

ADXS11-001, *Lm*-LLO IMMUNOTHERAPY TARGETING HPV-E7: PRELIMINARY SAFETY DATA FROM TWO PHASE 2 STUDIES IN WOMEN WITH CIN2/3 AND WITH RECURRENT/REFRACTORY CERVICAL CANCER

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INTRODUCTION

ADXS11-001 (ADXS-HPV) is a live attenuated *Listeria monocytogenes* (*Lm*) based immunotherapy developed for the treatment of HPV-associated dysplasia and malignancy. ADXS-HPV secretes an antigen-adjuvant fusion (*Lm*-LLO) protein consisting of a truncated fragment of the *Lm* protein listeriolysin O (LLO) fused to HPV16-E7.

The immune response to a live, metabolically competent pathogen is much more complex than the response to a synthetic or organic molecule. The therapeutic use of “living drugs” potentially enables a more comprehensive immune response with many complimentary mechanisms of action:

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| <ul style="list-style-type: none"> -Strong innate immune stimulation -Strong adaptive immune response -Epitope spreading | | <p style="text-align: center;">No adjuvant needed</p> <ul style="list-style-type: none"> -Stimulates synthesis of new immune cells, maturation of existing cells -Potential for memory generation after a short antigen exposure -Reduction in numbers and function of MDSCs and Tregs in tumors | <ul style="list-style-type: none"> -Stimulates chemotaxis and extravasation of activated immune cells -Primarily a cellular immune response |
|---|--|---|---|

Preclinical studies of ADXS11-HPV has been found to stimulate immune responses and demonstrate efficacy in mouse models. ADXS-HPV is the first construct to advance to the clinic, and has completed a Phase 1 study and 4 Phase 2 studies are ongoing to CIN 2/3, cervical cancer, and head and neck cancer. As of October 25, 2011, 266 doses have been administered to 119 patients. From this clinical experience, a clear pattern of treatment-related adverse events has emerged, which are consistent with the release of immunologic cytokines commonly associated with immune activation. Treatment is well-tolerated with transient side effects responding to symptomatic treatment.

LM-LLO-E7-07

A randomized, single blind, placebo controlled phase 2 study to assess the safety of ADXS11-001 for the treatment of Cervical Intraepithelial Neoplasia Grade 2/3.

- 15 Sites, US only

- N=120:

- Women 18-45 years of age with a diagnosis of late stage CIN Grade 2 or Grade 3
- Three cohorts of 40 subjects (30 active and 10 placebo)
- Doses of 5x10⁷ cfu, 3.3x10⁸ cfu, and 1x10⁹ cfu

- Primary objective:

- To determine a safe dose of ADXS11-011 for use in the treatment of CIN 2/3

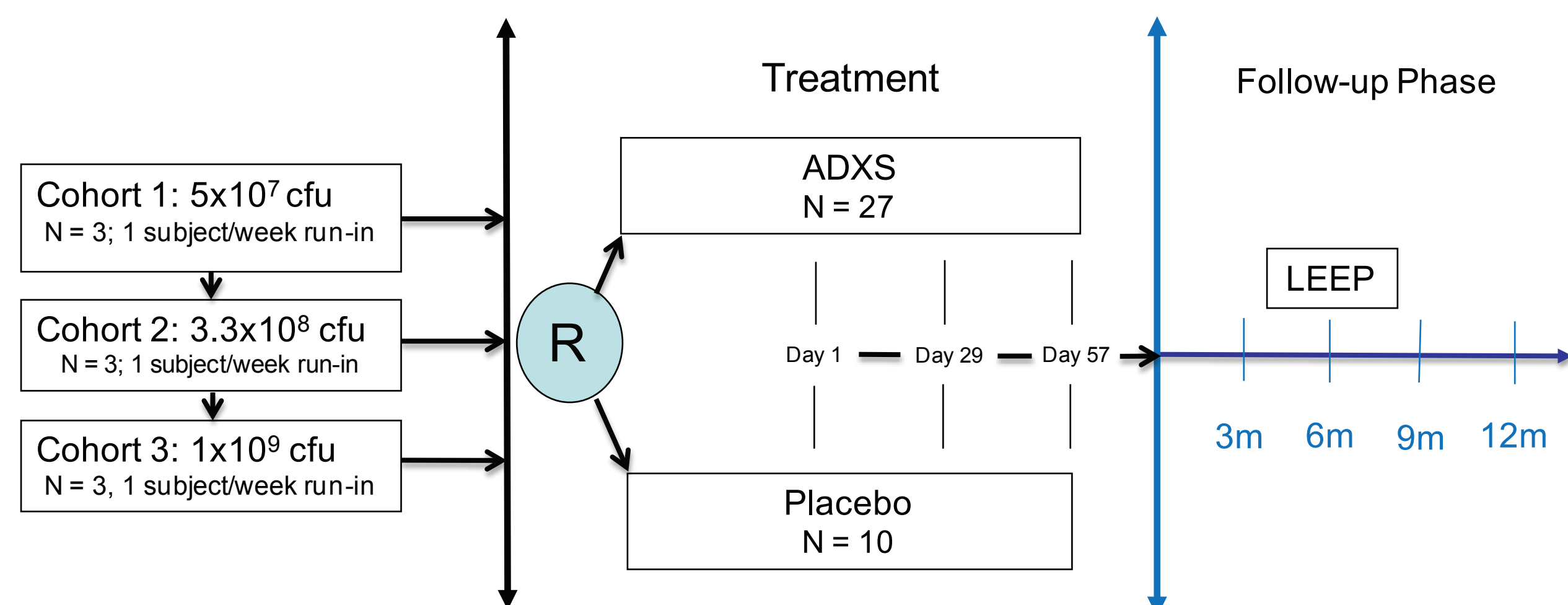
- Efficacy endpoints:

- Histologic regression of CIN 2/3 disease to Grade 1 or normal at the time of surgery
- The elimination or significant reduction in viral titers
- Colposcopic examination results

- Immunogenicity endpoints:

- Serum cytokines associated with dosing
- HLA typing of subjects for Class I and II antigens
- Immunohistochemical characterization of lesion infiltrating cells in active versus placebo treated subjects
- Genomic expression of relevant gene products known to be associated with a therapeutic immune response
- Evaluation of HPV reactive T cells by ELISpot and/or ELISA

**Trial Design: Lm-LLO-E7-07
CIN 2/3 (n = 120)**



Lm-LLO-E7-07 is designed to evaluate the safety and efficacy of 3 doses of ADXS-HPV (5x10⁷ cfu, 3.3x10⁸ cfu, and 1x10⁹ cfu). Each cohort consists of 30 active and 10 placebo subjects. Prior to randomization, an inpatient vanguard group of 3 subjects are doses 1 week apart to monitor safety. The remaining 27 active treatment subjects and 10 placebo subjects are randomized in each dosage group. The active treatment group receive ADXS-HPV at one of three dose levels given as 3 vaccinations separated by 4 weeks with an oral antibiotic regimen on day 3 subsequent to each dose. The control group receive placebo treatment for the same observation interval as the active treatment group. Subjects will be evaluated at screening, on days 1, 29, and 57 at the time of each dose administration, at 3 months, and at the time of LEEP surgery at 6 months. A final 1 year assessment will be made 6 months after LEEP.

**Safety Summary: Lm-LLO-E7-07
(As of October 25, 2011)**

35 subjects have been administered 92 doses of ADXS-HPV at 5x10⁷ cfu

- 19 subjects (54%) have reported 54 AEs
- 10 subjects (20%) report 32 AEs related/possibly related
 - 27 flu-like symptoms
 - 9 nausea (in 7 subjects)
 - 6 fever (in 4 subjects)
 - 5 chills (in 2 subjects)
 - 3 fatigue (in 2 subjects)
 - 3 vomiting (in 2 subjects)
 - 1 each headache, dizziness, neck pain, increased heart rate, sweats, body ache

4 subjects have been administered 4 doses of ADXS-HPV at 3.3x10⁸ cfu

Summary of Clinical Safety

- In Phase 2 trials: over 230 doses (5x10⁷ cfu - 1x10⁹ cfu) of ADXS-HPV administered to >125 patients safely.

- AEs comprised of flu-like symptoms

- Acute onset
- Resolve with symptomatic treatment (NSAIDs, anti-cholinergics)
- No evidence of infectious disease; antibiotics not required (antibiotics given prophylactically at 72 h)
- No delayed or cumulative toxicities observed
- No SAEs related to study drug

- In the Phase 1 trial: Dose Limiting Toxicity

- 30 doses (1x10⁹ - 1x10¹⁰ cfu) of the HPV16-E7 construct administered to 15 patients (without pre-medication)
- DLT diastolic hypotension (1x10¹⁰ cfu) (resolved with fluids). A function of the number of infectious particles.

Lm-LLO-E7-015

A randomized, active therapy controlled Phase 2 study to assess the safety and efficacy of ADXS11-001 +/- Cisplatin as 2nd line therapy for the treatment of recurrent cervix cancer.

- ~15 Sites, India only

- N=110:

- Women 18-60 years of age with recurrent, metastatic cervix cancer who have failed prior cytotoxic therapy
- ECOG performance status ≤ 2
- Two groups of 55 patients receiving ADXS11-001 or ADXS11-001 + cisplatin
 - ADXS11-001 given as 3 iv infusions one month apart, each dose followed by antibiotic at 3 days post-dosing
 - ADXS11-001 as an iv infusion followed by antibiotic beginning 3 days post-infusion, followed after 4 weeks by 5 weekly iv administrations of cisplatin, followed 4 weeks later by 3 iv infusions of ADXS11-001 at 4 week intervals with antibiotic beginning 3 days after each ADXS11-001 dose.

- Primary objective:

- To determine the safety and efficacy of ADXS11-001 +/- cisplatin

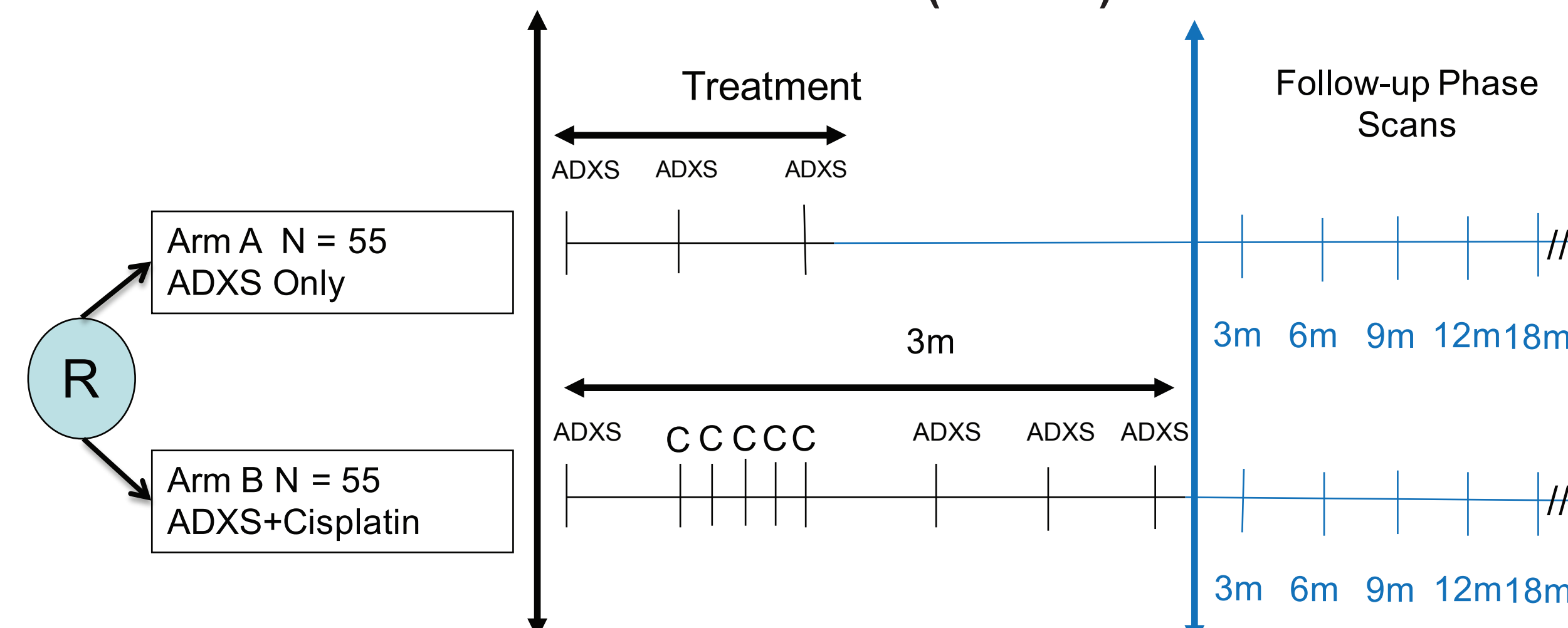
- Efficacy endpoints:

- Primary efficacy endpoint is overall survival
- Secondary efficacy endpoints are RR (RECIST) and PFS

Immunogenicity endpoints:

- Initial determination of HPV species and HLA typing
- At scheduled intervals, peripheral serum IFN-γ, IL-2, and IL-4 will be determined, and peripheral T cells will be assessed for their response and secretion of IFN-γ, IL-2, and IL-4.
- In patients for whom pre & post treatment biopsies can be obtained, infiltrating T cell phenotypes will be determined, including Tregs.

**Trial Design: Lm-LLO-E7-015
2nd line cervical (n = 110)**



Lm-LLO-E7-015 is designed to evaluate the safety and efficacy of ADXS-HPV +/- cisplatin. The ADXS-HPV only group receives ADXS-HPV (1x10⁹ cfu) given as 3 iv infusions one month apart, each dose is followed by antibiotic at 3 days post-dosing. The ADXS-HPV + cisplatin arm receive ADXS-HPV as an iv infusion (1x10⁹ cfu), followed by antibiotic beginning 3 days post-infusion, followed after 4 weeks of 5 weekly iv administrations of cisplatin (40mg/m²), followed 4 weeks later by 3 iv infusions of ADXS-HPV at 4 week intervals with antibiotic beginning 3 days after each ADXS11-001 dose.

Safety will be assessed at every visit. Efficacy will be determined from scans before the first dose of treatment and at 3, 6, 9, 12, and 18 months after treatment begins.

**Safety Summary: Lm-LLO-E7-015*
(As of October 25, 2011)**

65 subjects have been received 140 doses of ADXS11-001 at 1x10⁹ cfu

- 44 subjects (37%) have reported 217 AEs
- 27 subjects (27%) report 65 AEs related/possibly related
 - 33 chills/rigors/shivering (in 22 subjects)
 - 8 fever (in 6 subjects)
 - 4 vomiting (in 4 subjects)
 - 4 leucopenia (in 2 subjects)
 - 3 nausea (in 3 subjects)
 - 3 headache (in 3 subjects)
 - 1 each septicemia, weight loss, oral mucositis, mild flu-like symptoms, lymphocyte count decrease, hyponatremia, eosinophil count increase, constipation, candida, bacterial peritonitis, absolute neutrophil decrease
- Acute renal failure in 3 patients (2%)

*This is a terminal population with many disease related AE.

CONCLUSIONS

In clinical trials to date (P1 and P2), 119 subjects have received 266 doses of ADXS-HPV. ADXS-HPV can be safely administered to healthy young subjects as well as patients with advanced cancer. AEs are acute, non-cumulative, transient, and consist of flu-like symptoms that respond to symptomatic treatment or resolve on their own. No SAEs related to ADXS-HPV. In Lm-LLO-E7-015 (cervical cancer) all 4 patterns of therapeutic immune response have been seen, and the study is ongoing. Clinical trials are ongoing to evaluate the activity of this agent across the spectrum of diseases caused by HPV transformation from CIN 2/3 (US) through locally advanced cervical cancer (GOG) to advanced recurrent cervical cancer (India). ADXS-HPV is also being evaluated in a Phase 2 trial in HPV positive head and neck cancer (CRUK).