

## MEL 19: A Phase II Study of Everolimus in Combination with Paclitaxel and Carboplatin in Patients with Metastatic Melanoma

### *Fast Facts*

#### **Provided Drug: Everolimus**

#### **Inclusion Criteria**

1. Histologically confirmed metastatic melanoma.
2. Stage III or IV disease that is not amenable to resection.
3. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. If the patient has had previous radiation to the target lesion(s), there must be evidence of progression since the radiation.
4. ECOG Performance Status of 0 or 1 (Appendix A).
5. Life expectancy  $\geq 12$  weeks.
6. No prior cytotoxic chemotherapy or targeted therapy. Immunotherapy is allowed (i.e., interleukin-2 or interferon).
7. Adequate hematological function:
  - a. absolute neutrophil count (ANC)  $\geq 1500/\mu\text{L}$  and
  - b. platelets  $\geq 100,000/\mu\text{L}$  and
  - c. hemoglobin  $> 9$  g/dL
8. Adequate renal function: serum creatinine  $\leq 2.0$  mg/dL or calculated (measured) GFR  $\geq 50$  mL/min.
9. Adequate hepatic function:
  - a. serum bilirubin  $\leq 1.5$  x institutional upper limit of normal (ULN);
  - b. aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 2.5 \times$  ULN, or  $\leq 5 \times$  ULN in patients with documented liver metastases.
10. Normal PT, INR. Patients on coumadin anticoagulation are eligible if they are on a stable dose, with an INR in the therapeutic range.
11. Fasting serum cholesterol  $\leq 300$  mg/dL OR  $\leq 7.75$  mmol/L AND fasting triglycerides  $\leq 2.5$  x ULN. NOTE: In case one or both of these thresholds are exceeded, the patient can be included after initiation of appropriate lipid lowering medication.
12. Age  $\geq 18$  years.
13. Ability to swallow whole pills.
14. Patient must be accessible for treatment and follow-up.
15. Patients must be able to understand the investigational nature of this study and give written informed consent prior to study entry.

#### **Exclusion Criteria**

1. Previous treatment with an mTOR inhibitor (sirolimus, temsirolimus, everolimus), paclitaxel, or carboplatin.
2. Treatment with any investigational agent  $\leq 4$  weeks of protocol treatment.
3. Patients currently receiving anticancer therapies or who have received anticancer therapies  $\leq 3$  weeks of the start of the study drug (including radiation therapy, immunotherapy).
4. Patients who have had a major surgery or significant traumatic injury  $\leq 4$  weeks of start of study drug or patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia).
5. Patients receiving chronic, systemic treatment with corticosteroids (dose  $> 10$  mg daily of methylprednisolone or equivalent) or other immunosuppressive agents. Topical or inhaled steroids are allowed.
6. Immunization with attenuated live vaccine  $\leq 1$  week of study or anytime during study treatment period.
7. Patients with active brain metastases are ineligible. Patients with treated brain metastases are eligible if (1) radiation therapy was completed  $\geq 4$  weeks prior to study entry; (2) surgery was completed  $\geq 4$  weeks prior to study entry; (3) follow-up scan shows no disease progression; and (4) patient does not require steroids.
8. Any severe and/or uncontrolled medical conditions or other conditions that could affect participation in the study such as:
  - a. severely impaired lung function defined as a DLCO  $\leq 50\%$  of the normal predicted value and/or O<sub>2</sub> saturation  $\leq 88\%$  at rest on room air.
  - b. Symptomatic congestive heart failure of New York Heart Association Class III or IV (Appendix B).
  - c. unstable angina pectoris, symptomatic congestive heart, myocardial infarction  $\leq 6$  months of start of study drug, serious uncontrolled cardiac arrhythmia or any other clinically significant disease.
  - d. uncontrolled diabetes as defined by fasting serum glucose  $> 1.5$  x ULN.
  - e. active (acute or chronic) uncontrolled severe infections.
  - f. liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis.
9. Active, bleeding diathesis.

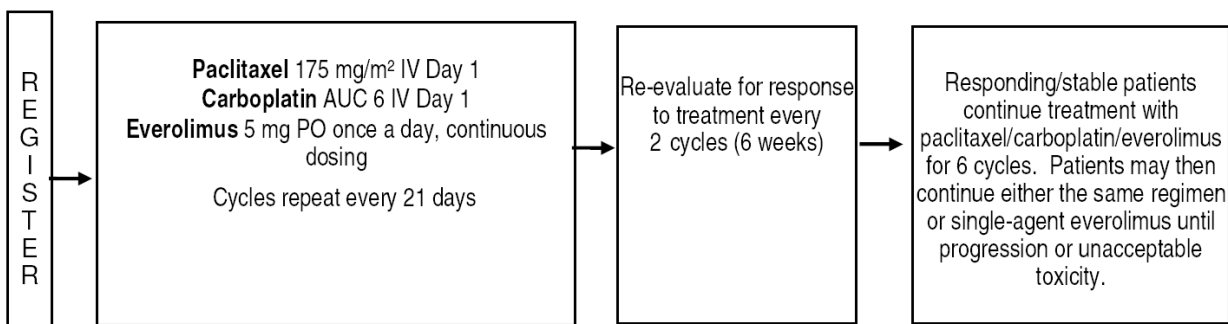
10. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of Everolimus (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
11. A known history of human immunodeficiency virus (HIV) seropositivity.
12. Known hypersensitivity to everolimus or other rapamycins (sirolimus, temsirolimus) or to its excipients.
13. Use of St. John's Wort is prohibited. Drugs or substances (e.g., grapefruits, star fruits, seville oranges, and their juices and products) known to be inhibitors or inducers of the isoenzyme CYP3A4 should be avoided (see Section 5.3.2.1). Co-administration with substrates, inducers, or inhibitors of P-glycoprotein should also be avoided (see Section 5.3.2.1).
14. Female patients who are pregnant or breastfeeding or adults of reproductive potential who are not using effective birth control methods. If barrier contraceptives are being used, these must be continued throughout the trial by both sexes. Hormonal contraceptives are not acceptable as a sole method of contraception. (Women of childbearing potential [WOCBP] must have a negative urine or serum pregnancy test within 7 days prior to administration of everolimus.) WOCBP should continue to use effective contraception for 8 weeks after ending everolimus treatment.
15. Other malignancies within the past 3 years except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin.
16. History of noncompliance to medical regimens. Patients unwilling to, or unable to, comply with the protocol.
17. History of any other disease, physical examination finding, or clinical laboratory finding that gives reasonable suspicion of a disease or a condition that may render the patient at high risk for treatment complications using these agents.

#### Pre-Study Parameters

1. History, PE, vitals, Ht, Weight, PS, AE evaluation and medication review
2. LABS: CBC, including diff. and platelets, CMP, fasting lipid profile, Serum pregnancy test (childbearing potential only)
3. Tumor measurement, CT of chest and abdomen, CT or MRI of the brain
4. Tumor tissue sample collection

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#### MEL 19 Treatment Schema:




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#### Study Drug Supply and Distribution:

- **Everolimus (RAD001, Afinitor<sup>®</sup>)** will be provided by Novartis Pharmaceuticals to SCRI ORC (as the Study Sponsor) for distribution to enrolled patients.
- **Paclitaxel** is commercially available.
- **Carboplatin** is commercially available.