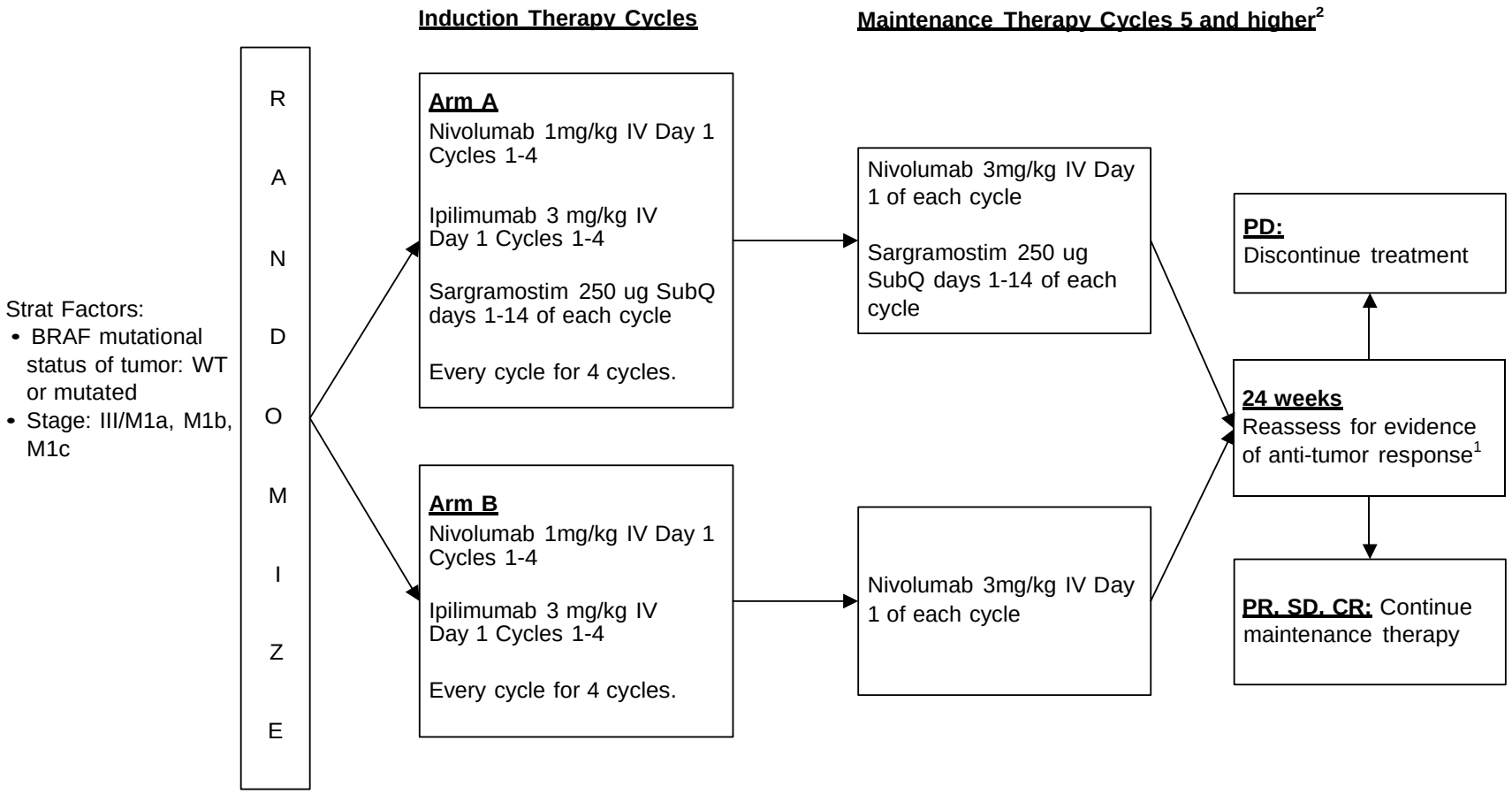
Schema



Accrual Goal= 400
1 cycle= 21 days

1. Scans will be done at week 12 but treatment should continue until week 24 regardless of progression unless treatment is contraindicated by Section 5.6.
2. Patients will receive protocol therapy until progressive disease, non-protocol therapy, or up to two years, whichever comes first.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

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 four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to randomization by the treating physician.

3.1 Phase II/III Eligibility Criteria

_____ 3.1.1 All patients must be ≥ 18 years of age.

_____ 3.1.2 ECOG Performance status: 0 or 1 (Appendix V)

_____ 3.1.3 Patients must have known BRAF mutational status of tumor; Wild-type (WT) or mutated, prior to randomization.

_____ 3.1.4 Women must not be pregnant or breast-feeding due to use of cytotoxic immunotherapy and risk of teratogenic side effects.

All females of childbearing potential must have a blood test or urine study within 2 weeks prior to randomization 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).

Female of childbearing potential? _____(Yes or No)

Date of blood test or urine study: _____

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_____ 3.1.5 Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of contraception or to abstain from sexual intercourse for at least one week prior to the start of the research study, and continuing for up to 23 weeks for women of childbearing potential and 31 weeks for sexually active males after the last dose of the study drugs.

3.1.6 Patients must have unresectable stage III or stage IV melanoma. Patients must have histological or cytological confirmation of melanoma that is metastatic or unresectable and clearly progressive.

3.1.7 Patients must have measurable disease per RECIST 1.1 criteria, as defined in Section 6.1. All sites of disease must be evaluated within 4 weeks prior to randomization.

3.1.8 Patients may have had prior systemic therapy in the adjuvant setting (e.g. interferon, BRAF, or MEK agents). Patients may have had prior anti-CTLA-4 in the adjuvant setting, if at least one year from last dose of treatment has passed prior to beginning treatment. Patients may not have had any prior PD-1/PD-L1 agent in the adjuvant setting.

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3.1.9 Patients may not have had any prior ipilimumab and/or anti-PD-1/PD-L1 agent in the metastatic setting.

3.1.10 Patients must have discontinued chemotherapy, immunotherapy or other investigational agents used in the adjuvant setting ≥ 4 weeks prior to randomization 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 ≥ 2 weeks prior to entering the study and recovered from any adverse events associated with treatment. Prior surgery must be ≥ 4 weeks from randomization and patients must be fully recovered from post surgical complications.

3.1.11 Patients must not receive any other investigational agents while on study or within four weeks prior to randomization.

3.1.12 Patients are excluded for receiving any non-oncology vaccine therapy used for prevention of infectious diseases for up to four weeks (28 days) prior to or after any dose of ipilimumab.

3.1.13 Patients are ineligible if they have any currently active CNS metastases. Patients who have treated brain metastases (with either surgical resection or stereotactic radiosurgery) that have been stable on head MRI or contrast CT scan for at least 4 weeks following treatment and within 4 weeks prior to randomization are eligible. Patients must not have taken any steroids ≤ 14 days prior to randomization for the purpose of managing their brain metastases. Patients with only Whole Brain irradiation for treatment of CNS metastases will be ineligible.

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3.1.14 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 > 3 years prior to the time of randomization.

3.1.15 Patients must have the following required values for initial laboratory tests obtained within 4 weeks prior to randomization (ULN: institutional upper limit of normal):

3.1.15.1 White Blood Count ≥ 3,000/uL

_____ 3.1.15.2 ANC ≥ 1,500/uL

_____ 3.1.15.3 Platelet Count ≥ 100,000/uL

_____ 3.1.15.4 Hemoglobin ≥ 9 g/dL

_____ 3.1.15.5 Serum creatinine ≤ 1.5 x ULN or serum creatinine clearance (CrCl) ≥ 40ml/min. (CrCl= Wt (kg) x (140-age)*/72 x Cr. level, *female x 0.85)

_____ 3.1.15.6 AST and ALT ≤ 3 x ULN (≤ 5 x ULN for patients with documented liver metastases)

_____ 3.1.15.7 Alkaline Phosphatase ≤ 2 x ULN (≤ 5x ULN for patients with known liver involvement and ≤ 7x ULN for patients with known bone involvement)

_____ 3.1.15.8 Total Bilirubin ≤ 1.5 x ULN except subjects with normal direct bilirubin or those with known Gilbert's syndrome

_____ 3.1.15.9 Serum LDH ≤ 10 X ULN

_____ 3.1.16 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, history of bleeding diathesis or need for concurrent anticoagulation (INR ≤ 1.5 and PTT within 1.1 x ULN), or psychiatric illness/social situations that would limit compliance with study requirements, interfere with subject's safety, or obtaining informed consent.

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_____ 3.1.17 Patients with HIV infection are ineligible. Due to the mechanism of action of ipilimumab and GM-CSF, activity and side effects in an immune compromised patient are unknown.

_____ 3.1.18 Patients with evidence of active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection are not eligible. Patients with cleared HBV and HCV (0 viral load) infection will be allowed.

3.1.19 Patients must not have autoimmune disorders or conditions of immunosuppression that require current ongoing treatment with systemic corticosteroids (or other systemic immunosuppressants), including oral steroids (e.g., prednisone, dexamethasone) or continuous use of topical steroid creams or ointments or ophthalmologic steroids. A history of occasional (but not continuous) use of steroid inhalers is allowed. Replacement doses of steroids for patients with adrenal insufficiency are allowed. Patients who discontinue use of these classes of medication for at least 2 weeks prior to randomization are eligible if, in the judgment of the treating physician investigator, the patient is not likely to require resumption of treatment with these classes of drugs during the study.

Exclusion from this study also includes patients with a history of symptomatic autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [e.g., Wegener's Granulomatosis]); motor neuropathy considered of autoimmune origin

(e.g., Guillain-Barre Syndrome and Myasthenia Gravis); other CNS autoimmune disease (e.g., Multiple sclerosis).

Patients with autoimmune hypothyroid disease or type I diabetes on replacement treatment are eligible.

3.1.20 Patients must not have a history of inflammatory bowel disease or diverticulitis (history of diverticulosis is allowed).

3.1.21 Patients must not have other significant medical, surgical, or psychiatric conditions or require any medication or treatment that in the opinion of the investigator may interfere with compliance, make the administration of the study drugs hazardous or obscure the interpretation of AEs, such as a condition associated with frequent diarrhea. Patients must not have an active infection requiring current treatment with parenteral antibiotics.

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