PROTOCOL ADXS001-02

PHASE 3 STUDY OF ADXS11-001 ADMINISTERED FOLLOWING CHEMORADIATION AS ADJUVANT TREATMENT FOR HIGH RISK LOCALLY ADVANCED CERVICAL CANCER: AIM2CERV (Advaxis IMmunotherapy 2 prevent CERVical recurrence)

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PROTOCOL APPROVAL

Protocol Number: ADXS001-02

Title of Protocol: Phase 3 Study of ADXS11-001 Administered Following Chemoradiation as Adjuvant Treatment for High Risk Locally Advanced Cervical Cancer: AIM2CERV

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Approved by:

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Date

Advaxis, Inc.

INVESTIGATOR SIGNATURE PAGE

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Version: 5 Dated 07Dec2020

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by Advaxis, Inc. and GOG prior to seeking approval from the approving Institutional Review Board (IRB)/Ethical Review Committee (ERC).

This study will be conducted in accordance with Good Clinical Practices (GCP), International Conference on Harmonisation (ICH) Guidelines, the Declaration of Helsinki, and local ethical and legal requirements.

Investigator Name:

_____ _____

Signature Date

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Printed Name

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SYNOPSIS

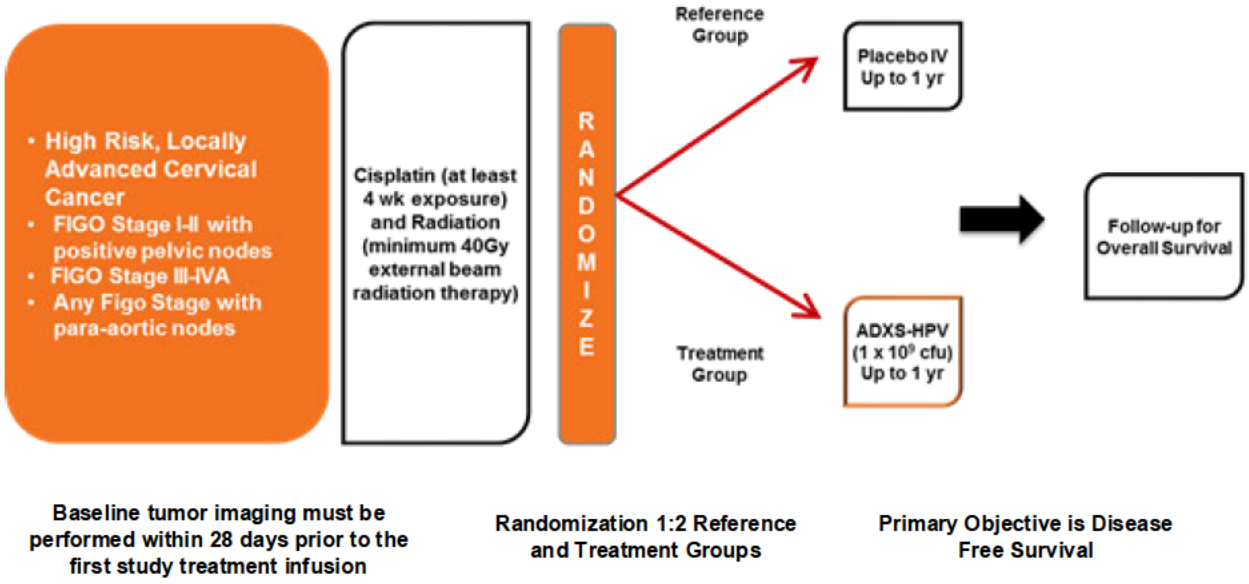
Study Title:	A Phase 3 Study of ADXS11-001 Administered Following Chemoradiation as Adjuvant Treatment for High Risk Locally Advanced Cervical Cancer: AIM2CERV
Study Phase	Phase 3
Clinical Indication	High-risk locally advanced carcinoma of the cervix (HRLACC) following concurrent chemotherapy and radiation therapy. This is a group of patients with a significant unmet need. The estimated probability of disease recurrence or death within 4 years of diagnosis is 50% and the prognosis is very grave for those who experience a recurrence.
Study Type	Interventional
Study Centers	Multicenter, Global
Route of Administration	Intravenous (IV)
Study Blinding	Double blinded, placebo-controlled
Number of Study Subjects	Approximately 450
Estimated Duration of Study	Approximately 55 months of recruitment, 1 year of treatment, and 1 year *Lm* surveillance follow up
Duration of Participation	Approximately 2 years
Reference Treatment Group	Placebo (Arm A)
Experimental Treatment Group	ADXS11-001 (Arm B)
Randomization Ratio	1:2 Arm A to Arm B
Primary Objective	Disease free survival (DFS)
Secondary Objectives	Safety & tolerability Overall survival (OS)
Exploratory Objective	[redacted]
Key Inclusion Criteria	• Subjects with: o Histological diagnosis of squamous cell, adenocarcinoma or adenosquamous carcinoma of the cervix who have undergone definitive therapy with a curative intent* • Subjects may have: o 2014 FIGO-Stage IB2, IIA2, IIB with any of the following pelvic lymph node metastases criteria: ▪ Biopsy proven pelvic node(s) ▪ 2 or more positive nodes by MRI/CT ≥1.5 cm shortest dimension ▪ 2 or more positive pelvic nodes by PET with standard uptake value ≥2.5 OR o All Stage IIIA, IIIB, IVA

	OR o Any FIGO stage with para-aortic lymph node metastases criteria (defined by 1 of the following): ▪ Biopsy proven para-aortic node(s) ▪ 1 or more positive para-aortic node(s) by MRI/CT >1.5 cm shortest dimension ▪ 1 or more positive para-aortic node(s) by PET with SUV >2.5 Subjects must have received definitive therapy with curative intent, which consist of at least 4 weeks of treatment with cisplatin and a minimum of 40 Gy external beam radiation therapy (EBRT). NOTE: Brachytherapy is permitted.
	• Subjects must be: o Age 18 years or older o GOG performance status 0 – 1 o ANC ≥1000 x 10^9/L o Platelets ≥75 x 10^9/L o Bilirubin ≤1.5 x ULN o AST or ALT ≤2.5 x ULN o Serum creatinine or measured creatinine clearance ≤1.5 x ULN o Toxicities resulting from definitive therapy must resolve to ≤Grade 1 prior to randomization, with the exception of peripheral neuropathy (sensory and motor) which must resolve to ≤Grade 2.
Key Exclusion Criteria	• Subjects who have not achieved disease-free status (e.g. no evidence of measurable disease or non-measurable disease per RECIST 1.1) after completion of CCRT administered with curative intent. • Subjects with FIGO stage IVB • Histologies other than described above (neuroendocrine cancers are excluded) • Has undergone a previous hysterectomy (defined as removal of the entire uterus), following neoadjuvant chemotherapy. • Has implanted medical device(s) that pose a high risk for colonization and/or cannot be easily removed (e.g., prosthetic joints, artificial heart valves, pacemakers, orthopedic screw(s), metal plate(s), bone graft(s), or other exogenous implant(s)). NOTE: More common devices and prosthetics which include arterial and venous stents, dental and breast implants and venous access devices (e.g. Port-a-Cath or Mediport) are permitted. Sponsor must be contacted prior to consenting any subject who has any other device and/or implant. • Who are receiving, plan, or anticipate on receiving PI3K or TNFα inhibitors.

	• Has a contraindication (sensitivity or allergy) to trimethoprim/sulfamethoxazole.
Stratification	Region (USA vs Rest of World), para-aortic lymph node metstastes, 2014 FIGO tumor stage
Methodology	Prime and Maintenance Phases This is a double-blind, placebo-controlled randomized study of ADXS11-001 administered in the adjuvant setting after completion of cisplatin-based CCRT in subjects with locally advanced cervical cancer at higher risk for recurrence (HRLACC), or death. The study will enroll subjects with high-risk disease as determined by prognostic factors such as tumor staging, nodal involvement, extent of nodal involvement, and location of nodal involvement. All eligible subjects will have received CCRT administered with curative intent according to institutional/national guidelines as well as meeting the minimum standards defined in the protocol. Subjects must initiate the Screening period within 14 weeks after the completion of CCRT. Baseline radiographic assessments and clinical laboratory assessments must be completed no longer than 28 days prior to and 3 days prior to the first study treatment infusion, respectively. Eligible subjects will be randomized 1:2 to receive either placebo or ADXS11-001 (1×10^9 CFU infused over [redacted]). Subjects will receive 1 infusion of study treatment (placebo or ADXS11-001, 1×10^9 CFU) administered every 3 weeks for 3 doses (Weeks 1, 4 and 7) for the first 3 months. This is called the Prime Phase at the study. Thereafter, subjects will receive study treatment every 8 weeks (Weeks 15, 23, 31, 39, and 47) for a total of 5 doses or until disease recurrence. This is called the Maintenance Phase. Subjects will receive a 7-day course of trimethoprim/sulfamethoxazole (Bactrim) or placebo starting 72 hours following the completion of study treatment administration during the Prime and Maintenance phases. The total treatment period will be approximately 1 year. *Lm* Surveillance Period Subjects will enter a 1-year *Lm* surveillance period beginning at the completion of study treatment or at the time of study discontinuation. This period is intended to help ensure the eradication of *Lm* bacteria in the body. It consists of a 3-week course of trimethoprim/sulfamethoxazole, initiated either 72 hours following the completion of the last dose of study treatment or immediately following study discontinuation. This study period consists of 12 months of follow-up which will involve contacting subjects dosed with ADXS11-001, by phone every 3 months (±1 week) to determine whether they have experienced for several days, the following symptoms that could potentially be associated with delayed listeremia: fever or chills, headache, nausea, confusion or changes in alertness. If listeremia is suspected, the 1-year *Lm* surveillance period also involves blood testing. Upon completing the *Lm* Surveillance period, as part of the End of Study procedures, site staff should educate subjects to contact the site or their primary care provider if they experience any of these symptoms, as applicable, to allow evaluation and treatment for listeremia, if suspected.
Criteria for Evaluation	Efficacy: DFS evaluated using progression-based evaluation methodology every 3 months, beginning 3 months after the first dose for the first 2 years and then every 6 months for the next 4 years for a total of 6 years; and OS

	Safety: assessed at every visit by comparing treatment-related adverse events (AEs); changes in physical examinations, vital signs measurements, clinical laboratory evaluations during the treatment period, and *Lm* surveillance blood cultures and listeremia-related adverse events (AEs) during the follow-up period; an independent Data Monitoring Committee (DMC) will evaluate and analyze accrued subject data periodically throughout the study treatment period.
Statistical Considerations	Statistical Analysis Plan provided as a separate document, is adjusted to assess data collected up to the time of early study termination rather than post 184 events previously planned for full maturity of the study.

Figure 1 Study Schema



1 OBJECTIVES

1.1 Primary Objective & Hypothesis

Objective: To compare the disease-free survival (DFS) of ADXS11-001 to placebo administered in the adjuvant setting following concurrent chemotherapy and radiotherapy (CCRT) administered with curative intent to subjects with high-risk locally advanced squamous, adenosquamous, or adenocarcinoma of the cervix (HRLACC).

Hypothesis: ADXS11-001 administered in the adjuvant setting following definitive therapy with CCRT will significantly improve DFS as compared with placebo.

1.2 Secondary Objectives

- To determine and compare the frequency and severity of adverse events (AEs) as assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for the regimens administered on this study.

- To evaluate the overall survival (OS) of ADXS11-001 administered in the adjuvant setting following definitive therapy of CCRT in subjects with HRLACC.

1.3 Exploratory Objective

[redacted]

2 BACKGROUND & RATIONALE

2.1 Background

2.1.1 Locally Advanced Cervical Cancer

Cervical cancer is the fourth most common cancer and the most common cause of mortality in women worldwide with 528,000 new cases reported annually, and an estimated 266,000 deaths in 2012 [1]. Early detection by routine screening of pre-neoplastic lesions has led to a large decline in mortality from cervical cancer in the Western hemisphere; however, cervical cancer is still the leading cause of cancer death in women worldwide and a significant cause of cancer death for poor and for uninsured women in the US. Approximately 13,000 cases of invasive cervical cancer FIGO stages IA-IVB are diagnosed annually in the US, 30% of which will present with bulky or locally advanced disease defined by FIGO (FIGO stage IIB-IVA) at the time of diagnosis that is not amendable to high cure rates with surgery or radiation therapy [2, 3].

Based on the results of multiple Phase 3 studies [4-8], the well-established standard of care for the treatment of locally advanced cervical cancer (LACC) is concurrent cisplatin-based CCRT [9]. Despite the widespread adoption of CCRT, a significant proportion of subjects will recur and ultimately die from their disease. Five-year survival rates decrease with stage of disease (e.g., IA~100%, IB2 and IIB ~50-75%; III ~30-50%, and IV ~15%). While FIGO staging is a useful predictor of both DFS and OS in subjects with LACC [10], additional factors such as presence or absence of lymph node metastases have emerged as more accurate predictors of prognosis. Taking into account FIGO stage and the presence or absence of lymph node metastases, we are better able to identify subjects who are at high risk for recurrence and for whom new therapeutic options are needed.

2.1.2 Relationship between Cervical Cancer and Human Papilloma Virus

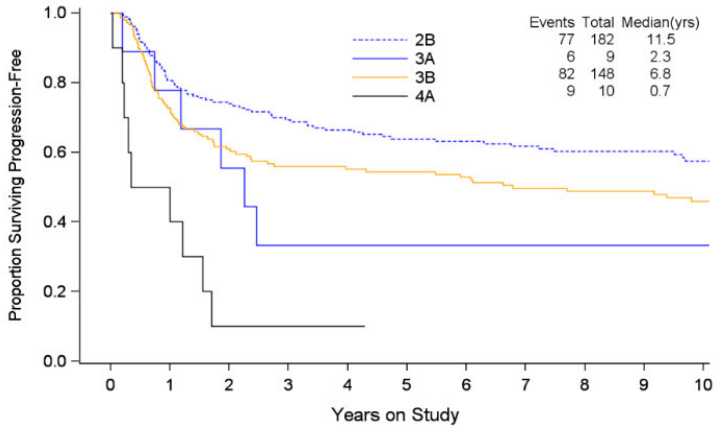
Squamous cell carcinoma of the cervix is largely the result of persistent infections with high-risk types of human papillomavirus (HPV). Ninety-five to 98% of cervical cancers have detectable amounts of HPV DNA. There are multiple high-risk HPV types and more than half of cervical cancer is caused by infection with the oncogenic HPV-16 [11]. HPVs inhabit

the squamous epithelium of the mucocutaneous surface and often infections are either harmless or cause minor subclinical disease. Cervical HPV infections are largely immunologically quiescent, but it is clear that the immune system can be effective in eliminating HPV infected cells in healthy people. Nevertheless, a significant percentage of women are not protected against cervical cancer that occurs after HPV infection with a number of different types, possibly owing to the inability to mount an effective immune response to the virus.

2.1.3 Rationale for Study and Selected Subject Population

Despite the widespread adoption of CCRT, a significant proportion of subjects will recur and ultimately die from their disease (5-year survival: IA~100% IB2 and IIb~50-75%; III~30-50%, and IV~15%) [10]. For example, in GOG-120, the probability of surviving progression-free decreased with increasing stage. As shown in (Figure 2), an analysis of only those subjects from GOG-120 treated with cisplatin-based chemotherapy and radiotherapy, reveals that the estimated probability of surviving recurrence-free for at least 3 years is 69%, 33%, 56% and 10% for subjects with stage 2B, 3A, 3B and 4A disease, respectively.

Figure 2 Kaplan Meier (KM) PFS curves by FIGO stage (GOG-120)

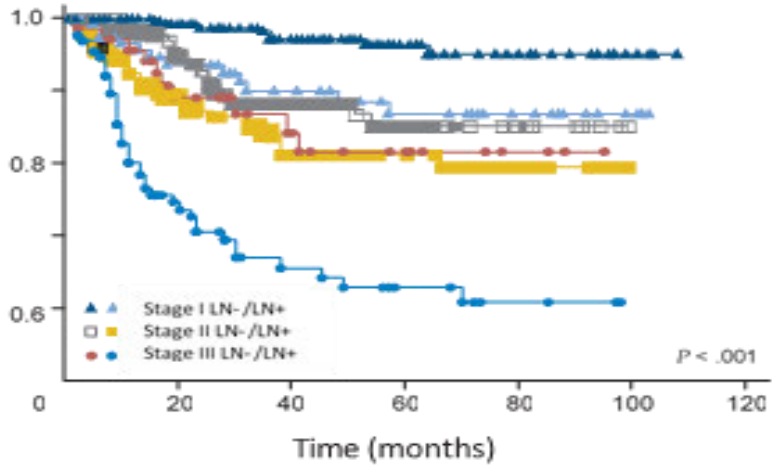


While FIGO staging is a useful predictor of both PFS and OS in subjects with LACC [10], lymph node metastases is the most important prognostic factor in early stage cervical cancer [12-15].

In subjects with advanced cervical cancer who are surgically staged and then treated with radiotherapy, 5-year PFS was 57% for node-negative subjects but decreased to 34% and 12% for subjects with pelvic and para-aortic lymph node (PALN) metastases, respectively [16]. An additional study evaluated 560 subjects with cervical cancer who underwent fluorodeoxy-glucose positron emission tomography (FDG-PET) lymph node staging. Treatment included surgery alone, surgery and postoperative radiation therapy, and definitive radiation or combination radiation and chemotherapy. Overall, 47% of subjects had lymph node involvement by FDG-PET at diagnosis. The frequency of lymph node metastasis increased

with clinical stage and was similar to that in historical surgical series. Within a stage, subjects with PET-positive lymph nodes had significantly worse disease specific survival than those with PET-negative lymph nodes (P<0.001) (Figure 3) [17].

Figure 3 KM disease-specific survival divided by FIGO and PET lymph node status



stage I, PET negative (dark blue triangle); stage I, PET positive (light blue triangle); stage II, PET negative (gray square); stage II, PET positive (gold square); stage III, PET negative (red circle); and stage III, PET positive (blue circle)

Further evaluation of standard uptake value (SUV) revealed important differences in the degree of "positivity." An analysis of 130 subjects with FIGO stage IB to IIA was undertaken to better understand the utility of pre-operative FDG-PET to predict recurrence in this population. Receiver operating characteristic (ROC) analysis identified that pelvic lymph nodes with a SUV $\geq$2.36 as the most significant cut-off value for predicting recurrence. Univariate analyses showed a significant association between recurrence and SUV_{LN} (P=0.001).

Finally, the presence of PALN metastases has been associated with even poorer prognosis. The percentage of LACC subjects with PALN metastases ranges from 2%-21% and is associated with FIGO disease stage [18]. An analysis of recurrence-free survival (RFS) and disease-specific survival based on location of nodes by stage reveals that subjects with PALN metastases demonstrate inferior survival to subjects with pelvic nodes (Figure 3) [17].

The FIGO staging system is sub-optimal towards accurately assessing the relative risk of recurrence in subjects with LACC because it does not take into account the presence or absence of lymph node metastases. Because of the importance of lymph node metastases, the National Comprehensive Cancer Network (NCCN) guideline recommends that the initial work-up of subjects with LACC include assessment of nodal disease by technologies such as computer tomography (CT), PET and/or magnetic resonance imaging (MRI). Because of the superiority of PET to MRI and/or CT in detecting nodal metastasis, the US Centers for Medicare and Medicaid Services has issued a national coverage determination paying for FDG-PET imaging for the detection of pretreatment metastases (e.g., staging) in newly

diagnosed cervical cancer subsequent to conventional imaging that is negative for extra pelvic metastasis [19].

As noted above, subjects with nodal disease, either pelvic or para-aortic, and subjects with FIGO stage III and IV represent a subset of subjects with LACC who are at greatest risk for recurrence and death from the disease and represent the population of LACC with the highest unmet need. Therefore, by restricting the study population to high risk disease, as determined by conventional and accepted diagnostic standards, we are focusing our evaluation of ADXS11-001 on those subjects who would have the highest potential to benefit and where the benefit/risk ratio is acceptable for treatment with experimental therapies.

2.1.4 ADXS11-001 Immunotherapy

ADXS11-001 is a live attenuated *Listeria monocytogenes* (*Lm*) bacteria bioengineered to secrete an antigen-adjuvant fusion protein (tLLO-HPV-E7) consisting of a truncated fragment of the listeriolysin O (tLLO) fused to the full length E7 peptide of HPV-16.

2.1.5 ADXS11-001 Mechanism of Action

ADXS11-001 is rapidly taken up by antigen presenting cells (APC) within the subject. This causes activation of the APC and results in a multi-factorial stimulation of innate immunity. To the subject, this activation can manifest as flu-like symptoms or symptoms associated with cytokine release syndrome (CRS) that occur during or in the hours immediately following administration. Once inside the APC, ADXS11-001 can escape the phagolysosome into the cytoplasm where it secretes the HPV-E7-tLLO fusion protein. This peptide, along with other *Lm* peptides, is very rapidly ubiquitinated and transported to the proteasome where the peptides are broken down and cross-presented through major histocompatibility complex (MHC) class 1 and class 2 pathways. This cross-presentation, in immunologic context of responding to a “perceived” acute infection, stimulates the development of adaptive immunity culminating in HPV-specific effector T-cells that can infiltrate into the tumor microenvironment (TME) and destroy tumor cells immunologically.

Advaxis *Lm*-LLO immunotherapies have broad effects on the immune system and the ability to neutralize mechanisms of immune tolerance. These *Lm*-LLO immunotherapies take advantage of the ability of *Lm* to present target antigens in the cytoplasm of APCs that generate a target-specific T-cell immunity. High avidity T-cells are generated where possible, but when they are not, *Lm* stimulates an up-regulation of T-cell responses to sub-dominant epitopes. Advaxis *Lm*-LLO immunotherapies secrete tumor peptides fused to LLO from multiple copies of plasmids. This increased LLO secretion triggers endocrine and exocrine signaling of the immune system that results in a relative reduction in the number and function of regulatory T-cells and myeloid-derived suppressor cells (MDSC) in the TME which enables tumor cell killing, even when the T-cells are of lower avidity. Tumor antigen specific T-cell immunity generated in the context of *Lm*-LLO immunotherapies can be effective even when targeting self-antigens or viral targets that are partially cross reactive. Preclinical and clinical evidence [20] have shown that treatment with ADXS11-001 has anti-tumor activity

against multiple types of high-risk HPV, including cross-reactivity activity where there are minor differences in HPV E7 T-cell epitopes.

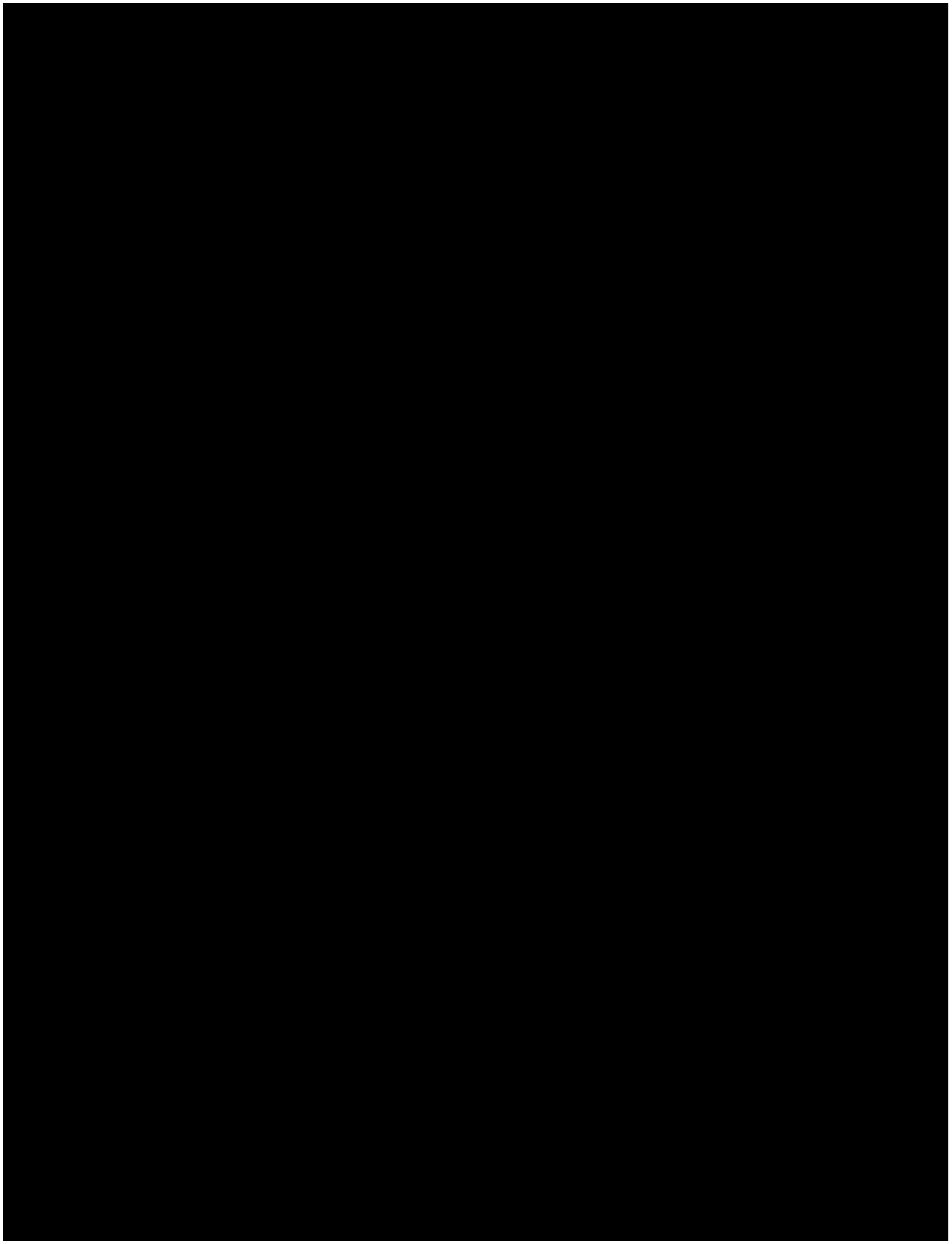
As an investigational drug product, ADXS11-001 has no direct effect on the tumor tissue but is designed to stimulate the subject's own immune system to generate an effective immune response targeting the tumor-associated antigen like HPV-E7.

2.1.6 Preclinical and Clinical Study Data

Refer to the Investigator's Brochure (IB) for detailed preclinical and clinical data.

2.1.7 Summary of Safety of ADXS11-001

Clinical investigation of ADXS11-001 is ongoing. Additionally, because ADXS11-001 shares the same attenuated *Lm* parental strain, vector backbone, and mechanisms of action with other *Lm*-based immunotherapies, a description of all clinical studies evaluating Advaxis' *Lm*-based immunotherapies is provided.



2.1.7.1 Biofilm-Associated Bacteremia

ADXS11-001 has been attenuated over [redacted] more in comparison to the wild-type (wt)-*Lm*. [redacted]

ADXS11-001 bacteremia (listeremia) is confirmed only after isolation of *Lm* from a normally sterile site, such as blood or spinal fluid (in the setting of nervous system involvement). Stool samples are of limited use as ADXS *Lm* strains are not shed. Listeriosis (as opposed to listeremia with attenuated *Lm*) is a systemic organ infection caused by invasive *Lm* infection and is highly unlikely to occur during study treatment due to the method of attenuation used in the Advaxis *Lm* platform. In a Phase 1 clinical study, in the absence of antibiotics, *Lm* was rapidly cleared from the blood. [redacted]

wt-*Lm* is known to form and persist within biofilms especially on medical devices despite antibiotic treatment [22]. Although rare, medical device–related infections such as ventriculo-peritoneal shunt infection, peritoneovenous shunt infection, and prosthetic joint infection have been reported after systemic listeriosis caused by wt-*Lm* [23-26]. ADXS11-001 is highly sensitive to antibiotics such as ampicillin and sulfamethoxazole/trimethoprim which can be an effective treatment regimen for listeria infection. This systemic organ infection caused by wild-type, invasive *Lm*, is highly unlikely to occur during study treatment with Advaxis *Lm* constructs due to the method of attenuation. However, subjects with a fixed medical device may be at risk for ADXS11-001 attachment to the surface of the device by establishing a biofilm. Therefore, subjects with implanted medical device(s) that pose a high risk for colonization and/or cannot be easily removed are excluded from this study. In addition, all subjects, will receive a course of oral antibiotics beginning on Day 4 (approximately 72 hours) after each dose of ADXS11-001 and for 3 weeks following the last dose of ADXS11-001 to help ensure the clearance of the ADXS11-001 bacteria. In addition, as the PI3K signaling pathway may be directly involved in the regulation of TNFα production, inhibition of the PI3K pathway may block the TNFα-mediated signaling pathway that could reduce resistance to bacterial infections [27, 28].

In the Phase 1 Lm-LLO-E7-01 study, in the absence of antibiotics administered to assist in *Lm* clearance following the completion of each dose administration, the attenuated bacteria *Lm* was shown to be rapidly cleared from the blood. No *Lm* bacteria was detected in the blood of any subject beyond 48 hours post-dosing in doses of up to 1 x 10^{10} CFU [21]. Importantly, there has not been any report of person-to-person transmission associated with use of *Lm*-based therapy in completed or ongoing clinical studies [21].

[redacted]

[redacted]

2.1.8 Summary of Efficacy for ADXS11-001 Studies in Cervical Cancer

2.1.8.1 Lm-LLO-E7-01: Phase 1 Experience

[redacted]

[redacted]

2.1.8.2 Lm-LLO-E7-15: Phase 2 Study of ADXS11-001 vs ADXS11-001 and Cisplatin in Recurrent, Refractory Cervical Cancer

[redacted]

[redacted]

2.1.8.3 GOG-0265: Phase 2 Evaluation of ADXS11-001 in Recurrent, Refractory Cervical Cancer

[redacted]

2.1.9 Rationale for ADXS11-001 Dose Selection/Regimen/Modification

The dose regimen for both placebo and ADXS11-001 consists of a Prime Phase followed by a Maintenance Phase:

- Prime Phase = 1 dose administered q3 weeks for a total of 3 doses followed by;
- Maintenance Phase = 1 dose administered q8 weeks for a total of 5 doses

Those subjects who complete the 12-month treatment period (Prime + Maintenance Phases) may receive a total of 8 doses of ADXS11-001 at 1 x 10^9 CFU or placebo.

The recommended Phase 2 dose and the Prime Phase schedule were determined by safety and efficacy results from the Phase 1 and 2 studies (described in Section 2.1.8.1 and 2.1.8.2, respectively). The Maintenance Phase of the study was included based on the 2 fundamental actions of *Lm*-LLO immunotherapy; (1) the generation of antigen specific lymphocytes; (2) and a reduction in the immune tolerance of the TME resulting from a reduction in the relative percentage and immune-suppressive function of Tregs and MDSCs in the TME. [redacted] In addition, the beneficial reduction of immune tolerance within the TME, attributable to the secretion of LLO, decreases as well. It is not known how long this effect persists after a single treatment with ADXS11-001, but clinical data suggest that this effect is not permanent. [redacted] Furthermore, a completed study in the adjuvant treatment of canine osteosarcoma demonstrated that after 2 months the antigen-specific T-cell response returns to baseline and that doses administered every 2 months were able to maintain elevated levels of T-cells [29]. Based on the previous studies completed in LACC the events of progression or recurrence, particularly in subjects with high risk disease, often occur within the first 12 months so therefore the Prime and Maintenance Phase dosing over a 12-month treatment period is hypothesized to be sufficient and able to potentially provide additional benefit to the subject.

2.2 Rationale for Endpoints

2.2.1 Efficacy Endpoints

The primary endpoint for this study is DFS measured from the time of randomization to recurrence or death. DFS was selected as the primary endpoint since only subjects who achieve disease-free status without evidence of measurable or non-measurable disease after definitive CCRT are eligible to participate.

DFS is the appropriate primary endpoint for this study based on the eligible study population because it is closely aligned with progression-free survival as a reliable surrogate endpoint for OS. An evaluation of PFS and OS of 14 randomized studies conducted in HRLACC between 1999 and 2014 is shown in (Table 2). In the 9 studies where both PFS and OS were available, 8 demonstrated that PFS and OS were closely correlated. PFS is also believed to be a more accurate endpoint and one that has been used as the primary endpoint for many studies in HRLACC. The RECIST 1.1 criteria which will be used in this study have been modified to assess disease recurrence only.

Table 2 Randomized Studies Evaluating Concomitant Chemoradiation in Cervical Cancer

	Treatments		Stage of Disease	No. of Subjects	PFS HR (95% CI)	OS HR (95% CI)
	Control	Experimental				
Thomas-1998	RT	RT+5FU	Ib-IVa	234	0.49 (0.25-0.97)	NA
Whitney-1999	RT+Hyd	RT+Cis+5FU	IIb-IVa	368	0.79 (0.60-1.04)	0.74 (0.55-0.99)
Rose-1999 a	RT+Hyd	RT+Cis	IIb-IVa	353	0.57 (0.42-0.78)	0.61 (0.44-0.85)
Rose-1999 b	RT+Hyd	RT+Cis+5FU+Hyd	IIb-IVa	350	0.55 (0.40-0.75)	0.58 (0.41-0.81)
Keys-1999	RT	RT+Cis	Bulky Ib	369	0.51 (0.34-0.75)	0.54 (0.34-0.86)
Roberts-2000	RT	RT+MitoC	Ib2-IVa	160	NA	NA
Brundage-2002	RT	RT+Cis	Ib-IVa	259	NA	1.10 (0.75-1.62)
Lorvidhaya-2003	RT	RT+MitoC+5FU	IIb-IVa	475	NA	NA
Eifel-2004	RT	RT+Cis+5FU	Ib-IVa	389	0.49 (0.36-0.66)	0.48 (0.36-0.66)
Lanciano-2005	RT+Cis	RT+5FU(PVI)	IIb-IVa	316	1.29 (0.93-1.80)	1.37 (0.96-1.97)
Duenas-Gonzalez-2011	RT+Cis	RT+Cis+Gem	IIb-IVa	515	0.68 (0.49-0.95)	0.68 (0.49-0.95)
Nagy-2012	RT+Cis(wkly)	RT+Cis(q3wk)	IIb-IIIb	326	NA	NA
DiSilvestro-2014	RT+Cis	RT+TPZ	Ib2-IVa	379	1.06 (0.65-1.71)	1.17 (0.65-2.11)
Sugiyama-2014	RT+placebo	RT+Z100	IIb-IVa	249	0.86 (0.57-1.29)	0.65 (0.40-1.04)

The utilization of DFS as the primary endpoint in this study will more efficiently evaluate the treatment effect and clinical benefit while limiting the number of study participants and reducing the time to reach an overall study conclusion. Overall survival will be evaluated as a secondary endpoint.

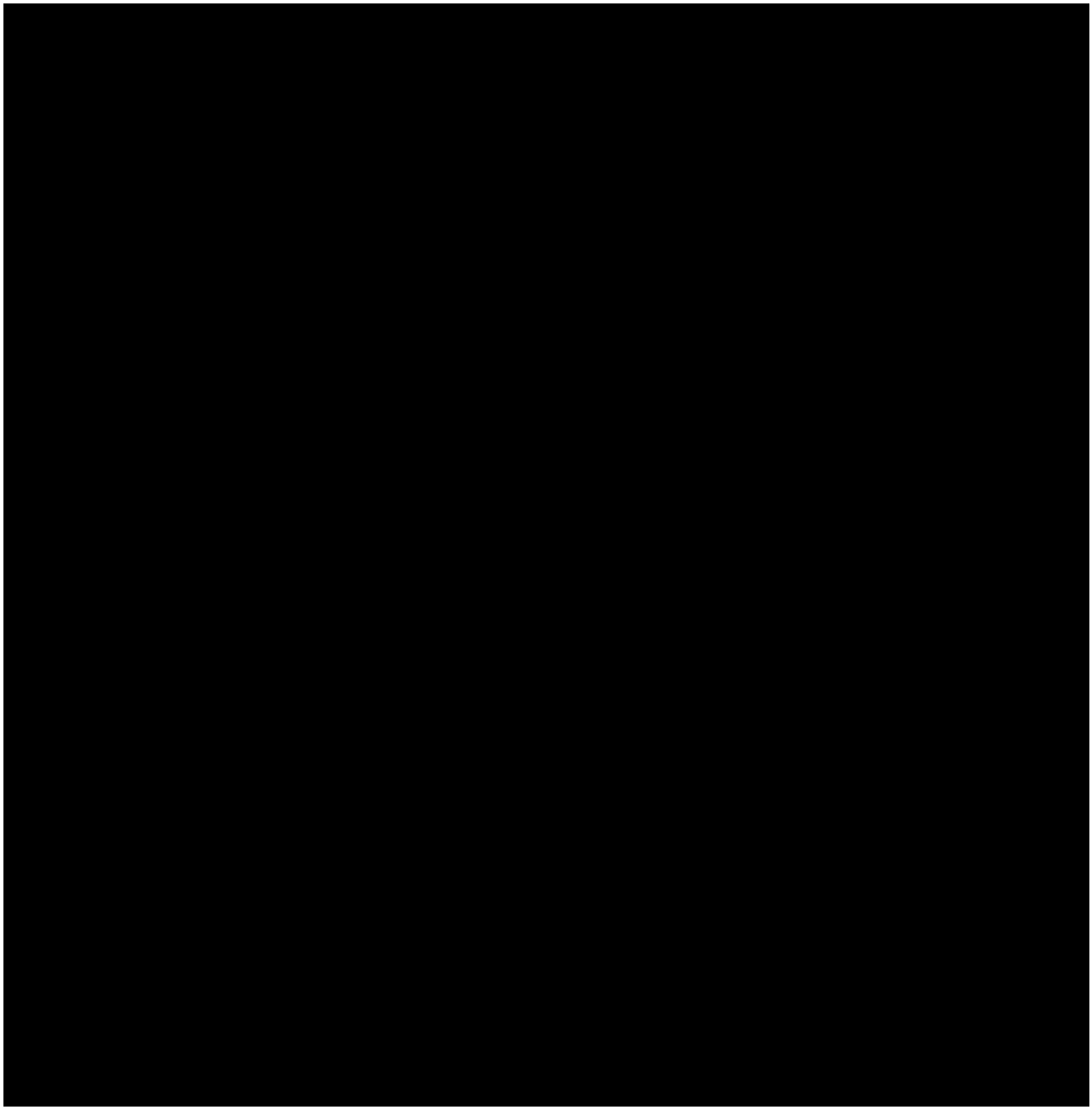
2.2.2 Safety Endpoints

The safety objective of this study is to determine and compare the frequency and severity of AEs as assessed by NCI CTCAE v 4.03 for the regimens administered on this study.

The safety of ADXS11-001 administration will be assessed according to the NCI CTCAE v 4.03 criteria which will be used to define the grades and levels of toxicity. These criteria will be applied to:

- Observation of the infusion site for swelling, irritation, immune reaction or other abnormalities
- Changes from baseline in physical examination findings and vital signs
- Changes from baseline in laboratory parameters (hematology, serum chemistry and urinalysis)
- Evidence of allergic and constitutional symptoms
- Other adverse events

Safety evaluations will be performed throughout the study. All subjects who received at least 1 dose of study treatment (placebo or ADXS11-001) will be evaluated for safety. The AE grade, attribution to drug, date of onset, duration of the event, outcome, impact on study treatment, any concomitant medications, procedures and/or therapies administered will be recorded.



3 SUBJECT ELIGIBILITY AND EXCLUSIONS

3.1 Inclusion Criteria

1. Prior to receiving CCRT with curative intent:

    a. Subjects must have a biopsy confirmed diagnosis of squamous cell, adenocarcinoma, or adenosquamous carcinoma of the cervix. Histologic confirmation of the original primary tumor is required.

b. FIGO Stage IB2, IIA2, IIB with any of the following pelvic lymph node metastases criteria (**2014 FIGO Staging**)

   i. Biopsy proven pelvic node metastases

   ii. 2 or more pelvic node(s) by CT or MRI measuring ≥1.5 cm in shortest dimension

   iii. 2 or more pelvic node(s) by PET with SUV ≥2.5 cm

OR

c. All FIGO Stage IIIA, IIIB, IVA

OR

d. Any FIGO Stage (except stage IVB) with para-aortic lymph node metastases criteria (as defined by any of the following)

   i. Biopsy proven para-aortic node

   ii. 1 or more positive para-aortic node by CT or MRI ≥1.5 cm shortest dimension

   iii. 1 positive para-aortic node by PET with SUV ≥2.5 cm

2. Must have received CCRT with curative intent according to either institutional or national guidelines (e.g., NCCN) with a minimum of at least 4 weeks exposure with cisplatin and a minimum of 40 Gy external beam radiation therapy (EBRT) (NOTE: Carboplatin-based CCRT is permitted; Neoadjuvant therapy is permitted).

3. Completed CCRT, defined as the last dose of radiation (including brachytherapy) or chemotherapy, must be completed by no more than 14 weeks prior to the initiation of the Screening Period (date of signed Informed Consent). Have performance status of 0 or 1 on the GOG Performance Scale

4. Demonstrate adequate organ function as defined in (Table 3). (NOTE: All screening labs should be performed within 3 days of treatment initiation.)

   NOTE: Toxicities resulting from CCRT must resolve to ≤ Grade 1 prior to randomization, with the exception of alopecia. Peripheral neuropathy (sensory and motor) must resolve to ≤ Grade 2.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematologic[a]	
Absolute neutrophil count (ANC)	≥1,000/mcL
Platelets	≥75,000/mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine **OR** Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 x upper limit of normal (ULN) **OR** ≥50 mL/min for subject with creatinine levels >1.5 x institutional ULN
Hepatic	
Serum total bilirubin	≤1.5 x ULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 ULN
AST (SGOT) and ALT (SGPT)	≤2.5 x ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 x ULN (NOTE: Subject is eligible if receiving anticoagulant therapy and PT or INR is within therapeutic range of intended use of anticoagulant therapy.)
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN (NOTE: Subject is eligible if receiving anticoagulant therapy and aPTT is within therapeutic range of intended use of anticoagulants.)

[a] Hematologic requirement cannot be met with the use of recent transfusions, or growth factor support (G-CSF, erythropoietin, etc.) within two weeks prior to treatment initiation.

[b] Creatinine clearance should be calculated per institutional standard.

5. Must be ≥18 years old at time of giving written informed consent

6. Subjects of childbearing potential must have a negative urine or serum pregnancy test prior to the study entry and be practicing 2 methods of study doctor approved birth control or be surgically sterile or abstain from heterosexual activity for the course of the study from Screening through 120 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for >1 year.

7. Cannot be breast-feeding

3.2 Exclusion Criteria

The subject must be excluded from participating in the study if the subject:

1. Has not achieved disease-free status (e.g. no evidence of measurable disease or non-measurable disease per RECIST 1.1) after completion of CCRT administered with curative intent.

2. Has FIGO Stage IVB (e.g. the cancer has spread to other parts of the body [any T, any N, M1]).

3. Has histologies other than squamous cell, adenocarcinoma, or adenosquamous carcinoma of the cervix.

    - Note: neuroendocrine cancers are excluded.

4. Is currently participating in or has participated in a study of an investigational agent or an investigational device within 4 weeks of the first dose of treatment.

5. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of' immunosuppressive therapy within 7 days prior to the first dose of study treatment.

6. Had any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for other invasive malignancy(ies) within 2 years. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

    - Note: Local treatment of isolated lesions for palliative intent (e.g., by local surgery or radiotherapy), basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or ductal carcinoma in situ of the breast that has/have been surgically cured is acceptable.

7. Has an 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. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects who require intermittent use of inhaled steroids or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.

8. Has an active infection requiring systemic therapy. (NOTE: Prior to dosing with study treatment, the subject must be at least 5 half-lives from their last dose of antibiotic.)

9. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for

the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.

10. Has implanted medical device(s) that pose a high risk for colonization and/or cannot be easily removed (e.g., prosthetic joints, artificial heart valves, pacemakers, orthopedic screw[s], metal plate[s], bone graft[s], or other exogenous implant[s]). NOTE: More common devices and prosthetics which include arterial and venous stents, dental and breast implants and venous access devices (e.g. Port-a-Cath or Mediport) are permitted. Sponsor must be contacted prior to consenting any subject who has any other device and/or implant.

11. Currently receiving or have a known plan to receive in the future a PI3K or TNFα inhibitors.

12. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.

13. Has a clinically active bacterial, fungal, parasitic or viral infection which require therapy, or who are HIV positive.

14. Has a contraindication (sensitivity or allergy) to trimethoprim/sulfamethoxazole.

15. Has a known allergy to any component of the study treatment(s) formulations.

16. Has undergone a major surgery, including surgery for a new artificial implant and/or device, within 6 weeks prior to the initiation of ADXS11-001 treatment. (NOTE: All toxicities and/or complications must have recovered to baseline or Grade 1 prior to the initiation of ADXS11-001 study therapy.) Consult with the Sponsor prior to enrolling subjects on the study who recently had a major surgery or have new artificial implant, and/or devices.

17. Has received a live vaccine within 30 days prior to the first dose of study treatment.

18. Has a history of other invasive malignancies within 3 years of randomization, with the exception of non-melanoma skin cancer and in situ melanoma. Subjects with other malignancies diagnosed more than 3 years ago who are relapse-free for at least 3 years may be enrolled. Subjects are also excluded if their previous cancer treatment contraindicates this protocol therapy.

19. Has bilateral hydronephrosis unless at least one side has been stented and renal function fulfils the required inclusion criteria.

20. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

21. Has an uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac

arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

22. Has liver cirrhosis or any other impaired hepatic function as determined by serum enzymes.

23. Has undergone a previous hysterectomy (defined as removal of the entire uterus), following neoadjuvant chemotherapy.

24. Has a medical history or conditions not otherwise previously specified which in the opinion of the Investigator should exclude participation in this study. The Investigator should feel free to consult the Sponsor for any question regarding eligibility.

25. Is or has an immediate family member (spouse or children) who is directly involved with this study, that is employed by the investigational site or Sponsor, unless prospective Institutional Review Board (IRB) approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

4 STUDY MODALITIES

The treatments to be used in this study are outlined below in (Table 4).

Table 4 Study Treatment

Arm	Drug	Dose	Route of Administration	Regimen
A	ADXS11-001 Placebo	NA	IV infusion over [redacted]	1 dose administered every 3 weeks (Weeks 1, 4 and 7) for 3 doses (Prime Phase), thereafter, subjects will receive 1 dose every 8 weeks (Weeks 15, 23, 31, 39, and 47) (Maintenance Phase)
A	Placebo matching trimethoprim/sulfamethoxazole	NA	Oral	trimethoprim/sulfamethoxazole placebo administered once daily for 7 consecutive days[1]
B	ADXS11-001	1×10^9 CFU	IV infusion over [redacted]	1 dose administered every 3 weeks (Weeks 1, 4 and 7) for 3 doses (Prime Phase), thereafter, subjects will receive 1 dose every 8 weeks (Weeks 15, 23, 31, 39, and 47) (Maintenance Phase)
B	Trimethoprim/sulfamethoxazole	80 mg trimethoprim / 400 mg sulfamethoxazole	Oral	trimethoprim/sulfamethoxazole administered once daily for 7 consecutive days[1]

[1]Subjects will receive a 3-week course of antibiotics or placebo at the indicated dosage following the final dose of study treatment or upon discontinuation of study drug, whichever occurs first.

4.1 ADXS11-001 (IND #13,712)

[redacted]

Details on the preparation, handling, administration and destruction are provided in the Pharmacy Manual.

4.1.1 Adverse Effects

Please refer to Section 2.1.7 for summary information on the ADXS11-001 AE profile and the ADXS11-001 IB for complete information regarding AEs.

4.1.2 Drug Accountability

The Investigator is responsible for keeping accurate records of the clinical supplies received from Advaxis or designee, the amount administered to subjects, and the amount remaining at the conclusion of the study.

4.1.3 Drug Ordering and Distribution

Drug will be supplied by Advaxis and distributed by Almac Clinical Services LLC. No supplies will be shipped to any site until regulatory approval has been obtained. There will NOT be an initial drug supply forwarded to any investigational site(s) until initial regulatory approval. Details regarding drug ordering and distribution are provided in the Pharmacy Manual.

4.1.4 How Supplied, Storage and Stability

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Details on the drug supply, storage and stability are provided in the Pharmacy Manual.

4.2 Concomitant Therapies and Procedures (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the course of the study. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the study, then discontinuation from study therapy may be required. The Investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the subject's primary physician. However, the decision to continue the subject on study therapy requires mutual agreement of the Investigator, the Sponsor, and the subject.

4.2.1 Acceptable Concomitant Therapies and Procedures

All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the electronic case report form (eCRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

4.2.1.1 Hematopoietic Growth Factors

While it is not expected that administration of ADXS11-001 may lead to neutropenia, hematopoietic growth factors may be used to treat emergent neutropenia as indicated by the current ASCO guidelines.

4.2.1.2 Major and Minor Surgeries and ADXS11-001 Treatment

No formal studies of the effect of ADXS11-001 on wound healing have been conducted. However, based on its mechanism of action it is not expected that administration of ADXS11-001 would complicate wound healing. Therefore, a subject may initiate or resume study treatment 2 weeks after minor surgery (i.e., surgery involving little risk to the life of the subject; specifically, an operation on the superficial structures of the body or a manipulative procedure that does not involve a serious risk) if the wound has completely healed and there are no wound healing complications. A subject who has wound healing complications following minor surgery, received major surgery or requires new implants and/or devices (permitted by the protocol) during the course of the study, must wait a minimum of 6 weeks and must have recovered from any toxicity (e.g., return to baseline or Grade 1) and/or complication before the next infusion of study treatment. Sponsor consultation is required prior to resuming study treatment for these subjects. If the treatment is delayed due to concomitant surgery beyond 12 weeks the subject may be discontinued from the study.

4.2.2 Prohibited Concomitant Therapies

Subjects are prohibited from receiving the following therapies during the screening and treatment period of this study:

- Anti-cancer therapy including, hormonal therapy, chemotherapy, radiation therapy, treatment with targeted agents (e.g., tyrosine kinase inhibitors).
- Immunotherapy (e.g., therapies for the treatment of rheumatoid arthritis) not specified in this protocol. However, immunotherapy for the treatment of allergies is allowed.
- Investigational agents other than ADXS11-001.
- PI3K and TNFα inhibitors

- Live vaccines (e.g., measles, mumps, rubella, chicken pox, yellow fever, BCG, rabies and typhoid) must not be given concomitantly with ADXS11-001. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

- Chronic use of systemic glucocorticoids since these have the potential to reduce the immune response. *However, glucocorticoids should be considered to manage symptoms from an event of suspected immunologic etiology (eg, symptoms associated with CRS, hypotension occurring during infusions)*. (NOTE: The use of occasional inhaled corticosteriods for the treatment of COPD and/or asthma is allowed.)

Subjects who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. Subjects may receive other medications that the Investigator deems to be medically necessary.

The Exclusion Criteria (Section 3.2) describe other therapies and procedures that are prohibited during this study.

4.3 Diet/Activity/Other Considerations

4.3.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

4.3.2 Contraception

ADXS11-001 may have adverse effects on a fetus in utero. Furthermore, it is not known if ADXS11-001 has transient adverse effects on the composition of sperm. Prior to enrollment, all study candidates with reproductive potential must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. Women of childbearing potential is defined as females who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or, are not postmenopausal (defined as amenorrhea ≥12 consecutive months or women on hormone replacement therapy with a documented serum follicle stimulating hormone level >35 mIU/ml). Even women who are using oral, implanted, or injectable contraceptive hormones or mechanical products, such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, who are practicing abstinence, and who have a sterile partner (e.g., vasectomy) should be considered of childbearing potential.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an

estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, all female study candidates of reproductive potential must adhere to the contraception requirement (described above) from Visit 1 through 120 days after the last study treatment administration. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

4.3.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment, the subject will immediately be removed from the study. The site will contact the subject by phone at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a SAE (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

4.3.4 Use in Nursing Women

The effects of ADXS11-001 on human milk are unknown. Therefore, subjects who are breast-feeding are not eligible for enrollment.

5 TREATMENT PLAN AND ENTRY/REGISTRATION PROCEDURE

5.1 Subject Entry and Registration

An Interactive Response Technology (IRT) system will be used for this study to register drug dispensation visits (ADXS11-001/placebo and antibiotics/placebo), obtain subject drug assignments, and manage site drug inventory. A blinded user manual will be provided to site personnel in the study manual. An unblinded manual will be provided in the pharmacy manual.

Additional details on subject entry and registration can be found in the study Administrative Binder.

5.2 Randomization and Treatment Plan

Subjects must initiate the Screening period within 14 weeks after the completion of CCRT (inclusive of brachytherapy, when applicable). The Screening Period is 28 days in duration and all examinations and assessments required by the protocol are expected to be completed within this period. Clinical laboratory assessments must be completed no more than 3 days prior to randomization to ADXS11-001 or placebo.

Eligible subjects will be randomized 1:2 to Arm A (placebo) or Arm B (ADXS11-001).

Study treatment (ADXS11-001or placebo) will be administered on Day 1 of the Week 1 visit. Study treatment may be administered ±3 days within Day 1 of each scheduled infusion for subsequent visits (e.g. Week 4, Day1 and Week 7, Day 1 visits).

- Arm A: Placebo administered IV over approximately [redacted] every 3 weeks (Weeks 1, 4 and 7 only) for 3 doses (Prime Phase), thereafter, subjects will receive an additional dose every 8 weeks (Weeks 15, 23, 31, 39, and 47) for 5 doses (Maintenance Phase). The *total treatment* period will be approximately 1 year.

- Arm B: ADXS11-001 administered IV over approximately [redacted] every 3 weeks (Weeks 1, 4 and 7 only) for 3 doses (Prime Phase), thereafter, subjects will receive an additional dose every 8 weeks (Weeks 15, 23, 31, 39, and 47) for 5 doses (Maintenance Phase). The *total treatment* period will be approximately 1 year.

5.2.1 Screening Period

The following evaluations will be performed to confirm subjects' eligibility:

- Informed consent
- Demographic information
- Medical, surgical, and cancer history
- Concomitant therapy review
- Adverse events review (collected from the time informed consent is obtained)
- Full physical examination
- Vital signs, height, weight
- Pelvic exam inclusive of cervical and vaginal cytology (**NOTE**: Exam should include a speculum examination with bi-manual pelvic and rectal examinations.)
- GOG performance status
- Routine Laboratory tests (hematology, coagulation profile, blood chemistry, urinalysis, pregnancy test): Subjects whose pre-treatment CBC reveals leukocytosis may need additional evaluation (e.g., UA, etc.) to rule out an active infection. Confirmed infection will result in a delay of study treatment and must be treated with appropriate antibiotic treatment. Screening labs must be performed within 3 days of dosing.

- Tumor Imaging: Baseline scans must be performed within 28 days of first study treatment infusion and must include contrast-enhanced CT of the chest, abdomen and a contrast-enhanced MRI or PET/CT of the pelvis. If a contrast-enhanced CT of the pelvis is performed, an MRI of the pelvis is still required.
    - The modality selected for a patient for imaging of the pelvis (either contrast-enhanced CT and MRI or PET/CT) must be used consistently for the patient throughout the study.

    - For subjects who have a medical contraindication to IV contrast, a contrast-enhanced MRI or PET/CT of the abdomen and pelvis may be performed. In these subjects, a non-contrast CT scan of the chest must also be performed.

      NOTE: Please refer to the Imaging Manual for details regarding imaging requirements, including but not limited to, image acquisition, collection and submission of scans for independent radiology review.

- Inclusion/Exclusion Review: Results of all screening evaluations must be reviewed by the principal Investigator or qualified designee to ensure that all eligibility criteria have been satisfied prior to subject randomization.

5.2.2 Subjects Who Fail to meet Screening Criteria

A subject who has a laboratory test results(s), vital signs, or other finding(s) that does not satisfy the eligibility criteria may have the test(s) repeated once. These tests may be repeated as soon as the Investigator believes the retest result is likely to be within the acceptable range to satisfy the entrance criteria but **must** be completed within the 28-day screening period. The subject will not be required to sign another informed consent form (ICF), and the original subject identification number will be used. In the event that the laboratory test(s) cannot be performed within the Screening period, or the re-test(s) does not meet the entrance criteria or the subject's medical condition has changed significantly during the Screening Period so that inclusion/exclusion criteria are no longer met, the subject is considered a Screen failure, and must be withdrawn from the study.

5.2.3 Treatment Period

During the treatment period, the following assessments will be performed prior to study treatment infusion:

- Physical examination (NOTE: A "focused" physical examination will be performed during the Prime Phase on Weeks 4 and 7 and during the Maintenance Phase on the Week 23 visit. Full physical exams should be performed on all other visits during the treatment period. (See Section 7.1, Schedule of Events).

- Vital signs and weight

- GOG performance status

- Routine laboratory tests (hematology profile, blood chemistry, urinalysis, pregnancy test). Lab tests must be completed within 3 days of study treatment dosing.*
- Prophylactic medication administration within the approximate pre-infusion window
- AE review
- Concomitant therapy/procedures review
- [redacted]
- Tumor imaging and pelvic examination will be performed at Weeks 12, 24, 36, and 48 in all subjects who have not experienced disease recurrence, even those who have discontinued treatment prior to early study termination.
    - Note: Cervical and vaginal cytology will be performed at Screening only unless deemed necessary by the treating physician.

**Prior to each study treatment, a subject must be thoroughly screened for an ongoing or active infection. Any subject whose pre-treatment CBC reveals leukocytosis may need additional evaluation (e.g. urinalysis, etc.) to rule out an active infection. Confirmed infection will result in a delay of study treatment and appropriate antibiotic treatment. Study treatment may resume following at least 5 half-lives from the subject's final antibiotic dose.*

5.2.3.1 Pretreatment Prophylaxis Regimen

Mild to moderate cytokine release symptoms (e.g., fever, chills, rigors, fatigue, headache, nausea, vomiting, tachycardia, shortness of breath, hypotension and rash) are commonly seen and typically occur 2-4 hours after ADXS11-001 infusion and often resolve within 12-24 hours. Prophylactic medications are intended to reduce the inflammatory response and minimize the occurrence of post-treatment symptoms. Therefore, it is strongly recommended that subjects receive the following pretreatment prophylaxis regimen:

IV Fluid Hydration:

- Normal saline (NOTE: A recommended fluid amount is 500 mL administered IV over approximately one hour but investigator discretion should be used to determine an individual subject's need based on her medical condition. Appropriate hydration has been determined to be a key component in helping to minimize post-treatment symptoms related to an immune-mediated response.)

Premedication Regimen:

- Antihistamine - PO or IV (e.g., diphenhydramine 25 mg or equivalent) [redacted] prior to the procedure, once
- NSAIDs - PO (e.g., naproxen 220 mg or ibuprofen 400 mg) [redacted] prior to the procedure, once
    - NOTE: Acetaminophen is prohibited for prophylaxis because it does not have anti-inflammatory properties required to assist in reducing adverse events associated with ADXS11-001 administration. When naproxen and ibuprofen are contraindicated an alternative anti-inflammatory should be used. Acetaminophen may be used for supportive care measures. Sponsor consultation is recommended.
- Antiemetic - PO or IV (e.g., promethazine or ondansetron) [redacted] prior to the procedure, once
- Histamine H2-receptor antagonist - PO or IV (e.g., famotidine 20 mg or equivalent) [redacted] prior to the procedure, once

IV fluids and pretreatment medications should be given on the day of dosing and completed at least [redacted] prior to the start of the assigned study treatment infusion. Do not substitute acetaminophen for the selected NSAID for prophylactic treatment since acetaminophen does not have similar anti-inflammatory properties that could ameliorate symptoms related to an immune-mediated response.

5.2.3.2 Administration of Study Treatment

ADXS11-001 and all other study medications must be administered through a temporary line, which will be removed prior to discharge.

[redacted]

[redacted]

5.2.3.3 Study Treatment Regimen

The treatment period consists of the Prime Phase (dosing every 3 weeks (± 3 days) for 3 total doses in the first 12 weeks and the Maintenance Phase (dosing every 8 weeks (± 3 days) for a total of 5 doses). Study treatment will be administered as an IV fusion over approximately [redacted] in 250 mL of normal saline. Vital signs will be taken immediately before each study treatment infusion. Treatment is to be done on an outpatient basis.

5.2.3.4 Pre-Treatment Assessment and Study Therapy Administration

The investigator or research staff must ensure that the subject's vital signs, laboratory results and physical condition are within normal limits with consideration given to the subject's prior medical history as well as information available based on her current participation in the study prior to the administration of study therapy. Study therapy must not be administered until all of the subject's assessments are within acceptable limits in the opinion of the investigator. In the situation where one or more of the subject's assessments are not within the normal limits for that subject, but in the opinion of the investigator study therapy dosing may proceed, then documentation must be made to note baseline values and the investigator's assessment that the findings were not clinically or medically significant.

5.2.3.5 Post-Treatment Monitoring

After study treatment administration, subjects will remain in the clinic to be monitored for safety for at least 4 hours. Vital signs will be taken [redacted] following each study treatment infusion. Four hours after the study treatment, the investigator must ensure the subject is in stable medical condition and in the investigator's opinion can be safely discharged before being released. The investigator must take action to provide appropriate medical care. After the completion of study treatment an NSAID and/or antiemetic may be given on Day 1 and Day 2, as needed. The prescribed dosage of the selected NSAID and antiemetic will be at the discretion of the Investigator.

5.2.4 Follow-up Period

Subjects who complete the one-year treatment period: The Follow-up period is defined as the portion of the study that begins after completion of the treatment period and will last for 1 year. The treatment period will be considered complete once the subject receives his/her last dose of study treatment in either the Prime or Maintenance phases. During the Follow-up Period, subjects will be contacted by phone every 3 months (±1 week) to determine whether

they have experienced for several days, the following symptoms that could potentially be associated with delayed listeremia: fever or chills, headache, nausea, confusion or changes in alertness. As part of the End of Study procedures, upon completing the *Lm* Surveillance period, site staff should instruct subjects to contact the site if they experience any of these symptoms, as applicable (refer to Section 6.2.6).

Subjects who discontinue early for reasons other than disease recurrence: Subjects will immediately enter the Follow-up Period (refer to Section 7.2.6.1.2), which will last for a total of 1 year *Lm* Surveillance period.

5.2.4.1 Lm Surveillance

Surveillance monitoring for the detection of *Lm* will be performed during the Follow-Up period. Surveillance will be initiated at the completion of study treatment according to the protocol or at the time of study discontinuation if earlier. See Section 6.2.6 Management and Surveillance of *Listeria* during Study Participation and Section 9 for further information.

Medications and antibiotics administered during the *Lm* surveillance period should also be captured in the eCRF along with any new procedures which are performed during this time.

Adverse events and serious adverse events experienced that are potentially associated with listeremia during the 1-year *Lm* surveillance monitoring phase will be reported and recorded in the eCRF. Adverse experiences will be graded and recorded throughout the study andfollow-up according to CTCAE V 4.03 (see Section 5.2.4 and 6).

5.2.4.2 End of Study Visit

The EOS visit will be performed on the last scheduled study visit day of the Follow-up phase (± 5 days), or earlier if the subject meets a reason for discontinuation during the Follow-up phase due to disease recurrence. All study procedures that are included for the scheduled visit and EOS visit will need to be performed. This can be done remotely. The following procedures will be performed for the EOS visit:

- Record adverse events
- Completion of end of *Lm* Surveillance Monitoring visit (can be done remotely)

5.3 Stratification

Treatment arms will be stratified based on the:

- Presence or absence of para-aortic lymph node metastases (yes vs no/unknown)

- Region (US vs Rest of World)
- FIGO stage (Stages I-II or III-IV) **(2014 FIGO Staging)**

6 TREATMENT MODIFICATION GUIDELINES

6.1 Treatment Delay/Discontinuation Guidelines

The study treatment dose will not be modified (i.e., reduced or increased). However, treatment may be delayed or discontinued for drug related severe and life-threatening toxicities, as shown below in (Table 5).

Table 5 Treatment Delay/Discontinuation Guidelines for Drug-Related Adverse Events

Toxicity	Grade	Hold Treatment	Timing for Restarting Treatment	Discontinue Study Treatment
Hematologic	1,2,3	No	N/A	N/A
	4	Yes	Toxicity resolves to ≤Grade 1 or baseline	Toxicity does not resolve to ≤Grade 1 or baseline within 3 weeks of AE onset
Non-hematologic, excluding cytokine release symptoms	1	No	N/A	N/A
	2-3	Yes	Toxicity resolves to ≤Grade 1 or baseline	Toxicity does not resolve to ≤Grade 1 or baseline within 3 weeks of AE onset[a]
	4	N/A	Permanent discontinuation from study treatment	Permanent Discontinuation from study treatment

[a]With investigator and sponsor agreement, subjects with a non-hematologic AE (e.g., alopecia, neuropathy) still at Grade 2 after 3 weeks may continue treatment if subject is asymptomatic and well-controlled.

Treatment may also be delayed at the discretion of the investigator for adverse events that are not drug-related, but which would either put the subject at risk from treatment, adversely affect the efficacy of study treatment, confound the interpretation of study results, or prevent the assessment of study results.

6.2 Supportive Care Guidelines Following Administration of Study Treatment

Subjects should receive appropriate supportive care measures as deemed necessary by the Investigator including but not limited to the items outlined below.

6.2.1 Symptoms Related to Immune Cell Activation

A subject may experience inflammatory symptoms associated with T-cell engagement and proliferation following the administration of ADXS11-001. Symptoms may include constitutional symptoms such as fever, chills, rigors, fatigue, headache, nausea, vomiting, rash tachycardia, hypotension, and shortness of breath which usually present several hours after the infusion and may last for up to 24 hours. These symptoms which are caused by an increase in cytokines such as IL- 6, TNFα and IFNγ occur after ADXS11-001 administration. This is the result of the body's immune response to the therapy. In most cases, the symptoms are usually CTCAE Grade 1 and 2, transient and resolve with appropriate medical management within 30 minutes to1 hour. The guidelines for the grading and management of symptoms related to immune cell activation are shown in Table 6.1-6.4

6.2.1.1 Grading and Management Guidelines for Acute Hypotension, Hypoxia, Encephalopathy, Organ Toxicity, Fever and Constitutional Symptoms

Table 6.1 Grading Scale for Hypoxia, Hypotension, and Organ Toxicity

Grade	Description of Severity
1	Fever (temperature $\geq$ 38°C) or Grade 1 organ toxicity
2	Symptoms require and respond to moderate intervention Oxygen requirement FiO_2 < 40% and/or subject requires intermittent supplemental oxygen, OR Hypotension responsive to IV fluids or low-dose of one vasopressor to maintain systolic blood pressure > 90 mmHg, OR Grade 2 organ toxicity
3	Needs oxygen to maintain O_2 saturation > 90% Oxygen requirement $FiO_2 \geq$ 40% and/or requiring BiPAP, OR Hypotension refractory to management for Grade 2 or where hospitalization is required, OR Grade 3 organ toxicity or Grade 4 transaminitis per CTCAE v5.0 criteria
4	Life-threatening signs and symptoms OR Requirement for ventilator support to maintain O_2 saturation > 90% OR Grade 4 organ toxicity (excluding Grade 4 transaminitis) per CTCAE v5.0 criteria

Table 6.2 Management Guidelines for Acute Hypotension, Hypoxia, Organ Toxicity, Fever and Constitutional Symptoms

Toxicity Grade	Sign/Symptom	Treatment	Instructions for Interruption of ADXS11-001	Modification for Subsequent infusions
1	Hypotension	• Supportive care	Not applicable	• Increase pretreatment IV fluids (e.g., 500 ml -1L normal saline)
1	Fever; Constitutional symptoms; Grade 1 organ toxicity	• Symptomatic management of constitutional symptoms and organ toxicity • Acetaminophen and hypothermia blanket as needed for fever • Ibuprofen if fever is not controlled with above, use with	Not applicable	• No modification

		caution or avoid if thrombocytopenic • IV fluids as needed		
2	Hypotension	• Fluids (500 – 1000 mL normal saline to keep systolic blood pressure > 90 mmHg) • If hypotension persists after IV fluid bolus, administer a vasopressor (e.g., epinephrine 0.3 mg IM) • If hypotension persists despite IV fluid bolus ± a low dose pressor, administer the IL-6 antagonist tocilizumab (8 mg/kg IV over 1 hour), and consider transfer to ICU • If hypotension persists despite these measures, treat with a high-dose corticosteroid. • If there are signs of hypo-perfusion or if there is rapid deterioration in the opinion of the clinician, consider the use of corticosteroids • Increase frequency of monitoring vital signs	• Immediately interrupt ADXS11-001 until AE(s) resolve to Grade ≤ 1 but for no less than 72 hours • Permanently discontinue ADXS11-001 if there is no improvement of AE(s) to ≤ Grade 1 within 7 days.	• Extend infusion time to 2 hours • Increase pretreatment IV fluids (e.g. 500 mL – 1L normal saline) • Upon evaluation, Glucocorticoid-Hydrocortisone or equivalent-50 mg, IV, may be incorporated as premedication
2	Hypoxia	• Use supplemental oxygen as needed • Use tocilizumab 8 mg/kg IV with or without corticosteroids as with Grade 2 hypotension (described above) • Increase frequency of monitoring vital signs • Restrict the administration of IV fluid, if possible	• Immediately interrupt ADXS11-001 until AE(s) resolve to Grade ≤ 1 but for no less than 72 hours • Permanently discontinue ADXS11-001 if there is no improvement of AE(s) to ≤ Grade 1 within 7 days.	• No modifications • Discussion with Sponsor recommended
2	Fever, Constitutional symptoms; Grade 2 organ toxicity	• Appropriate supportive care • Manage organ toxicity as per standard guidelines • If no improvement with supportive care, use tocilizumab 8 mg/kg IV with or without corticosteroids as described above for Grade 2 hypotension • Manage fever and constitutional symptoms as	• Immediately interrupt ADXS11-001 until AE(s) resolve to Grade ≤ 1 but for no less than 72 hours • Permanently discontinue ADXS11-001 if	• Extend infusion time to 2 hours • Consider increasing doses of prophylactic medications • Discussion with Sponsor recommended, but not required

		noted above for Grade 1 toxicity	there is no improvement of AE(s) to ≤ Grade 1 within 7 days.	

3	Hypotension	• IV fluid bolus (as for Grade 2 hypotension) and tocilizumab (8mg/kg IV over 1 hour)
		  ○ If an IV fluid bolus was previously administered it may be repeated, depending on the subject's hemodynamic status. However, IV fluid administration in the presence of hypoxia may lead to increased pulmonary edema (see guidance for hypoxia above)
		  ○ If no improvement, tocilizumab 8 mg/kg IV can be repeated every 8 hours for a total of 3 doses
		• Transfer subject for inpatient management
		• High dose vasopressors (e.g., Dopamine 10 µg/kg/min)
		• If hypotension worsens or is unresponsive to above measures, administer high dose corticosteroids (methylprednisolone or dexamethasone)
		• Monitor for neurologic signs and symptoms. **Consult neurology to assess for signs of elevated intracranial pressure** (e.g., papilledema) /cerebral involvement. See Table 6.3 and Table 6.4 below for grading and management of encephalopathy
		• Increase frequency of monitoring vital signs
			• Immediately interrupt ADXS11-001
			• Permanently discontinue ADXS11-001 if there is no improvement in AE(s) to ≤ Grade 2 within 5 days or AE ≤ Grade 1 within 7 days
				• Discuss with Sponsor

3	Hypoxia	• Use supplemental oxygen • Use tocilizumab 8 mg/kg IV with or without corticosteroids (as for Grade 3 hypotension) • Increase frequency of monitoring vital signs • Restrict the administration of IV fluid if possible	• Immediately interrupt ADXS11-001	• Discuss with Sponsor

3	Fever, Constitutional symptoms; Grade 3 organ toxicity	• Appropriate supportive care • Manage organ toxicity as per standard guidelines • Use tocilizumab 8 mg/kg IV with or without corticosteroids (as for Grade 3 hypotension) • Manage fever and constitutional symptoms above for Grade 1 toxicity	• Immediately interrupt ADXS11-001	• Discuss with Sponsor
4	Hypotension	• IV fluid bolus (as for Grade 2 hypotension) and tocilizumab • High-dose methylprednisolone	• Immediately interrupt ADXS11-001	• Permanently discontinue ADXS11-001
4	Hypoxia	• Mechanical ventilation • Tocilizumab, high-dose methylprednisolone, and supportive care	• Immediately interrupt ADXS11-001	• Permanently discontinue ADXS11-001
4	Fever, Constitutional symptoms; Grade 4 organ toxicity	• Appropriate supportive care • Manage organ toxicity as per standard guidelines • Tocilizumab, high-dose methylprednisolone, and supportive care • Manage fever and constitutional symptoms as noted for Grade 1 above • Increase frequency of monitoring vital signs	• Immediately interrupt ADXS11-001	• Permanently discontinue ADXS11-001

Note: Tocilizumab is a humanized, immunoglobulin G1k (IgG1k) anti-human IL-6R mAb approved by the FDA for treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to Disease-Modifying Anti-Rheumatic Drugs (DMARDs), for the treatment of active polyarticular juvenile idiopathic arthritis (PJIA), and active systemic juvenile idiopathic arthritis (SJIA) in patients 2 years of age and older, and for the treatment of adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome. Tocilizumab works by preventing IL-6 binding to both cell-associated and soluble IL-6 receptors**.** Dosing guidelines for tocilizumab are provided below.

Tocilizumab Dosing Guidelines [39]

- 8 mg/kg IV; maximum dose/infusion = 800 mg.
- If the subject's condition does not improve or stabilize within 8 hours of the tocilizumab dose, administration of a second dose of tocilizumab should be

considered. A total of three doses can be administered in a 24-hour period (maximum 800 mg/dose), and a maximum of 4 doses total can be administered.

- Tocilizumab may be administered with corticosteroids.

Table 6.3 Grading Scale for Encephalopathy

Grade	Description of Severity
1	Neurological assessment score (see below) – Mild (7-9)
2	Neurological assessment score (see below) – Moderate (3-6)
3	Neurological assessment score (see below) - Severe (0-2) OR Stage 1 or 2 papilledema[1] with CSF opening pressure less than 20 mmHg
4	Neurological assessment score Critical / obtunded OR Stage 3, 4, or 5 papilledema[1] or CSF opening pressure greater than or equal to 20 mmHg or cerebral edema

CARTOX 10-point neurological assessment (Assign one point for each task performed correctly; score of 10 = normal)
● Orientation to year, month, city, hospital, President: 5 points
● Name 3 objects (point to clock, pen, button): 3 points
● Ability to write a standard sentence (*e.g.,* Our national bird is the bald eagle): 1 point
● Count backwards from 100 by ten: 1 point
[1] Papilledema grading is performed according to Modified Frisén scale
CSF = cerebrospinal fluid

Table 6.4 Management Guidelines for Encephalopathy

Toxicity Grade	Treatment	Instructions for Interruption of ADXS11-001	Modification for Subsequent Infusions
1	• Vigilant supportive care; aspiration precautions; IV hydration • Withhold oral intake of food/medicines/fluids and assess swallowing • Convert all oral medications and/or nutrition to IV if swallowing is impaired • Avoid medications that cause CNS depression • Low doses of lorazepam (0.25-0.5 mg IV every 8 hours) or haloperidol (0.5 mg IV every 6 hours) may be used for agitated patients with careful monitoring • Neurology consultation • Daily CARTOX 10-point neurological assessment as in Table 6.3 • Fundoscopic exam to assess for papilledema	Not applicable	Discuss with Sponsor

Toxicity Grade	Treatment	Instructions for Interruption of ADXS11-001	Modification for Subsequent Infusions
	• MRI brain with and without contrast; diagnostic lumbar puncture with OP; MRI spine if focal signs exist; CT of brain may be performed if MRI brain is not feasible		
2	• Supportive care and neurological workup as per Grade 1 • IL-6 antagonist (tocilizumab[1]), if associated with other events such as refractory hypotension and/or hypoxia • Dexamethasone or methylprednisolone if refractory to tocilizumab[1] therapy, when it is administered • Consider ICU transfer if associated with other events such as hypotension or hypoxia	• Immediately interrupt ADXS11-001	Discuss with Sponsor
3	• Supportive care and neurological workup as per Grade 1 • ICU transfer is recommended • Tocilizumab[1], if associated with concurrent refractory hypotension and/or hypoxia and if not administered previously • Dexamethasone or methylprednisolone around the clock, if symptoms worsen despite tocilizumab therapy. Continue corticosteroids until improvement to Grade 1 and then taper or stop. • Low grade (Stage 1 or 2) papilledema with CSF OP less than 20 mmHg, acetazolamide as per Institutional guidelines • Consider repeat neuro-imaging (CT or MRI) every 2-3 days if persistent event greater than or equal to Grade 3	• Immediately interrupt ADXS11-001 • Permanently discontinue ADXS11-001	Not applicable
4	• Supportive care and neurological workup as per Grade 1 • ICU monitoring; consider mechanical ventilation for airway protection • Tocilizumab[1] and repeat neuro-imaging as per Grade 3 • High dose methylprednisolone • For high-grade (Stage 3, 4, or 5) papilledema, CSF OP greater than or equal to 20 mmHg, or cerebral edema, follow Institutional guidelines for high dose steroids, hyperventilation, hyperosmolar therapy, metabolic profile; CT scan daily.	• Immediately interrupt ADXS11-001 • Permanently discontinue ADXS11-001	Not applicable

[1]IL-6 antagonist (tocilizumab) administration - See Table 6.2

6.2.2 Nausea/Vomiting

Nausea and vomiting should be treated aggressively. In addition to the prophylactic antiemetic therapy subjects receive prior to each infusion, consideration should be given to subsequent administration of antiemetic therapy every 8 hours, as needed according to standard institutional practice. Subjects should also be strongly encouraged to maintain liberal oral fluid intake.

6.2.3 Hypotension

In some instances (~7% of subjects receiving ADXS11-001) CTCAE Grade 3 and 4 hypotension has been seen. The occurrence of hypotension may be related to increased levels of IL-6 which are strongly associated with capillary leak which manifests as hypotension due to the cytokines involved. Elevated IL-6 levels have been observed after infusion of ADXS11-001 with peak levels occurring 2-4 hours after infusion. Therefore, close monitoring of blood pressure is strongly recommended at baseline and during the post-infusion period.

[redacted] An updated algorithm for the grading and management of >Grade 3 hypotension, hypoxia, encephalopathy, and other constitutional symptoms has been developed.

Particularly, emerging evidence indicates that IL-6 antagonists, such as Tocilizumab, have demonstrated positive results in treating cytokine-induced hypotension [40-43]. Therefore, Tocilizumab is recommended for cases of hypotension which are refractory to supportive care (e.g., fluids and/or pressors; See Section 6.2.1).

6.2.4 Listeriosis and Listeria Infection - Identification and Management

A person with wild type (wt) listeriosis usually presents with fever and muscle aches which may be preceded by diarrhea or other gastrointestinal symptoms. In most cases, a person who is diagnosed with listeriosis has an "invasive" infection in which the bacteria has spread beyond the gastrointestinal tract. However, the symptoms will vary with the infected person. Pregnant women are at a higher risk and typically experience fever and other non-specific symptoms such as fatigue and aches. Infections during pregnancy can lead to miscarriage, stillbirth, premature delivery, or life-threatening infection of the newborn. In people other than pregnant women, symptoms can include headache, stiff neck, confusion, loss of balance

and convulsions in addition to fever and muscle aches. Listeriosis can present in different ways. In older adults and people with a compromised immune system septicemia and meningitis are the most common clinical presentations [44]. In these extreme cases, appropriate medical management may include an immediate evaluation with a brain CT scan or MRI and a lumbar puncture with the analysis of spinal fluid to rule out meningitis.

For symptomatic subjects, diagnosis is confirmed only after isolation of wt-*Lm* from a normally sterile site such as blood or spinal fluid (in the setting of nervous system involvement), or amniotic fluid/placenta (in the setting of pregnancy). Stool samples are of limited use and are not recommended. Wild-type *Listeria monocytogenes* can be isolated readily on routine media but care must be taken to distinguish this organism from other Gram-positive rods particularly diphtheroids. Selective enrichment media improve rates of isolation from contaminated specimens. Cultures will take approximately 1-2 days for growth. Importantly, a negative culture does not rule out infection in the presence of strong clinical suspicion. Serological tests are unreliable and not recommended at the present time [44].

Listeriosis can be successfully treated using a wide range of antibiotics. In contrast, listeriosis which is a systemic organ infection caused by wild-type, invasive *Lm* infection, is highly unlikely to occur during study treatment with Advaxis *Lm* constructs due to the method of attenuation used in the Advaxis *Lm* constructs. Bacteremia with attenuated ADXS11-001 (i.e., listeremia) can be documented in a blood culture taken within 24-72 hours after the infusion of ADXS11-001 and before the administration of antibiotics. It may or may not be associated with clinical signs and symptoms (e.g., fever, chills, headache, nausea, confusion or changes in alertness for several days) and it will limit itself by the time antibiotics are started (~72 h) (see Section 5.2.4). In preclinical studies, wt-*Lm* and ADXS11-001 are susceptible to the lowest tested concentration of the following antimicrobial agents:

[redacted]

6.2.5 Management of Listeria during Study Treatment Period

6.2.5.1 Management Immediately Following Completion of a Study Treatment Infusion

Each subject will be given a 7-day supply of trimethoprim/sulfamethoxazoleor matching placebo to be taken beginning approximately 72 hours following the completion of each dose of study treatment, except for the last dose (see Section 6.2.6 for a description of post-treatment antibiotics). Antibiotic treatment will consist of oral trimethoprim/ sulfamethoxazole (80 mg trimethoprim/400 mg sulfamethoxazole) administered once daily, or a matching placebo. Subjects who have an allergic reaction to or develop sensitivity to trimethoprim/sulfamethoxazole will be discontinued from the study. These subjects will be unblinded (Section 7.2.6.1.5) to confirm randomization to Arm B (ADXS11-001), and subjects confirmed randomized to Arm B will receive commercially available oral ampicillin 500 mg four times daily. In the rare case that a subject also has a contraindication to

ampicillin, the subject may receive another antibiotic to which Listeria is sensitive to (refer to Section 6.2.4 and the Investigator's Brochure) and there are no contraindications to administer it to the patient. Antibiotic treatment after each dose is intended to ensure elimination of ADXS11-001 and reduce the possibility of post-dose *Lm* persistence.

In cases where a subject experiences a fever (CTCAE Grade 1 or greater) 24 hours following the completion of the study treatment infusion NSAIDs and other appropriate measures to treat the fever should be started. In the event that the fever persists or worsens 24 hours after starting NSAIDs and other appropriate measures then treatment with oral antibiotics (e.g., Bactrim) should be considered based on the subject's medical condition. If the fever remains unresponsive to oral antibiotics after an adequate treatment course then the administration of IV antibiotics should be considered and a blood culture obtained to evaluate for listeremia in order to determine the appropriate treatment course for the subject.

6.2.6 Management of Listeria During the Follow-up Period

After completion of study treatment, subjects will undergo extended antibiotic treatment and then begin *Lm* surveillance for a period of 1-year. Subjects will begin a 3-week course of antibiotics beginning 72 hours after the 8th dose of study treatment. The 3-week course of antibiotics will also begin after a decision has been made to discontinue further study treatment prior to the 8th dose. Antibiotic treatment will consist of 3 weeks of oral trimethoprim/ sulfamethoxazole (80 mg trimethoprim/400 mg sulfamethoxazole) administered once daily or a matching placebo. Subjects for whom trimethoprim/ sulfamethoxazole is contraindicated due to allergy or other reasons will be discontinued from the study. These subjects will be unblinded (Section 7.2.6.1.5) to confirm randomization to Arm B (ADXS11-001), any subjects confirmed randomized to Arm B will receive commercially available oral ampicillin 500 mg four times daily. In the rare case that a subject also has a contraindication to ampicillin, the subject may receive another antibiotic to which Listeria is sensitive to (refer to Section 6.2.5, 6.2.6 and the Investigator's Brochure) and there are no contraindications to administer it to the patient. Extended treatment with 3-weeks of antibiotics is intended to reduce the possibility of post-treatment *Lm* persistence. Following the completion of the 3-week trimethoprim/sulfamethoxazole treatment, it is strongly recommended that a subject avoid having an implantable device which is not easily removed unless warranted based on the subject's medical condition. In this case, the investigator, subject and the subject's primary care provider should discuss the risk/benefit in order to make a well-informed decision.

Lm surveillance will begin at 3 months (±2 weeks) after the 8th dose of study treatment or after early treatment discontinuation, and will consist of contacting subjects by phone every 3 months (±1 week) to determine whether they have experienced the following symptoms that could potentially be associated with delayed listeremia: fever or chills, headache, nausea, confusion or changes in alertness for several days. The contact will be made to all subjects who have received at least one dose of Study treatment for 1-year (see Section 5.2.4). If the subject's response to having experienced any of the afore-mentioned symptoms is negative, the *Lm* surveillance would continue remotely through phone contacts. However, if the investigator, his/her research staff, other healthcare providers become aware of any positive

signs and symptoms of listeremia reported for a subject and listeremia is suspected, the subject should be tested for the presence of listeria in their blood culture, and treated as medically appropriate if a diagnosis of listeremia is made.

It is extremely important that the investigator, his/her research staff, other healthcare providers involved in the care of the subject as well as each subject participating in this study are educated and made aware of the signs and symptoms of listeremia and the potential for delayed listeremia. Educational materials for the investigator, research staff, health care providers and subjects will be prepared and educational training performed.

Thus, at the End of Study visit (which can be completed remotely via phone), subjects should be instructed to contact their primary care provider or the site if they experience any of the potential listeremia symptoms (i.e., fever or chills, headache, nausea, confusion or changes in alertness for several days).

For subjects who have completed the *Lm* surveillance period, the subject's primary care provider or the investigator should initiate evaluation of listeremia if suspected and treat accordingly.

A subject should be treated as medically appropriate if a diagnosis of listeremia is made. Listeremia can be treated using IV antibiotics such as ampicillin and gentamycin (**Note:** ADXS11-001 is resistant to streptomycin and chloramphenicol). An infectious disease consult should be obtained to ensure optimal management of listeremia. Based on each individual subject's case and at the discretion of the treating physician, the removal of any implanted device that has been present since treatment with ADXS11-001 was initiated may be warranted.

6.2.7 Management of Listeria in Subjects Who Withdraw Consent

A subject who has received at least one dose of study treatment and withdraws consent at any time during her participation in the study should be reminded of the recommended course of action with respect to the detection and management of listeria as summarized above.

7 STUDY PARAMETERS

7.1 Schedule of Events

Study Procedure		Treatment Period														
	Screening[4]	Prime Phase[1]				Maintenance Phase[2]							Follow-up Phase[3]	Post-Disease Recurrence Period[23]	End of Study or Early Discontinuation[24]
		Week														
	≤28 Days	1[5]	4[5]	7[5]	12	15[5]	23[5]	24	31[5]	36	39[5]	47[5]	48			
Administrative Procedures																
Informed consent[6]	X															
Inclusion/Exclusion criteria	X	X														
Demographics/Medical/Surgical history	X															
Prior Cancer History	X															
Concomitant Therapy/Procedure[7]	X	X	X	X		X	X		X		X	X		X	X	
Prophylactic medication[8]		X	X	X		X	X		X		X	X				
Contact IRT for Treatment Assignment & Re-Supply[25]		X	X	X		X	X		X		X	X				
Study treatment administration[9]		X	X	X		X	X		X		X	X				
Dispense Oral Prophylactic Antibiotics[10]		X	X	X		X	X		X		X	X		X	X	
Phone Call														X	X	
Clinical Procedures/Assessments																

Study Procedure		Treatment Period														
	Screening[4]	Prime Phase[1]				Maintenance Phase[2]								Follow-up Phase[3]	Post-Disease Recurrence Period[23]	End of Study or Early Discontinuation[24]
		Week														
	≤28 Days	1[5]	4[5]	7[5]	12	15[5]	23[5]	24	31[5]	36	39[5]	47[5]	48			
Review adverse events[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[12]	X	X	X	X		X	X		X		X	X	X	X		
Vital signs/Weight/Height[13]	X	X	X	X		X	X		X		X	X				
GOG performance status	X	X	X	X		X	X		X		X	X				
Pelvic examination[14]	X				X			X		X			X			
[redacted]																
LOCAL laboratory Procedures/Assessments[15]																
CBC with differential[16]	X		X	X		X	X		X		X	X				
Serum chemistry panel	X		X	X		X	X		X		X	X				
Coagulation profile[17]	X															
Urine Dipstick	X		X	X		X	X		X		X	X				
Pregnancy tests[18]	X		X	X		X	X		X		X	X				
Lm Surveillance Monitoring[19]													X	X	X	X
Efficacy Measurements																
Tumor imaging[20]	X				X			X		X			X			
[redacted]																

1 The Prime Phase is the first 3 months of the study treatment period following randomization.

2 The Maintenance Phase includes Months 4-12 of the study treatment period.

[3] Upon completion of the treatment period, subjects who have not had confirmed documented disease recurrence/recurrence, (as defined in Section 8.2.1 Definition of Recurrence) will continue with routine physical and pelvic examinations, tumor imaging and [redacted] until documented disease recurrence or death during the Follow-up Phase.

[4] Screening evaluations will be performed within the 28 day screening period, unless otherwise specified.

[5] At every study treatment infusion, the indicated procedures will be performed within the specified window(s).

[6] Informed Consent must be obtained prior to conducting screening evaluations.

[7] Concomitant therapies and procedures will be collected from the time informed consent is signed through 30 days past last dose, and should be recorded in the eCRF.

[8] Pretreatment prophylactic medication administration and IV hydration must be completed at least [redacted] before each study treatment infusion. The prescribed dosage of the selected prophylactic medications will be at the discretion of the Investigator.

[9] Study treatment (ADXS11-001or placebo) may be administered ±3 days within Day 1 of each scheduled infusion. The assigned study treatment will be administered every 3 weeks for a total of 3 doses during the Prime Phase and every 8 weeks for a total of 5 doses during the Maintenance Phase.

[10] All Subjects will receive a 7-day course of oral antibiotic therapy starting 72 hours after administration of each ADX11-001 treatment, except for the last treatment where subjects will receive a 3 week oral antibiotic course (instead of the 7-day course) to be initiated 72 hours following the last dose of study treatment (administered at Week 47) or immediately upon discontinuation of study treatment.

[11] All AEs/SAEs will be assessed from the time Informed Consent is obtained through 30 days past last dose. Beyond that point, report the signs and symptoms of listeremia during the *Lm* surveillance period. All AE/SAEs will be followed through resolution. All AEs/SAEs experienced must be recorded on the eCRF.

[12] Physical Examinations (PEs) will be performed up to 3 days prior to the administration of study treatment to confirm safety criteria for study treatment administration are met. Focused physical examination to be performed during the Prime Phase on Weeks 4 and 7, and during the Maintenance Phase on the Week 23 visit. Full physical exams should be performed on all other visits during the treatment period. In the follow-up phase, full physical exams should be performed if a blood culture positive for *Lm* is reported. PEs may be performed more frequently, as clinically indicated.

[13] Height measurement will be obtained at screening only. Monitor vital signs immediately [redacted] for the first 4 hours following the completion of every study treatment infusion. Weight will be taken prior to each study treatment infusion.

[14] Pelvic exam inclusive of speculum exam with bimanual pelvic and rectal examination and will occur during End of Study treatment period or Early Discontinuation from treatment period, as applicable. Cervical and vaginal cytology will be performed at Screening only unless deemed necessary by the treating physician.

[15] All laboratory procedures are to be completed and assessed by the Investigator no more than 3 days prior to the administration of study treatment to confirm safety criteria for study treatment are met.

[16] Prior to **each** study treatment, subjects must be thoroughly screened for an ongoing or active infection. Subject's whose pre-treatment CBC reveals leukocytosis may need additional evaluation (e.g. urinalysis, etc.) to rule out an active infection. Confirmed infection will result in a delay of study treatment and must receive appropriate antibiotic treatment. Study treatment may resume following at least 5 half-lives from the subject's final antibiotic dose.

[17] Coagulation tests will only be required at Screening as a baseline value.

[18] Urine pregnancy tests must be performed within 3 days prior to **each** study treatment infusion for subjects of childbearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

[19] *Lm* Surveillance Monitoring will include a 3-weeks course of oral antibiotics and routine monitoring of subjects via phone contact, and blood cultures if subjects report experiencing potential signs and symptoms of listeremia All assessments will be performed beginning on the 3rd month after the last dose of study treatment during the 1-year *Lm* surveillance monitoring period or immediately at the time of study discontinuation unless a subject withdraws her consent

[20] Contrast-enhanced CT of the chest, abdomen and a contrast-enhanced MRI or PET/CT of the pelvis are required. If a contrast-enhanced CT of the pelvis is performed, an MRI or PET/CT of the pelvis is still required, as described in the Advaxis Imaging Manual. The modality selected for a patient for imaging of the pelvis (either contrast-enhanced CT and MRI or PET/CT) must be used consistently for the patient throughout the study. Baseline tumor imaging must be performed within **28 days prior** to the first study treatment infusion. Imaging during the Treatment Period will occur at Weeks 12, 24, 36, and 48 as indicated provided a subject does not experience disease recurrence.

[21] [redacted]

[22] [redacted]

[23] Subjects with documented disease recurrence will complete the 1 year *Lm* Surveillance Period, be contacted by phone every 3 months (±1 week) to collect status of signs and symptoms of listeremia (see Section 5.2.4 and 6.2.6).

[24] At the completion of therapy, or upon the decision to discontinue/withdraw a subject prior to study completion, all treatment assessments will be completed. Subjects will then be contacted by phone every 3 months (±1 week) for *Lm* Surveillance monitoring for 1-year (see footnote 23).

[25] After all screening procedures have been completed, Investigators should utilize the IRT for treatment assignment. Subsequently, the IRT should be utilized on an as-needed basis for study drug resupply purposes.

7.2 Study Procedures

The Schedule of Events (Section 7) summarizes the study procedures to be performed at each visit. Individual study procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the Investigator.

7.2.1 Administrative Procedures

7.2.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in the study. Consent must be documented by the subject's dated signature on the most current Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved ICF or ICF addendum document along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated ICF should be given to the subject before participation in the study.

The initial ICF, any subsequent revised written ICF/ICF addendum and any written information provided to the subject must receive the IRB/IEC's approval/favorable opinion in advance of use. The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature.

The ICF will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

7.2.1.2 Eligibility Criteria

All inclusion and exclusion criteria will be reviewed by the Investigator or qualified designee to ensure that the subject qualifies for the study.

7.2.1.3 Subject Identification Card

A subject will be given a Subject Identification Card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The Investigator or qualified designee will provide the subject with a Subject Identification Card after the subject provides written informed consent.

7.2.1.4 Demographics/Medical/Surgical History

Demographic information, medical and surgical history, including surgical history for cancer will be obtained by the Investigator or qualified designee. Medical history will include all active conditions and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator.

7.2.1.5 Prior Cancer History

The Investigator or qualified designee will obtain prior and current details regarding disease status, including histopathologic confirmation of cancer, all prior cancer treatments and best response(s), if applicable (e.g., systemic, radiation and surgeries).

7.2.1.6 Prior/Concomitant Therapies and Procedures

The Investigator or qualified designee will review all prescription and nonprescription medication (excluding vitamins and nutritional supplements) taken by the subject from screening up to and including 30 days after the last administration of assigned study treatment when a subject discontinues her participation in the study; Protocol-mandated prophylactic medications and antibiotics administered during the 3-year *Lm* surveillance phase should also be captured in the eCRF along with any new procedures which are performed during this time. All of this information will be recorded in the subject's medical record and on the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Generic names should be used to eliminate confusion that may result from trade names.

7.2.1.7 Administer Prophylactic Medications

See Section 5.2.3.1 Pretreatment Prophylactic Regimen.

7.2.1.8 Study Treatment Administration

See Section 5.2.3.2 Placebo or ADXS11-001 Regimen.

7.2.1.9 Administer Oral Prophylactic Antibiotics

(1) During Study Treatment Period - All subjects will receive a 7-consecutive day course of oral antibiotic therapy starting approximately 72 hours (Day 4) after administration of each study treatment, except for the final dose of study treatment (either as per the Schedule of Events or upon discontinuation of study drug), at which time all subjects will receive a 3-week course of oral antibiotic therapy starting approximately 72 hours later (see (2), Post Study Treatment, below). Antibiotic therapy should consist of 80 mg trimethoprim/400 mg sulfamethoxazole tablet or matching placebo to be administered once daily for 7 consecutive days. Subjects who are not able to tolerate trimethoprim/ sulfamethoxazole will be discontinued from the study. These subjects will be unblinded (Section 7.2.6.1.5) to confirm randomization to Arm B (ADXS11-001), and subjects confirmed randomized to Arm B will receive commercially available oral ampicillin 500 mg four times daily. In the rare case that a subject also has a contraindication to ampicillin, the subject may receive another antibiotic to

which Listeria is sensitive to (refer to Section 6.2.5 and the Investigator's Brochure) and there are no contraindications to administer it to the patient. See Section 6.2.6 "Management and Surveillance of Listeria during Study Treatment Phase" for additional information.

(2) Post Study Treatment – All subjects will receive a 3-week course of oral trimethoprim/ sulfamethoxazole as defined in Section 7.2.1.9 (1) above to be initiated approximately 72 hours following the last dose of study treatment or immediately at the time of study discontinuation from the treatment period of the study. The dose and dosing instructions are also defined in Section 7.2.1.9 (1) above.

7.2.2 Clinical Procedures/Assessments

7.2.2.1 Adverse Event Monitoring

The Investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Schedule of Events and more frequently if clinically indicated. AEs will be recorded starting from the time that the first dose of study treatment is administered through the completion of the *Lm* surveillance period. Adverse and serious adverse events experienced during this period will be reported and recorded in the eCRF. Adverse experiences will be graded according to NCI CTCAE v 4.03 (see Section 10.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to study treatment.

7.2.2.2 Physical Examination

The Investigator or qualified designee will perform focused physical examinations (PE) during the Prime Phase on Weeks 4 and 7, and during the Maintenance Phase on the Week 23 visit. Full physical exams should be performed on all other visits.

The "full" PE will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular; abdomen (liver, spleen); extremities; groin, axillary and neck lymph nodes; assessment for edema and/or ascites, and a brief neurological exam; Gynecologic exam: external genitalia, speculum exam of the vagina, digital exam of the vagina and digital exam of the rectum/anus.

The "focused" PE will include the following assessments: examination of all symptomatic areas as well as skin; head; lungs; cardiovascular; abdomen (liver, spleen); extremities; groin, axillary and neck lymph nodes; assessment for edema and/or ascites; neurological exam.

A clinically significant finding or a worsening in a PE finding from the previous visit in the opinion of the Investigator or qualified designee will be recorded in the eCRF and reported as an AE.

PEs may be performed more frequently, as clinically indicated. An "Unscheduled Visit" form will be used to record this information in the eCRF.

7.2.2.3 Vital Sign Measurements

The Investigator or qualified designee will measure and record vital signs (including blood pressure, pulse rate, respiratory rate, and temperature) at the Screening Visit, prior to each assigned study treatment administration and [redacted] following each study treatment infusion. Weight will be collected prior to each study treatment infusion. Height will be measured at Screening Visit only.

A clinically significant finding or a worsening in a PE finding from the previous visit in the opinion of the Investigator or qualified designee will be recorded in the eCRF and reported as an AE.

7.2.2.4 Performance Status

The Investigator or qualified designee will assess GOG performance status (see Section 14.2 GOG Performance Scale).

7.2.2.5 Pelvic Examination

The investigator or qualified designee will perform a pelvic exam which will include a speculum exam with bimanual pelvic and rectal examination. Cervical and vaginal cytology will be performed at Screening only unless deemed necessary by the treating physician.

7.2.3 Laboratory Procedures/Assessments

Laboratory tests will be performed within 3 days prior to each dose of study treatment administered. **The laboratory results must be reviewed by the Investigator or qualified designee and found to meet all defined dosing criteria in order for a subject to receive study treatment (See** Table 7 Laboratory Tests**).**

Subjects must also be thoroughly screened for an ongoing or active infection prior to each treatment infusion. Subjects whose pre-infusion CBC reveals leukocytosis may need additional evaluation (e.g. a urinalysis) to rule out an active infection. Subjects with documented ongoing or active infection must receive appropriate antibiotic treatment for their underlying infection and return to ≤ CTCAE Grade 1 prior to dosing with study treatment. The Investigator should call the Sponsor to discuss a specific subject's case if there appears to be special circumstances which could result in resuming study treatment. In addition, the subject must also be at least 5 half-lives from their last dose of antibiotic.

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in (Table 7).

Surveillance monitoring for the detection of *Lm* will be initiated at the completion of study treatment according to the protocol or at the time of study discontinuation, if earlier. See Section 5.2.4 Follow-up Period for further details. All blood cultures that grow *Lm* will be reported to FDA as part of the Adverse Event and Serious Adverse Event monitoring during the *Lm* surveillance period.

Table 7 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	*Lm* Surveillance blood cultures*
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	
Absolute Neutrophil Count	C-Reactive Protein (CRP)*	Urine pregnancy test †	
	Carbon Dioxide ‡ *(CO_2 or bicarbonate)*		
	Creatinine		
	Calcium		
	Chloride		
	Erythrocyte Sedimentation Rate (ESR)*		
	Glucose		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total Protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

**Lm* surveillance Monitoring will include routine monitoring of CBC, CMP (including CRP, ESR) and blood cultures. All blood cultures positive for *Lm* will be reported to FDA as part of the Adverse Event and Serious Adverse Event monitoring during the *Lm* surveillance period.

[redacted]

7.2.5 Efficacy Assessments

The efficacy endpoints of the study are Disease Free Survival (DFS) and Overall Survival (OS). They will be assessed as follows:

7.2.5.1 Histologic/Cytologic Assessment for Disease Recurrence

Suspicion of recurrence can be based upon multiple clinical factors such as an abnormal physical and/or pelvic exam, including cytology and/or imaging. A biopsy and histologic examination and/or cytologic examination of a Fine Needle Aspirate (FNA) of a new suspected lesion is required to confirm disease recurrence when it is feasible in the opinion of the investigator.

A cytologic examination of a PAP smear is not acceptable to make a determination of recurrence however a cytologic examination of a Fine Needle Aspirate (FNA) of a new suspected lesion is acceptable to make a determination of recurrence.

7.2.5.2 Radiographic Assessments for Disease Recurrence

Baseline scans must be performed within 28 days of first study treatment infusion and must include contrast-enhanced CT of the chest and abdomen, plus a contrast-enhanced MRI of the pelvis; or a fluorodeoxyglucose (FDG) PET/CT of the chest, abdomen and pelvis. When PET/CT is used, the CT component of the PET/CT must be of diagnostic quality. Each anatomic area must be assessed using the same method at all time points (baseline and post-baseline) for each subject.

Note: The only acceptable methods of imaging the pelvis are MRI and PET/CT.

For subjects who have a medical contraindication to IV iodinated CT contrast, a non-contrast CT of the chest is acceptable; however, the abdomen must be imaged using a contrast-enhanced MRI. A non-contrast CT of the abdomen is not acceptable.

7.2.5.2.1 Unscheduled Radiographic Assessments

The schedule for radiographic assessments is detailed in Section 7.1 - Schedule of Events. Unscheduled radiographic assessments can occur and are based upon the clinical judgment of the investigator. Reasons for an unscheduled assessment may include, but are not limited to, clinical deterioration, subject complaint and/or findings stemming from a physical examination.

Any unscheduled imaging assessment should be analyzed by the site for recurrence and labelled in the eCRF as an "Unscheduled Visit." This assessment will also be submitted to the central imaging laboratory for evaluation. If the unscheduled imaging assessment occurs within 2 weeks of a scheduled visit, the unscheduled images should be evaluated with the nearest scheduled timepoint images. If disease recurrence is not confirmed on the evaluation of the images obtained at an unscheduled timepoint and within 2 weeks of a scheduled timepoint assuming all of the required scans were performed during the Unscheduled Visit then performing an additional radiographic assessment the next scheduled timepoint is not necessary.

7.2.6 Other Procedures

7.2.6.1 Withdrawal/Discontinuation and End of Study Visit

7.2.6.1.1 Discontinuation during Treatment Period Due to Disease Recurrence

When a subject meets a reason for discontinuation due to disease recurrence prior to the completion of the Treatment Period (Prime + Maintenance Phases), an End of Study (EOS) visit will be conducted and all applicable assessments, including physical examination, vital signs, performance status, pelvic examination, hematology and chemistry profile, urine dipstick, pregnancy test, as applicable, tumor imaging, dispense course of oral antibiotic, and [redacted] should be performed. Any AEs that are present at the time of discontinuation should be followed in accordance with the safety requirements outlined in Section 10. The subject will enter the Post-Disease Recurrence Period and *Lm* Surveillance Period will be initiated at this time.

7.2.6.1.2 Early Discontinuation

Early discontinuation is defined as discontinuation during the treatment period for a reason other than disease recurrence. During the Study Treatment Period, when a subject meets a reason for discontinuation other than disease recurrence prior to the completion of the Treatment Period (Prime + Maintenance Phases) all applicable DFS assessments (i.e.: tumor imaging, pelvic examinations, and [redacted]) should be performed in accordance with the Visit Schedule until early study termination, 6 years from the date of enrollment, disease recurrence, or death, whichever comes first. Any AEs that are present at the time of discontinuation should be followed in accordance with the safety requirements outlined in Section 10. The subject will enter the Follow-up Phase and the *Lm* Surveillance period will be initiated. Oral prophylactic antibiotics will be administered.

In subjects who have not experienced disease recurrence, physical exams, pelvic exams, and tumor imaging will occur at Weeks 12, 24, 36, and 48 during the first year (from date of enrollment) on trial, until early study termination, whichever comes first. During the second year, pelvic exams and tumor imaging will occur every 3 months (±1 week), and then every 6 months (±1 week) thereafter for four years, or until early study termination, whichever comes first. [redacted] so they coincide with the scheduled visits to assess tumor imaging and pelvic exams and with the

End of Study visit, which will occur 6 years from date of enrollment, or until early study termination, whichever comes first.

7.2.6.1.3 Discontinuation during the Follow-up Phase

During the Study Treatment phase, when a subject meets a reason for discontinuation from treatment, the EOS Visit should be conducted, after which the subject will enter the *Lm* Surveillance Period and will continue in accordance with the protocol requirements. During the Follow-up Phase, reasonable efforts should be made to have the subject contacted remotely and report any AEs that may occur during this phase.

7.2.6.1.4 Withdrawal of Informed Consent

In the event that any subject withdraws from the study treatment prior to completion, regardless of reason, reasonable efforts should be made to have the subject return for an EOS visit to have applicable assessments completed. The date the subject discontinued the study and specific reason for discontinuation will be recorded in the eCRF.

7.2.6.1.5 Blinding/Unblinding

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the investigator during the study. The subject's safety takes priority in determining if a treatment assignment should be unblinded during the study.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary (i.e. that it will alter the subject's immediate management, as in the case with subjects who discontinue due to the development of sensitivity to Bactrim). In many cases, the problem may be properly managed by assuming that the subject is receiving active product (ADXS11-001) and treated accordingly. It is highly desirable that the decision to unblind treatment assignment during the study be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind during the course of the study. The Principal Investigator should only call for emergency unblinding during the study AFTER the decision to discontinue the subject has been made.

For subjects who are receiving treatment and have not progressed, the Sponsor, subjects, investigator and site staff will be blinded to the study drug. Each investigative site must assign an unblinded pharmacist/designee, and an unblinded site monitor will be assigned by sponsor to provide oversight of drug supply and other unblinded study documentation. The Sponsor's central protocol team (including but not limited to clinical, statistics, data management) will remain blinded.

For this study, the method of unblinding is through the IVRS. For information on how to unblind for emergency, please consult the IVRS manual. In cases of accidental unblinding during the study, contact the Medical Monitor and ensure every attempt is made to preserve

the blind my minimizing the total amount of individuals that may become unblinded. Any request to unblind a subject for non-emergency purposes during the blinded portion of the study is required to be discussed with the Medical Monitor.

8 EVALUATION CRITERIA

8.1 Assessment of Disease

Assessment of disease will be performed to evaluate for the development of new disease, and will include:

- Physical exam
- Pelvic exam
- Tumor imaging
- Confirmatory biopsy (when it can be safely achieved in the opinion of the investigator)

8.1.1 Assessment of Disease Free Survival using Radiological Imaging Methodology

The primary endpoint of the study is DFS; therefore, the use of contrast-enhanced CT and MRI or PET/CT scans is to achieve the primary objective of identifying disease recurrence. RECIST 1.1 criteria is an accepted method for determining PFS in patients with metastatic disease where a primary goal of the study is to assess the ability of a drug to reduce or eradicate a tumor which was identified using radiological imaging. However, the patients who will be enrolled in this study will be unlike those enrolled in the majority of the studies which have used RECIST 1.1 because they must have no measurable or non-measurable disease at the baseline imaging assessment in order to be eligible to participate in the study. In addition, a primary objective of the study is to prevent tumor recurrence in accordance with the definitions provided in the following sections and not to achieve a tumor "response." Therefore, this study will only evaluate the ability of ADXS11-001 to prevent tumor recurrence and accordingly the only relevant designation for each timepoint measured by radiological imaging will be either "recurrence" or "no recurrence." As a result, modifications to the way that the RECIST 1.1 criteria will be implement are needed. The modifications to the way the RECIST criteria are applied are justified because this study population has: (1) has already received treatment for their cancer; (2) has no measurable or non-measurable disease by RECIST 1.1 criteria following CCRT with curative intent to follow during the study; (3) will be evaluated only for disease recurrence and (4) the results from a biopsy of the tumor being evaluated will be used as confirmation of disease. The intended "spirit" of RECIST 1.1 will be employed by using the terms and measurement criteria when they apply to this study and patient population.

A detailed description of tumor imaging assessments is provided below as well as in the Imaging Review Charter.

8.2 Determination of Disease Recurrence

The following criteria define the methodology which can be used to define disease recurrence.

- Clinical deterioration alone **cannot** be utilized as the sole determinant of recurrence and needs to be confirmed by either imaging or confirmatory biopsy.

- Results from the physical and/or pelvic exam, including cytologic assessment of a PAP smear, **cannot** be utilized as the sole determinant of recurrence and need to be confirmed by either radiographic imaging or confirmatory biopsy/fine needle aspirate of a suspected lesion.

- Results from biopsy/FNA of a suspected lesion can be utilized as the sole determinant of recurrence. However, results from radiographic imaging as determined by independent radiology review can only be utilized as the sole determinant of recurrence in the event that a tissue confirmation is not medically feasible in the opinion of the investigator. In cases where radiologic imaging confirms disease recurrence and a biopsy/FNA was obtained of the tumor being evaluated by imaging which is negative, then the subject will be considered to have disease recurrence. Histopathologic or cytologic assessment of tumor can occur by local lab.

8.2.1 Definition of Recurrence

The determination of recurrence must occur by definitive pathologic tissue confirmation (e.g., biopsy/fine needle aspirate). However, in those cases where it is not medically feasible to obtain a tissue sample then radiographic evidence, when confirmed by independent radiology review, will be used to determine recurrence.

8.2.1.1 Pathologic Definition of Recurrence

If a suspected lesion, especially in a previously irradiated field, is evaluated by histopathologic or cytologic examination and determined to be positive by biopsy/fine needle aspirate then the subject will be deemed to have progressed. Evaluation of suspected tumor material will occur at the site by a qualified pathologist.

8.2.1.2 Types of Radiographic Assessments

Three types of radiologic assessments will be performed in this study.

(1) Site Reads – These are performed on all subjects at baseline and follow-up time points. The site reads are used primarily for subject management.

(2) Confirmation of Recurrence Reads – These reads are performed by a small, limited pool of independent radiologists trained on the criteria and with expertise in radiologic evaluation of this subject group. If the results of the Site Read demonstrate recurrent disease (RD,) the images are electronically transmitted to the imaging core lab and within 72 hours from receipt the

results of an independent Confirmation of Recurrence (COR) will be transmitted to the site. The role of this reader is very targeted – to ONLY confirm or not confirm disease recurrence. The purpose of this assessment is to prevent subjects from being removed too early before true recurrence has actually occurred.

(3) Blinded Independent Read – Each subject will be separately evaluated by two readers for the RD parameters. When the two readers disagree on the presence or date of recurrence, a third expert reviewer (the Adjudicator) will review all results and select to agree with either reader A or B. The purpose of this read is to confirm RD. A separate radiology charter provides detailed information on all aspects of the radiographic assessments to be utilized for this protocol including adjudication. An independent radiology review will be conducted to confirm recurrence for all subjects. The independent radiology review will both an independent efficacy review and an independent review of COR.

In summary:

- The objective of the independent efficacy review is to prospectively determine when a subject enrolled in the study has developed a new tumor(s) that qualifies them for the recurrence determination. Expert and trained independent efficacy reviewers will interpret the images for the radiology review with no clinical information available. The independent efficacy review will provide the Sponsor with an assessment of the Time Point Response (TPR; NOTE: TPR will be limited to Recurrent Disease, [RD], non-RD, or Unable to Evaluate [UE] only; refer to Section 8.2.1.4) and the Date of Recurrence (if applicable) for each subject enrolled in the study.

- Separately, the independent COR review will provide the Sponsor and the investigator with a rapid confirmation of site-determined radiographic disease recurrence in instances when radiographic disease recurrence is suspected by the site radiologist. The purpose of this COR process is to provide the site PI with the best possible information regarding radiographic disease recurrence

- The population under evaluation by the independent efficacy reviewers will include all subjects enrolled on the ADXS001-02 study. For the purposes of the COR review, the population under evaluation by the independent COR reviewers will be all subjects suspected of having radiographic disease recurrence by the site radiologist and whose images were submitted to the central imaging lab for expedited COR review.

All treatment decisions remain the responsibility of the investigator.

A flow chart for the Independent Radiology Review Methodology can be found in Appendix 14.6.

8.2.1.2.1 Date of Recurrence

The Date of Recurrence is defined as the date of the first time point when RD is determined.

8.2.1.2.2 Assessment Date Conventions

It is acknowledged that an assessment may include several methods of evaluation performed over a period of several days within a window of time around an expected assessment date.

The convention to be followed when assessing each time point will be to assign a single date to evaluations performed within that time point. The Time Point Response (TPR) date will be recorded as the date of the first radiographic evaluation included in the series for that assessment.

8.2.1.3 Definition of Non-Disease Recurrence

An assessment of non-recurrent disease (Non RD) will be made when the criteria for RD has not been met and the TPR is neither UE nor NA.

8.2.1.4 Radiographic Assessment of Time Point Response

Radiographic assessments at each time point will be based on the presence or absence of new lesions. The time point assessment will be classified as either non-RD, RD or UE. This TPR is assessed with reference to Baseline for the evaluation of RD. The TPR for each time point will still be determined even in cases where the prior time point demonstrates RD. In addition, if an identified new lesion subsequently becomes UE it will continue to be considered present and classified as a RD.

Table 8 shows "Imaging Time Point Assignment of Response Including Biopsy Information." In situations where a biopsy result is negative for tumor, but results from imaging demonstrate disease recurrence then the final determination of RD will be based on the imaging results. In situations where a biopsy result is positive for tumor, but results from imaging do not demonstrate disease recurrence, then the final determination of RD will be based on the biopsy results.

Table 8 Imaging Time Point Assignment of Response Including Biopsy Information

Time Point Imaging Response	Biopsy Result[1]	Final Timepoint Imaging Response
RD	Not medically feasible	RD
	Positive for tumor	RD
	Negative for tumor	RD
UE	Not medically feasible	UE
	Positive for tumor	RD[1]
	Negative for tumor	UE
Non-RD	Not medically feasible	Non-RD
	Positive for tumor	RD[1]
	Negative for tumor	Non-RD

[1]A biopsy result, which is positive for disease, dictates a final timepoint response of recurrent disease irrespective of the imaging response.

9 DURATION OF STUDY

Subjects can receive assigned study treatment for up to 1 year. Subjects may refuse the study treatment at any time. Subjects who complete the Treatment Period or discontinue study treatment, will enter the Follow-up Phase (Section 5.2.4) for a total 1 year. During the Follow-up Period, all subjects will be contacted by phone every 3 months (±1 week) to determine whether they have experienced for several days, the following symptoms that could potentially be associated with delayed listeremia: fever or chills, headache, nausea, confusion or changes in alertness (see Section 6.2.6 for Management of Listeria During the Follow-up Period).

9.1 Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be discontinued from study treatment at the discretion of the Investigator should any untoward effect occur. In addition, a subject may be withdrawn by the Investigator or the Sponsor if enrollment into the study is inappropriate, the study plan is violated or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 9.1.

A subject may be discontinued from the study with no further follow-up or data collection for any of the following reasons:

- Screen Failure
- Subject Lost to Follow-Up

- Death
- Withdrawal of Consent by Subject
- Other (specify)

A subject may be discontinued from study treatment, but will continue to be followed for any of the reasons listed below:

- Confirmed Disease Recurrence
- Clinical Deterioration
- Adverse Event/Serious Adverse Event
- Sponsor Decision to Stop Study
- Withdrawal of Consent by Subject
- Investigator Decision
- Study Non-Compliance by Subject
- Subject has Positive Pregnancy Test

In all cases, the reason for and date of study discontinuation must be recorded in the eCRF and in the subject's medical records. The subject must be followed up to establish whether the reason was an AE, and, if so, this must be reported and monitored through resolution.

The Investigator must make every effort to contact subjects who discontinue the study prematurely or are lost to follow-up in order to schedule the end of therapy assessments. These attempts to contact such subjects must be documented in the subject's records. It is expected that three phone calls and sending a certified letter will be sufficient to establish diligence in efforts to contact the subjects.

All subjects who discontinue study treatment will continue to be followed and evaluated for recurrence as outlined in Section 7.1, Schedule of Events, for up to 5 years or death.

9.2 Subject Replacement Strategy

Subjects will not be replaced.

10 ADVERSE EVENT MONITORING AND REPORTING PROCEDURES

All Investigators have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the study treatment. It is the responsibility of the

Investigator to supply the medical documentation needed to support expedited AE reports in a timely manner.

10.1 Definitions

Adverse event (AE): any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of study treatment (ADXS11-001 or Placebo) is also an AE.

AE(s) may occur during the course of the study, from overdose (whether accidental or intentional), or from abuse and withdrawal.

AE(s) may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Serious adverse event (SAE): any AE occurring at any dose or during any use of ADXS11-001 or Placebo that:

- Results in death
- Is life threatening
- Results in persistent or significant disability/incapacity
- Results in or prolongs an existing inpatient hospitalization
- Is a congenital anomaly/birth defect
- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose
- Is another important medical event

Recurrence of the cancer under study is not considered an AE unless it results in hospitalization or death.

Overdose: any dose exceeding the prescribed dose by 100%. No specific information is available on the treatment of overdose of ADXS11-001. In the event of an overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment

should be provided if clinically indicated. If an AE(s) results from the overdose of ADXS11-001, the AE is reported as a SAE(s), even if no other seriousness criteria are met. An overdose without any associated clinical symptoms or abnormal laboratory results is reported as an AE.

10.2 Assessing and Recording Adverse Events

AEs will be recorded and assessed from the time the informed consent form is signed through 30 days past last dose. Beyond that point, AEs related to the signs and symptoms of listeremia should be assessed and reported during the *Lm* surveillance period. Events will be recorded on the AE eCRF. AEs will also be assessed to determine if it meets the definition of "serious." In the event that an AE meets the criteria for "serious" the appropriate SAE form will be completed and the event reported in accordance with the required time period. The reporting timeframe for SAEs is described in Section 10.2.5.

10.2.1 Evaluating Adverse Events

An Investigator who is a qualified physician will evaluate all AEs according to the NCI CTCAE v 4.03. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE eCRF. In these cases, when the intensity of an AE changes over time for a reporting period (e.g., between visits) each change in intensity will be reported as an adverse event until the AE resolves. For example, 2 separate AEs will be reported if a subject experiences Grade 1 diarrhea for 3 days, meeting the definition of an AE, and then after 3 days the AE increases to a Grade 3 intensity that lasts for 2 days and then resolves. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the AE definition and a stop date equal to the day that the event increased in intensity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date on the day that the event changed intensity again or resolved. For analysis purposes, this will be considered one AE for this subject and the maximum intensity will be recorded.

When possible, AEs should be described in terms of a change in the baseline status or with a diagnosis or summary term rather than as individual symptoms.

Criteria for Determining AE Severity: The descriptions and grading scales found in the revised NCI CTCAE v 4.03 will be utilized for AE reporting.

Criteria for Determining AE Causality: The following attribution categories must be used in assessing the relationship between the AE and the study treatment: If the Investigator does not know whether or not the investigational agent caused the event, then the event will be handled as "related to investigational agent."

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to investigational agent/intervention	Unrelated	The AE *is clearly* ***NOT*** *related* to the study treatment
	Unlikely	The AE *is* ***doubtfully related*** to the study treatment
Related to investigational agent/intervention	Possible	The AE ***may be related*** to the study treatment
	Probable	The AE ***is likely related*** to the study treatment
	Definite	The AE ***is clearly related*** to the study treatment

10.2.2 Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the AE CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g., anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 (severe) event, as per CTCAE V4.03, does not automatically indicate a SAE unless it meets the definition of serious, as defined in Section 10.1 "Definitions" and/or as per the Investigator's discretion.

10.2.3 Reporting Abnormal Test Findings

The criteria for determining whether an abnormal test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention: and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatments, or other; and or
- Test result is considered to be an AE by the Investigator or sponsor

Merely repeating an abnormal test, in the absence of any of the above conditions does not constitute an AE. An abnormal test result that is determined to be an error does not require reporting as an AE.

10.2.4 Reporting Events Related to Immune Cell Activation

The most relevant AEs to consider under this category are high-grade hypotension (refractory to fluids and vasopressors) and high-grade hypoxia. In the prior version of this protocol, these events were included under the term "cytokine release syndrome" (CRS) along with nausea, headache, tachycardia, rash, and shortness of breath as per NCI CTCAE v 4.03 criteria. However, the description and grading scales for CRS in the NCI CTCAE v. 4.03 are not adequate to appropriately capture the toxicity associated with ADXS11-011, as per a recent communication from FDA. Investigators therefore are discouraged from using umbrella terms such as "cytokine release syndrome" or "infusion reaction" and are instead strongly encouraged to list each symptom and associated Grade individually.

Considering these communications with FDA, > Grade 3 hypotension and >Grade 3 hypoxia, along with other high-grade organ toxicities, will be considered Events of Special Interest and for which new guidelines for grading and management have been developed (Table 6.1-6.4). These are intended to be guidelines for the investigators, who will treat patients according to institutional recommendations.

10.2.5 Immediate Reporting of Serious Adverse Events to the Sponsor

Any SAE, or follow up to a SAE, including death due to any cause other than recurrence of the cancer under study that occurs to any subject from the time the consent is signed through 30 days past last dose, , whether or not related to ADXS11-001. Beyond that point, SAEs related to the signs and symptoms of listeremia should be assessed and reported during the 1-year *Lm* surveillance period. SAEs must be reported within 24 hours to the Sponsor at Syneos Health Clinical Pharmacovigilance (Attn: Syneos SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@syneoshealth.com

Additionally, any SAE, considered by an Investigator who is a qualified physician to be related to ADXS11-001 that is brought to the attention of the Investigator at any time outside of the time period specified above also must be reported immediately to the Sponsor.

SAE reports and any other relevant safety information are to be forwarded to Syneos Health Clinical Pharmacovigilance (Attn: Syneos SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@syneoshealth.com).

All reports of overdose with AE(s) must be reported within 24 hours to Syneos Health Clinical Pharmacovigilance (Attn: Syneos SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@syneoshealth.com).

10.2.6 Reporting Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered AEs, it is the responsibility of Investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), that occurs during the study or within 120 days of completing the study, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects who become pregnant must be

followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as an SAE (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours of awareness to Syneos Health Clinical Pharmacovigilance (Attn: Syneos SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@syneoshealth.com).

10.3 Data Monitoring Committee

Details on safety monitoring, modifying or stopping the study early are found in the Data Monitoring Committee Charter. In general, consideration will be given to modifying the treatment or stopping the study early based on the reports of the DMC if:

1. the futility boundary is crossed in the planned, formal interim analysis (See Section 11.3)

2. a clearly more effective therapy becomes available

3. the toxicity associated with ADXS11-001 treatment appears to outweigh the potential benefit to the subjects

The toxicity would be considered excessive if in the ADXS11-001 arm there is a significantly higher than expected rate of life-threatening (Grade 4) AEs. The DMC will formally evaluate unblinded study reports which will provide detailed tabulations of all AEs by grade and treatment group on a regular, ongoing basis in accordance with the schedule as defined in the DMC Charter.

11 STATISTICAL CONSIDERATIONS

In the original study design (Protocol Version 1.1 – Version 4.1), a total of 450 subjects were to be randomly assigned (1:2) to Placebo (Arm A; control arm) or ADXS11 001 (Arm B; experimental arm). However, after the 110th subject was randomized, the Sponsor terminated the study and further enrollment early for reasons other than safety and efficacy. Therefore, the assessments and analyses in the Statistical Analysis Plan will apply only to the 110 subjects randomized by the time of early study termination.

All subjects enrolled in the study will be moved to the End of Treatment (EoT) visit by 31 July 2019 (except for 1 subject whose last dose occurring by 4 September 2019) and will not receive study treatment thereafter.

As per the original protocol, *Lm* surveillance will begin for all patients at 3 months (±2 weeks) after treatment discontinuation, and will consist of *Lm* safety evaluations only, as described in the protocol, for all subjects who have received at least one dose of study treatment.

However, efficacy evaluations will no longer be performed on any subjects after the early study termination date, e.g., 31 July 2019.

11.1 Sample Size Considerations

For a study involving a sample of subjects with the same distribution of stage as listed in (Table 9), the estimated probability of surviving disease-free for at least 4 years is approximately 50%. Thereafter, the probability of recurring or dying increases very slowly (2-3% per year). This study will be considered sufficiently mature for a final analysis when there are at least 184 subjects reported as having experienced either recurrence of their cancer or death due to any cause. This number of events provides 85% power for detecting a treatment hazard ratio (HR) of 0.620. The type I error will be set to 0.025 (accounting for interim analysis) for a one-tail test of the null hypothesis (HR=1) using stratified logrank procedure. A treatment hazard ratio of 0.620 is comparable to increasing the expected proportion alive and disease-free for at least 4 years from 0.500 to 0.651.

Table 9 Summary of Study Parameters and Targeted Sample Size

Design Parameter	
Type I error (1-sided)	0.025
Statistical power	0.85
Treatment: Reference allocation ratio	2:1
Interim analysis *	50% IT
Hazard ratio | H_A	0.620
Percent increase in DFS at 4 yrs. | H_A	0.151
Number of DFS events required**	184
Target accrual (N of subjects)***	450
Accrual duration****	55 months
Post-accrual follow-up duration****	20 months

*An interim analysis of safety and efficacy planned at 50% of the information time (IT)
**East version 5.4, H_A is the alternative hypothesis for power calculations.
***Assumes cumulative probability of recurring or dying on the reference treatment during the first 4 years is approximately 50%, and thereafter this probability does not increase. See Note on Target Accrual (below).
****The estimated duration of accrual and post-accrual follow-up depend on the expected average accrual rate and the number of investigative sites participating in the study. It is estimated that ~ 450 subjects will be enrolled in 55 months.

A Note on Target Accrual: The statistical power of this study is a function of the expected number of subjects experiencing either recurrence or death observed in each treatment group at the time of final analysis. The anticipated DFS event rate in this population is relatively high during the first 4 years of enrollment but declines considerably thereafter. Specifically, the cumulative probability of recurrence or death with the first 4 years is expected to be at least 50% (see Figure 4). However, for those who have not recurred during the first 4 years, the cumulative probability of recurrence or death during the subsequent 4 years is expected to be less than 10%. It is anticipated that about 30-40% will not experience a recurrence of

their cancer within their lifetime. The targeted accrual for this study is based on the expected (mean) number of recurrences or deaths that will be observed under the alternative hypothesis after following each subject for at least 4 years. However, the number of subjects experiencing either recurrence or death within 4 years of for a particular study is actually a random number. By chance alone, the actual number of DFS events in this study could be less than expected. Moreover, it is possible for more than planned low-risk subjects could be enrolled. Therefore, it is prudent to enroll slightly more subjects than the minimum. Assuming that there are no subjects who recur after the first 4-years of follow-up, as was done for this study to determine the target accrual, provides some protection for underestimating the actual proportion of subjects recurring in the study sample. It is worth noting that this study will include criteria, which were not used in GOG-219, to clinically determine node involvement (e.g., minimum size of nodes) that are intended to reduce the frequency of false-positives. Therefore, the DFS event rate observed in this study could be slightly higher than predicted by the historical data from GOG-219 (see Section 11.2.7).

11.2 Statistical Analysis Plan Summary

The full statistical analysis plan is detailed in a separate document, with information presented in this section adjusted as applicable to allow data analysis up to the time of early study treatment termination [i.e., after 110th subject was randomized, the Sponsor terminated the study and further enrollment, and all subjects moved to the End of Treatment (EoT) visit by 31 July 2019 (except for 1 subject whose last dose occurred on 2 September 2019)].

11.2.1 Study Design

This is a 2-arm, placebo-controlled, randomized (2:1 ADXS11-001/placebo), Phase 3 clinical study. The treatment for each enrolled subject will consist of either:

- Placebo (P)
- ADXS11-001 (E)

The general objective of this study is to evaluate the relative efficacy and safety of adding ADXS11-001 in the adjuvant setting following CCRT with curative intent for the treatment of women with HRLACC.

11.2.2 Definition of Study Populations for Analyses

The primary analysis population for the primary efficacy endpoints will be based upon the intention to treat (ITT) principle population. The ITT population includes all subjects enrolled into this study regardless of their eligibility or compliance with their assigned treatment. Secondary efficacy endpoints will be reported for the ITT population. Analyses of adverse events will include all subjects enrolled into this study who initiated their assigned study treatment.

11.2.3 Measures of Efficacy and Safety

The principal observations for evaluating the therapeutic efficacy and safety of the study regimens are:

1. Primary efficacy endpoint: DFS

2. Secondary efficacy endpoint: OS

Safety endpoints: frequency and severity of related AEs as defined by CTCAE v 4.03, changes in physical examinations, vital signs measurements, and clinical laboratory evaluations. An external DMC will evaluate and analyze accrued subject data periodically throughout the study.

For the analyses of the primary endpoint, the DFS duration for each subject will be assessed from the date of randomization to the date of first recurrence as determined by independent radiology review or death (due to any cause). For those subjects who have not recurred or died, the duration at risk of recurrence will be calculated up to the date of the subject's last disease assessment.

11.2.4 Enrollment and Treatment Allocation

Subjects are enrolled onto the study via a web-based enrollment and treatment randomization procedure. Treatments will be sequentially allocated from predetermined concealed lists consisting of randomly permuted study treatments balanced within blocks. The randomization procedure will allocate approximately twice as many subjects to ADXS11-001 than placebo within the 8 subgroups defined by the following factors:

1. Para-aortic node metastases (yes vs no/unknown).

2. Region (USA vs Rest of World)

3. FIGO Tumor Stage (Stage I, II vs Stage III, IV) **(2014 FIGO Staging)**

11.2.5 Primary Study Hypothesis

Disease-free survival is the primary endpoint of the study. The null hypotheses for the primary endpoint of DFS is:

Hp:E,DFS: ADXS11-001 following chemoradiation does not increase the duration of DFS compared with placebo in subjects with HRLACC.

11.2.6 Analytic Procedures for the Testing Hypothesis: Hp:E,DFS

The logrank procedure will be used to evaluate the primary study hypothesis. The logrank calculation will be stratified by 2014-FIGO tumor stage (I or II vs III or IV) system, region (US vs Rest of World), para-aortic node metastases (yes vs no/unknown). The analysis of DFS will consider all deaths as events, regardless of the cause of death. The impact of the

other potential prognostic/predictive factors will be explored in multivariate and/or subgroup analyses and will include, but not necessarily limited to, prior brachytherapy and radiation field at baseline. A sensitivity analysis will be performed to evaluate subjects who were determined to meet the criteria for recurrence based on radiographic imaging, but the results from biopsy were negative. The SAP will provide details for the sensitivity/supportive analyses which will be performed.

For the primary analysis, subjects will be grouped according to their randomly assigned treatment and subjects will be included in the analysis, regardless of their compliance with their assigned treatment plan. The primary analyses will use the duration of DFS as it is determined by the Independent Radiology Reviewer.

11.3 Interim & Final Analyses

As a result of early study termination, no interim analysis is to occur and the plans below described as per the original protocol are adjusted accordingly. The final analysis is clarified and detailed in the full statistical analysis plan in a separate document (see Section 11.2).

An independent Data Monitoring Committee (DMC) will periodically assess the safety data during the treatment phase. A description of the roles and responsibilities and details of the review processes are provided in a separate DMC charter.

An administrative analysis is planned prior to completing the enrollment of the targeted number of subjects onto this study. In this assessment the DMC will be given the opportunity to recommend an adjustment to the targeted total accrual (N = 450 subjects) when the Sponsor has positively determined that the number of DFS events required for study maturity will not be attained within a reasonable time closely associated with the projected follow-up period (e.g., 20 months). In this case, the Sponsor will provide the DMC with the following information from their analysis:

1- DFS events estimate using the Kaplan Meier method

2- A revised enrollment and DFS events projection based on the actual current rates compared with those used in the original assumptions

3- Other information as requested by the DMC

No treatment unblinding will be performed as part of this analysis. The Sponsor will perform the analysis when a sufficient number of subjects have been enrolled in order to ensure a robust sample size and allow the DMC time to review the information provided to them and make a recommendation for increasing the sample size. Based on the current enrollment assumptions it is estimated that the analysis will be performed after the 300th subject is

enrolled and the initial 12-week post-baseline imaging assessment are reviewed. The Sponsor will maintain close communication with the DMC to ensure the committee is aware of the current status of enrollment and the timing for the planned analysis. The DMC will prepare a document which will detail their recommendation and supporting rationale and provide it to the Sponsor. Any output supporting their recommendation will also be included.

A formal interim analysis which will only assess futility will be performed when there is at least, and as close to as administratively possible to, one-half the number of events (92 events) required for full maturity of the study. At this time the logrank test of the null hypothesis will be calculated as described in Section 4.3.1 of SAP and futility will be assessed. An O'Brien and Fleming-like spending function will be used. The O'Brien-Fleming-like alpha (and beta) spending function used in EAST has the functional form $\alpha(t)=2-2\Phi(Z\propto/2/\sqrt{t^*})$ for one-sided tests, where Φ denotes the standard normal distribution function and t* the information fraction. These functions require that the percent of information time be specified at the time of the interim analyses. The percent of information time (information fraction) will be calculated as the number of enrolled individuals who have reported experiencing disease recurrence or death, relative to the required number for the final analysis. The futility analysis will be "non-binding".

The interim analysis will be performed by an independent Study Reporting Statistician, otherwise unaffiliated with the study, who will provide the results only to the DMC. As detailed in the DMC charter, the DMC may consider making a recommendation to the Sponsor to discontinue the study if the p-value from the logrank test of the primary study hypothesis falls outside of the boundary for futility indicated by the O'Brien and Fleming-like boundary proposed by Lan and Demets [50] and computed using by East (Cytel).

The statistical boundary only serves as a trigger for the DMC to consider stopping the study. A complete assessment for stopping a study will involve considerations for the adverse events profile, impact on other study endpoints, and possibly external information. In the event the criteria for stopping are met, the interim results will be shared only with the Steering Committee members. The Sponsor in consultation with the DMC, Steering committee and other relevant individuals will have the authority to make the final decision regarding the outcome of the study. All members privy to the results as well as the results shared, and the sponsor's final decision will be documented and made available for regulatory review. In the event that additional individuals outside the steering committee are involved in the decision, the information shared and the individuals involved will also be documented.

11.4 Monitoring of Accrual and Event Rates

Administrative monitoring of accrual and event rate based on blinded data will be performed periodically by the Sponsor's blinded statistical team prior to completing the enrollment of the targeted number of subjects onto this study. The team will analyze the following information:

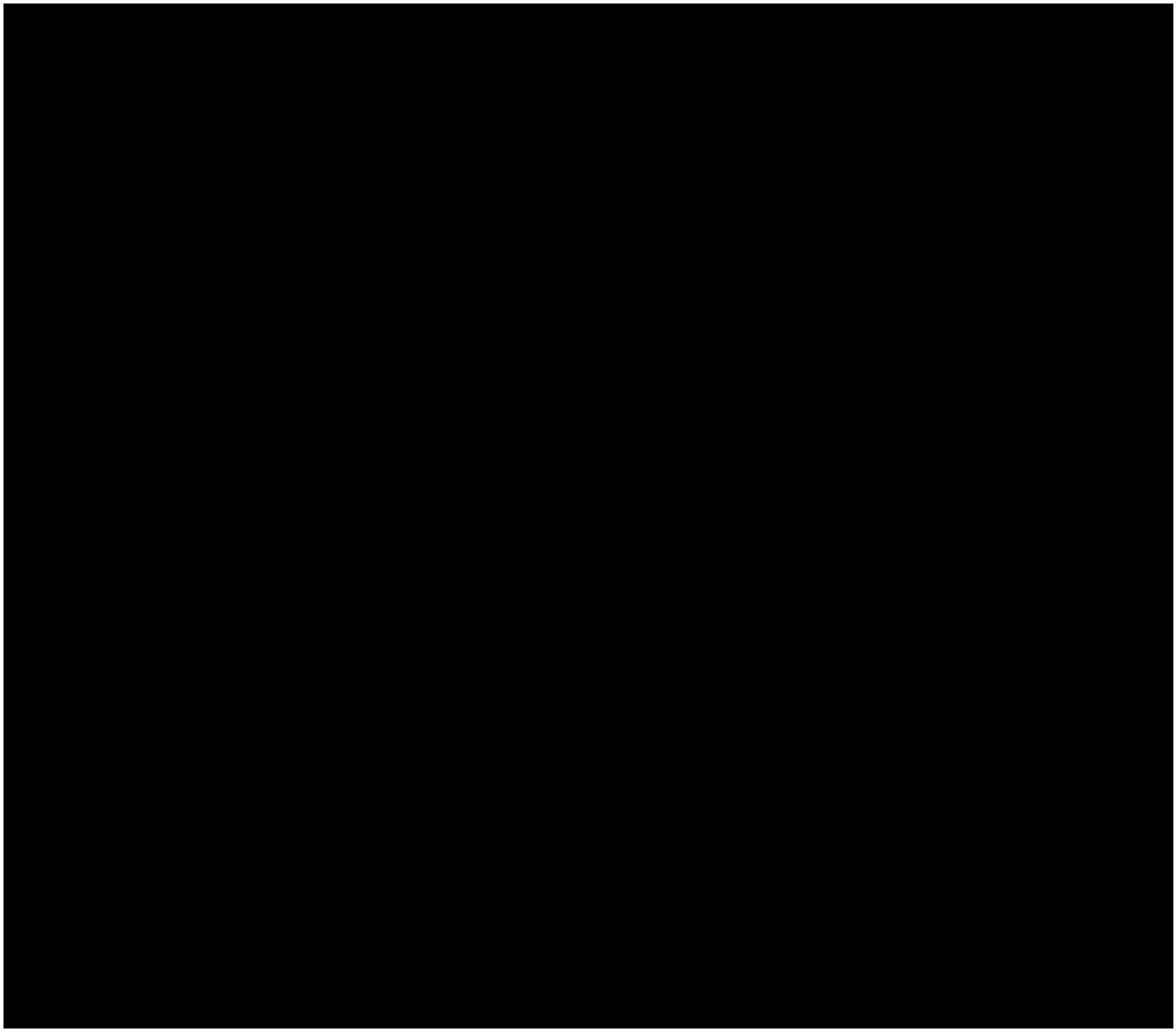
4- DFS events estimate using the Kaplan Meier method

5- A revised enrollment and DFS events projection based on the actual current rates compared with those used in the original assumptions

On the basis of this information, if the Sponsor determines that the number of DFS events required for study maturity will not be reached within reasonable time, then the Sponsor might consider increasing the targeted accrual beyond 450 subjects.

11.5 Estimated Study Duration

With an average accrual rate of 5 patients per month for the first 26 months and 11 patients per months thereafter, enrollment of 450 subjects will be completed in approximately 55 months. If the DFS event rate among those randomized to placebo is as displayed in Figure 4 and the true treatment HR is 0.62, the study will reach full maturity with 184 DFS events approximately 35 months after enrollment is complete.



12 ADMINISTRATIVE AND REGULATORY DETAILS

12.1 Confidentiality

The confidentiality of records and information that could identify subjects must be protected, respecting privacy and confidentiality rules in accordance with applicable regulatory requirements.

The Investigator will agree to maintain in confidence all information furnished by the Sponsor and all data generated in the study, except as provided or required by law, and will divulge such information to the IRB/IEC with the understanding that confidentiality will be maintained by the committee.

The identity of all subjects in this study must remain confidential, and only the initials of said subjects will appear on the eCRF. Qualified representatives from the relevant regulatory agencies, the Sponsor, or its agents may inspect the subject/study records. Subject data obtained during the study may be presented in scientific publications, but at no time will subject names be used.

12.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration (FDA) Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the Investigator's/Sub Investigator's responsibility to comply with any such request. The Investigator/Sub Investigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements.

The Investigator/Sub Investigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The Investigator/Sub Investigator(s) also consent to the transmission of this information to the Sponsor in the US for these purposes.

12.3 Compliance with Law, Audit and Debarment

International Conference on Harmonisation (ICH) Guidance on Good Clinical Practice ([GCP] CPMP/ICH/135/95) and the Sponsor require the Investigator to be aware of his/her obligations in the conduct of this study.

Representatives of the Sponsor must be allowed to visit all study site locations periodically to assess data quality and study integrity. On site, they will review study records and directly compare them with the original source documents, discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by auditors designated by the Sponsor and by government inspectors who must be allowed access to CRFs, source documents, and all other study files. Sponsor audit reports will be kept confidential.

THE INVESTIGATOR MUST NOTIFY THE SPONSOR PROMPTLY OF ANY INSPECTIONS SCHEDULED BY REGULATORY AUTHORITIES AND PROMPTLY FORWARD COPIES OF INSPECTION REPORTS TO THE SPONSOR.

12.4 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDA Modernization Act (FDAMA) and the FDA Amendments Act (FDAAA), the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to the Clinical Study's Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

12.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

12.6 Data Management

The Investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the Investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the Investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

13 ABBREVIATIONS

AEs	Adverse Events
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APC	Antigen Presenting Cell
ASCO	American Society for Clinical Oncology
AST	Aspartate aminotransferase
BCG	Bacillus Calmette–Guérin
BRM	Biologic Response Modifier
CCRT	Combination chemotherapy and radiotherapy
CFU	Colony Forming Unit
CIN	Cervical Intraepithelial Neoplasia
CMP	Comprehensive metabolic panel
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CTEP	Cancer Treatment Evaluation Program
CR	Complete response
CRP	C-reactive Protein
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Comprehensive Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DFS	Disease Free Survival
DLT	Dose limiting toxicity
DMC	Data monitoring committee
EBRT	External beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ERC	Ethical Review Committee
ESR	Erythrocyte sedimentation rate
[redacted]	
FDA	Food and Drug Administration
FDG-PET	Flurodeoxyglucose-positron emission tomography
FFPE	Formalin-fixed, paraffin-embedded
FIGO	International Federation of Gynecology and Obstetrics
GCP	Good Clinical Practice
GGT	Gamma glutyltransferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GOG	Gynecologic Oncology Group
Gy	Gray
HBsAg	Hepatitis B surface antigen
HCC	Hepatocellular cancer
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

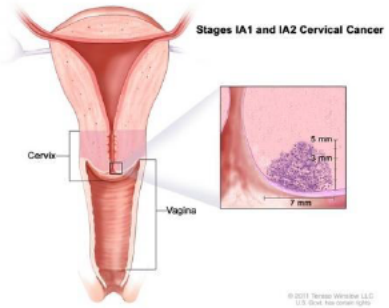
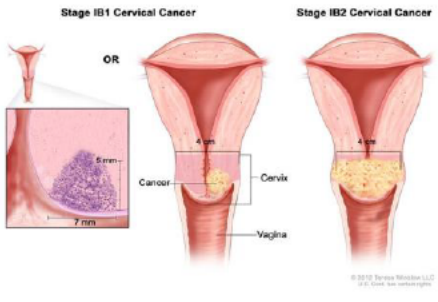
HPV	Human papilloma virus
HR	Hazard ratio
HRLACC	High risk locally advanced cervical cancer
HRQOL	Health related quality of life
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	International Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
irAE	Immune related adverse event
IV	Intravenously
LACC	Locally advanced cervical cancer
LFT	Liver Function Test
LLO	Listeriolysin O
Lm	*Listeria monocytogenes*
Lm-LLO	*Listeria monocytogenes* Listeriolysin O
MDSC	myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Complex
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti Inflammatory Drugs
OS	Overall survival
OTC	Over the counter
PALN	Para-aortic lymph node
PET	Positron emission tomography
PI3K	Phosphoinositide 3-kinase
PR	Partial response
[redacted]	
PWB	Physical Well Being
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Relapse free survival
ROC	Receiver operating characteristic
SAE	Serious Adverse Event
SD	Stable Disease
SOC	Standard of Care
SOP	Standard operating procedure
SUV	Standard uptake value
tLLO	Truncated LLO
TME	Tumor microenvironment
TNFα	Tumor necrosis factor alpha

TOI	Study Outcome Index
TSE	Treatment side effects
Tregs	Regulatory T cells
ULN	Upper limit of normal
US	United States
WBC	White blood cell
wt-*Lm*	wild type *Listeria monocytogenes*

14 APPENDICES

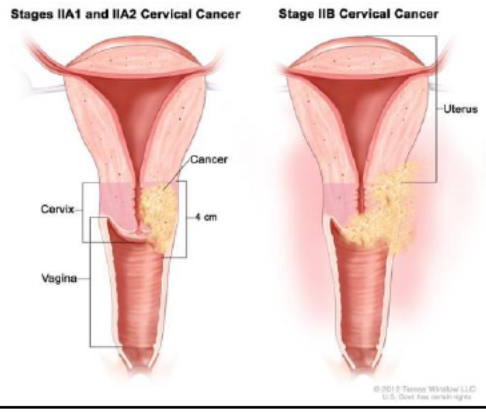
14.1 2014 FIGO Staging System

Table 11 Definitions of 2014-FIGO Stage I

Stage[a]	Description	Illustration
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded).	
IA	Invasive cancer identified only microscopically. (All gross lesions even with superficial invasion are Stage IB cancers.) Invasion is limited to measured stromal invasion with a maximum depth of 5 mm[b] and no wider than 7 mm.	
IA1	Measured invasion of stroma ≤3.0 mm in depth and ≤7.0 mm width.	
IA2	Measured invasion of stroma >3.0 mm and <5.0 mm in depth and ≤7 mm width.	
IB	Clinical lesions confined to the cervix or preclinical lesions greater than stage IA	
IB1	Clinical lesions no greater than 4 cm in size	
IB2	Clinical lesions >4 cm in size	

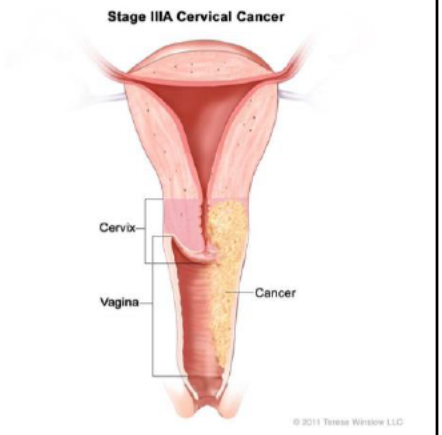
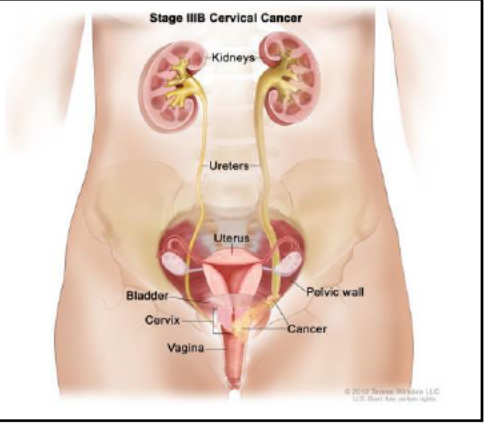
FIGO = Féderation Internationale de Gynécologie et d'Obstétrique
[a] Adapted from FIGO committee on gynecologic oncology (FIGO Committee on Gynecologic Oncology: 2014 FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. [51]
[b] The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space invasion should not alter the staging.

Table 12 Definitions of 2014-FIGO Stage II

Stage[a]	Description	Illustration
II	The carcinoma extends beyond the uterus but not extended onto the pelvic wall or to the lower third of the vagina	
IIA	Involvement of up to the upper 2/3 of the vagina. No obvious paramestudy involvement	
IIA1	Clinically visible lesion ≤4.0 cm	
IIA2	Clinically visible lesion >4.0 cm	
IIB	Obvious parametrial involvement but not onto the pelvic sidewall	

FIGO = Féderation Internationale de Gynécologie et d'Obstétrique
[a] Adapted from FIGO committee on gynecologic oncology (FIGO Committee on Gynecologic Oncology: 2014 FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. [51]

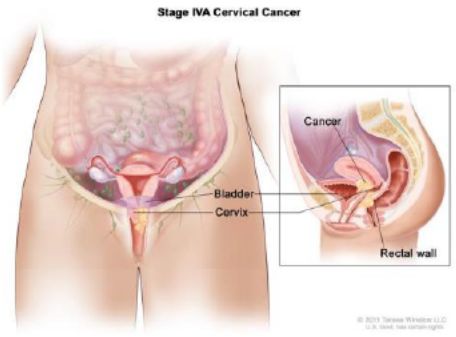
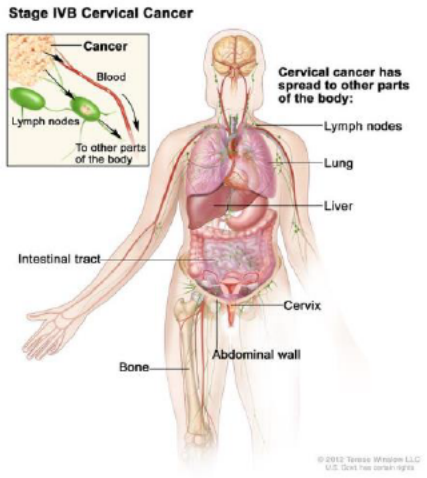
Table 13 Definitions of 2014-FIGO Stage III

Stage[a]	Description	Illustration
III	The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer-free space between the tumor and pelvic sidewall. The tumor involves the lower third of the vagina. All cases of hydronephrosis or nonfunctioning kidney should be included unless they are known to be due to other causes.	
IIIA	Involvement of the lower vagina but no extension onto pelvic sidewall.	
IIIB	Extension onto the pelvic sidewall, or hydronephrosis/non-functioning kidney.	

FIGO = Féderation Internationale de Gynécologie et d'Obstétrique

[a] Adapted from FIGO committee on gynecologic oncology (FIGO Committee on Gynecologic Oncology: 2014 FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. [51]

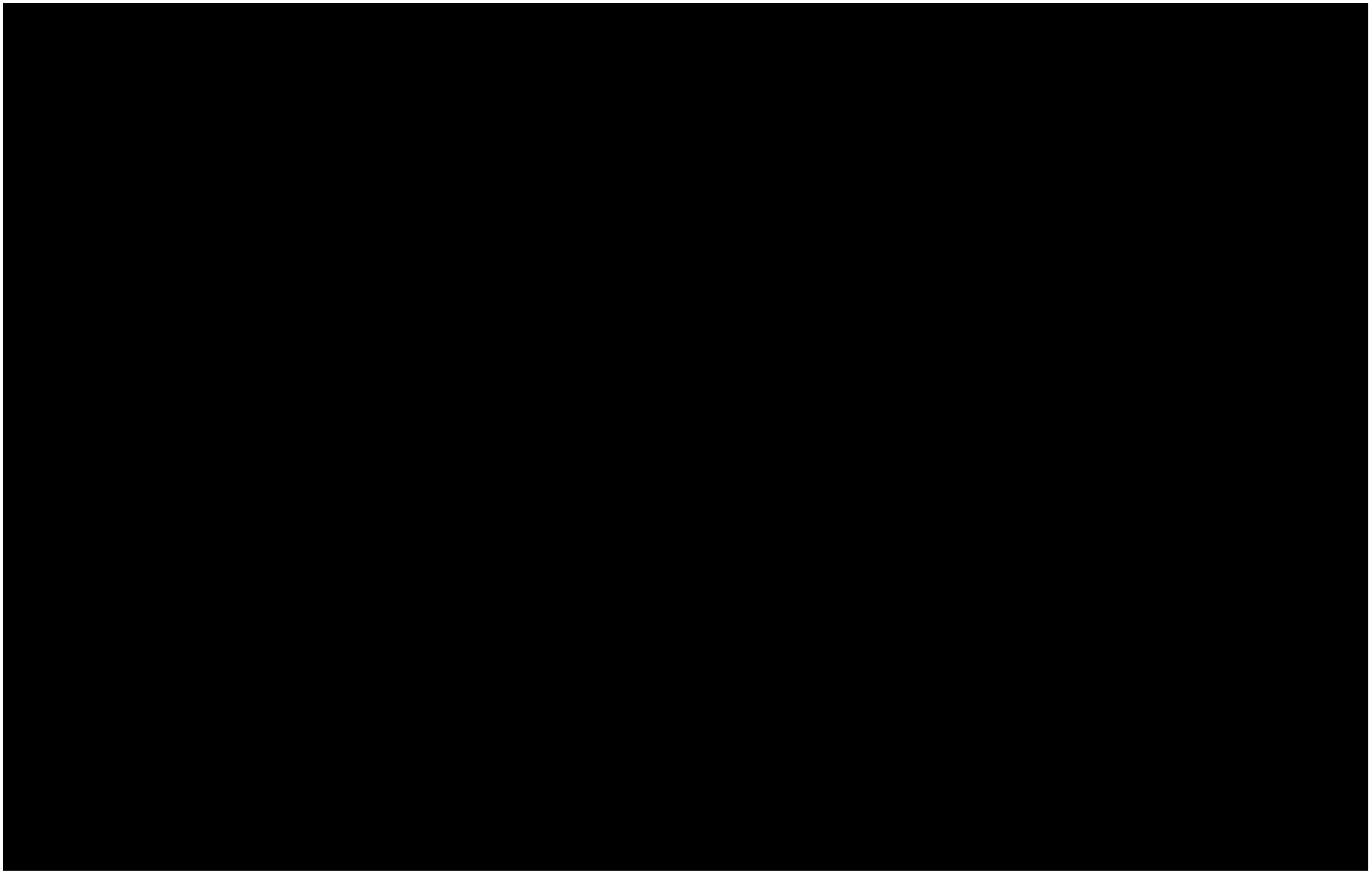
Table 14 Definitions of 2014-FIGO Stage IV

Stage[a]	Description	Illustration
IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.	
IVA	Spread to adjacent pelvic organs.	
IVB	Spread to distant organs.	

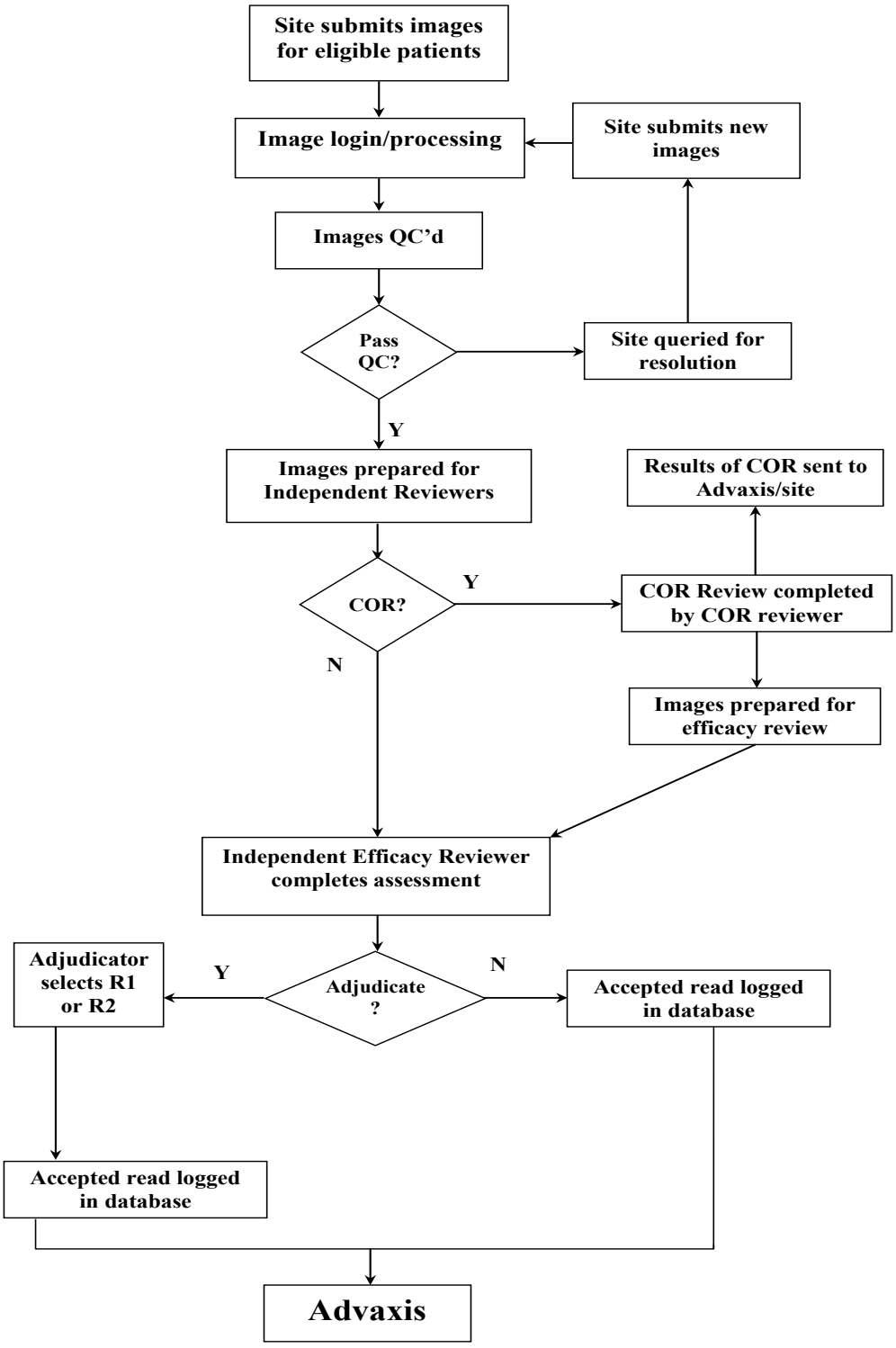
FIGO = Féderation Internationale de Gynécologie et d'Obstétrique
[a] Adapted from FIGO committee on gynecologic oncology (FIGO Committee on Gynecologic Oncology: 2014 FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. [51]

14.2 GOG Performance Status

Grade	Karnofsky Scale	Performance
0	90 & 100	Fully active
1	70 & 80	Restricted in physically strenuous activities, but ambulatory
2	50 & 60	Ambulatory; capable of self-care; unable to work; up to 50% if waking hours
3	30 & 40	Limited self-care; confined to bed or chair 50% of waking hours
4	10 & 20	Completely disabled; no self-care



14.6 Flow Chart of the Independent Review Methodology



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16 SUMMARY OF CHANGES WITHIN PROTOCOL AMENDMENT

#	Section	Revision	Rationale
1	Throughout	Protocol was updated to reflect approved End of Study Procedures as part of early study termination notifications to sites and Health Authorities, which included collection of AEs and SAEs during the *Lm* surveillance period for all AE/SAEs associated with listeremia. Further efficacy assessments post study termination in the Post-Treatment Follow-Up Period and Post-Disease Recurrence Period were deleted as no longer applicable.	Change made consistent with already approved procedures per "Appendix 1 - Study Closure Guidance Clarification Document" in Sponsor's early study termination notification submitted to authorities post 31 July 2019.
2	Synopsis, 5.2.4, 6.2.5, 6.2.6, 9	The *Lm* surveillance duration changing from 3-years to 1-year, along with remote surveillance and assessment of listeremia signs and symptoms (i.e., fever or chills, headache, nausea, confusion or changes in alertness experienced for several days) via phone contact in place of routine blood culturing every 3 months (-/+ 1 week). Blood culture is to occur if subjects report having experienced any of these symptoms, followed by treatment for listeremia if suspected.	Update made based on the Sponsor's assessment of *Lm* surveillance data from about 171 subjects participating across 7 Advaxis studies with *Lm*-based therapies, followed by FDA agreement on 10 November 2020 of this approach.
3	11, 11.2 ,11.3 Interim & Final Analyses	In the previous protocol version, the planned final analysis was to be performed after "184 DFS events" had occurred (defined as the time from randomization until death or recurrence). However, given the study treatment phase was terminated early, it is clarified that the data collected and analyzed up to the time of early study treatment termination will be analyzed [i.e., after 110th subject was randomized, the Sponsor terminated the study and further enrollment, and all subjects moved to the End of Treatment (EoT) visit by 31 July 2019 (except for 1 subject whose last dose occurred on 2 September 2019)].	Update made to reflect that SAP is provided as a separate document reflecting assessments up to the early study termination as of 31 July 2019