Phase 1 study evaluating high-dose ADXS11-001 treatment in women with carcinoma of the cervix

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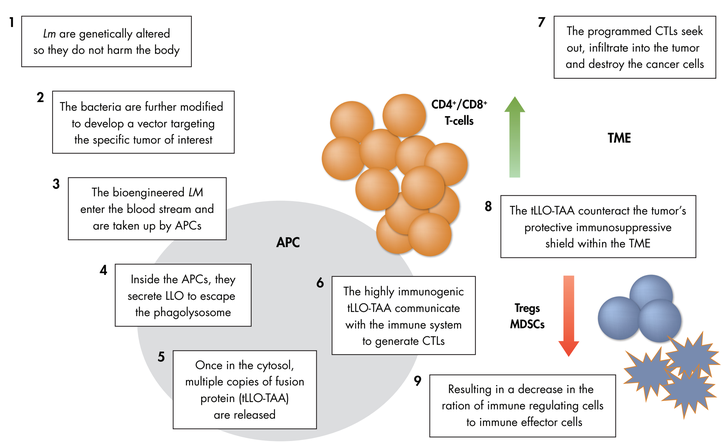
INTRODUCTION

- Cervical cancer is the second most common cancer in developing countries, where ~450,000 new cases are diagnosed annually, most at an advanced stage.[1]
- Prognosis of women with advanced cervical cancer is poor, with a 5-year survival rate of 15%.[2]
- Survival rates are also poor for women who have recurrent cancer, a population that is often resistant to the standard of care, cisplatin.[3]
- The primary etiologic agent of cervical cancer is the human papillomavirus (HPV).
  - Approaches that target this virus may have great utility in improving survival in cervical cancer
- ADXS11-001 is a non-pathogenic, attenuated, bioengineered *Listeria monocytogenes* (*Lm*)-listeriolysin O (LLO) immunotherapy for the treatment of HPV-associated cancer.
  - *Lm*-LLO immunotherapies access and direct antigen-presenting cells to stimulate antitumor T-cell immunity, stimulate and activate the immune system,[4,5] and simultaneously reduce tumor protection in the tumor microenvironment by neutralizing T-regulatory (Tregs) and myeloid-derived suppressor cells (MDSCs)[6] (**Figure 1**). This enables them to stimulate both innate and adaptive tumor-specific immunity
- ADXS11-001 secretes an HPV-E7 tumor antigen as a tLLO-E7 fusion protein, where tLLO refers to the truncated form of non-hemolytic listeriolysin O protein.[4]
- ADXS11-001 has been shown to be safe and well tolerated, and is associated with objective tumor responses and long-term survival in women with recurrent/refractory cervical cancer.[7,8,9]
- This Phase 1 study was conducted in order to further explore a possible dose-response relationship that has been identified in preclinical models, and to evaluate whether a higher dose than that used in the ongoing Phase 2 studies is safe and well tolerated in patients with metastatic or recurrent cervical carcinoma.

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

- The primary objective is to evaluate the tolerability and safety of ADXS11-001 in patients with persistent, metastatic or recurrent squamous or non-squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix.
- The secondary objectives are to:
  - Evaluate tumor response and progression-free survival (PFS) by Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 and immune-related RECIST (irRECIST)
  - Assess correlative immunologic studies of ADXS11-001 treatment

METHODS

STUDY DESIGN

- Phase I, dose-escalation, open-label, multicenter study (NCT02164461).
- Doses will be escalated in the standard 3 + 3 fashion, in 2 doses, starting with 5 x 10^9 colony-forming units (CFU) to a maximum dose level of 1 x 10^{10} CFU.
  - If no dose-limiting toxicities (DLTs) are observed at Dose Level 1 (5 x 10^9 CFU), then patients will be enrolled at the next dose level (1 x 10^{10} CFU)
  - If a DLT is seen in 1 of 3 patients, another 3 will be treated at that same dose
  - If a DLT is seen in 2 of 6 patients, then that dose level will be considered the maximum tolerated dose and the previous dose level will be selected as the recommended phase 2 dose (RP2D). The RP2D cohort will then be expanded to ~15 patients to further define safety and efficacy
  - If ≥ 2 DLTs are observed within 28 days of dosing at Dose Level 1, the starting dose of ADXS11-001 will be de-escalated to 1 x 10^9 CFU and a dose de-escalation cohort may be enrolled (Dose Level –1)
- Treatment cycles can be repeated at the RP2D (or less) for an individual patient until a discontinuation criterion is met.
- The end of study will be defined as 1 year after the last patient's first treatment or until that patient has met a discontinuation criterion.

DOSE-LIMITING TOXICITIES

- DLTs will only be assessed during the first 28 days of Cycle 1.
- The appearance of any of the following toxicities (graded using Common Terminology Criteria for Adverse Events [CTCAE] v4.0) will be considered a DLT if judged to be possibly, probably, or definitely related to therapy by the investigator:
  - Hematologic
    - Grade 4 hematologic toxicity
    - Febrile neutropenia (absolute neutrophil count < 1000/mm^3 with a single temperature of > 38.3° C or a sustained temperature of > 38° C for more than 1 hour)
    - Grade 3 thrombocytopenia lasting > 72 hours
    - Grade 4 thrombocytopenia
  - Non-hematologic
    - ≥ Grade 3 non-hematologic toxicity (excluding nausea, vomiting, and/or diarrhea lasting < 3 days and reversible with medical intervention)
    - Grade 3 non-hematologic laboratory values (excluding transient grade 3 laboratory value abnormalities, hematologic and non-hematologic)
    - Listeremia
    - Grade 3 cytokine release syndrome

INTERVENTIONS

- Patients will receive ADXS11-001 every 3 weeks during a 12-week treatment cycle.
  - ADXS11-001 will be administered in sequential cohorts of 3–6 patients with a minimum of 48 hours between initial dosing for each of the first 3 patients treated at each dose level
- Prophylactic anti-emetic medication prior to ADXS11-001 infusion and every 8 hours thereafter for 48 hours, as needed.
- Non-steroidal anti-inflammatory drugs prior to ADXS11-001 infusion with a second dose approximately every 4 hours thereafter on Days 1 and 2.
- Following each ADXS11-001 infusion, 1–2 g ampicillin twice daily (2–4 g per day) for 3 days, or trimethoprim/sulfamethoxazole DS (if penicillin allergic) 1–2 tablet(s) every 12 hours for 3 days beginning on Day 4 (72 hours).

PATIENT ELIGIBILITY

- Key patient eligibility criteria are described in **Table 1**.

Table 1. Key patient eligibility criteria

Key inclusion criteria
Adult patients (≥ 18 years)
Histologically confirmed persistent, metastatic or recurrent squamous or non-squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix with documented disease progression not amenable to surgery or standard RT at time of screening
Measurable and/or evaluable disease for response assessment per RECIST 1.1
≤ 2 prior regimens for treatment of the metastatic disease
ECOG PS ≤ 1
Adequate hematologic, hepatic, and renal function
Adverse events of any prior therapy resolved to baseline severity of grade < 2 (CTCAE v4.0)
Key exclusion criteria
Rapidly progressing disease OR life expectancy of < 6 months OR unable to receive at least 1 cycle of therapy
Received chemotherapy and/or curative RT ≤ 2 weeks or a live vaccine within 30 days of first ADXS11-001 dose
Known additional malignancy that is progressing or requires active treatment
Active autoimmune disease requiring systemic treatment within past 3 months or documented history of clinically severe autoimmune disease or a syndrome
Neuropathy ≥ grade 3 (CTCAE v4.0)
Diagnosis of immunodeficiency or is receiving systemic steroid therapy/any form of immunosuppressive therapy ≤ 7 days of first ADXS11-001 dose
Known history of human immunodeficiency virus and/or known active hepatitis B or C

CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status; RECIST, Response Evaluation Criteria In Solid Tumors; RT, radiotherapy.

ENDPOINTS

- Primary endpoint:
  - Safety will be assessed by comparing treatment-related adverse events (according to the CTCAE v4.0 criteria), DLTs, changes in physical examinations, vital sign measurements, and laboratory abnormalities
- Secondary endpoints:
  - Tumor assessment will be carried out at baseline, at Week 12 in Cycle 1, then every 12 weeks thereafter. Assessment of disease will be done using RECIST 1.1 and irRECIST criteria
  - Immunologic effects will be measured and evaluated by collection of peripheral blood for preparation of peripheral blood mononuclear cells (PBMCs) and serum immediately prior to each ADXS11-001 infusion and 2 weeks after every ADXS11-001 infusion in Cycle 1 only (Day 1 of Weeks 3, 6, 9, and 12)
    - PBMCs will be analyzed for the presence and quantitation of HPV-E7– and HPV-E6–specific CD8+ T cells through the Enzyme-Linked ImmunoSpot and other assays, as well as Tregs and MDSCs

STATISTICAL METHODS

- Descriptive statistics will be used to summarize and evaluate the safety and tolerability of ADXS11-001.
  - All patients who received at least 1 dose of ADXS11-001 will be included in the safety analyses
  - The RP2D of ADXS11-001 will be selected based on an observed DLT rate of < 33%
- PFS is defined as the time from first dose of study treatment until objective tumor progression or death. Patients who have not progressed or who are still alive at the time of evaluation will be censored for the analysis.
- Kaplan-Meier curves and descriptive statistics will be used to summarize PFS.
  - All patients who completed one 12-week cycle of ADXS11-001 treatment will be considered evaluable for response

TRIAL STATUS

- This phase 1 study is open and is currently enrolling at Georgia Regents University, Augusta, GA.
- To date, 3 patients have been enrolled at Dose Level 1.

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DISCLOSURES

Samir Khleif: Board member, Advaxis. David Mauro: Employee and shareholder, Advaxis. Sharad Ghamande, Cheryl Price, Donna Wheatley, Robbin Dobbins, Lisa Marshall and John Janik have no potential conflicts of interest to disclose.