy for previously resected disease with PD-1 or PD-L1 agents may also be eligible if disease recurrence

occurred while still receiving the PD-1 or PD-L1 therapy and no intervening therapy was received. Patients must have discontinued anti-PD-1 or anti-PD-L1 therapy at least 21 days prior to registration.

2. Patients must not have achieved a partial or complete response to the anti-PD-1 or anti-PD-L1 agents prior to progression per the treating physician.
3. Patients must not have had any systemic therapy, including anti-PD-1 or anti-PD-L1 agents, within 21 days prior to registration.
4. Patients must not have had prior radiation therapy within 14 days prior to registration (see Section 5.1c).
5. Patients must not have had:
    a. Prior treatment with ipilimumab or other CTLA-4 antagonists
    b. Systemic therapy between progression on the anti-PD-1 or anti-PD-L1 agents and registration.

   Note: Systemic therapy (including BRAF-targeting agents) prior to anti-PD-1 or anti-PD-L1 therapy is allowed.
6. Patients must not be planning to require any additional form of systemic anti-tumor therapy while on protocol treatment.

Clinical/laboratory Criteria

1. Patients must be ≥ 18 years of age
2. Patients must have Zubrod Performance Status of ≤ 2 (see Section 10.4).
3. Patients must have complete history and physical examination within 28 days prior to registration.
4. Patients must have adequate hematologic function as evidenced by all of the following within 28 days prior to registration: absolute neutrophil count (ANC) ≥ 1,500/mcL; hemoglobin ≥ 8 g/dL; and platelets ≥ 100,000/mcL
5. Patients must have adequate hepatic function as evidenced by all of the following within 28 days prior to registration: total bilirubin ≤ 2.5 x Institutional Upper Limit of Normal (IULN) (except patients with Gilbert's syndrome); and AST and ALT both ≤ 5 x IULN.
6. Patients must have adequate kidney function as evidenced by serum creatinine ≤ 2.0 x IULN within 28 days prior to registration.
7. Patients with a known history of HIV must have CD4 count ≥ institutional lower limit of normal within 28 days prior to registration.
8. Patients must not have known active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection prior to registration.
9. Patients must not have an active infection requiring systemic therapy at time of registration.
10. Patients must not have organ allografts
11. Patients must not have received systemic treatment with corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days prior to registration. Inhaled or topical steroids, and adrenal replacement doses ≤ 10 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease.
12. Patients must not have a history of immune-mediated pneumonitis or colitis that required interruption of therapy or treatment of steroids.
13. Patients with a known history of congestive heart failure (CHF), cardiomyopathy, myocarditis, myocardial infarction (MI), exposure to cardiotoxic medications, or with a clinical history suggestive of the above must have an EKG and Echocardiogram (ECHO) performed within 42 days prior to registration and as clinically indicated while on treatment.
14. Patients with new symptoms of congestive heart failure (CHF), cardiomyopathy, myocarditis, myocardial infarction (MI), or exposure to cardiotoxic medications must have a cardiology consultation, creatinine phosphokinase (CPK), and troponin testing at prestudy and as clinically indicated.

15. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage 0, I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for two years.
16. Patients must not be pregnant or nursing due to risk of fetal or nursing infant harm. Females of reproductive potential must have negative serum pregnancy test within 2 days prior to registration and agree to use an effective contraceptive method throughout the study and for 5 months after completion of protocol treatment. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. If at any point a previously celibate patient chooses to become heterosexually active during or within 5 months after protocol treatment, she is responsible for beginning effective contraceptive measures.
17. Males who are sexually active with women of reproductive potential must have agreed to use birth control throughout the study and for 7 months after completion of protocol treatment. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (vasectomy). If at any point a previously celibate patient chooses to become heterosexually active during or within 7 months after completion of protocol treatment, he is responsible for beginning effective contraceptive measures.

Specimen Submission Criteria

1. Patients must submit archival tissue (if available) for translational medicine as described in Section 15.1. Patients must also be willing to undergo biopsies and submit tissue and blood for translational medicine as described in Section 15.1.
2. Patients must be offered the opportunity to participate in specimen banking of leftover tissue for future research as described in Section 15.1b.

Regulatory Criteria

1. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.
2. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.