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

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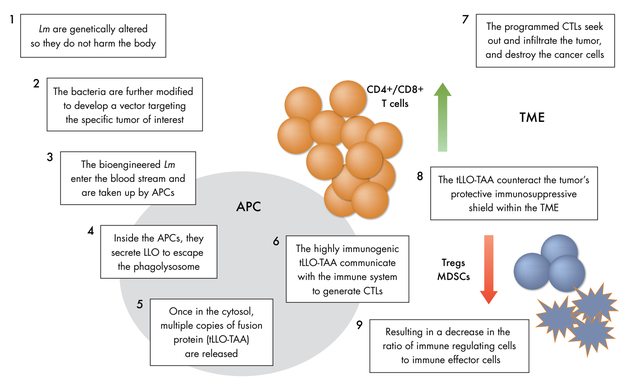
INTRODUCTION

- In 2012, the World Health Organization reported an estimate of 530,000 new cases of cervical cancer and 70,000 cervical cancer-related deaths worldwide, with more than 85% occurring in low- and middle-income countries.[1]
- Globally, the cervical cancer mortality rate is very high (52%),[1] with a 5-year survival rate of 15% for patients with advanced disease.[2] In patients with recurrent cervical cancer, the majority of recurrences occur within 2 years after diagnosis;[3] prognosis and survival rates are poor.[4]
- The primary causative agent of cervical cancer is the human papillomavirus (HPV).
- There are 13 high-risk cancer-causing HPV types, of which HPV-16 and -18 are accountable for 70% of precancerous cervical lesions and cervical cancers.[1]
  - HPV-16 accounts for approximately 53% of invasive cervical cancer cases in most countries, followed by HPV-18, which accounts for approximately 13%[5]
  - Improvement of patient survival remains a large unmet need and, therefore, treatment strategies that target this virus are an urgent necessity
- ADXS11-001 is a live, attenuated, nonpathogenic, bioengineered *Lm*-LLO immunotherapy developed for treatment of HPV-associated cancers,[6-8] such as cervical cancer.
  - ADXS11-001 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 is taken up by antigen-presenting cells (APCs), which are directed to induce and activate a new population of E7 antigen-specific T cells,[6] with tumor-specific cytotoxic potential
    - Simultaneously, ADXS11-001 reduces immune tolerance within the tumor microenvironment by neutralizing regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) **(Figure 1)**
- In women with advanced cervical cancer[8] and with recurrent/refractory cervical cancer,[9-11] ADXS11-001 has been found to be well tolerated, safe, and effective.
- The present Phase 1 trial has been initiated to evaluate whether a dose of ADXS11-001 higher than 1 x 10^9 colony-forming units (CFU), currently used in the ongoing Phase 2 trials, is safe and well tolerated.

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



APC, antigen-presenting cell; CTL, cytotoxic T lymphocyte; 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

- The primary objective is to evaluate the safety/tolerability of ADXS11-001 in patients with persistent, metastatic squamous or nonsquamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix.
- Secondary endpoints include evaluation of tumor response and progression-free survival (PFS), and assessment of correlative immunologic studies.

METHODS

STUDY DESIGN

- This is a Phase 1, dose-escalation, open-label multicenter study (NCT02164461).
- Dose-escalation is performed using the 3+3 design in 2 doses:
  - 5 x 10^9 CFU (Dose Level 1)
  - 1 x 10^{10} CFU (Dose Level 2)
- Safety/tolerability will be assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 for grading treatment-related adverse events, and by quantifying the dose-limiting toxicities (DLTs) experienced by patients who have received ADXS11-001.
- Computed tomography and magnetic resonance imaging will be used to assess tumor response as well as PFS as measured by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and immune-related RECIST (irRECIST).
- Immunologic effects (eg, changes in cytokine/chemokine levels) will be measured and evaluated by collection of peripheral blood for preparation of peripheral blood mononuclear cells and serum in cycle 1 of ADXS11-001 treatment.
- 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.

KEY ELIGIBILITY CRITERIA

- The patient key eligibility criteria are presented in **Table 1**.

Table 1. Key patient eligibility criteria

Key inclusion criteria
Adult female patients (≥18 years)
Histologically confirmed 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)
Lower than or equal to 2 regimens for disease in the metastatic setting. Subjects must have either documented disease progression OR become intolerant to prior therapy, in the metastatic setting
Measurable and/or evaluable disease for response assessment per RECIST v1.1
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
Treatment with chemotherapy and/or radiation therapy (except palliative radiation therapy for disease-related pain) within ≤2 weeks of first ADXS11-001 infusion
No recovery (ie, grade ≤1 at baseline) from AEs, with the exception of alopecia due to previously administered agent(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 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 and allergy to any component of the study drug(s) formulations
Known history of human immunodeficiency virus and/or known active hepatitis B or C
Known history of listeriosis or prior ADXS11-001 vaccine therapy

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

DOSE-LIMITING TOXICITIES

- DLTs will be evaluated during the first cycle of the dose-escalation portion of the trial for a period of 28 days for each patient, using NCI CTCAE v4.03.
  - If no DLTs are experienced in the 28-day DLT observation period at Dose Level 1, the next dose level (Dose Level 2) will be explored
  - If 1 DLT is experienced at Dose Level 2, then 3 additional subjects will be enrolled at that same dose level. If there is 1 DLT among the 6 subjects, then Dose Level 2 may be identified as the recommended Phase 2 dose (RP2D), and will be expanded to further define safety and efficacy
  - If ≥2 DLTs are observed within 28 days of dosing for subjects in the first dose cohort, 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)
- The occurrence of any of the toxicities mentioned in **Table 2** will be considered a DLT if judged to be possibly, probably, or definitely related to the therapy by the investigator.

Table 2. Toxicities that will be considered dose-limiting toxicities if judged to be possibly, probably, or definitely related to the ADXS11-001 therapy by the investigator

Toxicity categories	Criteria for dose-limiting toxicity
Hematologic	Grade 4 hematologic toxicity, febrile neutropenia, and grade 3 or 4 thrombocytopenia
Nonhematologic	≥ 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)

INTERVENTIONS

- Patients receive ADXS11-001, intravenously in a volume of 250 mL, every 3 weeks during a 12-week treatment cycle.
  - ADXS11-001 is administered in sequential cohorts of 3–6 patients, with a minimum of 48 hours between initial dosing for each patient treated at each dose level
- Each patient receives:
  - Prophylactic antiemetic medication prior to ADXS11-001 infusion and every 8 hours afterward, for 48 hours (if needed)
  - Nonsteroidal anti-inflammatory drugs prior to ADXS11-001 infusion, with a second dose approximately every 4 hours thereafter on days 1 and 2
  - Ampicillin twice daily (2–4 g per day) for 3 days; alternatively, if penicillin-allergic, patients receive trimethoprim/sulfamethoxazole DS 1–2 tablet(s) every 12 hours for 3 days starting on day 4 (72 hours) after each ADXS11-001 infusion

STATISTICAL METHODS

- Descriptive statistics will be used to summarize and evaluate the outcomes.
  - All patients who received at least 1 dose of ADXS11-001 will be included in the safety analyses
  - The RP2D will be selected based on an observed DLT rate of <33%
- Disease response will be tabulated for all patients who receive ADXS11-001.
- PFS is defined as the time from randomization 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.

RESULTS

- Enrollment into Dose Level 1 (n = 6) is complete.
  - Initially, 3 patients were enrolled into the first dose cohort
    - One patient experienced grade 3 hypotension as a DLT, which resulted in the enrollment of 3 additional patients
    - The patient with hypotension responded well to intravenous fluids and quickly recovered from the episode
- Enrollment into Dose Level 2 is complete (n = 3).
- Baseline characteristics of patients from both cohorts are summarized in **Table 3**.

Table 3. Patient baseline demographics and clinical characteristics

Preferred term	ADXS11-001 (cohort 1, n = 6)	ADXS11-001 (cohort 2, n = 3)	ADXS11-001 (cohorts 1 and 2, n = 9)
Mean age, years (SD)	51.3 (11.2)	54.7 (25.5)	52.4 (15.6)
Race			
Caucasian	4 (66.7%)	0 (0%)	4 (44.4%)
African American	2 (33.3%)	3 (100%)	5 (55.6%)
ECOG PS, n (%)			
0	4 (66.7%)	2 (66.7%)	6 (66.7%)
1	2 (33.3%)	1 (33.3%)	3 (33.3%)
Histology, n (%)			
Adenosquamous	1 (16.7%)	1 (33.3%)	2 (22.2%)
Squamous	5 (83.3%)	2 (66.7%)	7 (77.8%)
Median no. of chemotherapy cycles (min-max)	1.5 (0–4)	1 (1–4)	1 (0–4)
Prior treatment(s), n (%)			
Chemoradiation	6 (100%)	3 (100%)	9 (100%)
Surgery	4 (66.7%)	2 (66.7%)	6 (66.7%)

ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.

CONCLUSIONS

- A total of 32 cycles have been safely administered, including 5 cycles at the higher dose of 1 x 10^{10} CFU.

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DISCLOSURES

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