RANDOMIZED PHASE III TRIAL OF PEMBROLIZUMAB VS. PEMBROLIZUMAB/CETUXIMAB IN RECURRENT OR METASTATIC HEAD AND NECK SQUAMOUS CELL CARCINOMA WITH PLATINUM REFRACTORY DISEASE

Eligibility Criteria (see Section 3.0)

-Histologically confirmed squamous cell carcinoma (HNSCC) of oral cavity, oropharynx, hypopharynx, and larynx.

-Previously untreated for recurrent/metastatic disease incurable by local therapies.

-Measurable Disease as Defined in Section 11.0.

-Must have platinum-refractory disease defined as disease progression during or ≤ 6 months after completion of definitive therapy (chemo radiation therapy) or adjuvant (post-operative) therapy.

-Oropharynx Only: Combined positive score (CPS) of ≥1 for PD-L1 expression and negative results from testing of HPV status defined as p16 IHC and/or HPV ISH.

-Prior Treatment (See §3.2.5)

-Age ≥ 18 years

-ECOG Performance Status of ≤ 2

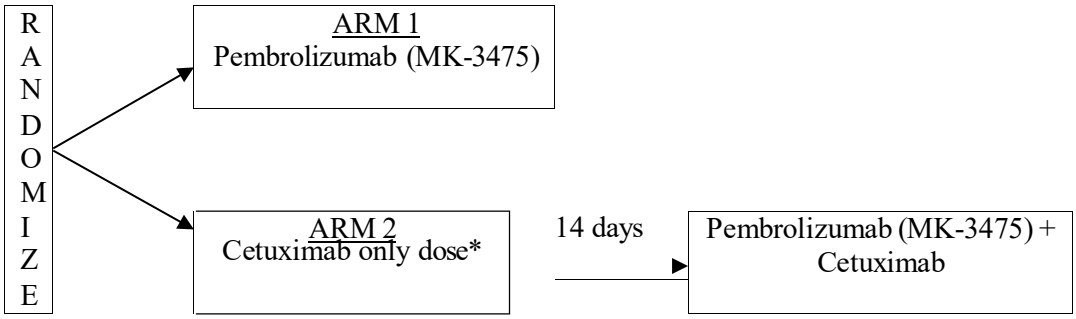
-Not pregnant and not nursing (See §3.2.10).

-Comorbid conditions (See §3.2.11)

Required Initial Laboratory Values	
ANC:	≥ 1500/mm^3
Platelet count:	≥ 100,000/mm^3
Hemoglobin (Hgb):	≥ 9 g/dL (if < 9 g/dL, then transfusions are acceptable to increase hemoglobin above 9 g/dL)
Creatinine:	≤ 1.5 x upper limit of normal (ULN)
OR	
Calc. creatinine clearance:	≥ 30 mL/min using the Cockcroft-Gault formula for participant with creatinine levels > 1.5 X institutional ULN
Total bilirubin:	≤ 1.5 x ULN
OR	
Direct Bilirubin:	< ULN for participant with total bilirubin > 1.5 X institutional ULN
AST/ALT:	≤ 3.0 X ULN unless liver metastases are present in which case < 5.0 X ULN

SCHEMA

1 Cycle = 42 days



*Patients will be treated with lead-in cetuximab 500mg/m^2 (Day -14 before Cycle 1 only) due to the risk of infusion reaction including anaphylaxis associated with cetuximab.

All treatment is to continue until a maximum of 18 cycles, disease progression or unacceptable adverse event. Patients will be followed for 5 years from registration or until death, whichever comes first.

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

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

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: for example, medical conditions such as uncontrolled infection, uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient. Clinicians should use their clinical judgement and have discussions with potential trial participants to assess their ability to follow protocol requirements safely.

Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Reproductive status and discussions about birth control measures should be documented in the patient's record. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom). Document the patient's reproductive status and the discussion about contraception in the patient's records.

3.2 Registration Eligibility Criteria (Step 1)

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). Please note that an optional signature line has been provided for use by institutions wishing to use the eligibility checklist as source documentation.

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.

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).

___ **3.2.1 Documentation of Disease:**

___ **Histologic Documentation:** Histologically confirmed diagnosis head and neck squamous cell carcinomas (HNSCC).

___ **Stage:** Previously untreated for recurrent and/or metastatic disease incurable by local therapies

___ **Tumor Site:** Primary tumor location of oral cavity, oropharynx, larynx, or hypopharynx.

Note: other primary tumor sites of HNSCC, including nasopharynx primary tumor are not eligible. Unknown primary tumors may be eligible and can be enrolled at the discretion of the treatment team with approval by the study chair.

___ **3.2.2 Measurable Disease as Defined in Section 11.0.**

___ **3.2.3 Must have platinum-refractory disease** defined as disease progression during or ≤ 6 months after completion of definitive therapy (chemoradiation therapy) or adjuvant (post-operative) therapy.

___ **3.2.4 Patient must have a combined positive score PD-L1 positive (CPS >/= 1) tumor.**

___ **3.2.5 Prior Treatment:**

___ Any radiation therapy must be completed ≥ 10 days prior to registration.

___ Patients should not have received any prior treatment in the recurrent or metastatic setting.

___ Prior therapy with anti PD-1/PD-L1 monoclonal antibody or cetuximab in the curative setting is allowed if last treatment dose was ≥ 6 months prior to registration without evidence of disease progression during that treatment period.

___ Patient has not received a live vaccine within 30 days prior to registration.

___ Patient does not have a history of any contraindication or has a severe hypersensitivity to any component of pembrolizumab or cetuximab (≥ Grade 3).

___ Patient has not received chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to registration.

___ Patient with oropharyngeal cancer only must have negative results from testing of HPV status defined as p16 IHC and/or HPV ISH.

Note: a CLIA certified ctHPVDNA assay can be used if tissue sample is not available.

___ **3.2.7 Age ≥ 18 years**

___ **3.2.8 ECOG Performance Status ≤ 2**

___ **3.2.9 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Platelet Count	≥ 100,000/mm^3
Hemoglobin (Hgb)	≥ 9 g/dL (if < 9 g/dL, then transfusions are acceptable to increase hemoglobin above 9 g/dL)
Creatinine	≤ 1.5 x upper limit of normal (ULN)
OR	
Calc. Creatinine Clearance	≥ 30 mL/min using the Cockcroft-Gault formula for participant with creatinine levels > 1.5 X institutional ULN
Total Bilirubin	≤ 1.5 x ULN
OR	
Direct Bilirubin	< ULN for participant with total bilirubin > 1.5 X institutional ULN
AST (SGOT)/ALT (SGT)	≤ 3.0 X ULN unless liver metastases are present in which case < 5.0 X ULN

___ **3.2.10 Not pregnant and not nursing,** because this study involves an agent that has known genotoxic, mutagenic, and teratogenic effects.

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

___ **3.2.11 Comorbid Conditions:**

___ Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen should be included.

___ **Brain metastases:** For treated/stable brain metastases: Patients with treated brain metastases are eligible if follow-up brain imaging after CNS-directed therapy shows no evidence of progression.

Patients with new or progressive brain metastases (active brain metastases) or leptomeningeal disease are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy.

___ **HIV:** HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months prior to registration are eligible for this trial.

___ **Hepatitis B:** For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

___ **Hepatitis C:** Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

___ **Cardiac function:** Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

___ **Active myocarditis:** Patients does not have a history of active myocarditis.

___ **Pulmonary disease:** Patients does not have a history of any form of pneumonitis or diffuse idiopathic or immune mediated interstitial pulmonary disease.

___ Patient does not have a history of solid organ transplantation.