

## **FAST FACTS**

### **S1404: A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma**

**Treatment:**    **MK-3475 200 (Pembrolizumab)** – *provided*  
                         **Interferon Alfa-2b** – *commercially available*  
                         **Ipilimumab** – *commercially available*

**\*See Study Schema on last page**

#### **STEP 1 REGISTRATION**

##### **Disease Related Criteria**

- a. Patients must have completely resected melanoma of cutaneous origin or of unknown primary in order to be eligible for this study. Patients must be classified as Stage IIIA (N2a), IIIB, IIIC, or Stage IV melanoma. Patients with non-ulcerated T1b N1a disease are not eligible. Patients with melanoma of mucosal or other non-cutaneous origin are eligible. Patients with melanoma of ocular origin are not eligible. Patients with a history of brain metastases are ineligible.
- b. 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.
- c. Patients with multiple regional nodal basin involvement are eligible. Gross or microscopic extracapsular nodal extension is permitted.
- d. Patients at initial presentation of melanoma must undergo an adequate wide excision of the primary lesion, if present. (See Section 18.1 for guidelines on surgical management.) Patients with previously diagnosed melanoma must have had all current disease resected with pathologically negative margins and must have no evidence of disease at the primary site or must undergo re-resection of the primary site. A full lymphadenectomy meeting the criteria outlined in Section 18.1 is required for all node positive patients including those with positive sentinel nodes. Patients with recurrent disease who have had a prior complete lymphadenectomy fulfill this requirement as long as all recurrent disease has been resected. For all patients, all disease must have been resected with negative pathological margins and no clinical, radiologic, or pathological evidence of any incompletely resected melanoma. Patients must be registered within 98 days of the last surgery performed to render the patient free of disease.

##### **Specimen Submission Criteria**

- e. Patients must have available and be willing to submit a minimum of five unstained slides from primary, lymph node, or metastatic site to determine PD-L1 expression as described in Section 15.2. The tumor tissue must be adequate for PD-L1 testing (defined as  $\geq 100$  tumor cells as confirmed by the treating institution's local pathologist). This must be documented by having a pathologist sign the S1404 Local Pathology Review Form (see section 18.4) prior to step 1 registration. The specimens may come from an archived block but must be submitted within 20 days from cutting the slides.

- f. Patients must be offered the opportunity to participate in specimen banking as outlined in Section 15.3
- g. Patients must be willing to have blood draws for PK/ADA analysis as outlined in Section 15.4, should the patient be randomized to the MK-3475 arm.

#### **Prior/Concurrent Therapy Criteria**

- h. Patients may have received prior radiation therapy, including after the surgical resection. All adverse events associated with prior surgery and radiation therapy must have resolved to  $\leq$  Grade 1 prior to registration.
- i. Patients must not have received neoadjuvant treatment for their melanoma. 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 the screening or treatment phases of the study.
- j. Patients must not be planning to receive concomitant other biologic therapy, radiation therapy, hormonal therapy, other chemotherapy, surgery or other therapy after step 2 registration.

#### **Clinical/Laboratory Criteria**

- k. Patients must be  $\geq$  18 years of age.
- l. All patients must have disease-free status documented by a complete physical examination and imaging studies within 42 days prior to registration. Imaging studies must include a total body PET-CT scan (with or without brain) or a CT of the chest, abdomen and pelvis. For patients with melanoma arising from the head and neck, dedicated neck imaging (CT with IVcontrast or PET-CT through the region) is required. If the patient has had unknown primary with disease in the axilla, neck imaging is required to assure region is clear of cancer. CT imaging should be done with intravenous contrast if there are no contraindications for it. Any other clinically-indicated imaging studies if performed (e.g. bone scan) must show no evidence of disease.
- m. All patients must have a CT or MRI of the brain within 90 days prior to registration. The brain CT or MRI should be performed with intravenous contrast (unless contraindicated).
- n. Patients must have adequate bone marrow function as evidenced by all of the following: ANC  $\geq$  1,500 microliter (mcL); platelets  $\geq$  100,000/mcL; Hemoglobin  $\geq$  10 g/dL. These results must be obtained within 42 days prior to registration.
- o. Patients must have adequate hepatic function as evidenced by the following: total bilirubin  $\leq$  1.5 x institutional upper limit of normal (IULN) (except Gilbert's Syndrome, who must have a total bilirubin  $<$  3.0 mg/dL), and SGOT (AST) and SGPT (ALT) and alkaline phosphatase  $\leq$  2 x IULN. These results must be obtained within 42 days prior to registration.
- p. Patients must have adequate renal function as evidenced by ONE of the following: serum creatinine  $\leq$  IULN OR measured or calculated creatinine clearance  $\geq$  60 mL/min. This result must have been obtained within 42 days prior to registration.

$$\text{Calculated creatinine clearance} = (140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)} / 72 \times \text{creatinine (mg/dl)}$$

- q. Patients must have LDH performed within 42 days prior to registration.
- r. Patients must have Zubrod Performance Status  $\leq$  1 (see Section 10.4).
- s. Patients must have a baseline ECG performed within 42 days of registration that is normal or considered not clinically significant by the site investigator.

- t. Patients must not have a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
- u. Patients must not have an active infection requiring systemic therapy.
- v. 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.
- w. Patients must not have received live vaccines within 42 days prior to registration. 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.
- x. Patients known to be HIV positive are eligible if they meet the following criteria within 30 days prior to registration: stable and adequate CD4 counts ( $\geq 350$  mm<sup>3</sup>), 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.
- y. Patients must not have known active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection prior to registration.
- z. Patients must not have a history or current evidence of any condition, therapy or laboratory abnormality that might confound the trial results, interfere with the patient's participation for the full duration of the trial, or indicate that participation in the trial is not in the patient's best interests, in the opinion of the treating investigator.
- aa. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, lobular carcinoma of the breast in situ, atypical melanocytic hyperplasia or melanoma in situ, adequately treated Stage I or II cancer (including multiple primary melanomas) from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for three years.
- bb. Women of childbearing potential must have a negative urine or serum pregnancy test within 28 days prior to registration. 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.
- cc. Patients who are able to complete questionnaires in English must participate in the quality of life assessments. (Those patients who cannot complete the quality of life questionnaires in English can be registered to S1404 without contributing to the quality of life studies.)

**Regulation Criteria**

- dd. Patients must be informed of the investigational nature of this study and must sign and give written informed consent for this protocol in accordance with institutional and federal guidelines.
- ee. 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.

**STEP 2 REGISTRATION (Randomization)**

An e-mail notification from the SWOG Statistical Center should be received within 10 business days of submitting tissue as described in Section 15.2.

The following additional criteria must be met in order for a patient to be considered eligible for registration to the randomized trial. Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at [melanomaquestion@crab.org](mailto:melanomaquestion@crab.org) prior to registration.

- a. Patients must not be registered until receiving confirmation from the SWOG Statistical Center that the patient's tissue specimen was adequate for PD-L1 testing. Patients must be registered within 7 working days of receiving the e-mail notification.
- b. Women of childbearing potential must plan to have a urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a negative serum pregnancy test will be required.
- c. No tests or exams are required to be repeated for Step 2 registration (Randomization). However, patients who are known to have a change in eligibility status after Step 1 registration are not eligible for Step 2 registration. For example, ANC is not required to be repeated between Step 1 and Step 2 registration, but the most recent ANC performed before Step 2 registration is required to be  $\geq 1,500$  mcL.

**Pre-Study Parameters**

1. History & Physical, PS & Toxicity
2. CBC, diff, plts
3. CMP, LDH, CrCl
4. Triglycerides
5. T3 T4 TSH, Pregnancy test
6. Whole body PET/CT  
or CT neck, chest, abd & pelvis
7. Brain MRI or CT with contrast
8. EKG

