Cancer Research Consortium of West Michigan
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# FAST FACTS

## S1801 - A PHASE II RANDOMIZED STUDY OF ADJUVANT VERSUS NEOADJUVANT MK-3475 (PEMBROLIZUMAB) FOR CLINICALLY DETECTABLE STAGE III-IV HIGH RISK MELANOMA

### ELIGIBILITY CRITERIA

**STEP 1 REGISTRATION (Randomization)**

**Disease Related Criteria**

1. Patients must have resectable melanoma in order to be eligible for this study. Patients must have clinically detectable Stage III (clinically detectable N1b, N1c, N2b, N2c, N3b and N3c) or Stage IV resectable melanoma. Patients with melanoma of mucosal or acral origin are eligible. Patients with melanoma of uveal origin are not eligible. Patients with a history of brain metastases are not eligible.

   Clinically detectable is defined as disease that is apparent and measurable via physical examination or radiographic imaging (Section 10.1). Note: Planned surgery must be documented on the **S1801** Planned Surgery Form.

2. Patients are eligible for this trial either at initial presentation of their melanoma or at the time of the first detected nodal, satellite/in-transit, distant metastases, or recurrent disease in prior lymphadenectomy basin or distant site. Nodal, satellite/in-transit metastasis, distant metastases or disease in a prior complete lymphadenectomy basin must have been confirmed histologically by H & E stained slides.

3. Patients with multiple regional nodal basin involvement are eligible. Gross or microscopic extracapsular nodal extension is permitted.

4. Patients must have histologically proven Stage IIIB or higher. This would entail pathologic confirmation beyond the primary or initial diagnosis of melanoma involving fine needle aspiration cytology or biopsy confirmation of any N-category or M-category resectable site.

**Prior/Concurrent Therapy Criteria**

1. Patients must not have received previous neoadjuvant treatment for their melanoma. Patients may have received prior non-immunotherapy adjuvant therapy. Patients must not have had prior immunotherapy including, but not limited to ipilimumab, interferon alfa-2b, high dose IL-2, PEG-IFN, anti-PD-1, anti-PD-L1 intra-tumoral, or vaccine therapies. Patients must not be planning to receive any of the prohibited therapies listed in Section 7.2 during treatment phases on the study.

2. Patients must not be planning to receive concomitant other biologic therapy, hormonal therapy, other chemotherapy, surgery, while on protocol therapy.

3. Patients may have received prior radiation therapy, including after prior surgical resection. All adverse events associated with prior surgery and radiation therapy must have resolved to ≤ Grade 1 prior to randomization.

**Clinical/Laboratory Criteria**

1. Patients must be ≥ 18 years of age.

2. All patients must have disease status documented by a complete physical examination and imaging studies within 42 days prior to randomization. Imaging studies must include a CT of the chest, abdomen, and pelvis with intravenous

contrast (unless contraindicated). For patients with melanoma arising from the head and neck, dedicated neck imaging (CT with intravenous contrast) is required. If the patient has unknown primary with disease in the axilla, neck imaging is required. CT imaging must be done with intravenous contrast if there are no contraindications for it. Extremity melanomas must be imaged using CT with intravenous contrast or MRI with and without gadolinium. Note: PET-CT scans are NOT acceptable to establish eligibility. Non-iodinated CT scans that are part of common PET-CT imaging protocols do not provide contrast for difficult to ascertain areas such as the neck and liver, and do not provide enough CT detail to perform appropriate RECIST 1.1 measurements. As such, a PET-CT with non-contrast CT or non-diagnostic quality CT images is considered insufficient for the detection of melanoma.

3. All patients must have a CT or MRI of the brain within 42 days prior to randomization. The brain CT or MRI should be performed with intravenous contrast (unless contraindicated).

4. Patients must have adequate bone marrow function as evidenced by all of the following: ANC ≥ 1,500/microliter (mcL); platelets ≥ 100,000/mcL; Hemoglobin ≥ 10 g/dL. These results must be obtained within 42 days prior to randomization.

5. Patients must have adequate hepatic function as evidenced by the following: total bilirubin ≤ 1.5 x institutional upper limit of normal (IULN) (except patients with Gilbert's Syndrome, who must have a total bilirubin < 3.0 mg/dL), and SGOT (AST) and SGPT (ALT) and alkaline phosphatase ≤ 2 x IULN. These results must be obtained within 42 days prior to randomization.

6. Patients must have LDH performed within 42 days prior to randomization.

7. Patients must have adequate renal function as evidenced by calculated creatine clearance > 30 mL/min. The creatinine level (mg/dL) used in the calculation must be obtained within 42 days prior to randomization.
Calculate creatinine clearance = (140-age) x wt (Kg) x 0.85 (if female)
72 x creatinine (mg/dL

8. Patients must have Zubrod Performance Status ≤ 2 (see Section 10.14).

9. Patients must not have a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

10. Patients must not have an active infection requiring systemic therapy.

11. Patients must not have active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

12. Patients must not have received live vaccines within 42 days prior to randomization. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, shingles, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed. NOTE: The COVID-19 vaccines (currently available and those in the pipeline for FDA emergency use authorization or FDA approval) do not contain live virus, and therefore, COVID-19 vaccination does not affect or preclude eligibility for the **S1801** trial. For patients who have undergone lymphadenectomy, vaccines should be delivered to a limb with an intact lymph node basin (Sentinel lymph node biopsy in a limb is acceptable). The vaccine should not be administered in a limb that has undergone lymphadenectomy.

13. Patients known to be HIV positive are eligible if they meet the following criteria within 30 days prior to randomization: stable and adequate CD4 counts (≥ 350 mm3), and serum HIV viral load of < 25,000 IU/ml. Patients may be on or off anti-viral therapy so long as they meet the CD4 count criteria.

14. Patients must not have known active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection prior to randomization. Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

15. Prior malignancy is allowed providing it does not require concurrent therapy.

16. Women of childbearing potential must have a negative urine or serum pregnancy test within 28 days prior to randomization. Women/men of reproductive potential must have agreed to use an effective contraceptive method for the course of the study through 120 days after the last dose of study medication. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. 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 patient 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. Patients must not be pregnant or nursing due to unknown teratogenic side effects.

17. Patients must be deemed medically fit to undergo surgery by the treating medical/surgical team.

**Specimen Submission Criteria**

1. Patients must be willing to submit the following surgical specimens: either all tissue blocks from the surgical specimen or two slides per block [(1) H&E slide and (1) unstained slide OR (2) unstained slides if H&E stained slides cannot be provided)

2. Patients must be offered the opportunity to participate in specimen banking as outlined in Section 15.2.

**STEP 2 REGISTRATION (Surgery)**

1. Patients randomized to Arm 2 (Neoadjuvant arm) must be willing to submit tissue to determine pathologic response as described in Section 15.2 regardless of number of pre-operative doses of MK-3475 (pembrolizumab) received. Determination of pathologic response cannot be done on less than the full surgical specimen.

2. Patients must have disease assessments by CT chest/abdomen/pelvis with IV contrast, and neck CT with IV contrast if primary head and neck melanoma, performed within 42 days (and no more than 49 days) before the planned date of surgery. MRI combined with non-contrast CT is an acceptable alternative for patients with CT contrast allergy, but imaging must encompass total body.

3. Patients must register to Step 2 within 3 days prior to planned date of surgery.

**STEP 3 REGISTRATION (Adjuvant Therapy)**

1. Patients must have undergone surgery prior to Step 3 registration. The Step 2 surgery must have completely resected their melanoma.
   - Patients with gross positive residual disease at the time of surgery do not qualify as having disease-free status, and, therefore, such patients are not eligible to register for adjuvant therapy.
   - Patients with microscopic residual disease (i.e., positive margins) can be treated with re-excision or radiation, per site discretion, to render the patient disease-free prior to registration of adjuvant therapy.
   - Disease-free status must be documented by a complete physical examination and radiographic imaging studies within 42 days prior to Step 3 registration. Imaging studies must include a CT of the chest, abdomen, and pelvis (unless contraindicated). Extremity melanomas must be imaged using CT with intravenous contrast or MRI with and without gadolinium. CT imaging must be done with intravenous contrast if there are no contraindications for it.

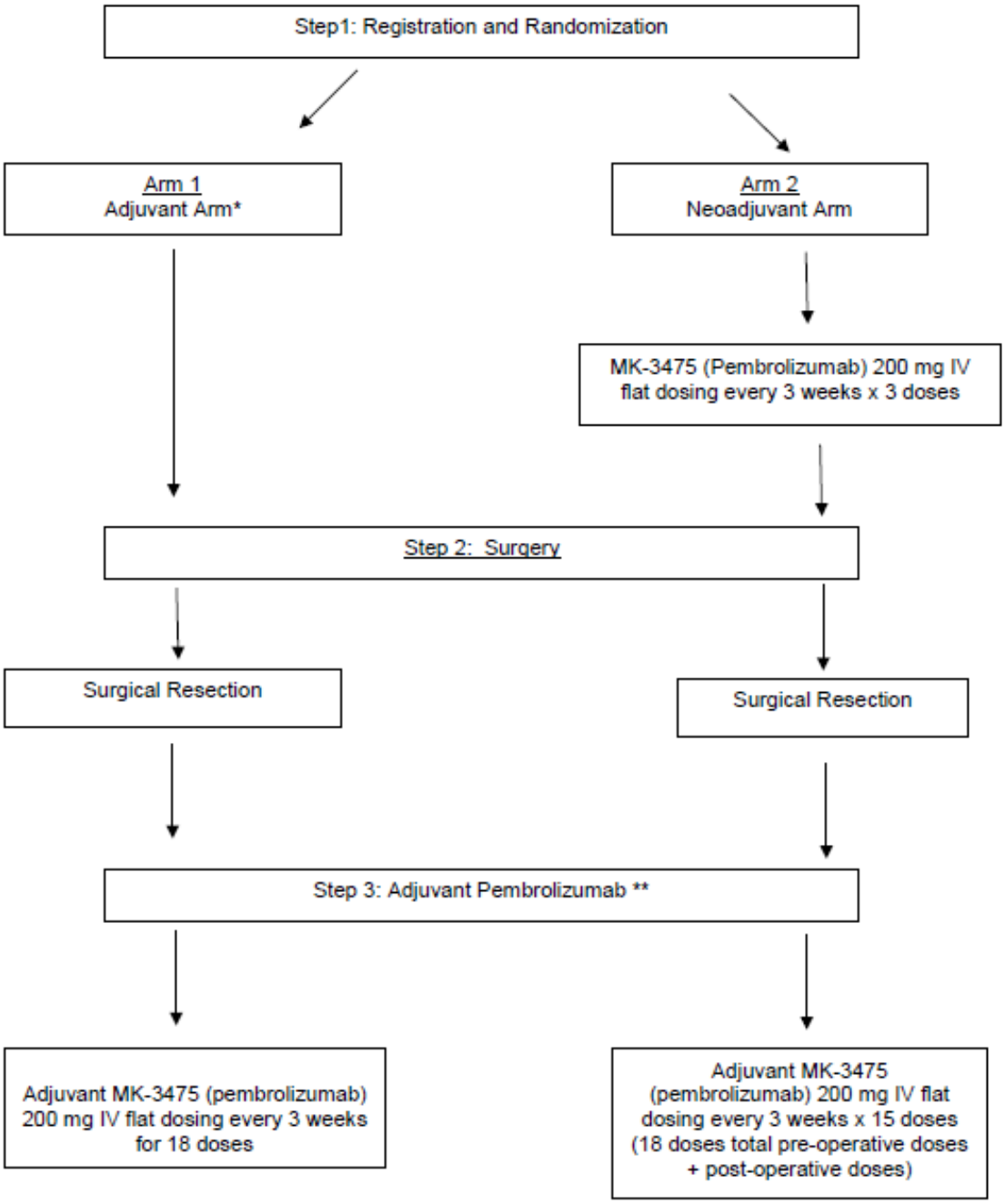
- For patients with melanoma arising from the head and neck, dedicated neck imaging (CT with IV contrast, unless contraindicated) is required.
- If the patient has had unknown primary with disease in the axilla, neck imaging is required to assure the region is clear of cancer.
- Any other clinically-indicated imaging studies if performed (e.g., bone scan) must show no evidence of disease.

**2.** Patients must be registered to Step 3 no more than 84 days after date of Surgery.

**3.** Patients with R0 or R1 resections must have disease-free status documented by a complete physical examination and imaging studies within 42 days prior to Step 3 Registration. These patients must have disease assessment by CT chest/abdomen/pelvis with IV contrast, and neck CT with IV contrast if primary head and neck melanoma. MRI combined with non-contrast CT is an acceptable alternative for patients with CT contrast allergy.

**4.** Patients with R2 resections are not eligible for Step 3 and must be removed from study treatment per Section 7.4.

**SCHEMA**




* **Patients on Adjuvant arm must be registered to Step 2 (Surgery) within 17 days (preferably within 14 days) after randomization and must undergo surgical resection within 17 days (preferably within 14 days) after Step 2 registration.**

** **See Section 7.1 for dosage and timing. Patients must start adjuvant therapy with 84 days of surgery.**