High-dose treatment with ADXS11-001, a *Listeria monocytogenes*-listeriolysin O (*Lm*-LLO) immunotherapy, in women with cervical cancer: a phase I, dose-escalation study

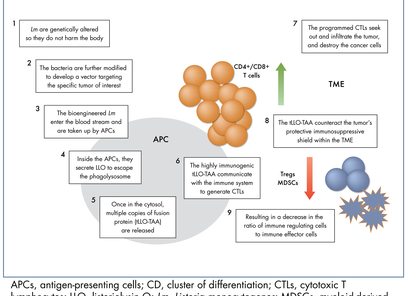
Sharad Ghamande[1], Tom Hare[2], Donna Wheatley[1], Lisa Hatch[1], Bunja Rungruang[1], John Janik[1], Samir N. Khleif[1]

[1]Georgia Cancer Center, Augusta University, Augusta, GA, USA; [2]Advaxis, Inc., 305 College Road East, Princeton, NJ, USA

INTRODUCTION

- Worldwide, cervical cancer is the second most frequent cancer, with an estimated 530,000 new cases in 2012. Of the estimated 270,000 cervical cancer-related deaths, more than 85% occur in low- and middle-income countries.[1]
- Globally, the mortality rate from cervical cancer is very high (52%),[1] with a poor prognosis for patients with advanced disease (5-year survival rate of 15%).[2] There remains no agent proven to extend survival among those patients who are refractory to first-line chemotherapy with or without bevacizumab.[3]
- The human papillomavirus (HPV) is the primary etiologic agent of cervical cancer; HPV-16 and -18 are accountable for 70% of cervical cancers and precancerous cervical lesions.[1]
  - Treatment strategies that target this virus have the potential to improve the survival of patients with cervical cancer, a significant unmet need for this patient population.
- Axalimogene filolisbac (AXAL or ADXS11-001) is a live, attenuated, nonpathogenic, bioengineered *Lm*-LLO immunotherapy for treatment of HPV-associated cancers.[4-6]
  - AXAL secretes an HPV-E7 tumor antigen as a truncated LLO-E7 fusion protein (tLLO-HPV-E7) that stimulates both innate and adaptive tumor-specific immunity
    - tLLO-HPV-E7, taken up by antigen-presenting cells (APCs), are directed to induce and activate a new population of E7 antigen-specific T cells[4] with tumor-specific cytotoxic potential
    - Within the tumor microenvironment, AXAL simultaneously reduces immune tolerance by neutralizing regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) (**Figure 1**)
- AXAL has been demonstrated to be well tolerated, safe, and active in women with advanced cervical cancer.[7-9]
- The present Phase 1 trial has been initiated to determine the clinical feasibility of AXAL at a higher dose than that currently used in ongoing Phase 2 and 3 trials (1×10^9 colony-forming units [CFU]).

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



APCs, antigen-presenting cells; CD, cluster of differentiation; CTLs, cytotoxic T lymphocytes; LLO, listeriolysin O; *Lm*, *Listeria monocytogenes*; MDSCs, myeloid-derived suppressor cells; TAA, tumor-associated antigen; tLLO, truncated LLO; TME, tumor microenvironment; Tregs, regulatory T cells.

OBJECTIVES

PRIMARY OBJECTIVE

- To evaluate the tolerability and safety of AXAL in patients with persistent, metastatic or recurrent squamous and nonsquamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix.

SECONDARY OBJECTIVES

- To evaluate tumor response and progression-free survival (PFS), and assess correlative immunologic studies of AXAL treatment.

METHODS

STUDY DESIGN AND INTERVENTION

- Phase 1 open-label, multicenter, dose-escalation study (NCT02164461).

TREATMENTS

- AXAL was provided to patients intravenously in a volume of 250 mL, every 3 weeks during a 12-week treatment cycle.
- At least 30 minutes prior to AXAL infusion each patient completed a prophylactic regimen consisting of nonsteroidal anti-inflammatory drugs (NSAIDs), antihistamines, antiemetics, and histamine H2 receptor antagonists to mitigate and manage potential immune response seen with administration of immunotherapy. Additional doses of NSAIDs or antiemetics will be provided on days 1 and/or 2 following the infusion, as needed.
- All patients received a 7-day course of oral antibiotic therapy starting 72 hours after each administration of AXAL treatment.
- Dose-escalation occurred according to a 3+3 design to determine dose-limiting toxicities (DLTs), maximum tolerated dose, and subsequent recommended Phase 2 dose (RP2D). Two dose levels were assessed: 5×10^9 CFU (Dose Level 1) and 1×10^{10} CFU (Dose Level 2).
  - DLTs were defined as: grade 4 hematologic toxicity, febrile neutropenia, and grade 3 or 4 thrombocytopenia, grade ≥3 nonhematologic toxicity (excluding nausea, vomiting, and/or diarrhea lasting <3 days and reversible with medical intervention); grade 3 nonhematologic laboratory values (excluding transient grade 3 laboratory value abnormalities, hematologic and nonhematologic, reversible within 5 days and without necessity for medical intervention); grade ≥3 cytokine release syndrome symptoms that persist for >24 hours despite symptomatic treatment; listeremia – persistent (for 48–72 hours post-dose) symptoms consistent with listeremia (eg, fever and muscle aches, often preceded by diarrhea or other gastrointestinal symptoms)
- Maximum tolerated dose was defined as the highest dose level at which 2 of 6 patients experience a DLT.
- RP2D was determined based on an observed DLT rate of <33%.

ELIGIBILITY CRITERIA

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

Table 1. Key patient eligibility criteria

Key inclusion criteria
Adult female patients (≥18 years) with histologically confirmed, measurable and/or evaluable disease as defined by RECIST 1.1
Persistent metastatic or recurrent squamous or nonsquamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix with documented disease progression (not amenable to surgery or standard radiotherapy)
Received ≤2 prior regimens for disease in the metastatic setting. (At the discretion of the investigator and the sponsor, patients who have had >2 prior therapies in the metastatic setting MAY be eligible)
Patient should not have any major existing comorbidities or medical conditions that will preclude therapy, in the view of the principal investigator
ECOG PS ≤1
Adequate hematologic, hepatic, and renal function
Key exclusion criteria
Rapidly progressing disease OR life expectancy of <6 months OR unable to receive at least 1 cycle of therapy
Major surgery, including surgery for a new artificial implant and/or medical device, within 6 weeks prior to initiation of study treatment
Implanted medical device(s) that pose a high risk for colonization and/or cannot be easily removed (eg, prosthetic joints, artificial heart valves, pacemakers, orthopedic screw[s], metal plate[s], bone graft[s], or other exogenous implant[s])
Presence of known additional malignancy that is progressing or requires active treatment
Active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents
Presence of neuropathy (sensory and motor) grade ≥3 per NCI CTCAE v4.03
Diagnosed with immunodeficiency or received systemic steroid therapy/immunosuppressive therapy within 7 days or a live vaccine within 30 days of first ADXS11-001 dose
Has known active central nervous system metastases and/or carcinomatous meningitis
Known contraindication to study antibiotics or nonsteroidal anti-inflammatory drugs, trimethoprim/sulfamethoxazole and ampicillin, or an allergy to any component of the study drug(s) formulation
Known history of human immunodeficiency virus and/or known active hepatitis B or C
Known history of listeriosis or prior AXAL therapy

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

SAFETY AND EFFICACY MEASUREMENTS

- Safety and tolerability were assessed in all patients who received at least 1 dose of AXAL according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 for grading treatment-related adverse events (TRAEs), and by quantifying the DLTs experienced by patients who had received AXAL.
- DLTs were evaluated during the first 28 days of Cycle 1 during the dose-escalation portion of the trial.
- Tumor response was assessed by computed tomography and magnetic resonance imaging at 8-week intervals by Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 and immune-related RECIST (irRECIST). PFS for tumor progression was also measured using RECIST and irRECIST criteria.
- Immunologic effects (eg, changes in cytokine/chemokine levels) were measured and evaluated by collection of peripheral blood for preparation of peripheral blood mononuclear cells and serum in Cycle 1 of AXAL treatment.
- End of study was defined as 1 year after the last patient's first treatment or until that patient has met a criterion for study discontinuation.

STATISTICAL METHODS

- Safety analyses and evaluations of disease response include all patients who received at least 1 dose of AXAL.
- PFS was defined as the time from randomization until objective tumor progression or death, and was summarized through the use of Kaplan-Meier curves and descriptive statistics.
  - Patients who had not progressed or who were still alive at the time of evaluation were censored for the analysis

RESULTS

PATIENT POPULATION AND TREATMENT EXPOSURE

- Enrollment into Dose Level 1 (n = 6) and Dose Level 2 (n = 3) is complete.
  - Three patients were initially enrolled into Dose Level 1
    - Grade 3 hypotension was experienced by 1 patient and characterized as a DLT; this resulted in the enrollment of 3 additional patients
    - The hypotensive patient responded well to intravenous fluids and quickly recovered from the episode
- Baseline demographics and clinical characteristics of patients from the dose-escalation phase are summarized in **Table 2**.

Table 2. Patient baseline demographics and clinical characteristics

Demographic	N = 9
Age (median, range)	53 (30–81)
Race	
White	4 (44%)
Black/African-American	5 (56%)
Baseline ECOG PS	
0	7 (78%)
1	2 (22%)
Prior lines of systemic therapy (median, range)	2 (0–5)
0	1
1	2
2	3
3	1
>3	2
Prior radiation	9 (100%)
Prior chemoradiation	8 (89%)
Prior bevacizumab	6 (67%)

ECOG PS, Eastern Cooperative Oncology Group performance status.

- Distribution of AXAL doses received in Dose Level 1 and Dose Level 2 is presented in **Table 3**.

Table 3. AXAL treatment exposure (doses received)

	Dose Level 1 (n = 6)	Dose Level 2 (n = 3)
Total doses received (median, range)	5.5 (1–6)	2 (1–11)*

*n = 1 patient who remains on treatment and received 5 doses at 1×10^{10} CFU and 6 doses at 1×10^9 CFU. The dose reduction was not safety related, but rather the result of a clinical development program-wide decision not to further explore the higher dose.

SAFETY/TOLERABILITY

- All patients (9; 100%) had at least 1 AE, with 8/9 (89%) patients experiencing TRAEs.
  - In patients with TRAEs: 89% had grade 1–2 TRAEs; 1 patient in Dose Level 1 experienced a treatment-related serious AE (grade 3 hypotension, only reported DLT); and no grade 4 TRAEs were reported
  - Most common TRAEs occurring in 3 or more patients were chills, hypotension, vomiting, tachycardia, headache, fever, and nausea
- Safety findings among patients enrolled in the dose-escalation phase are summarized in **Table 4**.

Table 4. Total number of TRAEs and TRAEs ≥10%, all grades (dose-escalation phase)

	Grade 1–4	Grade 1	Grade 2	Grade 3	Grade 4
Total TRAEs	102	67	34	1	0
TRAEs occurring in ≥10% of patients, n (%)					
Chills	7 (78%)	4 (44%)	3 (33%)	-	-
Hypotension*	4 (44%)	-	3 (33%)	1 (11%)	-
Vomiting	4 (44%)	2 (22%)	2 (22%)	-	-
Tachycardia†	4 (44%)	2 (22%)	2 (22%)	-	-
Headache‡	3 (33%)	2 (22%)	1 (11%)	-	-
Fever	3 (33%)	2 (22%)	1 (11%)	-	-
Nausea§	3 (33%)	-	3 (33%)	-	-

TRAEs, treatment-related adverse events.
*Hypotension, worsening hypotension.
†Tachycardia, sinus tachycardia.
‡Headache, worsening headache, intermittent headache.
§Nausea + intermittent nausea.

EFFICACY

- Investigator assessment of tumor best overall response was reported in 8/9 (89%) treated patients (**Table 5**).
  - One (11%) patient experienced a partial response (PR), and 1 (11%) had stable disease for at least 8 weeks. Six (67%) had progressive disease
  - Clinical history and images representative of the durable PR are shown in **Figure 2**

Table 5. Efficacy (best RECIST v1.1 response, per investigator assessment)

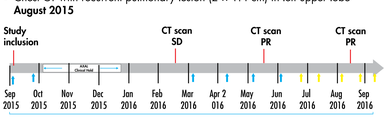
	Dose Level 1 (n = 6)	Dose Level 2 (n = 3)
Complete response	0	0
Partial response	0	1*
Stable disease	0	1†
Progressive disease	5	1
Not evaluable	1	0

RECIST, Response Evaluation Criteria In Solid Tumors.
*n=1 patient remains on study and PR is best overall response to date.
†Patient withdrew from study following first documentation of SD.

Figure 2. Case study: partial response to AXAL following prolonged stable disease

53-year-old African American diagnosed with Stage IIIB squamous cell carcinoma of the cervix in **January 2014**

- Concurrent chemoradiation (carboplatin AUC 1/paclitaxel 50 mg/m^2 qwk + radiation × 6 doses followed by HDR × 5 applications → total radiation dose of 7500 cGY at point A) completed **May 2014**
- Chest CT with enlarging pulmonary lesion in left upper lobe **July 2014** → carboplatin AUC 4.5/paclitaxel 135 mg/m^2 x 2 cycles, but carboplatin reaction = switch to cisplatin 50 mg/m^2 and addition of bevacizumab in cycle 4
  - Total of 9 cycles
  - PET/CT **February 2015** → CR
  - Consolidation bevacizumab × 6 cycles completed **June 2015**
- Chest CT with recurrent pulmonary lesion (2 × 1.4 cm) in left upper lobe **August 2015**



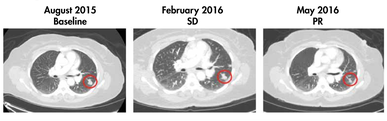
Survival to date – pretreated metastatic squamous cell cervical cancer (post-bevacizumab): 12 months

AXAL 1×10^9 CFU ↑ AXAL 1×10^{10} CFU

AXAL well tolerated

- Grade 1 transient chills/rigors, nausea, vomiting, diarrhea, tachycardia, rash, headache, body ache
- Grade 2 nausea (× 2) and 1 episode of Listeria-positive blood culture requiring a single dose debay

CT images



AUC, area under the curve; CFU, colony-forming units; cGY, centigray; CT, computed tomography; CR, complete response; HDR, high-dose radiation; PET, positron emission tomography; PR, partial response; qwk, every week; SD, stable disease.

CONCLUSIONS

- The RP2D of AXAL was determined to be 1×10^{10} CFU.
- AXAL was well tolerated, with only 1 grade 3 TRAE reported.
- Antitumor activity was demonstrated at the RP2D, with 1 patient experiencing prolonged SD that subsequently upgraded to an ongoing PR.

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DISCLOSURES

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