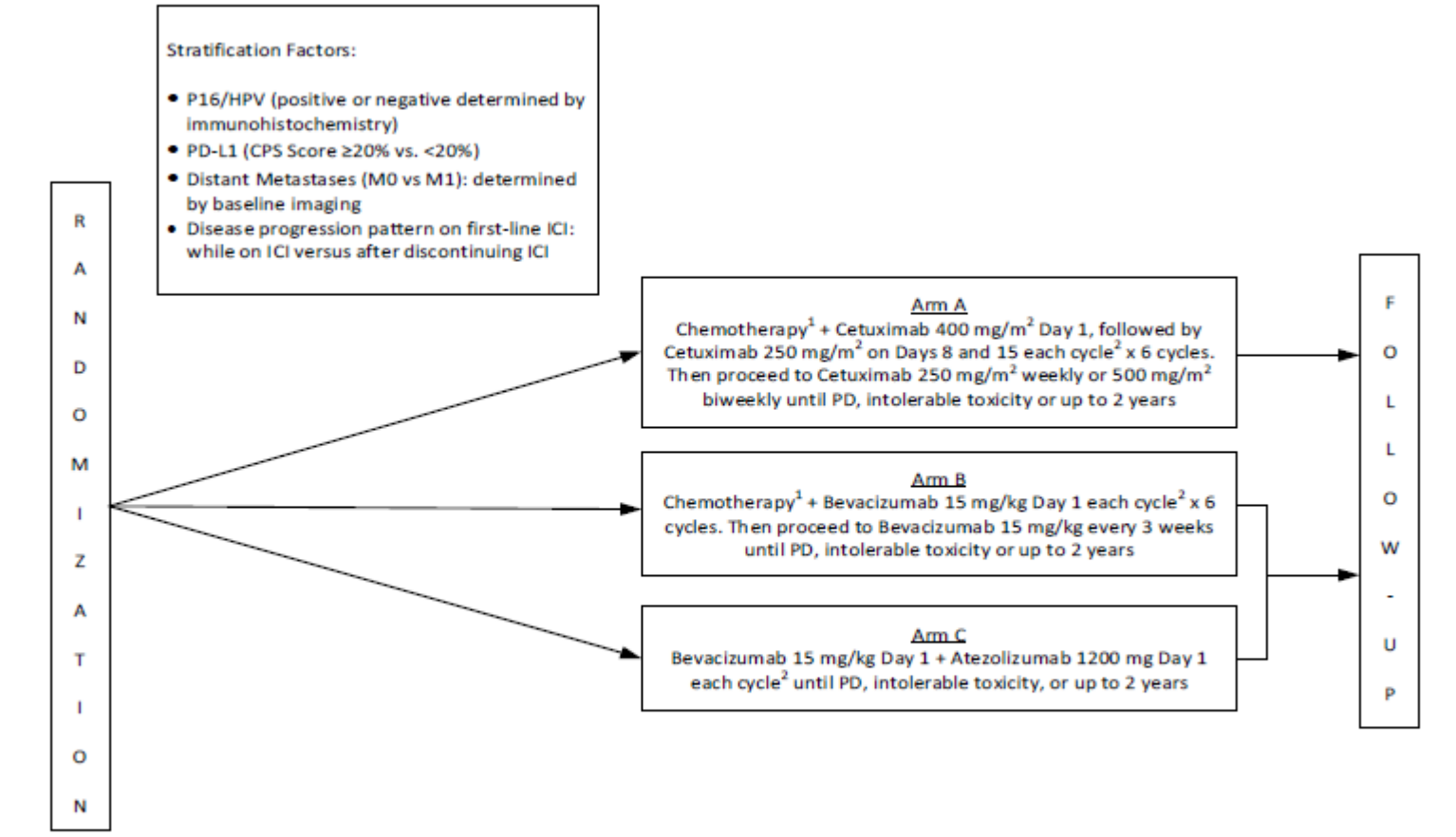
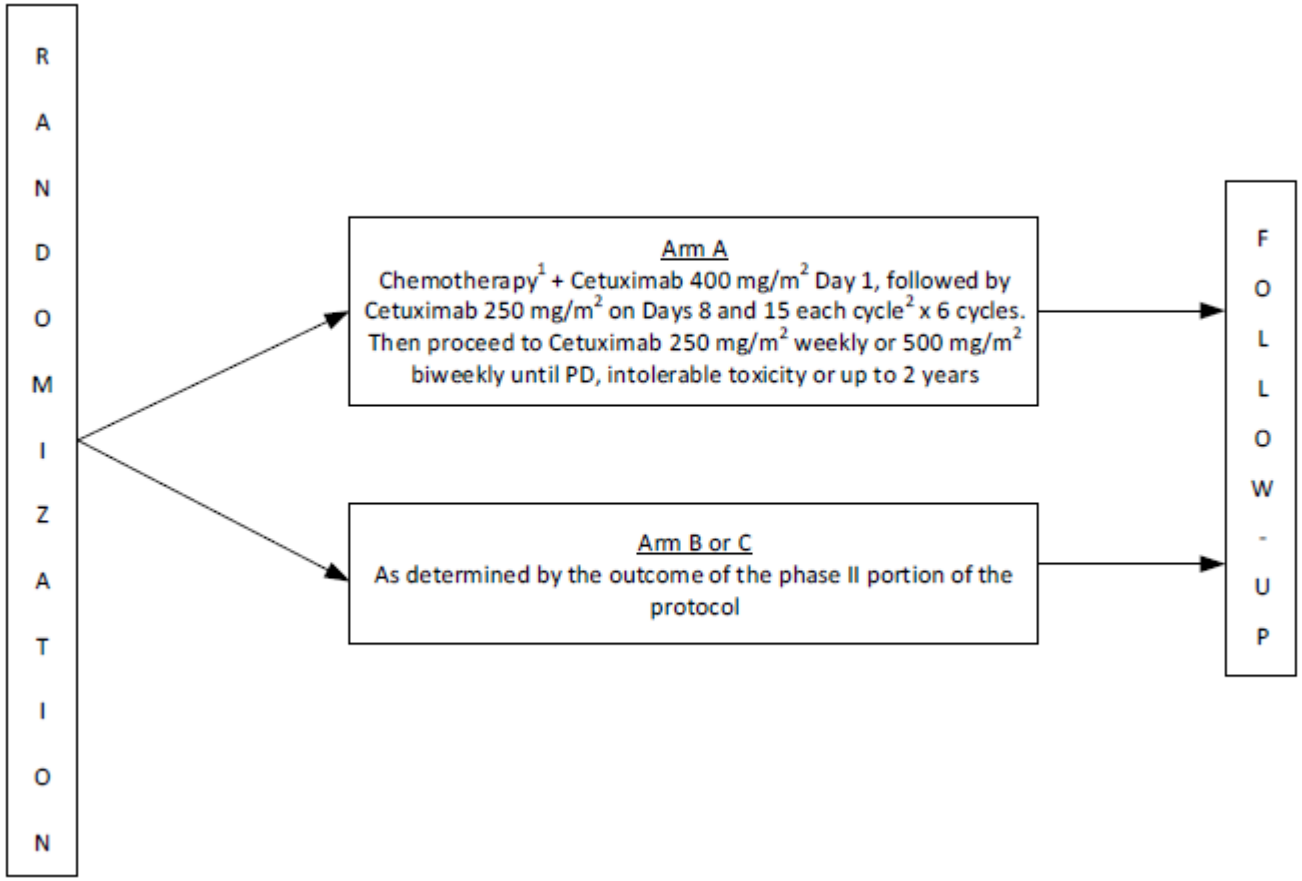
Schema

Phase II



1. Arm A and B: Chemotherapy consists of Docetaxel 75mg/m² IV Day 1, Investigator Choice of Cisplatin 75mg/m² IV Day 1 or Carboplatin AUC 5 IV Day 1. Please refer to Section 5.1 for more details
2. One cycle = 21 days

Phase III



1. Arm A: Chemotherapy consists of Docetaxel 75mg/m^2 IV Day 1, Investigator Choice of Cisplatin 75mg/m^2 IV Day 1 or Carboplatin AUC 5 IV Day 1. Please refer to Section 5.1 for more details
2. One cycle = 21 days

Phase III sample size = 214

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit, and require reporting to the IRB of record as non-compliance.

All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to randomization by the treating physician.

3.1 Eligibility Criteria

_____3.1.1 Patient must have histologically confirmed squamous cell carcinoma of the head and neck (HNSCC) (excluding SCC of salivary glands, and skin).

_____3.1.2 Patient must have measurable disease as defined by RECIST v1.1 criteria in Section 6. Measurements must be obtained within 4 weeks prior to randomization

_____3.1.3 Patient must be ≥ 18 years of age.

_____ 3.1.4 Patient must have an ECOG performance status 0-1.

_____3.1.5 Patient must have received prior therapy with an immune checkpoint inhibitor (ICI) in the first-line setting for recurrent/metastatic disease with at least stable disease for at least 12 weeks by iRECIST. Prior combination immunotherapies are permitted, but patient must not have had any prior chemotherapy, cetuximab or any prior antiangiogenic treatment (e.g., bevacizumab, ziv-aflibercept, ramucirumab, sorafenib, sunitinib, pazopanib, regorafenib, lenvatinib, etc.). Patient must have completed any prior investigational therapy at least 28 days prior to randomization.

NOTE: Patients who received chemotherapy or cetuximab in combination with radiation for curative-intent treatment of locally-advanced disease and did not progress for at least 6 months thereafter, will not be excluded.

_____ 3.1.6 Patient must not have a history of ≥ grade 3 immune-related adverse event on prior ICI therapy. Patients who developed grade 3 endocrinopathies but are now stable on hormone supplementation and/or a daily prednisone dose of ≤ 10 mg (or equivalent doses of another glucocorticoid), will be permitted on this trial.

_____ 3.1.7 Patient must not have a history of PD-1 inhibitor-induced hyper-progression, defined as 100% increase in tumor burden within 8 weeks (or 50% within 4 weeks) of initiating ICI and associated with clinical deterioration.

_____ 3.1.8 Patient must not have any of the following criteria due to the possibility of increased risk for tumor bleeding with bevacizumab therapy:

- Prior carotid bleeding,
- Tumors that invade major vessels (e.g., the carotid) as shown unequivocally by imaging studies,
- Central (e.g., within 2 cm from the hilum) lung metastases that are cavitary as shown unequivocally by imaging studies,
- Any prior history of bleeding related to the current head and neck cancer,
- History of gross hemoptysis (bright red blood of ½ teaspoon or more per episode of coughing) within 3 months prior to randomization.

_____ 3.1.9 Patient must not have uncontrolled hypertension, a history of hypertensive crisis or hypertensive encephalopathy, or a history of grade 4 thromboembolism.

_____ 3.1.10 Patient must not have a history of coagulopathy or hemorrhagic disorders.

_____ 3.1.11 Patient must not have a history of thrombosis (e.g., pulmonary embolism or deep venous thrombosis) currently requiring therapeutic anticoagulation (prophylactic use of anticoagulation is allowed).

_____ 3.1.12 Patient must not be receiving chronic daily treatment with aspirin (> 325 mg/day) or non-steroidal anti-inflammatory agents (NSAID's) known to inhibit platelet function. The use of anti-platelet agents [e.g., dipyridamole (Persatine), ticlopidine (Ticlid), clopidogrel (Plavix)] is allowed only if patient is not receiving aspirin or NSAID's known to inhibit platelet function. The use of direct oral anticoagulant therapies such as dabigatran (Pradaxa) and rivaroxaban (Xarelto) is not allowed while on study due to bleeding risk.

_____ 3.1.13 Patient must have PD-L1 expression ≥1% by CPS in the tumor and/or immune cells.

NOTE: Enrolling centers should test for PD-L1 CPS preferably using the SP263 assay. Where this is not feasible, any

using their preferred CLIA-certified assay will be accepted. It is preferred for SOC PD-L1 assessments to be done on post-first line ICI samples if available, but SOC PD-L1 assessments on pre-ICI samples will be accepted for eligibility.

_____ 3.1.14 Patient must not have a severe infection within 4 weeks prior to randomization, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia. Patients must not have active tuberculosis.

_____ 3.1.15 Patient must not have a history of non-infectious pneumonitis requiring steroids at doses greater than or equal to 10 mg per day of prednisone or the equivalent on first line immunotherapy.

_____ 3.1.16 Patient must not have a history of solid organ transplantation or stem-cell transplant.

_____ 3.1.17 Patient must not be on immunosuppressive medication within 7 days prior to randomization except for: intranasal, inhaled, or topical steroids, local steroid injection, systemic corticosteroids at doses less than or equal to 10 mg per day of prednisone or the equivalent, or steroids used as premedication for hypersensitivity reactions.

_____ 3.1.18 Patient must not have an active autoimmune disease that requires systemic treatment within 2 years prior to randomization. Patients who are receiving replacement therapy for adrenal or pituitary insufficiency will not be excluded.

_____ 3.1.19 Patient must not have had a severe hypersensitivity reaction to any of the drug components used on this protocol or to chimeric or humanized antibodies or fusion proteins.

_____ 3.1.20 Patient must not have received any live vaccine within 30 days prior to randomization and while participating in the study (and continue for 5 months after the last dose of Atezolizumab on Arm C). Live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Patients are permitted to receive inactivated vaccines and any non-live vaccines including those for the seasonal influenza and COVID-19 (Note: intranasal influenza vaccines, such as Flu-Mist® are live attenuated vaccines and are not allowed). If possible, it is recommended to separate study drug administration from vaccine administration by about a week (primarily, in order to minimize an overlap of adverse events).

_____ 3.1.21 Patient must not be pregnant or breast-feeding due to the potential harm to an unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used.

All patients of childbearing potential must have a blood test or urine study within 14 days prior to randomization to rule out pregnancy.

A patient of childbearing potential is defined as anyone, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3)

has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Patient of child-bearing potential?_____(Yes or No)

Date of blood test or urine study: _____

_____ 3.1.22 Patients must not expect to conceive or father children by using accepted and effective method(s) of contraception or by abstaining from sexual intercourse for the duration of their participation in the study and for 2 months after the last dose of treatment for patients assigned to Arm A and for 6 months after the last dose of protocol treatment for patients assigned to Arms B or C.

NOTE: Patients must also not breastfeed while on treatment and for 2 months after the last dose of treatment for patients assigned to Arm A and for 6 months after the last dose of treatment for patients assigned to Arms B or C.

_____ 3.1.23 Patient must have the ability to understand and the willingness to sign a written informed consent document. Patients with impaired decision-making capacity (IDMC) who have a legally authorized representative (LAR) or caregiver and/or family member available will also be considered eligible.

3.1.24 Patient must have adequate organ and marrow function as defined below (these labs must be obtained ≤ 14 days prior to protocol randomization):

_____Leukocytes ≥ 3,000/mcL

Leukocytes:_____Date of Test:_____

_____Absolute neutrophil count (ANC) ≥ 1,500/mcL

ANC:_____Date of Test:_____

_____ Lymphocyte ≥ 500/mcL

Lymphocyte:_____Date of Test:_____

_____Platelets ≥ 100,000/mcL

Platelets:_____Date of Test:_____

_____ Hgb > 9 g/dL (Note: Patient may be transfused to meet this criteria)

Hgb:_____Date of Test:_____

_ Total bilirubin ≤ 2.0x institutional upper limit of normal (ULN) (≤5.0 x institutional ULN if hepatic metastases present or ≤ 3 x ULN for patients with known Gilbert's disease)

Total Bilirubin:_____Institutional ULN:_____

Hepatic metastases present?_____(Yes or No)

Gilbert's disease present? _ (Yes or No)

Date of Test:_____

_____ AST (SGOT)/ALT (SGPT) ≤ 2.5 × institutional ULN (< 5.0 x institutional ULN if hepatic metastases present)

AST:_____Institutional ULN:_____

Date of Test:_____

ALT:_____Institutional ULN:_____

Date of Test _____

Hepatic metastases present?_____(Yes or No)

Alkaline phosphatase < 2.5 x institutional ULN (< 5.0 x institutional ULN if hepatic or bone metastases present)

Alkaline phosphatase:_____Institutional ULN:_____

Date of Test:_____

Hepatic or bone metastases present?_____(Yes or No)

_ Creatinine ≤ 1.5 x institutional ULN

Creatinine_____Institutional ULN

Date of Test:_____

_____3.1.25 Patients with uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL or corrected serum calcium > ULN) must have their calcium levels corrected prior to randomization.

_____3.1.26 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of randomization are eligible for this trial.

_____3.1.27 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

_____3.1.28 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.

_____3.1.29 Patients with treated brain metastases are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression. Patients must not have untreated brain metastases or leptomeningeal disease.

_____3.1.30 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 are eligible for this trial.

_____ 3.1.31 Patients must not have uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently). Patients may have indwelling catheters (e.g., PleurX®).

_____ 3.1.32 Patient must not have significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to randomization, or unstable arrhythmia or unstable angina at the time of randomization.

_____3.1.33 Patient must not receive any other chemotherapy, immunotherapy, antitumor hormonal therapy (excluding contraceptives and replacement steroids), radiation therapy, or experimental medications while on protocol treatment. Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to randomization and patients must be recovered from the effects of radiation (there is no required minimum recovery period).

——— 3.1.34 Patient must not have had a surgical procedure (including open biopsy, surgical resection, wound revision, or any other major surgery involving entry into a body cavity) or significant traumatic injury within 28 days prior to randomization, or anticipation of need for major surgical procedure while on protocol treatment.

_____3.1.35 Patient must not have any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of the agents used in this protocol, may affect the interpretation of the results, or may render the patient at high risk from treatment complications.

_____3.1.36 Patient must not have a history of abdominal fistula, GI perforation, intra-abdominal abscess, or active GI bleeding within 6 months prior to randomization.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.