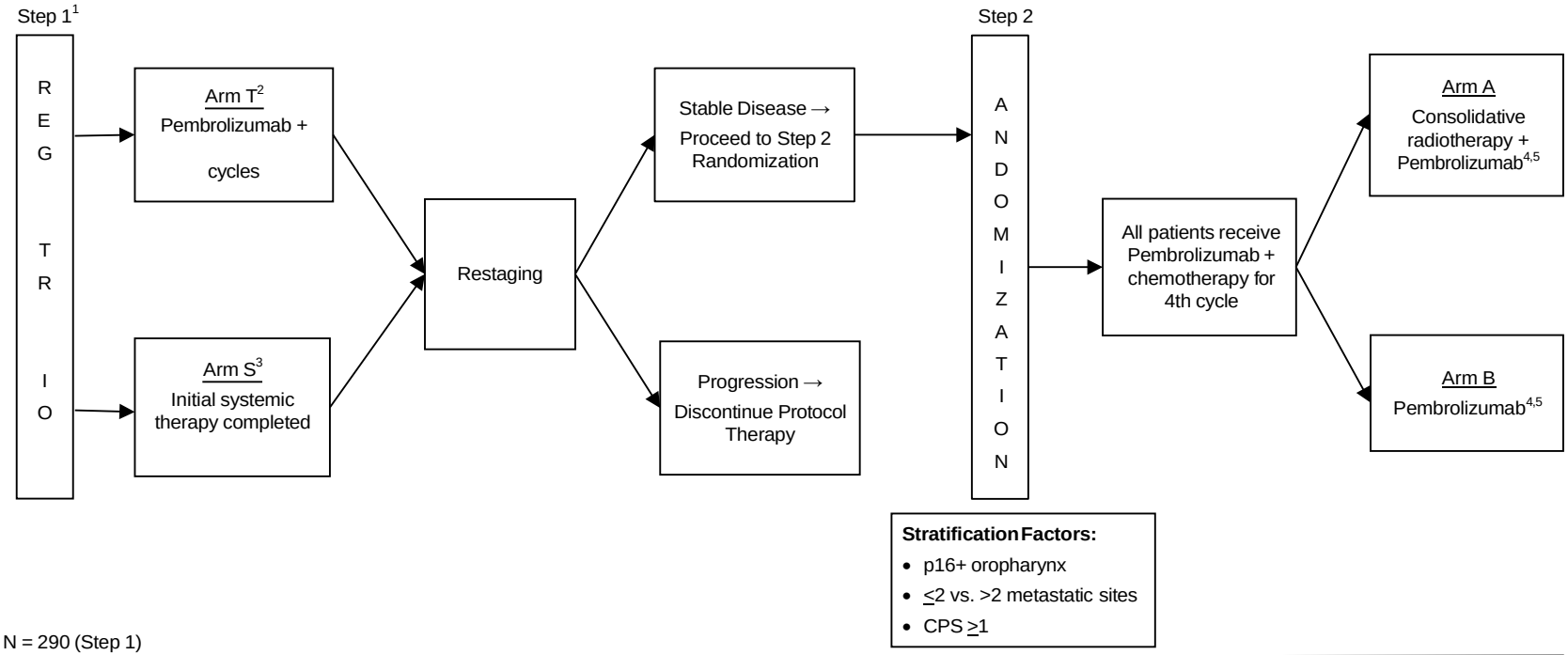
Schema



1. PET-CT imaging is strongly recommended at baseline and 12-14 weeks from the conclusion of radiotherapy (Arm A) or from the start of cycle 7 (Arm B).
2. Patients who have not started any initial systemic therapy or who have started but not completed their initial systemic therapy will be enrolled on Arm T to complete their 3 cycles of initial systemic therapy. See Section 5.1 for details regarding the systemic therapy options.
3. Patients who have completed 3 cycles of initial systemic therapy as defined in Section 5.1 prior to enrollment on Step 1 will be enrolled on Arm S and proceed directly to Step 2 randomization (after verifying eligibility).
4. Patients will receive maintenance treatment on Step 2 until progression or a total of 2 years. Thereafter, patients will be followed for survival.
5. Patients on Arm A: At the time of progression, any future treatment will be at the investigator's discretion. Patients on Arm B: At the time of progression, if all progression is within sites of disease present at registration, treating oncologists are encouraged but not required to treat progressing disease per Arm A (See Sections 5.1.2 and 5.2) while continuing Pembrolizumab. If the decision is not to treatment per Arm A, any future treatment will be at the investigator's discretion.

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@ecog-acrin.org) or the Group's Regulatory Officer (EA.RegOfficer@ecog-acrin.org).

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

NOTE: Patients who completed their 3 cycles of initial systemic therapy (Pembrolizumab plus either cisplatin/carboplatin with 5-fluorouracil or carboplatin with paclitaxel as defined in Section 5.1) prior to enrolling on this study and have no evidence of disease progression since treatment initiation may register on to Arm S on Step 1. Patients can proceed directly to Step 2 randomization after confirming Step 1 and Step 2 eligibility. Patient must be randomized to Step 2 within 21 days after completing their last cycle of initial systemic treatment.

NOTE: Patients who started their 3 cycles of initial systemic therapy (Pembrolizumab plus either cisplatin/carboplatin with 5-fluorouracil or carboplatin with paclitaxel as defined in Section 5.1) prior to enrolling on this study may register to Arm T to complete their initial therapy.

3.1 Eligibility Criteria – Step 1 Registration

_____ 3.1.1 Patient must be ≥ 18 years of age.

_____ 3.1.2 Patient must have biopsy-proven metastatic squamous cell carcinoma, originating in the oral cavity, larynx, oropharynx, or hypopharynx, with active disease present in both the head and neck and distant sites.

NOTE: The tumor from an oropharynx primary site must have known p16 status; p16 positive cancer of unknown primary is allowed as well, provided the disease presentation in consistent with a head and neck primary.

_____3.1.3 Patient can have prior surgical resection of a primary cancer in the head and neck at any previous time, however, residual/recurrent disease in the head and neck must be present on baseline imaging.

_____3.1.4 Patients must not have prior head and neck radiotherapy.

_____3.1.5 Any effects from prior cancer therapy for other diseases must be fully resolved and not pose a problem for giving the treatment on this trial.

_____3.1.6 Patient must have 4 or fewer metastatic sites prior to starting any treatment, with thoracic nodal disease considered a single site if encompassable in a tolerable radiotherapy hypofractionated field (i.e., 15 fractions or less).

NOTE: Contiguous/adjacent metastases treatable in a single stereotactic field may be considered a single site.

NOTE: Patients with additional indeterminate findings such that the total number of metastatic sites would be more than 4 may be enrolled if a non-malignant etiology to these findings is a reasonable consideration.

_____3.1.7 Patient must have ECOG Performance Status 0-1

_____3.1.8 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.

_____3.1.9 Patients must have measurable disease as defined in Section 6.1.1, as follows:

3.1.9.1 For patients who have not started any initial systemic therapy (with pembrolizumab + chemotherapy as defined in Section 5.1) must have measurable disease documented by CT of the neck and chest, and abdomen obtained within 28 days prior to Step 1 registration.

3.1.9.2 For patients who have started or completed their 3 cycles of initial systemic therapy (with pembrolizumab + chemotherapy as defined in Section 5.1) must have measurable disease documented by CT of the neck, chest and abdomen obtained within 28 days prior to the start of their initial systemic therapy.

_____3.1.10 Patient must have adequate organ and marrow function as defined below (these labs must be obtained ≤ 28 days prior to Step 1 registration or prior to the start of any chemotherapy if on Arm T):

Leukocytes ≥ 3,000/mcL

Leukocytes:_____Date of Test:_____

- Absolute neutrophil count (ANC) ≥ 1,500/mcL

  ANC:_____Date of Test:_____

- Platelets ≥ 100,000/mcL

  Platelets:_____Date of Test:_____

- Total bilirubin ≤ institutional upper limit of normal (ULN). Patients with a total bilirubin > 1.5 x ULN, that is attributed to confirmed Gilbert's syndrome, are allowed after consultation and approval from their treating physician.

  Total Bilirubin:_____Institutional ULN:_____

  Gilbert's Syndrome:_____(Yes or No)

  Date of Test:_____

_____AST(SGOT)/ALT(SGPT) ≤ 3.0 × institutional ULN

  AST:_____Institutional ULN:_____

  Date of Test:_____

  ALT:_____Institutional ULN:_____

- Creatinine clearance: GFR ≥50 mL/min/1.73m^2 (for patients receiving carboplatin-based regimens, GFR **>** 30 mL/min/1.73m^2)

  GFR:_____Date of Test:_____

  Carboplatin based regimen:_____(Yes or No)

_____3.1.11 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of Step 1 registration are eligible for this trial.

_____3.1.12 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

_____3.1.13 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.

_____3.1.14 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.

_____3.1.15 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.

_____ 3.1.16 Patient must not have an active autoimmune disease (i.e., inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, etc.) that has required systemic treatment (i.e., disease modifying agents, corticosteroids, or immunosuppressive

drugs) in past 2 years. Replacement therapy (i.e., thyroxine, insulin, physiologic corticosteroid replacement) is not considered a form of systemic treatment and is allowed.

_____3.1.17 Patients on Arm S must have received chemoimmunotherapy consistent with Section 5.1.

_____3.1.18 Patients will be enrolled in the QOL study if the patient can read and understand English, Spanish, French or Chinese (simplified or traditional characters).

NOTE: Sites cannot translate the associated QOL forms.

_____3.1.19 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 Step 1 registration 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 childbearing potential?_____(Yes or No)

Date of blood test or urine study: _____

_____3.1.20 Patients of childbearing potential and/or sexually active patients must not expect to conceive or father children by using an accepted and effective method(s) of contraception or by abstaining from sexual intercourse for the duration of their participation in the study. Patients of childbearing potential must continue contraceptive measures for 4 months after the last dose of protocol treatment and must not breastfeed while on study treatment through 4 months after the last dose of protocol treatment.

_____ 3.1.21 Patient must not have received any live vaccine within 30 days prior to Step 1 registration and while participating in the study. 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.

Physician Signature Date

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

3.2 Eligibility Criteria Step 2 Randomization

_____ 3.2.1 Patient must have ECOG Performance Status 0-2.

_____ 3.2.2 Patient must have completed 3 cycles of initial systemic chemotherapy.

_____ 3.2.3 For patients registered to Arm S on Step 1, patients must have at least stable disease after completing 3 cycles of Pembrolizumab + chemotherapy, as defined in Section 5.1.

_____3.2.4 Patient must have no signs of progression (CR/PR or SD) on restaging imaging (consisting of neck, chest, and abdomen CT). Restaging imaging must have been done after completion of initial systemic chemotherapy with pembrolizumab + chemotherapy on Step 1 and within 7 days prior to step 2 randomization. Patients with stable or responding radiologic response are eligible for Step 2.

Physician Signature Date

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