AIM2CERV: a randomized phase 3 study of adjuvant AXAL immunotherapy following chemoradiation in patients who have high-risk locally advanced cervical cancer (HRLACC)

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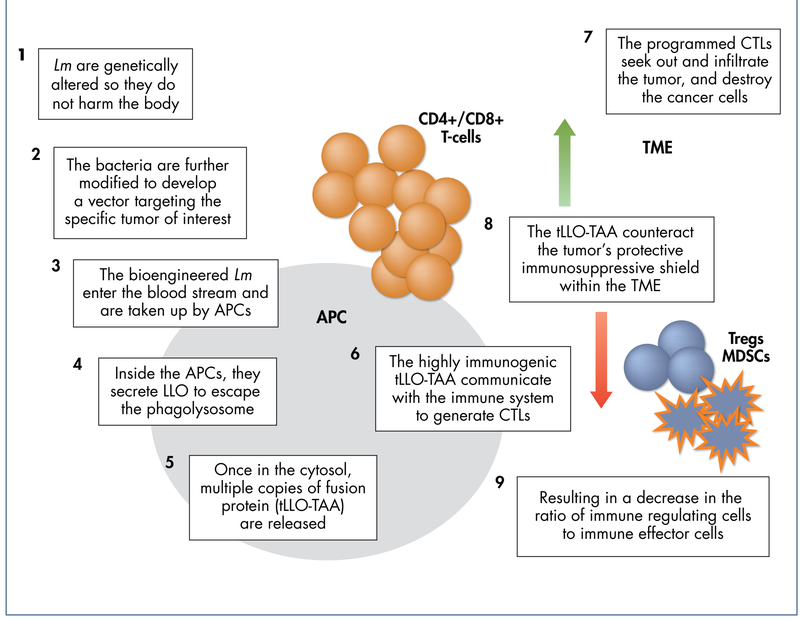
INTRODUCTION

- Cervical cancer is the fourth most common cancer in women, accounting for 7.5% of all female cancer deaths worldwide[1]; the majority of these deaths occur in women with LACC (International Federation of Gynecology and Obstetrics [FIGO] stages IIB–IVA).[2]
- Despite the widespread adoption of cisplatin-based concurrent chemotherapy and radiation therapy (CCRT) as the standard of care for LACC,[3] a significant proportion of patients will have disease recurrence and ultimately die from their disease.[4] Four-year survival rates decrease with stage of disease (eg, II: 64.2%–65.8% and III: 37.7%–51.4%).[4]
  - Therapies for patients with HRLACC are significant unmet need.[3]
- The most common cause of cervical cancer is persistent infection with high-risk types of human papillomavirus (HPV); in particular, HPV 16 and HPV 18 account for 70% of precancerous cervical lesions and cervical cancers.[5]
  - Therapeutic strategies targeting this virus may be useful for improving survival in cervical cancer.
- Axalimogene filolisbac (AXAL or ADXS11-001) is a live, irreversibly attenuated Listeria monocytogenes (*Lm*)-listeriolysin O (LLO) immunotherapy developed for the treatment of HPV-associated cancers[6-8] (**Figure 1**).
  - AXAL secretes an HPV E7 tumor antigen as a truncated LLO-E7 fusion protein (tLLO-HPV-E7) that is taken up by antigen-presenting cells (APCs).
  - Uptake of tLLO-HPV-E7 by APCs induces HPV-specific cytotoxic T-cell generation and reduces immune tolerance in the tumor microenvironment.
- Clinical studies have demonstrated that AXAL is well tolerated, safe, and effective in women with advanced cervical cancer[9] and with recurrent/metastatic cervical cancer.[10-12]
- Recently, AXAL received US Food and Drug Administration (FDA) Fast Track Designation for the treatment of HRLACC.[13]
- The present phase 3 study was initiated to evaluate the efficacy of AXAL as an adjuvant treatment for HRLACC in patients who have received cisplatin-based CCRT with curative intent.

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, regulatory T cell.

OBJECTIVES

- The primary objective is to compare disease-free survival (DFS) of AXAL to placebo administered following CCRT with curative intent in patients with HRLACC.
- Secondary objectives are to assess the safety and tolerability and evaluate overall survival (OS).
- Exploratory objectives will determine if there is an association between HPV subtypes and DFS/OS and patient-reported outcomes (PROs).

METHODS

STUDY DESIGN

- This is a phase 3 double-blind, placebo-controlled, multinational, multicenter, randomized study (NCT02853604) being conducted under a Special Protocol Assessment agreement with the FDA.
  - The study will enroll approximately 450 patients at 150 sites.
- Key patient eligibility criteria are described in **Table 1**.

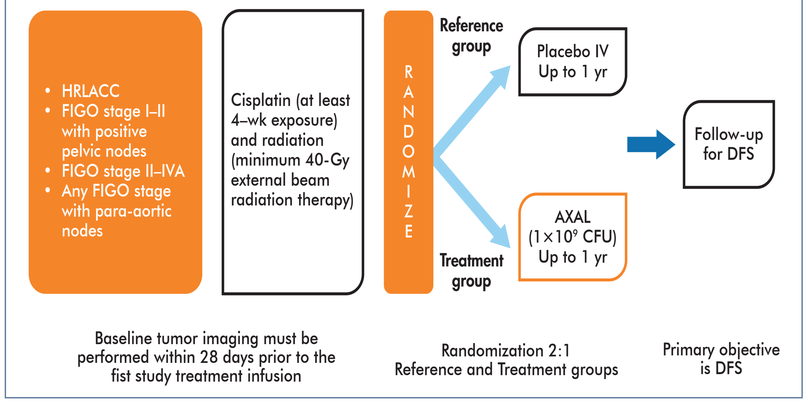
Table 1. Key patient eligibility criteria

Key inclusion criteria
Adult female patients (≥18 years)
Histologically confirmed squamous cell, adenocarcinoma, or adenosquamous carcinoma of the cervix, and ≥1 of the following • FIGO stage IB2, IIA2, IIB with pelvic lymph node metastases criteria, as defined by 1 of the following: a) biopsy-proven pelvic nodes, b) ≥2 positive pelvic nodes by MRI/CT ≥1.5-cm diameter, or c) ≥2 positive pelvic nodes by PET with SUV ≥2.5 • All FIGO stage IIIA, IIIB, IVA • Any FIGO stage with para-aortic lymph node metastases criteria, as defined by 1 of the following: a) biopsy-proven para-aortic node(s), b) ≥1 positive para-aortic node(s), by MRI/CT >1.5-cm diameter, or c) ≥1 positive para-aortic node(s) by PET with SUV ≥2.5
Completion of CCRT with curative intent, with • ≥4 weeks of cisplatin treatment and ≥40-Gy EBRT • CCRT completed ≤10 weeks prior to the screening visit
GOG PS 0 or 1
Adequate hematologic, renal, and hepatic function
Key exclusion criteria
FIGO stage IVB
Residual disease following completion of CCRT with curative intent
Histologies other than squamous cell, adenocarcinoma, or adenosquamous carcinoma of the cervix
Implanted medical device(s) that pose a high risk for colonization and/or cannot be easily removed
Underwent previous hysterectomy, or hysterectomy planned as part of the initial cervical cancer therapy
Active autoimmune disease requiring systemic treatment within 3 months prior to first study treatment dose, or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents
Diagnosed with immunodeficiency, or received systemic steroid therapy/immunosuppressive therapy within 7 days prior to first study treatment dose, or received a live vaccine within 30 days prior to first study treatment dose
Received concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for invasive malignan-cy within 2 years prior to first study treatment dose
Known contraindication (sensitivity or allergy) to trimethoprim/sulfamethoxazole and/or ampicillin, known allergy to any component of the study drug(s) formulations
Known clinically active bacterial, fungal, parasitic, or viral infection that requires therapy, or HIV-positive status

CCRT, concurrent chemotherapy and radiation therapy; CT, computed tomography; EBRT, external beam radiation therapy; GOG PS, Gynecologic Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; HIV, human immunodeficiency virus, MRI, magnetic resonance imaging; PET, positron emission tomography; SUV, standard uptake value.

- Patients will be stratified based on the presence of para-aortic lymph metastases (yes vs no/unknown), region (US vs rest of the world), and FIGO stage (stages I–II or III–IV), and randomly assigned (2:1) to AXAL or placebo (**Figure 2**).
- Patients will receive 1 infusion of placebo or AXAL (1×10⁹ colony-forming units [CFU] over 60 minutes) every 3 weeks for 3 doses (weeks 1, 4, and 7) for the first 3 months (induction phase). Thereafter, patients will receive treatment every 8 weeks for 5 doses (weeks 15, 23, 31, 39, and 46) or until disease recurrence (maintenance phase).
- The total treatment period will be approximately 1 year.
- All patients will receive:
  - A pretreatment prophylaxis regimen consisting of nonsteroidal anti-inflammatory drugs (NSAIDs), antihistamines, antiemetics, and histamine H2 receptor antagonists at least 30 minutes prior to each infusion; if needed, additional doses of NSAIDs or antiemetics will be provided on days 1 and/or 2 following the infusion.
  - A 7-day course of oral antibiotic therapy (eg, trimethoprim/sulfamethoxazole or ampicillin) or matching placebo starting 72 hours after each infusion.
- At the completion of study treatment or at the time of study discontinuation, patients will enter a 3-year *Lm* surveillance period to ensure the eradication of *Lm* bacteria. Surveillance will consist of a 6-month course of trimethoprim/sulfamethoxazole, ampicillin, or matching placebo and a 2.5-year follow-up including routine monitoring (every 3 months) of complete blood test, comprehensive metabolic panel, and blood cultures.
  - Antibiotic therapy will begin either 72 hours following the last infusion of study treatment or immediately following study discontinuation.
- Patients will be followed up for disease recurrence/progression after completion of study treatment for a total of 5 years or until death, whichever occurs earlier.
  - Information regarding anticancer treatment(s) and interventions as well as survival following confirmed disease recurrence/progression will be collected.

Figure 2. Study design



CFU, colony-forming units; DFS, disease-free survival; FIGO, International Federation of Gynecology and Obstetrics; HRLACC, high-risk locally advanced cervical cancer; IV, intravenous.

STUDY ASSESSMENTS

- Tumor biopsy will be obtained, when determined to be feasible in the opinion of the investigator, for confirmation of disease recurrence.
- Radiographic tumor assessment will be conducted by contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) at baseline, weeks 12, 24, 36, and 48. During the follow-up period, tumor imaging will be performed every 3 months for the first year, every 6 months for an additional 4 years (or until death).
  - Response Evaluation Criteria In Solid Tumors version 1.1 in this protocol have been modified to assess disease recurrence only when a tumor biopsy could not be obtained.
- Adverse events and laboratory values (including *Lm* surveillance blood cultures) will be assessed at each study visit according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
- An independent data monitoring committee) will periodically evaluate and analyze accrued patient data throughout the study.
- HPV genotyping will be performed at the week 1 visit to evaluate the association between HPV subtypes and DFS/OS.
- PROs will be assessed at baseline, at weeks 12, 24, 36, and 48 after beginning treatment, and then every 3 months for the first year, and every 6 months for an additional 4 years (or until death) during the follow-up period via the Functional Assessment of Cancer Therapy-Cervix Trial Outcome Index (FACT-Cx TOI), PROMIS Cancer Fatigue Short Form 4a, and Brief Pain Inventory single item.

STATISTICAL METHODS

- Efficacy analyses will include all patients enrolled in the study, regardless of their eligibility or compliance with their assigned treatment.
- Safety analyses will include all patients who received at least 1 infusion.
- The study will be considered sufficiently mature for a final analysis when there are at least 184 events, which will provide 85% statistical power for detecting a treatment hazard ratio of 0.620.
  - An interim analysis that will only assess futility will be performed when there is at least one-half the number of DFS events required for full maturity of the study. An O'Brien and Fleming-like spending function will be used.
- The log-rank procedure will be used to evaluate the null hypothesis for the primary endpoint of DFS (Hp:E,DFS).
- Mixed-effects models will be used to estimate and compare the mean FACT Treatment side-effects scores, the mean FACT-Cx Physical Well-Being subscale scores (7 items), and the FACT-Cx TOI (29 items) for the treatment groups.

TRIAL STATUS

- The trial was open for recruitment in September 2016 with an estimated primary completion date of June 2020.

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