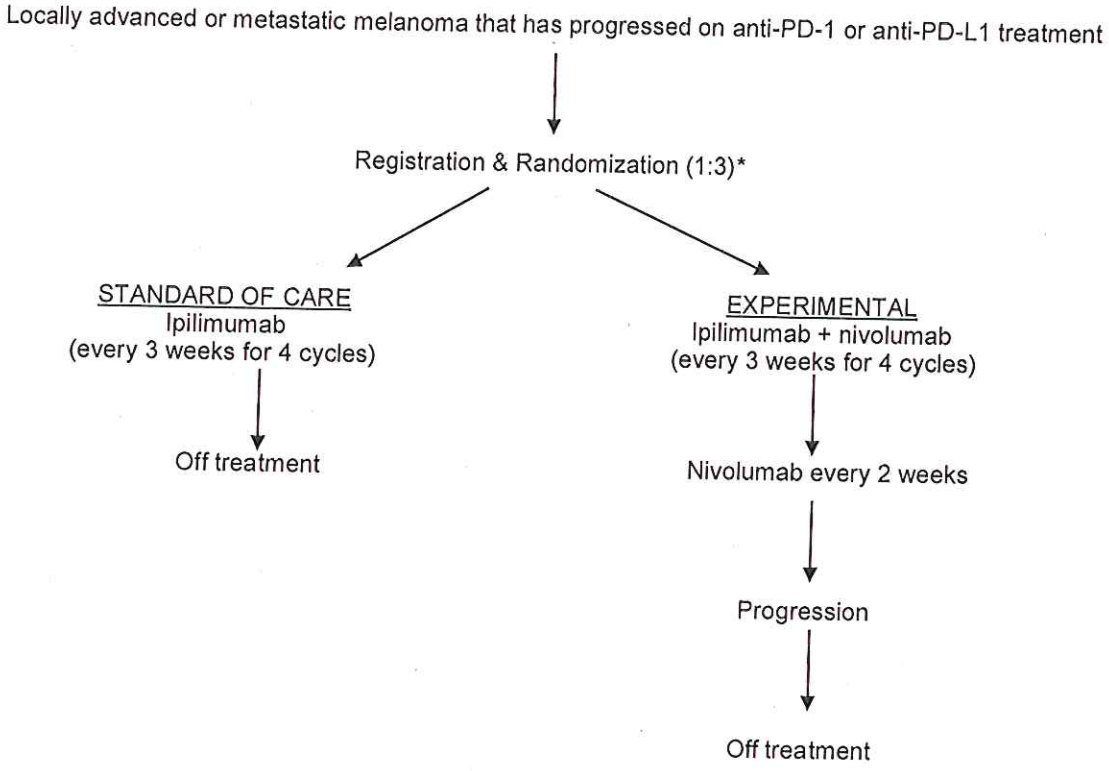
**SCHEMA**




NOTE: This study includes mandatory specimen submission. See Section 15.0 for details.

* For every patient randomized to receive standard of care, there will be three randomized to receive the experimental regimen (see Section 11.0).

## 5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 or melanomaquestion@crab.org prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. **If Day 14 or 28 falls on a weekend or holiday, the limit may be extended to the next working day.**

### 5.1 Disease Related Criteria

a. 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.

b. Patients must have measurable disease per RECIST 1.1 (see Section 10.1). CT scans or MRIs used to assess measurable disease must have been completed 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.

c. 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.

### 5.2 Prior/Concurrent Therapy Criteria

a. Patients must have had prior treatment with anti-PD1 or anti-PD-L1 agents and had documented disease progression either while on these agents or after stopping therapy with these agents without intervening therapy. Patients must have discontinued anti-PD-1 or anti-PD-L1 therapy at least 21 days prior to registration.

b. Patients must not have achieved a confirmed partial or complete response to the anti-PD-1 or anti-PD-L1 agents prior to progression.

c. Patients must not have had any systemic therapy, including anti-PD-1 or anti-PD-L1 agents (see Section 5.1c), within 21 days prior to registration.

d. Patients must not have had prior radiation therapy within 14 days prior to registration.

e. Patients must not have had:

1. Prior treatment with ipilimumab or other CTLA-4 antagonists

2. 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.

f. Patients must not be planning to require any additional form of systemic anti-tumor therapy while on protocol treatment.

5.3 Clinical/Laboratory Criteria

a. Patients must be ≥ 18 years of age.

b. Patients must have Zubrod Performance Status of ≤ 2 (see Section 10.4).

c. Patients must have complete history and physical examination within 28 days prior to registration.

d. 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.

e. 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.

f. Patients must have adequate kidney function as evidenced by serum creatinine ≤ 2.0 x IULN within 28 days prior to registration.

g. Patients with a known history of HIV must have CD4 count ≥ institutional lower limit of normal within 28 days prior to registration.

h. Patients must not have known active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection prior to registration.

i. Patients must not have an active infection requiring systemic therapy at time of registration.

j. Patients must not have organ allografts.

k. 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.

l. Patients must not have a history of immune-mediated pneumonitis or colitis that required interruption of therapy or treatment of steroids.

m. 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.

n. 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.