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FROM: MEG COLAHAN
PROTOCOL SECTION

DATE: OCTOBER 18, 2016

RE: PROTOCOL GOG-0265 – CLOSURE

Protocol Title: "A Phase II Evaluation of ADXS11-001 (NSC 752718, BB-IND #13,712) in the Treatment of Persistent or Recurrent Squamous or Non-Squamous Cell Carcinoma of the Cervix"

Study Chair: Warner K. Huh, M.D.; (205) 934-4986; email: whuh@uabmc.edu

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Effective October 24, 2016, GOG-0265 is closed to patient entry.

The GOG Foundation and Advaxis, Inc. have agreed to close GOG-0265 to patient entry. This decision was at the request of the Sponsor (Advaxis): GOG-0265 was previously placed on a FDA clinical hold, and subsequent review of Stage 2 data was consistent with Stage 1; a phase III study of the agent has already been initiated.

Follow-up of patients already entered onto GOG-0265 will continue per protocol.

Members of the study team will be reaching out to you soon to discuss next steps for closing out the study.

SUMMARY OF CHANGES

NCI Protocol #: GOG-0265
Local Protocol #: GOG-0265

NCI Version Date: 05/20/2016
Protocol Date: 06/27/2016

#	Section(s)	Page(s)	Change
1	Title Page	1	To reflect the date of closure.

PROTOCOL GOG-0265

A PHASE II EVALUATION OF ADXS11-001 (NSC 752718, BB-IND#13,712) IN THE TREATMENT OF PERSISTENT OR RECURRENT SQUAMOUS OR NON-SQUAMOUS CELL CARCINOMA OF THE CERVIX

NCI Version Date: 05/20/2016

Includes Amendments #1-13

POINTS:

PER CAPITA- 20

MEMBERSHIP- 6 **(10/22/2012)**

TR PER CAPITA – Award based on specimen submission with 1.0 point for FFPE and 1.0 point for each serum specimen (MAX = 13 points). **(05/06/2013)**

Lead Organization: NRG/NRG Oncology **(02/02/2015)**

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SCHEMA **(12/23/2013) (03/09/2015) (06/27/2016)**

ADXS11-001 will be given once every 28 days (60 minute intravenous infusion of 1 x 10^9 cfu in 250 ml of normal saline) until disease progression or adverse events prohibit further therapy.

OPEN TO PATIENT ENTRY MAY 23, 2011; REVISED OCTOBER 17, 2011; REVISED FEBRUARY 6, 2012; REVISED OCTOBER 22, 2012; REVISED AND OPEN TO PATIENT ENTRY GROUP WIDE MAY 6, 2013; REVISED DECEMBER 23, 2013; TEMPORARILY CLOSED TO PATIENT ENTRY MAY 5, 2014; REVISED AND REOPENED TO PATIENT ENTRY FEBRUARY 2, 2015; REVISED MARCH 9, 2015; REVISED JUNE 27, 2016; CLOSED TO PATIENT ENTRY OCTOBER 24, 2016

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1.0 OBJECTIVES

1.1 Primary Objectives

1.1.1 To evaluate the tolerability, safety and nature and degree of toxicity of ADXS11-001 by the numbers of patients with dose limiting toxicities (DLTs) and adverse events as assessed by the CTCAE v4.0. **(12/23/2013)**

1.1.2 To assess the activity of ADXS11-001 for patients with persistent or recurrent carcinoma of the cervix with the frequency of patients who survive for at least 12 months after initiating therapy.

1.2 Secondary Objectives

1.2.1 To characterize the distribution of progression-free survival and overall survival.

1.2.2 To examine the proportion of patients with objective tumor response.

1.3 Exploratory Objectives

1.3.1 To assess changes in clinical immunology based upon serum cytokines and to correlate any observed changes with clinical response including progression-free survival, overall survival, tumor response, DLTs and adverse effects.

1.3.2 To examine associations between presence and type of high-risk human papillomavirus (H-HPV) and measures of clinical response and serum cytokine levels.

2.0 BACKGROUND AND RATIONALE

2.1 Cervical Cancer and Its Relationship to the Human Papillomavirus (HPV) **(06/27/2016)**

Cervical cancer is the fourth most common cancer and the most common cause of mortality in women worldwide with 528,000 new cases reported annually, and an estimated 266,000 deaths in 2012.[1] Worldwide, over half a million women are diagnosed with cervical cancer each year, predominantly in under-developed countries, where most cases present at an advanced stage due to lack of effective cervical cancer screening systems.[2] In the United States (US), it is estimated that 12,340 women were diagnosed with cancer of the cervix, and 4,030 women died of the disease in 2013.[3]

The human papilloma virus (HPV) is now recognized to be the primary etiologic agent for cervical carcinogenesis, and cervical cancer is the first cancer recognized by the World Health Organization to be 100% attributable to an infection with high-risk HPV genotypes.[2] However, the majority of HPV-infected individuals have an asymptomatic course, with clearance of the virus occurring within 1 or 2 years in 90% of cases. Ten percent of individuals experience persistent HPV infection, which increases their risk of developing invasive cancers. Ultimately, approximately one-half of the 10% of

individuals with persistent HPV infection will develop malignant disease, a process that may take up to 30 years.[4]

Although many HPV types have been associated with cervical neoplasia, types 16, 18, 31, 35, 39, 45, 51, 52, 56, and 58 cause most invasive cancers and are considered "high-risk" HPV-genotypes. HPV-16 accounts for approximately 53% of invasive cervical cancer (ICC) cases in most countries, followed by HPV-18, which accounts for approximately 13%.[5] The high-risk HPV genotypes produce 2 oncoproteins, designated E6 and E7, which bind and inactivate the tumor suppressor's p53 and retinoblastoma protein (pRB), respectively. The E6 mediated inhibition of p53 blocks apoptosis, whereas E7 inhibition of pRB abrogates cell cycle arrest leading to deregulated cellular proliferation and ultimately malignancy.[5]

Persistent HPV infection may lead initially to abnormal changes in cervical cells, termed cervical dysplasia or cervical intraepithelial neoplasia (CIN). However, CIN is a distinct clinic pathological entity from ICC and defines premalignant lesions (namely CIN 2/3) that, if left untreated, may eventually progress to ICC. However, these lesions have a high rate of spontaneous remission and can be curatively treated with a minor gynecologic surgical procedure such as loop electrical electrosurgical procedure or a cone biopsy.

In the US, most cases of ICC are detected at early stages because of the implementation of cervical cancer screening programs. Staging of ICC is usually based on the American Joint Committee on Cancer or the International Federation of Gynecology and Obstetrics system, which are similar. Approximately 60% of ICC cases are diagnosed at stage I, 25% at stage II, 10% at stage III, and 5% at stage IV.[6] Standard treatments for ICC include surgery, radiation alone, chemotherapy alone, or combination radiation/chemotherapy. Surgery and radiation therapy are considered to be equally effective for early-stage, small-volume disease. For more advanced disease, that is not reliably curable by surgery, additional treatments including radiation and potentially systemic chemotherapy are required. Several clinical trials have shown an overall survival advantage with cisplatin concurrent with radiation therapy (chemoradiation), and chemoradiation with cisplatin is the currently recommended treatment for locally advanced cervical cancer.[7] Platinum doublet chemotherapy with or without bevacizumab is currently recommended as standard of care for patients with recurrent or primary metastatic (stage IVB) cervical cancer that is not amenable to surgery or radiation.[7] In general, survival correlates with stage, with a 5-year survival for stage IA of almost 100%, stage IB2 and IIB 50%–75%, stage III 30%-50%, and stage IV 15%. For locally recurrent disease, pelvic exenteration can lead to a 5-year survival rate of 32%-62% in selected patients.[7] Although most cases of early-stage cervical cancer can be cured, treatments are associated with significant long-term morbidity[7] and most have an impact on fertility. Cisplatin, the most commonly used and most active therapy, has produced response rates ranging from 20%-30% and overall survival of less than 10 months.[8] In addition, patients with recurrent disease will typically have already received cisplatin concurrent with radiotherapy as a first-line therapy, and may no longer be sensitive to cisplatin.[9][9] In view of the low level of success with cytotoxic therapies, and the poor

prognosis of patients with advanced cervical cancer, there is certainly an unmet medical need for novel, more efficacious, less toxic therapeutic approaches for ICC.

Doublets containing cisplatin (GOG-0169 and GOG-0179) demonstrated superiority over single-agent platinum.[10,11] The GOG completed GOG-0204, a phase III, four-arm study comparing three cisplatin containing doublets (gemcitabine, vinorelbine, or topotecan) to a control arm of cisplatin/paclitaxel.[8] No therapy was superior to cisplatin and paclitaxel, and the results demonstrated a trend towards improved quality of life, progression-free survival, and overall survival in the cisplatin/paclitaxel arm. Thus, paclitaxel/cisplatin remained the preferred platinum-based chemotherapy backbone for metastatic or recurrent cervical cancer. On August 14, 2014, the FDA approved the use of bevacizumab in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic cervical cancer. This approval was based on the results of the GOG-0240 study,[12] which noted a statistically significant improvement in OS for the bevacizumab plus chemotherapy arm (med OS of 16.8 months for bevacizumab plus chemotherapy vs. 12.9 months for chemo alone P=0.0132).

Despite this, there continues to be a large unmet medical need for agents with different mechanisms of action (such as antiangiogenics, checkpoint inhibitors, or therapeutic HPV immunotherapies) that when used alone or in combination can improve the survival of patients with recurrent cervical cancer.[8]

2.2 HPV Vaccines

Squamous cell carcinoma of the cervix requires the constitutive expression of the HPV oncoproteins E6 and E7. Thus, the E6 and E7 antigens have been an intense focus of cancer immunotherapies using a variety of vaccine vectors. Because of the intra-cellular localization of these antigens, these therapies are mostly directed at cellular immune responses. The ability to deliver antigen to the cytosolic compartment of APCs in order to develop HLA class I presentation to induce CD8+ cytotoxic T cell responses is widely believed to be necessary for developing an effective therapeutic anti-tumor vaccine.

Several approaches have been employed to develop therapeutic HPV vaccines against cervical cancer. Peptide-based vaccines using E7 peptide have been shown to generate cytotoxic T lymphocytes (CTLs) that were protective against HPV-16 E7 positive tumors.[13-14] One Phase I/II clinical trial immunized 19 terminally ill cervical cancer patients with HLA-A*0201-restricted HPV 16 E7 peptide and demonstrated safety, but no CTL responses were detected.[15] Another Phase II clinical trial in end-stage cervical cancer patients used E6 or E7 HLA-A*0201-binding peptides pulsed onto cytokine-stimulated autologous peripheral blood mononuclear cells (PBMCs). The trial showed that 11 of 16 patients evaluated developed cytotoxic responses.[16] Despite this early success, peptide-based vaccines have the disadvantage of sometimes leading to tolerance rather than activation. Also, peptide-based vaccines require the identification of epitopes associated with a particular MHC allele. Women who do not share a particular allele would not be eligible for treatment.

Protein-based vaccines deliver the entire protein for APC processing. Several studies have confirmed the ability to generate HLA class I-restricted CTL responses.[17,18]A few protein vaccines have been tested for the treatment of genital warts or dysplasia in humans[19-22] and have demonstrated safety and modest immune responses.

Vaccination with live-recombinant viruses has the advantage of high-efficiency DNA transduction and gene-expression. Adenovirus and vaccinia are the two most common viral vectors in use. Phase I/II trials of vaccinia virus expressing E6 and E7 (TA-HPV) demonstrated the vaccine to be safe, but only 1 of 8 patients demonstrated an immune response.[23] A multi-center trial in Europe utilizing this vaccine is currently awaiting long-term clinical outcome data. Recombinant adenovirus encoding multiple tumor-associated CTL epitopes demonstrated a protective anti-tumor effect against an HPV 16-transformed cell line.[24] One main disadvantage of using these viral vectors is that effectiveness may depend on host immunity. In the case of vaccinia, pre-existing immunity secondary to prior vaccination against smallpox may attenuate a vaccine's efficiency. In the case of adenovirus, the host may mount a significant humoral and cellular response to the adenoviral vector, thereby precluding the effectiveness of multiple immunizations. In addition, adverse events that occur often cannot be controlled. For instance, in the 1960's, smallpox vaccination was the cause of a substantial number of adverse events and resulted in a lethal infection in approximately one out of one million people who received this live vaccinia vaccine.[25] Recently the use of adenovirus for gene therapy has also resulted in a fatality.[26] Dendritic cell (DC) based vaccines and modified tumor cell-based vaccines have also been investigated with limited success in preclinical models.

The literature provides many references to support the idea that many HPV species respond to therapeutic agents based upon HPV-16 E7.[27] A phase II study, conducted by the New York Phase II Consortium (an NCI-sponsored consortium), immunized 31 healthy women with biopsy-proven Cervical Intraepithelial Neoplasia (CIN) III with three, monthly subcutaneous vaccinations with 500 mcg of SGN-00101 [Heat Shock Fusion Protein-Based Immunotherapy (HspE7)]. Of the 31 evaluable patients, 32% (10/31) had a complete pathologic response; 39% (12/31) had a partial response and 29% (9/31) had stable disease. The overall response rate was 71% (22/31, 95% C.I.=55-87%). No patient progressed. Fifty-five percent (17/31) were HPV-16 positive prior to vaccination and one patient had HPV-16 subsequently detected. These results suggest all cervical cancer patients (not just those who are HPV-16 positive) would benefit from the vaccine targeted at HPV-16 E7. Further, it supports the idea that HPV epitopes are sufficient similar to allow efficacy in other HPV types. Research completed by Nventa, formerly Stressgen, reports extremely high efficacy using the HPV-16 E7 antigen even in non-HPV-16 positive patients; which demonstrates the antigen has immuno-therapeutic activity across HPV types.[28] Davidson et al. reported cross reactivity to the E7 antigen and responses in patients with other HPV types in a trial of a vaccinia based HPV-16 E7 vector tested in the clinical treatment of high grade vulval intraepithelial neoplasia (VIN).[29] Luxton et al, reported that 22% of responding women treated with HPV-16 E7 peptide epitopes for the treatment of cervical dysplasia or neoplasia were negative for HPV-16 DNA.[30] Slevy et al. reported that B cell epitopes of HPV-16 E7 are cross

reactive with HPV-18.[31] Krchnak et al, found while investigating HPV-16 E7 epitopes that of the 9 overlapping peptides that were made to map the immunogenic domains, some epitopes were type-specific and others were cross reactive with other HPV types.[32] Additional support for the cross reactivity of HPV-16 E7 with other HPV types has been demonstrated in human HLA-A2 transgenic mice.[33] It further appears that certain HPV-16 E7 epitopes are conserved across genera, as Nilges et al demonstrated that "…cross-reactivity represents the inherent nature of the T-cell repertoire" with cross reactivity between HPV-16 E7 and Coronovirus protein OC43 NS2.[34]

2.3 Recombinant Listeria monocytogenes (Lm) as a Vaccine Vector

The advantages that *Listeria monocytogenes* possesses as a vaccine vector are rooted in its biology. It is a beta hemolytic gram-positive facultative intracellular bacterium that has been used to study cell mediated immunity for decades.[35] *Listeria* preferentially infects APC, and unlike other intracellular bacteria like *Salmonella*, *Listeria* escape into the cytoplasm of the host cell by disrupting the phagosomal membrane. Also unlike *Salmonella, Listeria* is a gram positive organism, thus does not release endotoxin, a rate limiting attribute of *Salmonella.* Because *Listeria* quickly leaves the circulation becoming an intracellular infection, and because it replicates in the cytoplasm, humoral immunity does not play a major role in combating *Listerial* infections. Peptides derived from *L. monocytogenes* in the phagolysosome and the cytosol can be presented by the MHC Class I and Class II molecules, inducing both CD4+ and CD8+ T-cell responses. *Listeria* has other useful properties, such as stimulating monopoiesis, stimulating the differentiation and maturation of APC, and the generation of a particularly strong innate immune response.[36]

Advaxis builds upon this unique attribute of *Listeria* by engineering the release of E7 antigen as a fusion protein to a non-hemolytic fragment of the *Listeria* protein Listeriolysin O (LLO), resulting in more potent and broad CTL responses to the target antigen. The HPV tumor antigen proteins E6 and E7 are constitutively expressed in the nucleus of HPV associated tumors. Most therapies targeting these antigens are directed at cellular immune responses. The ability to deliver antigen to the cytosolic compartment of APCs in order to develop HLA Class I presentation to induce CD8+ cytotoxic T cell responses appears to be an important aspect of developing an effective therapeutic anti-tumor vaccine.

LLO is a virulence factor of Lm as it enables the bacterium to escape from the phagolysosome and thus become virulent. As such, it appears to have evolved as a target of the immune system and stimulates many potentially therapeutic immune responses by itself, independent of the microbe. By using it as part of a fusion protein along with an antigen this vaccine secretes a combined antigen-adjuvant directly within both the phagolysosome and cytoplasm of APC.

There is evidence that Lm also gets into tumors, probably carried by infected macrophages and neutrophils. One potential consequence of this is the observed ability of live *Listeria* vaccines that secrete an LLO-antigen fusion, but not those that secrete

only an antigen, to diminish regulatory T cells within the tumor, but not in the spleen or peripheral tissues.[37, 38]

2.4 Listeria monocytogenes Expressing HPV 16-E7 (ADXS11-001 Immunotherapy) **(06/27/2016)**

ADXS11-001 is a live attenuated *Listeria monocytogenes* (*Lm*) 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 (truncated LLO, tLLO) fused to the full length E7 peptide of HPV-16.

ADXS11-001 is manufactured for Advaxis, Inc. by Cobra Biomanufacturing PLC in the UK at EU and FDA certified facilities, and with open Drug Master Files in place on both continents. Clinical materials have been manufactured under GMP conditions and in compliance with GMP regulations, and are so documented.[39-51]

2.5 ADXS11-001 Mechanism of Action **(06/27/2016)**

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

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

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

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

2.6 Summary of Previous Clinical Studies **(06/27/2016)**

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

2.6.1 ***Lm*-LLO-E7-07: Phase 1 Experience**

In the initial Phase 1 dose escalation study (Lm-LLO-E7-01), ADXS11-001 was assessed in 15 subjects with previously treated metastatic, refractory or recurrent invasive cervical cancer.[52] ADXS11-001 was administered as an intravenous (IV) infusion at doses of 1×10^9 to 1×10^{10} CFU followed by a second dose 3 weeks later. Overall, ADXS11-001 infusion was safely administered and well tolerated in end-stage subjects who had failed multiple prior therapies.

No pre-medications were given in this study and all subjects experienced flu-like symptoms and/or symptoms associated with CRS. The most commonly reported AEs were pyrexia (100%), vomiting (60%), chills, headache and anemia (53.3% each), nausea and tachycardia (46.7% each), and musculoskeletal pain (26.7%). At all doses, AEs were acute and transient in most subjects, and responded to non-prescription symptomatic treatment with no observed listeriosis or *Lm* shedding. A total of 9 (60%) subjects experienced Grade 3 AEs, and in 6 (40%) of those subjects AEs were considered treatment-related (pyrexia in 3 subjects, fatigue in 1 subject, and increased gamma-glutamyltransferase [GGT] levels in 2 subjects). No Grade 4 AEs were observed. The highest dose of 1×10^{10} CFU led to a dose-limiting toxicity (DLT) of Grade 2 diastolic hypotension. Under typical interpretation of a DLT (as defined per the protocol) in Phase 1 clinical studies in refractory cancers, this AE would not have met the criteria for DLT. Two deaths occurred during the study period and were considered unrelated to ADXS11-001 administration. Although not designed to assess efficacy, stable disease (SD) was reported in 7 of 13 (54%) evaluable subjects, and 1 subject (8%) had an unconfirmed partial tumor response. Based on the AE profile, all subsequent studies incorporate the administration of NSAIDs and antiemetic medications pre- and post-infusion to help reduce the incidence and severity of AEs related to cytokine release. As an additional precaution, a course of oral antibiotics is initiated on Day 3 post-dosing of ADXS11-001 to assist in clearance of the *Lm.*

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

Lm-LLO-E7-15, was a randomized, multicenter, actively controlled Phase 2 study evaluating the safety and efficacy of ADXS11-001 alone compared with ADXS11 001 + cisplatin in 110 subjects with advanced cervical cancer that recurred after prior cytotoxic

therapy, including chemotherapy and/or radiotherapy. Eligible subjects were randomized 1:1 to ADXS11-001 or ADXS11-001 + cisplatin. Subjects in the ADXS11-001 group received 1 cycle (3 doses of 1 x 10^9 CFU) of ADXS11-001 at 28-day intervals. Subjects in the ADXS11-001 + cisplatin group received a single dose of ADXS11-001, followed 28 days later by 5 weekly doses of cisplatin (40 mg/m^2), followed 28 days later by 1 cycle of ADXS11-001; as a precautionary measure, a course of oral antibiotics was given to ensure clearance of the *Lm* . After first dosing, subjects were followed at 3, 6, 9, 12, and 18 months; 109 subjects received 264 doses of ADXS11-001.

The primary endpoint of the study was OS. Of 109 enrolled subjects, 89 (81.7%) subjects at 3 months, 70 (64.2%) at 6 months, 49 (45%) at 9 months, 35 (32%) at 12 months, and 24 (22%) at 18 months were alive, suggesting that ADXS11-001 is an active agent in recurrent cervical cancer. There was no statistically significant difference in the median duration of OS between ADXS11-001 and ADXS11-001 + cisplatin ($p = 0.9993$), nor was there any statistically significant effect of disease status, prior therapy, or Eastern Cooperative Oncology Group (ECOG) performance status on OS between treatment groups.

Of 69 subjects in the efficacy population, 10% of subjects had an objective tumor response. Complete response (CR) was recorded as the best response in 5 subjects (3 ADXS11-001; 2 ADXS11-001 + cisplatin), partial response (PR) in 6 subjects (3 ADXS11-001; 3 ADXS11-001 + cisplatin), SD in 31 subjects (16 ADXS11-001; 15 ADXS11-001 + cisplatin), and progressive disease (PD) in 27 subjects (13 ADXS11-001; 14 ADXS11-001 + cisplatin). Tumor response at 3, 6, 9, 12, and 18 months was comparable between treatment groups. The disease control rate was 39% (42/109). Results of the safety profile are shown in Table 1.

2.6.3 GOG-0265: Phase 2 Evaluation of ADXS11-01 in Recurrent, Refractory Cervical Cancer

GOG-0265 is an ongoing study being conducted by the GOG, through sponsorship by the NCI Cancer Therapy Evaluation Program (CTEP). It is a 2-stage study designed to evaluate ADXS11-001 (3 doses of 1 x 10^9 administered every 4 weeks) in subjects with advanced, metastatic, or recurrent squamous or non-squamous carcinoma of the cervix who have had at least 1 prior systemic chemotherapeutic regimen in the metastatic setting. The primary objectives of the study are to evaluate:

The tolerability, safety, nature and degree of toxicity of ADXS11-001 by the numbers of subjects with DLTs and AEs as assessed by CTCAE v 4.03
To assess the activity of ADXS11-001 for subjects with persistent or recurrent carcinoma of the cervix by the frequency of subjects who survive for at least 12 months after initiating therapy

Twenty-nine subjects were enrolled to Stage 1 of the study, of which 3 were never treated with ADXS11-001. Among the 26 subjects, 8 (30%) had 1 prior therapy, 14 (54%) had 2 prior therapies and 4 (16%) had 3 prior therapies for treatment of their metastatic disease.

The study is being conducted according to the GOG's standard Simon 2-stage design (for recurrent/refractory cervical cancer). A Stage 1 efficacy bar of 20% 12-month survival was established as a predetermined criterion (by a logistic regression model from 17 studies conducted by GOG in over 500 subjects with recurrent/refractory cervical cancer) to be met in order for the study to proceed to Stage 2. Based on the historical data in subjects with recurrent/refractory cervical cancer, the expected 12-month survival rate is 10-15%.

As of May 2015, Stage 1 of GOG-0265 is complete with 26 subjects receiving at least 1 dose of ADXS11-001. Stage 2 of the study opened on March 11, 2015 and will enroll approximately 37 subjects. The study has been amended to allow for treatment with ADXS11-001 until disease progression as per RECIST 1.1, and to limit the number of prior therapies in the metastatic setting to no more than 1 prior therapy.

2.7 Summary of Safety of ADXS11-001 **(06/27/2016)**

As of January 1, 2015, 573 doses of ADXS11-001 have been administered to 229/230 enrolled subjects at doses of 5 x 10^7, 3.3 x 10^8, 1 x 10^9, 3.3 x 10^9, and 1 x 10^{10} CFU. In the Phase 1 study, 100% of subjects (n=15) have experienced flu-like AEs or symptoms associated with cytokine release syndrome. The incorporation of NSAIDs and antiemetic medications pre and post infusions has effectively reduced the incidence of these symptoms from 100% to 37%. In addition, a course of antibiotics is given 3 days after each dose of ADXS11-001 as a precautionary measure to ensure clearance of the *Lm*. From the clinical experience in 230 subjects, a clear pattern of mild to moderate treatment-related AEs consistent with cytokine release symptoms (e.g., constitutional symptoms such as fever, chills, rigors, headache, nausea, vomiting, tachycardia, shortness of breath, hypotension, and rash) are commonly seen and typically appear 2-4 hours after infusion. Symptoms either self-resolve or respond quickly to symptomatic treatment.

A summary of AEs in >5% of patients by MedDRA system organ class and preferred term is presented in Table 1. There have been no Grade 3-4 drug related AEs observed in over 5% of the patient population (see Table 2).

Table 1 Number (%) of Subjects with Adverse Events >5% Incidence (Safety Population, N=230)

System Organ Class (SOC),Preferred Term, n % [1]	**Grades 1-4 (N=230)**	**Grade 3-4 (N=230)**
Blood And Lymphatic System Disorders		
Anaemia	80 (34.8 %)	35 (15.2 %)
Cardiac Disorders		
Tachycardia	13 (5.7 %)	-
Gastrointestinal Disorders		
Abdominal Pain	34 (14.8 %)	4 (1.7 %)
Constipation	29 (12.6 %)	1 (0.4 %)
Diarrhoea	16 (7.0 %)	3 (1.3 %)
Nausea	64 (27.8 %)	2 (0.9 %)

System Organ Class (SOC),Preferred Term, n % [1]	**Grades 1-4 (N=230)**	**Grade 3-4 (N=230)**
Vomiting	46 (20.0 %)	4 (1.7 %)
General Disorders And Administration Site Conditions		
Chills	89 (38.7 %)	2 (0.9 %)
Disease Progression	-	-
Fatigue	41 (17.8 %)	2 (0.9 %)
Oedema Peripheral	14 (6.1 %)	-
Pain	19 (8.3 %)	3 (1.3 %)
Pyrexia	71 (30.9 %)	3 (1.3 %)
Investigations		
Alanine Aminotransferase Increased	12 (5.2 %)	2 (0.9 %)
Aspartate Aminotransferase Increased	14 (6.1 %)	2 (0.9 %)
Blood Alkaline Phosphatase Increased	15 (6.5 %)	2 (0.9 %)
Blood Creatinine Increased	16 (7.0 %)	6 (2.6 %)
Gamma-Glutamyltransferase Increased	14 (6.1 %)	3 (1.3 %)
Haemoglobin Decreased	12 (5.2 %)	2 (0.9 %)
White Blood Cell Count Decreased	20 (8.7 %)	7 (3.0 %)
Metabolism And Nutrition Disorders		
Decreased Appetite	21 (9.1 %)	-
Hypoalbuminaemia	28 (12.2 %)	9 (3.9 %)
Hypocalcaemia	13 (5.7 %)	2 (0.9 %)
Hypokalaemia	15 (6.5 %)	4 (1.7 %)
Hyponatraemia	19 (8.3 %)	9 (3.9 %)
Musculoskeletal And Connective Tissue Disorders		
Back Pain	17 (7.4 %)	3 (1.3 %)
Nervous System Disorders		
Dizziness	12 (5.2 %)	-
Headache	41 (17.8 %)	-
Respiratory, Thoracic And Mediastinal Disorders		
Dyspnoea	14 (6.1 %)	1 (0.4 %)
Vascular Disorders		
Hypotension	16 (7.0 %)	2 (0.9 %)
Note: [1] Percentage is calculated using column header count as denominator for percentage calculation.		

Table 2 Number (%) of Subjects with Adverse Events >5% with Respect to Relationship (Possibly Related, Probably Related and Related) (Safety Population, N=230)

System Organ Class (SOC),Preferred Term, n % [1]	**Grades 1-4 (N=230)**	**Grade 3-4 (N=230)**
Blood And Lymphatic System Disorders		
Anaemia	18 (7.8 %)	2 (0.9 %)
Gastrointestinal Disorders		
Nausea	47 (20.4 %)	-
Vomiting	31 (13.5 %)	2 (0.9 %)
General Disorders And Administration Site Conditions		
Chills	78 (33.9 %)	2 (0.9 %)
Fatigue	27 (11.7 %)	1 (0.4 %)
Pyrexia	57 (24.8 %)	3 (1.3 %)
Nervous System Disorders		
Headache	36 (15.7 %)	-
Vascular Disorders		
Hypotension	15 (6.5 %)	2 (0.9 %)
Note: [1] Percentage is calculated using column header count as denominator for percentage calculation.		

2.7.1 Delayed/Late Listeria Infection

ADXS11-001 has been attenuated over 4 logs more in comparison to wild-type (wt)-*Lm*. ADXS11-001 is cleared by SCID mice lacking a functioning cellular immune system and by gamma interferon knockout mice lacking adaptive immunity. ADXS11-001 has been shown to be nonpathogenic in mouse models.

In a Phase 1 clinical study, in the absence of antibiotics, *Lm* was rapidly cleared from the blood. No *Lm* was detected in the blood of any subject beyond 48 hours post-dosing and no *Lm* was detected in the urine and feces in any subject at the highest dose of ADXS11-001 tested (1 x 10^{10} CFU).[53]

Wild type *Lm* is known to form and persist within biofilms, especially on medical devices despite antibiotic treatment.[54] Although rare, medical device–related infections such as ventriculo-peritoneal shunt infection, peritoneovenous shunt infection, and prosthetic joint infection have been reported.[55-58] ADXS11-001 is highly sensitive to antibiotics such as ampicillin and sulfamethoxazole/trimethoprim, which can be an effective treatment regimen for listeria infection. Therefore, subjects with implanted medical device(s) that pose a high risk for colonization and/or cannot be easily removed are excluded from this study. In addition, all subjects will receive a course of oral antibiotics beginning on Day 4 (approximately 72 hours) after each dose of ADXS11-001 and for 6 months following the last dose of ADXS11-001 to aid in the eradication of the bacteria.

As of September 2015, approximately 263 subjects have received approximately 675 doses of ADXS11-001. During the course of treatment in this subject population,

there has been one reported case of Grade 3 listeriosis (0.38%). The subject was a 56 year old female who was enrolled in November 2012 in Study GOG-0265. During the course of her participation in the study, she suffered a motor vehicle accident, and as a result, required multiple orthopedic surgeries involving the placement of hardware and a bone graft. After completing her participation in the study, she went on to receive multiple other treatments for her metastatic cervical cancer including an investigational PI3K inhibitor. Two and a half years after completing her last administration of ADXS11-001, she presented to the hospital with mental confusion and a fever. Blood cultures were positive for *Lm*. Subsequent analyses revealed that the isolate was the same as ADXS11-001 but without the plasmid. The subject was admitted to the hospital and treated with IV ampicillin. She became afebrile and was discharged home 3 days after her admission. Prior to her discharge, a lumbar puncture and a CT of the brain were recommended but the patient refused. Two weeks later, the subject presented with acute respiratory distress caused by her metastatic disease and died. The Investigator ruled the cause of death was due to disease progression (metastatic cervical cancer). It is hypothesized that dosing of attenuated *Lm* soon after her bone graft likely resulted in biofilm formation, which protected the organisms from both the immune system and antibiotics. At no time while the subject was on study or during the 2.5 years post-study did she show signs or symptoms of listeriosis. Genomic sequencing confirmed by PCR later revealed that the *Lm* was avirulent, and therefore incapable of spreading cell-to-cell. The *Lm* isolate also remained highly susceptible to multiple antibiotics. Please see Section 6.3- "Listeriosis and Listeria Infection – Identification and Management." **(06/27/2016)**

2.8 Rationale for Survival Endpoint and Confirmation of Progression **(5/23/2011)**

Unlike cytotoxic therapies which directly kill tumor cells and diminish tumor size, immunotherapies work through different pathobiologic mechanisms and often work more slowly. First, they effect changes in the immune system and then those changes exert a therapeutic effect on the disease. This process may take months to fully occur. In patients with rapidly progressive disease such as melanoma, immunotherapies have been observed to result in strong objective responses even in patients whose disease progressed initially after the onset of treatment[59-61]; which would be defined as a therapeutic failure under RECIST criteria and would be a response not observed at all if the evaluation model was based upon progression free survival (PFS), as the patient would not have been evaluated on-study subsequent to initial disease progression. However these patients experienced overall survival matching those who had exhibited traditional PR and CRs. Whereas PFS is an adequate surrogate for overall survival when treating with cytotoxic agents, multiple studies of immunotherapy have demonstrated that PFS does not correlate with overall survival and therefore is an inadequate surrogate for overall survival in immunotherapy. **(5/23/2011)**

The patient population in this current trial has historically been associated with a median life expectancy of approximately 6 months, making the collection of survival data practical. Because tumor-measurement based response and PFS based on RECIST are

inadequate surrogates for clinical benefit and survival in immunotherapy, time to death is the primary efficacy endpoint in this trial. **(5/23/2011)**

Because a positive response to an immunotherapy treatment will always involve the infiltration of tumor-specific white blood cells and local inflammation in the tumor tissue at some point, the total lesion size circumscribed by the "tumor" area will typically have an initial increase in size before it begins to shrink. For this reason, particular care must be applied when using tumor measurement-based criteria like RECIST to make clinical decisions about determining disease progression. **(5/23/2011)**

2.9 Rationale for restricting enrollment to patients who have received only one prior chemotherapy regimen **(12/23/2013) (06/27/2016)**

Immunotherapy of cancer is an indirect form of cancer treatment. In order for patients to derive potential clinical benefit, they need to mount an immunologic response after the treatment is administered in order for their immune system to resist progression, or induce tumor responses against their malignancy. For ADXS11-001, clinical benefit is presumed to be based on the generation of tumor-antigen specific adaptive immunity, infiltration of those cells into the tumor and a reduction in regulatory T-cell (Treg) and myeloid-derived suppressor cell (MDSC) mediated immunologic tolerance within the tumor microenvironment. The best responses in-vitro were seen after three treatments because each subsequent treatment has a "booster effect" resulting in greater numbers of antigen specific cytotoxic T-cells. It takes time for such an immunologic response to develop and ultimately be reflected in the growth characteristics of a patients tumors. For this reason most immunotherapies are not typically assessed until after 12 weeks and apparent minor asymptomatic progressions are re-evaluated after 3-4 additional weeks to confirm progression when there are no alternative treatment options available.

Unfortunately, many late-stage cervical cancer patients that have failed multiple chemotherapy regimens do not live for very long and the multiple prior chemotherapies can impair their hematologic capacity and reduce their relative immunologic function. In the "run-in" phase, several patients expired from disease progression before they were able to receive all three ADXS11-001 treatments and/or be assessed. For these reasons, amending the protocol to enroll patients who have not received more than one prior chemotherapy regimen in the recurrent setting better enables the opportunity for clinical benefit and assessment in this refractory patient population.

2.10 Rationale for Additional Treatment Cycles **(03/09/2015)**

ADXS11-001 treatment essentially employs two critical pathobiologic effects that work together to contribute toward clinical benefit in patients. One can be described as its "vaccine effect" which results in the generation of tumor antigen specific cytotoxic T cells which replicate and distribute throughout the body and have been shown to concentrate in tumors. The second is the ability of Lm-LLO vectors to induce a relative reduction in the number of immunologic inhibitory cells, Tregs and MDSCs in the tumor

microenvironment coupled with a greatly reduced capacity of Tregs and MDSCs to secrete the inhibitory cytokines IL-10 and arginase-1 (respectively).

Each time a patient receives an infusion of ADXS11-001, more T-cells are generated which can migrate to the tumors and mediate CD8+ T cell killing of tumor cells. Repeated dosing every 3-4 weeks x three has been established in animal models to develop a "booster effect" resulting in a greater number of antigen-specific CD8 T cells. Larger numbers of antigen specific T-cells in the periphery as well as infiltrating tumors consistently results in better tumoricidal effects. Therefore more T cells equals better tumor killing. Furthermore, in these models, higher doses (CFUs) consistently resulted in a greater number of antigen specific CD8+ T cells, which engenders better tumorcidal activity, therefore establishing a clear "dose effect". Unlike most vaccine approaches, Advaxis LM-LLO vectors do not generate neutralizing antibodies which enables the potential of giving repeating cycles of treatment to patients who could potentially benefit. Together, since repeating doses of ADXS11-001 generates more tumoricidal CD8+ Tcells and since there is no contraindication to giving repeating cycles of treatment. Patients with bulky and/or resistant tumors may benefit from adding repeated cycles of treatment beyond the initial 3-dose cycle. Each subsequent cycle can generate more cancer fighting cells and could deepen or help maintain clinical benefit achieved from the initial cycle of treatment. This is particularly relevant in settings where additional treatment options are limited.

The ability of Lm-LLO vectors to reduce the number and function of inhibitory Treg and MDSCs within the tumor microenvironment is a relatively recent discovery that is exclusively associated with Advaxis Lm-LLO vectors like ADXS11-001. The precise mechanism is still under investigation, but it clearly involves a relative reduction in the % of T regs and MDSCs coupled with a massive change in the ratio of effector to suppressor cells in the tumor micro-environment (TME). It is also clearly linked to the secretion of the tLLO fusion peptide by the live attenuated vectors. Furthermore, in animal models the suppressor cells remaining in the TME virtually lose their ability to secrete inhibitory cytokines for a generation. The duration of this change in suppressor function in patients remains undetermined thus far. However, clinical evidence would suggest that it is temporary because there is no evidence of autoimmunity and also since, after one 3-dose treatment cycle, partial tumor responses were observed that remained constant for several months and subsequently begin to grow again after 6 or 9 months.

Each administration of the live attenuated vectors results in a new secretion of the tLLO fusion peptide which would thereby re-establish the conditions that inhibit suppressor cell activity within the tumor microenvironment. Therefore repeating doses or cycles of treatment could benefit the patient by helping to overcome tolerance in the tumor microenvironment.

Taking all of these things together, if a patient has resistant or bulky disease, tolerates initial treatment well and still has evidence of residual tumor, they may benefit from receiving repeating cycles of treatment. Each administration generates more tumor-

specific CD8+ T cells which can fight against the tumors as well as re-establish a tumor microenvironment beneficial to effector T cell activity.

In the case of recurrent cervical cancer, there are limited treatment options. ADXS11-001 has been shown to improve survival and generate tumor responses, including complete responses, in some patients after only one 3-dose cycle of treatment. While the median duration of response to one cycle was 9.5 months, it remains to be determined whether additional cycles of treatment might have further prolonged or even furthered these clinical benefits. Since ADXS11-001 is relatively well tolerated and there is no contraindication to repeated dosing, and since each administration can generate more effector cells and re-establish a tumor microenvironment favorable to tumorcidal activity and since additional treatment options are limited; we propose to allow repeated cycles of treatment for patients entered in the second stage of accrual to GOG-0265 who tolerate their initial treatments and still have residual evidence of tumors.

2.11 Inclusion of Women and Minorities **(12/23/2013)**

The Gynecologic Oncology Group and GOG participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire cervical cancer population treated by participating institutions.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

3.1.1 Patients must have persistent or recurrent squamous or non-squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix with documented disease progression (disease not amenable to curative therapy). Histologic confirmation of the original primary tumor is required via the pathology report.

3.1.2 Patient must have measurable disease as defined by RECIST 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be ≥ 10 mm when measured by CT, MRI, or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest x-ray. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI.

3.1.3 Patient must have at least one "target lesion" to be used to assess response on this protocol as defined by RECIST 1.1 (Section 8.1). Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

3.1.4 Patients must not be eligible for a higher priority GOG protocol, if one exists. In general, this would refer to any active GOG Phase III or Rare Tumor protocol for the same patient population.

3.1.5 Patients must have a GOG performance Status of 0 or 1. **(12/23/2013)**

3.1.6 Recovery from effects of recent surgery, radiotherapy, or chemotherapy **(06/27/2016)**

3.1.6.1 Any hormonal therapy directed at the malignant tumor must be discontinued at least one week prior to registration. Continuation of hormone replacement therapy is permitted.

3.1.6.2 Any other prior therapy directed at the malignant tumor, including chemotherapy, biologic/targeted (non-cytotoxic) agents and immunologic agents, must be discontinued at least three weeks prior to registration. **(02/06/2012)**

3.1.6.3 Any prior radiation therapy must be completed at least 4 weeks prior to registration. **(02/06/2012)**

3.1.7 Prior therapy **(12/23/2013)**

3.1.7.1 Patients must have had one prior systemic chemotherapeutic regimen for management of advanced, metastatic, or recurrent carcinoma of the cervix.

Chemotherapy administered concurrent with primary radiation (e.g.; weekly cisplatin) is not counted as a systemic chemotherapy regimen for management of advanced, metastatic, or recurrent disease. Adjuvant chemotherapy given following the completion of radiation therapy (or concurrent chemotherapy and radiation therapy) is not counted as a systemic chemotherapy regimen for management of advanced, metastatic, or recurrent disease (e.g.; paclitaxel and carboplatin for up to 4 cycles). **(02/06/2012)**

3.1.7.2 Patients are allowed to receive, but are not required to receive, biologic/targeted (non-cytotoxic) therapy as part of their primary therapy and/or as part of their therapy for advanced, metastatic, or recurrent disease (e.g., bevacizumab). **(02/06/2012)**

3.1.8 Patients must have adequate: **(06/27/2016)**

3.1.8.1 Bone marrow function: Platelet count greater than or equal to 75,000/mcl and ANC count greater than or equal to 1,000/mcl. Lymphocyte count greater than or equal to 700/mcl. Hemoglobin count greater than or equal to 9 g/dL **or** greater than or equal to 5.6 mmol/L. (Note: ANC, Platelets, Hemoglobin requirement cannot be met by the use of recent transfusions, or growth factor support (G-CSF, erythropoietin, etc.) within 2 weeks prior to treatment initiation.)

3.1.8.2 Renal function: creatinine less than or equal to 1.5 x institutional upper limit normal (ULN) **or** measured or calculated creatinine clearance greater than or equal to 50 mL/min for subject with creatinine levels greater than 1.5 x institutional ULN. (GFR can also be

used in place of creatinine or CrCl) (Creatinine clearance should be calculated per institutional standard.)

3.1.8.3 Hepatic function: Total bilirubin less than or equal to 1.5 x ULN. AST, ALT, less than or equal to 3 x ULN, and alkaline phosphatase less than or equal to 2.5 x ULN. **(02/06/2012)**

3.1.8.4 Coagulation function: INR or PT and aPTT less than or equal to 1.5 x ULN, unless patient is receiving anticoagulant therapy as long as PT or INR is within therapeutic range of intended use of anticoagulants.

3.1.8.5 Neurologic function: Neuropathy (sensory and motor) less than or equal to Grade 1.

3.1.9 Patients must have signed an approved informed consent and authorization permitting release of personal health information.

3.1.10 Patients must meet pre-entry requirements as specified in Section 7.0.

3.1.11 Patients of childbearing potential must have a negative serum pregnancy test prior to the study entry and must agree to ongoing use of 2 methods of study doctor approved birth control or abstain from heterosexual activity for the course of the study from Screening through 120 days after the last dose of study medication. Patients of childbearing potential are those who have not been surgically sterilized or have not been free from menses for >1 year. **(5/23/2011) (06/27/2016)**

3.1.12 Patients cannot be lactating.

3.1.13 Patients must be $\geq$ 18 years old.

3.1.14 Patients must be able to swallow pills.

3.2 Ineligible Patients

3.2.1 Patients who have received prior therapy with ADXS11-001.

3.2.2 Patients who are currently receiving or who have received an investigation therapy within 30 days prior to registration. **(06/27/2016)**

3.2.3 Patients who are currently receiving or who have received any PI3K inhibitor within 30 days prior to registration. **(06/27/2016)**

3.2.4 Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer and other specific malignancies as noted in Sections 3.23 and 3.24, are excluded if there is any evidence of other malignancy being present within the last three years. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.

3.2.5 Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis OTHER THAN for the treatment of cervical cancer within the last three years are excluded. Prior radiation for localized cancer of the breast, head and neck, or skin is permitted, provided that it was completed more than three years prior to registration, and the patient remains free of recurrent or metastatic disease.

3.2.6 Patients who have received prior chemotherapy for any abdominal or pelvic tumor OTHER THAN for the treatment of cervical cancer within the last three years are excluded. Patients may have received prior adjuvant chemotherapy for localized breast cancer, provided that it was completed more than three years prior to registration, and that the patient remains free of recurrent or metastatic disease.

3.2.7 Patients with a contraindication (e.g. sensitivity/allergy) to trimethoprim/sulfamethoxazole or ampicillin. **(5/23/2011) (10/22/2012) (06/27/2016)**

3.2.8 Patients allergic to NSAIDs. **(06/27/2016)**

3.2.9 Patients with active infection requiring systemic therapy or who are dependent on or currently receiving antibiotics that cannot be discontinued before dosing. (Note: Subjects who discontinue an antibiotic prior to dosing must wait at least 5 half-lives after the last dose of antibiotic before receiving any ADXS11-001 infusion). **(06/27/2016)**

3.2.10 Patients with a diagnosis of immunodeficiency, or who are dependent on or have received systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment with the exception of topical corticosteroids and occasional inhaled corticosteroids, as indicated. **(5/23/2011) (10/22/2012) (06/27/2016)**

3.2.11 Patients with uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.12 Patients with liver cirrhosis or any other impaired hepatic function as determined by serum enzymes (see Section 3.183). **(06/27/2016)**

3.2.13 Patients known to be seropositive for HIV and/or active hepatitis, even if liver function studies are in the eligible range.

3.2.14 Patients with a prior history of a splenectomy and/or sickle cell trait/disease.

3.2.15 Patient has implanted medical device(s) that pose a high risk for colonization and/or cannot be easily removed (e.g., prosthetic joints, artificial heart valves, pacemakers, orthopedic screw(s), metal plate(s), bone graft(s), or other exogenous implant(s)). NOTE: More common devices and prosthetics which include arterial and venous stents, dental and breast implants and venous access devices (e.g., Port-a-Cath or Mediport) are permitted. Sponsor must be contacted prior to consenting any subject who has any other device and/or implant. **(06/27/2016)**

3.2.16 Any patient currently requiring or anticipated to require tumor necrosis factor (TNF) blocking agent (e.g., infliximab) therapy for diagnosis of rheumatologic disease or inflammatory bowel disease (e.g., ankylosing spondylitis, Crohn disease, plaque psoriasis, psoriatic arthritis, rheumatoid arthritis or ulcerative colitis). **(06/27/2016)**

3.2.17 Patient has undergone a major surgery, including surgery for a new artificial implant and/or device, within 6 weeks prior to the initiation of ADXS11-001 treatment. NOTE: All toxicities and/or complications must have recovered to baseline or Grade 1 prior to the initiation of ADXS11-001 study therapy. Sponsor must be consulted prior to enrolling patients on the study who recently had a major surgery or have new artificial implant, and/or devices. **(06/27/2016)**

3.2.18 Patient has a known allergy to any component of the study treatment formulations. **(06/27/2016)**

3.2.19 Patient has a history of listeriosis or prior ADXS11-001 therapy. **(06/27/2016)**

4.0 STUDY MODALITIES

4.1 ADXS11-001 (IND #13,712)

4.1.1 IND Sponsor: Advaxis Inc. **(03/09/2015)**
To obtain a copy of the IND effective letter or for questions pertaining to the IND, institutions should contact **(5/23/2011)**:

Robert Ashworth
Advaxis Inc.
Phone: 609-250-7508
e-mail: ashworth@advaxis.com **(06/27/2016)**

4.1.2 Description: **(03/09/2015) (06/27/2016)**

ADXS11-001 is a free flowing isotonic, aqueous, cream colored suspension at a pH of 6.8-7.8 supplied in a DIN 2R glass vial (4mL), stoppered with a grey rubber stopper and sealed with an aluminum seal and a blue flip off cap that must be stored frozen at -80 ± 10°C.

4.1.3 How Supplied, Storage and Stability: **(12/23/2013) (03/09/2015) (06/27/2016)**

ADXS11-001 is provided on dry ice via bonded courier delivery with temperature monitors in 1.2 mL vials of which 1.0 ml is to be used in the preparation of a dose. ADXS11-001 must be received frozen on dry ice and immediately stored at -80 ± 10°C. ADXS11-001 is stable for 6 hours when stored at room temperature (temperatures at or below 25°C [77°F]). This 6 hour time allows for vial thaw, preparation of infusion and

administration. **The 60 minute ADXS11-001 infusion at room temperature must be completed within 6 hours of product vial removal from freezer**.

4.1.4 Storage and Stability: **(12/23/2013) (03/09/2015) (06/27/2016)**

ADXS11-001 must be received frozen on dry ice and immediately stored at -80 ± 10°C. Even though ADXS11-001 is non-pathogenic, all *L. monocytogenes* species are classified as Biosafety Level 2 (BSL-2) according to the Biosafety in Microbiological and Biomedical Laboratories (BMBL) 5th Edition. Universal precautions and institutional guidelines should be used when handling investigational drugs and human specimens.

Aseptic technique must be strictly observed throughout the preparation procedure including the use of a biologic safety cabinet or hood since ADXS11-001 is live, attenuated *L. monocytogenes.*

Prior to preparation, the frozen vial of ADXS11-001 should be thawed at room temperature at or below 25°C (77°F) for approximately 5 to 10 minutes.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the drug product vial if extraneous particulate matter other than slightly turbid white to off white suspension is observed.

Do not use ADXS11-001 if discoloration is observed.

Each dose of ADXS11-001 must be prepared in sterile 0.9% Sodium Chloride Injection, USP (normal saline) and patient must be dosed within 6 hours of drug product removal from the freezer.

ADXS11-001 MUST **NOT** BE MIXED WITH OTHER DILUENTS.

Once the vial is removed from the freezer, the ADXS11-001 product is stable at room temperature (temperatures at or below 25°C [77°F]) for 6 hours. The 6 hours includes the drug product vial thaw, dose preparation, room temperature storage of the prepared dose in the IV bag AND the duration of infusion.

DO NOT ADMINISTER THE PRODUCT AS AN (INTRAVENOUS [IV] PUSH OR BOLUS).

DO NOT COMBINE, DILUTE OR ADMINISTER IT AS AN INFUSION WITH OTHER MEDICINAL PRODUCTS.

ADXS11-001 **and all other IV study medications** must be administered through a temporary IV, which will be removed prior to discharge.
If a patient has an existing portacath or infusion port, it must not be used for any purpose on the day of infusion (Day 1) through approximately 72 hours following the administration of ADXS11-001 and after the initiation of oral antibiotics (Day

4). For example, if a patient had an infusion on a Monday, the portacath or infusion port cannot be used again until Thursday, after the patient has taken the first dose of antibiotics.
In order to prevent accidental use of the portacath or infusion port, additional safety measures must be implemented at the study site. Reminder stickers that state, "DO NOT USE PORTACATH/INFUSION PORT" must be attached to the following items:

- Portacath/infusion port site
- All study medication IV bags
- In front of patients chart (when applicable)

(06/27/2016)

4.1.5 Handling Precautions: **(05/06/2013) (03/09/2015) (06/27/2016)**

ADXS11-001 is classified a BSL-2, minimally pathogenic. Precautions as stated in the BMBL 5th Edition[61] [62] include:

Agent: ADXS11-001, live attenuated genetically engineered live vaccine (5/23/2011) ***ADXS11-001 is a live attenuated strain of Listeria monocytogenes (Lm)*** that has been attenuated such that it is cleared by severe combined immunodeficiency (SCID) mice lacking cellular immunity and gamma interferon knock-out mice lacking adaptive immunity. It has also been altered such that it is impossible for it to recombine with wild-type *Lm*. In the Phase 1 study no bacterial shedding was detected from any subjects treated with ADXS11-001. It is considered as a non-infectious BSL-1 agent for transport by the CDC.

Wild type *Listeria* is Gram-positive, non-spore-forming, facultative bacilli that are hemolytic and catalase-positive. It is a naturally occurring bacterium that is present in the environment and is known to cause illness in some people when they eat foods contaminated with *Lm*. Although healthy adults and children can contract a wild-type *Listeria* infection, they do not usually become seriously ill. People at risk of severe illness from wild-type *Listeria* are pregnant women, newborns, and persons with impaired immune function.

Even though ADXS11-001 is non-pathogenic, all *Lm* species are classified as BSL-2 according to the BMBL 5th Edition. Universal precautions and institutional guidelines should be used when handling investigational drugs and human specimens. Except for the transmission of mother to fetus, human-to-human transmission of *Lm* is not known to occur.[63] Shedding studies completed in Phase 1 demonstrated that, in the absence of antibiotics, ADXS11-001 was rapidly cleared from the blood with no *Lm* detected in the blood of any subject beyond 48 hours post-dosing, and no *Lm* was detected in the urine and feces in any subject at the highest dose of ADXS11-001 tested (1×10^{10} CFU).[64] .

Based on the mechanism of action of ADXS11-001 and the inability of *Lm* to be transferred from human-to-human, there is no need for subjects who receive ADXS11-001 to avoid contact with people who are elderly, pregnant, newborns, or have weakened immune systems.

Precautions as stated in the BMBL 5th Edition include:

Wild-type L. monocytogenes poses a potential hazard to laboratory personnel. The Gram-positive, non-spore-forming, aerobic bacilli are hemolytic and catalase-positive. Bacteria have been isolated from soil, dust, human food, animals, and asymptomatic humans. Most cases of listeriosis have arisen from eating contaminated food products, most notably soft cheeses, raw meat, and unwashed raw vegetables. Although healthy adults and children can contract a Listeria infection, they do not usually become seriously ill. At risk of severe illness are pregnant women, newborns, and persons with impaired immune function.

Laboratory Hazards: Wild-type Listeria monocytogenes are ubiquitous in the environment and may be found in feces, cerebrospinal fluid (CSF), and blood, as well as food and environmental materials. Ingestion is the most common mode of exposure, but wild-type *Listeria* can also cause eye and skin infections following a direct exposure. Wild-type Lm infections in pregnant women occur most often in the third trimester and may precipitate labor. Transplacental transmission of *Lm* poses a grave risk to the fetus and may result in disseminated abscesses contributing to a mortality rate of nearly 100%.

Recommended Precautions: BSL-2 practices, containment equipment, and facilities are recommended for activities with clinical specimens and cultures known or suspected to contain the agent. Gloves and eye protection should be worn while handling the agent. Pregnant women who work with *Lm* in the clinical or research laboratory setting should be fully informed of the potential hazards associated with the organism, including potential risks to the fetus.

Disposing of Contaminated Materials:

Gloves should be used while cleaning spills. Unless ingested orally or parenterally no pathologic hazard exists. Contaminated materials can be disposed of in sealed containers as medical waste (e.g. closed plastic bags). Spills should be washed and cleaned with the application of commercial chlorine bleach (e.g. Clorox). See Section 4.1.12.

4.1.6 Drug preparation and administration: **(03/09/2015) (06/27/2016)**
Only sterile containers will be used in the preparation of these materials. They may be autoclaved glassware, disposable containers, or other sterile materials as provided for within each institution's SOP.

Please note that ADXS11-001, the Investigational Study Drug, is a live, highly attenuated microbe, L monocytogenes, which can multiply, thus increasing the dosage, or die off, thus decreasing the dosage. ADXS11-001 is stable for 6 hours when stored at room temperature (temperatures at or below 25°C [77°F]). This 6 hour time allows for vial thaw, preparation of infusion and administration. **The 60 minute ADXS11-001 infusion at room temperature must be completed within 6 hours from product vial removal from the freezer.**

A dose of study drug is prepared in the following manner:

Remove the appropriate number of vials from -80 ± 10°C and thaw the vials at room temperature for approximately 5 to 10 minutes. Gently agitate mildly by hand to ensure that the study drug is in suspension. Prepare the dose and infusion volume of ADXS11-001 as described below.

To make a dose of 1 x 10^9 cfu: Thaw 1 vial of the ADXS11-001 study drug at room temperature (temperatures at or below 25°C [77°F]). Gently agitate the vial mildly by hand to ensure that the study drug is in suspension. Withdraw 0.53 mL of ADXS11-001 suspension and add it to the infusion bag for a final volume of 250 mL and mix thoroughly.

Each prepared dose of ADXS11-001 must be administered at room temperature (temperatures at or below 25°C [77°F]) within 6 hours from product vial removal from the freezer. This includes vial thaw, room temperature storage of the vial, dose preparation, storage of the infusion suspension in the IV bag and the duration of the infusion. Administer ADXS11-001 at room temperature intravenously over a 60-minute infusion time.

The time the vial is removed from the freezer is to be recorded (T0). **(5/23/2011)**

Doses will be administered to patients who have received the prophylactic medication specified in the protocol as a 60 minute intravenous (IV) infusion. The actual time of administration is to be recorded (T1). The actual time the infusion is completed is to be recorded (T2).
PLEASE SEE Section 4.1.4 for important information regarding the use of a temporary IV line and the placement of reminder stickers.

4.1.7 Adverse Effects: **(03/09/2015) (06/27/2016)**

4.1.7.1 Please refer to Section 2.6 for summary information on the ADXS11-001 AE profile.

4.1.7.2 ADXS11-001 is a live attenuated bioengineered nonpathogenic strain of *Lm*, and one that is known to stimulate a strong innate immune response characterized by high levels of cytokine release from immune cells into the general circulation. This pattern of side effects is consistent with other immunotherapy agents.

4.1.7.3 The most likely AEs associated with ADXS11-001 are comprised primarily of individual flu-like symptoms (e.g., fever, chills, body ache, and fatigue) or cytokine release symptoms (e.g., headache, nausea, vomiting, tachycardia, shortness of breath, hypotension and rash). The symptoms usually present within 2-4 hours after the completion of infusions and are often mild to moderate and transient in nature or respond quickly to symptomatic treatment. In rare instances they may last up to 24 hours. No cumulative toxicity has been observed.

Less likely AE's include increase heart rate, low blood pressure, muscle aches, headaches, allergic reaction, changes in blood chemistry, changes in blood counts, and short term changes in liver function.

Rare but serious AEs include high fever, difficulty breathing and hypotension. **(5/23/2011) (12/23/2013)**

4.1.7.4 Like all *Listeria*, ADXS11-001 has a tropism for the liver. Transient asymptomatic elevations of ALT and alkaline phosphatase were observed after dosing in phase 1 trials without prophylactic medication administration. For that reason, patients with significant liver disease are excluded, and particular attention is to be paid to hepatic abnormalities. **(5/23/2011)**

Please reference the ADXS11-001 Investigator Brochure for complete information regarding adverse effects.

4.1.8 Drug Ordering and Distribution: **(12/23/2013) (03/09/2015) (06/27/2016)**

ADXS11-001 will be supplied by Advaxis and distributed by Almac Clinical Services LLC. No supplies will be shipped to any site until regulatory approval has been obtained. There will **NOT** be an initial drug supply forwarded to all investigational sites upon initial regulatory approval.

The designated person(s) from each participating institution must complete a GOG-0265 "Pharmacy Information Form" and submit to the GOG Administrative Office along with the required regulatory documents (see Section 5.0) and GOG will forward to Advaxis.

4.1.8.1 Initial and Subsequent Drug Requests: **(12/23/2013) (03/09/2015)**
When a patient is registered, the study site is to complete a "Drug Order Request Form" and e-mail the completed form to Almac and Advaxis.

ATTN: palogistics.clinicalservices@almacgroup.com

CC: larry.haines@almacgroup.com
logistics@advaxis.com

Study drug is not patient specific. You may order multiple vials of study drug to accommodate more than one patient depending upon the enrollment expectations at your site and storage capacity at -80 ± 10°C. (4 vials are required per patient to cover the first three months of treatment protocol).

ADXS11-001 will be shipped from Almac Clinical Services directly to the institution. Shipments will be made Monday through Thursday for Tuesday through Friday delivery per the table below. To ensure ample time for delivery, drug requests must be received by Almac before 12:00 pm Eastern Standard Time (EST) Monday through Wednesday.

If the drug request is received prior to 12 noon, that will be considered Day 1. Study drug will be shipped Day 2 to arrive on site Day 3 before 10:30 am local time.

Orders in (by 12 PM EST)	Shipment Out	Expected Delivery
Monday	*Tuesday*	*Wednesday*
Tuesday	*Wednesday*	*Thursday*
Wednesday	*Thursday*	*Friday*
Thursday	*Monday*	*Tuesday*
Friday	*Monday*	*Tuesday*

EST = Eastern Standard Time

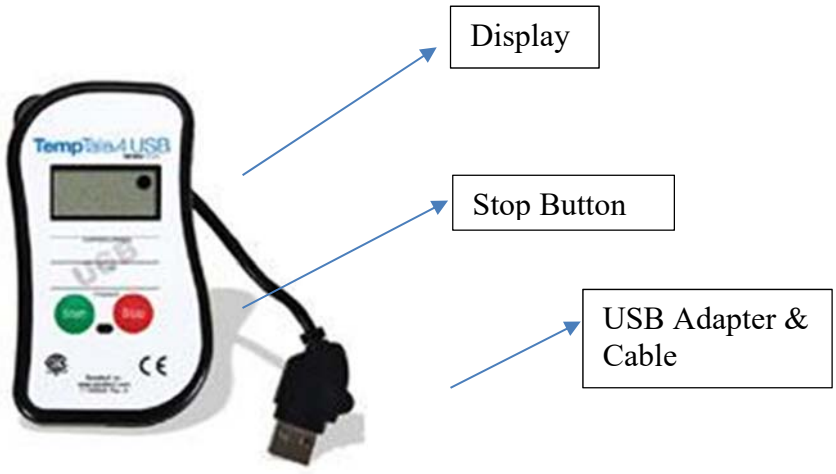
4.1.9 Cold Chain Verification **(12/23/2013) (03/09/2015) (06/27/2016)**
Cold chain verification must be completed immediately before unpacking the shipment, by carefully following the instructions below:

TempTale USB4 Temperature Recorder Review Instructions

Please note that study drug is shipped at -70°C and has a TempTale USB4 (temperature monitor) included in the box. It is imperative that all study drug shipments be stored at -80 ± 10°C immediately after being removed from the shipping container.

Cold Chain Verification must be completed immediately before unpacking the shipper, by carefully following the instructions below:

TempTale USB4 Temperature Recorder



Stopping the Monitor:
On receipt of the shipment, the TempTale USB4 temperature recorder should be stopped. For this the **RED stop button is held down firmly for 3 seconds**. A hexagonal "STOP" icon appears in the upper right hand corner of the display.

Alarm:

A small blinking "BELL" icon  is on the display after the device has been stopped. This means that during the transport a significant temperature excursion occurred. Please follow steps 1-6.

Plug the USB cable into your computer.
Copy both files from the USB device into an e-mail.
Specify the subject header with **Protocol Name, Site Name/No. and Shipment No**.
Please send an e-mail with both attachments to Almac and Advaxis via the following e-mail addresses:
coldchainteampa@almacgroup.com
logistics@advaxis.com
The medication contained in this shipment **must not be dispensed to patients** until a positive written feedback from Advaxis is available.

Please store the affected medication separately and wait until confirmation of supply usability is received.

No Alarm:
If the device has been stopped and no blinking "BELL" icon is visible, verification that the medication was shipped under good conditions is complete. No further actions from your side are necessary. Please discard the temperature logger. You can use the medication immediately.

No study drug should be administered to any patients unless the TempTale has been reviewed and the shipment has been verified or authorized for clinical use.

For questions about TempTale and drug shipment, please email the following:

Almac: palogistics.clinicalservices@almacgroup.com
CC: larry.haines@almacgroup.com
logistics@advaxis.com

4.1.10 Drug Accountability: All study drug must be accounted for by using the NCI Drug Accountability Form during the course of this study. The pharmacist or qualified research staff member will maintain inventory records. The records will include details of materials received, the date dispensed, the patient identification number, initials of patient receiving the dose, and documentation of drug destruction following notification from the Sponsor or completion/termination of the study. 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. **(06/27/2016)**

4.1.11 Drug Destruction: All investigational product can be discarded in accordance with the Institution's policies for Biohazard Waste Disposal or by using the steps shown below for ADXS11-001 destruction. **(06/27/2016)**

The used or unused vials of ADXS11-001 can be treated with a 10% bleach solution for disinfection. Use a 10% solution of Clorox® (or any similar commercial chlorine bleach solution containing 5.25% sodium hypochlorite (NaClO) for disinfection. **(03/09/2015)**

1. Treat unopened or opened vials(s) with a minimum volume of 0.25 mL of bleach solution to sterilize its contents.
2. Empty the disinfected chemical solution in drain, run water to remove residual materials from drain and discard empty vials into designated biohazardous waste container, as applicable.
3. The residual IV bags or other components used for preparing the drug product should also be inactivated with bleach and discarded in similar manner as explained in steps 1 and 2.

4.1.12 Accidental Spills: All accidental spills shall be handled in compliance with applicable site safety procedures or following the guidance below:

- In the event there is an accidental spill of ADXS11-001, isolate the area and notify others in the vicinity.
- Put on appropriate personal protective equipment (PPE) if not already worn (e.g. gown or lab coat, gloves and loose fitting mask with eye shield or goggles).
- Remove any broken glass or sharps and place them into sharps container.
- Place paper tower over the spill
- Saturate the paper-towel(s) with bleach starting at the outside of the spill and working towards the center. Allow the 10% bleach solution to remain on area for approximately 10 min.
- Dispose the paper towel(s) in a biohazardous waste container.
- Clean the remaining disinfectant with additional paper towels, as needed.
- Discard all materials including PPEs, in the designated biohazardous waste container(s).
- Inform the Principal Investigator (PI) and other appropriate personnel, e.g. Research Manager, Pharmacy Manager.

4.1.13 Exposure to ADXS11-001: All exposure incidences shall be handled in compliance with applicable site safety procedures or following the guidance below:

In the event of an accidental exposure, remove and dispose of contaminated PPEs or clothing into the designated biohazardous waste containers.

For skin contamination: thoroughly wash the affected area immediately with soap and water.
For needle stick injury: wash the affected area thoroughly with soap and water and cover the area with a sterile gauze dressing. Notify the PI who will determine appropriate medical actions to be taken.

For eye contamination: immediately and thoroughly rinse the affected area for up to 15 minutes using an eyewash; making the water flow across the affected eye from the nose

to the outer corner of the eye. If only one eye is contaminated, avoid contaminating the other eye (position your head so the affected eye must be below the other eye). Notify PI who will determine appropriate medical actions to be taken.

It will be the investigator's responsibility to ensure that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures and that:
the coordinating institution has been alerted to drug destruction and has been sent hospital destruction policy, if applicable
arrangements have been made for the disposal
appropriate records of the disposal have been documented.

A separate (NCI) Drug Accountability Form must be completed for Drug Destruction. (12/23/2013)

4.1.14 Investigator Brochure: the most current version of the ADXS11-001 investigator brochure can be downloaded on the GOG-0265 Web page. If there are any questions pertaining to the IB, please contact:

Robert Ashworth
Advaxis Inc.
Phone: 609-250-7508
email: ashworth@advaxis.com **(5/23/2011) (12/23/2013) (06/27/2016)**

4.2 Pathology Requirements

See Section 3.1 for eligibility. No Slides Required.

5.0 TREATMENT PLAN AND ENTRY/REGISTRATION PROCEDURE

Before patient entries will be accepted, submit the following documents to the GOG Administrative Office via mail **(Attn: Regulatory Department, Protocol GOG-0265):**

- IRB approval*
- IRB-approved informed consent
- IRB Membership list or FWA assurance letter
- Institutional Biosafety Committee (IBC) approval
- Waiver from the BSL-2 categorization of the wild type *Listeria monocytogenes* OPTIONAL. May be submitted by sites which restrict work with BSL-2 agents **(10/17/2011 (05/06/2013)**
- Study-specific signed original FDA Form 1572 for institution PI**
- Current Biographical Sketch (no more than two pages) for institution PI**
- Current CV (signed and dated within one year) for sub-investigators listed on FDA Form 1572
- Medical license for institution PI and sub-investigators listed on the FDA Form 1572
- Lab license, certificates, and required Normal Lab Values (NLV) for labs listed on FDA Form 1572
- Signed GOG Investigator Signature Page for PI****(12/23/2013)**
- Signed GOG Financial Disclosure Form for all investigators listed on FDA Form 1572****(12/23/2013)**
- Pharmacy Information Form**

The GOG Administrative Office will receive the regulatory documents and submit them to Advaxis for review and approval. Upon Advaxis approval, Advaxis will submit the PI Biographical Sketch, IRB approval, IRB approved informed consent and Institutional Biosafety Committee Approval to the NIH Office of Biotechnology Activities (OBA). **No patient can be enrolled until the NIH OBA has received these documents.** Upon receipt at the NIH OBA, Advaxis will notify GOG of institution approval and GOG will then notify the institution that they have been regulatory approved.

Please allow 7-10 days for processing of regulatory documents before screening the first patient. All copies of the above should be filed into a study-specific regulatory binder at your institution.

* When submitting the IRB approval to the GOG, the CTSU IRB Certification Form must be used (form can be downloaded at www.ctsu.org). All initial, continuing and amendment reviews must be sent to the GOG Administrative Office.

** Please see GOG-0265 protocol documentation page to download forms by clicking on the "Regulatory Forms" link.

5.1 Patient Entry and Registration

For patients in the safety lead-in, the GOG Statistical and Data Center's web-based patient reservation system (available at the GOG web menu page) will be used, in which slots for particular patients are reserved. Reservations are not transferrable to other patients, and if the patient is not enrolled within the required timeframe, the reservation is then cancelled and the slot is then made available to other patients and sites. If all slots are reserved, patients can be added to a waiting list for that dose level. NOTE: The safety lead-in has been completed. **(03/09/2015)**

All site staff will use OPEN to enroll patients to this study. OPEN can be accessed at on the GOG web menu page and clicking on the OPEN link.

Prior to accessing OPEN site staff should verify the following:

All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group web site as a tool to verify eligibility.
All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
To perform registrations, the site user must have been assigned the 'Registrar' role on the GOG or CTSU roster.
To perform registrations you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

5.2 Treatment Plan **(06/27/2016)**

ADXS11-001 will be given at a dose of 1 x 10^9 cfu intravenously once every 28 days until clinical progression has been determined, confirmed radiologic disease progression, intolerable toxicity or the patient refuses further treatment. The drug will be given as a 250 mL infusion over 60 minutes and will be given on Day 1 of each cycle. All subjects will receive a 7 day course of oral antibiotic therapy starting approximately 72 hours (Day 4) after each ADXS11-001 infusion.

During Study Treatment Phase - All subjects will receive a 7-day course of oral antibiotic therapy starting approximately 72 hours (Day 4) after administration of ADXS11-001. Antibiotic therapy should consist of either 160 mg trimethoprim/800 mg sulfamethoxazole (DS) tablet administered 3 times during the 7 consecutive days or 80 mg trimethoprim/400 mg sulfamethoxazole administered daily for 7 consecutive days. For subjects who develop a sulfa allergy, that precludes completion of this required antibiotic course, treatment with ampicillin 500 mg 4 times daily for 7 consecutive days should be administered.

Post Study Treatment - All subjects will receive a 6-month course of oral trimethoprim/sulfamethoxazole (or ampicillin for subjects who develop a sulfa allergy that precludes completion of the full oral trimethoprim/sulfamethoxazole course) to be initiated approximately 72 hours following the last dose of study treatment or at the time of study discontinuation. The dose of trimethoprim/sulfamethoxazole consists of either 160 mg trimethoprim/800 mg sulfamethoxazole (DS) tablet administered 3 times a week or 80 mg trimethoprim/400 mg sulfamethoxazole administered daily. The dose of ampicillin consists of 500 mg 4 times daily. Review the approved product labeling for trimethoprim/sulfamethoxazole and ampicillin, and monitor antibiotic tolerance as dosing adjustments may be necessary.

The study includes a safety lead-in, in which the dose limiting toxicities of the study agent will be assessed in the first 6 patients enrolled. Further accrual will be held until all 6 patients have completed 28 day observation after cycle 1 treatment (See Section 5.3).

During the safety lead in, all enrolling sites will be required to participate in a regularly scheduled teleconference with the Study Chair, Phase I Safety Lead-in Chair and Phase I Committee Chair, and their assigned delegates. Conference calls during phase II will be at the discretion of the Study Chair and the Chair of the Developmental Therapeutics Committee of the GOG. **(5/23/2011)**
NOTE: The safety lead-in has been completed (03/09/2015)

Chemotherapy Guidelines: See the GOG General Chemotherapy Guidelines (Appendix IV). **(02/06/2012)**

5.2.1 Pretreatment Prophylaxis **(06/27/2016)**

Mild to moderate flu-like symptoms and cytokine release symptoms (e.g., constitutional symptoms such as fever, chills, rigors, fatigue, headache, nausea, vomiting, tachycardia, shortness of breath, hypotension and rash) are commonly seen and typically occur 2-4 hours after ADXS11-001 infusion and often resolve within 12-24 hours. Prophylactic medications are intended to reduce the inflammatory response. Subjects should receive the following pretreatment prophylaxis regimen.

IV Fluid Hydration:
Normal saline (e.g., 500 mL over 30 minutes)

Premedication Regimen:
Antihistamine – PO or IV (e.g. diphenhydramine 25 mg or equivalent), once
NSAIDs - PO (e.g., naproxen 220 mg or ibuprofen, 400 mg), once
Antiemetic - PO or IV (e.g., promethazine or ondansetron), once
Histamine H2-receptor antagonist – PO or IV (e.g., famotidine 20 mg or equivalent), once

Pretreatment medication should be given on the day of dosing and completed at least 30 minutes prior to the start of the study treatment. Additional NSAID doses and antiemetic administration should be given per label or package insert post initial administration on Day 1 and Day 2, as needed. The prescribed dosage of the selected NSAID and antiemetic will be at the discretion of the Investigator.

Do not substitute acetaminophen for the selected NSAID for prophylactic treatment since acetaminophen does not have similar anti-inflammatory properties that could ameliorate cytokine release symptoms.

Antiemetics such as promethazine or ondansetron will continue to be given as described above. Thus, subjects will leave the study site with doses of the NSAID and antiemetic to take later in the day, as appropriate.

PLEASE SEE Section 4.1.4 for important information regarding the use of a temporary IV line and the placement of reminder stickers.

5.2.2 ADXS11-001 Regimen **(06/27/2016)**

5.2.2.1 Within 4 days of Day 1 of each cycle (prior to dosing with ADXS11-001) patients must have blood work obtained to include creatinine (See Section 7.1 for mandatory labs). NOTE: If creatinine > 1.5 x ULN (CTCAE v4.0 Grade 2 or higher) then dose will be held until recovery to Grade 1 or less. The maximum dose delay to allow for recovery is 3 weeks. In the safety lead-in, patients whose serum creatinine is >1.5 x ULN and who do not recover to ≤1.5xULN and who do not complete at least 2 of the 3 planned courses will be replaced (up to a maximum of three replacements), unless their serum creatinine is >3.0 x ULN (these patients will be considered DLTs and will not be replaced). All treated patients in the lead-in will be counted in the phase II efficacy evaluation. **(5/23/2011)**

On Day 1, ADXS11-001 will be administered as a 60 minute intravenous infusion of 1 x 10^9 cfu in 250 mL of normal saline. Treatment is to be done on an outpatient basis. Patients will be observed in the outpatient area for 8 hours following the ADXS11-001 infusion. Vital signs will be taken pre-dose, every 30 minutes (+/- 5 minutes) for the next 4 hours and at approximately 8 hours after the infusion, as a safety measure. Patients will return on Day 2 for toxicity assessment and vital signs 24 hours (+/- 2 hours) after dose. Patients will return Day 4 (approximately 72 hours after dosing) for toxicity assessment and vital signs. **(10/22/2012) (12/23/2013) (03/09/2015)**

PLEASE SEE Section 4.1.4 for important information regarding the use of a temporary IV line and the placement of reminder stickers.

Day 1 of each treatment: At 8 hours after the dose, the patient must have a temperature less than 38.5 degrees C and other vital signs (heart rate, blood pressure, and respiration) must be within normal limits. The patient must not show signs or symptoms of moderate-severe nausea, vomiting, or headache. If the patient does not meet these discharge criteria, the patient should be admitted to the hospital for observation and treatment of side effects.

A subject who experiences a fever (CTCAE Grade 1 or greater) 24 hours following the completion of ADXS11-001 infusion should be started on NSAIDS, hydration and other appropriate measures to treat the fever. In the event that the fever persists or worsens 48 hours following the completion of ADXS11-001 infusion then oral or broad spectrum IV antibiotics should be considered based on the subject's medical condition. If the fever remains unresponsive to oral/IV antibiotics 72 hours following the completion of the infusion then a blood culture should be obtained to evaluate for listeremia and determine the appropriate treatment course for the subject.

Should a diagnosis of listeriosis be made at any point after treatment with ADXS11-001 and the 6-month course of oral antibiotics are completed, immediate and intensive IV antibiotic treatment (ampicillin +/- gentamycin or other IV antibiotic regimen as indicated) is required An infectious disease consult should be obtained. Based on each individual subject's case and at the discretion of the treating physician, the removal of any foreign medical object that has been present since treatment with ADXS11-001 was initiated may be warranted. It is extremely important that the Investigator, his/her research staff, other healthcare providers involved in the care of the subject as well as each subject participating in this study are educated and made aware of the signs and symptoms of listeriosis and the potential for delayed listeremia/listeriosis. Educational materials for the Investigator, research staff, health care providers and subjects will be prepared and educational training performed. **(06/27/2016)**

5.2.3 Safety Follow-up/Post-Treatment Visits **(06/27/2016)**

Safety follow-up will be conducted via an office visit or telephone call at 30 days (± 5 days) after the last ADXS11-001 infusion to confirm the resolution of any ongoing AEs and SAEs. Additional unscheduled visits may be considered as needed and at the discretion of the Investigator.

Surveillance monitoring for the detection of *Lm* will be initiated at the completion of study treatment according to the protocol or at the time of study discontinuation if earlier. This surveillance monitoring period will consist of a 6-month course of oral antibiotics and obtaining blood cultures at regular intervals. The blood cultures will be performed on all subjects who have received at least 1 dose of ADXS11-001. Blood cultures will occur every 3 months (±1 month) for 3 years beginning 3 months after the last dose of

study treatment. Patient who enter supportive care phase of illness and are no longer having regular blood work (e.g., hospice care) will no longer be required to have blood cultures performed.This testing may be performed at the investigational site or at another acceptable location following consultation with the Sponsor.

5.3 Dose Limiting Toxicities FOR PHASE I SAFETY LEAD_IN PORTION ONLY **(06/27/2016)**

The 6 patients enrolled in the safety lead-in and the patients in the first stage of the study will be evaluated for Dose Limiting Toxicities (DLT) during the 28 days following the completion of all treatment (Day 84). DLTs are defined as either hematologic or non-hematologic toxicities (assessed in accordance with the CTEP CTCAE Version 4), which cause any of the following:

5.3.1 Hematologic Toxicity:

5.3.1.1 Dose delay of greater than 3 weeks due to failure to recover counts.

5.3.1.2 Study treatment-related febrile neutropenia.

5.3.1.3 Grade 4 neutropenia lasting > 7 days.

5.3.1.4 Study treatment-related Grade 4 thrombocytopenia or bleeding associated with Grade 3 thrombocytopenia.

5.3.2 Non-Hematologic Toxicity:

5.3.2.1 Study treatment-related Grade 3 or Grade 4 non-hematological toxicity excluding alopecia and fatigue.

5.3.2.2 Documented bacterial meningitis

5.3.2.2 Clinical sepsis requiring ICU admission and/or pressors

5.3.2.3 Documented persistent listeremic event (defined by a positive blood culture for Listeria at greater than or equal to 72 hours after dosing). **(5/23/2011)**

5.3.2.4 Grade 3 or 4 hypotension sufficient to warrant therapeutic intervention

5.3.2.5 Grade 3 or 4 nausea, vomiting, constipation, or diarrhea is not a DLT unless there is no resolution to Grade 1 or less despite adequate medical intervention.

5.3.2.6 Grade 3 or 4 transaminitis is not a DLT unless there is no resolution to Grade 1 or less in less than or equal to 7 days

5.3.3 Treatment delay of greater than 14 days.

5.3.4 Any drug-related death

5.4 Concurrent Therapies and Procedures **(06/27/2016)**

All prescription and nonprescription medication (excluding vitamins, nutritional supplements and hormone replacement therapy) taken by the subject from screening and up to and including completion of the 30 day post treatment safety follow-up will be recorded in the medical record and on the CRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Generic names should be used to eliminate confusion that may result from trade names. Protocol-mandated prophylactic medications, antibiotics and procedures administered/performed following the completion of study treatment, including during the 30 day post treatment safety follow-up period, should also be captured on the CRF. The 6 month antibiotic accountability details during the Lm Surveillance period should be captured on the CRF.

Study subjects should be reminded that acetaminophen should not be used for pretreatment prophylaxis associated with the foreseeable AEs related to the study treatment since this medication can interfere with treatment.

Medications 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 specifically prohibited during the trial, discontinuation from trial therapy may be required. The Investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy rests with the Investigator and/or the subject's primary physician. However, the decision to continue the subject's on-trial therapy requires the mutual agreement of the Investigator, the Sponsor, and the subject.

Subjects are prohibited from receiving the following therapies during the screening and treatment phases of this trial:

- Anti-cancer systemic chemotherapy, targeted therapy or biological therapy
- Surgical anti-cancer treatment. The sponsor should be notified of any emergency surgeries that occur and prior to planned elective surgeries.
- PI3K inhibitors and TNFα blocking agents
- Immunotherapy not specified in this protocol
- Investigational agents other than ADXS11-001
- Radiation therapy (except palliative radiation therapy for disease-related pain with a consult with the sponsor's medical monitor)
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed.
- Acetaminophen is not to be used for premedication but may be used for supportive care measures. NSAIDs, such as naproxen and ibuprofen have been evaluated and are confirmed not to interfere with efficacy.

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.

6.0 TREATMENT MODIFICATIONS AND SUPPORTIVE CARE **(5/23/2011) (06/27/2016)**

The dose of ADXS11-001 will not be modified (e.g., reduced or increased). However, treatment may be delayed or discontinued for toxicities, as shown in the table below.

NOTE: Any patients with a treatment delay of > 3 weeks will not receive any further ADXS11-001 treatment.

Please note all CTCAE grading below refers to version 4.0. **(02/062012)**

Treatment Delay/Discontinuation Guidelines for Drug Related Adverse Events				
Toxicity	**Grade**	**Hold treatment**	**Timing for restarting treatment**	**Discontinue Treatment**
Hematologic	1,2,3	No	N/A	N/A
	4	Yes	Toxicity resolves to ≤Grade 1 or baseline	Toxicity does not resolve to ≤Grade 1 or baseline within 3 weeks
Non-hematologic, excluding cytokine release symptoms and DLTs	1	No	N/A	N/A
	2-3	Yes	Toxicity resolves to ≤Grade 1	Toxicity not resolved to ≤Grade 1 within 3 weeks of last infusion[a]
	4	N/A	Permanent treatment discontinuation	Permanent Discontinuation from Treatment

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

6.1 Additional Guidelines for the Management of Hematologic Toxicity (**06/27/2016**)

6.1.1 Initial treatment modifications will consist of cycle delay as indicated in the above table. The use of hematopoietic cytokines and protective reagents are restricted as noted: **(02/06/2012)**

6.1.1.1 Patients will NOT receive prophylactic G-CSF.

6.1.1.2 Patients will NOT receive prophylactic thrombopoietic agents.

6.1.1.3 Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia. Treating physicians should be aware of the recent changes in prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) which note that there is a potential risk of

shortening the time to tumor progression or disease-free survival, and that these agents are administered only to avoid red blood cell transfusions. They do not alleviate fatigue or increase energy. They should not be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted. http://www.fda.gov/Medwatch/safety/2007/safety07.htm

6.2 Supportive Care Guidelines **(06/27/2016)**

The major safety findings with ADXS11-001 occurring in >5% of subjects, as of February 2015 (n=230) and being possibly, probably or definitely related include anaemia (7.8%), chills (33.9%), fatigue (11.7%), fever (24.8%), nausea (20.4%), vomiting (13.5%), headaches (15.7%), and hypotension (6.5%). Most are Grade 1-2 in severity. Subjects should receive appropriate supportive care measures as deemed necessary by the treating Investigator including but not limited to the items outlined below.

6.2.1 Cytokine Release Symptoms are a constellation of inflammatory symptoms resulting from cytokine elevations associated with T cell engagement and proliferation. Symptoms related to cytokine release may include constitutional symptoms such as fever, chills, rigors, fatigue, headache, nausea, vomiting, rash, tachycardia, hypotension and shortness of breath which usually presents several hours after the infusion and lasts for up to 24 hours. These symptoms are caused by an increase in cytokines such as TNFα, IFNγ and IL-6, all of which have been shown to occur after ADXS11-001 administration, resulting from the body's immune response to the therapy. Although, symptoms are often Grade 1-2 and transient, resolving with symptomatic management within 30 minutes to 1 hour, in rare instances (~1%) Grade 3-4 hypotension has been seen. Therefore, close monitoring of blood pressure is strongly recommended at baseline, and during the post-infusion period. Increased levels of IL-6 have been strongly associated with capillary leak which manifests as hypotension due to the cytokines involved. We have observed elevated IL-6 levels after infusion of ADXS11-001, with peak levels occurring 2-4 hours after infusion. Emerging evidence indicates that IL-6 antagonists, such as tocilizumab, have demonstrated good results in treating cytokine-induced hypotension[65-68] and are therefore recommended for cases of severe hypotension refractory to supportive care (e.g., fluids and/or pressors).

The management of cytokine release symptoms and guidelines for subsequent treatment modifications for subjects who have experienced these AEs are shown in the table below.

Recommended Management Guidelines for Adverse Events Associated with Cytokine Release

Toxicity	NCI CTCAE Grade or Severity	Treatment	Modification for Subsequent infusions
Hypotension	1 Mild	Supportive care	Increase pretreatment IV fluids (e.g., 500 ml -1L normal saline)
All other cytokine release symptoms (e.g. chills, rigors, fever, nausea, vomiting)	1	Supportive care	No modification
Hypotension	2 Moderate	Fluids and 1 dose of pressor (e.g. 0.3 mg epinephrine IM) Increase monitoring of vital signs If hypotension persist for more than one hour consider low dose corticosteroids (e.g. hydrocortisone 100 mg IV)	Extend infusion time to 2 hours. Increase pretreatment IV fluids (e.g. 500 ml -1L normal saline) Incorporate Glucocorticoid- Hydrocortisone or equivalent- 50 mg, IV, as premedication
All other cytokine release symptoms (e.g. chills, rigors, fever, nausea, vomiting)	2	Appropriate supportive care measure	Extend infusion time to 2 hours. Consider increasing doses of prophylactic medications
Hypotension	3 Severe	Fluids, high dose pressors (e.g. Dopamine 10 µg/kg/min) +1 dose tocilizumab*(4mg/kg over 1 hour) If hypotension worsens or is unresponsive to above measures, administer corticosteroids If the subject's condition does not improve or stabilize within 24 hours of the tocilizumab dose, administration of a second dose of tocilizumab +/- corticosteroids should be considered.	Discuss with Sponsor
All other cytokine release symptoms (e.g. chills, rigors, fever, nausea, vomiting)	3	Appropriate supportive care measures	Extend infusion time to 2 hours. Consider increasing doses of prophylactic dose of NSAID, or antiemetic as appropriate
Hypotension/	4	Vigilant supportive care	Permanently discontinue

Recommended Management Guidelines for Adverse Events Associated with Cytokine Release

Toxicity	NCI CTCAE Grade or Severity	Treatment	Modification for Subsequent infusions
Organ toxicity, mechanical ventilation	Life threatening	Fluids High dose pressors, Tocilizumab (4mg/kg over 1 hour) +/- corticosteroids (hydrocortisone 100 mg IV infused over 30 seconds administered every 2 hours until symptoms resolve to <Grade 1)	

***** Tocilizumab is a humanized, immunoglobulin G1k (IgG1k) anti-human IL-6R mAb approved for treatment of adult subjects with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to Disease-Modifying Anti-Rheumatic Drugs (DMARDs), for the treatment of active polyarticular juvenile idiopathic arthritis (PJIA), and active systemic juvenile idiopathic arthritis (SJIA) in subjects 2 years of age and older. Tocilizumab works by preventing IL-6 binding to both cell-associated and soluble IL-6Rs. Although, it is not indicated for the treatment of cytokine release symptoms emerging clinical experience at several institutions has concluded that tocilizumab is an effective treatment for severe or life-threatening cytokine release symptoms.[65-68]

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

6.2.3 Hypersensitivity/Anaphylaxis/Infusion Site Extravasation:
While there is some overlap between infusion reactions symptoms and cytokine release symptoms, infusion reactions symptoms typically occur during the infusion, while cytokine release symptoms typically occur after the infusion and are mediated by a different mechanism of action. Signs/symptoms of infusion reactions 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; pruritic/itching; rash/ desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); and vomiting.

The table below shows the management guidelines for subjects who experience an infusion reaction associated with administration of ADXS11-001.

Recommended Management Guidelines for Infusion Reactions

NCI CTCAE Grade	Management
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.	Stop Infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics 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. 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	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. Subjects who experience a Grade 4 reaction should be permanently discontinued from study. Subjects who experience a grade 3 reaction may be discontinued. Discussion with the Sponsor is recommended

6.3 Listeriosis and Listeria Infection – Identification and Management **(06/27/2016)**

A person with (wt) listeriosis usually presents with fever and muscle aches, sometimes preceded by diarrhea or other gastrointestinal symptoms. Almost everyone who is diagnosed with listeriosis has an "invasive" infection, in which the bacteria spread beyond the gastrointestinal tract. The symptoms vary with the infected person. Pregnant

women typically experience fever and other non-specific symptoms, such as fatigue and aches. However, infections during pregnancy can lead to miscarriage, stillbirth, premature delivery, or life-threatening infection of the newborn. In people other than pregnant women, symptoms can include headache, stiff neck, confusion, loss of balance, and convulsions in addition to fever and muscle aches. Listeriosis can present in different ways. In older adults and people with immunocompromising conditions, septicemia and meningitis are the most common clinical presentations.[69] Subjects may need immediate evaluation with a brain CT scan or MRI and a lumbar puncture with the analysis of spinal fluid to rule out meningitis.

For symptomatic subjects, diagnosis is confirmed only after isolation of Lm from a normally sterile site, such as blood or spinal fluid (in the setting of nervous system involvement), or amniotic fluid/placenta (in the setting of pregnancy). Stool samples are of limited use and are not recommended. Lm can be isolated readily on routine media, but care must be taken to distinguish this organism from other Gram-positive rods, particularly diphtheroids. Selective enrichment media improve rates of isolation from contaminated specimens. You can expect that the cultures will take approximately 1-2 days for growth. Importantly, a negative culture does not rule out infection in the presence of strong clinical suspicion. Serological tests are unreliable, and not recommended at the present time.[69]

Listeriosis is treated with a wide range of antibiotics. In preclinical studies, wt-Lm and ADXS11-001 are susceptible to the lowest tested concentration of the following antimicrobial agents: ampicillin, amoxicillin/K clavulanate, ciprofloxacin, erythromycin, gentamicin, penicillin, tetracycline, trimethoprim/sulfamethoxazole and vancomycin (IV). ADXS11-001 is resistant to both s*treptomycin* and chloramphenicol.

6.3.1 Management and Surveillance of Listeria during Study Participation

In the event a subject experiences a persistent fever lasting 72 hours after receiving study treatment then the oral antibiotic regimen will be replaced by broad spectrum IV antibiotic treatment. If symptoms consistent with sepsis occur close to ADXS11-001 administration or at any time after ADXS11-001 administration, immediate medical attention must be sought. A microbial culture will be taken to identify the agent of sepsis and antibiotic sensitivity testing should be performed to confirm susceptibility. An infectious disease consult should be obtained for further management of these subjects.

All subjects will receive a 6-month course of an oral antibiotic regimen as a prophylactic measure following the completion of the last dose of ADXS11-001 treatment or at the time of study discontinuation. This additional safety measure is intended to eradicate *Lm* from the body.

Lm surveillance monitoring will also be initiated following the completion of the last dose of ADXS11-001 treatment or at the time of study discontinuation. This monitoring will blood cultures for the detection of *Listeria*. Testing will be performed on all subjects

who have received at least 1 dose of ADXS11-001 and occur every 3 months (±1 month) for 3 years beginning 3 months after the last dose of study treatment.
Should a diagnosis of listeriosis be made at any point after treatment with ADXS11-001 and the 6-month course of oral antibiotics are completed, immediate and intensive IV antibiotic treatment (ampicillin +/- gentamycin or other IV antibiotic regimen as indicated) is required An infectious disease consult should be obtained. Based on each individual subject's case and at the discretion of the treating physician, the removal of any foreign medical object that has been present since treatment with ADXS11-001 was initiated may be warranted. It is extremely important that the Investigator, his/her research staff, other healthcare providers involved in the care of the subject as well as each subject participating in this study are educated and made aware of the signs and symptoms of listeriosis and the potential for delayed listeremia/listeriosis. Educational materials for the Investigator, research staff, health care providers and subjects will be prepared and educational training performed.

6.4 Major and Minor Surgeries and ADXS11-001 Treatment (**06/27/2016**)

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

7.0 STUDY PARAMETERS

7.1 Observations and Tests

The following observations and tests are to be performed and recorded on the appropriate form(s): **(5/23/2011) (02/06/2012) (06/27/2016)**

Parameter	Pre-Therapy	Day 1 of each cycle	Day 2 of each cycle (24 hours post dosing)	Days 3&4 of each cycle for first 6 patients and Day 4 for all other patients (72 hours post dosing)	Off of all study therapy[11]
History & Physical	1, 2	X#	X#	X#	
Performance Status	1	X#	X#	X#	
Toxicity Assessment	3	X#	X#	X#	X
Prior/Concomitant Medications	3	X			
Non Drug Treatment/Procedures	2, 3	X	X	X	X
Vital signs (Blood pressure, temperature, pulse, respiratory rate).	1	10	10	10	
CBC/Differential/ Platelets	3	4, 5			
Electrolytes, BUN, creatinine, Ca, Mg, PO_4	3	4, 5			
Bilirubin, AST, ALT, Alkaline Phosphatase	3	4, 5			
Lm Surveillance Monitoring					6
Urinalysis	3	4 **(05/06/2013)**			
Serum pregnancy test (for patients capable of childbearing)	9				
Chest imaging (X-ray or CT of the chest)	1				7

Radiographic tumor measurement (of the abdomen and pelvis)	1				8

The first 6 patients will have a daily History and Physical, Performance Status, Toxicity Assessment, and Vital Signs for four days of each cycle. All other patients will have a History and Physical, Performance Status on Day 1 only and Toxicity Assessment and Vital Signs on Days 1, 2, and 4 of each cycle. NOTE: The safety lead-in has been completed. **(03/09/2015)**

Notes:
1. Must be obtained within 28 days prior to initiating protocol therapy.
2. History includes medical, prior cancer and surgical histories. Surgical history includes documentation of non-cancer surgeries, including, but not limited to artificial (prosthetic) joints, implants and/or devices, such as port/stent implant placed prior to study enrollment.
3. Must be obtained within 14 days prior to initiating protocol therapy.
4. If grade 4 neutropenia is documented (ANC <500/mcl) obtain twice per week until grade 3 or less. If grade 3 or 4 AST, ALT, alkaline phosphatase, total bilirubin, or creatinine obtain twice per week until resolved to grade 1 or less.
5. Must be obtained within 4 days of re-treatment with protocol therapy.
6 *Lm* surveillance will includes a 6 month post ADS11-001 oral antibiotic treatment to mitigate the risk of delayed listeria infection and routine monitoring of blood cultures. Following completion of study treatment blood cultures will be performed every 3 months (±1 month) for 3 years beginning 3 months after the subject's last dose of study treatment.
7. Repeat chest-x-ray if initially abnormal or if required to monitor tumor response. Chest-x-ray is not required if a chest CT is performed as part of the tumor measurement.
8. First follow-up CT scan should be at 12 weeks (provided patient remains clinically stable) then every 8 weeks for first 6 months and then every 3 months thereafter, until patient is put on non-protocol therapy. **(5/23/2011)**
Patients with progressive disease (irPD) detected before or at the 12-week imaging assessment, but without rapid clinical deterioration, require confirmation of irPD with a second, consecutive scan obtained ≥ 4 weeks from the initial documentation. Patients will continue to receive study treatment until irPD is confirmed at this later time point. (See section 8.2.) **(10/22/2012) (03/09/2015)**
9. Obtain within 48 hours prior to patient enrolling into study.
10. Patients will be observed in the chemotherapy outpatient area for 8 hours following the ADXS11-001 infusion. Vital signs will be taken pre-dose, every 30 minutres (+/- 5 minutes) for 4 hours after dose, approximately 8 hours after dose, 24 hours (+/- 2hours) and 72 hours (Day 4) after dose.
11. Follow-up is every three months for the first 3 years and every 6 months for the next 2 years (see Section 9). **(5/23/2011)**

7.2 Pathology Requirements: **(02/06/2012)**

- Pathology report for histologic confirmation of primary tumor
- Pathology report for recurrent or persistent disease if histologically documented
- Slides not required- no Central Pathology Review
- All reports should be mailed to the GOG SDC in Buffalo, NY or uploaded via SEDES.

7.3 Translational Research

7.3.1 Specimen Requirements **(05/23/2011) (10/17/2011) (10/22/2012) (05/06/2013)**

If the patient gives permission for her specimens to be used for translational research, then the participating institution is required to submit the patient's specimens as outlined below.

A detailed description of the specimen requirements can be found in Appendix I.

Required Specimen (Specimen Code)	**Collection Time Point**	**Ship To**
FFPE Primary Tumor (FP01)* 1st Choice: block 2nd Choice: 15 unstained slides (charged, 5µm)	Prior to all treatment	Ship to the GOG Tissue Bank within 8 weeks of registration[1]
FFPE Metastatic Tumor (FM01)* 1st Choice: block 2nd Choice: 15 unstained slides (charged, 5µm)	*Optional if FP01or FR01 is submitted* Prior to all treatment	
FFPE Recurrent Tumor (FR01)* 1st Choice: block 2nd Choice: 15 unstained slides (charged, 5µm)	*Optional if FP01or FM01 is submitted* Prior to starting ADXS11-001	
Pre-Dose 1 Serum (SB01) prepared from 7-10mL of blood drawn into a plain red top tube	Prior to dose 1 of ADXS11-001	Ship to the GOG Tissue Bank within 2 weeks of study entry[1]
2 Hour Post-Dose 1 Serum (SB02) prepared from 7-10mL of blood drawn into a plain red top tube	2 hours after dose 1 of ADXS11-001	
8 Hour Post-Dose 1 Serum (SB03) prepared from 7-10mL of blood drawn into a plain red top tube	8 hours after dose 1 of ADXS11-001	
24 Hour Post-Dose 1 Serum (SB04) prepared from 7-10mL of blood drawn into a plain red top tube	24 hours after dose 1 of ADXS11-001	
Pre-Dose 2 Serum (SB05) prepared from 7-10mL of blood drawn into a plain red top tube	Prior to dose 2 of ADXS11-001	Ship to the GOG Tissue Bank within 6 weeks of study entry[1]
2 Hour Post-Dose 2 Serum (SB06) prepared from 7-10mL of blood drawn into a plain red top tube	2 hours after dose 2 of ADXS11-001	
8 Hour Post-Dose 2 Serum (SB07) prepared from 7-10mL of blood drawn into a plain red top tube	8 hours after dose 2 of ADXS11-001	
24 House Post-Dose 2 Serum (SB08) prepared from 7-10mL of blood drawn into a plain red top tube	24 hours after dose 2 of ADXS11-001	
Pre-Dose 3 Serum (SB09) prepared from 7-10mL of blood drawn into a plain red top tube	Prior to dose 3 of ADXS11-001	Ship to the GOG Tissue Bank within 10 weeks of study entry[1]
2 Hour Post-Dose 3 Serum (SB10) prepared from 7-10mL of blood drawn into a plain red top tube	2 hours after dose 3 of ADXS11-001	
8 Hour Post-Dose 3 Serum (SB11) prepared from 7-10mL of blood drawn into a plain red top tube	8 hours after dose 3 of ADXS11-001	
24 Hour Post-Dose 3 Serum (SB12) prepared from 7-10mL of blood drawn into a plain red top tube	24 hours after dose 3 of ADXS11-001	

* A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the GOG Tissue Bank.

[1] Ship specimens as described in Appendix I to: GOG Tissue Bank / Protocol GOG-0265, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: 614-722-2865, Fax: 614-722-2897, Email: gogbank@nationwidechildrens.org **(12/23/2013)**

7.3.2 Laboratory Testing

7.3.2.1 Serum Cytokines

Serum specimens will be batch shipped to Advaxis. Serum specimens will be used to assess the concentrations of IFN-γ and IL-2, as the flu-like response to ADXS11-001 is presumed to be mediated by the release of cytokines into the systemic circulation. **(5/23/2011)**

7.3.2.2 HPV Typing

Unstained slides will be shipped to Advaxis for HPV testing and genotyping. **(5/23/2011)**

7.3.3 Future Research

Details regarding the banking and use of specimens for future research can be found in Appendix I.

7.4 Quality of Life

Not applicable.

8.0 EVALUATION CRITERIA

8.1 Antitumor Effect – Solid Tumors **(10/22/2012)**

In this study, disease parameters (section 8.11) and methods for tumor evaluation (Section 8.12)--but **not** evaluation of tumor response--will be in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) guideline Version 1.1.[69]

RECIST 1.1 response criteria are primarily designed to evaluate the early effects of cytotoxic agents, and depend on tumor shrinkage to demonstrate biologic activity. However, clinical evidence of tumor responses seen with immunotherapeutic agents such as ADXS11-001 can take longer to achieve, and may occur after a period of disease stabilization or following an initial increase in tumor burden. In light of the limitations of utilizing RECIST1.1 to evaluate immunomodulatory agents, immune-related response criteria (irRC) have been proposed to systematically detect the novel response patterns observed with immunologic agents.[70] Therefore, in this study, tumor response will be evaluated with an irRC modification of RECIST v1.1. (See also Section 8.2).
(06/27/2016)

8.1.1 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan, as ≥20 mm by chest x-ray, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters.

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal/pelvic masses (identified by physical exam and not CT or MRI), are considered as non-measurable.

Notes:
Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion which can be reproducibly measured should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease), including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

8.1.2 Methods for Evaluation of Disease:

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are

clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans), but NOT lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, subsequent image acquisitions should use the same type of scanner and follow the baseline imaging protocol as closely as possible. If possible, body scans should be performed with breath-hold scanning techniques.

FDG-PET/CT: At present, the low-dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, FDG-PET/CT may be used in this study if the CT portion of this study is a diagnostic quality CT with contrast (oral and IV) allowing for tumor measurements. If it is not of diagnostic quality, a diagnostic CT scan must be done. While FDG-PET/CT scan response assessments need additional study, it is reasonable to incorporate the use of FDG-PET/CT scanning to complement CT scanning in tumor assessment. If a post-baseline FDG-PET/CT scan shows evidence of a new lesion, progressive disease must be confirmed ≥ four weeks later by CT scan, and classification of progressive disease will be made based on irRECIST criteria below. **(10/22/2012)**

Note: A "positive" FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete

pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

It is mandatory to obtain cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when measureable disease has met criteria for response or stable disease. This confirmation is necessary to differentiate response or stable disease versus progressive disease, as an effusion may be a side effect of the treatment.

8.1.3 Response Criteria (RECIST 1.1) **(10/22/2012)**

THIS SECTION IS FOR REFERENCE ONLY. Refer to Section 8.2 for response criteria to be used in this study.

Determination of response should take into consideration all target (See 8.131) and non-target lesions (See 8.132) and if appropriate, biomarkers (See 8.133). **(06/27/2016)**

8.1.3.1 Evaluation of Target Lesions

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 the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the 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. PD must be confirmed after 3-4 weeks in the absence of clinical deterioration. (Note: the appearance of one or more small new lesions is not considered progression if when added to total tumor burden it does not increase by 20%). PD need not be confirmed if accompanied by other evidence of clinical deterioration (decreasing performance status, organ function, other clinical impression). **(5/23/2011)**

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

Not evaluable (NE): When at least one target lesion is not evaluated at a particular time point.

8.1.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis)

Non-CR/Non-PD: Persistence of one or more non-target lesion(s)

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase and be considered with the total tumor burden. **(5/23/2011)**

Not evaluable (NE): When at least one non-target lesion is not evaluated at a particular time point.

Although a clear progression of only "non-target" lesions is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

8.1.3.3 Evaluation of Biomarkers

Biomarker measurements are not used to determine response or progression in this study.

8.1.3.4 Evaluation of Best Overall (unconfirmed) Response

The best overall response is the best time point response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum recorded since baseline). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria in some circumstances.

Time Point Response for Patients with Measurable Disease at baseline (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions*	Time Point Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD**	Yes or No	PD
Any	Any	Yes	PD

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion
** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Time Point Response for Patients with only Non-Measurable Disease at baseline (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions*	Time Point Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD**
NE	No	NE
Unequivocal PD*	Yes or No	PD
Any	Yes	PD

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion

** 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

8.1.3.5 Best Overall Confirmed Response

Confirmation of CR and PR for determination of best overall response is required for studies with a primary endpoint that includes response.

Confirmed CR and PR for best overall confirmed response

Time Point Response First time point	Time Point Response Subsequent time point	BEST overall confirmed response
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

*If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR or SD, not CR at the first time point. Under these circumstances, the original CR should be changed to PR or SD and the best response is PR or SD.

In non-randomized trials where response is part of the primary endpoint, confirmation of CR or PR is needed to deem either one the "best overall response." **Responses (CR and PR) require confirmation at greater than or equal to 4 weeks from initial documentation.**

For this study, the minimum criteria for SD duration is 6 weeks.

Patients with a global deterioration of health status requiring discontinuation of treatment or die without objective evidence of disease progression at that time should be reported to be off study treatment due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

8.2 Response Assessment: Immune-Related RECIST **(10/22/2012)**

As previously noted, this study will assess tumor response with an immune-related modification of RECIST 1.1 (see Table 8.2-1 below).

Determination of response via irRECIST should take into consideration all target and non-target lesions.

A key distinction between standard RECIST 1.1 criteria and immune-related response criteria is that irRECIST requires early evidence of progressive disease (i.e., a determination of irPD ≤ 12 weeks after starting study treatment) be confirmed by repeat, consecutive imaging ≥ 4 weeks after the initial documentation in the absence of rapid clinical deterioration. During this interim ≥ 4 week period, patients should continue to be followed per protocol, including continued dosing of the study drug(s).

Additionally, the immune-mediated responses expected from ADXS11-001 require activation of the immune system prior to the observation of clinical responses, and such immune activation may take weeks to months to be clinically evident. Some patients with advanced cancer may have objective volume increase of tumor lesions within 12 weeks following the start of dosing on study. Such patients may not have had sufficient time to develop the required immune activation or, in some patients, tumor volume increases may represent infiltration of lymphocytes into the original tumor. In traditional oncology studies, such increases in tumor volume during the first 12 weeks of the study would constitute progressive disease and lead to discontinuation of study treatment and of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response. Therefore, in this study, the first imaging assessment will be performed at Week 12, followed by assessment every 8 weeks thereafter.

Table 8.2-1 Tumor Response Evaluation: Comparison Between 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)*

*** Patients with an initial finding of progressive disease (irPD) before or at the 12 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 12 weeks of the study).**

8.2.1 Response in Measurable Lesions

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 (TA), 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 TA, 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.

8.2.2 Response in Non-measurable Lesions

At each TA, 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 TA, 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.

8.2.3 Evaluation of Biomarkers
None.

8.2.4 Overall Response
The OR according to the irRC is derived from the responses in measurable lesions (based on TMTB) as well as the presence of any non-measurable lesions as follows:

Complete Response (irCR): Complete disappearance of *all lesions* (whether measurable or not); lymph nodes must decrease to < 10 mm in shortest dimension.

Partial Response (irPR): Decrease in TMTB ≥ to 30% relative to baseline.

Stable Disease (irSD): Not meeting criteria for irCR or irPR, in absence of irPD.

Progressive Disease (irPD): Increase in TMTB ≥ 20% relative to nadir.

The immune-related best overall response (irBOR) is the best irRC OR over the study as a whole, recorded between the date of first dose until the last TA prior to subsequent therapy (including tumor resection surgery) for the individual patient in the study. As with the primary definitions of tumor response, early progression (i.e., irPD occurring prior to Week 12) will not preclude an irBOR of irCR, irPR or irSD resulting from the Week 12 assessment. An assessment of irPD at or after Week 12 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 8.2-2 Best Overall Response (irBOR)

Target Lesions Baseline (Index) and New Measurable Lesions	**Non-Target Lesions***		**irRC Overall Response**
Total Measurable Tumor Burden (TMTB)	**Baseline Lesions**	**Unequivocal New Lesions**	
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

***NOTE: 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 TA, their measurement will at that point start to contribute to the TMTB. To achieve unequivocal progression of non-target lesions, there must be an overall level of substantial worsening in non-target disease that is of a magnitude that the treating physician would feel 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 schedule assessment.**

8.3 Duration of Response **(10/22/2012)**

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for irCR or irPR (whichever is first recorded) until the first date that recurrent or progressive disease (irPD) is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall irCR is measured from the time measurement criteria are first met for irCR until the first date that irPD is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for irPD are met. **(02/06/2012)**

8.4 Recurrence **(10/22/2012)**

Recurrence is defined as newly evident disease for patients who have no evidence of disease at baseline or progressive disease for patients who have strictly non-measurable disease at baseline.

8.5 Recurrence-Free Survival **(10/22/2012)**

Recurrence-Free Survival (RFS) is defined as the duration of time from study entry to time of recurrence or death, whichever occurs first.

8.6 Progression-Free Survival **(10/22/2012)**

Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of progression or death, whichever occurs first.

8.7 Survival **(10/22/2012)**

Survival is defined as the duration of time from study entry to time of death or the date of last contact.

9.0 DURATION OF STUDY

9.1 Patients will continue treatment until disease has progressed and been confirmed or progressed in the setting of clinical deterioration or intolerable toxicity intervenes. The patient can refuse the study treatment at any time. **(5/23/2011) (03/09/2015)**

9.2 Patients will be followed (with physical exams and histories) every three months for the first three years and then every six months for the next two years. Patients will be monitored for delayed toxicity and survival for this 5 year period with Q forms submitted to the GOG Statistical and Data Center, unless consent is withdrawn. **(5/23/2011) (06/27/2016)**

9.3 Surveillance monitoring for the detection of *Lm* will be initiated at the completion of study treatment according to the protocol or at the time of study discontinuation if earlier. This surveillance monitoring period will consist of a 6-month course of oral antibiotics and blood cultures at regular intervals. This surveillance monitoring will be performed on all subjects who have received at least 1 dose of ADXS11-001. Blood cultures will occur every 3 months (± 1 month) for 3 years beginning 3 months after the last dose of study treatment. This testing may be performed at the investigational site or at another acceptable location following consultation with the Sponsor. **(06/27/2016)**

10.0 STUDY MONITORING AND REPORTING PROCEDURES

10.1 IND Sponsor: Advaxis Inc., IND #13,712

10.2 ADVERSE EVENT REPORTING FOR AN INVESTIGATIONAL AGENT **(5/23/2011) (03/09/2015) (06/27/2016)**

Timely and complete reporting of safety information assists Advaxis in identifying any untoward medical occurrence, thereby allowing: (1) the protection of the safety of study subjects, (2) a greater understanding of the overall safety profile of ADXS11-001, (3) recognition of dose-related ADXS11-001 toxicities, (4) appropriate modification of study protocols, (5) improvements in study design or procedures, and (6) adherence to worldwide regulatory requirements.

All Investigators have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the study treatment. It is the responsibility of the Investigator to supply the medical documentation needed to support expedited AE reports in a timely manner.

Adverse events (AEs) will be reported to FDA according to 21 CFR 312.32.

10.2.1 Definition of Adverse Events (AE)

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

AE(s) may 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.

AEs 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.

All AEs will be recorded from the time the consent form is signed through 30 days following cessation of treatment during the study treatment period of the study.

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

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset and end dates, severity (grade of the event), Investigator's opinion of the relationship to ADXS11-001 (see definitions below), treatment/action required for the AE, and information regarding resolution/outcome.

Overdose: any dose exceeding the prescribed dose by 100%. No specific information is available on the treatment of overdose of ADXS11-001. In the event of an overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. If an AE(s) results from the overdose of ADXS11-001, the AE is reported as a SAE(s), even if no other seriousness criteria are met. An overdose without any associated clinical symptoms or abnormal laboratory results is reported as an AE.

AEs and other symptoms will be graded according to the expanded NCI CTCAE v 4.0. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov). The CTCAE v4.0 Manual is also available on the GOG member web site (http://www.gog.org under MANUALS).

10.2.1.1 Evaluating Adverse Events

An Investigator who is a qualified physician will evaluate all AEs according to the NCI CTCAE v 4.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the CTEP-AERS report.

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

Criteria for Determining AE Severity: The descriptions and grading scales found in the revised NCI CTCAE v 4.0 will be utilized for AE reporting.

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

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

10.2.1.2 Reporting Abnormal Test Findings

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

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

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

10.2.1.3 Reporting Cytokine Release Syndrome

As per NCI CTCAE v 4.03, CRS is defined as a disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath. Subjects must have experienced ALL symptoms for an AE to be documented as CRS. Individual symptoms associated with CRS should not be reported as CRS, but should be reported as separate AEs.

10.2.1.4 Adverse Event Follow-Up

AEs and SAEs related to ADXS11-001 (definitely, probably or possibly) should be followed to resolution or stabilization and reported as SAEs if they become serious. This also applies to subjects experiencing AEs that cause interruption or discontinuation of ADXS11-001 or those experiencing AEs that are present at the end of their participation in the study; such subjects should receive post treatment follow-up as appropriate. If an ongoing AE changes in its severity or in its perceived relationship to ADXS11-001, an amendment to the CTEP-AERS report should be submitted.

10.2.2 Reporting Expedited Adverse Events

Depending on the phase of the study, use of investigational agents, and role of the pharmaceutical sponsor, an expedited AE report may need to reach multiple destinations. For patients participating on a GOG trial, all expedited AE reports should be submitted by using the CTEP Adverse Event Reporting System (AERS). All reports are reviewed by GOG before final submission to CTEP-AERS. Submitting a report through CTEP-AERS serves as notification to GOG, and satisfies the GOG requirements for expedited AE reporting. All adverse reactions will be immediately directed to the Study Chair for

further review. **Additionally, all CTEP-AERS reports for this study will be sent to the GOG Phase I Committee Chair and the GOG Safety Review Committee Chair.**

The requirement for timely reporting of adverse events to the study sponsor is specified in the Statement of Investigator, Form FDA-1572. In signing the FDA-1572, the investigator assumes the responsibility for reporting AEs to the study sponsor. In compliance with FDA regulations, as contained in 21 CFR 312.64, AEs should be reported by the investigator.

10.2.3 Phase 1, 2 and 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a non-CTEP IND/IDE within 30 Days of the Last Administration of the Investigational Agent.

Phase 1, 2 and 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a non-CTEP IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

Death
A life-threatening adverse event
An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
A congenital anomaly/birth defect.
Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to GOG via CTEP-AERS within 24 hours of learning of the AE, followed by a complete report within 3 calendar days of the initial 24-hour report.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	24-Hour 3 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:
"24-Hour; 3 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:
All Grade 3, 4, and Grade 5 AEs
Grade 1 and 2 AEs resulting in hospitalization or prolongation of hospitalization

NOTE: Deaths clearly due to progressive disease should **NOT** be reported via CTEP-AERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting:

In addition to the standard SAE expedited reporting criteria, the following adverse events also require CTEP-AERS reporting, regardless of attribution:

- Bacterial meningitis ≥ grade 3 with or without hospitalization
- Hypotension ≥ grade 3 with or without hospitalization
- Sepsis ≥ grade 4 with or without hospitalization
- Acute and delayed listeria infection

Please refer to the ADXS11-001 Investigator Brochure for information regarding adverse effects when determining expectedness of an event for the purpose of expedited reporting via CTEP-AERS.

10.2.4 Procedures for Expedited Adverse Event Reporting:

10.2.4.1 CTEP-AERS Expedited Reports: Expedited reports are to be submitted using CTEP-AERS available at http://ctep.cancer.gov. The CTEP, NCI Guidelines: Adverse Event Reporting Requirements for expedited adverse event reporting requirements are also available at this site.

AML/MDS events must be reported via CTEP-AERS (in addition to routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplatic syndrome, or 3) Treatment related secondary malignancy.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to the GOG Regulatory Affairs Department by telephone at 215-854-0770. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

10.2.5 Reporting to Advaxis: The GOG Regulatory Department will forward the CTEP-AERS report to Advaxis for all serious adverse events (SAEs) **within 24 hours of discovery or notification of the event.**

Advaxis PV CRO:	inVentiv Health Clinical Pharmacovigilance
Attn:	iHC SAE Reporting (**email**: i3drugsafetyPV@inventivhealth.com
or FAX:	866-880-9343)

10.3 GOG DATA MANAGEMENT FORMS

The following forms must be completed and submitted to the GOG Statistical and Data Center (SDC) in accordance with the schedule below. All forms except the BDR Form **must** be submitted via the SDC Electronic Data Entry System (SEDES) which is available through the GOG website (www.gogstats.org). The BDR Form should be submitted via mail. The GOG Uploader Application in SEDES is an alternate method for submitting pathology reports and BDR to the GOG SDC. **(5/23/2011)**

Form (10/22/2012)	**Due within**		**Copies***	**Comments**
	Weeks	**Event**		
Form R (Registration Form)	2	Registration	1	Mandatory Submission via SEDES
Specimen Consent Application	1	Registration	N/A	Complete online
Form OHR (Recurrent Gynecologic Cancer – On Study History Form)	2	Registration	1	Mandatory Submission via SEDES
Form DR (Pre-Treatment Summary Form)	4	Registration	1	Mandatory Submission via SEDES
Form BDR (Pre-Treatment Body Diagram Form)	4	Registration	1	Submit to SDC via postal mail or upload online via SEDES
Form irRECIST (Immune Related RECIST Form) baseline	4	Registration	1	Mandatory Submission via SEDES
Primary disease:** Pathology Report	6	Registration	1**	Submit to SDC via postal mail or via report uploader in SEDES
Recurrent or Persistent Disease:** Pathology Report (only if histologically documented)	6	Registration	1**	
Concomitant Medications Form **(06/27/2016)**	4	Registration	1	Mandatory Submission via SEDES
Form D2R (Cycle Dose Drug Form)	2***	Completion of each cycle of therapy	1	Mandatory Submission via SEDES
Form irRECIST (Immune Related RECIST FORM)	2	Clinical response assessment	1	Mandatory Submission via SEDES
Form T (Common Toxicity Reporting Form)	2***	Beginning of each subsequent cycle	1	Mandatory Submission via SEDES
Form Q0 (Treatment Completion Form)	2	Completion of study Rx and change in Rx	1	Mandatory Submission via SEDES

Form Q (Follow-Up Form)	2	Disease progression; death; normal follow-up	1	Mandatory Submission via SEDES quarterly for 2 years, semi-annually for 3 more years
Form SP-FP01-0265**** for FFPE primary tumor **(05/06/2013)**	8	Registration	N/A	Submit via SEDES†
Form SP-FM01-0265**** for FFPE metastatic tumor (optional) **(05/06/2013)**	8	Registration	N/A	Submit via SEDES†
Form SP-FR01-0265**** for FFPE recurrent tumor (optional) **(05/06/2013)**	8	Registration	N/A	Submit via SEDES†
Form SP-SB01-GOG-0265 for pre-dose 1 serum	2	Registration	N/A	Submit via SEDES†
Form SP-SB02-GOG-0265 for 2 hour post-dose 1 serum	2	Registration	N/A	Submit via SEDES†
Form SP-SB03-GOG-0265 for 8 hour post-dose 1 serum	2	Registration	N/A	Submit via SEDES†
Form SP-SB04-GOG-0265 for 24 hour post-dose 1 serum	2	Registration	N/A	Submit via SEDES†
Form SP-SB05-GOG-0265 for pre-dose 2 serum	6	Registration	N/A	Submit via SEDES†
Form SP-SB06-GOG-0265 for 2 hour post-dose 2 serum	6	Registration	N/A	Submit via SEDES†
Form SP-SB07-GOG-0265 for 8 hour post-dose 2 serum	6	Registration	N/A	Submit via SEDES†
Form SP-SB08-GOG-0265 for 24 hour post-dose 2 serum	6	Registration	N/A	Submit via SEDES†
Form SP-SB09-GOG-0265 for pre-dose 3 serum	10	Registration	N/A	Submit via SEDES†
Form SP-SB10-GOG-0265 for 2 hour post-dose 3 serum	10	Registration	N/A	Submit via SEDES†
Form SP-SB11-GOG-0265 for 8 hour post-dose 3 serum	10	Registration	N/A	Submit via SEDES†
Form SP-SB12-GOG-0265 for 24 hour post-dose 3 serum	10	Registration	N/A	Submit via SEDES†

* The number of required copies including the original form which must be sent to the Statistical and Data Center.
** Pathology slides for Central Pathology Committee Review are not required on this study.
*** For patients in the safety lead-in, the T and D2R forms are due within **72 hours** after completing each cycle.
**** A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the GOG Tissue Bank. **(05/06/2013)**
† Form SP must be submitted online via SEDES regardless of whether the specimen is submitted for research. **(05/06/2013)**

This study will be monitored by the **Abbreviated** Clinical Data Update System (CDUS) Version 3.0 Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

11.0 STATISTICAL CONSIDERATIONS

The primary objective of this study is to assess the tolerability, toxicity, and efficacy of the study agent, ADXS11-001, in patients with recurrent or persistent cervical cancer. The primary measure of efficacy will be overall survival at 12 months.

We note here that the change in treatment regimen from stage 1 (three cycles of treatment) to stage 2 (unlimited cycles) complicates the interpretation of the trial. Under the reasonable but not certain assumption that extended treatment (i.e., >3 doses) is more effective than 3 doses: at the end of the study, if we reject the null hypothesis of inactivity, then we can conclude that the extended regimen is effective. **(03/09/2015)**

11.1 This is a single-arm, two-stage Phase II study, and no randomization is involved; however, patient registration will be accomplished in the usual fashion. For patients in the safety lead-in, patient entry will be accomplished via the GOG Statistical and Data Center's Phase I reservation and registration system.

11.2 The principle parameters to be employed to evaluate the primary and secondary objectives are:

11.2.1 Primary Endpoints:

11.2.1.1 Number of patients with DLTs.

11.2.1.2 Frequency and severity of adverse effects as assessed by CTCAE v 4.0.

11.2.1.3 The proportion of patients who survive for at least 12 months

11.2.2 Secondary Endpoints:

11.2.2.1 Distribution of overall survival

11.2.2.2 Distribution of progression-free survival

11.2.2.3 The proportion of patients who have objective tumor response (complete or partial)

11.2.3 Exploratory Endpoints:

11.2.3.1 Changes in clinical immunology based upon serum and their relationship with clinical response

11.3 Of the 25 patients **enrolled in stage 2** 11 patients were still on treatment at the time the clinical hold went into effect. It is clear that the latter patients should be replaced because they did not receive treatment per protocol (i.e., until progression). However, including just patients who had progressed or died or who had otherwise come off study treatment, while excluding patients still on treatment at the time of the clinical hold, would

introduce bias into the assessment of the efficacy of the study treatment. Therefore, all patients **enrolled in stage 2** prior to the clinical hold will be excluded from efficacy analyses and will be replaced. All treated patients will be included in all safety analyses. **(5/23/2011) (06/27/2016)**

11.3.1 The anticipated period of active accrual for the 6 patients in the safety lead-in is approximately 4 months.

11.3.2 The anticipated period of active accrual for the first stage (with a target of 21 patients plus 6 patients from the safety lead-in) is approximately 15 months. **(5/23/2011)**

Thirty-seven patients were originally planned for Stage 2. As described above in Section 11.3, all **stage 2 patients accrued prior to the clinical hold** (October 1, 2015) will be replaced. Therefore, a two-stage total of 90 patients will be targeted (including 29 enrolled in the first stage [26 treated], 25 in Stage 2 [all to be replaced], and **37 to be accrued in order to complete stage 2**, and thus have 63 evaluable patients. Once accrual reopens, we expect accrual of 37 patients to complete in approximately twelve months (based on an accrual rate of about 3 patients per month for the year prior to the clinical hold going into effect). **(06/27/2016)**

11.4 The study plan is a single arm, 2-stage phase II clinical trial. The study also includes a safety lead-in, in which the dose limiting toxicities of the study agent will be assessed in the first 6 patients enrolled.

Safety Lead-in
In Phase I trials, five patients have been treated with ADXS11-001 at the dose used in this study ($1x10^9$ cfu). No DLT has occurred in these patients or in the 5 patients at lower doses. We will examine in detail the DLT data for the first 6 patients in this study before enrolling the rest of the study's patients.

We denote by θ the probability of a DLT at the $1x10^9$ cfu dose. In the traditional 3+3 phase I design used in the dose escalation phase, the implicit (but not technically correct) goal of the MTD estimation process is to obtain a dose that has a probability of a DLT less than 0.33. We focus our consideration on the probability that θ [i.e., Pr(DLT) at the $1x10^9$ cfu dose], is higher than a target of 0.33.

As proposed by Gönen[71], we utilize a Bayesian interpretation of θ, in which θ is considered to be a random variable with a probability distribution. We combine the data observed in our trial with a prior probability distribution for θ to obtain a posterior distribution for θ. The DLT data is binomially distributed (DLT yes/no). The conjugate prior for the binomial distribution is the beta distribution, so we assume the prior for θ, $p(\theta)$, to be Beta(α, β). We denote the number of DLT-evaluable patients treated at the $1x10^9$ cfu in the dose safety lead-in to be N_S, and of these we denote the number with DLTs to be X_S. The posterior for θ at the end of the safety lead-in is thus $p(\theta|X_1)$, is thus Beta($\alpha+X_S$, $\beta+ N_S - X_S$). **(10/22/2012)**

We specify a prior for θ that considers the information we have from the Phase I trial (0 DLTs out of 5 patients treated). We use a Beta(α, β) with α=2 and β=6, which is the prior curve in Figure 11.1. This reflects the belief that the pr(DLT) for the $1x10^9$ cfu dose is most likely around 0.1 to 0.2.

Figure 11.1 also shows the posterior distributions for θ given all various possible DLT results we may see in the safety lead-in of six patients. Under the different posterior distributions for θ, we can calculate the probability that θ exceeds a target of 0.33 given the data we have observed. These are shown in Table 11.3. For example, if we observe 0/6 patients with DLTs safety lead-in, there is 0.04 probability that θ exceeds a target of 0.33; whereas, if we see 3/6 patients with DLTs in the expanded cohort, there is a 0.56 probability that θ exceeds a target of 0.33.

Given these probabilities at the end of the safety lead-in, we can make informed decisions regarding the appropriateness of the choice of the phase II dose. We can also use similar calculations to determine the probability that our MTD is too high after <u>partial</u> enrollment of the expanded cohort is enrolled, e.g., if the first three patients in the expanded cohort all have DLTs, the probability that θ exceeds our target of 0.33 is 0.57.

Figure 11.1: Prior and Posterior Distributions for θ, the Pr (DLT) at $1x10^9$ cfu dose

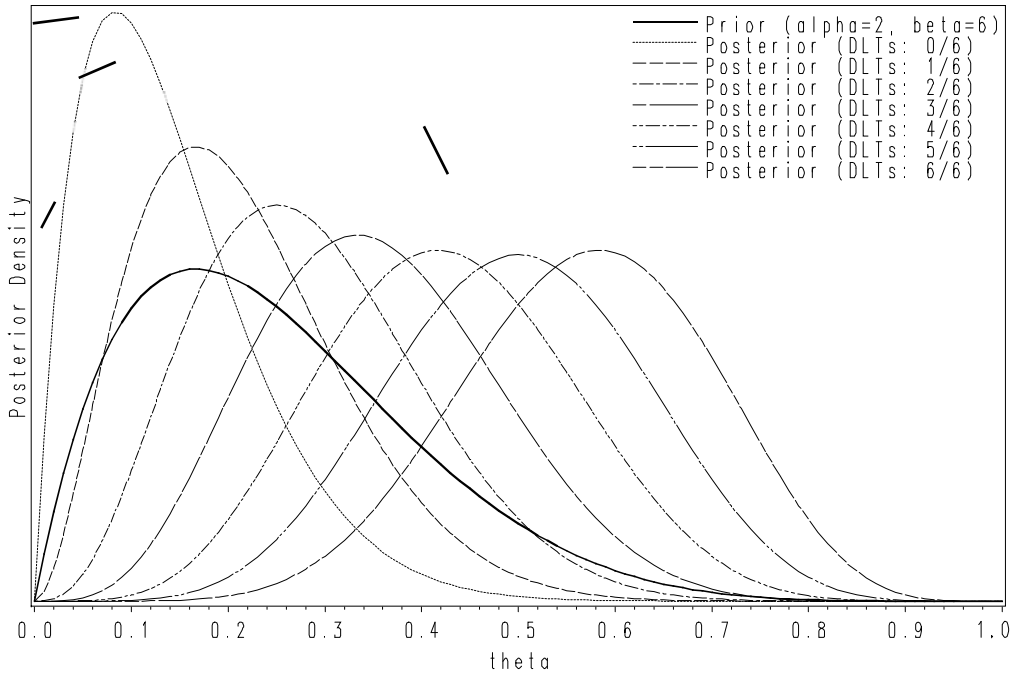


Table 11.1: Prior and Posterior Probabilities that θ [Pr(DLT)] Exceeds a Target of 0.33

	Probability that θ Exceeds a Target of 0.33
Prior (prior to Safety Lead-In)	
	0.27
Posterior (at End of Safety Lead-In)	

X_s	
0	0.04
1	0.14
2	0.33
3	0.56
4	0.77
5	0.90
6	0.97

Phase II End point and design selection
Survival at 12 months is the primary endpoint of the study for the reasons described above in section 2.6.

The guiding principle in selecting the design for this study is to limit the number of patients treated with clinically ineffective therapies; yet to estimate efficacy with reasonable precision for those agents that are clinically active. However, the accrual is complicated by the logistics of managing a multi-center phase II study. When the targeted sample size is attained, those patients who have already been approached will be permitted to register. Strict adherence to a two-stage sampling design with 'optimal' early stopping rules is not practical. Instead, flexible stopping rules are used that tend to maximize the probability of rejecting the treatment when the agent is indeed not active.

Historical Data and Design Parameters
The design parameters for this study arise from considering the results from the GOG 0127 and 0227 study queues. The patients enrolled into those studies are expected to behave similarly to those eligible for this study. The purpose of those studies was to evaluate cytotoxic and cytostatic salvage regimens. Those studies also implemented two-stage stopping guidelines. While clinical response is the primary endpoint in those studies, the survival times are also available. The conclusions from those studies are that the agents studied had at most modest activity, except for protocol 0227-C, in which the agent was deemed active, is excluded. All of the other sections concluded that the agent had limited activity, insignificant activity, or the like. The estimated probability of surviving for at least 12 months is summarized in Table 11.2.

We utilize a method proposed by Korn et al[73] in which a logistic regression model was built based on past studies (shown in Table 11.2) to predict the probability of a patient surviving at least 12 months. The following terms were examined to determine if they were significantly related to 12-month survival:

- age (linear and quadratic terms)
- cell type (squamous vs. other [unspecified adenocarcinoma, mucinous adenocarcinoma, adenosquamous])
- performance status (0 vs. 1 vs. 2 or 3)
- number of prior chemotherapy regimens (0 or 1 vs. 2)
- prior radiotherapy
- extra-pelvic disease

- grade
- race (black, white, other)
- stage.

A backward elimination procedure was used, with $p \leq 0.20$ required for terms to remain in the model. This resulted in the selection of age, age^2, performance status, and race for the predictive model. The same variables were selected when stepwise selection was used, with $p < 0.20$ required for entry and to remain in the model. Models were also built excluding variables (stage, grade, number of prior chemotherapy regimens, and extra-pelvic disease) for which some patients had missing values; variable selected based on these models also matched the above. **(10/22/2012)**

Between-trial variability was assessed using two methods. First, as proposed by Korn et al[72], we compared the proportion of patients surviving at 12 months in each protocol (r_i based on n_i patients in protocol i, i=1, …, k; k=17 protocols) with the overall proportion surviving at 12 months (r based on n patients). If r_i was outside the following interval, it was considered different from the overall event rate:

$$r \pm z_{1-0.025/k} \sqrt{\frac{n - n_i}{n \cdot n_i} r(1-r)}$$

None of the trials had rates that differed significantly from the overall event rate.

The second method to assess between-trial variability was to build a proportional hazards model with protocol section, and then to add the variables that were predictive to determine if they removed the significance of protocol section. With the first model, protocol section had a statistically significant effect: p=0.0764 (based on 16 degrees of freedom). When age, age^2, performance status, and race were included in the model, protocol section was no longer significant: p=0.7662. **(10/22/2012)**

The predictive model is shown in Table 11.3. We will use this model to compute the expected (null) proportion of patients surviving 12 months in this planned trial. We will then compare the actual proportion of patients surviving 12 months with the null value using the score chi-square test. The model's predicted probabilities of survival are presented graphically by race, performance status, and age in Figure 11.2.

Table 11.2: Protocols 0127 and 0227: Probability of Surviving 12 Months by Study Section

Protocol	N of Evaluable Patients	Proportion Surviving at Least 12 Months (SE)†
0127-B	34	0.18 (0.07)
0127-C	44	0.22 (0.06)
0127-D	29	0.14 (0.06)
0127-F	40	0.22 (0.07)
0127-H	24	0.17 (0.08)
0127-K	25	0.16 (0.07)
0127-L	44	0.18 (0.06)
0127-M	25	0.00 (0.00)
0127-N-1	32	0.28 (0.08)
0127-N-2	32	0.22 (0.07)
0127-P	23	0.30 (0.10)
0127-Q	32	0.28 (0.08)
0127-R	27	0.30 (0.09)
0127-S	23	0.22 (0.09)
0127-T	25	0.28 (0.09)
0127-U	25	0.24 (0.09)
0227-D	25	0.16 (0.07)
All	*509*	*0.21 (0.02)*

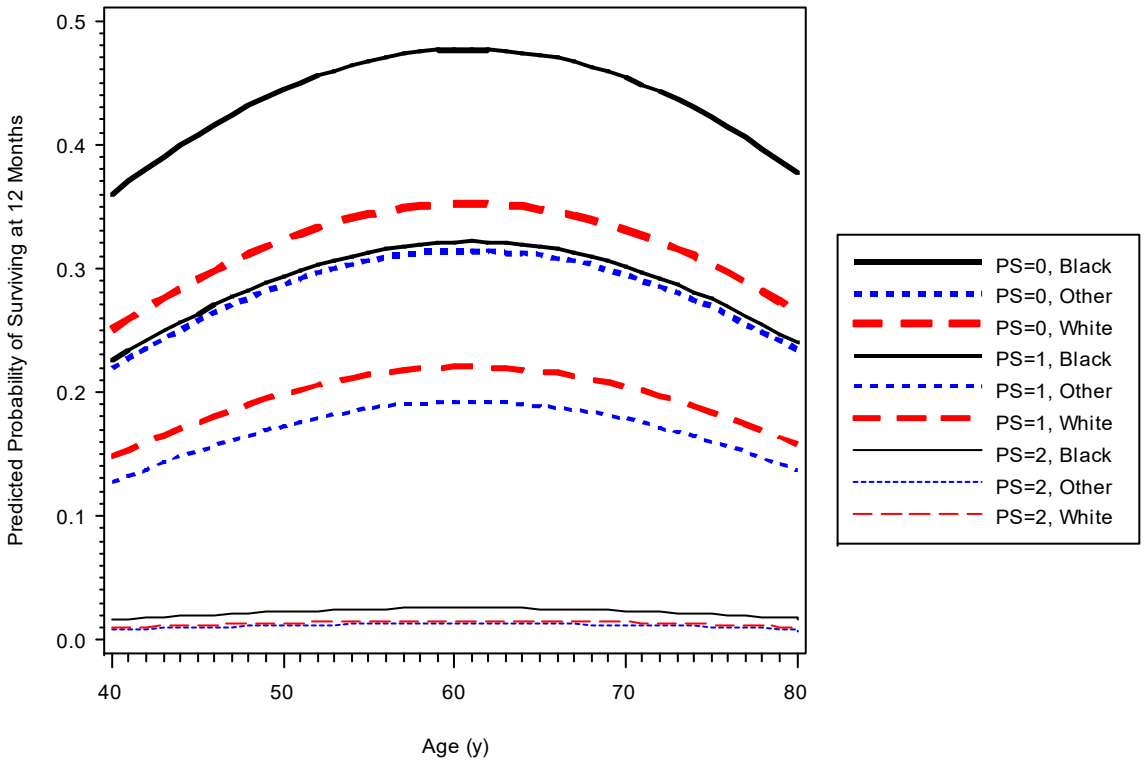
† Product limit estimate of the probability of surviving at least 12 months, standard error in parentheses.

Table 11.3: Predictive Logistic Regression Model for Survival at 12 Months

Parameter	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept	-4.2306	1.8878	5.0222	0.0250
age	0.136	0.0741	3.3687	0.0664
age*age	-0.00112	0.000711	2.4713	0.1159
Performance Status=0	0.0	NA	NA	NA
Performance Status=1	-0.6552	0.2324	7.9486	0.0048
Performance Status=2,3	-3.5418	1.0197	12.0645	0.0005
Race=Black	0.0	NA	NA	NA
Race=Other	-0.688	0.525	1.7171	0.1901
Race=White	-0.5172	0.2882	3.2192	0.0728

$p < 0.0001$ for Performance Status (with 2 df)
$p = 0.1674$ for Race (with 2 df)]
NA: not applicable.

Figure 11.2: Predicted Survival at 12 Months by Age, Race, and Performance Status



For sample size calculation, we assume the expected null proportion of patients surviving 12 months (denoted by π) to be the overall percentage across all trials (of inactive agents) in the 127 and 227 queues: 21% ≈ 20%. We size the study to have 90% power to detect a 15% increase in 12-month survival (to 35%) at a one-sided significance level of 0.10. We utilize a two-stage design, and we use the optimal sample size as proposed by Simon[73] to set the targeted sample size for each stage: n_1=27 (including 6 patients from safety lead-in), and n_2=36 (n=63). However, the actual method of Simon is not applicable here because of the dynamic nature of the null proportion of patients surviving 12 months (i.e., the null value for the proportion of patients surviving 12 months depends on the observed patient characteristics). The design is inherently flexible in that while we target these sample sizes, the actual attained sample sizes will be utilized in the analyses of stage 1 and overall. **(5/23/2011) (10/22/2012)**

A conditional power approach will be utilized to determine if the second stage of accrual should be undertaken. Conditional on the results from the first stage, the power to detect a statistically significant result at the end of the trial (after stage 2) will be calculated. For this calculation, the 12-month survival probability in the second stage (p_2) will be based on the estimated probability from the first stage ($\hat{p}_2^{(\text{Mod})}$):

$$\hat{p}_2^{(\text{Mod})} = \hat{p}_1 + se(\hat{p}_1) = \hat{p}_1 + \sqrt{\hat{p}_1(1-\hat{p}_1)/n_1}$$

This "simple optimistic but plausible alternative" was proposed by Pepe and Anderson[74] and is shown to yield reasonable operating characteristics below. **(10/22/2012)**

If the conditional power at the end of stage 1 is <20%, then the trial will be stopped, otherwise, if clinical judgment indicates, the trial will continue to the second stage.

Table 11.4 11.4 displays the operating characteristics of the trial. These are based on 10,000 simulated trials resampled from data of the trials listed in Table 11. 11.2. The type I error control is maintained at <0.10, and power is maintained at 90%. Under the null, the trial has 49.5% chance of stopping at the end of the first stage.

If the result of the first stage becomes ineluctable with respect to the decision to open to a second stage, the second stage may be initiated sooner.

Table 11.4: Operating Characteristics of Trial (5/23/2011)

	PET	Probability of Rejecting H_0 at end of study
Under null (p≈0.20)	0.495	α = 0.075
Under alternative (p≈0.35)	0.058	$1-\beta$ = 0.900
PET = probability of early termination, i.e., at end of stage 1 Based on 10,000 simulations of data resampled from the studies in listed Table 11. 11.2. Trial is stopped early if conditional power is <20% at the end of stage 1. n_1=27 (including 6 patients from safety lead-in), n_2=36, n=63.		

11.5 Evaluability for efficacy and toxicity

Only those patients who are deemed "ineligible" or who receive no therapy will be eliminated from the analysis. All patients who receive any therapy will be evaluated for both treatment efficacy and toxicity. While on occasion circumstances may prevent the determination of treatment efficacy, such patients will be included in the analysis and labeled as "indeterminate". This category will be listed and reflected in the calculation of the response rate.

11.6 Data Safety and Monitoring

Data sheets from patients on this protocol will be reviewed before each semi-annual meeting and will be reviewed by the Study Chairperson in conjunction with the Statistical and Data Center. In some instances, because of unexpectedly severe toxicity, the Statistical and Data Center may elect, after consultation with the Study Chairperson and the Medical Oncology Committee, to recommend early closure of a study.

The frequency and severity of all toxicities will be tabulated from submitted case report forms and summarized for review by the study chairperson, the Developmental Therapeutics Committee, and the GOG Safety Review Committee in conjunction with each semi-annual GOG meeting. For studies sponsored by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI), standardized toxicity reports are also submitted to the drug and disease monitors at the Investigational Drug Branch (IDB) and Clinical Investigation Branch (CIB). The initial overall review of

toxicity is usually performed after completion of the first stage of accrual, at which point accrual is generally suspended pending formal analysis of response and toxicity.

All serious and/or unexpected events are communicated to the Study Chair, sponsor, and regulatory agencies as mandated in the protocol. These reports are reviewed by the Study Chair (or designated co-chair) within two working days for consideration of investigator notification, amendment, or immediate study suspension. **Additionally, all SAEs of sepsis, hypotension, or meningitis will be reviewed by the GOG Phase I Committee Chair and by the GOG Safety Review Committee Chair within 24 hours for consideration of investigator notification, amendment, or immediate study suspension.** All participating institutions will then receive notification of the toxicities and reason for study suspension. Under these circumstances, accrual cannot be re-activated until the study is reviewed by the GOG Safety Review Committee (SRC). However, patients currently receiving treatment may continue to receive treatment in accordance protocol guidelines at the discretion of their physicians, unless directed otherwise. **(02/06/2012)**

In addition to the safety run-in of six patients to assess safety and in addition to the routine monitoring of safety described above this section, an additional assessment of safety and tolerability will done at the end of the first stage of accrual. At that point, we will examine the numbers of patients with DLTs; if this number of patients exceeds the numbers in the Table 11.5 below (allowing for a range of possible accrual values), consideration will be given to stopping the trial due to excessive toxicity; discussion will occur between the study chair, study statistician, and the chair of the Developmental Therapeutics Committee.

Table 11.5: Cutpoints for DLTs at the End of Stage 1

n	*c*	Pr($X > c$) given *Prob(DLT)*= 0.2	Pr($X > c$) given *Prob(DLT)*= 0.4
24	8	.036	.672
25	8	.047	.726
26	9	.023	.775
27	9	.030	.691
28	9	.039	.741
29	9	.049	.785
30	10	.026	.709
n = 1st stage accrual c = cutpoint for number of DLTs X = observed number of patients with DLTs			

11.7 Secondary and Exploratory Analyses

Overall survival and progression-free survival will be characterized with Kaplan-Meier plots and estimates of the median time until death or progression.

Changes in serum cytokines will be examined with descriptive statistics and graphics, and their relationship with survival and tumor response will be examined with proportional hazards and logistic regression models, as appropriate.

11.8 Anticipated Gender and Minority Inclusion **(5/23/2011)**

This study restricts entry to women by nature of the site of the disease. The table below shows the projected numbers of patients by racial/ethnic subgroup (based on GOG protocol series 0127 and 0227) assuming 63 total patients are accrued. There are no data that support differences in the intervention effects between racial/ethnic subgroups; therefore, the study design does not involve race. However, subsets defined by white and non-white will be analyzed in this study to investigate this important question with the current therapies. The trial is registered at clinicaltrials.gov, and all patients who meet eligibility criteria are invited to participate.

Ethnic Category	**Sex/Gender**					
	Females			**Males**		**Total**
Hispanic or Latino	5	+	0		=	5
Not Hispanic or Latino	58	+	0		=	58
Ethnic Category: Total of all subjects	63(A1)	+	0	(B1)	=	63 (C1)
Racial Category						
American Indian or Alaskan Native	1	+	0		=	1
Asian	2	+	0		=	2
Black or African American	10	+	0		=	10
Native Hawaiian or other Pacific Islander	1	+	0		=	1
White	49	+	0		=	49
Racial Category: Total of all subjects	63 (A2)	+	0	(B2)	=	63 (C2)

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APPENDIX I – TRANSLATIONAL RESEARCH SPECIMEN PROCEDURES **(05/06/2013) (06/27/2016)**

Summary of Specimen Requirements (10/17/2011) (10/22/2012)

If the patient gives permission for her specimens to be collected and used for this optional translational research component, then participating institutions within the United States are required to submit the patient's specimens as outlined below (unless otherwise specified).

Required Specimen (Specimen Code)	**Collection Time Point**	**Ship To**
FFPE Primary Tumor (FP01)* 1st Choice: block 2nd Choice: 15 unstained slides (charged, 5µm)	Prior to all treatment	Ship to the GOG Tissue Bank within 8 weeks of registration[1]
FFPE Metastatic Tumor (FM01)* 1st Choice: block 2nd Choice: 15 unstained slides (charged, 5µm)	*Optional if FP01or FR01 is submitted* Prior to all treatment	
FFPE Recurrent Tumor (FR01)* 1st Choice: block 2nd Choice: 15 unstained slides (charged, 5µm)	*Optional if FP01or FM01 is submitted* Prior to starting ADXS11-001	
Pre-Dose 1 Serum (SB01) prepared from 7-10mL of blood drawn into a plain red top tube	Prior to dose 1 of ADXS11-001	Ship to the GOG Tissue Bank within 2 weeks of study entry[1]
2 Hour Post-Dose 1 Serum (SB02) prepared from 7-10mL of blood drawn into a plain red top tube	2 hours after dose 1 of ADXS11-001	
8 Hour Post-Dose 1 Serum (SB03) prepared from 7-10mL of blood drawn into a plain red top tube	8 hours after dose 1 of ADXS11-001	
24 Hour Post-Dose 1 Serum (SB04) prepared from 7-10mL of blood drawn into a plain red top tube	24 hours after dose 1 of ADXS11-001	
Pre-Dose 2 Serum (SB05) prepared from 7-10mL of blood drawn into a plain red top tube	Prior to dose 2 of ADXS11-001	Ship to the GOG Tissue Bank within 6 weeks of study entry[1]
2 Hour Post-Dose 2 Serum (SB06) prepared from 7-10mL of blood drawn into a plain red top tube	2 hours after dose 2 of ADXS11-001	
8 Hour Post-Dose 2 Serum (SB07) prepared from 7-10mL of blood drawn into a plain red top tube	8 hours after dose 2 of ADXS11-001	
24 House Post-Dose 2 Serum (SB08) prepared from 7-10mL of blood drawn into a plain red top tube	24 hours after dose 2 of ADXS11-001	
Pre-Dose 3 Serum (SB09) prepared from 7-10mL of blood drawn into a plain red top tube	Prior to dose 3 of ADXS11-001	Ship to the GOG Tissue Bank within 10 weeks of study entry[1]
2 Hour Post-Dose 3 Serum (SB10) prepared from 7-10mL of blood drawn into a plain red top tube	2 hours after dose 3 of ADXS11-001	
8 Hour Post-Dose 3 Serum (SB11) prepared from 7-10mL of blood drawn into a plain red top tube	8 hours after dose 3 of ADXS11-001	

24 Hour Post-Dose 3 Serum (SB12) prepared from 7-10mL of blood drawn into a plain red top tube	24 hours after dose 3 of ADXS11-001	

* A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the GOG Tissue Bank **(10/22/2012)**

[1] Ship specimens to: GOG Tissue Bank / Protocol GOG-0265, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: 614-722-2865, Fax: 614-722-2897, Email: gogbank@nationwidechildrens.org **(12/23/2013)**

Obtaining a GOG Bank ID for Translational Research Specimens (10/22/2012)

Only one GOG Bank ID (# # # # - # # - G # # #) is assigned per patient. All translational research specimens and accompanying paperwork must be labeled with this coded patient number. A GOG Bank ID can be obtained online via the Tissue Bank Portal on the GOG website (under Tools on the Web Menu page).

Obtain the GOG patient study ID for all GOG protocols with translational research specimen requirements before requesting a Bank ID from the Tissue Bank Portal. **Be sure to indicate if the patient has a previous GOG # when registering.** This will ensure that the patient is only assigned one Bank ID. The GOG ID – Bank ID Lookup on the Tissue Bank Portal can be used to search for an existing Bank ID. **(02/06/2012)**

Please contact GOG User Support if you need assistance or have assigned more than one Bank ID to a patient (Email: support@gogstats.org; Phone: 716-845-7767).

III. Requesting Specimen Kits

One single-chamber specimen kit will be provided per patient for the collection and shipment of serum for each time point (Dose 1, Dose 2, and Dose 3). **(12/23/2013)**

Translational research specimen kits can be ordered online via the Kit Management link on the GOG website (under Data Entry on the Web Menu page). Each site may order a maximum of two specimen kits per protocol per day (daily max = 6 kits).

Please contact the GOG Tissue Bank if you need assistance (Email: GOGBank@nationwidechildrens.org; Phone: 866-GOG-BANC/866-464-2262).

Be sure to plan ahead and allow time for kits to be shipped by ground transportation.

Note: Unused materials and kits should be returned to the GOG Tissue Bank.

IV. Labeling Translational Research Specimens

A waterproof permanent marker or printed label should be used to label each translational research specimen with:

GOG Bank ID (# # # # - # # - G # # #)
GOG protocol number (GOG- # # # #)

specimen code (see section I)
collection date (mm/dd/yyyy)
surgical pathology accession number (tissue specimens only)
block number (tissue specimens only)

Note: If labeling slides, only label on the top, front portion of the slide. Do not place a label on the back of the slide or over the tissue. The label must fit on the slide and should not be wrapped around the slide or hang over the edge.

V. Submitting Archival Formalin-Fixed, Paraffin-Embedded Tumor (10/22/2012) (12/23/2013)

Formalin-fixed, paraffin embedded (FFPE) tissue should be the most representative of the specimen type (primary, metastatic, recurrent). Primary and metastatic tumor should be collected prior to all treatment. Recurrent tumor should be collected prior to the study treatment. Only one block may be submitted per tissue type.

Every attempt should be made to provide a tumor block; however, if a block cannot be provided on a permanent basis, then 15 unstained sections (charged, 5µm) should be submitted. All tissue sections should be cut sequentially from the same block.

The type of specimen (block or slides) should be specified on Form SP.

If submitting recurrent tumor, include a comment on Form SP noting whether the tumor is from the primary site or a metastatic site.

All FFPE tissue should be submitted with the corresponding pathology report.

VI. Submitting Serum Specimens

1. Label cryovials and a 15mL conical tube as described above. Use 2mL cryovials if serum will be shipped to the GOG Tissue Bank.

2. Draw 7-10mL of blood into red top tube(s).

3. Allow the blood to clot at 4°C (or in a bucket with ice) for at least 30 minutes but no longer than 3 hours.

4. Centrifuge the blood at 1000g for 15 minutes at 4ºC (preferred) or room temperature to separate the serum (top, straw-colored layer) from the red blood cells (bottom, red layer).

5. Transfer the serum into a 15mL conical tube and gently mix.

6. Quickly, evenly dispense (aliquot) the serum into the pre-labeled cryovials and cap the tubes securely. Place a minimum of 0.25mL into each cryovial.

7. Immediately **freeze the serum in an upright position** in a -70ºC to -80ºC freezer or by direct exposure with dry ice until ready to ship. If a -70ºC to -80ºC freezer is not available for storage, store and ship on dry ice within 24 hours of collection.

VII. Submitting Form SP

Form SP must be submitted via SEDES for each required specimen regardless of whether the specimen is submitted for research.

A copy of the SEDES-completed Form SP must accompany each specimen shipped to the GOG Tissue Bank. Handwritten forms will not be accepted.

Note: A copy does not need to be sent if the specimen is not collected.

Retain a printout of the completed form for your records.

Please contact GOG User Support if you need assistance (Email: support@gogstats.org; Phone: 716-845-7767).

VIII. Shipping Translational Research Specimens

A SEDES-completed copy of Form SP must be included for each translational research specimen.

A. FFPE Tissue

FFPE tissue and a copy of the corresponding pathology report should be shipped using your own shipping container at your own expense to:

GOG Tissue Bank / Protocol GOG-0265
Nationwide Children's Hospital
700 Children's Dr, WA1340
Columbus, OH 43205
Phone: 614-722-2865
Fax: 614-722-2897
E-mail: gogbank@nationwidechildrens.org

Do not ship FFPE tissue for Saturday delivery.

B. Frozen Serum

Frozen serum should be shipped using the specimen kits provided to the GOG Tissue Bank (address above).

Frozen specimens should be shipped **Monday through Thursday for Tuesday through Friday delivery**. Do not ship frozen specimens on Friday or the day before a holiday. Note: Saturday delivery is not available for frozen specimens.

Frozen specimens should be stored in an ultra-cold freezing/storage space (i.e., ultra cold ≤-70ºC freezer, liquid nitrogen, or direct exposure with dry ice) until the specimens can be shipped.

Instructions for Shipping Frozen Specimens

Pre-fill the kit chamber about 1/3 full with dry ice.

Place the frozen specimens from each time point in a separate zip-lock bag.

Place the zip-lock bags in the biohazard envelope containing absorbent material. Do not put more than 25 vials in the biohazard envelope. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible before sealing both envelopes.

Place the Tyvek envelope containing the frozen specimens into the kit and fill the chamber to the top with dry ice.

Insert a copy of Form SP for each specimen.

Place the cover on top of the kit. Tape the outer box of the kit closed with filament or other durable sealing tape. Please do not tape the inner chamber.

Print a pre-paid FedEx air bill using the Kit Management application (found under Data Entry on the Web Menu page). Attach the air bill.

Attach the dry ice label (UN1845) and the Exempt Human Specimen sticker.

Arrange for FedEx pick-up through your usual Institutional procedure or by calling 800-238-5355.

IX. Distributing Translational Research Specimens

The GOG Statistical and Data Center and the GOG Tissue Bank will coordinate the distribution of specimens to approved investigators.

Investigators will not be given access to any personal identifiers.

Investigators will be responsible for the direct supervision and oversight of translational research and for keeping accurate records.

Investigators will ensure the results are linked to the appropriate specimen-specific identifiers and are responsible for transferring relevant laboratory data to the Statistical and Data Center.

At the discretion of the Chair of the Committee on Experimental Medicine and the Director of the GOG Tissue Bank, investigators may be required to ship any specimens (or by-products) remaining after the completion of the translational research to the GOG Tissue Bank.

A. FFPE (06/27/2016)

Unstained sections of tumor will be batch shipped upon trial completion to Advaxis:

Advaxis, Inc.
ATTN: Dr. Jun Zou
305 College Road East
Princeton, NJ 08540
Phone: 609-250-7502
Fax: 609-452-9818
Email: zou@advaxis.com

B. Frozen Serum

An aliquot of frozen serum will be batch shipped upon trail completion to Advaxis (address above).

X. Banking Translational Research Specimens for Future Research

Specimens will remain banked in the GOG Tissue Bank and made available for approved research projects if the patient has provided permission for the use of her specimens for future health research. The patient's choices will be recorded on the signed informed consent document and electronically via the online Specimen Consent Application. At the time of specimen selection for project distribution, the most recent consent information will be used.

GOG institutions can amend the patient's choices regarding the future use of her specimens at any time if the patient changes her mind.

If the patient revokes permission to use her specimens, the GOG Tissue Bank will destroy or return any remaining specimens. The patient's specimens will not be used for any <u>further</u> research; however, any specimens distributed for research prior to revoking consent cannot be returned or destroyed. In addition, the patient cannot be removed from any research that has been done with her specimens distributed prior to revoking consent.

Note: If return of specimens is requested, shipping will be at the institution's expense.

APPENDIX II- PATIENT DRUG CALENDAR – NAPROXEN or IBUPROFEN
(12/23/2013) (**06/27/2016**)

Visit Log is returned every four weeks

Patient Name: _____ Patient Study ID_____
Date: _____Infusion #: _____

This is a calendar to help you track when you have taken your naproxen or ibuprofen. Each time you return to your doctor's office for the next infusion, please bring this calendar with you and you will be provided with a new one. When taking the Naproxen OR ibuprofen it should be taken within 30 minutes before the ADXS11-001 dose, 4 hours after the infusion is completed then you can take Naproxen OR ibuprofen as needed. If you have any questions at any time please contact your study doctor's office.

Naproxen OR Ibuprofen	**AM Dose**	**PM Dose**
Day of ADXS11-001 Infusion	Time _____ (220mg/400 mg)	Time _____ (220mg/400mg)
Record any additional doses of Naproxen or Ibuprofen taken below:		
Date	Time	Dose (220mg/400mg)

APPENDIX III - PATIENT DRUG CALENDAR –
TRIMETHOPRIM/SULFAMETHOXAZOLE (BACTRIM) REGULAR STRENGTH
(12/23/2013) (06/27/2016)

(02/06/2012)

Visit Log is returned every four weeks

Patient Name: _____ Patient Study ID_____
Date: _____ Infusion #: _____

This is a calendar to help you track when you have taken your trimethoprim/sulfamethoxazole. You will take trimethoprim/sulfamethaxazole for a 7 day course after receiving the ADXS11-001 (Days 4-10). Each time you return to your doctor's office for the next infusion, please bring this calendar with you and you will be provided with a new one. . When taking the regular strength trimethoprim (80mg)/ sulfamethoxazole (400 mg), it should be taken once daily during the 7 day course. If you have any questions at any time please contact your study doctor's office.

	Date/Day of Week	**Time**
DAY 1 ADXS11-001 Infusion	**Date:** _____ **Day:** _____	
Trimethoprim-sulfamethoxazole Regular Strength1 tablet for 7 days		
Day 4 (post-infusion)	**Date:** _____ **Day:** _____	
Day 5 (post-infusion)	**Date:** _____ **Day:** _____	
Day 6 (post-infusion)	**Date:** _____ **Day:** _____	
Day 7 (post-infusion)	**Date:** _____ **Day:** _____	
Day 8 (post-infusion)	**Date:** _____ **Day:** _____	
Day 9 (post-infusion)	**Date:** _____ **Day:** _____	
Day 10 (post-infusion)	**Date:** _____ **Day:** _____	

APPENDIX IV - PATIENT DRUG CALENDAR –
TRIMETHOPRIM/SULFAMETHOXAZOLE (BACTRIM) DOUBLE STRENGTH (DS) **(06/27/2016)**

Visit Log is returned every four weeks

Patient Name: _____ Patient Study ID_____
Date: _____ Infusion #: _____

This is a calendar to help you track when you have taken your trimethoprim/sulfamethoxazole Double Strength (DS). You will take trimethoprim/sulfamethaxazole for a 3 days over 7 days after receiving the ADXS11-001 (Days 4-10). Each time you return to your doctor's office for the next infusion, please bring this calendar with you and you will be provided with a new one. . When taking the double strength trimethoprim (160mg)/ sulfamethoxazole (800 mg), it should be taken once daily on days 4, 7 and 10. If you have any questions at any time please contact your study doctor's office.

	Date/Day of Week	**Time**
DAY 1 ADXS11-001 Infusion	**Date: _____** **Day: _____**	
Trimethoprim-sulfamethoxazole Double Strength 1 tablet for 3 days		
Day 4 (post-infusion)	**Date: _____** **Day: _____**	
Day 7 (post-infusion)	**Date: _____** **Day: _____**	
Day 10 (post-infusion)	**Date: _____** **Day: _____**	

APPENDIX V - PATIENT DRUG CALENDAR – AMPICILLIN **(06/27/2016)**

This calendar is to be used for patients who are not able to receive trimethoprim/sulfamethoxazole

Visit Log is returned every four weeks

Patient Name: _____ Patient Study ID_____

Date: _____ Infusion #: _____

This is a calendar to help you track when you have taken your your ampicillin. You will take ampicillin for 7 days after receiving the ADXS11-001. Each time you return to your doctor's office for the next infusion, please bring this calendar with you and you will be provided with a new one. When taking the ampicillin, it should be taken four times a day. If you have any questions at any time please contact your study doctor's office.

	DATE/DAY of Week	**Time**	**Time**	**Time**	**Time**
DAY 1 ADXS11-001 Infusion	**Date: _____** **Day: _____**				
Ampicillim 500 mg 4 times a day for 7 days					
Day 4 (post-infusion)	**Date: _____** **Day: _____**				
Day 5 (post-infusion)	**Date: _____** **Day: _____**				
Day 6 (post-infusion)	**Date: _____** **Day: _____**				
Day 7 (post-infusion)	**Date: _____** **Day: _____**				
Day 8 (post-infusion)	**Date: _____** **Day: _____**				
Day 9 (post-infusion)	**Date: _____** **Day: _____**				
Day 10 (post-infusion)	**Date: _____** **Day: _____**				

APPENDIX VI – Post Study Treatment PATIENT DRUG CALENDAR –
TRIMETHOPRIM/SULFAMETHOXAZOLE (BACTRIM) REGULAR STRENGTH
(06/27/2016)

Post Study Treatment (6 month course)

Patient Name: _____ Patient Study ID_____

Date to begin 6-month antibiotic course: _____

This is a calendar to help you track when you have taken your trimethoprim/sulfamethoxazole after you have completed your treatment with ADXS11-001. When taking the regular strength trimethoprim (80mg)/ sulfamethoxazole (400 mg), it should be taken once daily during the 6-month course. If you have any questions at any time please contact your study doctor's office Each time you return to your doctor's office, please bring this calendar with you.

Trimethoprim/Sulfamethoxazole Regular Strength Patient Pill Calendar for 6 month post-treatment Prophylaxis

Trimethoprim/ Sulfamethoxazole daily	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Week 1	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 2	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 3	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 4	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 5	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 6	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:

Week 7	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 8	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 9	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 10	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 11	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 12	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 13	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 14	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 15	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 16	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 17	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 18	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:

Week 19	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 20	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 21	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 22	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 23	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:
Week 24	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:

APPENDIX VII **-**Post Study Treatment PATIENT DRUG CALENDAR – TRIMETHOPRIM/SULFAMETHOXAZOLE (BACTRIM**)** DOUBLE STRENGTH **(06/27/2016)**

Post Study Treatment (6 month course)

Patient Name: _____ Patient Study ID_____

Date to begin 6-month antibiotic course: _____

This is a calendar to help you track when you have taken your trimethoprim/sulfamethoxazole after you have completed your treatment with ADXS11-001. When taking the double strength trimethoprim (160mg)/ sulfamethoxazole (800 mg), it should be taken three times a week (every Monday, Wednesday and Friday) during the 6-month course. If you have any questions at any time please contact your study doctor's office Each time you return to your doctor's office, please bring this calendar with you.

Trimethoprim/Sulfamethoxazole Patient Pill Calendar for 6 month post-treatment Prophylaxis

Trimethoprim/ Sulfamethoxazole 3 times/ week	Monday	Wednesday	Friday
Week 1	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 2	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 3	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 4	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 5	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 6	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____

Week 7	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 8	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 9	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 10	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 11	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 12	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 13	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 14	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 15	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 16	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 17	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 18	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____

Week 19	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 20	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 21	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 22	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 23	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____
Week 24	Date: _____ Time: _____	Date: _____ Time: _____ -	Date: _____ Time: _____

APPENDIX VIII – Post Study Treatment PATIENT DRUG CALENDAR –AMPICILLIN
Post Study Treatment (6 month course) (06/27/2016)

(Ampicillin is to be used only for patients who cannot take sulfamethaxozole/trimethoprim)

Patient Name: _____ Patient Study ID_____

Date to begin 6-month antibiotic course: _____

This is a calendar to help you track when you have taken your ampicillin after you have completed your treatment with ADXS11-001. Each time you return to your doctor's office, please bring this calendar with you. When taking the ampicillin, it should be taken four times a day every day for 6 months. If you have any questions at any time please contact your study doctor's office.

Ampicillin 4 doses per day	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Week 1	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:
Week 2	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:
Week 3	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:

	Time:	Time:	Time:	Time:	Time:	Time:	Time:
Week 4	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:
Week 5	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:
Week 6	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:
Week 7	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:
Week 8	Date: Time: Time:	Date: Time: Time:	Date: Time: Time:	Date: Time: Time:	Date: Time: Time:	Date: Time: Time:	Date: Time: Time:

	Time: Time:	Time: Time:	Time: Time:	Time: Time:	Time: Time:	Time: Time:	Time: Time:
Week 9	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:
Week 10	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:
Week 11	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:
Week 12	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:
Week 13	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:

	Time: Time: Time:	Time: Time: Time:	Time: Time: Time:	Time: Time: Time:	Time: Time: Time:	Time: Time: Time:	Time: Time: Time:
Week 14	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:
Week 15	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:
Week 16	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:
Week 17	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:
Week 18	Date:	Date:	Date:	Date:	Date:	Date:	Date:

	Time: Time: Time: Time:	Time: Time: Time: Time:	Time: Time: Time: Time:	Time: Time: Time: Time:	Time: Time: Time: Time:	Time: Time: Time: Time:	Time: Time: Time: Time:
Week 19	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:
Week 20	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:
Week 21	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:
Week 22	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:

Week 23	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:
Week 24	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:	Date: Time: Time: Time: Time:

APPENDIX IX - GOG GENERAL CHEMOTHERAPY GUIDELINES (**06/27/2016**)

- For 21 or 28 day cycles, a patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.
- It will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window before and after the protocol-defined date" for "Day 1" treatment of 21 or 28 day cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (day 3 past due).
- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window," for example; "Day 8 chemotherapy" can be delivered on Day 7, Day 8, or Day 9 and "Day 15 chemotherapy" can be given on Day 14, Day 15, or Day 16.
- Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose).
- Chemotherapy doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for < 10% weight changes.