FAST FACTS

A091903 - A RANDOMIZED PHASE II TRIAL OF ADJUVANT NIVOLUMAB WITH OR WITHOUT CABOZANTINIB IN PATIENTS WITH RESECTED MUCOSAL MELANOMA

Pre-Registration Eligibility Criteria (Step 0)

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later wouldbe considered Day 7.

Histologically proven mucosal melanoma by local pathology.

Central PD-L1 tumor tissue submission

Tumor tissue is mandatory prior to registration/randomization to perform PD-L1 testing that will be used for stratification. It should be obtained as soon after pre-registration as possible. See Sections 4.3.3 and 6.2 for more information.

Registration Eligibility Criteria (Step 1)

Receipt of the central PD-L1 testing results available.

- Report is required for randomization of Resection R0 or R1 patients;
- Testing must be started in Step) but results can be reported after registration for Resection R2 patients.

Disease status—Resected R0 or R1 disease patients

Patients eligible for randomization have resected R0 or R1 disease (with negative margins or positive microscopic margins) that must meet one of the following 4 criteria as defined below:

1) Regional LN involvement; OR
2) In-transit metastases/satellite primary disease; OR
3) Single localized, primary disease meeting one of the following site-specific requirements:

Head/Neck

–Sinonasal (including nasopharynx): any primary lesion [9-11];
–Nasal or oral cavity: pT4a or above, given slightly improved OS [9-11]
NOTE: Conjunctival: does not meet the qualification for eligibility.
–Anorectal – any primary lesion [12-14]
–Vaginal/Cervical – any primary, as they have 5 year OS rates of 5-25% [15-17]
–Urinary Tract – any primary urethral or bladder tumor
–Penile
–Vulvar– AJCC cutaneous Stage IIB or higher [18]
–Esophageal/Gallbladder – any primary

4) Locoregionally Recurrent following prior resection, meeting at least one of theabove criteria

In addition, patients must have undergone cross-sectional imaging of the brain, chest,abdomen and pelvis with no evidence of distant metastatic disease.

Disease status—Non-resected R2 or metastatic disease patients

Non-resected R2 or metastatic disease that is assessable and measurable radiographically or by physical examination as defined by Section 11.0.

Prior Treatment:

No prior systemic checkpoint inhibitor therapy of mucosal melanoma, including in the adjuvant setting, is allowed. Prior adjuvant chemotherapy or interferon is allowed.

No other active, concurrent malignancy that requires ongoing systemic treatment or interferes with radiographic assessment of melanoma response as determined by the investigator. Exceptions may allow for adjuvant NED cancers undergoing hormone basedtherapy may be eligible pending the other eligibility criteria are met and the PI affirms thehormonal agent would not change the melanoma response.

Any radiation must have completed 28 days prior to randomization and the patient must have adequately recovered from its effects.

For resectable patients only: Surgery must have completed 28 days prior to randomization.

For resectable patients only: Surgery must have completed no more than 84 days prior torandomization.

Not pregnant and not nursing, because this study has an agent that has known genotoxic, mutagenic and teratogenic effects.

Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 7days prior to registration is required.

Age ≥ 18 years

ECOG Performance Status 0-2

Required Initial Laboratory Values: Absolute

Neutrophil Count (ANC) ≥ 1,500/mm^3 Platelet Count ≥ 100,000/mm^3

Creatinine ≤ 1.5 x upper limit of normal (ULN) **OR** CrCl ≥ 50mL/min/1.73 m^2 forpatients with creatinine levels above institutional normal

Albumin ≥ 2.8g/dL

Total Bilirubin ≤ 1.5 x upper limit of normal

(ULN)AST / ALT ≤ 2.5 x upper

limit of normal (ULN)

No cardiovascular disease, including:

No history of acute coronary syndromes (including myocardial infarction and unstable angina), coronary artery bypass graft (CABG) coronary angioplasty, or stenting within 6 months prior to study entry.

No history of current Class II or higher congestive heart failure as defined by the New YorkHeart Association (NYHA) functional classification system.

No refractory hypertension defined as a blood pressure of systolic >140 mmHg and/or diastolic >90 mmHg despite adequate attempts at anti-hypertensive therapy.

No history of myocarditis.

No history of syncope of cardiovascular etiology, uncontrolled cardiac arrhythmia, Historyof Mobitz II second degree or third degree heart block without a permanent pacemaker in place, myocardial ischemia or infarction, severe or unstable angina, New York Heart Association (NYHA) class II to IV heart failure, or stroke/transient ischemic attack (TIA)within the past 3 months.

No QTcF >500msec. Note: if initial QTcF is found to be > 500 ms, two additional EKGs separated by at least 3 minutes should be performed. If the average of these three consecutive results for QTcF is ≤500 ms, the subject meets eligibility in this regard.

No underlying hematologic issues, including:

Congenital bleeding diathesis

GI bleeding requiring intervention within the past 6 months, unless directly related tomucosal melanoma

Active hemoptysis within 42 days prior to study enrollment.

Active tumor lesions with cavitations or tumor lesions which invade, encase, or abut majorblood vessels. The anatomic location and characteristics of primary tumors or metastases as well as the medical history should be carefully reviewed in the selection of subjects fortreatment with cabozantinib/placebo.

Pulmonary emboli or deep vein thromboses (DVT) that require an active anticoagulation regimen.

No known or suspected history of cytopenia (low WBC, hemoglobin or platelet count) of greater than 3 months duration with an unknown cause, myelodysplastic syndrome, or hematologic malignancies.

No clinical, laboratory or radiographic evidence of an active bacterial, fungal, or viral infection requiring treatment at the time of pre-registration (e.g., active symptoms of COVID-19 infection or a post-infectious symptomatic autoimmune syndrome, serious bacterial infections requiring antibiotics).

No known or suspected gastrointestinal disorder affecting absorption of oral medications.

Comorbid conditions:

No active autoimmune disease or any condition requiring systemic treatment with either corticosteroids (>10 mg daily of prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

No history of autoimmune motor neuropathy (e.g., Guillain-Barre Syndrome, MyastheniaGravis) or non-infectious pneumonitis.

No history of severe allergic reactions to an unknown allergen or any components of the study drugs or its excipients.

No history of gastrointestinal perforation or abdominal fistula.

No clinically suspected CNS (leptomeningeal or parenchymal) metastases. Patients with ahistory of CNS metastasis(s) will be allowed as long (1) as the metastatic site(s) were adequately treated as demonstrated by clinical and radiographic improvement, AND (2) the patient has recovered from the intervention (no residual adverse events > CTCAE Grade 1), AND (3) the patient has remained without occurrence of new or worsening CNSsymptoms for a period of 28 days prior to enrollment.

No history of seizure or any condition that may increase the patient's seizure risk (e. g., prior cortical stroke, significant brain trauma) within 2 years.

No clinically active or chronic liver disease resulting in moderate/severe hepatic impairment (Child-Pugh Class B or C), ascites, coagulopathy or bleeding due to liver dysfunction.

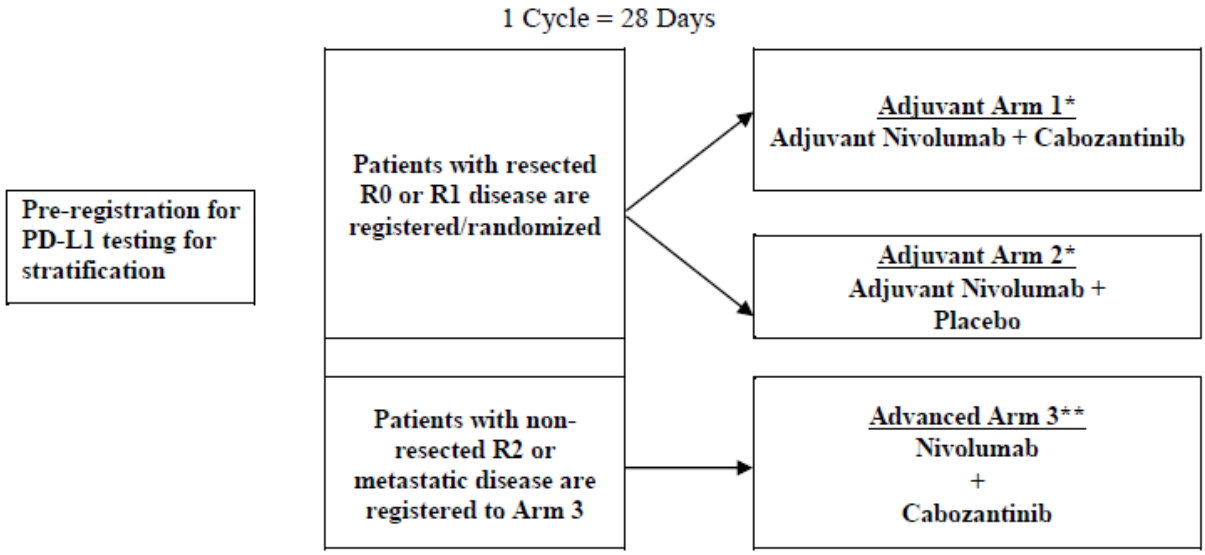
No untreated spinal cord compression or evidence of spinal metastases with a risk of impending fracture or spinal cord compression. Spinal metastases must have completed planned radiation or surgical therapy prior to registration.

Concomitant medications

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this study. Patients on strong CYP3A4 inhibitors must discontinue the drug for 5 days prior tothe start of study treatment. See Section 8.1.9 for more information.

Chronic concomitant treatment with strong CYP3A4 inducers is not allowed. Patients mustdiscontinue the drug 5 days prior to the start of study treatment. See Section 8.1.10 for more information.

Schema



Patients will be stratified by: Primary Site; PD- L1 (high vs. low); Node Status; and Receipt of RT

* Treatment in **resected R0 or R1 disease randomize group** is to continue for 1 year or until disease progression or unacceptable adverse event.

** Treatment in **R2 Non-resected or metastatic disease group** is to continue for 2 years or until disease progression or unacceptable adverse events.

All patients will be in clinical follow up every 3 months until disease progression; thereafter, survival follow-up every 6 months for 5 years from registration or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.