Cancer Research Consortium of West Michigan
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FAST FACTS

S2000 - A RANDOMIZED PHASE 2 TRIAL OF ENCORAFENIB + BINIMETINIB + NIVOLUMAB VS IPILIMUMAB + NIVOLUMAB IN BRAF-V600 MUTANT MELANOMA WITH SYMPTOMATIC BRAIN METASTASES

ELIGIBILITY CRITERIA

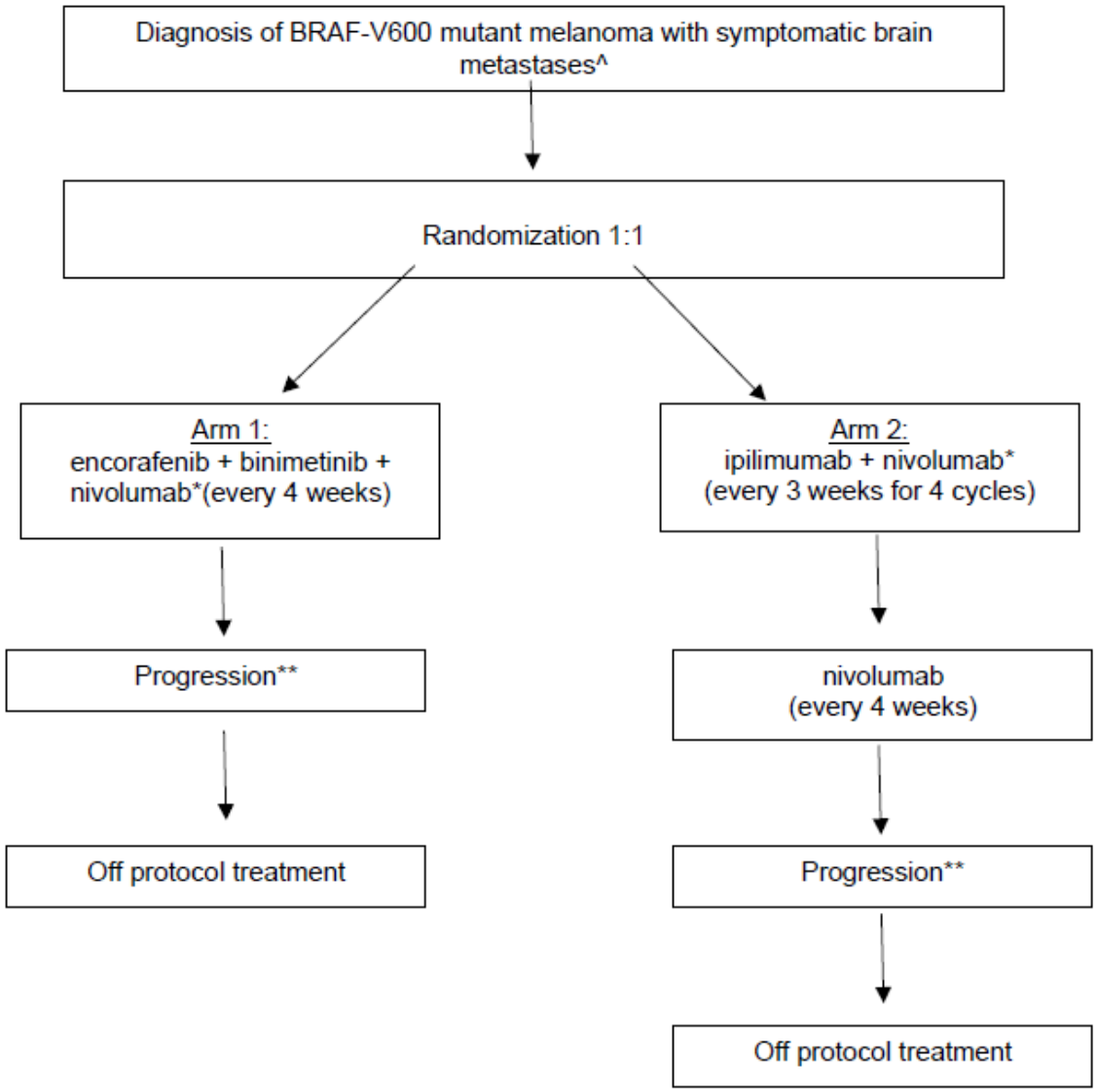
1. *Disease Related Criteria*
    a. Participants must have histologically and pathologically confirmed melanoma that has metastasized to the brain. Brain metastases must be symptomatic at baseline defined as having neurologic symptoms and/or requiring steroids. Leptomeningeal disease is permitted.
    b. Any primary (cutaneous, acral/mucosal,etc) or unknown origin are permitted, except that participants with uveal primary are not eligible.
    c. Participants must have BRAF-V600 mutant melanoma documented by a CLIA-certified laboratory.
    d. All Participants must have an MRI of the brain within 28 days prior to registration and must have central nervous system metastases with at least one measurable brain metastasis ≥ 0.5cm in size (per modified RECIST 1.1. Section 10.4) that has not been irradiated, or has progressed (in the opinion of the treating physician) after prior radiation therapy. Participating sites MUST use MRI slice thickness of ≤1.5 mm (on the highest resolution T1 weighted contrast enhanced sequence) and are recommended to adhere to the 'minimum' BTIP-BM compliant MRI acquisition protocol. (Appendix 18.5). CT of the head cannot substitute for brain MRI. (NOTE: All CNS disease must be documented on BOTH the Brain Metastases Baseline Tumor Assessment Form, using modified RECIST, and the Baseline Tumor Assessment Form (RECIST 1.1) using RECIST 1.1.) See section 15.1b for guidelines and submission instructions for required image submission via TRIAD.
    e. Participants may have measurable or non-measurable extracranial disease (see Section 10.1). All measurable disease must be assessed within 28 days prior to randomization; all non-measurable disease must be assessed within 42 days prior to randomization. Please note, while any extracranial disease will also be assessed and followed, Participants are NOT required to have extracranial disease for randomization. NOTE: All disease must be assessed and documented on the Baseline Tumor Assessment Form (RECIST 1.1). CNS disease must be documented on BOTH the Brain Metastases Baseline Tumor Assessment Form, using modified RECIST, and the Baseline Tumor Assessment Form (RECIST 1.1) using RECIST 1.1. See section 15.1b for guidelines and submission instructions for required image submission via TRIAD.
2. *Prior/Concurrent Therapy Criteria*
    a. Participants must not have received prior systemic therapy for metastatic disease. Prior systemic therapy received only in the neoadjuvant and/or adjuvant setting (e.g., BRAF/MEK inhibitor therapy, anti-PD-1 therapy or anti-CTLA4 therapy, alfa-interferon, etc.) is permitted. If patients received prior neoadjuvant/adjuvant therapy, they must have had eventual disease relapse prior to randomization.
    b. Participants must not have had prior radiation therapy within 7 days prior to randomization.
    c. Participants must not be planning to require any additional form of systemic anti-tumor therapy for melanoma while on protocol treatment.
    d. Participants may be receiving corticosteroids for brain metastases at a dose of up to 8 mg of dexamethasone per day (or equivalent). The dose must not have exceeded 8 mg per day for at least 3 days prior to randomization.
    e. Participants must not be planning to use hormonal contraceptives.
3. *Clinical/Laboratory Criteria*
    a. Participants must be ≥ 18 years of age.

b. Participants must have Zubrod Performance Status ≤ 2 (see Section 10.7).
c. Participants must have complete history and physical examination within 28 days prior to randomization.
d. Participants must be able to swallow and retain pills.
e. Participants must have adequate organ and marrow function as defined below within 28 days prior to randomization.:
    - Hemoglobin ≥ 8.0 g/dL
    - absolute neutrophil count ≥1,500/mcL
    - platelets ≥75,000/mcL
    - total bilirubin ≤ 3 x institutional upper limit of normal (ULN)
    - AST and ALT ≤3 × institutional ULN (in participants with liver metastases ≤ 5 × ULN)
    - creatinine ≤ 2.0 institutional ULN
f. Participants with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, must have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification (see Appendix 18.1). To be eligible for this trial, participants must be class 2B or better.
g. Participants must not have a serious active infection requiring systemic therapy at time of randomization in the opinion of the treating physician.
h. Participants must not have active autoimmune disease that has required treatment in the past 6 months with use of biologic disease modifying agents (.e.g. infliximab, adalimumab) Patients on non-biologic disease modifying agents (e.g. methotrexate) or patients on corticosteroids ≤10 mg prednisone daily or equivalent (to treat auto-immune disease), or on replacement therapy (e.g., thyroxine, insulin) are eligible if deemed in the best interest of the patient by treating physician.
i. Participants must not have had Grade 3 or 4 immune-related adverse events on ipilimumab or nivolumab that required more than 12 weeks of immune suppression with corticosteroids.
j. Participants must not have had adverse events related to encorafenib and/or binimetinib specifically, that required discontinuation of one or both drugs. (Please note this does not apply to other BRAF/MEK inhibitor drugs.)
k. Participants with a prior or concurrent malignancy whose natural history or treatment (in the opinion of the treating physician) does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
l. Participants must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective method of contraception. (NOTE: Patients must agree to not use hormonal contraceptives, as encorafenib can result in decreased concentration and loss of efficacy.) 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. However, if at any point a previously celibate participant chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.
m. Participants with known human immunodeficiency virus (HIV)-infection are eligible providing they are on effective anti-retroviral therapy and have undetectable viral load at their most recent viral load test and within 90 days prior to randomization.
n. Participants with a known history of hepatitis C virus (HCV) infection must have been treated and cured. Participants with HCV infection who are currently on treatment must have an undetectable HCV viral load prior to randomization.

4. *Specimen Submission Criteria*
    a. Participants must agree to participate in image banking as outlined in Section 15.1, Images must be submitted submitted via the Triad System as outlined in Section 15.1b.

b. Participants must be offered the opportunity to participate in specimen and blood collections as outlined as outlined in Section 15.2.

SCHEMA



* **See Section 7.1 for dosage and timing.**
** **Participant may continue on treatment after progression. Please see Section 7.5.**
^symptomatic brain metastases are defined as having neurologic symptoms and/or requiring steroids.