Update #09

**ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY**

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**PROTOCOL UPDATE TO ALLIANCE A091802**

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**PHASE II RANDOMIZED TRIAL OF AVELUMAB PLUS CETUXIMAB VERSUS AVELUMAB ALONE IN ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA OF THE SKIN (CSCC)**

| | | | |
|---|---|---|---|
| X | **Update:** | | **Status Change:** |
| | Eligibility changes | | Pre-Activation |
| | Therapy / Dose Modifications / Study Calendar changes | | Activation |
| X | Informed Consent changes | | Closure |
| | Scientific / Statistical Considerations changes | | Suspension / temporary closure |
| | Data Submission / Forms changes | | Reactivation |
| X | Editorial / Administrative changes | | |
| X | Other: Updated CAEPR for avelumab | | |

***The changes included in this update to A091802 have been made in response to the NCI Request for Rapid Protocol Amendment (RRA) from [redacted] This Action Letter is posted on the A091802 study page on the CTSU website. The revised CAEPR for avelumab with the new risk has been added to the protocol. Therefore, the model consent form has been revised to incorporate the new risk, consistent with the NCI Model Consent Template instructions.***

***No recommended IRB level of review is provided by the Alliance since the CIRB is the IRB of record for this trial.***

***The site has 30 days after the posting of this amendment to implement it at their site. Please refer to the amendment application and CIRB guidelines for further instructions.***

***Reconsent is required for all populations of the study.***

**UPDATES TO THE PROTOCOL:**

**Title Page**

- [redacted]
- [redacted]
- [redacted]

**CTSU Address and Contact Information**
This section has been completely updated to reflect current CTSU boilerplate language.

**Section 4.1 (Investigator and Research Associate Registration with CTEP)**
- This section's heading has been completely updated to the following to reflect current CTSU boilerplate language: "Investigator and Research Associate Registration with CTEP."
- This section has been completely updated to reflect current CTSU boilerplate language.

**Section 4.2 (Cancer Trials Support Unit Registration Procedures)**
- This section's heading has been completely updated to the following to reflect current CTSU boilerplate language: "Cancer Trials Support Unit Registration Procedures."
- This section has been completely updated to reflect current CTSU boilerplate language.
- Section 4.2.1 (Additional site registration requirements) has been added to reflect current CTSU boilerplate language. All subsequent sections have been renumbered.
- Sections 4.2.2 (Downloading Site Registration Documents) and 4.2.5 (Delegation of Task Log [DTL]) has been completely updated to reflect current CTSU boilerplate language.
- The order of the following sections has been switched and it is now the following to reflect current CTSU boilerplate language: Sections 4.2.3 (Submitting Regulatory Documents) and 4.2.4 (Checking Site Registration Status). Additionally, the content of the sections has been completely updated to reflect current CTSU boilerplate language.

**Section 4.5 (Patient Registration/Randomization Procedures)**
This section has been completely updated to reflect current CTSU boilerplate language.

**Section 6.1 (Data Collection and Submission)**
This section has been completely updated to reflect current CTSU boilerplate language.

**Section 6.2 (Data Quality Portal)**
This section has been completely updated to reflect current CTSU boilerplate language.

**Section 9.1.1 (Rave-CTEP-AERS integration)**
This section has been completely updated to reflect current CTSU boilerplate language.

**Section 9.4.1 (Comprehensive Adverse Events and Potential Risks list [CAEPR] for Avelumab [NSC 799232])**
The CAEPR for avelumab has been updated from Version 2.0, April 23, 2019 to Version 2.1, June 27, 2023. Changes from Version 2.0 to Version 2.1 include the following:
- Added New Risk:
  - Rare but Serious: Arthritis; Bullous dermatitis; Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (immune-mediated renal dysfunction); Erythema multiforme; Erythroderma; Eye disorders - Other, specify (iritis); Hemolysis; Hepatobiliary disorders - Other (hepatotoxicity); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (histiocytic necrotizing lymphadenitis); Nervous system disorders - Other (demyelination); Rhabdomyolysis; Skin and subcutaneous tissue disorders - Other (pemphigoid); Skin and subcutaneous tissue disorders - Other (psoriasiform dermatitis); Stevens-Johnson syndrome; Toxic epidermal necrolysis; Vasculitis
  - Also Reported on Avelumab Trials But With Insufficient Evidence for Attribution: Acute kidney injury; Allergic reaction; Anaphylaxis; Anal hemorrhage; Ascites; Atrial fibrillation; Bronchopulmonary hemorrhage; Dysphagia; Enterocolitis; Gastrointestinal disorders - Other (enteritis); General disorders and administration site conditions - Other

(general physical health deterioration); Hematuria; Hypercalcemia; Hypotension; Investigations - Other (thyroxine free decreased); ; Nervous system disorders - Other (Miller fisher syndrome); Pleural effusion; Proctitis; Purpura; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease); Skin and subcutaneous tissue disorders - Other (drug eruption); Skin and subcutaneous tissue disorders - Other (lichen planus); Skin hypopigmentation; Small intestinal obstruction; Thromboembolic event

- Increase in Risk Attribution:
  - Changed to Likely from Less Likely: Nausea
  - Changed to Less Likely from Also Reported on Avelumab Trials But With Insufficient Evidence for Attribution: Back pain; Constipation; Dizziness; Dyspnea; Edema limbs; Headache; Hypertension Weight loss
- Decrease in Risk Attribution:
  - Changed to Also Reported on Avelumab Trials But With Insufficient Evidence for Attribution from Less Likely: Flu like symptoms; Pruritus
- Provided Further Clarification:
  - Footnote #2 previously reported as "Immune-mediated adverse reactions have been reported in patients receiving avelumab. Adverse events potentially related to avelumab may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of avelumab), administration of corticosteroids and supportive care." is now reported as "Avelumab being a member of class of agents involved in the inhibition of "immune checkpoints" may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) adrenal insufficiency, arthritis, autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous dermatitis, colitis, dermatitis psosiasiform, demyelination, Nervous system disorders - Other (non-infectious encephalitis) , hyperglycemia, erythema multiforme, exfoliative dermatitis, Guillain-Barré syndrome, hemolytic anemia, hepatic failure histiocytic necrotizing lymphadenitis, hypophysitis, hypopituitarism, Infusion related reaction, iritis, myocarditis, myasthenia gravis, myositis, nephritis and renal dysfunction, pancreatitis, pemphigoid pneumonitis, rhabdomyolysis, sarcoidosis , Stevens-Johnson syndrome(SJS)/toxic epidermal necrolysis (TEN), Thyroid Disorders (hypothyroidism/hyperthyroidism), uveitis, vasculitis. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of of avelumab), administration of corticosteroids and supportive care.

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**UPDATES TO THE MODEL CONSENT:**

**What risks can I expect from taking part in the treatment study?**

The tables under the "Possible Side Effects of Avelumab" heading have been updated per CAEPR Version 2.1 with the following risk list change:

- Added New Risk:
  - Rare: Painful and enlarged lymph nodes; Swelling and redness of the skin; Skin: itching; rash, blisters including inside the mouth; loss of skin pigment
- Increase in Risk Attribution:

    - Changed to Common from Occasional: Nausea
    - Changed to Occasional from Also Reported on Avelumab Trials But With Insufficient Evidence for Attribution (i.e. Added to Risk Profile): Constipation; Dizziness; Swelling of the body; Headache; Shortness of breath; High blood pressure which may cause headaches, dizziness, blurred vision; Weight loss
- Decrease in Risk Attribution:
    - Changed to Also Reported on Avelumab Trials But With Insufficient Evidence for Attribution from Occasional (i.e. Removed from Risk Profile): Flu-like symptoms including body aches; Itching
- Provided Further Clarification:
    - Swelling and redness of the eye (under Rare) is now reported as Swelling and redness of the eye with a chance of blindness (under Rare).

**A replacement protocol document and model consent form have been issued.**

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**ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL**

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ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A091802

# PHASE II RANDOMIZED TRIAL OF AVELUMAB PLUS CETUXIMAB VERSUS AVELUMAB ALONE IN ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA OF THE SKIN (cSCC)

*Industry-supplied agent(s): Avelumab (NSC# 799232; IND# 143349); IND holder: Alliance*
*Commercial agent(s): Cetuximab (NSC# 714692)*
**ClinicalTrials.gov Identifier: NCT03944941**


Study Chair

[redacted]

Community Oncology Co-Chair

[redacted]

Experimental Therapeutics Rare Tumors Committee Co-Chair

[redacted]

Experimental Therapeutics Rare Tumors Committee Co-Chair

[redacted]

Primary Statistician

[redacted]

Protocol Coordinator

[redacted]

Data Manager

[redacted]


Participating Organizations:

Alliance/Alliance for Clinical Trials in Oncology (lead), ECOG-ACRIN / ECOG-ACRIN Cancer Research Group, NRG / NRG Oncology, SWOG / SWOG

**Study Resources:**

**Expedited Adverse Event Reporting**

[redacted]

**Medidata Rave® iMedidata portal**

[redacted]

**OPEN (Oncology Patient Enrollment Network)**

[redacted]

**Biospecimen Management System**

[redacted]

**Protocol Contacts:**

**A091802 Nursing Contact**

[redacted]

**A091802 Pharmacy Contact**

[redacted]

**Alliance Biorepository at Washington University (WUSTL)**

[redacted]

**Drug Distribution Contact**

[redacted]

| **Protocol-related questions may be directed as follows:** | |
|---|---|
| **Questions** | **Contact (via email)** |
| Questions regarding patient eligibility, treatment, and dose modification: | Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager |
| Questions related to data submission, RAVE or patient follow-up: | Data Manager |
| Questions regarding the protocol document and model informed consent: | Protocol Coordinator |
| Questions related to IRB review | Alliance Regulatory Inbox [redacted] |
| Questions regarding CTEP-AERS reporting: | Pharmacovigilance Inbox [redacted] |
| Questions regarding specimens/specimen submissions: | Alliance Biorepository at WUSTL |
| Questions regarding drug supply | McKesson Clinical Research Services |
| Questions regarding drug administration | Pharmacy Contact |

## CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

| For regulatory requirements: | For patient enrollments: | For data submission: |
|---|---|---|
| Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal.<br>(Sign in at [redacted] and select the Regulatory > Regulatory Submission.)<br><br>Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] to receive further instruction and support.<br><br>Contact the CTSU Regulatory [redacted] for regulatory assistance. | Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at [redacted]<br><br>Contact the CTSU Help Desk with any OPEN-related questions by phone or email: [redacted] | Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions. |

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website ([redacted]).

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.

**For clinical questions (i.e., patient eligibility or treatment-related)** see the Protocol Contacts, Page 2.

**For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission)** Contact the CTSU Help Desk by phone or email:
CTSU General Information Line – [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative.

PHASE II RANDOMIZED TRIAL OF AVELUMAB PLUS CETUXIMAB VERSUS AVELUMAB ALONE IN ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA OF THE SKIN (CSCC)

**Pre-Registration Eligibility Criteria**

Available sample for PD-L1 testing (See §3.2.1)

**Registration Eligibility Criteria (see Section 3.3)**

Biopsy proven advanced cutaneous squamous cell carcinoma.

Measurable disease as defined in Section 11.0

**Required Initial Laboratory Values**

Absolute neutrophil count (ANC): ≥ 1500/mm$^3$
Platelet count: ≥ 100,000/mm$^3$
Calc. creatinine clearance: ≥ 30 mL/min
Total bilirubin: ≤ 1.5 x ULN
AST/ALT: ≤ 2.5 x ULN

**Prior Treatment**

Patients who received prior treatment with cetuximab as palliative treatment for advanced cSCC (as defined in §3.3.1) are excluded. Patients that received cetuximab based chemoradiation (either definitive or adjuvant) 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 prior cetuximab and had a severe infusion reaction requiring discontinuation of cetuximab are excluded.

No prior treatment with anti-PD-1 or anti PD-L1 mAbs

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.

**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.

Not pregnant and not nursing (See §3.3.5)

Age ≥ 18

ECOG Performance Status 0-2

No “currently active” second malignancy with the exception of other non-melanoma skin cancers or cervical carcinoma in situ (See §3.3.8)

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

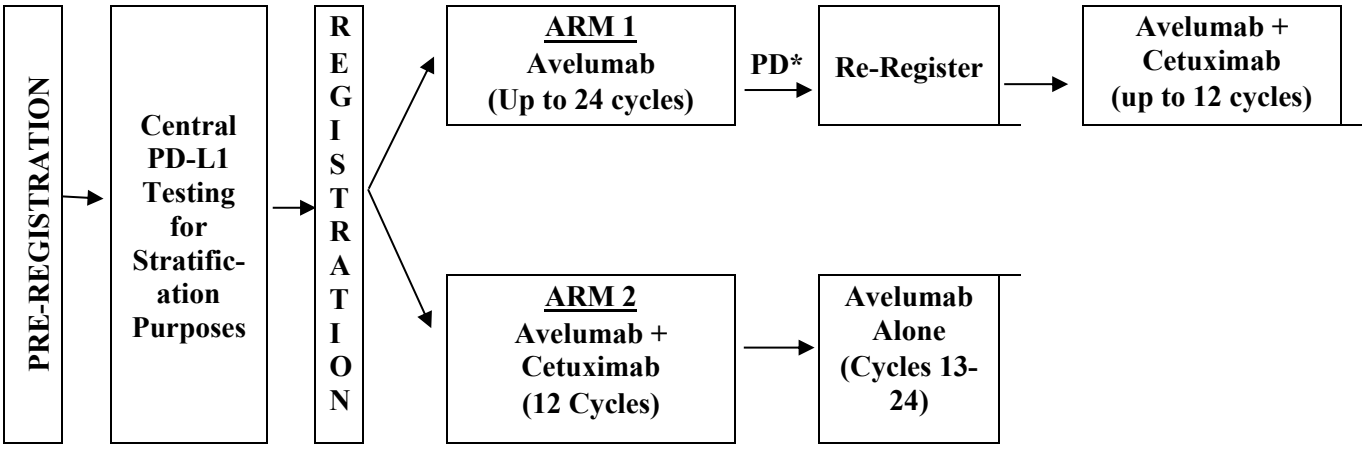
No history of the following:

- Autoimmune disease (including inflammatory bowel disease) with the exception of patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment.
- No currently active non-infectious pneumonitis or history of 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.
- No active infection requiring systemic treatment
- No use of immunosuppressive medication ≤ 7 days of registration (See § 3.3.12)
- No other severe acute or chronic medical conditions (See § 3.3.12)

**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.**

## Table of Contents

## 1.0 BACKGROUND

Cutaneous squamous cell carcinoma (cSCC) is one of the most common cancers with an estimated 700,000 new cases diagnosed each year in the United States [1, 2]. While most will have an excellent prognosis, as many as 12,572 patients per year have nodal metastasis and the number of deaths from cSCC per year in the USA is upwards of 8791, which approaches the annual melanoma-related deaths per year [2, 3]. For patients with locally advanced cSCC without a surgical option or metastatic disease, systemic treatment options are limited. There is limited data with predominantly case series with various chemotherapy agents used for squamous cell carcinomas of other sites [4]. Prospective trials have been conducted with anti-EGFR monoclonal antibodies as well as tyrosine kinase inhibitors in advanced disease. Cetuximab showed a RR of 27% and DCR of 70% however duration of activity was very short with a median PFS and OS of 4 and 8 months respectively [5]. Gefitinib was tested in advanced disease with zero responses and DCR of 27% [6]. More recently, a prospective trial was conducted with anti PD-1 mAb Cemiplimab in 59 patients with advanced cSCC. Treatment with Cemiplimab led to a RR of 47%, and a 12 month PFS and OS of 52.5% and 80.6% respectively [22]. This led to the approval by the FDA of Cemiplimab for the treatment of metastatic cSCC or locally advanced cSCC who are not candidates for curative surgery or curative radiation.

### 1.1 Rationale for the Use of Avelumab in cSCC

There is a significant rationale for the use of avelumab in cSCC. The development of cSCC is intricately tied to the immune system. The risk of developing cSCC is significantly increased with immunosuppression, for example organ transplant patients on immunosuppressive medication have a nearly 65 fold increase in risk of development of cSCC, and increased incidence is directly correlated with the degree of immunosuppression [7, 8]. In addition to DNA damage, UV radiation suppresses the immune system and the degree of UV radiation induced immunosuppression correlates with increased development of cSCC. UV radiation has been observed to suppress cell-mediated immunity, suppress dendritic cell activation of T cells, increase T regs and M2 macrophages, and skew the immune response towards a Th2 type response [7,9,10]. Immunotherapy has been evaluated in advanced cSCC with promising results. Interferon alpha (IFN-α) has been studied with 13-cis-retinoic acid and Cisplatin in prospective trials. In combination with 13-cis-retinoic acid RR was 68% with 25% achieving a CR [11]. In combination with cisplatin the overall response rate was 34% with 17% of patients having a CR and those that had a CR having duration of response of a median of 34 months. Response rates in patients with locally advanced disease were an impressive 67% [12]. However, IFN-α never made it to mainstream practice because of significant toxicity making it hard to tolerate. Our group evaluated PD-L1 and PD-1 expression by CD8 T cells in 70 patients with cSCC requiring surgical resection. Defining positive expression as greater than 5%, 26% of all tumors were PD-L1 positive, and 80% had CD8 T cells in the tumor microenvironment that expressed PD-1. Looking at the percentages of the tumor involved by CD8 T cells, a median of 40% of the tumor was infiltrated by CD8 T cells in these cSCC patients [13]. Additional rationale for checkpoint blockade in cSCC comes from mutational analysis. Higher somatic mutational burden has been shown as a strong predictor of response to checkpoint blockade retrospectively in melanoma and NSCLC and prospectively in mismatch repair deficient colon cancer [14-16]. Whole exome sequencing of aggressive cSCC samples showed a higher mutational rate then even reported in melanoma, with a median of 61.2 mutations/Mb, and mutations were largely clonal [17]. Additionally, as discussed above, treatment with anti-PD-1 mAb cemiplimab was associated with a RR of 47% [22].

### 1.2 Rationale for the Use of Avelumab plus Cetuximab in cSCC

There is a significant rationale for the combination of avelumab and cetuximab. Cetuximab is an IgG1 mAb against EGFR. IgG1 mAbs induce the innate immune system through NK cell

mediated antibody dependent cellular cytotoxicity (ADCC) and can additionally stimulate adaptive immunity [18]. In patients with head and neck cancer, treatment with IgG1 mAb cetuximab, induces the development of EGFR specific CD8 T cells in the peripheral blood. In vitro, in the presence of EGFR expressing tumor cells, cetuximab induced the activation of NK cells with IFNγ secretion, leading to cross talk and maturation of dendritic cells and subsequent antigen presentation and induction of EGFR specific CD8 T cells [19]. Additionally, Th1 polarizing cytokines were induced as well as chemokines like CXCL10 improving T cell migration. Importantly, IgG1 mAb induced NK cell mediated DC maturation lead to presentation of not just EGFR but additionally MAGE-A3 for example [19]. EGFR overexpression is consistently observed in cSCC [6]. In a murine model, treatment with an anti-ErbB-2 mAb, mimicking IgG1 mAb Trastuzumab, lead to increase in IFNγ producing CD8 T cells in the tumor microenvironment with induction of PD-L1 expression by tumor cells. Combination with Anti-PD-1 mAb showed synergy and improved therapeutic efficacy compared to either mAb given alone [20]. Thus IgG1 monoclonal antibody cetuximab induces innate and adaptive immunity recruiting immune cell to the tumor microenvironment that can benefit from blockade of the PD-1:PD-L1 axis [18]. Avelumab is also an IgG1 mAb which induces ADCC and so this combination in particular has the potential to induce a stronger immune response than cetuximab in combination with other anti-PD-1/PD-L1 mAbs.

### 1.3 Impact of the Trial

In summary, there is a significant rationale for the use of avelumab including in combination with cetuximab in this patient population. This trial will importantly evaluate the safety and efficacy of this combination in advanced cSCC and will be an important step in improving outcomes in this patient population.

## 2.0 OBJECTIVES

### 2.1 Primary Objective

To evaluate whether treatment with avelumab plus cetuximab prolongs progression free survival (PFS) compared to avelumab alone.

### 2.2 Secondary Objectives

**2.2.1** To evaluate the confirmed objective response rate of each treatment arm.

**2.2.2** To evaluate the clinical benefit rate of each treatment arm.

**2.2.3** To evaluate the PFS of cetuximab plus avelumab in patients that have progressed on single agent avelumab.

**2.2.4** To evaluate the OS for each treatment arm.

**2.2.5** To evaluate toxicity across treatment arms of avelumab plus cetuximab and avelumab alone.

### 2.3 Correlative Objective

**2.3.1** To examine the association between PD-L1 expression and RR, CBR, PFS and OS in both patients receiving cetuximab and avelumab as well as avelumab alone.

## 3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

### 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 (either definitive or adjuvant) 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 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.

## 4.0 PATIENT REGISTRATION

### 4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at [redacted] Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

- Investigator (IVR) ─ MD, DO, or international equivalent;
- Non-Physician Investigator (NPIVR) ─ advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP) ─ clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave; acting as a primary site contact, or with consenting privileges
- Associate (A) ─ other clinical site staff involved in the conduct of NCI-sponsored trials; and

- Associate Basic (AB) ― individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

| Documentation Required | IVR | NPIVR | AP | A | AB |
|---|---|---|---|---|---|
| FDA Form 1572 | ✓ | ✓ | | | |
| Financial Disclosure Form | ✓ | ✓ | ✓ | | |
| NCI Biosketch (education, training, employment, license, and certification) | ✓ | ✓ | ✓ | | |
| GCP training | ✓ | ✓ | ✓ | | |
| Agent Shipment Form (if applicable) | ✓ | | | | |
| CV (optional) | ✓ | ✓ | ✓ | | |

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following::

- Addition to a site roster;
- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the **NCI RCR** page on the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at [redacted]

## 4.2 Cancer Trials Support Unit Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website.

This study is supported by the NCI CTSU.

**IRB Approval**

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB.

International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling [redacted]

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an Active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

### 4.2.1 Additional site registration requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (U.S. sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

### 4.2.2 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website [redacted];
- Click on *Protocols* in the upper left of the screen:
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *Alliance*, and protocol number *A091802*.
- Click on *Documents*, *Protocol Related Documents,* and use the *Document Type* filter and select *Site Registration* to download and complete the forms

provided**.** (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

### 4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission.*

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] to receive further instruction and support.

### 4.2.4 Checking Site Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go:
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

### 4.2.5 Delegation of Task Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and to activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List.

## 4.3 Patient Pre-Registration Requirements (Step 0)

- **Informed consent:** The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.
- **Protected Health Information:** Paraffin Tumor tissues collected for this study will be sent directly to MD Anderson, which is a CLIA certified lab. These samples will be labeled with patient initials, DOB, gender, study ID, pathology accession number and collection date.

- **Central PD-L1 Testing:** Patients who meet the pre-registration eligibility criteria will be pre-registered using the OPEN registration system (see Section 4.5) in order to submit specimens for central PD-L1 testing. Once a patient is pre-registered, unstained slides from diagnostics should be sent to the MD Anderson CLIA lab along with a completed "A091802 CLIA Laboratory PD-L1 Sample Submission Form", per Section 6.0 and Correlative Science Manual. Failure to submit this form with the specimens will delay turnaround time for central PD-L1 testing. PD-L1 results are required for ALL patients to be registered for stratification purposes.

## 4.4 Patient Registration Requirements (Step 1)

- **Confirmation of PD-L1 results:**

  Sites will be notified via e-mail within 5 business days of receipt, that the PD-L1 result is available.

  After receiving the results via e-mail, the patient can be registered using the OPEN system per Section 4.5.

  Registration must occur within 28 days of specimen submission. The same patient ID number obtained at pre-registration from the OPEN system should be used to register the patient. Please contact Alliance Patient Registration office at [redacted] if registration problems occur.

## 4.5 Patient Registration/Randomization Procedures

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs' registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at [redacted] or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at [redacted] For any additional questions, contact the CTSU Help Desk at [redacted]

### 4.6 Randomization Method

After a patient is registered they will be assigned to one of the two treatment arms (avelumab + cetuximab or avelumab alone) in a 1:1 ratio utilizing a dynamic allocation algorithm based on the methods by Pocock and Simon [22]. The goal of the algorithm is to maintain arm balance with respect to the stratification factors mentioned in Section 4.8.

In order to ensure that treatment assignment is not deterministic a level of randomness has been added to the algorithm such that patients will be assigned to the arm that leads to more imbalance 10% of the time.

### 4.7 Re-Registration at Crossover

- Upon confirmation of progression by RECIST 1.1 (per Section 11.3), by the treating investigator, patients who were initially assigned to avelumab alone will be allowed to cross over to avelumab + cetuximab as long as ECOG PS is still 0-2.
- Follow the OPEN enrollment procedures detailed in Section 4.5.

### 4.8 Stratification Factors

HIV positive vs. negative

PD-L1 positive vs. negative

## 5.0 STUDY CALENDAR

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

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.

To be completed ≤ 28 DAYS before registration: All laboratory studies, history and physical, and any scan of any type which is utilized for tumor measurement per protocol.

| | Prior to Registration* | Days 1 and 15 of each cycle * | Post treatment follow up** | At PD, withdrawal, or removal*** |
|---|---|---|---|---|
| **Tests & Observations** | | | | |
| History and Physical, Weight, PS**** | X | | X | X |
| Directed Physical Exam | | X | | |
| Height | X | | | |
| Pulse, Blood Pressure | X | X | X | X |
| ECG | X (1) | | | |
| CTCAE Adverse Event Assessment | | X | C | X |
| Registration Fatigue/Uniscale Assessment | X(2) | | | |
| **Laboratory Studies** | | | | |
| Complete Blood Count, Differential, Platelets | X | X | D | X |
| Serum Creatinine | X | X | D | X |
| Albumin, Glucose | X | X | D | X |
| AST, ALT, Alk. Phos., Bili | X | X | D | X |
| Magnesium | X | X | D | X |
| TSH with Reflex Free T4 | X(3) | | | |
| Serum or Urine HCG | X(4) | | | |
| CD4 Count and HIV Viral Load (#) | X | | | |
| Tumor PD-L1 Analysis | X | | | |
| **Staging** | | | | |
| Tumor Measurements | X | A | X | |
| Radiographic Imaging | X(5) | B | X | |
| **Correlative studies: For patients who consent to participate** | | | | |
| Tumor Tissue | See Section 6.3.4. | | | |
| Research Blood Draw (6) | Baseline, day 1 of cycle 4, day 1 of cycle 7, at time of completion of study treatment, and/or at progression (blood draw at first visit post imaging that confirms progression). | | | |

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 5 days prior to treatment. For subsequent cycles, labs, scans, tests and observations may be obtained ≤ 24 hours prior to day of treatment.

** For patients who complete all study therapy or who ended study therapy early for any reason other than progression , physical examination and staging scans are required 12 weeks (+/- 7 days) after the end of treatment, then every 12 weeks (+/- 7 days) until disease progression unless consent is withdrawn for clinical follow up. If this consent is withdrawn these patients will follow up as per Section 12.3.

*** Patients with progressive disease will go to survival follow-up at 30 days (+/- 7 days) and 90 days (+/- 7 days) from Off-treatment date for safety follow-up. Subsequently they will be in survival follow-up every 6 months from date of most recent contact for up to 2 years after progression.

**** Drug dosages do not need to be changed unless the calculated dose changes by ≥ 10%.

\# Only for HIV positive patients a CD4 count and viral load should be obtained.

1 As clinically indicated.

2 To be completed after registration and ≤ 21 days prior to treatment.

3 TSH with reflex free T4 will be obtained prior to registration and then as clinically indicated during study treatment. Free T4 is only done if the TSH is abnormal.

4 For women of childbearing potential. Must be done ≤ 7 days prior to registration and then as clinically indicated during study treatment.

5 Baseline imaging should include a CT or MRI of the chest/abdomen/pelvis for all patients to adequately evaluate for distant metastatic disease. The patient should also undergo CT or MRI imaging for the primary site of their cSCC as applicable. For example, a patient with a cSCC of the head and neck should undergo CT neck in addition to CT chest/abdomen/pelvis. CT scans should be done with IV and oral contrast unless allergy prevents administration. If MRI is chosen as imaging modality for following target/non-target lesions then MRI should be used for evaluation of response during the study. CT is encouraged over MRI.

6 When research blood draw is done on day 1 of a cycle it will be done before the treatment is given.

A. After every 3 cycles (beginning prior to Cycle 4) until evidence of progression. Scans may be done up to 7 days prior to beginning the next cycle. Imaging can be done earlier if clinically indicated based on the investigators judgment. Confirmatory scans should also be obtained at least 4 weeks following documentation of objective response (see Section 11.0). If a patient completes all study therapy and has not progressed at that time the patient will have repeat imaging 12 weeks (+/- 7 days) after the end of treatment, then every 12 weeks (+/- 7 days) until disease progression, as per Section 12.3.

B. Response assessment should include assessment of all sites of disease and use the same imaging method as was used at baseline. All patients should also undergo a CT of the chest/abdomen/pelvis in addition to a CT of the primary site of active disease if applicable in addition to a CT of the primary site of active disease if applicable.

C. Done at post-treatment follow-up visit.

D. Done as clinically indicated during post-treatment follow-up visit.

# 6.0 DATA AND SPECIMEN SUBMISSION

## 6.1 Data Collection and Submission

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only or Rave SLA role must have at a minimum an Associates (A) registration type.

Refer to [redacted] for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study-specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the *Data Management* section under the Rave resource materials (*Medidata Account Activation and Study Invitation Acceptance*). Additional information on iMedidata/Rave is available on the CTSU members' website in the *Data Management* > *Rave* section or by contacting the CTSU Help Desk at [redacted]

### 6.1.1 Supporting Documentation to be Submitted to the Alliance

This study requires supporting documentation for diagnosis, response and progression. Supporting documentation will include pathology clinical notes (including labs and imaging). These must be submitted at the following time points:

- Pathology reports from diagnosis should be submitted 10 days prior to registration or at progression if applicable.
- The PD-L1 results from MD Anderson should be submitted prior to registration.
- Radiology reports will be required at each measurement (baseline, during treatment, and during event monitoring, per Section 5.0). Supporting documentation is to be submitted via Rave.

## 6.2 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

## 6.3 Specimen Collection and Submission

### 6.3.1 Prospective PD-L1 analysis

Tissue will be submitted within 14 days of pre-registration. Archival tissue can be used for PD-L1 analysis. If archival tissue is not available that is adequate for PD-L1 analysis a new biopsy will be required. PD-L1 status (positive/negative) will be required before randomization.

### 6.3.2 A091802-Biobanking

All participating institutions must ask patients for their consent to participate in the biobanking planned for Alliance A091802, although patient participation is optional. For patients who consent to participate (model consent question, "I agree that my samples and related health information may be kept in a biobank for use in future health research." Biomarker studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 14.0.

### 6.3.3 Correlative Science Manual (CSM)

The Alliance A091802 Correlative Science Manual (CSM) contains instructions for specimen collection, processing and shipping. The manual can be found on the BioMS, CTSU, and CTSU websites. Questions regarding the CSM should be addressed to the contacts specified in the manual.

### 6.3.4 Overview of Specimen Requirements

| | ≤ 14 days of pre-registration | Baseline ≤ 28 days of registration | Day 1 of Cycle 4,7 | At progression | Completion of study treatment |
|---|---|---|---|---|---|
| **Mandatory for <u>all</u> patients registered to A091802:** | | | | | |
| **Unstained slides from diagnostic tissue for PD-L1 analysis** | X | | | | |
| **For patients registered to A091802 biobanking, submit the following:** | | | | | |
| **Tumor tissue block or slides** | | X | | | |
| **Peripheral whole blood (purple top EDTA)** | | 3x10ml | 3x10ml | 3x10ml | 3x10ml |
| **Whole blood in STRECK tubes** | | 2x8ml | 2x8ml | 2x8ml | 2x8ml |

## 7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 7 days of registration.

For questions regarding treatment, please see the study contacts page.

It is acceptable for individual drug doses to be delivered +/- a 48-hour (business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Wednesday through the following Tuesday. This also includes a situation when both cetuximab and avelumab are given and avelumab cannot be completed if there was a significant delay as a result of an infusion reaction to cetuximab. Every effort should be made be to keep day 15 dosage on that day however a +/- 24 hour (business day) window for day 15 is allowable. Day 1 and Day 15 dosages should be at least 13 days apart. In addition, patients are permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

Every cycle will be 28 days. One cycle of avelumab includes drug given day 1 and 15. One cycle of cetuximab includes drug given day 1 and 15. When the combination of avelumab and cetuximab is given (Arm 2), the first 12 cycles will include both cetuximab and avelumab. If the patient has not progressed after the first 12 cycles than avelumab alone will be given for up to another 12 cycles or until progression (up to 24 total cycles for the study). For patients receiving avelumab alone (Arm 1), avelumab will be continued until progression or for up to 24 cycles. A patient that is randomized to Arm 1 and receives avelumab alone and progresses will then receive avelumab plus cetuximab as detailed above for Arm 2. Combination avelumab and cetuximab after avelumab failure will be given

for up to 12 cycles. Avelumab will be given at 800mg IV q2 weeks. Cetuximab will be given at standard dosing of 500mg/m$^2$ IV q2 weeks.

Arm 1:

| Agent[1] | Dose [2] | Route[3] | Schedule | Cycle Length[5] |
|---|---|---|---|---|
| Avelumab[4] | 800mg | IV | Cycles 1-24<br>Days 1, 15 | 28 days |

1 Refer to Section 8.1.2 for information on premedications.

2 Refer to section 10.1 for rounding rules for dosage.

3 Refer to section 10.3 for infusion time of avelumab.

4 Refer to section 10.3 for additional details on avelumab preparation.

5 If the patient has not progressed after the first 12 cycles of avelumab alone, the avelumab will be given for another 12 cycles or until progression (up to 24 cycles total for the study).

Arm 2 and Crossover from Arm 1

| Agent[1] | Dose [2] | Route[3] | Schedule | Cycle Length |
|---|---|---|---|---|
| Cetuximab | 500mg/m$^2$ | IV | Cycles 1-12<br>Days 1, 15 | 28 days |
| Avelumab[4] | 800mg | IV | Cycles 1-24<br>Days 1, 15 | 28 days |

1 Refer to Section 8.1.2 for information on premedications.

2 Refer to Section 10.1 for rounding rules for dosage.

3 Refer to Section 10.3 for infusion volume and administration of avelumab. Infusion time for cetuximab will be as per institutional standards. On days when both drugs are given, avelumab will be given after cetuximab.

4 Refer to Section 10.3 for additional details on avelumab preparation.

5 Refer to Section 10.2 for additional details on cetuximab preparation and administration.

On cycle 1 day 1 cetuximab at 500mg/m$^2$ IV and avelumab at 800mg IV (see Section 10.3 for additional details on avelumab preparation and administration). Cetuximab (see Section 10.2 for additional details on cetuximab preparation and administration) will be given first and patient will be observed for 1 hour post completion of cetuximab to ensure no infusion reaction has occurred before receiving avelumab. Patients will be observed for 2 hours post avelumab on day 1, cycle 1 and 1 hour post starting cycle 1 day 15 for the first 4 doses. Cetuximab will continue to be given before avelumab on treatment days. If after the 2$^{nd}$ cycle no infusion reactions have occurred patients will be observed for 30 minutes after cetuximab and 30 minutes after avelumab. The instructions in this paragraph apply to Arm 2 and if a patient crosses over from Arm 1 to combination avelumab plus cetuximab.

## 8.0 DOSE AND TREATMENT MODIFICATIONS

### 8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

- Patients should not receive any other treatment which would be considered treatment for the cSCC or impact the primary endpoint.

This includes any surgical intervention, radiotherapy, cryotherapy, ablation, etc., performed on the target lesions.

- Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.
- Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given as pre-medication for infusions, as treatment for infusion reactions, or immune related adverse events; and hormones administered for non-disease-related conditions (e.g., insulin for diabetes).
- Antiemetics may be used at the discretion of the attending physician, with the exception of steroids above.
- Palliative radiation therapy may be administered during the study for symptomatic bone lesions. Any other form of palliative radiation required including whole brain irradiation given for new documented CNS disease would require removal from the study.

### 8.1.1 Alliance Policy Concerning the Use of Growth Factors

The following guidelines are applicable unless otherwise specified in the protocol.

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 33: 3199-3212, 2015 and American Society of Clinical Oncology – American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer. J Clin Oncol 28:4996-5010, 2010.

Epoetin (EPO): Use of epoetin in this protocol is prohibited

White Blood Cell Growth Factors (Includes: filgrastim (G-CSF), pegfilgrastim) and other FDA approved white blood cell growth factor biologics)

1. White blood cell growth factor treatment for patients on protocols that do not specify their use is discouraged.
2. White blood cell growth factor may not be used:
    a. To avoid dose delays.
    b. For the treatment of febrile neutropenia, the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastim/pegfilgrastim) must be documented and reported. (e.g. on CRFs per protocol requirements)
    c. If White blood cell growth factors are used, they must be obtained from commercial sources. Selection of white blood cell growth factor products should be per institutional guidelines.

### 8.1.2 Hypersensitivity/infusion reactions

**Cetuximab:**

Premedication with antihistamines is recommended before cetuximab infusion. Treat hypersensitivity and infusion reactions to cetuximab as per institutional standards. Patients who experience Grade 1, 2, or 3 infusion reactions should have the infusion rate permanently reduced by 50% and continue to receive antihistamine premedication prior to administration. Patients who experience Grade 3 infusion reactions requiring hospital admission or Grade 4 will be discontinued from the study if they have received less than 6 cycles of cetuximab. If they have received at least 6 cycles when this occurs they will permanently discontinue cetuximab and just continue on avelumab.

**Avelumab:**

Avelumab should be administered in a setting that allows for access to and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids, epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access. In order to mitigate avelumab infusion-related reactions, a premedication regimen of 25 to 50mg IV or oral equivalent diphenhydramine and 650mg IV or oral equivalent acetaminophen/paracetamol (as per local practice) is mandatory approximately 30 to 60 minutes prior to each of the first 4 doses of avelumab. Because diphenhydramine is given as a pre-medication prior to cetuximab, if it has been at least 3 hours since prior dose of diphenhydramine should be given again as pre-medication for avelumab unless sedation of patient precludes to being given at the discretion of the treating investigator. Patients will be observed in the clinic for at least 2 hours after Cycle 1 day 1 and for at least 1 hour starting Cycle 1 day 15, after each infusion of avelumab. If, following the 4$^{th}$ dose of avelumab, no infusion-related reactions are observed, no further premedication will be required for subsequent administrations and patients will require only 30 minutes of observation following the infusion. Infusion of avelumab will be stopped in case of Grade ≥2 infusion-related, allergic, or anaphylactic reactions. If an infusion/allergic reaction occurs, the patient must be treated according to the best available medical practice, with parameters on rate reduction and discontinuation shown in Table 1 below.

Table 1 Treatment Modification for Symptoms of Avelumab Infusion Related Reactions

| CTCAE Grade | Treatment Modification for Avelumab |
|---|---|
| Grade 1<br>Mild transient reaction; infusion interruption not indicated; intervention not indicate | Decrease the avelumab infusion rate by 50% and monitor closely for any worsening |
| Grade 2<br>Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, | Temporarily discontinue avelumab infusion<br>Resume infusion at 50% of previous rate once infusion-related reaction |

| | | |
|---|---|---|
| | narcotics, IV fluids); prophylactic medications indicated for ≤ 24 | has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening |
| | Grade 3 or Grade 4<br>Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae<br>Grade 4: Life-threatening consequences; urgent intervention indicated | Stop the avelumab infusion immediately and disconnect infusion tubing from the subject.<br>Participants have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment. |

**Note:** Once the avelumab infusion rate has been decreased by 50% due to an infusion-related reaction, it must remain so for all subsequent infusions.

If on the day of treatment, as a result of management of infusion reaction to either cetuximab or avelumab there is not enough time to complete the infusion with required observation period, then treatment should be restarted the next day (within 24 hours).

**Additional Modifications for Patients with Grade 2 Avelumab Infusion-Related Reactions:** In the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in Table 1(including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids, and the infusion should not be resumed for that cycle. At the next cycle, the Investigator may consider the addition of H2-blocker antihistamines (e.g., famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication. Prophylactic steroids are NOT permitted.

**Management of Avelumab related Severe Hypersensitivity Reactions and Flu-like Symptoms**

Many monoclonal antibody therapies can induce flu-like symptoms and hypersensitivity reactions, including impaired airway, decreased oxygen saturation (<92%), confusion, lethargy, hypotension, pale/clammy skin, and cyanosis. Patient should be placed on monitor immediately and epinephrine injection and dexamethasone infusion should be available for immediate access.

For prophylaxis of flu-like symptoms, 25mg indomethacin or comparable nonsteroidal antiinflammatory drugs (NSAID) dose (e.g., ibuprofen 600mg, naproxen sodium 500mg) may be administered at Investigator discretion 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (e.g., paracetamol or ibuprofen) and rigors (e.g., meperidine) may be given to patients at the discretion of the Investigator.

**Management of Avelumab-Related Tumor Lysis Syndrome**

Avelumab can induce antibody-dependent cell-mediated cytotoxicity (ADCC), so there is a potential risk of tumor lysis syndrome. Should this occur, patients should be treated as per local guidelines and the management algorithm.

## 8.2 Dose Modifications

### 8.2.1 Dose modification and management of adverse events from avelumab

No dose modifications of avelumab are permitted in this study, but the next infusion may be omitted based on persisting toxicity, as outlined in the next sections.

**Management of Avelumab Immune-Related Adverse Events**

Because inhibition of PD-L1 stimulates the immune system, avelumab may cause toxicity by increasing the immune response, leading to inflammatory reactions collectively referred to as immune-related adverse events (irAEs). Immune-related adverse events described with this class of drugs include pneumonitis, colitis, hepatitis, endocrinopathies including thyroid disorders (hyperthyroidism, hypothyroidism, thyroiditis), adrenal insufficiency, rash, nephritis and renal dysfunction, eye disorders (includinguveitis, iritis), and other immune-mediated reactions including myositis and myocarditis. Any AE which may have an underlying immune-mediated mechanism including those described above, and without other clear etiologies, should be considered immune-related and managed according to guidelines described in this section.

Treatment of irAEs is mainly dependent upon severity (NCI CTCAE grade v5.0):

General Approach.

Grade 1 or 2: treat symptomatically or with moderate-dose steroids, more frequent monitoring;

Grade 1 or 2 (persistent): manage similar to high grade AE (Grade 3 to 4)

Grade 3 or 4: treat with high-dose corticosteroids.

Treatment of irAEs should follow guidelines set forth in Table 2 below.

**Table 2: Management of Immune-related Adverse Reactions from Avelumab**

| Gastrointestinal irAEs | | |
|---|---|---|
| Severity of Diarrhea/Colitis (NCI-CTCAE v5) | Initial Management | Follow-up Management |
| Grade 1 | Continue avelumab therapy<br>Symptomatic treatment (e.g. loperamide) | Close monitoring for worsening symptoms<br>Educate subject to report worsening immediately<br>If worsens:<br>Treat as Grade 2, 3 or 4. |

| | | |
|---|---|---|
| Grade 2 | Withhold avelumab therapy<br>Symptomatic treatment<br>Consider starting 1 to 2 mg/kg/day prednisone IV or equivalent | If improves to Grade ≤ 1:<br>Resume avelumab therapy<br>If persists > 5-7 days or recurs:<br>Treat as Grade 3 or 4. |
| Grade 3 to 4 | Withhold avelumab for Grade 3.<br>Permanently discontinue avelumab for Grade 4 or recurrent Grade 3.<br>Start 1 to 2 mg/kg/day prednisone IV or equivalent<br>Add prophylactic antibiotics for opportunistic infections if indicated<br>Consider lower endoscopy | If improves:<br>Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).<br>If worsens, persists > 3 to 5 days, or recurs after improvement:<br>Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis. |
| Dermatological irAEs | | |
| Grade of Rash<br>(NCI-CTCAE v5) | Initial Management | Follow-up Management |
| Grade 1 to 2 | Continue avelumab therapy<br>Symptomatic therapy (for example, antihistamines, topical steroids) | If persists > 1 to 2 weeks or recurs:<br>Withhold avelumab therapy<br>Consider skin biopsy<br>Consider 0.5-1 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper.<br>If worsens:<br>Treat as Grade 3 to 4. |

| | | |
|---|---|---|
| Grade 3 to 4 | Withhold avelumab for Grade 3.<br>Permanently discontinue for Grade 4 or recurrent Grade 3.<br>Consider skin biopsy<br>Dermatology consult<br>Start 1 to 2 mg/kg/day prednisone or equivalent<br>Add prophylactic antibiotics for opportunistic infections if indicated | If improves to Grade ≤ 1:<br>Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). |
| Pulmonary irAEs | | |
| Grade of Pneumonitis<br>(NCI-CTCAE v5) | Initial Management | Follow-up Management |
| Grade 1 | Consider withholding avelumab therapy<br>Monitor for symptoms every 2 to 3 days<br>Consider Pulmonary and Infectious Disease consults | Re-assess at least every 3 weeks<br>If worsens:<br>Treat as Grade 2 or Grade 3 to 4. |
| Grade 2 | Withhold avelumab therapy<br>Pulmonary and Infectious Disease consults<br>Monitor symptoms daily; consider hospitalization<br>Start 1 to 2 mg/kg/day prednisone or equivalent<br>Add prophylactic antibiotics for opportunistic infections if indicated<br>Consider bronchoscopy, lung biopsy | Re-assess every 1 to 3 days<br>If improves:<br>When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper<br>If not improving after 2 weeks or worsening:<br>Treat as Grade 3 to 4. |
| Grade 3 to 4 | Permanently discontinue avelumab therapy.<br>Hospitalize. | If improves to Grade ≤ 1:<br>Taper steroids over at least 1 month |

| | | |
|---|---|---|
| | Pulmonary and Infectious Disease consults.<br>Start 1 to 2 mg/kg/day prednisone or equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Consider bronchoscopy, lung biopsy | If not improving after 48 hours or worsening:<br>Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil) |
| Hepatic irAEs | | |
| Grade of Liver Test Elevation<br>(NCI-CTCAE v5) | Initial Management | Follow-up Management |
| Grade 1 | Continue avelumab therapy | Continue liver function monitoring<br>If worsens:<br>Treat as Grade 2 or 3 to 4. |
| Grade 2 | Withhold avelumab therapy<br>Increase frequency of monitoring to every 3 days. | If returns to Grade ≤ 1:<br>Resume routine monitoring; resume avelumab therapy.<br>If elevation persists > 5 to 7 days or worsens:<br>Treat as Grade 3 to 4. |
| Grade 3 to 4 | Permanently discontinue avelumab therapy<br>Increase frequency of monitoring to every 1 to 2 days<br>Start 1 to 2 mg/kg/day prednisone or equivalent<br>Add prophylactic antibiotics for opportunistic infections if indicated<br>Consult gastroenterologist/ hepatologist<br>Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted | If returns to Grade ≤ 1:<br>Taper steroids over at least 1 month<br>If does not improve in > 3 to 5 days, worsens or rebounds:<br>Add mycophenolate mofetil 1 gram (g) twice daily<br>If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines. |

| Renal irAEs | | |
|---|---|---|
| Grade of Creatinine Increased (NCI-CTCAE v5) | Initial Management | Follow-up Management |
| Grade 1 | Continue avelumab therapy | Continue renal function monitoring<br>If worsens:<br>Treat as Grade 2 to 3 or 4. |
| Grade 2 to 3 | Withhold avelumab therapy<br>Increase frequency of monitoring to every 3 days<br>Start 1 to 2 mg/kg/day prednisone or equivalent.<br>Add prophylactic antibiotics for opportunistic infections if indicated<br>Consider renal biopsy | If returns to Grade ≤1:<br>Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper.<br>If worsens:<br>Treat as Grade 4. |
| Grade 4 | Permanently discontinue avelumab therapy<br>Monitor creatinine daily<br>Start 1 to 2 mg/kg/day prednisone or equivalent.<br>Add prophylactic antibiotics for opportunistic infections if indicated<br>Consider renal biopsy<br>Nephrology consult | If returns to Grade ≤1:<br>Taper steroids over at least 1 month. |

| Cardiac irAEs | | |
|---|---|---|
| Myocarditis | Initial Management | Follow-up Management |
| New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis. | Withhold avelumab therapy.<br>Hospitalize.<br>In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. | If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy.<br>If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is |

| | | |
|---|---|---|
| | Cardiology consult to establish etiology and rule-out immune-mediated myocarditis.<br>Guideline based supportive treatment as per cardiology consult*<br>Consider myocardial biopsy if recommended per cardiology consult. | suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis. |
| Immune-mediated myocarditis | Permanently discontinue avelumab.<br>Guideline based supportive treatment as appropriate as per cardiology consult*<br>Start 1 to 2 mg/kg/day prednisone or equivalent<br>Add prophylactic antibiotics for opportunistic infections if indicated | Once improving, taper steroids over at least 1 month.<br>If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A). |

*Local guidelines, or e.g. ESC or AHA guidelines

ESC guidelines website: [redacted]

AHA guidelines website: [redacted]

Endocrine irAEs

| Endocrine Disorder | Initial Management | Follow-up Management |
|---|---|---|
| Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus) | Continue avelumab therapy<br>Endocrinology consult if needed<br>Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. | Continue hormone replacement/suppression and monitoring of endocrine function as appropriate. |

| | | |
|---|---|---|
| | Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis) | |
| Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus) | Withhold avelumab therapy<br>Consider hospitalization<br>Endocrinology consult<br>Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate.<br>Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis) | Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression).<br>Continue hormone replacement/suppression and monitoring of endocrine function as appropriate. |
| Hypopituitarism/Hypophysitis (secondary endocrinopathies) | If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH):<br>Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women)<br>Hormone replacement/suppressive therapy as appropriate<br>Perform pituitary MRI and visual field examination as indicated<br>If hypophysitis confirmed: | Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement).<br>In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented.<br>Continue hormone replacement/suppression therapy as appropriate. |

| | | |
|---|---|---|
| | Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month<br><br>Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month<br><br>Add prophylactic antibiotics for opportunistic infections if indicated | |
| Other irAEs (not described above) | | |
| Grade of other irAEs (NCI-CTCAE v5) | Initial Management | Follow-up Management |
| Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE | Withhold avelumab therapy pending clinical investigation | If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy<br><br>If irAE is confirmed, treat as Grade 2 or 3 irAE. |
| Grade 2 irAE or first occurrence of Grade 3 irAE | Withhold avelumab therapy<br><br>Consider for G2 and start 1 to 2 mg/kg/day prednisone or equivalent for any G3<br><br>Add prophylactic antibiotics for opportunistic infections if indicated<br><br>Specialty consult as appropriate | If improves to Grade ≤ 1:<br><br>Taper steroids over at least 1 month and resume avelumab therapy following steroids taper. |
| Recurrence of same Grade 3 irAEs | Permanently discontinue avelumab therapy<br><br>Start 1 to 2 mg/kg/day prednisone or equivalent<br><br>Add prophylactic antibiotics for opportunistic infections if indicated | If improves to Grade ≤ 1:<br><br>Taper steroids over at least 1 month. |

| | | |
|---|---|---|
| | Specialty consult as appropriate | |
| Grade 4 | Permanently discontinue avelumab therapy<br>Start 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed<br>Add prophylactic antibiotics for opportunistic infections if indicated<br>Specialty consult | If improves to Grade ≤ 1:<br>Taper steroids over at least 1 month |
| Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency<br><br>Persistent Grade 2 or 3 irAE lasting 12 weeks or longer | Permanently discontinue avelumab therapy<br>Specialty consult | |

Abbreviations: ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine kinase MB; CT= computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PRL=prolactin;T4=thyroxine; TSH=thyroid stimulating hormone; ULN=upper limit of normal.

### 8.2.2 Management of treatment related adverse events from cetuximab

In general, treatment with cetuximab will be withheld for drug related Grade 4 hematologic toxicities and for non-hematologic toxicity Grade 3 and subsequent doses modified as per Table 4 below. Dose modifications will be applied for all subsequent doses.

**Dermatologic Toxicity**

The dosing of cetuximab will be delayed 1 to 2 weeks in the case of severe (Grade 3 or 4) acneiform rash. Cetuximab should be discontinued and treatment with cetuximab should be delayed for up to 12 weeks. If dermatologic toxicity improves after the delay then the dose of cetuximab will be reduced as indicated in Table 3. If dermatologic toxicity does not improve after the delay cetuximab will be permanently discontinued.

Table 3: Dermatologic treatment related toxicity from cetuximab

| Severe Acneiform Rash<br>(≥ Grade 3) | Dose Interruption | Outcome | Dose Modification |
|---|---|---|---|
| 1st occurrence | Delay treatment:<br>Grade 3 up to 12 weeks<br>Grade 4 up to 12 weeks | Improved | None, continue at 500mg/m$^2$ |
| 2nd occurrence | Delay treatment:<br>Grade 3 up to 12 weeks<br>Grade 4 up to 12 weeks | Improved | Permanently reduce dose to 400mg mg/m$^2$ |
| 3rd occurrence | Delay treatment<br>Grade 3 up to 12 weeks<br>Grade 4 up to 12 weeks | Improved | Permanently reduce to 300 mg/m$^2$ |
| 4th occurrence | Discontinue | N/A | N/A |

Table 4: Other Non-Hematologic and Hematologic treatment related toxicity from cetuximab

| Toxicity | Grade | Hold Treatment | Dose Modification | Treatment Discontinuation |
|---|---|---|---|---|
| Hematologic | 1,2,3 | No | No | NA |
| | 4 | Yes until recovers to <G3 | Yes, 400 mg/m$^2$ | If toxicity does not resolve within 12 weeks of last infusion or occurs again |
| Non-hematologic | 1,2 | No | No | NA |
| | 3,4 | Yes, until resolves to at least G1 | Restart treatment at 400 mg/m$^2$ | If toxicity does not resolve to G1 or less within 12 weeks of treatment or after re-challenge at dose reduction it occurs again, treatment will be permanently discontinued. |

AERS reporting may be required for some adverse events (See Section 9.0)

If toxicity is related only to cetuximab and mandates holding cetuximab, then avelumab should be continued in the interim. If toxicity is related only to avelumab and mandates holding avelumab, then cetuximab should be continued in the interim. If a patient has significant toxicity from cetuximab requiring permanent discontinuation than a patient can continue avelumab alone and remain on study as long as at least 4 cycles of cetuximab have been completed. If a patient develops toxicity from avelumab mandating permanent discontinuation of avelumab than a patient will be taken off of trial because of adverse events.

### 8.2.3 Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation. Physicians may consult the published guidelines of the American Society of Clinical Oncology Appropriate Chemotherapy Dosing for Obese Adult Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 30(13): 1553-1561, 2012.

## 9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at [redacted] Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

## 9.1 Routine Adverse Event Reporting (Rave-CTEP-AERS)

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, the Form, "Adverse Events" is used for routine AE reporting in Rave.

### 9.1.1 Rave-CTEP-AERS integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. **Sites must initiate all AEs for this study in Medidata Rave**.

**Treatment-emergent AEs:** All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period, and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of

the investigational study agent/intervention are collected using the Late Adverse Events form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query-free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form (i.e., checking the box *Send All AEs for Evaluation* and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at [redacted] or by email at [redacted] if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at [redacted] Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: *Protocols > Documents> Protocol Related Documents> Adverse Event Reporting*; and
- Additional resources: *Resources > CTSU Operations Information> User Guides & Help Topics*.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at [redacted]

### 9.1.2 Solicited Adverse Events

The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment by CTCAE, PRO-CTCAE, or both.

| **CTCAE v5.0 Term** | **CTCAE v5.0 System Organ Class (SOC)** |
|---|---|
| Rash Acneiform | Skin and subcutaneous tissue disorders |
| Diarrhea | Gastrointestinal Disorders |

| | |
|---|---|
| Hypomagnesemia | Metabolism and Nutrition disorders |

## 9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

| Attribution | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| **Unrelated** | | | **a** | **a** | **a** |
| **Unlikely** | | | **a** | **a** | **a** |
| **Possible** | | **a** | **a, b** | **a, b** | **a, b** |
| **Probable** | | **a** | **a, b** | **a, b** | **a, b** |
| **Definite** | | **a** | **a, b** | **a, b** | **a, b** |

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

## 9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: [redacted]
All appropriate treatment areas should have access to a copy of the CTCAE.

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

### 9.3.1 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

**FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**

**NOTE:** Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

**ALL SERIOUS** adverse events that meet the above criteria MUST be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

| Hospitalization | Grade 1 and Grade 2 Timeframes | Grade 3 – 5 Timeframes |
|---|---|---|
| Resulting in Hospitalization ≥ 24 hrs | 10 Calendar Days | 24-Hour 5 Calendar Days |
| Not resulting in Hospitalization ≥ 24 hrs | Not required | |

**NOTE**: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

**Expedited AE reporting timelines are defined as:**

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

**Expedited 24-hour notification followed by complete report within 5 calendar days for:**

- All Grade 3, 4, and Grade 5 AEs

**Expedited 10 calendar day reports for:**

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

### 9.3.2 Expedited AE reporting timelines defined

"24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.

"10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

### 9.3.3 Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements

All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

Grade < 4 hematosuppression (leukopenia (including all types of white blood cells, anemia, thrombocytopenia) and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.

Death due to progressive disease should be reported as Grade 5 “Disease progression” in the system organ class (SOC) “General disorders and administration site conditions.” Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

Pregnancy loss is defined in CTCAE as “Death in utero.” Any Pregnancy loss should be reported expeditiously, as Grade 4 “Pregnancy loss” under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

A neonatal death should be reported expeditiously as Grade 4, “Death neonatal” under the General disorders and administration SOC.

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors.

**Secondary Malignancy:**

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

**Second Malignancy:**

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

CTEP-AERS reports should be submitted electronically.

## 9.4 CAEPRs

### 9.4.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Avelumab (NSC 799232)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system.

Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' [redacted] for further clarification. Frequency is provided based on 2082 patients. Below is the CAEPR for Avelumab.

**Version 2.1 June 27, 2023[1]**

| Adverse Events with Possible Relationship to Avelumab (CTCAE 5.0 Term) [n= 2082] | | |
|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | |
| | Anemia | |
| | | Hemolysis |
| CARDIAC DISORDERS | | |
| | | Myocarditis[2] |

| Adverse Events with Possible Relationship to Avelumab (CTCAE 5.0 Term) [n= 2082] | | |
|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** |
| | | Pericarditis[2] |
| ENDOCRINE DISORDERS | | |
| | | Adrenal insufficiency[2] |
| | | Endocrine disorders - Other (autoimmune thyroiditis)[2] |
| | | Endocrine disorders - Other (immune-mediated renal dysfunction)[2] |
| | | Hyperthyroidism[2] |
| | | Hypophysitis[2] |
| | | Hypopituitarism[2] |
| | Hypothyroidism[2] | |
| EYE DISORDERS | | |
| | | Eye disorders - Other, specify (iritis)[2] |
| | | Uveitis[2] |
| GASTROINTESTINAL DISORDERS | | |
| | Abdominal pain | |
| | | Colitis[2] |
| | Constipation | |
| | Diarrhea | |
| Nausea | | |
| | Pancreatitis[2] | |
| | Vomiting | |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | |
| | Chills | |
| | Edema limbs | |
| Fatigue | | |
| | Fever | |
| HEPATOBILIARY DISORDERS | | |
| | | Hepatic failure[2] |
| | | Hepatobiliary disorders - Other (autoimmune hepatitis, immune-related hepatitis) [2] |
| | | Hepatobiliary disorders - Other (hepatotoxicity)[2] |
| IMMUNE SYSTEM DISORDERS | | |
| | | Autoimmune disorder[2] |
| | | Cytokine release syndrome[3] |
| | | Immune system disorders - Other (sarcoidosis) [2] |
| INFECTIONS AND INFESTATIONS | | |
| | Infection[4] | |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | |
| | Infusion related reaction[2,3] | |
| INVESTIGATIONS | | |
| | Alanine aminotransferase increased | |

| Adverse Events with Possible Relationship to Avelumab (CTCAE 5.0 Term) [n= 2082] | | |
|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** |
| | Alkaline phosphatase increased | |
| | Aspartate aminotransferase increased | |
| | Blood bilirubin increased | |
| | CPK increased | |
| | Creatinine increased | |
| | GGT increased | |
| | Lipase increased | |
| | Lymphocyte count decreased | |
| | Neutrophil count decreased | |
| | Platelet count decreased | |
| | Serum amylase increased | |
| | Thyroid stimulating hormone increased | |
| | Weight loss | |
| METABOLISM AND NUTRITION DISORDERS | | |
| | Anorexia | |
| | | Hyperglycemia[2] |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | |
| | Arthralgia[2] | |
| | | Arthritis[2] |
| | Back pain | |
| | Generalized muscle weakness | |
| | Muscle cramp | |
| | Myalgia[2] | |
| | | Myositis[2] |
| | Pain in extremity | |
| | | Rhabdomyolysis[2] |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | | |
| | | Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (histiocytic necrotizing)[2] lymphadenitis)[2] |
| NERVOUS SYSTEM DISORDERS | | |
| | Dizziness | |
| | | Encephalopathy[2] |
| | | Guillain-Barre syndrome[2] |
| | Headache | |
| | | Myasthenia gravis[2] |
| | | Nervous system disorders - Other (demyelination)[2] |
| | | Nervous system disorders - Other (non-infectious encephalitis) [2] |
| | | Nervous system disorders - Other (non-infectious meningitis) [2] |

| Adverse Events with Possible Relationship to Avelumab (CTCAE 5.0 Term) [n= 2082] | | |
|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** |
| | | Peripheral motor neuropathy[2] |
| | | Peripheral sensory neuropathy[2] |
| RENAL AND URINARY DISORDERS | | |
| | | Renal and urinary disorders - Other (immune related nephritis)[2] |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | |
| | Cough | |
| | Dyspnea | |
| | | Pneumonitis[2] |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | |
| | | Bullous dermatitis[2] |
| | Eczema | |
| | | Erythroderma[2] |
| | | Erythema multiforme[2] |
| | Rash acneiform | |
| | Rash maculo-papular[2] | |
| | | Stevens-Johnson syndrome[2] |
| | | Toxic epidermal necrolysis[2] |
| | | Skin and subcutaneous tissue disorders - Other (pemphigoid)[2] |
| | | Skin and subcutaneous tissue disorders - Other (psoriasiform dermatitis)[2] |
| VASCULAR DISORDERS | | |
| | Hypertension | |
| | | Vasculitis[2] |

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [redacted]Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Avelumab being a member of class of agents involved in the inhibition of “immune checkpoints” may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) adrenal insufficiency, arthritis, autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous dermatitis, colitis, dermatitis psosiasiform, demyelination, Nervous system disorders - Other (non-infectious encephalitis) , hyperglycemia, erythema multiforme, exfoliative dermatitis, Guillain-Barré syndrome, hemolytic anemia, hepatic failure histiocytic necrotizing lymphadenitis, hypophysitis, hypopituitarism, Infusion related reaction, iritis, myocarditis, myasthenia gravis, myositis, nephritis and renal dysfunction, pancreatitis, pemphigoid pneumonitis, rhabdomyolysis, sarcoidosis , Stevens-Johnson syndrome(SJS)/toxic epidermal necrolysis (TEN), Thyroid Disorders (hypothyroidism/hyperthyroidism), uveitis, vasculitis. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of of avelumab), administration of corticosteroids and supportive care.

[3]Infusion reactions, including high-grade hypersensitivity reactions, anaphylaxis, and cytokine release syndrome, which have been observed following administration of avelumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of avelumab.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

**Adverse events reported on Avelumab trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Avelumab caused the adverse event:**

**CARDIAC DISORDERS** - Atrial fibrillation; Palpitations; Sinus tachycardia
**EYE DISORDERS** - Blurred vision; Dry eye
**GASTROINTESTINAL DISORDERS** - Abdominal distension; Anal hemorrhage; Ascites; Dry mouth; Dyspepsia; Dysphagia; Enterocolitis; Flatulence; Gastrointestinal disorders - Other (enteritis); Mucositis oral; Proctitis; Small intestinal obstruction
**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Flu like symptoms[3]; General disorders and administration site conditions - Other (general physical health deterioration); Localized edema; Malaise; Non-cardiac chest pain; Pain
**IMMUNE SYSTEM DISORDERS** - Allergic reaction; Anaphylaxis
**INVESTIGATIONS** - Electrocardiogram QT corrected interval prolonged; Investigations - Other (thyroxine free decreased); Investigations - Other (c-reactive protein increased); Weight gain
**METABOLISM AND NUTRITION DISORDERS** - Dehydration; Hypercalcemia; Hypoalbuminemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Bone pain
**NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare); Tumor pain
**NERVOUS SYSTEM DISORDERS** - Dysesthesia; Dysgeusia; Nervous system disorders - Other (Miller fisher syndrome); Tremor
**RENAL AND URINARY DISORDERS** - Acute kidney injury; Hematuria; Proteinuria
**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Bronchopulmonary hemorrhage; Hypoxia; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)
**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Alopecia; Dry skin; Hyperhidrosis; Pruritus; Purpura; Skin and subcutaneous tissue disorders - Other (drug eruption); Skin and subcutaneous tissue disorders - Other (lichen planus); Skin hypopigmentation
**VASCULAR DISORDERS** - Flushing; Hot flashes; Hypotension; Thromboembolic event

**Note**: Avelumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

## 10.0 DRUG INFORMATION

### 10.1 General Considerations:

The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

It is not necessary to change the doses of cetuximab due to changes in weight unless the calculated dose changes by ≥10%.

## 10.2 Cetuximab (NSC# 714692)

*Procurement*

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

*Formulation*

Commercially available for injection 2 mg/mL (50 mL, 100 mL).

*Preparation, Storage and Stability*

Refer to package insert for complete preparation and dispensing instructions. Store intact vials at refrigeration temperature (2ºC to 8ºC or 36ºF to 46ºF), do not freeze or shake. Reconstitution is not required. Appropriate dose should be added to empty sterile container; do not shake or dilute. Preparations in infusion containers are stable for up to 12 hours under refrigeration (2ºC to 8ºC or 36ºF to 46ºF) and up to 8 hours at controlled room temperature (20ºC to 25ºC or 68ºF to 77ºF). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° C to 8° C. Discard any unused portion of the vial.

*Administration*

Administer via I.V. infusion; Administer the initial dose over 2 hours. The maximum infusion rate is 10 mg/minute. Do not administer as I.V. push or bolus. Do not shake or dilute. Premedication with antihistamines is recommended. Administer through a low protein-binding 0.22 micrometer in-line filter. Use 0.9% NaCl to flush line at the end of infusion.

*Drug Interactions*

There are no known interactions where it is recommended to avoid concomitant use.

*Pharmacokinetics*

**Distribution:** Vd: ~2-3 $L/m^2$

**Half-life elimination**: ~112 hours (range: 63-230 hours)

*Adverse Events*

Consult the package insert for the most current and complete information. Refer to the package insert pertaining to the following boxed warnings: Severe infusion reactions and cardiopulmonary arrest. Cetuximab is contraindicated in patients with known sever reactions to cetuximab.

**Common known potential toxicities, > 10%:**

Central nervous system: Fatigue, malaise, pain, peripheral sensory neuropathy, headache, insomnia, confusion, chills, rigors, anxiety, depression

Dermatologic: Desquamation, acneiform eruption, radiodermatitis, xeroderma, rash, dry skin, pruritus, nail changes, acne vulgaris, paronychia, palmar-plantar erythrodysesthesia, skin fissure, alopecia

Endocrine & metabolic: Weight, loss, hypomagnesemia, dehydration, hypocalcemia, hypokalemia

Gastrointestinal: Diarrhea, vomiting, abdominal pain, constipation, stomatitis, nausea, weight loss, anorexia, dyspepsia, xerostomia

Hepatic: Increased serum ALT, increased serum AST, increased serum alkaline phosphatase

Infection: infection, infection without neutropenia

Neuromuscular & skeletal: Weakness, bone pain, arthralgia

Ophthalmic: conjunctivitis

Respiratory: Dyspnea, cough, pharyngitis

Miscellaneous: fever, infusion related reaction

**Less common known potential toxicities, 1% - 10%:**

Cardiovascular: Cardiorespiratory arrest, ischemic heart disease

Dermatologic: Hypertrichosis

Gastrointestinal: Dysgeusia

Immunologic: Antibody development

Infection: Sepsis

Renal: Renal failure

**Rare known potential toxicities, <1% (Limited to important or life-threatening):**

Abscess formation, aseptic meningitis, blepharitis, bronchospasm, bullous pemphigoid, cardiac arrhythmia, cellulitis, cheilitis, corneal ulcer, electrolyte disturbance, hoarseness, hypotension, interstitial pulmonary disease, keratitis, loss of consciousness, mucosal inflammation, myocardial infarction, pulmonary embolism, shock, skin infection, Stevens-Johnson syndrome, stridor, toxic epidermal necrolysis.

*Nursing Guidelines*

- Patients should be closely monitored during the infusion for signs of anaphylaxis and standard resuscitative medications should be available during and for one hour following the cetuximab infusion.

  **CAUTION:** Infusion reactions may occur during or following cetuximab administration. Most infusion reactions occur with the first infusion of cetuximab, but some patients' first infusion reactions have been reported following subsequent doses (as far out as the 8$^{th}$ dose). The infusion reaction may occur during the infusion, or be delayed until any time after the infusion. A nurse should be present in the immediate treatment area throughout the infusion and observation period. A physician should be in close proximity to the patient treatment area. Should an infusion reaction occur, the patient should be treated according to institutional guidelines. Patient should be instructed to report any delayed reactions to the investigator immediately. Patients who have had severe reactions should not receive further doses of cetuximab.

- Vital signs should be taken prior to, during, post and 1 hour post infusion.
- Patient should be observed for 1 hour following the loading dose and each maintenance dose.
- Premedicate with 50 mg of IV diphenhydramine, or other specific premedications called for in the protocol, prior to each dose.
- Patients should be taught to wear sunscreen and hats and limit sun exposure while receiving treatment.
- Recommend that all infusions be run on a volumetric pump. Infusion rate **MUST NEVER EXCEED 10MG/MINUTE (5 ML/MINUTE).**

- Monitor CBC and instruct patient to report any signs or symptoms of infection, unusual bruising, or bleeding to the health care team.
- Monitor LFTs.
- Fever and chills may occur. Discuss with MD about premedication with an antipyretic.
- Monitor for signs and symptoms of gastrointestinal side effects, including nausea, constipation, diarrhea, and vomiting. Administer antiemetics and antidiarrheals and/or stool softeners as indicated and evaluate their effectiveness.
- Instruct patient to report rash.
- Hypomagnesemia is a complication of cetuximab therapy. Instruct patients to report any of the following signs or symptoms as these may be signs of the disorder. Neuromuscular: muscle weakness, muscle cramps, painful swallowing; CNS: Irritability, combativeness, disorientation, psychosis, vertigo, seizures; Cardiac: irregular and/or fast heartbeat. Any or all of the symptoms may or may not be present in the patient with this condition. If patients present with any of these symptoms, inform MD and a magnesium level should be checked.
- Sensory neuropathy has been seen. Assess for this and inform MD if this develops.

### 10.3 Avelumab (IND# 143349, NSC# 799232, IND Holder: Alliance)

*Procurement*

Avelumab is an investigational fully human IgG1 antibody directed against programmed death-ligand 1 (PD-L1). Avelumab 200 mg (20 mg/mL) vials are supplied by EMD Serono Research & Development Institute, Inc. and distributed by McKesson Clincial Research Services . Use the order form on the A091802 study specific page on the Alliance or CTSU web site to order avelumab.

At the end of the trial, any expired or remaining supplies should be destroyed according to institutional procedure.

*Investigator Brochure Availability*

The investigator brochure for Avelumab may be obtained by contacting the Alliance Central Protocol Operations Program office at [redacted]

*Formulation*

Avelumab is a sterile, clear and colorless concentrate for solution available in a concentration of 20 mg/mL. Each single-use vial contains 200 mg of avelumab as a preservative-free acetate-buffered solution (pH 5.2) containing Mannitol, and Polysorbate 20 (Tween 20).

*Preparation, Storage and Stability*

Allow each vial to equilibrate to room temperature. Avelumab drug product must be diluted into a 250 mL 0.9% saline solution (sodium chloride injection) infusion bag; alternatively, a 0.45% saline solution can be used if needed. Use a disposable syringe equipped with a needle of suitable size to inject a volume of avelumab into the infusion bag. Gently invert the mixture 10 times. Infusion bags must not be shaken, in order to avoid foaming or excessive shearing of the protein solution. The preparation must be carefully inspected as it should result in a homogeneous looking clear, colorless solution, free of visible particles. No other drugs should be added to the solution containing avelumab. Protect from light.

Avelumab drug product must be stored at 2ºC to 8ºC until use, and it must not be frozen. Rough shaking of avelumab product must be avoided. It is recommended that the diluted avelumab solution is used immediately. If not used immediately, the diluted drug product can be stored up

to 4 hours at room temperature or up to 24 hours at 2ºC to 8ºC. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

*Administration*

Administer the diluted solution over 60 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micron). Do not co-administer other medications through the same intravenous line.

Pre-medicate patients with an antihistamine and acetaminophen prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab infusions based upon clinical judgment and the presence or severity of prior infusion reactions.

*Drug Accountability*

Receipt and dispensation of avelumab should be recorded on and NCI compliant Investigational Agent Accountability Record [redacted]

Within 90 days after the last patient is treated at the institutions, drug may be destroyed per institutional procedures with documentation on the drug accountability form.

*Drug Interactions*

Avelumab is not expected to have drug-drug interactions with other medications because it is primarily metabolized via catabolic pathways and is not expected to alter the expression of Cytochrome P450 enzymes.

*Pharmacokinetics*

**Absorption**: Avelumab is administered intravenously and is 100% bioavailable. Steady-state concentrations are expected to be reached by the 3rd dosing cycle (10 mg/kg every 2 weeks), and the accumulation ratio is 1.25.

**Distribution**: The geometric mean volume of distribution at steady state for a subject receiving 10 mg/kg was 4.72 L.

**Metabolism:** Avelumab is degraded by proteolytic catabolism. Cytochrome P450 does not contribute to its metabolism.

**Excretion:** Avelumab is eliminated by proteolytic degradation. Based on population pharmacokinetic analyses in patients with solid tumors, the total systemic clearance was 0.59 L/day. The terminal half-life elimination was 6.1 days in patients receiving 10 mg/kg every 2 weeks.

*Adverse Events*

Consult the package insert for the most current and complete information.

**Very Common (> 10%):** Anemia, nausea, diarrhea, vomiting, abdominal pain, fatigue, pyrexia, peripheral edema, infusion related reaction, weight decreased, decreased appetite, back pain, arthralgia, cough, dyspnea

**Common (≥ 1% - < 10%):** Hypothyroidism, chills, pneumonitis, rash, pruritus, rash maculopapular

**Uncommon (≥ 0.1% - < 1%):** Adrenal insufficiency, hyperthyroidism, thyroiditis, autoimmune thyroiditis, adrenocortical insufficiency acute, hypopituitarism, uveitis, colitis, autoimmune colitis, enterocolitis, autoimmune hepatitis, acute hepatic failure, hepatic failure, hepatitis, drug hypersensitivity, anaphylactic reaction, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, blood creatine phosphokinase increased, transaminases

increased, diabetes mellitus, myositis, Guillian-Barré syndrome, tubulointerstitial nephritis, rash pruritic, erythema, rash generalized, rash erythematous, rash macular, rash papular, dermatitis exfoliative, erythema multiforme, pemphigoid, pruritis generalized

Adverse reactions with observed fatal outcome in the avelumab clinical development programs included: immune-related pneumonitis, immune-related hepatitis, and immune-related myocarditis.

*Nursing Guidelines*

- Avelumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.
- Diarrhea can be seen, but is less common than that seen with anti-CTLA-4 agents. However, it can be severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.
- Rash/pruirits/dermatitis is seen. Rarely Steven Johnson Syndrome has been seen and can be life threatening. Patients should report any rash to the study team. Treat per section 9.0 and monitor for effectiveness.
- Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.
- Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.
- Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysistis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well" . Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.
- Patients who are started on steroid therapy for any side effects of avelumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.
- Fatigue is common and may or may not be associated with immune related side effects. Assess patient's fatigue level prior to each cycle of therapy and report any changes to the study team.
- Other rare side effects include Guillian-Barre syndrome, nephritis, myocarditis, infusion reaction, and cytopenias. Instruct patients to report and side effects to the study team immediately.

## 11.0 MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using RECIST 1.1 with modifications (as discussed below).

## 11.1 Schedule for Assessment of Disease

- Baseline imaging should include a CT or MRI of the chest/abdomen/pelvis for all patients to adequately evaluate for distant metastatic disease. The patient should also undergo CT or MRI imaging for the primary site of their cSCC as applicable. For example, a patient with a cSCC of the head and neck should undergo CT neck in addition to CT chest/abdomen/pelvis. CT scans should be done with IV and oral contrast unless allergy prevents administration. If MRI is chosen as imaging modality for following target/non-target lesions then MRI should be used for evaluation of response during the study. CT is encouraged over MRI.
- Repeat imaging to evaluate for response will be done after each third cycle, for example before every 4$^{th}$ cycle and will be used to determine whether every 4$^{th}$ cycle is given to the patient. This schedule will continue until progression of disease or completion of all protocol specified treatment. For those that complete all protocol specified treatment without progression or patients who ended treatment early for any reason (without progression), physical examination and staging scans are required 12 weeks (+/- 7 days) after the end of treatment, then every 12 weeks (+/- 7 days) until disease progression unless consent is withdrawn for clinical follow up. These schedules apply to all arms (i.e. avelumab plus cetuximab, avelumab monotherapy, or avelumab plus cetuximab after failure of avelumab monotherapy).

## 11.2 Assessment of Disease

### 11.2.1 Definitions

Measurable Lesions: Lesions that can be accurately measured in at least one dimension with longest diameter at least 10 mm on CT scan (or >20mm by X-ray). Cystic lesions thought to represent cystic metastasis can be considered as measurable lesions.

Malignant Lymph Nodes: To be considered pathologically enlarged and measurable, a lymph node must be at least 15 mm in the short axis when assessed by CT scan.

Non-measurable Lesions: All other lesions < 10 mm or lymph nodes <15mm in the short axis by CT scan.

Target Lesions: All measurable lesions up to a maximum of 2 lesions per organ and up to 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement. In this circumstance, the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

### 11.3. Evaluation of Disease Response Determination Will be Defined Based on RECIST 1.1

Table 1. Definition of Response in Target Lesions.

| **Response** | Definition |
|---|---|
| Complete Response (CR) | Disappearance of all target lesions |
| Partial Response (PR) | At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters |
| Progressive Disease (PD) | At least a 20% increase in the sum of the diameters of target lesions compared to the nadir (smallest) sum of target lesions, or any new lesions |
| Stable Disease (SD) | Neither sufficient decrease to qualify as a PR or sufficient increase to qualify as PD |

Per RECIST 1.1, response should be confirmed by a repeat imaging. The scan for confirmation of response may be performed at the earliest 4 weeks after imaging that showed response (if clinically indicated) or at the next scheduled scan.

Lesions that can be measured clinically on physical exam (skin lesions or palpable lymph nodes) will be measured by the investigator with the longest axis recorded. These measurements can be used to guide clinical decision making, for example prompting an earlier CT scan to evaluate disease. However, only measurements based on radiology will be used to determine response.

Table 2. Assessment of Non-Target Lesions Response

| Response | Definition |
|---|---|
| Complete Response (CR) | Disappearance of all non-target lesions |
| Incomplete Response/Stable Disease (SD) | Persistence of one or more non-target lesion |
| Progressive Disease | Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions |

Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence.

Table 3. Best Overall Response

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | PR/SD | No | PR |
| PR | Non-PD | No | PR |
| SD | Non-PD | No | SD |

| | | | |
|---|---|---|---|
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

Given the observed pattern of response with immune checkpoint inhibitors (anti-PD-1 mAb, antiPD-L1 mAb, and Anti-CTLA4 mAb) where some patients develop evidence of progressive disease by RECIST 1.1, with significant increase in size of target lesions and/or new lesions, followed by regression of disease to SD or PR/CR, all imaging showing progressive disease by RECIST 1.1, in the absence of significant clinic deterioration of the patient will be confirmed with a repeat CT scan at least 4 weeks from the initial imaging showing progression. Clinically stable patients will continue treatment in the interim before this scan. If progressive disease is confirmed on subsequent imaging, the patient will be defined as having progressive disease and will be taken off of the study. Progressive disease by RECIST 1.1 with clinical deterioration by the patient will be counted as progressive disease, and study treatment will be discontinued without confirmation of progressive disease with repeat scan.

Determination of clinical deterioration is at the discretion of the treating physician as defined by progression of disease at critical sites requiring urgent intervention (for example cord compression), or development of signs and symptoms of disease progression and/or significant decline in ECOG performance status.

## 12.0 END OF TREATMENT/INTERVENTION

### 12.1 Duration of Protocol Treatment

Protocol treatment is to continue for up to 24 months. Please see the study calendar (Section 5) and the treatment section (Section 7) for treatment and following up time periods.

### 12.2 Criteria for Discontinuation of Protocol Treatment/Intervention

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study treatment
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance
    - Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
- Termination of the study by sponsor
    - The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

## 12.3 Follow-up

### 12.3.1 Follow- up for Patients Who Complete Therapy Without Progression

For those that complete all required protocol therapy without progression or who ended study therapy early for any reason other than progression, physical examination and staging scans are required 12 weeks (+/- 7 days) after the end of treatment, then every 12 weeks (+/- 7 days) until disease progression. These schedules apply to all arms (i.e. avelumab plus cetuximab, avelumab monotherapy, or avelumab plus cetuximab after failure of avelumab monotherapy).

### 12.3.2 Follow-up for Patients Who Stop Study Treatment/Intervention Early

Patients with progressive disease will go to survival follow-up at 30 days (+/- 7 days) and 90 days (+/- 7 days) from off-treatment date for safety follow-up. Subsequently they will be in survival follow-up every 6 months from date of most recent contact for up to 2 years after progression.

## 12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

## 12.5 Managing Ineligible Patients and Registered Patients Who Never Receive Protocol Intervention

**Definition of ineligible patient**

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

**Follow-up for ineligible patients who continue with protocol treatment**

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

**Follow-up for ineligible patients who discontinue protocol treatment**

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

**Follow-up for patients who are registered, but who never start study treatment**

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Baseline and off-treatment notice data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

# 13.0 STATISTICAL CONSIDERATIONS

## 13.1 Study Design

The study population in this randomized two arm phase II trial is patients with advanced cutaneous squamous cell carcinoma of the skin (cSCC). The trial is designed to compare progression-free survival (PFS) in patients receiving avelumab + cetuximab (Arm 2) versus avelumab alone (Arm 1). The PFS for avelumab plus cetuximab after avelumab failure (crossover) will not count towards the primary PFS comparison.

## 13.2 Statistical Design and Analysis for the Primary Endpoint

### 13.2.1 Primary Endpoint:

The primary endpoint for this trial is PFS. A patient's PFS time will be the number of days between registration and evidence of disease progression (or death). All registered patients meeting the eligibility criteria who received any quantity of the protocol therapy and did not have a major treatment violation will be part of the analysis group for the primary endpoint. Patients that do no progress will be censored at their last valid tumor measurement.

### 13.2.2 Statistical Design:

Data from Midgen et al. [22] showed a 12-month PFS rate of 53% with anti-PD-1 cemiplimab in cutaneous SCC. Based on this result we will utilize a randomized two arm trial superiority design (i.e. one-sided) that will be able to detect an increase of 75% in median PFS (from 12 to 21 months). It will have a significance rate of 0.2 and a power of 80%. The design requires 37 PFS events before the primary endpoint can be assessed and we will enroll 54 total evaluable patients (27 per arm). If, after the 37th event, the hazard ratio (using the avelumab alone arm as reference) is less than 0.758, then there will be sufficient evidence to reject the null hypothesis and declare that avelumab + cetuximab arm is superior, thus warranting further study in this disease population.

### 13.2.3 Analysis Plan:

The main analysis with regards to the primary endpoint is described above, in Section 13.2.2. In short, the study will be declared promising if, after the 37$^{th}$ PFS event, the hazard ratio (using the avelumab alone arm as the reference) is less than 0.758.

## 13.3 Sample Size, Accrual Time, and Study Duration

### 13.3.1 Sample Size, Accrual Rate and Study Duration:

The chosen design requires 37 PFS events. We will accrue 54 evaluable patients (randomized patients that are eligible, do not have major protocol violations, and do not cancel study participation prior to receiving drug). In order to attain this amount of evaluable patients we plan to enroll an additional 5 patients, meaning the maximum possible accrual for this phase II study is 59. The study team anticipates that accrual will happen at approximately 2 patients per month. Thus, the accrual portion of the trial should take approximately 30 months.

As of amendment #07, the study has experienced significantly more patients than expected that do not continue study participation past screening. Specifically, of the 58 patients that were screened for study participation, only 46 were registered, meaning nearly 21% of all patients screened were not registered. In order to account for this rate going forward, as well as to allow for any patients that are registered but deemed non-evaluable, the study will plan to screen a maximum of N=79 patients. The study team will monitor the rate of

patients that are actually registered as well as the number of evaluable patients. Once we have 59 registered patients, we will temporarily close the study to accrual and assess if we have at least 54 patients that are evaluable for the primary endpoint.

### 13.3.2 Primary Endpoint Completion Date for ClinicalTrials.gov Reporting:

For purpose of ClinicalTrials.gov reporting, the estimated Primary Endpoint Completion Date (PECD) for this study is 42 months after the study has begun enrollment. This estimate is based on the accrual rate and expected time to attain the required events to assess the primary endpoint under the alternative hypothesis (i.e. that treatment with avelumab + cetuximab is superior to avelumab alone).

## 13.4 Supplementary Analysis Plans

### 13.4.1 Secondary Endpoints

Confirmed Objective Response Rate (RR): A patient will be declared a success for RR if they achieve a PR or better on two consecutive evaluations (at least 8 weeks apart). The number of successes will be divided by the number of evaluable patients to estimate the RR for each treatment arm and exact 95% confidence intervals will be calculated based on the properties of the binomial distribution.

Clinical Benefit Rate (CBR): A patient will be declared a success for CBR if they are stable or responding and remain on study treatment for 8 cycles. The CBR is then estimated as the number of successes divided by the total number of evaluable patients. An exact 95% confidence interval will be constructed around the CBR using the properties of the binomial distribution.

Progression-free Survival (PFS): The progression-free survival time for a given patient is the number of days between enrollment and documented progression (or death). In addition to the analyses for the primary endpoint we will explore the PFS for those patients that crossover to combination therapy (avelumab + cetuximab) after progressing on avelumab alone (baseline time being the time of crossover). The Kaplan-Meier method will be used to calculate a median PFS as well as a 95% confidence interval.

Overall Survival (OS): The overall survival time for a given patient is the number of days between enrollment and or death. The Kaplan-Meier method will be used to calculate a median OS as well as a 95% confidence interval. These analyses will be performed for each treatment arm. Patients that do not have recorded deaths will be censored at their last follow up.

Safety/Toxicity: Maximum grade adverse events will be summarized in a tabular setting by treatment arm.

### 13.4.2 Correlative Endpoint

PD-L1 status will be determined for each patient (positive if $\geq$1% and negative otherwise). This status will then be compared to RR, CBR, OS, and PFS by study arm and comparisons will be made when appropriate (i.e. if the sample size justifies such a comparison). For RR and CBR chi-squared test will be used and hazard ratios will be used for OS and PFS.

## 13.5 Adverse Event Stopping Rule

The Alliance Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the study statistician. Additionally, in order to ascertain if the study treatments are safe for patients, the following adverse event stopping rules will be employed. These rules will also act as a safety lead in as,

while cetuximab combined with pembrolizumab was well tolerated at full doses in colorectal cancer patients [23], there is no available safety data on the combination of cetuximab and avelumab nor in this patient population. Accrual will not stop while assessing these rules. The following rules will be applied separately to 4 groups: (A) Avelumab + cetuximab arm, HIV negative patients, (B) Avelumab + cetuximab arm, HIV positive patients, (C) Avelumab alone arm, HIV negative patients, and (D) Avelumab alone arm, HIV positive patients. If either group of HIV positive patients (groups B and D) crosses the rule then the protocol will be amended to exclude HIV patients from further enrollment. If either group of non-HIV positive patients (groups A and C) crosses the rule then accrual will be suspended while the study team evaluates the data, develops a plan, and receives approval for re-opening from the DSMB.

- If at any point during the first 10 patients at least 3 patients experience at least 1 grade 4+ non-hematologic adverse event that is deemed at least possibly related to study treatment, or
- If at any point after the first 10 patients at least 30% of all patients experience at least 1 grade 4+ non-hematologic adverse event that is deemed at least possibly related to study treatment.

## 13.6 Study Reporting

### 13.6.1 Alliance DSMB

This study will be monitored by the Alliance Data Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every six months as per NCI guidelines.

### 13.6.2 Clinical data Update System (CDUS)

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site [redacted]

**Note:** If your study has been assigned to CDUS-Complete reporting, all adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

### 13.6.3 Result Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the "ClincialTrails.gov" web site. The primary and secondary endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov. This will include study results, as stated in the Final Rule.

## 13.7 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of study treatment in subsets defined by race, gender, or ethnicity. Although there is insufficient power to detect small or moderate effects, we will, as always, report the results by gender and ethnicity in exploratory analyses.

There is no reason to believe that there will be a gender difference, with respect to accrual, in this disease population. Additionally, the study team believes that the study will enroll approximately 5% racial minorities.

| **DOMESTIC PLANNED ENROLLMENT REPORT** | | | | | |
|---|---|---|---|---|---|
| **Racial Categories** | **Ethnic Categories** | | | | **Total** |
| | **Not Hispanic or Latino** | | **Hispanic or Latino** | | |
| | **Female** | **Male** | **Female** | **Male** | |
| American Indian/ Alaska Native | 0 | 0 | 0 | 0 | 0 |
| Asian | 1 | 0 | 0 | 0 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 0 | 0 | 1 |
| Black or African American | 1 | 1 | 0 | 1 | 3 |
| White | 36 | 36 | 1 | 0 | 73 |
| More Than One Race | 0 | 1 | 0 | 0 | 1 |
| **Total** | 38 | 39 | 1 | 1 | 79 |

## 14.0 BIOBANKING FOR FUTURE CORRELATIVE SCIENCE

Alliance protocol A091802 has both mandatory tumor testing for PD-L1 analysis and optional testing for future correlative studies. The optional tissue and blood/serum collection for future studies must be offered to all patients enrolled on Alliance A091802 (although patients may opt to not participate). This tissue collection does not require separate IRB approval. Testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

### 14.1 PD-L1 Analysis

Tumor plus tumor infiltrating immune cell (TII) PD-L1 expression will be analyzed by IHC to determine if the patient is positive (expression levels $\geq$1%) or negative (expression levels <1%) on fresh or archival tissue. The Dako automated IHC assay (22C3 mouse antibody) will be used to analyze the percent of tumor cells plus TII with membranous PD-L1 expression. This is an FDA approved qualitative IHC assay. In addition to positive/negative PD-L1 status the percentage of expression for each patient will be quantified and reported. Analysis will occur on FFPE tumor samples which can either be from a new biopsy or archival tissue. The MD Anderson Cancer Center will be carrying out the PD-L1 analysis. PD-L1 expression will be used to stratify patients (positive vs. negative) for randomization.

## 14.2 Biobanking for Future Research

An amendment or proposal for any correlative science studies to be performed on biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines. Amendments to the protocol and/or proposals for use of biological samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

## 15.0 REFERENCES


1. Rogers HW, Weinstock MA, Harris AR et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. Arch Dermatol 2010; 146: 283-287.
2. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. J Am Acad Dermatol 2013; 68: 957-966.
3. Thompson AK, Kelley BF, Prokop LJ et al. Risk Factors for Cutaneous Squamous Cell Carcinoma Recurrence, Metastasis, and Disease-Specific Death: A Systematic Review and Meta-analysis. JAMA Dermatol 2016; 152: 419-428.
4. Bejar C, Maubec E. Therapy of advanced squamous cell carcinoma of the skin. Curr Treat Options Oncol 2014; 15: 302-320.
5. Maubec E, Petrow P, Scheer-Senyarich I et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. J Clin Oncol 2011; 29: 3419-3426.
6. Glisson BS. Phase II study of gefitinib in patients with metastatic/recurrent squamous cell carcinoma of the skin. Journal of Clinical Oncology, 2006 Annual Meeting Proceedings Vol 24, No 18S, 2006:5531 Abstract 2006.
7. Yu SH, Bordeaux JS, Baron ED. The immune system and skin cancer. Adv Exp Med Biol 2014; 810: 182-191.
8. Berg D, Otley CC. Skin cancer in organ transplant recipients: Epidemiology, pathogenesis, and management. J Am Acad Dermatol 2002; 47: 1-17; quiz 18-20.
9. Ullrich SE. Mechanisms underlying UV-induced immune suppression. Mutat Res 2005; 571: 185-205.
10. Ullrich SE. Sunlight and skin cancer: lessons from the immune system. Mol Carcinog 2007; 46: 629-633.
11. Lippman SM, Parkinson DR, Itri LM et al. 13-cis-retinoic acid and interferon alpha-2a: effective combination therapy for advanced squamous cell carcinoma of the skin. J Natl Cancer Inst 1992; 84: 235-241.
12. Shin DM, Glisson BS, Khuri FR et al. Phase II and biologic study of interferon alfa, retinoic acid, and cisplatin in advanced squamous skin cancer. J Clin Oncol 2002; 20: 364-370.
13. Varki V, Ioffe OB, Bentzen SM, et al. PD-L1, B7-H3, and PD-1 expression in immunocompetent vs. immunosuppressed patients with cutaneous squamous cell carcinoma. Cancer Immunol Immunother 2018.
14. Snyder A, Makarov V, Merghoub T et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 2014; 371: 2189-2199.
15. Rizvi NA, Hellmann MD, Snyder A et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015; 348: 124-128.
16. Le DT, Uram JN, Wang H et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015; 372: 2509-2520.
17. Pickering CR, Zhou JH, Lee JJ et al. Mutational landscape of aggressive cutaneous squamous cell carcinoma. Clin Cancer Res 2014; 20: 6582-6592.

18. Ferris RL, Lenz HJ, Trotta AM et al. Rationale for combination of therapeutic antibodies targeting tumor cells and immune checkpoint receptors: Harnessing innate and adaptive immunity through IgG1 isotype immune effector stimulation. Cancer Treat Rev 2017; 63: 48-60.

19. Srivastava RM, Lee SC, Andrade Filho PA et al. Cetuximab-activated natural killer and dendritic cells collaborate to trigger tumor antigen-specific T-cell immunity in head and neck cancer patients. Clin Cancer Res 2013; 19: 1858-1872.

20. Stagg J, Loi S, Divisekera U et al. Anti-ErbB-2 mAb therapy requires type I and II interferons and synergizes with anti-PD-1 or anti-CD137 mAb therapy. Proc Natl Acad Sci U S A 2011; 108: 7142-7147.

21. Reck M, Rodriguez-Abreu D, Robinson AG et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016; 375: 1823-1833.

22. Migden, Michael R., et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med (2018).

23. Boland PM, Hutson A, Maguire O, et al. A phase Ib/II study of cetuximab and pembrolizumab in RAS-wt mCRC. J Clin Oncol. 2018;36(suppl 4S; abstr 834).

## APPENDIX I REGISTRATION FATIGUE/UNISCALE ASSESSMENTS

Registration Fatigue/Uniscale Assessments

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and entered into Medidata Rave at the time of registration.

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

Your level of fatigue, on the average in the past week including today?

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No Fatigue | | | | | | | | | | Fatigue as bad as it can be |

your overall quality of life in the past week including today?

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| As bad as it can be | | | | | | | | | | As good as it can be |