No active infection requiring systemic treatment

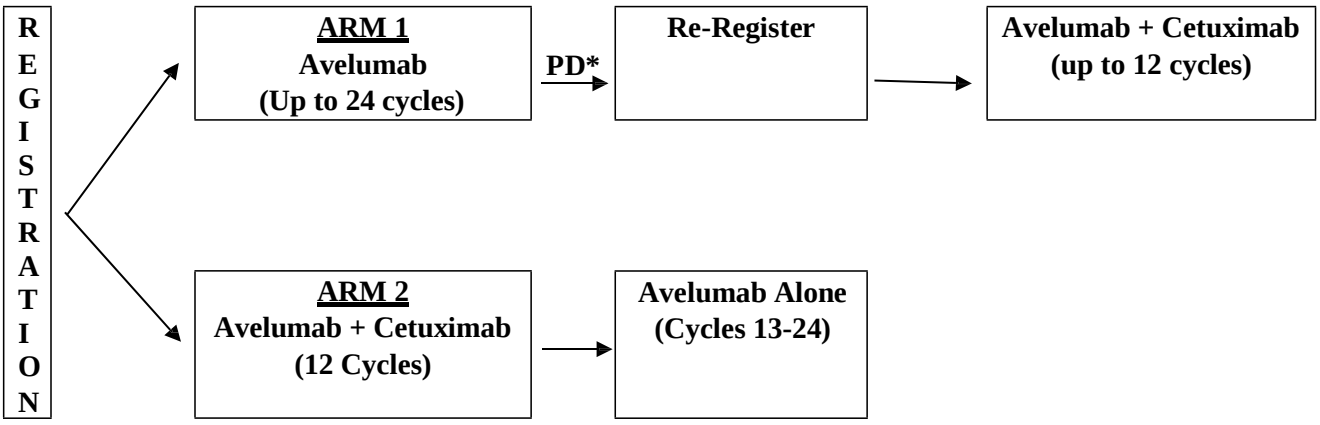
No currently active non-infectious pneumonitis

No use of immunosuppressive medication ≤ 7 days of registration (See § 3.3.12)

Chronic concomitant treatment that are strong inhibitors of CYP3A4 are not allowed on this study. Patients on strong CYP3A4 inhibitors must discontinue the drug for 14 days prior to registration on the study.

Schema

1 Cycle = 28 Days



Treatment is to continue until disease progression or unacceptable adverse event or until the end of the 24 cycle treatment period, whichever comes first. After patients end active treatment, they will be followed for an additional 2 years or until death, whichever comes first.

* Patients that are randomized to avelumab alone and progress will then continue on avelumab with the addition of cetuximab for up to 12 additional cycles.

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

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study and for at least 2 months after the last dose of study medication due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom). Women should also not breastfeed during the study and for at least 2 months after the last dose of study medication.

  A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.2 Pre-Registration Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

___ 3.2.1 Provide adequate tissue for PD-L1 Testing

Fresh tissue or archival tissue can be used. Sample must be at least core needle biopsy. Fine needle aspiration is not adequate. This specimen submission is mandatory prior to registration as results will be used for stratification. See Section 6.2 for details on specimen submission.

3.3 Registration Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

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 would be considered Day 7.

___ 3.3.1 Documentation of Disease:

Histologic Documentation: Biopsy-proven advanced cutaneous squamous cell carcinoma. Advanced disease is defined as either metastatic cutaneous squamous cell carcinoma or locally advanced cutaneous squamous cell carcinoma not amenable to curative surgical resection, or the patient declines surgical resection.

___ **3.3.2 Measurable disease as defined in Section 11.0.**

The patient must have at least one lesion that is measurable disease based on RECIST 1.1.

___ **3.3.3 Prior Treatment**

- Patients who received prior treatment with cetuximab as palliative treatment for advanced cSCC are excluded. Patients that received cetuximab based chemoradiation as prior treatment for locally advanced disease are eligible as long as the last dosage was given ≥ 6 months prior to registration.
- Patients who received cetuximab as part of definitive therapy in the adjuvant setting are eligible as long as the last dosage was given ≥ 6 months prior to registration.
- Patients who received prior cetuximab and had a severe infusion reaction requiring discontinuation of cetuximab are excluded.
- Patients treated with prior anti-PD-1 or anti-PD-L1 mAbs are excluded.
- Patients cannot have received treatment with radiation or chemotherapy including another investigational agent within 2 weeks of registration. Other than as stated above for cetuximab there are no limits on the number of lines of other therapies given for advanced cSCC.

___ **3.3.4 Prior Surgery**

If patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

___ **3.3.5 Not pregnant and not nursing**

This study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.

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

___ **3.3.6 Age ≥ 18 years**

___ **3.3.7 ECOG Performance Status 0-2**

3.3.8 Patients with a "currently active" second malignancy will be excluded with the exception of other non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for 3 years.

___ **3.3.9** If HIV positive the HIV viral load must be <200 copies/mL and CD4 count >200 If an HIV positive patient is on HAART the patient must have been so for > 4 weeks.

___ **3.3.10 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC) ≥ 1,500/mm^3

Platelet Count ≥ 100,000/mm^3

Calc. Creatinine Clearance > 30 mL/min

Total Bilirubin ≤ 1.5 x upper limit of normal (ULN)

AST / ALT ≤ 2.5 x upper limit of normal (ULN)

___ **3.3.11 No history of the following:**

- Autoimmune disease (including inflammatory bowel disease) with the exception of patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not currently requiring immunosuppressive treatment.
- Non-infectious pneumonitis that required steroids within 5 years.
- Organ transplant including prior stem cell transplant.
- Receipt of a live vaccine ≤ 4 weeks.
- Cerebral vascular accident/stroke within 6 months of enrollment.
- Myocardial infarction within 6 months of enrollment.
- Active unstable angina.
- Congestive heart failure (≥ New York Heart Association Classification Class II).
- Serious cardiac arrhythmia requiring medication. Whether an arrhythmia is considered "serious" is at the discretion of the investigator.

___ **3.3.12 Comorbid conditions (excluded)**

- Active infection requiring systemic treatment
- Use of immunosuppressive medication ≤ 7 days of registration, EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); b. Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)."
- Other severe acute or chronic medical conditions including but not limited to immune colitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

___ **3.3.13 Concomitant medications**

Chronic concomitant treatment that are strong inhibitors of CYP3A4 are not allowed on this study. Patients on strong CYP3A4 inhibitors must discontinue the drug for 14 days prior to registration on the study.