PROTOCOL ADXS001-04

PHASE 1-2 STUDY OF ADXS11-001 or MEDI4736 ALONE OR IN COMBINATION IN RECURRENT/METASTATIC CERVICAL OR HPV+ HEAD & NECK CANCER

SPONSOR: Advaxis, Inc.
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IND NUMBER: **16256**

EudraCT NUMBER: **N/A**

Original: October 9, 2014
Amendment 1.1: February 2, 2015
Amendment 2: May 8, 2015

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PROTOCOL APPROVAL

Protocol Number:	ADXS001-04
Title of Protocol:	Phase 1-2 Study of ADXS11-001 or MEDI4736 Alone or In Combination In Recurrent/ Metastatic Cervical or HPV+ Head & Neck Cancer
Amendment 2:	May 8, 2015

Prepared by:

[redacted] Advaxis Inc.

8/MAY/15
Date

Appr[redacted]

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[redacted], Advaxis Inc.

8-MAY-2015
Date

SIGNATURE PAGE

Protocol No.:	ADXS001-04
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Amendment 2:	May 8, 2015

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. 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 (GCPs), International Conference on Harmonization (ICH) Guidelines, local ethical and legal requirements, and the spirit of the Declaration of Helsinki.

Investigator Name:

Signature	Date
Printed Investigator Name	Site #

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1.0 SUMMARY

Sponsor: Advaxis, Inc.	**Name of Finished Product:** ADXS11-001 MEDI4736	**Type of Treatment:** **ADXS11-001:** *Lm*-LLO Immunotherapy **MEDI4736:** MEDI4736 is a human monoclonal antibody (mAb) of the IgG1κ subclass that inhibits binding of programmed cell death-1 ligand (PD-L1) to programmed cell death-1 (PD-1) and CD8

Study Title:	Phase 1-2 Study of ADXS11-001 or MEDI4736 Alone or In Combination In Recurrent/ Metastatic Cervical or HPV+ Head & Neck Cancer
Trial Phase	Phase I/II
Clinical Indication	Locally advanced, or metastatic squamous or non-squamous carcinoma of the cervix or HPV+ squamous cell carcinoma of the Head and Neck
Trial Type	Interventional
Study Centers	Multicenter, US-only
Route of Administration	Intravenous (IV)
Trial Blinding	Open label, unblinded
Number of Trial Subjects	Approximately 66 • 6-18 in Phase 1 (Part A) portion of study • 48 in Phase 2 (Part B) portion of study
Estimated Duration of Trial	Approximately 4 years
Duration of Participation	Each subject will participate in the trial for up to 4 years from the time the subject signs ICF through the final contact. Treatment will continue for up to 1 year or until the subjects has either documented progression, unacceptable adverse events, withdrawn due to investigator's discretion, subject withdraws consent, pregnancy, or noncompliance with study procedures or treatments. During treatment, subjects who achieve a CR should receive at least 1 additional cycle of treatment. Subjects who stop study treatment after a CR may be eligible for an additional 1 year of study retreatment if they progress within 1 year of stopping study treatment and the study is open. After the end of treatment, each subject will be followed for adverse events for a minimum of 30 days and for serious adverse events for 90 days.
Randomization Ratio	There is no randomization in the Part A portion of the study. The Part B portion of the study will have a 1:1:2 randomization of ADXS11-001: MEDI4736: ADXS11-001+MEDI4736, respectively
Methodology	This is a 2 part study in subjects with either metastatic squamous or non-squamous carcinoma of the cervix or metastatic HPV+ squamous cell cancer of the head and neck (SCCHN). Part A of the study is a Phase 1 dose escalation evaluation of the combination of ADXS11-001 and MEDI4736. The Phase 1 portion of the study will utilize a "3+3" design which will dictate dose escalation and de-escalations. Once a maximum tolerated dose is identified and subjects from Part A have been followed for the 28-day DLT period, Part B of the study will commence. Part B of the

Sponsor: Advaxis, Inc.	**Name of Finished Product:** ADXS11-001 MEDI4736	**Type of Treatment:** **ADXS11-001:** *Lm*-LLO Immunotherapy **MEDI4736:** MEDI4736 is a human monoclonal antibody (mAb) of the IgG1κ subclass that inhibits binding of programmed cell death-1 ligand (PD-L1) to programmed cell death-1 (PD-1) and CD8
	study will be a Phase 2 randomized design where subjects will be randomized 1:1:2 to ADXS11-001: MEDI4736: ADXS11-001+MEDI4736. Stratification will be based upon disease type. Safety will be assessed at every visit by comparing treatment-related adverse events (AEs), changes in physical examinations, vital signs measurements, and laboratory abnormalities.	
Criteria for Evaluation	Safety: recorded AEs, changes in physical examinations, vital signs measurements and clinical laboratory evaluations Efficacy: Response rates as measured by RECIST 1.1 and irRECIST, duration of response, PFS	

2.0 TRIAL DESIGN

Specific procedure to be performed during this trial, as well as the prescribed times and associated visit window are outlined in the Study Flow Charts - Section 6.0. Details of each procedure are provided in Section 7.1 - Trial Procedures.

This is a multi-center, open-label, 2 part randomized study of ADXS11-001 and MEDI4736 administered as monotherapy or in combination to subjects with metastatic squamous or non-squamous carcinoma of the cervix or metastatic HPV+ squamous cell carcinoma of the head and neck (SCCHN).

2.1 ADXS11-001 + MEDI4736 Combination Therapy

Part A of the study will be Phase 1 analysis of ADXS11-001 given in combination with MEDI4736. A standard 3+3 study design will guide enrollment, dose escalations, and de-escalations during Part A. The dose limiting toxicity (DLT) evaluation period will be 28 days. The dose of ADXS11-001 will be held at 1 x 10^9 cfu; escalating doses of MEDI4736 (3 mg/kg and 10 mg/kg) will be evaluated as Dose Level 1 and Dose Level 2, respectively. Dose Level -1 will be ADXS11-001 (1 x 10^9 cfu) and MEDI4736 (1 mg/kg), and will be explored if Dose Level 1 is not tolerated, as dictated by the 3+3 design. ADXS11-001 will be dosed every 4 weeks. MEDI4736 will be dosed every 2 weeks. Subjects will continue on therapy for up to 1 year or until they discontinue due to documented progression, unacceptable toxicity, Investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatments or procedure requirements, administrative reasons, or withdrawal from the study. The primary objective of Part A is to determine the saftey and tolerability of the treatment combination. Secondary endpoints will include evaluation of response rates, duration of response and progression free survival (PFS) as determined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and secondarily by irRECIST. Response and progression will be determined by the investigator.

2.2 ADXS11-001 vs MEDI4736 vs ADXS11-001 +MEDI4736

Part B of the study will start once subjects from Part A have been followed through the 28-day DLT period. Part B will be a Phase 2 design which will randomize subjects 1:1:2 to ADXS11-001 : MEDI4736 : ADXS11-001+MEDI4736. Randomization will be stratified based upon disease type. ADX11-001 will be adminstered every 4 weeks. MEDI4736 will be adminstered every 2 weeks. [redacted] Subjects will continue on therapy for up to 1 year or until they discontinue due to documented progression, unacceptable toxicity, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatments or procedure requirements, administrative reasons, or withdrawal from the study. Subjects who achieve a complete response (CR) should receive at least 1 additional cycle of treatment. Crossover to another treatment arm will not be allowed. Adverse events will be monitored throughout the study and graded in severity according to to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

After the end of treatment, each subject, regardless of whether they particpate in Part A or Part B, will be followed for a minimum of 30 days for adverse event monitoring (serious adverse events will be collected for up to 90 days) after the end of treatment. Subjects will have post treatment follow up visits for disease status, including non-study cancer treatment and disease progression, for up to 3 years.

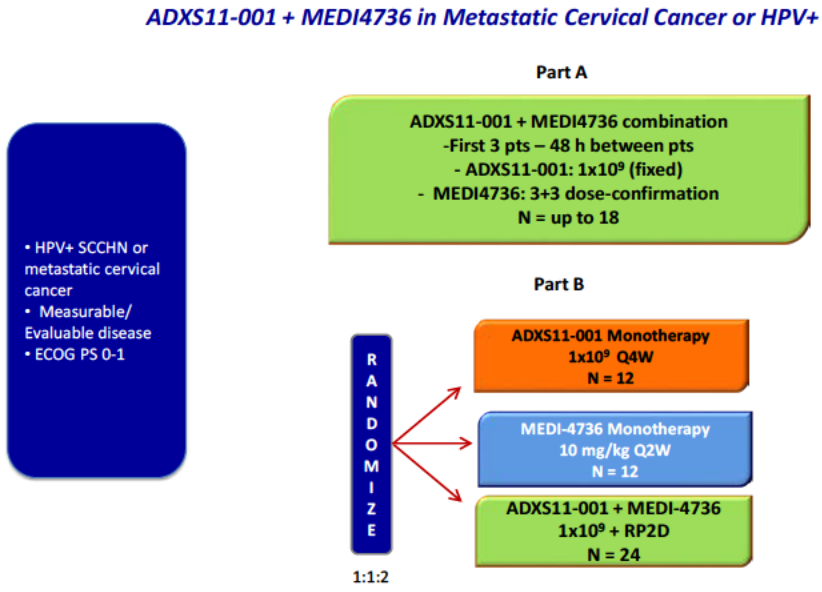
Safety and efficacy analysis will be performed for both parts of the study. Subject disposition, demographic and baseline characteristics will be summarized separately for Part A and Part B. Adverse events will be classified and summarized by system organ class (SOC) and preferred term, incidence, severity, and causality. All subjects who receive at least 1 dose of study drug will be included in the safety analyses.

Statistical analysis for efficacy will be perrformed by treatment arm and disease type. Although it may lack statistical power, statistical testing for treatment comparisons will be

performed as a reference. Tumor response will be evaluated by RECIST 1.1 criteria and secondarily by irRECIST criteria. The overall response rate will be summarized by frequency counts and percentage, and will be tested by Fisher's Exact test. PFS is defined as the time from randomization until objective tumor progression or death. Subjects who have not progressed or died will be censored for the analysis. Kaplan-Meier (KM) curves and descriptive statistics will be used to summarize PFS. The percentage of subjects with PFS and the 95% confidence intervals will be provided. PFS and duration of response will be summarized using KM method and tested by the Log-Rank test controlled by disease type.

Furthermore, disease response will be tabulated for all subjects who receive ADXS11-001 monotherapy, MEDI4736 monotherapy, or ADXS11-001 + MEDI4736 combination therapy.

2.3 Trial Diagram



3.0 OBJECTIVES & HYPOTHESES

3.1 Part A - Primary Objectives & Hypothesis

Objective: To evaluate the safety and tolerability of ADXS11-001 administered in combination with MEDI4736 across 2 dose levels by NCI CTCAE v 4.03.

Objective: To select recommended dose for Part B of the study based on number of DLTs seen in subjects enrolled in Part A.

Hypothesis: ADXS11-001 administered in combination with MEDI4736 will be well tolerated at the maximum doses combined.

3.2 Part A - Secondary Objective

Objective: To evaluate preliminary signs of efficacy by RECIST 1.1 and irRECIST.

3.3 Part A - Exploratory Objective

Objective: [redacted]

3.4 Part B - Primary Objectives & Hypothesis

Objective: To evaluate tumor response and PFS by RECIST 1.1 and irRECIST of ADXS11-001 and MEDI4736 administered as monotherapy and in combination.

Objective: To evaluate the safety and tolerability of ADXS11-001 administered in combination with MEDI4736 by NCI CTCAE v 4.03.

Hypothesis: ADXS11-001 and MEDI4736 will demonstrate signs of clinical activity.

3.5 Part B - Exploratory Objective

Objective: [redacted]

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 ADXS11-001 Immunotherapy

ADXS11-001 is *Lm*-LLO immunotherapy, developed for the treatment of HPV-associated cancers. ADXS11-001 is 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. Because the vector is live attenuated bacteria, it is rapidly taken up by antigen presenting cells (APC) after intravenous (IV) administration. This

causes activation of the APC and results in a multifactorial stimulation of innate immunity including triggering *Lm*-specific PAMP (pathogen-associated molecular patterns) receptors, DAMP (damage-associated molecular patterns) receptors, and TLRs (toll-like receptors). To the subject, this activation can manifest as flu-like symptoms or cytokine release symptoms that occur during or in the hours immediately following administration.

Once inside the APC, ADXS11-001 can escape the phagolysosome into the cytoplasm of the APC where it secretes the tLLO-HPV-E7 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 MHC Class 1 and Class 2 MHC pathways. This cross-presentation, in immunologic context of responding to a "perceived" acute infection, stimulates the development of adaptive immunity culminating in HPV-specific T effector cells that infiltrate the tumor microenvironment and destroy tumor cells immunologically.

Simply stated, the live attenuated vector is taken up into the immune system and presents the tumor antigen fused to immunogenic *Lm* peptides along with the rest of the *Lm* associated antigens. The immune system then "perceives" the HPV-E7 expressing cells as potentially "*Lm* infected", and generates CD8+ T cells that can infiltrate malignant tissue and destroy HPV-E7 expressing tumor cells.

As a drug product, ADXS11-001 is administered as an IV infusion given every 3-4 weeks. It is administered as a "therapeutic" vaccine or immunotherapy. It 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 a tumor-associated antigen like HPV-E7. Clinical benefit can manifest as a slowing of tumor growth, a stabilization of tumors, or a partial or complete response of the tumors. Collectively, the spectrum of clinical benefits is captured as relative delays in tumor progression and/or improved survival.

4.1.2 MEDI4736

MEDI4736 is a human monoclonal antibody (mAb) of the IgG1κ subclass that inhibits binding of programmed cell death-1 ligand (PD-L1) to programmed cell death-1 (PD-1) and CD8. MEDI4736 is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. MEDI4736 contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to complement protein C1q and the Fcγ receptors involved in triggering effector function [1].

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. Programmed cell death ligand 1 is one such protein, and is upregulated in a broad range of cancers with a high frequency, with up to 88% expression in some indications. In a number of these cancers, including lung [2], renal [3-5], pancreatic [6-8], and ovarian cancer [9], tumor cell expression of PD-L1 is associated with reduced survival and an unfavorable prognosis. For example, in ovarian cancer, the 5-year survival rate in patients with low expression of PD-L1 was 80.2% compared to 52.6% in patients with high expression levels of PD-L1 [9]. In lung cancer, only 20% of patients with tumors expressing PD-L1 survived for more than 3 years compared to 49% of patients with tumors lacking PD-L1 expression [2]. Along with PD-L1 expression data generated internally, these data suggest that an antibody targeting PD-L1 has the potential to affect multiple solid tumor types.

Programmed cell death ligand 1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell [10, 11]. This results in reduced T-cell activation and fewer

activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination [12].

Based on in vitro studies, an antibody that blocks the interaction between PD-L1 and its receptors can relieve PD-L1-dependent immunosuppressive effects and enhance the cytotoxic activity of antitumor T cells [13]. The levels of tumor-infiltrating lymphocytes, and more specifically cytotoxic T cells, have been correlated with improved prognosis in a number of cancers including colorectal, melanoma, and lung [14], suggesting that an antitumor immune response is beneficial to patients. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of several preclinical studies using mouse tumor models support this hypothesis [15-18]. In these studies, antibodies directed against PD-L1 or its receptor, PD-1, demonstrated antitumor activity.

Stimulating an antitumor immune response is a mechanism employed successfully by a number of approved cancer therapies. For example, aldesleukin (Proleukin®), a recombinant human interleukin (IL)-2, in renal cancer [19] and sipuleucel-T (Provenge®) in prostate cancer [20] both directly stimulate immune activation. Ipilimumab (Yervoy®) also stimulates the immune response, but does so by blocking the T-cell co-inhibitory molecule, CTLA-4, thereby removing an immunosuppressive signal.

Blocking PD-L1 is an approach similar to CTLA-4 inhibition, but with some distinct differences. First, the expression of CTLA-4 and its ligands is restricted to the hematopoietic system and thus, the site of action for molecules targeting CTLA-4 is solely the peripheral lymphoid organs. In contrast, PD-L1 is expressed on cells of the hematopoietic system and on a range of tumor types. Therefore, targeting PD-L1 should have additional effects within the tumor microenvironment. Second, CTLA-4 plays an early and critical role in controlling T-cell activation. This is reflected in the phenotype of CTLA-4 knockout mice, which die between 3 and 4 weeks of age due to lymphoproliferative disease and tissue destruction. In

contrast, PD-L1 acts later in the process of T-cell activation [21] and is considered less critical to the control of initial T-cell activation. This is reflected in the phenotype of PD-L1 knockout mice, which are viable and have normal T-cell numbers and activation levels but show increased T-cell activation in response to antigen and increased susceptibility in certain autoimmune models [22, 23]. Similarly, mice lacking PD-1, a PD-L1 receptor, show strain-specific phenotypes that are milder than those seen in CTLA-4 knockouts [24, 25]. Therefore, inhibition of the PD-L1/PD-1 pathway might be expected to result in less toxicity relative to CTLA-4 inhibition. In support of these findings, recent Phase 1 clinical studies assessing the tolerability of agents targeting PD-1 have demonstrated a toxicity profile that is more favorable than that of CTLA-4 [26-29].

4.1.3 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for detailed Preclinical and Clinical data.

4.2 Rationale

4.2.1 Rationale for the Combination ADXS11-001 & MEDI4736

Human papilloma viruses are spread by direct human contact. Infection of squamous mucosal epithelial cells by high risk strains of HPV can result in the transformation of squamous epithelial to a pre-malignant phenotype that can progress to malignancy. High risk HPV strain E6 and E7 gene products interfere with the expression and function of the host tumor suppressor gene products of P53 and Rb in the host cell. This process can occur in the uterine cervix and can lead to cervical cancer, the oropharyngeal mucosa of the tonsils or base of the tongue, and lead to squamous cell carcinoma of the oropharynx, or the mucosal epithelium of the anus leading to anal cancer.

While it is estimated that 80% of sexually active individuals are exposed to oncogenic strains of HPV, the percentage that develop dysplastic or malignant lesions is considerably less. This is presumably because many individuals can clear the viral infection immunologically. However, in some individuals, the virus is not cleared and expressions of viral gene products can lead to malignancy over time.

Various mechanisms have been proposed for the resistance of human solid tumors to immune recognition and obliteration, including the recruitment of regulatory T cells, myeloid-derived suppressor cells (MDSC), and local secretion of inhibitory cytokines that mediate immune tolerance in tissue or tumor microenvironments. The occurrence of HPV-induced cancer is strongly associated with failure to mount a strong HPV-specific type 1 T-helper and cytotoxic T-lymphocyte response [30-32]. Cervical cancers are known to be infiltrated by regulatory T cells (Tregs) that are specific for HPV antigens. The lack of CD8+ T cells migrating into the tumor cell nests, the induction of HPV16-specific regulatory T cells, and the influx of Tregs into the tumor prevent the immune system from eliminating malignant cells [33, 34]. Moreover, the ratio between the tumor-infiltrating CD8+ T cells and co-infiltrating CD4+Foxp3+ regulatory T cells is an independent prognostic factor for overall survival [35], indicating the key role of these different types of T cells in cervical cancer.

However, the inhibitory action of HPV-specific Tregs within the tumor microenvironment is not the only mediator of immune tolerance contributing to the immunologic resistance of HPV-associated malignancy. Recent evidence also suggests that tumors can co-opt physiologic mechanisms of tissue protection from inflammatory destruction via up-regulation of immune inhibitory ligands.

Antigen-induced activation and proliferation of T cells are regulated by the expression of both co-stimulatory and co-inhibitory receptors and their cognate ligands collectively referred to as immune “checkpoints”. Signaling through these receptors modulates the initiation, amplification, and subsequent resolution of adaptive immune responses. In the absence of co-inhibitory signaling, persistent T- cell activation can lead to excessive tissue damage in the setting of infection as well as autoimmunity. In the context of cancer, in which immune responses are directed against antigens specifically or selectively expressed by tumor cells, these immune checkpoints can represent major obstacles to the generation and maintenance of clinically meaningful antitumor immunity. Therefore, efforts have been made in the clinical arena to investigate blockade of immune checkpoints as a novel therapeutic approach to cancer.

CTLA-4 and PD-1 are 2 such checkpoint receptors being actively targeted in the clinic. [redacted]

PD-L1 has been reported to be expressed on the cell surface of 70% of HPV+ H&N squamous cell carcinoma (HPV-HNSCC) and only 29% of HPV negative tonsil cancers [38]. PD-L1 expression was restricted to the tumor periphery at the interface between tumor cell nests and inflammatory stroma in most tumors and diffusely expressed throughout the tumor nests in a small percentage. Similarly, for cervical dysplasia, PD-1 and PD-L1 expression on cervical T cells and dendritic cells, respectively, is associated with high-risk HPV positivity and the level of expression increases in parallel with increasing cervical intraepithelial neoplasia (CIN) grade up through invasive cervical cancer [39]. The majority of TILs found in cervical cancer express PD-1 and expression of PD-L1 correlates with impaired cell mediated immunity.

While PD-L1 expression on SCCHN can be variable, PD-1 is always expressed on a high proportion of TILs – much higher than on peripheral blood T cells. This difference in interferon gamma (IFN-γ) production between the PD-1(+) TILs are found to have a decreased ability to secrete IFN-γ and tumor necrosis factor alpha (TNFα) compared to PD-1(-) TILs and peripheral blood T cells suggesting that PD-1 expression within the tumor microenvironment marks TILs that are functionally suppressed in their capacity to produce effector cytokines.

The mechanism of action of ADXS11-001 includes the generation of tumor antigen (HPV E7) specific T-cells after presentation by a live attenuated bacterial vector. In addition, there is a consistent reduction in both the relative number and function of Tregs and MDSCs in the tumor microenvironment, overcoming an important mechanism of immunologic tolerance. [redacted].

Treatment with *Lm*-based vectors results in powerful stimulation of both innate and adaptive immunity. Part of this response includes an up-regulation of the expression of PD-1 on antigen presenting cells and T-cells as well as an increase of PD-L1 expression on tissues. Increased interaction of these negative checkpoint ligands may limit the potential immune response associated with ADXS11-001 treatment.

[redacted]

MEDI4736 binds to PD-L1 and prevents its ligation to PD-1 and subsequent inhibition of immune effector cells. PD-1 expression on HPV-associated tumors is a mediator of immune tolerance, active in HPV-associated cancers, that is distinct from the activity of Tregs and MDSCs. MEDI4736 is under clinical investigation in head and neck cancer and several other malignancies. [redacted]

Administering ADXS11-001 in combination with MEDI4736 to treat HPV-associated malignancies would potentially combine complimentary mechanisms of action in a

combination immunotherapy. The ADXS11-001 vector would provide strong innate and adaptive stimulation with the live vector serving as the equivalent of multiple immune adjuvants and gain access to the cytoplasm of the APCs within the subject. Inside the APCs the HPV-E7 peptide fused to tLLO would be secreted, ubiquitinated and cross-presented through both MHC Class 1 and Class 2 pathways resulting in HPV-specific T-cells. MEDI4736 would be able to block the negative inhibition of proliferation and T-cell activation caused by PD-1: PD-L1 and PD-L2 binding which should result in a greater number of tumor antigen-specific T cells. The Advaxis vector is also likely to increase PD-L1 expression by tumor cells along with PD-1 on lymphocytes. Advaxis vectors have been shown to increase chemokine expression by tumors and chemokine receptor expression in tumor draining lymph nodes, which will help the T cells traffic to the tumor microenvironment. Once they arrive at the tumors, MEDI4736 will block the PD-L1 expressed on the surface or periphery of the tumors at the interface with the immunologic stroma allowing the activated T cells to better infiltrate the tumor microenvironment. Upon their entry into the tumor microenvironment, the relative number of immunosuppressive Tregs and MDSCs will have been reduced and their immunosuppressive secretion of transforming growth factor (TGF) beta, IL-10 and arginase-1 markedly reduced, allowing better immunologic elimination of HPV-E7 expressing tumor cells. In addition, *Lm*-LLO immunotherapy like ADXS11-001 can be given repeatedly without the development of neutralizing antibodies in the same manner as MEDI4736. This allows for repeated administration of the vector along with MEDI4736 for extended repeating treatments.

[redacted] This study will investigate the safety of these 2 agents in combination.

4.2.2 Rationale for Trial and Selected Subject Population

The mechanism of oncogenesis from high-risk HPV infection in squamous mucosal epithelium is consistent, whether the site of infection is the cervix or the oral or anal mucosa. Persistence of the virus and its inhibition of tumor suppressor functions can lead to the development of dysplasia or malignant carcinoma. Both cervical cancer and SCCHN resist

immunologic clearance in part, through the development of immunologic tolerance that is mediated by expression of ligands for immunologic checkpoints such as PD-L1 on tumor tissue, and the presence of HPV-specific regulatory T cells and MDSCs within the tumor microenvironment.

Cervical cancer and HPV+ SCCHN have a significant rate of successful treatment from primary surgery often followed by radiation and chemotherapy. However, approximately 33% of cervical cancers recur after primary therapy. The majority of recurrent cervical cancers are not considered curable, and the subject will ultimately die from the malignancy. Globally, cervical cancer is the number 2 cause of cancer death for women. Similarly, 10-25% of subjects with HPV+ oropharyngeal cancer will experience progression within 3 years of completing primary therapy and have a 2-year survival of approximately 54% [41, 42]. The incidence of HPV+ SCCHN is growing at an epidemic rate in western countries, including the USA.

[redacted]

4.2.3 Rationale for Dose Selection/Regimen/Modification

4.2.3.1 ADXS11-001 Dose Selection

ADXS11-001 is a live attenuated Gram Positive bacterial immunotherapy vector. Adverse events (AEs) with this class of agents seem to be directly related to innate immune effects associated with the infusion of the live attenuated bacteria. These typically consist of certain flu-like and cytokine release syndrome symptoms that are almost exclusively low grade, have an onset within hours of infusion, and have not been either cumulative or associated with any

delayed onset symptoms, including potential autoimmune symptoms. These symptoms typically self-resolve, or respond readily to symptomatic treatment. The symptoms appear to be related to the number of cfu infused over time. Pretreatment with oral nonsteroidal anti-inflammatory drugs (NSAIDs) and antiemetics reduces the incidence of these symptoms by almost 50%. With ADXS11-001, live bacteria cannot be recovered from subjects after 24 hours and a course of antibiotics is given on Day 4 to ensure clearance of the vector.

There is no specific target blood level that needs to be achieved in order for ADXS11-001 to be effective in order to compete with a target or bind to a receptor; therefore, maximum concentration (C_{max}), minimum concentration ($C_{min,}$), and half-life of ADXS11-001 are not relevant beyond the clinical observation of a maximum tolerated cfu. In the current trial, the dose of 1 x 10^9 cfu was imposed.

[redacted]

[redacted]

4.2.3.2 MEDI4736 Dose Selection

MEDI4736 has shown the following activity as an anti-PD-L1 molecule:

- MEDI4736 binds to PD-L1 and blocks its interaction with PD-1 and CD80.
- MEDI4736 can relieve PD-L1-mediated suppression of human T-cell activation in vitro.
- MEDI4736 inhibits tumor growth in a xenograft model via a T-cell dependent mechanism.

[redacted]

[redacted]

4.2.4 Rationale for Endpoints

4.2.4.1 Efficacy Endpoints

The evaluation of efficacy for both the parts of the study will utilize computer tomography (CT) to assess tumor response as well as PFS as measured by RECIST 1.1 and irRECIST. These endpoints are well established and commonly used to evaluate signs of clinical activity and efficacy.

4.2.4.2 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of ADXS11-001 alone, MEDI4736 alone, and ADXS11-001 in combination with MEDI4736 in subjects with previously treated locally advanced or metastatic SSCHN or cervical cancer. The primary safety analysis will be based on subjects who experience toxicities as defined by NCI CTCAE v 4.03. Safety will be assessed by quantifying the toxicities and grades, including SAEs and events of clinical interest (ECI) experienced by subjects who have

received ADXS11-001, MEDI4736, or ADXS11-001 + MEDI4736 combination therapy. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes.

4.2.4.3 [redacted]

[redacted]

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Inclusion Criteria

This study will include subjects with either SCCHN or cervical cancer.

For subjects with SCCHN to be eligible they must have:

- Histopathological diagnosis of squamous cell cancer of the head & neck
- Confirmation of HPV positivity. Subjects with prior confirmation of HPV+ positivity will be eligible, provided documentation of the result is provided to sponsor. However if the subject's HPV status is unknown, either fresh tumor tissue or formalin-fixed paraffin embedded tissue will need to be provided to a central or local lab for evaluation. Details of sample requirement and shipping can be found in the study Laboratory Manual for samples being sent to the central laboratory.
- Metastatic disease that is deemed incurable by local therapy
- Must have received at least 1 platinum-based therapy for disease in the recurrent/metastatic setting. Subjects must have either documented disease progression OR become intolerant to prior therapy in the metastatic setting.
    - Subjects who have received > 1 prior systemic therapy in the metastatic setting MAY be eligible only after consultation with the Sponsor.

For subjects with carcinoma of the cervix to be eligible they must have:

- Histopathological diagnosis of squamous, non-squamous, adenosquamous, carcinoma or adenocarcinoma of the cervix
- Metastatic disease that is deemed incurable by local therapy
- Must have received at least 1 platinum-based therapy for disease in the recurrent/metastatic setting. Subjects must have either documented disease progression OR become intolerant to prior therapy in the metastatic setting.
    - Subjects who have received > 1 prior systemic therapy in the metastatic setting MAY be eligible only after consultation with the Sponsor
- HPV positivity is NOT a requirement for eligibility

ALL subjects must also:

1. Have disease amenable and accessible for biopsy. This criterion applies to Part B only.
2. Provide tissue from an [redacted], if available.
3. Be willing and able to provide written informed consent for the trial.
4. Be ≥ 18 years of age on day of signing informed consent.
5. Have measurable disease based on RECIST 1.1.
6. Have a performance status of 0 or 1 on the ECOG Performance Scale.
7. Demonstrate adequate organ function as defined in Table 1.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
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[a] 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 **OR** ≤5 X ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or INR is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as aPTT is within therapeutic range of intended use of anticoagulants

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

8. Female subjects of childbearing potential (not surgically sterilized or not free from menses for > 1 year):

    a. must have a negative urine or serum pregnancy test result within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

    b. must be willing to use 2 methods of birth control through 120 days after the last dose of study treatment (Section 5.7.2).

9. Male subjects must agree to use an adequate method of contraception starting with the first dose of study treatment through 120 days after the last dose of study therapy.

10. Must have a washout period of at least **14** days from completing prior standard of care therapy to the initiation of study therapy. For subjects who have been treated with either prior investigational therapy, including, but not limited to anti-PD-1, anti-PD-L1 or CTLA4 therapy, a washout period of **28** days is required*. *(* If a subject received a therapy where delayed toxicity is a concern or expected (e.g., skin reaction with RT or mucositis with 5FU) then additional wash out should be considered after discussion with the medical monitor.)*

5.1.2 Subject Exclusion Criteria

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

1. Has not recovered (i.e., ≤Grade 1 or at baseline) from adverse events, with the exception of alopecia, due to a previously administered agent.

2. Has any prior Grade ≥3 immune-related adverse event (irAE) while receiving immunotherapy, including anti-CTLA-4 treatment, or any unresolved irAE >Grade 1.

3. Has any pulmonary, ocular, or central nervous system (CNS) toxicity while receiving prior immunotherapy that has not resolved to ≤Grade 1.

4. Requires additional immunosuppression beyond corticosteroids for resolution of immune-related AEs from prior immunotherapy.

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

6. 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 trial treatment.

7. Has any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for invasive malignancy within 2 years. Concurrent use of hormones for non-cancer-

related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

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

b. Has known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of study drug and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to the first dose of study drug. Note: subjects with ≤Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

8. 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 that require intermittent use of bronchodilators 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.

9. Has evidence of interstitial lung disease or active, non-infectious pneumonitis, active or prior documented inflammatory bowel diseases (e.g., Crohn's disease, ulcerative colitis)

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

11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

13. Has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).

14. Has known active hepatitis B (e.g., HBsAg reactive) or hepatitis C (e.g., HCV RNA [qualitative] is detected).

15. Has irreversible toxicity that may be exacerbated by study drugs. However, irreversible toxicity that is not reasonably expected to be exacerbated by study drug(s) may be included (e.g., hearing loss) after consultation with the sponsor medical monitor.

16. Has a contraindication to administration of [redacted]

17. Has a known allergy to any component of the study drug(s) formulations.

18. Has contraindication to administration of non-steroidal anti-inflammatory drugs (NSAIDs).

19. Has a major surgical procedure (as defined by the investigator) within 30 days prior to the first dose of study drug(s) or still recovering from prior surgery.

    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy at the discretion of the Investigator.

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

21. In the opinion of the investigator, has rapidly progressing disease, OR has life expectancy of less than 6 months, OR would be unable to receive at least 1 cycle of therapy.

22. Has uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs from MEDI4736 or compromise the ability of the subject to give written informed consent.

23. Has a history of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia, risk of pulmonary toxicity, or evidence of active pneumonitis on screening chest CT scan.

5.2 Trial Treatments

The treatments to be used in this trial are outlined below in Table 2. Trial treatment should begin on the day of randomization or as close as possible to the date on which treatment is allocated/assigned.

Table 2 Trial Treatment

Drug	Dose	Route of Administration	Regimen
Part A (Combination therapy)			
ADXS11-001	1 x 10^9 (fixed)	IV infusion	Q4W
MEDI4736[a]	3 mg/kg (starting dose)	IV infusion	Q2W
Part B			
ADXS11-001 (monotherapy)	1 x 10^9 (fixed)	IV infusion	Q4W
MEDI4736 (monotherapy)	10 mg/kg	IV infusion	Q2W
Combination	RP2D	IV infusion	Q2W

[a] In Phase 1, the MEDI4736 3 mg/kg starting dose will be escalated/de-escalated to determine a recommended dose for Phase 2 combination therapy; in Phase 2, the MEDI4736 monotherapy dose will be 10 mg/kg

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

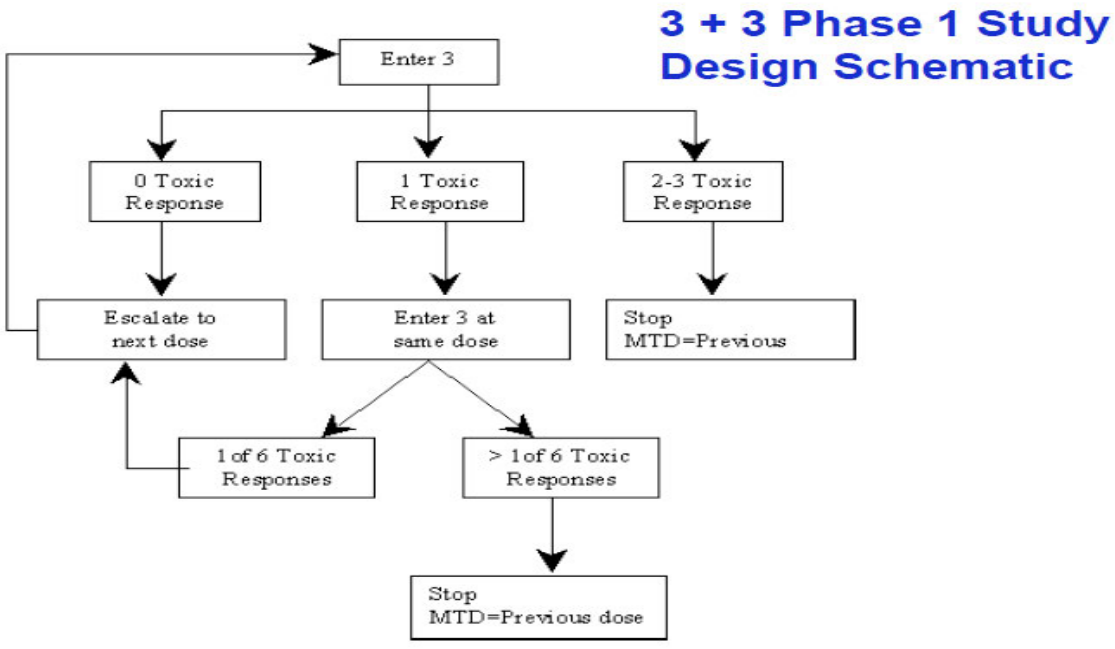
The rationale for selection of doses to be used in this trial is provided in Section 4.2.3 – Rationale for Dose Selection.

Details on the dose calculation, preparation and administration are provided in the Pharmacy Manual. Dose levels to be explored in Part A are shown below.

Dose Level	ADX11-001	MEDI4736
1	1 x 10^9 cfu (Q4wks)	3 mg/kg (Q2wks)
2	1 x 10^9 cfu (Q4wks)	10 mg/kg (Q2wks)
-1	1 x 10^9 cfu (Q4wks)	1 mg/kg (Q2wks)

Part A of the study is a Phase 1 3+3 design of ADXS11-001 and MEDI4736 combination therapy. MEDI4736 and ADXS11-001 will be administered in sequential cohorts of 3-6 subjects with a minimum of 48 hours between initial dosing for each of the first 3 subjects enrolled in the study. The first cohort will enroll a minimum of 3 subjects according to a standard 3+3 design shown schematically below.

Figure 1 3 + 3 Design Schematic



- Subjects in the first cohort will receive a dose of MEDI4736 at 3 mg/kg and ADXS11-001 1 x 10^9 cfu (Dose Level 1).

- If no DLTs are experienced, the next dose level of ADXS11-001 1 x 10^9 cfu + MEDI4736 at 10 mg/kg (Dose Level 2) will be explored.
- If 1 DLT is experienced, 3 additional subjects will be enrolled. If there is 1 DLT among 6 subjects, the next dose level will be explored.
- If ≥ 2 DLTs are observed in the first dose cohort, the starting dose of MEDI4736 will be de-escalated to 1 mg/kg and a dose de-escalation cohort will be enrolled (Dose Level -1).

All decisions regarding dose escalation or de-escalation will be guided by the 3+3 study design and will be made by the sponsor in consultation with investigators. The sponsor reserves the right to expand the number of subjects in each of the cohorts to better evaluate safety and tolerability, and to evaluate other doses.

The dose that will be utilized in Part B will be the highest maximal dose level evaluated in Part A that has an observed DLT rate of <33%.

Dose escalation/de-escalation decisions for MEDI4736 will use pre-defined DLT criteria (Section 5.2.1.1 – Dose Limiting Toxicities). Subjects who complete the DLT period may dose-escalate to the RP2D if approved by the sponsor.

5.2.1.2 Dose Limiting Toxicities

Dose-limiting toxicities will be evaluated during the Phase 1 combination dose-determination phase. All toxicities will be graded using NCI CTCAE v 4.03. The period for evaluating DLT will be from the first dose of investigational product through 28 days post initial dose for each subject. The occurrence of any of the following will be considered a DLT, if judged by the investigator to be possibly, probably or definitely related to combination therapy.

1. Any ≥Grade 4 irAE
2. Any ≥Grade 3 colitis
3. Any ≥Grade 3 non-infectious pneumonitis irrespective of duration

4. Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤Grade 1 or baseline within 14 days of AE onset

5. Liver transaminase elevation ≥5x but ≤8x ULN that does not downgrade to Grade 2 within 5 days after onset with optimal medical management, including systemic corticosteroids. Transaminase elevation >8x ULN or total bilirubin >5x ULN will be considered a DLT regardless of duration or reversibility.

6. Any increase in AST or ALT >3x ULN and concurrent increase in total bilirubin >2x ULN (Hy's Law).

7. Bacterial meningitis documented by symptoms and confirmed by lumbar puncture culture results

8. Listeremia: persistent (for 48-72 hours) symptoms consistent with listeremia (e.g., fever and muscle aches, often preceded by diarrhea or other gastrointestinal symptoms)

9. ≥Grade 3 flu-like symptoms or cytokine release syndrome symptoms that persist for >24 hours after study drug administration despite symptomatic treatment.

10. ≥Grade 2 allergic reaction (not due to antibiotic): will receive no further doses.

11. Any drug-related "non-irAE" ≥Grade 3 except for the exclusions listed below.

- Grade 3 fatigue for ≤7days
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic.
- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.).

- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction that resolves within 6 hours with appropriate clinical management.
- Grade 3 or Grade 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility.
- Grade 3 or Grade 4 lymphopenia.
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days.
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days.

irAEs are defined as AEs of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT. While the rules for adjudicating DLTs in the context of dose escalation are specified above, an AE not listed above may be defined as a DLT after consultation with the sponsor and investigators, based on the emerging safety profile.

5.2.1.3 Treatment Modification

In Part A, dose escalation/de-escalation for MEDI4736 in the combination will be based on defined DLT criteria (Section 5.2.1.1); the ADXS11-001 combination therapy dose is 1 x 10^9 cfu (fixed). In the event of DLT, the investigator will determine relatedness to the study treatment combination.

With ADXS11-001 treatment, a clear pattern of treatment-related AEs consistent with cytokine release has emerged consisting of transient Grade 1 or 2 (mild-moderate) flu–like or cytokine release syndrome symptoms (such as chills, nausea and vomiting), the majority of which occur within the first 6 hours **after** infusion (see also Section 5.6.1). Symptoms either self-resolve or respond quickly to symptomatic treatment. There has been no evidence of listeriosis, no persistent symptoms, no delayed symptoms, and no evidence of cumulative

toxicity in subsequent doses. Treatment modification guidelines for cytokine release syndrome symptoms are shown in Table 3. Treatment modification guidelines for irAEs are shown in Table 4 below.

Table 3 Treatment Modification Guidelines for ADXS11-001 Cytokine Release Syndrome symptoms

Toxicity	Grade	Modification
1st episode of symptoms associated with CRS (e.g. Nausea, vomiting, chills, rigors, hypotension, fever)	1-2	No modification on subsequent ADXS11-001 infusion
	3-4	• Extend infusion time [redacted] • Consider increasing prophylaxis dose of NSAIDS • Consider incorporating pretreatment fluids to manage hypotension.
Second episode of CRS	1-2	No modifications
	3	Discussion with sponsor required
	4	If symptoms have not ameliorated from aforementioned modifications, subject should be discontinued from study

Table 4 Dose Modification Guidelines for Immune-related Adverse Events - MEDI4736 Monotherapy and Combination Arms

Severity	Immune-related Adverse Events (irAEs)[a]	All Other Events
Grade 1	None	None
Grade 2	**For endocrinopathy**: Hold MEDI4736/Combination dose; do not hold ADXS11-001 (unless during combination therapy). When endocrinopathy is controlled, resume MEDI4736/Combination administration at next scheduled dose. **For dermatologic irAEs**: MEDI4736/Combination may be dosed at the next scheduled time point. **For pneumonitis:** Hold MEDI4736/Combination until resolution to ≤Grade 1. If resolution to ≤ Grade 1 occurs within 3 days of the initiation of maximal supportive care (including corticosteroids)[b], resume MEDI4736/Combination administration at next scheduled dose. Otherwise, discontinue MEDI4736/Combination. **For all other irAEs:** Hold MEDI4736/Combination until resolution to ≤Grade 1. If resolution to ≤Grade 1 does not occur within 30 days of irAE onset, discontinue MEDI4736/Combination	Hold MEDI4736/Combination until resolution to ≤Grade 1 or baseline. If resolution to ≤Grade 1 does not occur within 30 days, discontinue MEDI4736/ Combination
Grade 3	**For endocrinopathy:** Hold MEDI4736/Combination dose. When endocrinopathy is controlled, resume MEDI4736/Combination administration at next scheduled dose. **For dermatologic irAEs:** Hold MEDI4736/Combination until resolution to ≤Grade 1 or baseline. If resolution to ≤Grade 1 or baseline does not occur within 30 days, discontinue MEDI4736/Combination. **For elevations in transaminases:** For elevations in transaminases up to 8 × ULN, hold MEDI4736/Combination until resolution to ≤Grade 1 or baseline. If elevations downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days of onset, resume MEDI4736/Combination administration at next scheduled dose. Otherwise, discontinue MEDI4736/Combination. For elevations in transaminases >8 × ULN, discontinue MEDI4736/Combination. **For elevations in bilirubin:** For elevations in bilirubin up to 5 × ULN, hold MEDI4736/Combination until resolution to ≤ Grade 1 or baseline. If elevations downgrade to ≤ Grade 2 (< 3 × ULN) within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume MEDI4736/Combination administration at next scheduled dose. Otherwise, discontinue MEDI4736. **For all other irAEs:** Discontinue MEDI4736/Combination.	Hold MEDI4736/Combination until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume MEDI4736/ Combination administration at next scheduled dose. Otherwise, discontinue MEDI4736/Combination.
Grade 4	Discontinue MEDI4736/Combination.	Discontinue MEDI4736/Combination.

AE = adverse event; irAE = immune-related adverse event; ULN = upper limit of normal.

[a] Management of irAEs may require administration of immunosuppressive medications (and/or hormone replacement therapy for endocrinopathies). Resolution of irAEs managed in this manner in the timeframes specified is acceptable.

[b] Subjects who require corticosteroids for resolution must have discontinued corticosteroids. Subject can restart study therapy upon resolution of irAE and cessation of corticosteroid treatment for 14 days.

5.2.2 Timing of Dose Administration

Trial treatment should be administered after all procedures/assessments have been completed as detailed in the Study Flow Charts (Section 6.0). Trial treatment may be administered [redacted] due to administrative reasons but only after consultation with the sponsor. All trial treatments will be administered on an outpatient basis. The Procedures Manual contains specific instructions for dose calculation, reconstitution, preparation of the infusion fluid, and administration.

5.2.2.1 Combination Dosing (Part A & Part B)

For Combination dosing, MEDI4736 will be given Q2W (Weeks 1, 3, 5, and 7 of each 8-week cycle) and ADXS11-001 will be given Q4W (Weeks 1 and 5 of each 8-week cycle).On days when both treatments are administered (Weeks 1 and 5 of each cycle), subjects will first receive the MEDI4736 infusion in 250 mL [redacted] after end of MEDI4736 infusion, subjects should be premedicated with NSAIDS and oral antiemetics (Section 7.1.4.2). **The ADXS11-001 infusion can begin [redacted] after the subject has been premedicated.** When given the same day as MEDI4736, ADXS11-001 will be given ***in 100 mL*** of normal saline [redacted], to reduce the potential for fluid overload.

Any subject administered ADXS11-001 will also receive antibiotics. Specific details of antibiotic regimen are provided in Section 7.1.4.2.

5.2.2.2 ADXS11-001 Monotherapy (Part B)

In Part B , the dose for ADXS11-001 monotherapy will be 1 x 10^9 cfu administered in 250 mL of normal saline infused [redacted] Q4W (Weeks 1 and 5 in each 8-week cycle). Subjects should be premedicated with NSAIDS and oral antiemetics and received antibiotic as indicated in Section 7.1.4.2.

5.2.2.3 MEDI4736 Monotherapy (Part B)

In Part B, the dose for MEDI4736 monotherapy will be 10 mg/kg administered in 250 mL of normal saline infused [redacted] in duration Q2W (Weeks 1, 3, 5, and 7 in each 8-week cycle).

5.2.3 Trial Blinding/Masking

This is an open-label trial; therefore, the sponsor, investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

All subjects in Part A will receive combination therapy. Subjects participating in Part B will be allocated by random assignment 1:1:2 to ADXS11-001 monotherapy, MEDI4736 monotherapy, or ADXS11-001+ MEDI4736 combination therapy.

5.4 Stratification

In Part B, all 3 treatment arms will be stratified by disease (SCCHN or cervical cancer).

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination 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 trial therapy or vaccination schedule requires the mutual agreement of the Investigator, the Sponsor, and the subject.

5.5.1 Acceptable Concomitant Medications

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 case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications, administered after 30 days after the last dose of trial treatment, for SAEs and ECIs should be recorded as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Anti-cancer therapy including but not limited to, hormonal, chemotherapy, radiation therapy, treatment with targeting agents (e.g. Tyrosine kinase inhibitors). However occasional radiation therapy for palliation of pain is allowed
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor. Radio-pharmaceuticals (e.g., radium, strontium, etc.) are not acceptable.
- Immunotherapy not specified in this protocol
- Investigational agents other than ADXS11-001 and MEDI4736
- Live vaccines (e.g., measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, typhoid and intranasal influenza vaccines (e.g. Flu-Mist®). Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.
- Chronic use of systemic glucocorticoids have the potential to reduce the immune response therefore should be used with caution. However, glucocorticoids should

be considered to manage symptoms of cytokine release (e.g. Fever, headache, hypotension, chills, rigors, etc.). Topical use of steroids is allowed. The occasional use of steroids for the treatment of COPD and or asthma is allowed.

- Anti-infectives should be avoided, except where mandated by the protocol. However, subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

- Acetaminophen should not be substituted for the selected NSAID for pretreatment prophylaxis since acetaminophen does not have similar anti-inflammatory properties that could ameliorate cytokine release syndrome symptoms. Acetaminophen can be used after dosing for supportive care measures.

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 trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describe other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.6 Supportive Care Guidelines

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

5.6.1 Cytokine Release Syndrome

CRS per CTCAE V4.03 is characterized clinically by nausea, headache, tachycardia, hypotension, rash and shortness of breath. These side effects can develop soon after the administration of the *Lm*-LLO immunotherapies and can last for several hours. The clinical

syndrome is caused by a sudden increase in TNFα, IFNγ and IL-6 release, all of which have been shown to occur after *Lm*-LLO immunotherapy administration, resulting from the body's immune response to the therapy.

- Symptoms associated with CRS have been seen in subjects with ADXS11-001 administration. Symptoms are often grade 1-2 and transient, resolving with symptomatic management within 30 minutes-1 hour. In rare instance <5%, grade 3 rigors and hypotension have been seen.

- Prophylaxis with NSAIDs and anti-emetics have been shown to reduce both the severity, time to resolution and incidence. Supportive measure which include fluids for hypotension and continued use of NSAIDs are recommended.

- In cases of grade 3 hypotension that are not responsive to IV fluids consider use of low dose systemic corticosteroids (e.g. 100 mg, IV hydrocortisone infused over 30 seconds every 2 hours until resolution to Grade 1 or baseline or 500 mg IV hydrocortisone infused over 10 minutes every 2 hours until resolution to Grade 1 or baseline).

For subjects who experience symptoms associated with CRS, refer to Table 3 for treatment modifications for subsequent infusions

5.6.2 Diarrhea

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.

- All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

5.6.3 Nausea/vomiting:

Nausea and vomiting should be treated aggressively. Consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

5.6.4 Management of Infusion Reactions

With any infusional therapy there is the possibility of an infusion reaction. Signs and symptoms usually develop **during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion**. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritus/itching; rash/desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); vomiting. See Table 5 for treatment guidelines for subjects who experience an infusion reaction.

Table 5 Treatment Guidelines for Infusion Reactions

NCI CTCAE Grade	Treatment
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	1. Stop Infusion and monitor symptoms. 2. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics 3. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.
Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilatory support indicated	1. Stop Infusion. 2. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine 3. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. 4. Hospitalization may be indicated. 5. Subject experiencing Grade 4 reactions will be permanently discontinued from further trial treatment administration. Subjects with Grade 3 reactions may continue after discussion with the sponsor.

5.6.5 Listeremia

Persistent (for 48-72 hours) symptoms consistent with listeremia (e.g., fever and muscle aches, often preceded by diarrhea or other gastrointestinal symptoms) will require obtaining a quantitative blood culture. Symptoms that persist for >72 hours following dosing must be treated with an IV course of an appropriate antibiotic such as amoxicillin, ampicillin, ciprofloxacin, erythromycin, gentamycin, penicillin, trimethoprim/sulfamethoxazole, or vancomycin. ADXS11-001 is resistant to both streptomycin and chloramphenicol. Clinical sepsis requiring intensive care admission and/or pressors will automatically result in discontinuation of further doses.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

The study drug(s) may have adverse effects on a fetus in utero. Furthermore, it is not known if the study drug(s) has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, 2) postmenopausal (has not had menses for greater than 1 year), or 3) not heterosexually active for the duration of the study. The 2 birth control methods can be either 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Males may enroll if they are willing to use 1 method of birth control. Subjects should start using birth control from screening throughout the study period up to 120 days after the last dose of study therapy.

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 they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 7.2.2 - Reporting of Pregnancy and Lactation to the Sponsor. 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.

5.7.3 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 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 serious adverse experience (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. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the sponsor and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

It is unknown whether the study drug(s) is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial 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 trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.3 – Other Procedures.

A subject must be discontinued from the trial, with no further data reporting, for the following reasons:

- The subject withdraws consent
- Subject death
- The subject is lost to follow-up

A subject must be discontinued from study treatment, but will continue to be followed, for the following reasons:

- Confirmed radiographic disease progression
    - *Note*: For unconfirmed radiographic disease progression, please see RECIST 1.1 criteria
    - *Note*: A subject may continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see RECIST 1.1 criteria, after discussion with the sponsor.
- Unacceptable adverse experiences as described in Section 7.2
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Completed 12 months of treatment with study drug(s)
    - *Note: 12 months of study medication is calculated from the date of first dose. Subjects who stop treatment after 12 months may be eligible for additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.4.2.1.*
- Administrative reasons
- Sponsor decision to terminate the trial

- Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk

The End of Treatment and Follow-up visit procedures are listed in Section 6.0 - Study Flow Chart and Section 7.1.4 -Visit Requirements. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (90 days for serious adverse event monitoring or the initiation of a new anticancer therapy as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up tumor assessments until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up.

5.9 Subject Replacement Strategy

During Part A, subjects who discontinue for any reason other than toxicity will be replaced.

During Part B, subjects will not be replaced.

5.10 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

In the event of Sponsor decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Trial Flow Chart for Combination (Part A)

Trial Period:	**Screening Phase**		**Treatment Period**								**End of Treatment**			
Treatment Cycle/Title:	Pre-screening	Screening	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Discon	Follow-up **Phone call**	Follow up	Follow Up
Scheduling Window (Days):		-28 to -1	± 3[1]		± 3		± 3		± 3		At time of Discon	30 days post	90 days post	Every 8 weeks post
Administrative Procedures														
Pre-screening Consent (H&N subjects only)	X													
HPV+ Test (H&N subjects only)	X													
Informed Consent		X												
Inclusion/Exclusion Criteria, Subject ID Card		X												
Demographics and Medical History		X												
Prior and Concomitant Medication Review		X	X		X		X		X					
MEDI4736 Administration (Q2wk)			X		X		X		X					
ADXS11-001 Administration (Q4wk)[2]			X				X							
Clinical Procedures/Assessments														
Review Adverse Events			X		X		X		X		X	X	X	
Physical Examination[3]		X	X		X		X		X		X			
Vital Signs and Weight[4]		X	X		X		X		X		X			
ECOG Performance Status		X	X		X		X		X		X			
Tumor Imaging[5]		X	X								X			X
Laboratory Assessments[6]														
Pregnancy Test – Urine or Serum β-HCG		X	X		X		X		X					
PT/INR and aPTT		X	X		X		X		X		X			
CBC with Differential		X	X		X		X		X		X			
Comprehensive Serum Chemistry Panel		X	X		X		X		X		X			
Urinalysis		X	X		X		X		X		X			
T3, T4 and TSH		X	X		X		X		X		X			

Trial Period:	**Screening Phase**		**Treatment Period**								**End of Treatment**			
Treatment Cycle/Title:	Pre-screening	Screening	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Discon	Follow-up **Phone call**	Follow up	Follow Up
Scheduling Window (Days):		-28 to -1	± 3[1]		± 3		± 3		± 3		At time of Discon	30 days post	90 days post	Every 8 weeks post
Tissue/Blood Collection														
[redacted]														
PK Assessment[9]			X		X		X		X		X		X	
Immunogenicity (ADA) Assessment (serum)[10]			X				X		X		X		X	
[redacted]														

1 - The +/- 3 day window does not apply to Cycle 1, Week 1. This window is applicable in all subsequent cycles.

2 - Subjects will receive prophylactic NSAIDS and antiemetics [redacted] before each ADXS11-001 infusion. Subjects will also receive a course of oral antibiotics to be started 3 days after each ADXS11-001 infusion

3 - ECG and O_2 saturation by pulse oximetry at baseline screening only

4 - Vital signs are to be monitored [redacted] following each ADXS11-001 infusion.

5 - Tumor Assessments will be done in screening and Week 1 (± 1 week), starting at ***Cycle 2***. Evaluations will continue every 8 weeks (± 1 week) during treatment and for subjects in follow up who discontinue treatment for reasons other than disease progression; duration of follow up will be up to 3 years.

6 - Screening lab that are done within 5 days of initiating treatment can be used for C1D1 laboratory tests.

7 - [redacted]

8 - [redacted]

9 - PK Assessment: Serum will be collected at Cycle 1 Day 1 (pre-dose and end of infusion), at Weeks 3 and 5 (pre-dose only) and at Week 7 (pre-dose and end of infusion). For all subsequent cycles, serum will be collected at Week 7 (pre-dose only) with the exception of Cycle 3 where serum will be collected at Week 7 (pre-dose and end of infusion). Serum will also be collected at end of treatment and at the 90-day post treatment follow up visit.

10 - Immunogenicity (ADA) Assessment: Serum will be collected at Cycle 1 Day 1 (pre-dose only), at Weeks 5 and 7 (pre-dose only). For all subsequent cycles, serum will be collected at Week 7 (pre-dose only). Serum will also be collected at end of treatment and at the 90-day post treatment follow up visit.

11 [redacted]

12

6.2 Trial Flow Chart for ADXS11-001 Monotherapy (Part B)

Trial Period:	**Screening Phase**		**Treatment Period**								**Follow up**		
Treatment Cycle/Title:	Pre-screening	Screening	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Discon	Follow-up Phone Call[2]	Follow Up
Scheduling Window (Days):		-28 to -1	± 3[1]				± 3				At time of Discon	30/90 days post discon	Every 8 weeks post discon
Administrative Procedures													
Pre-screening Consent (H&N Subjects only)	X												
HPV+ Test (H&N subjects only)	X												
Informed Consent		X											
Inclusion/Exclusion Criteria		X											
Subject Identification Card		X											
Demographics and Medical History		X											
Prior and Concomitant Medication Review		X	X				X						
ADXS11-001 Administration (Q4wk)[3]			X				X						
Clinical Procedures/Assessments													
Review Adverse Events			X				X				X	X	
Physical Examination[4]		X	X				X				X		
Vital Signs and Weight[5]		X	X				X				X		
ECOG Performance Status		X	X				X				X		
Tumor Imaging[6]		X	X								X		X
Laboratory Assessments[7]													
Pregnancy Test – Urine or Serum β-HCG		X	X				X						
PT/INR and aPTT		X	X				X				X		
CBC with Differential		X	X				X				X		
Comprehensive Serum Chemistry Panel		X	X				X				X		
Urinalysis		X	X				X				X		

Trial Period:	**Screening Phase**		**Treatment Period**								**Follow up**		
Treatment Cycle/Title:	Pre-screening	Screening	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Discon	Follow-up Phone Call[2]	Follow Up
Scheduling Window (Days):		-28 to -1	± 3[1]				± 3				At time of Discon	30/90 days post discon	Every 8 weeks post discon
Tissue/Blood Collection													
[redacted]													

1 - The +/- 3 day window does not apply to Cycle 1, Week 1. This window is only applicable in all subsequent cycles.

2 - Safety Follow up will be conducted via telephone. Safety Follow up at 30 days (± 1 week) for AEs and at 90 days (± 1 week) for SAEs.

3 - Subjects will receive prophylactic NSAIDS and antiemetics [redacted] before each ADXS11-001 infusion. Subjects will also receive a course of oral antibiotics to be started 3 days after each ADXS11-001 infusion

4 - ECG and O_2 saturation by pulse oximetry at baseline screening only

5 - Vital signs are to be monitored [redacted] following each ADXS11-001 infusion.

6 - Tumor Assessments will be done in screening and Week 1 (± 1 week), starting at Cycle 2. Evaluations will continue every 8 weeks (± 1 week) during treatment and for subjects in follow up who discontinue treatment for reasons other than disease progression; duration of follow up will be up to 3 years.

7 - Screening lab that are done within 5 days of initiating treatment can be used for C1D1 laboratory tests.

8 - [redacted]

9 - [redacted]

10 - [redacted]

11 [redacted]

6.3 Trial Flow Chart for MEDI4736 Monotherapy arm (Part B)

Trial Period:	**Screening Phase**		**Treatment Period**								**End of Treatment**			
Treatment Cycle/Title:	Pre-screening	Screening	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Discon	Follow-up Phone Call	Follow up	Follow Up
Scheduling Window (Days):		-28 to -1	± 3[1]		± 3		± 3		± 3		At time of Discon	30 days post	90 days post	Every 8 weeks post
Administrative Procedures														
Pre-screening Consent (H&N subjects only)	X													
HPV+ Test (H&N subjects only)	X													
Informed Consent		X												
Inclusion/Exclusion Criteria		X												
Subject Identification Card		X												
Demographics and Medical History		X												
Prior and Concomitant Medication Review		X	X		X		X		X					
MEDI4736 Administration (Q2wk)			X		X		X		X					
Clinical Procedures/Assessments														
Review Adverse Events			X		X		X		X		X	X	X	
Physical Examination[2]		X	X		X		X		X		X			
Vital Signs and Weight		X	X		X		X		X		X			
ECOG Performance Status		X	X		X		X		X		X			
Tumor Imaging[3]		X	X								X			X
Laboratory Assessments[4]														
Pregnancy Test – Urine or Serum β-HCG		X	X		X		X		X					
PT/INR and aPTT		X	X		X		X		X		X			
CBC with Differential		X	X		X		X		X		X			
Comprehensive Serum Chemistry Panel[7]		X	X		X		X		X		X			
Urinalysis		X	X		X		X		X		X			
T3, T4 and TSH		X	X		X		X		X		X			
Tissue/Blood Collection														

Trial Period:	**Screening Phase**		**Treatment Period**								**End of Treatment**			
Treatment Cycle/Title:	Pre-screening	Screening	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Discon	Follow-up Phone Call	Follow up	Follow Up
Scheduling Window (Days):		-28 to -1	± 3[1]		± 3		± 3		± 3		At time of Discon	30 days post	90 days post	Every 8 weeks post
[redacted]														
PK Assessment[7]			X		X		X		X		X		X	
Immunogenicity (ADA) Assessment (serum)[8]			X				X		X		X		X	
[redacted]														

1 – The +/- 3 day window does not apply to Cycle 1 Week 1. This window is only applicable in subsequent cycles.

2 - ECG and O2 saturation by pulse oximetry at baseline screening only

3 - Tumor Assessments will be done in screening and Week 1 (± 1 week), starting at Cycle 2. Evaluations will continue every 8 weeks (± 1 week) during treatment and for subjects in follow up who discontinue treatment for reasons other than disease progression; duration of follow up will be up to 3 years.

4 - Screening lab that are done within 5 days of initiating treatment can be used for C1D1 laboratory tests.

5 [redacted]

6 - [redacted])

7 - PK Assessment: Serum will be collected at Cycle 1 Day 1 (pre-dose and end of infusion), at Weeks 3 and 5 (pre-dose only) and at Week 7 (pre-dose and end of infusion). For all subsequent cycles, serum will be collected at Week 7 (pre-dose only) with the exception of Cycle 3 where serum will be collected at Week 7 (pre-dose and end of infusion). Serum will also be collected at end of treatment and at the 90-day post treatment follow up visit.

8 - Immunogenicity (ADA) Assessment: Serum will be collected at Cycle 1 Day 1 (pre-dose only), at Weeks 5 and 7 (pre-dose only). For all subsequent cycles, serum will be collected at Week 7 (pre-dose only). Serum will also be collected at end of treatment and at the 90-day post treatment follow up visit.

9 - [redacted]

10 [redacted]

6.4 Trial Flow Chart for Combination Therapy (Part B)

Trial Period:	Screening Phase		Treatment Period								End of Treatment			
Treatment Cycle/Title:	Pre-screening	Screening	Wk1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Discon	Follow-up Phone Call	Follow up	Follow Up
Scheduling Window (Days):		-28 to -1	± 3[1]		± 3		± 3		± 3		At time of Discon	30 days post	90 days post	Every 8 weeks post
Administrative Procedures														
Pre-screening Consent (H&N subjects only)	X													
HPV+ Test (H&N subjects only)	X													
Informed Consent		X												
Inclusion/Exclusion Criteria		X												
Subject Identification Card		X												
Demographics and Medical History		X												
Prior and Concomitant Medication Review		X	X		X		X		X					
MEDI4736 Administration (Q2wk)			X		X		X		X					
ADXS11-001 Administration (Q4wk)[2]			X				X							
Clinical Procedures/Assessments														
Review Adverse Events			X		X		X		X		X	X	X	
Physical Examination[3]		X	X		X		X		X		X			
Vital Signs and Weight[4]		X	X		X		X		X		X			
ECOG Performance Status		X	X		X		X		X		X			
Tumor Imaging[5]		X	X								X			X
Laboratory Assessments[6]														
Pregnancy Test – Urine or Serum β-HCG		X	X		X		X		X					
PT/INR and aPTT		X	X		X		X		X		X			
CBC with Differential		X	X		X		X		X		X			
Comprehensive Serum Chemistry Panel		X	X		X		X		X		X			
Urinalysis		X	X		X		X		X		X			
T3, T4 and TSH		X	X		X		X		X		X			
Tissue/Blood Collection														
[redacted]														

Trial Period:	**Screening Phase**		**Treatment Period**								**End of Treatment**			
Treatment Cycle/Title:	Pre-screening	Screening	Wk1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Discon	Follow-up Phone Call	Follow up	Follow Up
Scheduling Window (Days):		-28 to -1	± 3[1]		± 3		± 3		± 3		At time of Discon	30 days post	90 days post	Every 8 weeks post
[redacted]														
PK Assessment[10]			X		X		X		X		X		X	
Immunogenicity (ADA) Assessment (serum)[11]			X				X		X		X		X	
[redacted]														

1 - The +/- 3 day window does not apply to Cycle 1, Week 1. This window is only applicable in all subsequent cycles.

2 - Subjects will receive prophylactic NSAIDS and antiemetics [redacted] before each ADXS11-001 infusion. Subjects will also receive a course of oral antibiotics to be started 3 days after each ADXS11-001 infusion

3 - ECG and O_2 saturation by pulse oximetry at baseline screening only

4 - Vital signs are to be monitored [redacted] following each ADXS11-001 infusion.

5 - Tumor Assessments will be done in screening and Week 1 (± 1 week), starting at ***Cycle 2***. Evaluations will continue every 8 weeks (± 1 week) during treatment and for subjects in follow up who discontinue treatment for reasons other than disease progression; duration of follow up will be up to 3 years.

6 - Screening lab that are done within 5 days of initiating treatment can be used for C1D1 laboratory tests.

7 - [redacted]

8 - [redacted]

9 - [redacted]

10 - PK Assessment: Serum will be collected at Cycle 1 Day 1 (pre-dose and end of infusion), at Weeks 3 and 5 (pre-dose only) and at Week 7 (pre-dose and end of infusion). For all subsequent cycles, serum will be collected at Week 7 (pre-dose only) with the exception of Cycle 3 where serum will be collected at Week 7 (pre-dose and end of infusion). Serum will also be collected at end of treatment and at the 90-day post treatment follow up visit.

11 - Immunogenicity (ADA) Assessment: Serum will be collected at Cycle 1 Day 1 (pre-dose only), at Weeks 5 and 7 (pre-dose only). For all subsequent cycles, serum will be collected at Week 7 (pre-dose only). Serum will also be collected at end of treatment and at the 90-day post treatment follow up visit.

12 - [redacted]

13 - [redacted]

6.5 Retreatment Flow Chart

		Retreatment Period (up to 1 Year)					Every 8 weeks
	Rebaseline	Week 1	Week 3	Week 5	Week 7	Week 8	After 1 year of retreatment
Informed re-consent	X						
Inclusion/Exclusion criteria	X	X					
Medical history (update)	X						
Prior/Concomitant medication	X	X	X	X	X		
MEDI4736 Administration		X	X	X	X		
Prophylactic Medications[1] (ADXS11-001 only)		X		X			
ADXS11-001 Administration		X		X			
PO antibiotics and instructions[2] (ADXS11-001 only)		X		X			
AE/SAE Assessment[3]		X	X	X	X		
Physical examination[4]	X	X	X	X	X		
Vital signs[5]	X	X	X	X	X		
ECOG performance status	X	X	X	X	X		
CBC with Differential[6]	X	X	X	X	X		
Chemistry Panel[6,7]	X	X	X	X	X		
PT/INR and aPTT[7]	X	X	X	X	X		
Urinalysis[7]	X	X	X	X	X		
T3, T4 and TSH[7]	X	X	X	X	X		
Pregnancy test	X	X	X	X	X		
Tumor Imaging[8]		X					X

1 - Subjects will receive prophylactic NSAIDS and antiemetics [redacted] before each ADXS11-001 infusion

2 - Subjects will receive a course of oral antibiotics to be started 3 days after each ADXS11-001 infusion

3 Safety Follow up will be conducted via telephone. Safety Follow up at 30 days (± 1 week) for AEs and at 90 days (± 1 week) for SAEs.

4 ECG and O_2 saturation by pulse oximetry at re-baseline only

5 - Vital signs are to be monitored [redacted] following each ADXS11-001 infusion.

6 - Subjects must meet hepatic and renal function eligibility criteria prior to dosing

7 – Refer to Table 9 for a full listing of laboratory tests

8 – Tumor Assessments will be on Week 1 (± 1 week), starting at ***Cycle 2***. Evaluations will continue every 8 weeks (± 1 week) during treatment and continue for subjects in follow up who discontinue retreatment for reasons other than disease progression; duration of follow up will be up to 3 years.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedure details are described in detail below. It may be necessary to

perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Additional evaluations/testing deemed necessary by the Sponsor for reasons related to subject safety will be incorporated into a protocol amendment but can be implemented prior to IRB approval for safety concerns. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

Consent must be documented by the subject's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The pre-screen consents, initial informed consent form, any subsequent revised initial informed consent form, any re-consent forms and any written information provided to the subject must receive the IRB'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 trial. 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.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial 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.

7.1.1.4 Medical History

A medical history 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. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.5.2 Concomitant Medications/Therapies

The investigator or qualified designee will record medication/therapy, if any, taken by the subject during the trial. All medications/therapies related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.6 Disease Details and Treatments

7.1.1.6.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.6.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.03 (see Section 13.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with the study drug(s) exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See Section 5.2.1.1 regarding the identification, evaluation and management of AEs of a potential immunological etiology.

Please refer to Section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Physical Examination

The investigator or qualified designee will perform a physical examination during the screening period (including baseline screening ECG and O_2 saturation by pulse oximetry), prior to the administration of each dose of trial treatment and at treatment discontinuation as

specified in the Trial Flow Chart (Section 6.0). Clinically significant abnormal findings should be recorded as medical history.

7.1.2.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment, [redacted] following each ADXS11-001 infusion and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, and blood pressure. Height will be measured at screening only and weight will be measured pre-dose at each visit.

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section13.1 ECOG Performance Status) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart- Section 6.1.

7.1.2.5 Tumor Imaging and Assessment of Disease

Computed tomography (CT) and magnetic resonance imaging (MRI) will be considered the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT should be performed with contiguous cuts of 10 mm or less. Spiral CT scan should be performed using a 5 mm contiguous reconstruction algorithm (as a general rule, lesion diameter should be no less than double the slice thickness). Lesions on chest x-rays will be acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable. Ultrasound is not an acceptable method to measure disease.

Assessment of disease will be done using both RECIST 1.1 criteria and irRECIST criteria.

7.1.2.6 Measurable and Non-measurable Lesions and Disease

Measurable lesions will be those that can be accurately measured in at least one dimension with the longest diameter ≥10 mm (for spiral CT scan or MRI scan, ≥5 mm). Measurable disease will be present if the subject has 1 or more measurable lesions.

Non-measurable lesions/disease will be all other lesions (or sites of disease), including small lesions (those with all measurements <10 mm or <5 mm with spiral CT/MRI), or any of the following: bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitis, cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions, and lesions occurring within a previously irradiated area unless they are documented as new lesions since the completion of radiation therapy.

7.1.2.7 Target/Non-Target Lesions

All measurable lesions, up to a maximum of 2 per organ and 5 in total, should be identified as target lesions to be measured and recorded at baseline. The target lesions should be representative of all involved organs. Target lesions will be selected based on their size (the lesion with the longest diameter) and suitability for accurate repeated measurements. At baseline, a sum of the longest diameters for all target lesions will be calculated and recorded as the baseline tumor burden. The baseline sum will be used as the reference point to determine the objective tumor response of the target lesions.

Measurable lesions other than the target lesions and all sites of non-measurable disease will be identified as non-target lesions and will be recorded at baseline. Non-target lesions will be evaluated at the same time points as target lesions.

7.1.2.8 Response in Measureable Lesions (RECIST 1.1)

At baseline, the sum of the longest diameters (SumD) of all target lesions (up to 2 lesions per organ, up to total 5 lesions) is measured. At each subsequent tumor assessment, the SumD of the target lesions and of new, measurable lesions (≥10mm; up to 2 new lesions per organ,

total 5 new lesions) are added together to provide the total measurable tumor burden (TMTB):

TMTB = SumD target lesions + SumD new, measurable lesions

Percentage changes in TMTB per assessment time point describe the size and growth kinetics of both old and new measurable lesions as they appear. At each tumor assessment, the response in target and new measurable lesions is defined based on the change in TMTB.

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

7.1.2.9 Immune-Related Response in Measureable Lesions (irRECIST)

In addition to evaluation using RECIST 1.1 criteria, an immune response adaptation of RECIST will be applied to this trial. The essential differences between irRECIST and RECIST criteria are as follows:

New measureable lesions do not necessarily constitute progressive disease and they should be added into the total tumor burden. New non-measurable lesions do not constitute disease progression but will prevent the determination of an irCR.

Apparent disease progression should be confirmed after 4 weeks in the absence of symptoms consistent with clinical deterioration.

At baseline, the sum of the longest diameters (SumD) of all target lesions (2 per organ and 5 in total) is measured. At each subsequent tumor assessment, the SumD of the target lesions and of new, measurable lesions (≥10 mm [lymph nodes ≥15 mm in shortest diameter]; up to 2 new lesions per organ, total 5 new lesions) are added together to provide the total measurable tumor burden (TMTB):

TMTB = SumD target lesions + SumD new, measurable lesions

Percentage changes in TMTB per assessment time point describe the size and growth kinetics of both old and new measurable lesions as they appear. At each tumor assessment, the response in target and new measurable lesions is defined based on the change in TMTB (after ruling out irPD) as follows:

- Complete Response (irCR): complete disappearance of all target and new, measurable lesions, with the exceptions of lymph nodes which must decrease to <10 mm in short axis
- Partial Response (irPR): decrease in TMTB ≥30% relative to baseline (see below)
- Stable Disease (irSD): not meeting criteria for irCR or irPR, in absence of irPD
- Progressive Disease (irPD): increase in TMTB ≥20% relative to nadir

7.1.2.10 Response in Non-measurable Lesions (RECIST 1.1)

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively.

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

When the patient also has measurable disease, to achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-

target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

In the event that the patient has only non-measurable disease, the same general concepts apply as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease (i.e., an increase in tumor burden representing an additional 73% increase in 'volume' which is equivalent to a 20% increase diameter in a measurable lesion).

7.1.2.11 Immune-Related Response in Non-measurable Lesions (irRECIST)

At each tumor assessment, the presence of any new, non-measurable lesions is assessed. The presence of such lesions will rule out an overall response of irCR. An increase in the size or number of new, non-measurable lesions does not necessarily imply an overall response of irPD; if these lesions become measurable (≥10 mm) at a subsequent tumor assessment, their measurement will at that point start to contribute to the TMTB.

In addition, the response in non-target lesions is defined as follows:

- Complete Response (irCR): complete disappearance of all non-target lesions
- Stable Disease (irSD): non-target lesions are stable
- Progressive Disease (irPD): unequivocal increases in number or size of non-target lesions. To achieve unequivocal progression of non-target lesions, there must be an overall level of substantial worsening of non-target disease that is of a magnitude that the treating physician would feel it is important to change therapy.

NOTE: Equivocal findings of progression of non-target lesions (e.g., small and uncertain new lesions; cystic changes or necrosis in existing lesions) should be considered irSD, and treatment may continue until the next scheduled assessment.

7.1.2.12 Overall Response

Overall response will be determined based on RECIST 1.1 criteria and by irRECIST criteria (Table 1). Overall response according to irRECIST is derived from the responses in measurable lesions (based on TMTB) and the presence of any non-measurable lesions.

Table 6 Tumor Response Evaluation: Comparison of RECIST 1.1 and irRECIST

Criteria	RECIST1.1	irRECIST
New measurable lesions (≥ 10 mm)	Always represents PD	Incorporated into tumor burden
New non-measurable lesions (< 10 mm)	Always represents PD	Does not define progression but precludes irCR
Non-Target lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions	Disappearance of all lesions
PR	≥ 30% decrease in the sum of the longest diameter of all target lesions compared with baseline, in absence of new lesions or unequivocal progression of non-target lesions	≥ 30% decrease in tumor burden compared with baseline
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study	Neither a 30% decrease in tumor burden compared with baseline nor a 20% increase compared with nadir can be established
PD	At least 20% increase in sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. The appearance of one or more new lesions is also considered progression.	At least 20% increase in tumor burden compared with nadir (at any single time point)[a]

irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; BOR = best overall response; CR = complete response; irCR = immune-related complete response; PD = progressive disease; PR = partial response; SD = stable disease;

[a] Patients with an initial finding of progressive disease (irPD) before or at the 9-week imaging assessment, but without rapid clinical deterioration, require confirmation of irPD with a second, consecutive scan obtained ≥ 4 weeks from the initiation documentation. Patients will continue to receive study treatment until irPD is confirmed at this later time point. Best overall response (BOR) will therefore include responses occurring at any time before disease progression and after early progression (i.e., within the first 8 weeks of the study).

7.1.2.12.1 Best Overall Response (RECIST 1.1)

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The

patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions (Table 7).

Table 7 Best Overall Response (RECIST 1.1)

Target Lesions	Non-Target Lesions		
Baseline (Index) and New Measurable Lesions	Baseline Lesions	Unequivocal New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable at a particular time point; PR = partial response; SD = stable disease; PD = progressive disease

7.1.2.12.2 Immune-related Best Overall Response (irRECIST)

The immune-related best overall response (irBOR) is the best irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment prior to subsequent therapy (including tumor resection surgery) for the individual subject in the study (Table 8). As with the primary definitions of tumor response, early progression (i.e., irPD occurring prior to Week 9) will not preclude an irBOR of irCR, irPR or irSD resulting from the Week 9 assessment. An assessment of irPD at or after Week 9 will preclude a subsequent irBOR of irCR, irPR or irSD. However, any post-progression clinical activity in subjects with irBOR of irPD may be summarized for exploratory purposes.

Table 8 Immune-related Best Overall Response (irBOR)

Target Lesions Baseline (Index) and New Measurable Lesions	Non-Target Lesions[a]		
Total Measurable Tumor Burden	Baseline Lesions	Unequivocal New Lesions	irRC Overall Response
irCR	irCR	No	irCR
irCR	irSD	No	irPR
irPR	irCR or irSD	No	irPR
irSD	irCR or irSD	No	irSD
irPD	Any	Yes or No	irPD
Any	Unequivocal Progression	Yes or No	irPD
Any	Any	Yes	irPD

irCR = immune-related complete response; irPR = immune-related partial response; irSD = immune-related stable disease; irPD = immune-related progressive disease

[a] Any increase in the size or number of non-measurable lesions does not necessarily imply an overall response of irPD. If these lesions become measurable (≥10 mm) at a subsequent assessment, their measurement will at that point start to contribute to the total measurable tumor burden. To achieve unequivocal progression of non-target lesions, there must be substantial worsening in non-target disease that is of a magnitude that the Investigator feels it is important to change therapy. Equivocal findings of progression of non-target lesions (e.g., small and uncertain new lesions; cystic changes or necrosis in existing lesions) should be considered irSD, and treatment may continue until the next assessment.

7.1.2.13 [redacted] Correlative Studies Blood Sampling

7.1.2.13.1 [redacted]

[redacted]

[redacted]

7.1.2.13.2 Correlative Studies Blood Sampling

Details for collection, storage and shipping can be found in the Laboratory Manual.

- [redacted]
- [redacted]

- **PK Assessment:** Serum will be collected at Cycle 1 Day 1 (pre-dose and end of infusion), at Weeks 3 and 5 (pre-dose only) and at Week 7 (pre-dose and end of infusion). For all subsequent cycles, serum will be collected at Week 7 (pre-dose only) with the exception of Cycle 3 where serum will be collected at Week 7 (pre-dose and end of infusion). Serum will also be collected at end of treatment and at the 90-day post treatment follow up visit.

- **Immunogenicity (ADA) Assessment:** Serum will be collected at Cycle 1 Day 1 (pre-dose only), at Weeks 5 and 7 (pre-dose only). For all subsequent cycles, serum will be collected at Week 7 (pre-dose only). Serum will also be collected at end of treatment and at the 90-day post treatment follow up visit.

- [redacted]

- [redacted]

7.1.2.14 Safety Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Laboratory Manual.

7.1.2.14.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in **Table 9**. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Laboratory Manual.

Subjects must meet all lab criteria prior to dosing. Laboratory tests can be performed no more than 3 days prior to dosing. If screening laboratory tests are performed within 5 days prior to initial study treatment, they can be used for C1D1 labs. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

Table 9 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	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	*results are noted)*	Free tyroxine (T4)
	(CO_2 or biocarbonate)	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Creatinine		PK
	Calcium		
	Chloride		Blood for correlative studies
	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.

7.1.3 Other Procedures

7.1.3.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 12 months of treatment may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.4.2.1. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.4.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.3.2).

7.1.4 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.4.1 Screening

Screening period – will start when the first screening evaluation is performed. This does not include signing of Informed Consent or wash out periods. Screening evaluations will be performed within 28 days prior to the first treatment administration, unless otherwise specified.

Informed Consent - each subject must sign a copy of the most current IRB/IEC approved informed consent document. A copy of the signed document will be maintained with the subject's records.

Inclusion/Exclusion Criteria - all inclusion and exclusion criteria will be reviewed by the Investigator or qualified designee to ensure that the subject qualifies for the trial

Medical History/Prior and Concomitant Medications - past or current medical conditions, current medications, medications taken within 28 days of study entry, histological confirmation of cancer, tumor staging (refer to the most current American Joint Committee on Cancer Staging Manual, the fifth edition or higher), and prior cancer therapies and best response(s), if applicable.

Complete physical exam - including baseline ECG and O_2 saturation by pulse oximetry

Pregnancy test - A rapid pregnancy test will be performed for all women of child bearing potential. A positive rapid pregnancy test must be confirmed by serum.

HPV genotyping – specimen collection for confirming HPV+ will be collected for SCCHN subjects, if necessary. Details regarding collection, preparation and shipping specimen can be found in the laboratory manual.

Laboratory Procedures (hematology, chemistry, urinalysis, other) – must be performed within 28 days prior to first dose of study treatment. Screening lab that are done within 5 days of initiating treatment can be used for C1D1 laboratory tests.

Tumor Imaging/Disease Assessment - CT scan or MRI for determination of unidimensional measurements and disease response. Baseline tumor imaging/disease assessment must be performed within 28 days prior to the first dose of study treatment.

Analysis of [redacted] – [redacted]

[redacted]

[redacted]

Correlative studies: Blood will be collected as indicated in Section 7.1.2.13.2.

7.1.4.2 Treatment Period

Subjects will be treated for up to 1 year. Subjects should arrive at the study center early on the days of their scheduled treatment in order to be evaluated, have laboratory specimens collected before treatment commences, allow for infusion timing, and take study prophylactic NSAIDs and antiemetic medication, as described below.

During the time the subjects are at the study site, the infusion line will be left in place to administer parenteral drugs, if necessary. Subjects will remain at the study center for a minimum of [redacted] after study treatment for safety observation, and if necessary, treatment of side effects. Subjects may receive NSAIDs every 4 hours and antiemetics every 8 hours after receiving each ADXS11-001 infusion, as needed.

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. Adverse events will be graded and recorded throughout the study and follow-up according to NCI CTCAE v 4.03. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Physical Examination - evaluation by body system.

Vital Signs - blood pressure, pulse rate, respiratory rate, and temperature will be checked and recorded prior to any infusions and [redacted] following the ADXS11-001 infusion. Height and weight will be measured at screening, and weight will be measured pre-dose at every visit.

ECOG Performance Status - according to ECOG criteria.

Laboratory Procedures (hematology, chemistry, urinalysis, other) – must be performed no more than 3 days prior to dosing. Screening lab that are done within 5 days of initiating treatment can be used for C1D1 laboratory tests. Please see Section 7.1.2.14.1 for details.

Prophylactic Medications – Subjects will receive a dose of NSAIDS (e.g. naproxen or ibuprofen) and antiemetics (e.g. promethazine or ondansetron) [redacted] prior to all ADXS11-001 infusions. Subjects should continue to receive NSAIDS, every 4 hours as needed, following the ADXS11-001 infusions.

PO Antibiotics with Instructions – Subjects will receive a 3 day course of one of the following oral antibiotics (amoxicillin, ampicillin, ciprofloxacin, erythromycin, gentamycin, penicillin, trimethroprim/sulfamethoxazole, or vancomycin), to be started on **Day 4** (72 hours) after each ADXS11-001 infusion. ADXS11-001 is resistant to both streptomycin and chloramphenicol. In the event a subject experiences a persistent fever present at 72 hours after receiving ADXS11-001, the oral regimen will be replaced by IV administration

Correlative studies: Blood will be collected as indicated in Section 7.1.2.13.2.

Analysis of [redacted]

Tumor Imaging/Disease Assessment - CT scan or MRI for determination of unidimensional measurements and disease response. Imaging studies and tumor assessments will be performed every 8 weeks starting with Day 1 of Cycle 2.

Pregnancy test - A rapid pregnancy test will be performed within 72 hours of each treatment administration (combination or monotherapy) for all women of child bearing potential prior to treatment. A positive rapid pregnancy test must be confirmed, prior to dosing, by serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of βHCG).

7.1.4.2.1 Re-Treatment Period

Subjects who attain a CR during treatment or complete 1 year of treatment may discontinue treatment with the option of an additional 1 year of treatment at the same treatment they were previously assigned if:

- during the first 12 months of the subject's follow up period (Section 7.1.4.3.2), disease progression is noted
- other subjects are still currently being treated
- subject still meets eligibility criteria
- sponsor and investigator are in agreement

Subjects will be re-consented and must meet all baseline inclusion exclusion to receive subsequent therapy. Eligibility criteria will only be evaluated prior to retreatment and not prior to every subsequent cycle.

Retreatment Visit schedule is outlined in Section 6.5 – Retreatment Study Flow. Re-baseline evaluations will be performed within 28 days prior to the first retreatment administration.

7.1.4.3 Post-Treatment Visits

7.1.4.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days (±5 days) after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.1.4.3.2 Follow-up Visits

90 day post treatment visit – Blood will be collected for PK/ADA/[redacted] markers on all subjects assigned to receive MEDI4736 monotherapy or Combination therapy.

8-week post treatment visit - Subjects who discontinue trial treatment or retreatment for a reason other than disease progression should be assessed every 8 weeks (± 1 week) by radiologic imaging to monitor disease status for up to three years. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment as detailed in Section 7.1.4.2.1.

Subjects who are in the follow up phase and experience disease progression may have the option to be retreated, after discussion with the sponsor. Details are provided in Section 6.5 –Retreatment Flow Chart and Section 7.1.4.2.1– Retreatment Period

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, 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 the Sponsor's product, is also an adverse event.

The Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Advaxis for human use.

Adverse events may occur during the course of the use of Advaxis' product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events 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.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in Section 7.2.3.1.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

7.2.1 Definition and Reporting of an Overdose

For purposes of this trial, an overdose will be defined as any dose exceeding 20% over the prescribed dose of ADXS11-001 or MEDI4736. No specific information is available on the treatment of overdose. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of the study drug(s), the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Advaxis' product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as

a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to inVentiv Health Clinical Pharmacovigilance (Attn: iHC SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@inventivhealth.com).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male 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 serious events (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 inVentiv Health Clinical Pharmacovigilance (Attn: iHC SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@inventivhealth.com)

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Advaxis' product 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

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Advaxis' product, must be reported within 24 hours to the Sponsor at inVentiv Health Clinical Pharmacovigilance (Attn: iHC SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@inventivhealth.com).

Non-serious Events of Clinical Interest will be forwarded to inVentiv Health Clinical Pharmacovigilance (Attn: iHC SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@inventivhealth.com) and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Advaxis' product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

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

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Advaxis Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to inVentiv Health Clinical Pharmacovigilance (Attn: iHC SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@inventivhealth.com) at the time of submission to FDA.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to inVentiv Health Clinical Pharmacovigilance (Attn: iHC SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@inventivhealth.com).

Events of clinical interest for this trial include:

1. Pneumonitis - Pneumonitis has been reported in association with use of anti-PD-L1/anti-PD-1 antibodies [36]. Initial work-up should include a high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is recommended.

2. Hypersensitivity Reactions - Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy [36]. As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of mAbs can be caused by various mechanisms, including

acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the mAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritis, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

- Subjects with Grade 1 and 2 hypersensitivity (including anaphylactic reaction) and infusion-related reactions should be treated according to standard medical practices. If a subject experiences a grade 3 or 4 infusion reaction, the infusion will be discontinued immediately, and no subsequent infusions may be given.

- A grade 3 or 4 infusion reaction will require immediate treatment, including the use of epinephrine, bronchodilators, and/or glucocorticoids for symptomatic bronchospasm; IV fluids and/or pressors for hypotension; and immediate and permanent discontinuation of study drug(s) with appropriate supportive care.

3. Hepatic Function Abnormalities (Hepatotoxicity) - Increased transaminases have been reported during treatment with anti-PD-L1 [36].

   Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 x ULN **and concurrent** increase in bilirubin to greater than 2 x ULN (i.e., Hy's Law cases). Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product(s).

If an event of hepatic function abnormality is considered to be related to a pre-existing condition and does not represent a worsening of this condition and/or is considered to be within the range of normal physiological fluctuation for the subject, the event does not meet the definition of an AE and does not need to be recorded as such.

If the underlying diagnosis for the hepatic function abnormality is known (including progression of pre-existing disease such as primary or metastatic malignancy), the diagnosis should be recorded as an AE/SAE.

In the event a subject develops any of the following AEs, a detailed narrative of the event should be reported as an ECI to the Sponsor within 24 hours:

- Grade ≥3 diarrhea
- Grade ≥3 colitis
- Grade ≥2 pneumonitis
- Grade ≥3 hypo- or hyperthyroidism

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Advaxis' product, must be reported within 24 hours to the Sponsor.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

The following attribution categories will be used in assessing the relationship between the AE and the study drug:

Table 10 Evaluating Adverse Events

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This is a Phase 1-2 study of ADXS11-001 or MEDI4736 alone or combination in locally advanced, or metastatic, squamous or non-squamous carcinoma of the cervix or HPV+ squamous cell carcinoma of the head and neck.

There are 2 phases in this study with different objectives. For safety, the analysis will be performed for Part A and Part B separately and combined. The efficacy analysis will be performed for Part A and Part B separately. SAS 9.2 or higher will be used for data analysis.

Subject disposition, demographic and baseline subject characteristics will be summarized separately for Part A and Part B. Adverse events will be classified and summarized by type, incidence, severity, and causality. All adverse events will be summarized by subject, treatment, and disease. All subjects who receive at least 1 dose of study treatment will be included in the safety analyses.

Statistical analysis for efficacy will be summarized by treatment arm and disease type. Although it may lack statistical power, statistical testing for treatment comparisons will be performed as a reference. Tumor response will be evaluated by RECIST criteria and secondarily by irRECIST criteria. The overall response rate will be summarized; frequency counts and percentage and will be tested by the Fisher's Exact test. PFS is defined as the time from randomization until objective tumor progression or death. Subjects who have not progressed or who are still alive at the time of evaluation will be censored for the analysis. Kaplan-Meier (KM) curves and descriptive statistics will be used to summarize PFS. The percentage of subjects with PFS and the 95% confidence intervals will be provided. PFS and duration of response will be summarized using KM method and tested by the Log-Rank test controlled by disease type.

Furthermore, the disease response will be tabulated for all subjects who receive ADXS11-001 monotherapy, MEDI4736 monotherapy or ADXS11-001 + MEDI4736 combination therapy.

8.2 Safety Monitoring

An external Data Safety Monitoring Committee will not be established for this study. A periodic safety review will be applied by an internal safety review team with medical capabilities to review individual and summary data collected in the safety and clinical databases. Findings having immediate implication for the management of subjects on study will be communicated to all Investigators in the timeframe associated with unexpected and drug-related SAEs.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

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

[redacted]

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Advaxis or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 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 case record form (CRF). 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.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US 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 United States for these purposes.

10.3 Compliance with Law, Audit and Debarment

International Conference on Harmonization (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.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

10.5 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 trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 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.

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12.0 SUMMARY OF CHANGES

Section	**Page**	Revision	Rationale
General		Minor editing, spelling and section placement changes were made throughout to clarify, correct and improve readability	Administrative/clarifications
General	**11**	Updated description of MEDI4736 in Summary	Align
General		Added language throughout regarding antibiotic use	Align
General		Removed all language regarding [redacted] in Part A (Phase 1) of the study	Based on investigator feedback
5.1.1	31	Revised lab eligibility in Table 1	Aligned with current requirement in protocol
5.1.2	34	Updated Exclusion #13	Based on investigator feedback
5.1.2	34	Updated Exclusion #16	Align to update on allowed antibiotics
5.1.2	35	Added Exclusion #18 regarding contraindication to NSAIDS	To clarify required use of NSAIDs per protocol
5.2.1.4	42	Table 3, Treatment Modification Guidelines	Updated for clarity
5.5.2	51	Added sentence regarding Acetaminophen use	Clarification
5.5.2	51	Updated Prohibited Medications list	Clarification
5.6	52	Revised Supportive Care Guidelines	Updated for clarity
5.6.1	52	Added Cytokine Release Syndrome supportive care guidelines	Updated and expanded for clarity
5.7.2	59	Included details of birth control requirement for male subjects	Clarification
6.0	63	Updated all Trial Flow Charts	Clarifications and footnote corrections. Remove tumor biopsies in Part A
7.1.2.13.2	86	Updated Correlative Studies Blood Sampling	Added additional text for clarification
7.1.2.14.1	88	Added detail regarding lab test timing	Clarification
7.1.4.1	90	Include sentence regarding consent signing verse screening	To ensure adequate time for protocol required wash out periods
7.2.5	105	Removed Table 10	Removed duplicate AE evaluation descriptions
8.2	108	Added Safety Monitoring section	Based on investigator feedback

13.0 APPENDICES

13.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Oken MM et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

13.2 Common Terminology Criteria for Adverse Events V4.03 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for adverse event reporting. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

13.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* Eisenhauer EA, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

In addition, volumetric analysis will be explored by central review for response assessment.

14.0 ABBREVIATIONS

ADXS11-001	*Lm*-LLO Immunotherapy for HPV associated diseases
AEs	Adverse Events
APC	Antigen Presenting Cell
CD4	Cytotoxic T cell, effector T cell, Memory T cell
CD8	Helper T cell, Regulatory T cell
CAT	chloramphenicol acetyl transferase
CFU	Colony Forming Unit
CIN	Cervical Intraepithelial Neoplasia
CR	Complete response
CTL	Cytotoxic T lymphocyte
DCR	Disease Control Rate
DLT	Dose limiting toxicity
DTH	delayed-type Hypersensitivity
GGT	Gamma glutyltransferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GOG	Gynecologic Oncology Group
HPV	Human papilloma virus
HspE7	Heat Shock Fusion Protein-Based Immunotherapy
IV	Intravenously
IFN	Interferon
LEEP	Loop Electrosurgical Excision Procedure
LFT	Liver Function Test
LLO	Listeriolysin O
Lm	*Listeria monocytogenes*
*Lm*dd	An attenuated strain of *Listeria monocytogenes* with deletions in two genes (*dal* and *dat*)
Lm-LLO	*Listeria monocytogenes* Listeriolysin O
MDSC	myeloid-derived suppressor cells
MHC	Major Histocompatibility Complex
MIC	Minimum inhibitory concentration
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NSAID	Non-Steroidal Anti Inflammatory Drugs
PBMC	Peripheral blood mononuclear cell
PR	Partial response
PSA	Prostate-specific antigen
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SOC	Standard of Care
TAA	Tumor Associated Antigen(s)
TCR	T-cell receptor

TIL	Tumor infiltrating lymphocytes
tLLO	Truncated LLO
Tregs	Regulatory T cells
wt-*Lm*	wild type *Listeria monocytogenes*