

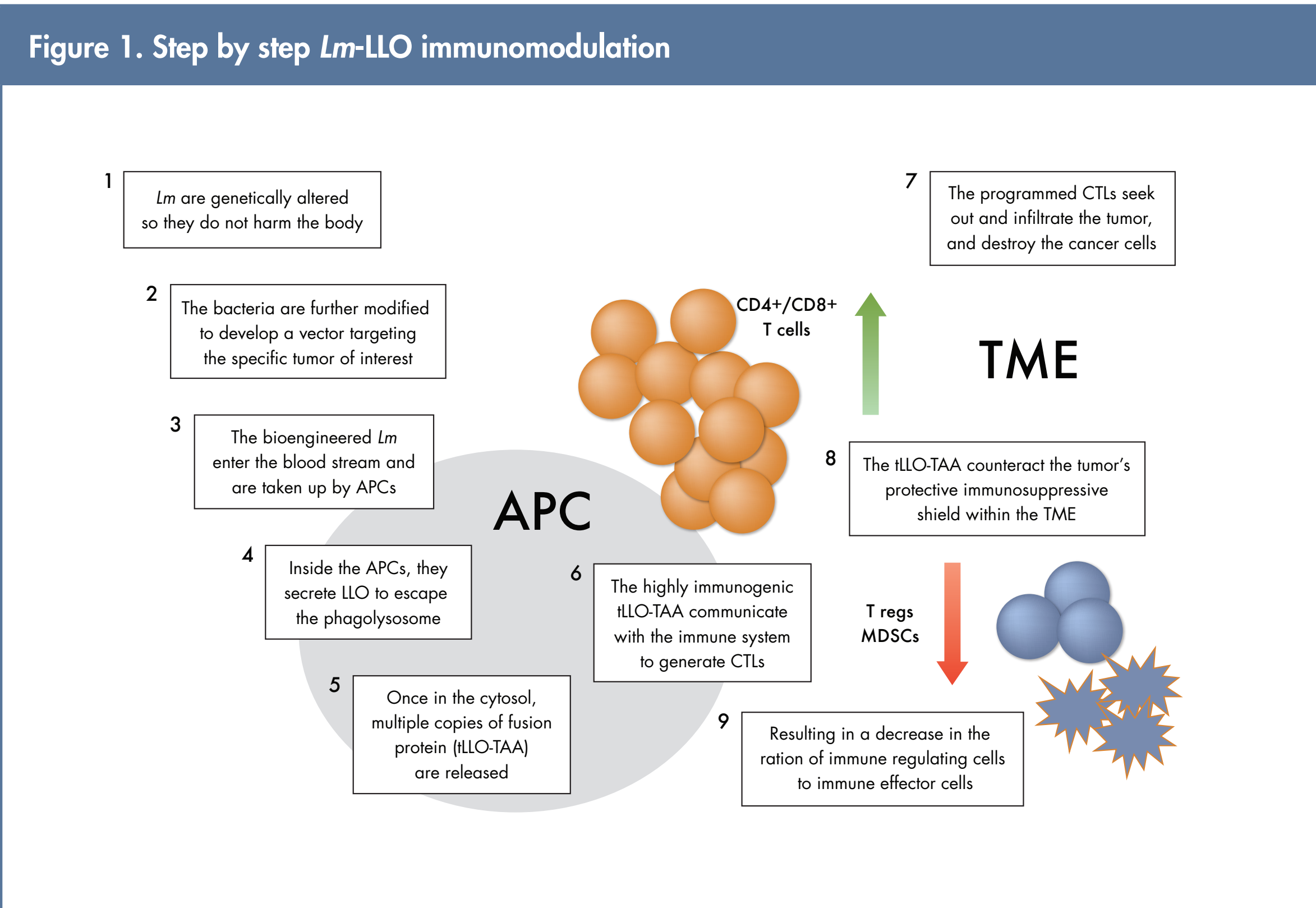
Phase 1/2 study of ADXS11-001 or MEDI4736 (Durvalumab) immunotherapies alone and in combination, in patients with recurrent/metastatic cervical or human papillomavirus (HPV)-positive head and neck cancer

Ezra E.W. Cohen¹, Kathleen N. Moore², Brian M. Slomovitz³, Christine H. Chung⁴, Matthew L. Anderson⁵, Shannon R. Morris⁶, David Mauro⁷, Barbara Burtness⁸

¹University of California, San Diego, La Jolla, CA, USA; ²University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; ³Sylvester Comprehensive Cancer Center, Miami, FL, USA; ⁴Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; ⁵Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, TX, USA; ⁶MedImmune, LLC, Gaithersburg, MD, USA; ⁷Advaxis Inc., Princeton, NJ, USA; ⁸Yale Medical Oncology, New Haven, CT, USA

INTRODUCTION

- The World Health Organization reported approximately 270,000 deaths from cervical cancer in 2012 worldwide.¹
- The 5-year survival rate of patients with advanced cervical cancer is 15%.² Patients with recurrent cancer are usually cisplatin resistant and have poor survival rates.³
- The HPV is the primary etiologic agent of cervical cancer. Of the 13 cancer-causing types of HPV, types 16 and 18 are responsible for 70% of cervical cancers and precancerous cervical lesions.¹
- Similarly, in HPV-positive oropharyngeal cancer, 10%–25% of patients experience progression within 3 years of completing primary therapy and have a 2-year survival of approximately 54%.^{4,5} A retrospective analysis of specimens from the Surveillance, Epidemiology, and End Results Program's Residual Tissue Repository Program determined the incidence rates for HPV-positive oropharyngeal cancers in the USA has increased from 0.8 per 100,000 during 1988–1990 to 2.6 per 100,000 during 2003–2004.⁶
 - Treatment strategies that target this virus may have great utility in improving survival in cervical cancer and squamous cell carcinoma of the head and neck (SCCHN)
- ADXS11-001 is a nonpathogenic, live, attenuated, bioengineered *Listeria monocytogenes* (*Lm*)-listeriolysin O (LLO) immunotherapy developed for the treatment of HPV-associated cancers.^{7,9}
- ADXS11-001 secretes the tLLO-HPV-E7 fusion protein (tLLO refers to the truncated form of LLO), which is rapidly taken up by antigen-presenting cells (APCs), stimulating adaptive immunity and resulting in the activation and release of HPV-specific T cells.⁷
 - Lm*-LLO immunotherapies stimulate both innate and adaptive tumor-specific immunity. They direct APCs to stimulate and activate the immune system, culminating in HPV-specific T-cell activation while simultaneously reducing tumor immunosuppression in the tumor microenvironment by neutralizing regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) (**Figure 1**)
- ADXS11-001 has been demonstrated to be safe, well tolerated, and effective in women with advanced cervical cancer¹⁰ and with recurrent/refractory cervical cancer.¹¹⁻¹³
- Durvalumab (MEDI4736), a human monoclonal antibody (mAb) of the IgG1κ subclass, blocks the binding of programmed cell death protein ligand 1 (PD-L1) to programmed cell death protein-1 (PD-1) and CD80.
- Blocking PD-L1 relieves the inhibition of PD-L1–dependent immunosuppressive effects and enhances the cytotoxic effect of antitumor T cells.
 - Antibodies directed against PD-L1 or its receptor, PD-1, demonstrated antitumor activity in several preclinical studies using mouse tumor models^{14,16}
 - Additionally, a preclinical study demonstrated that the combination of ADXS11-001 and an anti–PD-L1 mAb significantly retards tumor growth and prolongs survival in animals¹⁷
 - Preliminary results from the durvalumab Phase 1 clinical study in patients with SCCHN demonstrated an overall response rate was 11% (7/62) for all patients: 18% (4/22) for PD-L1–positive patients and 6% (3/37) for PD-L1–negative patients (NCT01693562)¹⁸
- Thus, there is a strong rationale for combination therapy with these two investigational agents to treat recurrent, HPV-positive SCC of either the cervix or head and neck.
- The present Phase 1/2 trial (NCT02291055) has been initiated to determine the safety, tolerability, and efficacy of ADXS11-001 and durvalumab each administered as monotherapy or in combination to patients with recurrent/metastatic cervical or HPV-positive SCCHN.



OBJECTIVES

- The objectives of the study are outlined in **Table 1**.

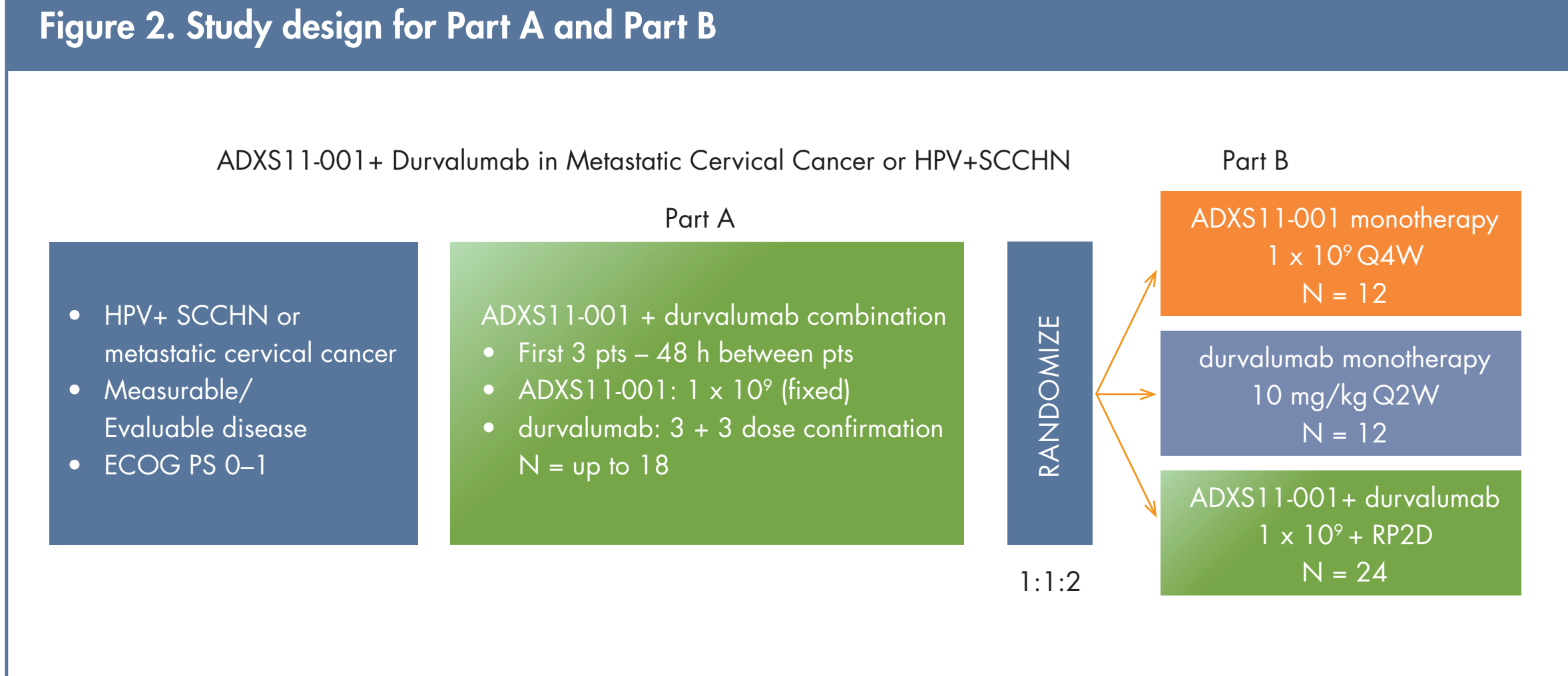
Table 1. Study objectives		
	Part A (Phase 1) ADXS11-001 + durvalumab combination therapy	Part B (Phase 2) ADXS11-001 vs durvalumab vs ADXS11-001 + durvalumab
Primary objective(s)	- Evaluate safety and tolerability across 2 dose levels - Determine the RP2D for Part B	- Evaluate tumor response and PFS by RECIST and irRECIST - Evaluate safety and tolerability
Secondary objective	Evaluate preliminary signs of efficacy (response rates, duration of response, and PFS) by RECIST 1.1 and irRECIST	
Exploratory objective	Evaluate associations between biomarkers of immunologic response and biologic activity across multiple dose levels	

irRECIST, immune-related Response Evaluation Criteria In Solid Tumors; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; RP2D, recommended Phase 2 dose.

METHODS

STUDY DESIGN

- The study is divided into 2 parts: Part A (Phase 1 design) and Part B (Phase 2 design). (**Figure 2**)
- Part A:
 - Phase 1, dose-escalation, open-label, multicenter study
 - Doses for ADXS11-001 will be fixed at 1 × 10⁹ colony-forming units (CFU), while those for durvalumab will be escalated in the standard 3 + 3 fashion, beginning at 3 mg/kg
 - If no dose-limiting toxicities (DLTs) are observed at Dose Level 1 (ADXS11-001 at 1 × 10⁹ CFU + durvalumab at 3 mg/kg), patients will be treated at Dose Level 2 (ADXS11-001 at 1 × 10⁹ CFU and durvalumab at 10 mg/kg)
 - If 1 DLT is experienced, 3 additional patients will be enrolled. If there is 1 DLT among 6 patients, the next dose level will be explored
 - If ≥ 2 DLTs are observed at the first dose level, the dose of durvalumab will be de-escalated to 1 mg/kg in a newly enrolled dose–de-escalation cohort (Dose Level –1)
 - Dose Level –1 (ADXS11-001 at 1 × 10⁹ CFU and durvalumab at 1 mg/kg) will be evaluated if Dose Level 1 is not tolerated
 - The dose level at which a DLT rate of <33% has been observed will be selected as the recommended Phase 2 dose (RP2D) for Part B
- Part B:
 - Phase 2, open-label, randomized multicenter study
 - Randomization will be stratified based on disease type in a 1:1:2 ratio to ADXS11-001 : durvalumab : ADXS11-001 + durvalumab
 - Doses for ADXS11-001 monotherapy will be fixed at 1 × 10⁹ CFU, durvalumab monotherapy at 10 mg/kg, and the combination at the RP2D determined in Part A
 - Biopsies will be performed during the 28-day screening period and at week 1 of cycle 2 to assess molecular markers of response and markers indicative of mechanism of action
 - Adverse events (AEs) will be monitored throughout the study and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03)
- In both parts/phases:
 - ADXS11-001 will be administered every 4 weeks (Q4W) and durvalumab every 2 weeks (Q2W)
 - Patients will receive treatment up to 1 year or until they discontinue due to disease progression, unacceptable toxicity, investigator's decision to withdraw the patient, patient withdrawal of consent, pregnancy of the patient, or noncompliance with trial treatments or procedure
 - All patients will be followed for a minimum of 30 days for AEs, 90 days for serious AEs (SAEs), and up to 3 years for disease status at the end of treatment
 - Patients receiving ADXS11-001 will receive antibiotics 72 hours after each ADXS11-001 infusion.
 - Patients will continue to receive NSAIDs every 4 hours as needed following the ADXS11-001 infusions.



DOSE-LIMITING TOXICITIES

- DLTs will be evaluated during Part A/Phase 1 combination dose-determination phase for a period of 28 days after the first dose for each patient, using NCI CTCAE v4.03.
- The occurrence of any of the toxicities shown in **Table 2** will be considered a DLT if judged by the investigator to be possibly, probably, or definitely related to the combination therapy.

Table 2. Dose-limiting toxicities	
Toxicity categories	Criteria for dose-limiting toxicity
Hematologic	Grade 3 or 4 febrile neutropenia
Nonhematologic	Any increase in aspartate transaminase or alanine transaminase >3× ULN and simultaneous increase in total bilirubin >2× ULN
	Liver transaminase elevation ≥5× but ≤8× ULN; does not downgrade to grade 2 ≤5 days after onset with optimal medical management, including systemic corticosteroids
	Transaminase elevation >8× ULN or total bilirubin >5× ULN
	≥ Grade 2 allergic reaction not due to antibiotics
	≥ Grade 3 cytokine release syndrome symptoms or flu-like symptoms that persist for >24 hours despite symptomatic treatment
irAEs	Listeremia
	Any grade 3 irAE (excluding colitis or pneumonitis) not downgraded to grade 2 ≤3 days despite medical intervention including corticosteroids or not downgraded to ≤ grade 1 or baseline within 14 days of AE onset
	Any ≥ grade 4 irAE
	Any ≥ grade 3 colitis
	Any ≥ grade 3 noninfectious pneumonitis (irrespective of duration)
	Bacterial meningitis

AE, adverse events; irAE, immune-related adverse events; ULN, upper limit of normal.

PATIENT ELIGIBILITY

- Key patient eligibility criteria are described in **Table 3**.

Table 3. Key patient eligibility criteria	
Key inclusion criteria	
Adult patients (≥18 years)	
Histologically confirmed metastatic SCCHN or metastatic squamous/nonsquamous cervical carcinoma/adenocarcinoma deemed incurable by local therapy with documented disease progression on (or intolerance to) ≥1 prior platinum-based therapy in the recurrent/metastatic setting. Confirmation of HPV positivity needed for SCCHN; not a requirement for cervical carcinoma	
Measurable and/or evaluable disease for response assessment per RECIST 1.1	
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	
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	
Requires additional immunosuppression beyond corticosteroids for resolution of irAEs from prior immunotherapy	
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	
Received concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for invasive malignancy within 2 years	
Known contraindication to study antibiotics or NSAIDs 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	
Not recovered (ie, ≤ grade 1 or at baseline) from AEs, with the exception of alopecia, due to a previously administered agent. Any prior grade ≥3 irAE while receiving immunotherapy, including anti–CTLA-4 treatment, or any unresolved irAE ≥ grade 1	

CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T lymphocyte antigen 4; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; irAEs, immune-related adverse events; NSAIDs, nonsteroidal anti-inflammatory drugs; RECIST, Response Evaluation Criteria In Solid Tumors; SCCHN, squamous cell carcinoma of the head and neck.

ENDPOINTS

- Safety
 - Safety will be assessed by grading treatment-related AEs (per NCI CTCAE v4.03 criteria) and by quantifying the toxicities (DLTs) and grades, including SAEs and events of clinical interest experienced by patients who have received ADXS11-001, durvalumab, or ADXS11-001 + durvalumab combination therapy
 - The RP2D of ADXS11-001 will be selected based on an observed DLT rate of <33%
- Efficacy
 - 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 (ir)RECIST. Tumor assessment will be carried out at baseline/screening, at week 1 of cycle 2, and then every 8 weeks thereafter
- Exploratory
 - Immunologic effects will be measured and evaluated by collection of peripheral blood for preparation of peripheral blood mononuclear cells and serum immediately prior to ADXS11-001 infusion and at weeks 5 and 7. For all subsequent cycles, serum will be collected at week 7 (pre-dose only)

STATISTICAL METHODS

- Statistical Analysis Software v9.2 or higher will be used for data analysis.
- Descriptive statistics will be used to summarize and evaluate the safety and tolerability of Part A and Part B separately and combined.
 - All patients who received at least 1 dose of ADXS11-001 will be included in the safety analyses
- The overall response rate will be summarized; frequency counts and percentage will be tested by Fisher's exact test.
- 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.

TRIAL STATUS

- Five of the nine trial centers in the United States are recruiting patients for the study, and as of October 2015, five patients have been enrolled.

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Ezra E.W. Cohen: On advisory boards of and/or consultant at Merck, Pfizer, Eisai and Bayer. Kathleen N. Moore: On advisory boards of Genentech/Roche; Immunogen; Amgen, Advaxis, Merrimack, and Astra Zeneca. No speakers boards or stock ownership. Brian M. Slomovitz, Christine H. Chung, Matthew L. Anderson: On speakers bureau of Astra Zeneca. Shannon R. Morris: Employee and stock holder at MedImmune LLC. David Mauro: Employee and shareholder of Advaxis, Inc. Barbara Burtness: On advisory boards of Bayer, Amgen, Merck, DMSC at MedImmune, Chair, DMSB at VentriRX, Steering Committee member at Boehringer Ingelheim, Expert witness at J&J, Investigator at Merck.