A Phase II/III Trial of Chemotherapy + Cetuximab vs Chemotherapy + Bevacizumab vs Atezolizumab + Bevacizumab Following Progression on Immune Checkpoint Inhibition in Recurrent/Metastatic Head and Neck Cancers

**Study Schema**

**Phase II accrual = 216 patients**

*Arm A and B: Chemotherapy consists of Docetaxel 75 mg/m² IV Day 1, Investigator Choice of Cisplatin 75 mg/m² IV Day 1 or Carboplatin AUC 5 IV Day 1

†One cycle = 21 days

For Phase III, patients will be randomized to Arm A (same as above), OR Arm B/C (as determined by the outcome of Phase II).

Phase III accrual = 214 patients
Study Objectives

**Primary Objectives**
- Phase II: To evaluate progression-free survival (PFS)
- Phase III: To evaluate overall survival (OS)

**Secondary Objectives**
- To evaluate OS for the subset of patients with high PD-L1 expression, defined as Combined Positive Score (CPS) ≥ 20% on all study arms
- To evaluate the toxicity of each study arm

Refer to the protocol for imaging objectives (Section 2.3) and exploratory objectives (Section 2.4)

Eligibility Criteria*

**Main Inclusion Criteria**
- ≥ 18 years of age, ECOG PS 0–1, adequate organ and marrow function defined per protocol
- Histologically confirmed squamous cell carcinoma of the head and neck (HNSCC) (excluding SCC of salivary glands, Epstein-Barr Virus–associated nasopharynx and skin)
- Measurable disease (defined by RECIST v1.1); measurements must be obtained within 4 weeks prior to randomization
- Must have disease progression after prior therapy with an immune checkpoint inhibitor (ICI) in the first-line setting for recurrent/metastatic disease. Must have received first-line ICI for at least 6 weeks. Patients who have recurred/progressed within 12 weeks of ICI administered in the definitive setting for locally advanced disease are eligible if local therapies are not feasible
- Prior combination immunotherapies are permitted, but patient must not have had prior antiangiogenic treatment (e.g., bevacizumab, ziv-aflibercept, ramucirumab,

*When evaluating patients for this study, please refer to the full protocol for complete list of eligibility criteria.
sorafenib, sunitinib, pazopanib, regorafenib, lenvatinib, etc.)
– Patients who received platinum/taxanes in the locally-advanced or recurrent/metastatic setting and did not progress for at least 4 months thereafter are eligible
– Patients who received cetuximab in the locally-advanced setting and did not progress for at least 4 months thereafter are also eligible
• Must have PD-L1 expression ≥ 1% by CPS in the tumor and/or immune cells

Main Exclusion Criteria
• History of ≥ grade 3 immune-related adverse event on prior ICI therapy (except those that could be managed with steroids) and ICI could eventually be resumed
  – Patients who developed grade 3 endocrinopathies but are stable on hormone supplementation and/or a daily prednisone dose of ≤ 10 mg (or equivalent doses of another glucocorticoid) are permitted
• 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
• Uncontrolled hypertension, history of hypertensive crisis or hypertensive encephalopathy, or history of grade 4 thromboembolism
• History of coagulopathy or hemorrhagic disorders
• History of solid organ transplantation/stem-cell transplant

(Continued)
Main Exclusion Criteria (cont)

• Uncontrolled pleural effusion, pericardial effusion or ascites requiring recurrent drainage procedures (once monthly or more)

• History of abdominal fistula, GI perforation, intra-abdominal abscess, or active GI bleeding within 6 months of randomization