Hight-dose treatment with ADSX11-001, a Listeria monoxytheron-microbiolysis in O (Lm-LLO) immunotherapy, in women with cervical cancer: a phase I, dose escalation study

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INTRODUCTION

• Worldwide, cervical cancer is the second most frequent cancer in women, with an estimated 569,000 cases in 2012. Of the estimated 270,000 cervical cancer-related deaths in 2012, 80% occur in low and middle-income countries.
• Obesity is the only modifiable risk factor for cervical cancer, with a very high (32%), with a poor prognosis for patients with advanced disease (5-year survival rate of 15%). There remains no known agent proven to extend survival for long-term patients who are refractory to traditional chemotherapy with or without concurrent radiation.
• The human papillomavirus (HPV) is the primary etiologic agent of cervical cancer. However, HPV infection occurs in 70% of all cervical cancers and precancerous lesions.
• Treatment strategies that target this virus have the potential to improve the survival of patients with recurrent or refractory disease, in particular patients with persistent disease.

• Axalimogene filolisbac (AXAL or ADXS11-001) is a Listeria monocytogenes mutant that is engineered to secrete Listeria monocytogenes listeriolysin O (Lm-LLO). AXAL is being developed for advanced solid tumors and for cervical cancer in high-risk HPV-positive disease.
• AXAL is a live, attenuated, nonpathogenic, bioengineered Lm monocytogenes immunomodulation vector.
• AXAL secretes an HPV16 E7 tumor antigen as a truncated LLO-exposed fusion protein (SLLO-E7) that can induce both innate and adaptive tumor-specific immunity.
• SLLO-E7, when taken up by antigen-presenting cells (APCs), is detected by innate and activates a new population of E7-specific T cells with tumor-specific recognition.
• Within the tumor microenvironment, AXAL simultaneously modifies host-immune system to downregulate the regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC). (Figure 1)
• AXAL has been demonstrated to be well tolerated, safe, and active in women with advanced cervical cancer.
• The study hypothesis is that AXAL will be clinically effective for the treatment of cervical cancer.

• The primary objective of the study was to determine the clinical feasibility of AXAL at a dose higher than the current dose 2 (1×10^9 CFU) and 2 (1×10^10 CFU) (with and without bevacizumab).3

METHODS

STUDY DESIGN AND INTERVENTION

Phase I, open-label, multicenter, dose-escalation study [NCT02146414]

TREATMENTS

• AXAL was provided to patients intravenously in a volume of 250 mL at the National Institutes of Health (NIH) site and at the study investigator site.
• At least 30 minutes prior to AXAL infusion each patient completed a prophylactic regimen consisting of antihistamine, anti- pyretic, corticosteroid and antihypertensive agents. (Figure 1)
• All patients received a 7-day course of oral antibiotic therapy starting 72 hours after each administration of AXAL.
• Dose-escalation occurred according to a 3+3 design to determine the maximum tolerated dose (MTD), maximum tolerated dose, and subsequent recommended Phase 2 dose regimen for dose escalation (Cycle 1: Dose Level 1 and Cycle 2: Dose Level 2).4

PATIENT POPULATION AND TREATMENT EXPOSURE

• Enrollments into Dose Level 1 (n = 1) and Dose Level 2 (n = 3) is complete.

RESULTS

PAIRED SAMPLES COMPARISON AND STATISTICAL TESTS

Table 5: Paired bone densities and anatomical characteristics

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<th>Age (years), range</th>
<th>p-value</th>
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<tr>
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<tr>
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<tr>
<td>Caucasian</td>
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DISCLOSURES