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Window of opportunity trial of HPV E7 antigen-expressing *Listeria*-based therapeutic vaccination prior to robotic surgery for HPV-positive oropharyngeal cancer

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Introduction

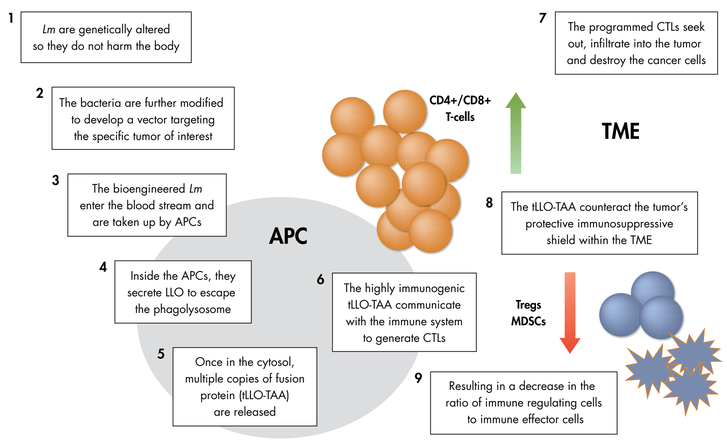
- In the USA, the prevalence of human papillomavirus (HPV)-associated oropharyngeal cancer (HPVOPC) is increasing (225% from 1988 to 2004).[1,2]
  - Patients tend to be younger and have a favorable prognosis, with a 69% reduction in the risk of death compared with HPV-negative patients[1,2]
- Most HPVOPC patients present with advanced stage, and standard chemoradiation regimens can be associated with significant toxicity.[3]
  - It is a paradox of treatment that patients who have a good prognosis are at risk of therapy-related long-term poor quality-of-life outcomes

Immunotherapy has the potential to reduce toxicity through de-escalation of chemoradiation regimens, and potentially enhance long-term disease control.

- *Listeria monocytogenes* (*Lm*)-listeriolysin O (LLO) immunotherapies have been shown to generate antigen-specific T-cell responses and neutralize T-regulatory (Treg) and myeloid-derived suppressor cells (MDSCs) that protect the tumor microenvironment against immunologic attack (**Figure 1**).[4]
- **ADXS11-001** is an attenuated, genetically modified *Lm* vector that secretes an HPV-E7 tumor antigen as tLLO-E7 fusion protein; tLLO refers to the truncated form of non-hemolytic LLO protein.[5]
- **ADXS11-001** can be combined with different treatment modalities, and data in cervical cancer support potential clinical benefit.[6,7]

We hypothesize that ADXS11-001 neoadjuvant immunotherapy will induce a robust HPV-specific cytotoxic T-lymphocyte (CTL) response in the blood and tumor of HPVOPC patients who are vaccinated prior to surgery.

Figure 1. Step by step *Lm*-LLO immunomodulation



APC, antigen-presenting cell; CTL, cytotoxic T-lymphocyte; LLO, listeriolysin O; *Lm*, *Listeria monocytogenes*; MDSC, myeloid-derived suppressor cell; TAA, tumor-associated antigen; tLLO, truncated LLO; TME, tumor microenvironment; Treg, T-regulatory cell.

Objectives

To determine the immunogenicity of ADXS11-001 treatment in patients with stage II–IV HPV-positive squamous cell carcinoma of the oropharynx.

- Primary endpoint: change from baseline in HPV-specific CD8+ CTL responses in peripheral blood at the time of surgery.
- Secondary endpoint: change from baseline in HPV-specific CD8+ CTL responses in peripheral blood at various time points after surgery.
- Exploratory endpoint: changes in the profile of tumor-infiltrating effector (natural killer [NK] cells, CD4+ and CD8+ T-cells) and suppressor (Treg and MDSC) immunocytes.

To evaluate the tolerability, safety, and nature and degree of ADXS11-001 toxicity in patients with HPVOPC.

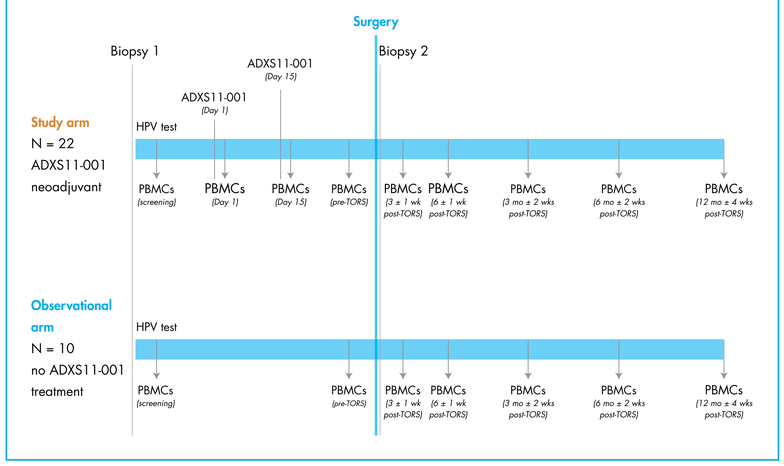
- Primary endpoint: adverse events assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Methods

Window of opportunity, non-randomized, single-arm phase 2 trial of neoadjuvant ADXS11-001 treatment before standard of care transoral robotic surgery (TORS) in patients with stage II–IV HPVOPC (NCT02002182; Figure 2).

- Patients in the **ADXS11-001** treatment arm (study arm) will be enrolled according to a Simon's two-stage design.
  - Initial cohort of 9 patients enrolled before preliminary analysis, and a subsequent cohort of 13 patients enrolled if statistical criteria are met
  - **ADXS11-001** will be administered as an intravenous infusion at a dose of 1×10^9 colony forming units at Days 1 and 15
  - Ibuprofen, diphenhydramine, and an antiemetic will be given before **ADXS11-001** infusion, with ibuprofen also administered after infusion; a course of amoxicillin (or alternative antibiotic) will be administered 72 hours after each **ADXS11-001** dosing
- An observational arm of up to 10 patients, who will undergo TORS without previous treatment with **ADXS11-001**, will also be enrolled.
- Standard of care TORS will be performed in all patients.
- Adjuvant radiation/chemoradiation will be as per standard of care (4–6 weeks after TORS).
- Blood, tumor specimens, and tumor-infiltrating lymphocytes will be collected at different time points from study patients (**Figure 2**), and processed and stored prior to analysis.

Figure 2. Study design and schedule



mo, months; PBMCs, peripheral blood mononuclear cells; TORS, transoral robotic surgery; wk, week.

Key inclusion criteria

- Adult patients (≥ 18 years) with newly diagnosed, biopsy proven, stage II–IV HPVOPC.
- Eligible to undergo TORS with or without neck dissection.
- Eastern Cooperative Oncology Group performance status ≤ 2.
- Able to understand and give informed consent.

Key exclusion criteria

- Active cancer at another site, or history of cancer within the past 3 years.
- Prior systemic chemotherapy or radiotherapy.
- Immunosuppressive condition, or taking immunosuppressive medication.
- Liver disease or other medical contraindication to study medications.

Blood and tumor assessments

- Blood and tumor analyses include immunophenotyping and characterization of HPV-specific T-cell responses in blood, seroreactivity to HPV and cancer-testis antigens in blood, and immunophenotyping and molecular profiling of tumor tissue (summarized in **Table 1**).
- Tissue-based changes will be correlated with comprehensive analysis of immune changes in peripheral blood.

Table 1. Laboratory studies

Assay	Questions to be answered
ELISPOT for HPV-E7-reactive T-cells in peripheral blood	Does **ADXS11-001** induce robust systemic antigen-specific immunity?
IHC/IF for tumor-infiltrating CD8+ T-cells and other immunocytes	Do **ADXS11-001**-induced T-cells penetrate the tumor? Is the overall balance of suppressor and effector immune cells in the TME improved after treatment?
Immunophenotyping of suppressor and effector immune cell subsets in blood by **flow cytometry**	Does **ADXS11-001** improve the systemic balance of suppressor and effector immunocytes?
Seroreactivity to HPV antigens and HNSCCA-associated cancer-testis antigens in blood	Does targeting a foreign viral antigen (E7) lead to epitope spreading and induction of a broad-based response to self-derived tumor antigens?
Immune gene expression signatures in TME by **Nanostring**	Is **ADXS11-001** associated with an "immune response signature" of altered gene expression? Can we identify potential molecular targets for combination therapy?
Multiplex serum cytokine and soluble immunomodulator levels by **Luminex** analysis	Does **ADXS11-001** induce a durable inflammatory/cytokine signature?
T-cell receptor diversity profiling by Immunoseq **TCR deep sequencing**	How does **ADXS11-001** treatment affect the depth and breadth of the tumor-infiltrating T-cell repertoire?

ELISPOT, Enzyme-Linked ImmunoSpot; HNSCCA, human head and neck squamous cell carcinoma antigen; HPV, human papillomavirus; IF, immunofluorescence; IHC, immunohistochemistry; TCR, T-cell receptor; TME, tumor microenvironment.

Statistical considerations

- The trial is designed to conclude that **ADXS11-001** treatment is highly immunogenic and worth further investigation if post-treatment T-cell responses in peripheral blood at least two-fold greater than pretreatment baseline response are observed in > 75% of patients.

Trial status

- This phase 2 study is open and actively enrolling at Icahn School of Medicine at Mount Sinai, NY, USA (Site PI Brett Miles). The IND for this study is held by the Baylor College of Medicine (FDA IND#15688, PI Andrew Sikora).
- Eight of a maximum of 22 **ADXS11-001**-treated patients and 2 of a maximum of 10 observational patients have been enrolled to date.

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Disclosures

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