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PROTOCOL ADXS142-03

A PHASE 1-2 DOSE-ESCALATION AND SAFETY STUDY OF ADXS31-142 ALONE AND OF ADXS31-142 IN COMBINATION WITH PEMBROLIZUMAB (MK-3475) IN PATIENTS WITH PREVIOUSLY TREATED METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

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PEMBROLIZUMAB (MK-3475): 110080

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Amendment 8:	August 5, 2016
Amendment 9:	**April 21, 2017**

PROTOCOL APPROVAL

Protocol Number: ADXS142-03

Title of Protocol: A Phase 1-2 Dose-Escalation and Safety Study of ADXS31-142 Alone and of ADXS31-142 in Combination with Pembrolizumab (MK-3475) in Patients with Previously Treated Metastatic Castration-Resistant Prostate Cancer

Amendment 9: April 21, 2017

Prepared by:

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24-Apr-2017
Date

Approved by:

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[redacted] MD
Advaxis, Inc.

24 APR 2017
Date

INVESTIGATOR SIGNATURE PAGE

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

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

Investigator Name:

Signature	Date
PI Name (Printed)	Site #

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1 TRIAL SUMMARY

Abbreviated Title	Phase 1-2 Dose-Escalation and Safety Study of ADXS31-142 Alone and ADXS31-142 + Pembrolizumab (MK-3475) Combination Therapy in Patients with Previously Treated Metastatic Castration-Resistant Prostate Cancer (mCRPC)
Trial Phase	1-2
Clinical Indication	Previously treated mCRPC
Trial Type	Dose determining with expansion
Type of control	None
Route of administration	ADXS31-142 – IV; pembrolizumab (MK-3475) - IV
Trial Blinding	Open-label
Treatment Groups	ADXS31-142 monotherapy; ADXS31-142 + pembrolizumab (MK-3475) combination therapy
Number of trial subjects	Approximately 51
Estimated duration of trial	Approximately 7 years
Duration of Participation	Approximately 5 years

2 TRIAL DESIGN

2.1 Trial Design

This is a Phase 1-2, open-label, multicenter, dose-determining safety and tolerability study with a Phase 2 expansion cohort.

2.1.1 Part A – ADXS31-142 Monotherapy

Part A of the study will be an open-label, Phase 1, multicenter, non-randomized, dose-determining trial of ADXS31-142 monotherapy in subjects with metastatic castration-resistant prostate cancer (mCRPC). The dose-determining phase was intended to select a recommended Phase 2 dose (RP2D) of ADXS31-142 for Part B. The starting dose level of ADXS31-142 monotherapy is 1 x 10^9 colony forming units (cfu) (DL 1) (Table 6). The study was originally designed to evaluate higher dose cohorts as well dose 5 x 10^9 cfu, 1 x 10^{10} cfu. Based on safety data from other Advaxis trials that use similar constructs, it was decided that escalation to 5 x 10^9 cfu or 1 x 10^{10} cfu would no longer be included in this study design. This is based on overall review of the safety data across the *Lm*-based program of clinical trials, which established that the starting dose of 1 x 10^9 cfu is more tolerable than higher doses. Up to 21 subjects will be entered (with a minimum of 6 subjects treated at the recommended dose before proceeding to the next phase). After consultation with the Sponsor and investigator, the RP2D of ADXS31-142 will be selected.

2.1.2 Part B – ADXS31-142 + Pembrolizumab (MK-3475) Combination Therapy

Part B of the study will be an open-label, Phase 1-2, multicenter, non-randomized dose-determining trial of ADXS31-142 in combination with pembrolizumab (MK-3475) in subjects with mCRPC. Part B will consist of a dose-determination phase followed by an expansion cohort phase. The dose-determining phase is intended to select a RP2D for the combination. A modified 3+3 design will be used to determine the dose of ADXS31-142 in combination with pembrolizumab (MK-3475).

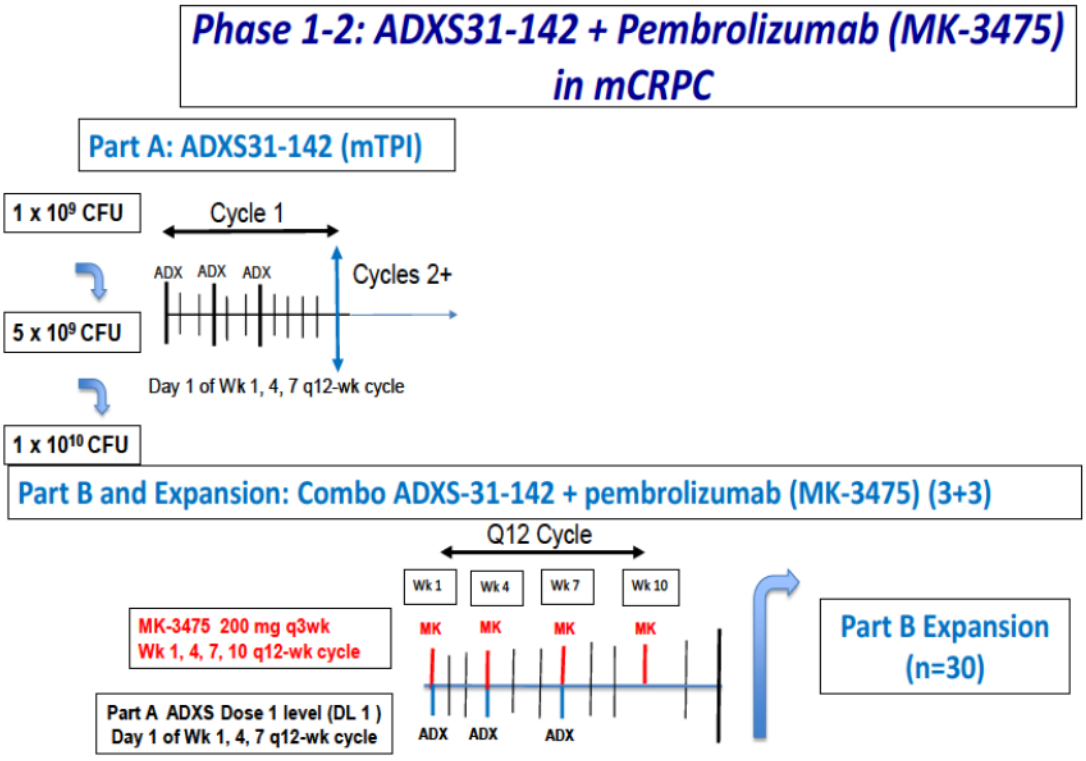
During the dose-determining stage, subjects will be entered at a dose of 1×10^9 of ADXS31-142 (see Table 7) in combination with pembrolizumab (MK-3475) at 200 mg. If this dose combination is not tolerable, then Dose Level -1 at a dose of 0.5×10^9 of ADXS31-142 in combination with pembrolizumab (MK-3475) at a dose of 200 mg will be evaluated. Dose-determination will continue until identification of a recommended RP2D for the combination to be used in the expansion cohort. A minimum of 6 subjects will be treated at the RP2D before initiating the expansion cohort.

The expansion cohort will be open for enrollment once the RP2D of ADXS31-142 in combination with pembrolizumab (MK-3475) is selected in the Part B dose-determination phase. Further assessment of the RP2D will be explored in up to 30 subjects with mCRPC to evaluate the safety and clinical activity of ADXS31-142 in combination with pembrolizumab (MK-3475).

Adverse events will be monitored from the time informed consent is obtained and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version (v) 4.03.

Treatment with ADXS31-142 or ADXS31-142 in combination with pembrolizumab (MK-3475) will continue until documented disease progression, unacceptable adverse event(s) (AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, subject experiences a complete response and receives one additional cycle of treatment, noncompliance with trial treatment or procedure requirements, completion of 24 months of treatment with ADXS31-142 and pembrolizumab (MK-3475), or administrative reasons. Subjects who attain an investigator-confirmed irCR, after receiving at least 2 cycles of therapy, may consider stopping pembrolizumab (MK-3475) and continue treatment with ADXS31-142 only. In addition, all subjects will participate in a 3-year *Lm* Surveillance Monitoring period. Subjects who discontinue treatment for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating other anti-cancer treatment, withdrawing consent, becoming lost to follow-up, or until the Sponsor ends the study (Refer to Section 7.1.5.3). The primary objectives of the trial are to establish a maximum tolerated dose (MTD) or maximum allowable dose (MAD) and to determine safety and tolerability of ADXS31-142 in combination with pembrolizumab (MK-3475) in subjects with mCRPC.

2.2 Trial Design



3 OBJECTIVES & HYPOTHESES

3.1 Primary Objectives & Hypotheses

Objective: Part A: to evaluate safety and tolerability of ADXS31-142 monotherapy and select the RP2D in subjects with mCRPC

Hypothesis: ADXS31-142 monotherapy has acceptable safety and tolerability in subjects with mCRPC

Objective: Part B: to evaluate safety and tolerability of ADXS31-142 in combination with pembrolizumab (MK-3475) and to establish the RP2D for this combination in subjects with mCRPC

Hypothesis: ADXS31-142 + pembrolizumab (MK-3475) combination therapy has acceptable safety and tolerability in subjects with mCRPC

3.2 Secondary Objectives

Objective: to evaluate anti-tumor activity and progression free survival (PFS) signal of ADXS31-142 monotherapy and ADXS31-142 + pembrolizumab (MK-3475) combination therapy using RECIST 1.1, immune-related Response Evaluation Criteria in

Solid Tumors (irRECIST) and Prostate Cancer Working Group 2 (PCWG2) criteria [38] to inform design of a subsequent randomized Phase 2 trial

3.3 Exploratory Objective

Objective: [redacted]

Objective: [redacted]

Objective: [redacted]

4 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 ADXS31-142 Immunotherapy

ADXS31-142 is a live attenuated *Listeria monocytogenes* (*Lm*)-LLO immunotherapy developed for the treatment of prostate cancer. ADXS31-142 is bioengineered to secrete an antigen-adjuvant fusion protein (tLLO-PSA) consisting of a truncated fragment of the listeriolysin (tLLO) fused to human PSA.

Advaxis' *Lm*-LLO immunotherapy vectors actually infect the antigen-presenting cells (APCs) and secrete listeriolysin O (LLO)-tumor antigen fusion proteins within the cytoplasm of the APC thereby allowing the generation of a new population of tumor antigen-specific cytotoxic T lymphocytes (CTLs) driven by the adjuvant properties of LLO. These tumor-specific CTLs can then take advantage of the acute immunologic response to the live vector to facilitate infiltration into the tumor, enabling them to access and destroy tumor cells.

The advantages that *Lm* possesses as a 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 [1]. *Listeria* preferentially infects APCs, and unlike other intracellular bacteria like *Salmonella*, *Listeria* escapes 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. *Listeria* has other useful properties, such as stimulating monopoiesis, stimulating the differentiation and maturation of APCs, and the generation of a particularly strong innate and

adaptive cellular immune response [2]. The ability to deliver antigen to the cytosolic compartment of APCs in order to develop human leukocyte antigen Class I presentation to induce CD8+ cytotoxic T-cell responses appears to be an important aspect of developing an effective therapeutic anti-tumor therapy. Peptides derived from *Lm* in the phagolysosome and the cytosol can be presented by both the major histocompatibility complex (MHC) Class I and Class II molecules, inducing both CD4+ and CD8+ T cell responses. 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* vectors that secrete an LLO-antigen fusion, but not those that secrete only an antigen, to diminish regulatory T-cells (Tregs) within the tumor, but not in the spleen or normal peripheral tissues [3, 4].

4.1.1.2 Anti-PD-1 Antibody Pembrolizumab (MK-3475)

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator brochure.

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [39]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and prognosis in various malignancies [40-52]. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells seem to correlate with improved prognosis and long-term survival in many solid tumors [48, 53-61].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control [60]. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD L2) . The structure of murine PD-1 alone and in complex with its ligand were first resolved [61], and more recently the NMR-based structure of the human PD-1 extracellular region and analysis of its interactions with its ligands were also reported [62]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail, which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70, which are involved in the CD3 T-cell signaling cascade 63]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 64]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and

CD8+ T-cells, B-cells, Tregs and Natural Killer cells 62]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells [66], as well as subsets of macrophages [67] and dendritic cells [68].

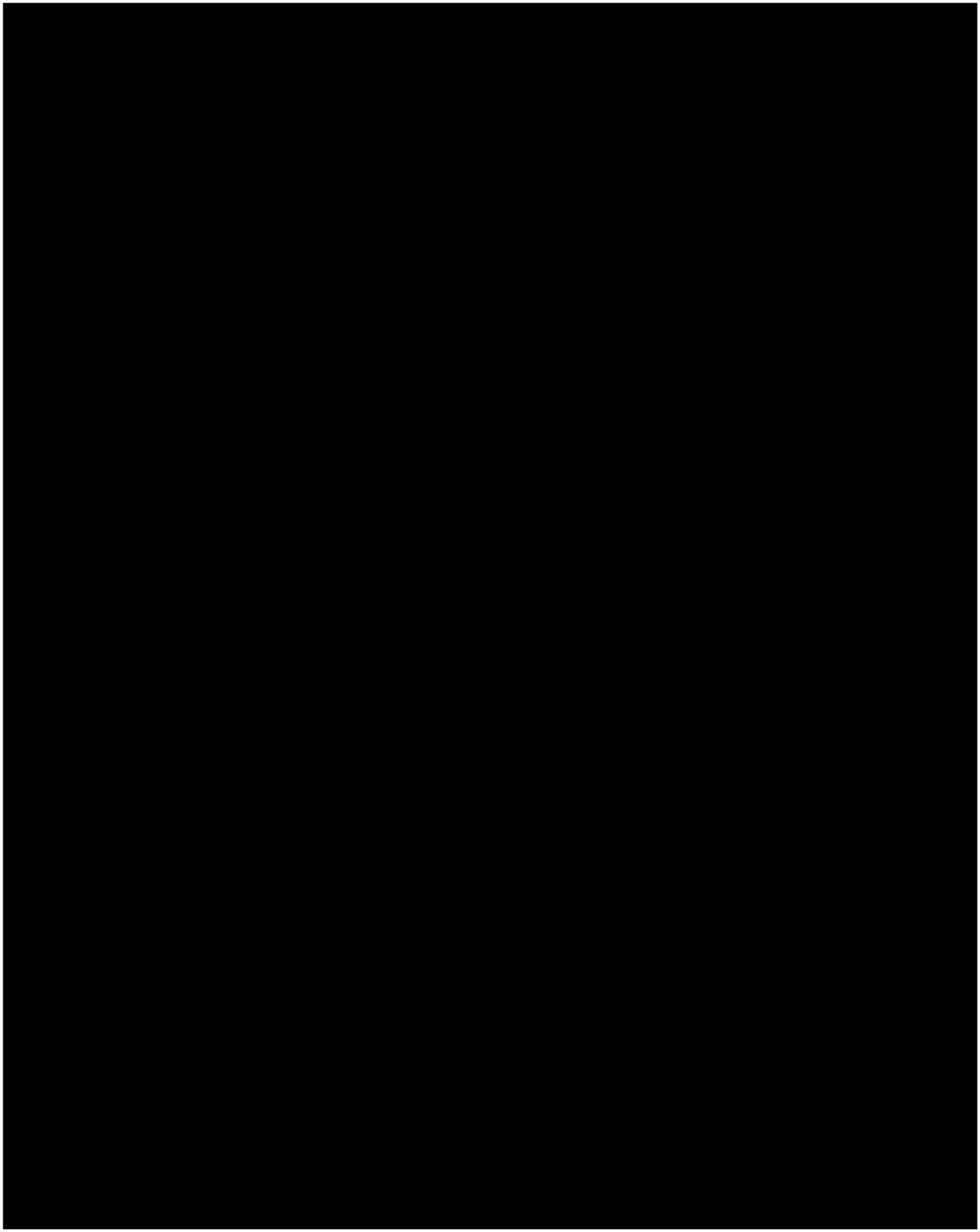
The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types [69] PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells (APCs) found in lymphoid tissue or chronic inflammatory environments [69]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the T cell receptor. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [5]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor [70,71], which, via its interaction with the PD-1 receptor on tumor specific T cells, plays a critical role in immune evasion by tumors [72]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer [73].

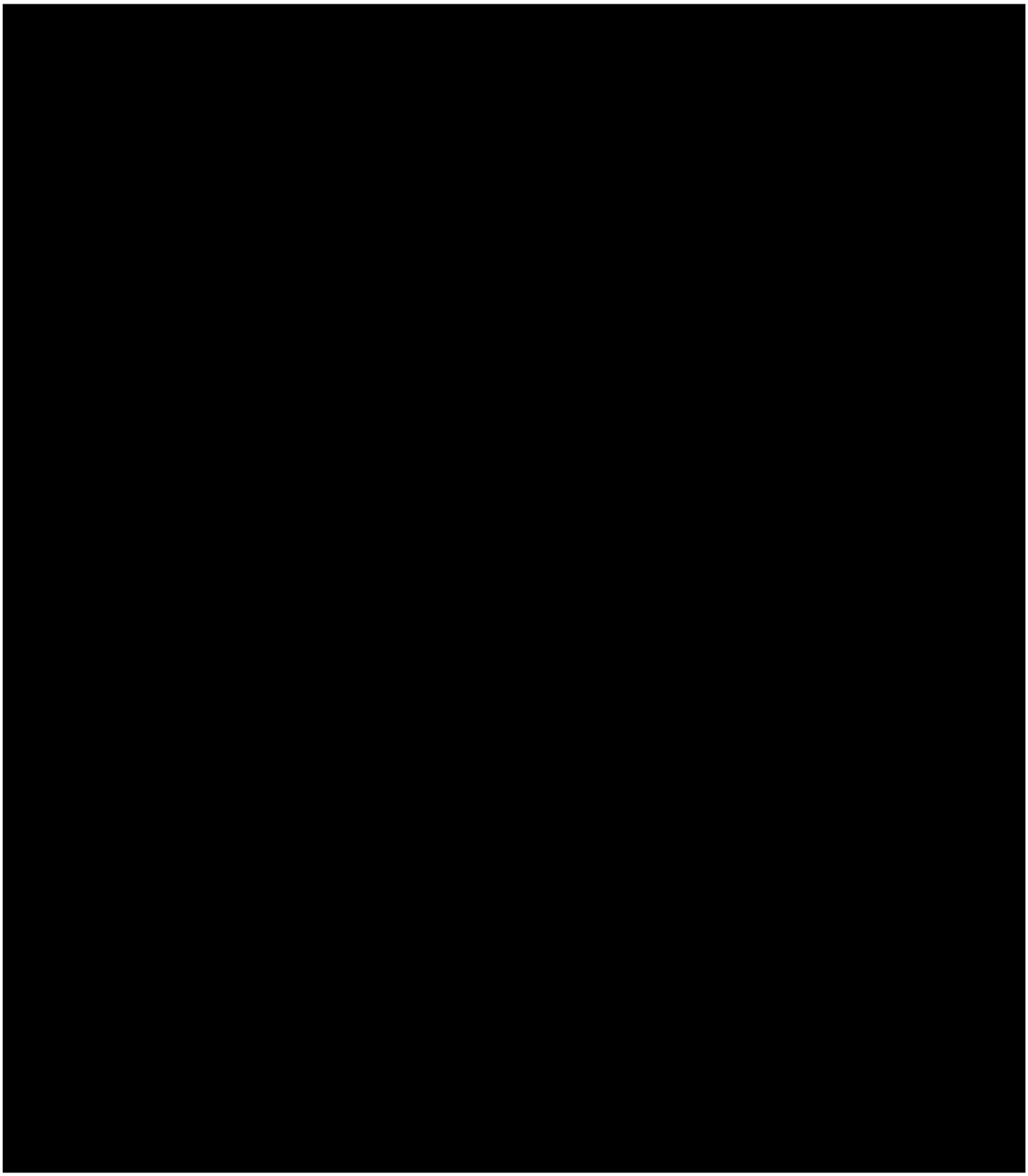
4.1.2 Preclinical and Clinical Trial Data

Refer to the respective IB for preclinical and clinical data.

4.1.3 Summary of Safety of ADXS31-142 based on ADXS11-001

Because *Lm*-LLO immunotherapies are based on a common platform technology and are engineered and manufactured in a similar manner, the clinical safety information obtained to date for ADXS11-001, another *Lm*-LLO immunotherapy for the treatment of HPV-associated cancers, may be helpful in appreciating any toxicity due to ADXS31-142. As of February 2015 clinical safety data, ADXS11-001 has been administered to 230 enrolled subjects. [redacted]





4.1.4 Delayed/Late Listeria Infection

[redacted]

[redacted] 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 5.6.1.9 "Listeria Infection Identification and Management".

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Prostate cancer has characteristics that make immunotherapy attractive. First, there are many tumor-associated antigens such as PSA, prostatic acid phosphatase (PAP), and prostate-specific membrane antigen (PSMA) that are cancer-specific or prostate tissue-specific. Second, the

prostate is a dispensable organ. Therefore, elimination of all prostate cells would not interfere significantly with major organ function or general quality of life (post-castration) and any potential autoimmunity to prostate cells generated from immunotherapy would not impact patient safety. Third, there is evidence that prostate cancer is an immunologically "visible" disease. Spontaneous autoantibodies, as shown by phage protein microarrays, indicate that a nascent immune response may be already present, with the potential to be amplified [26]. It has been reported that initiation of chemical castration may result in lymphocyte infiltration into prostate tissue. Sipuleucel T, an immunotherapy directed against PSMA has recently been shown to improve the survival of men with prostate cancer. Eugene Kwon and others have reported anecdotal observation of a downstaging of prostate cancer in men with locally advanced non-resectable disease treated with ipilimumab [27]. Lastly, prostate cancer tends to be a slow-growing disease. Since immunotherapy relies on the generation, proliferation, and infiltration of effector cells and is not directly cytotoxic to tumors, it takes time to begin to see tumor shrinkage in response to immunotherapy. A modest rate of disease progression could allow more time to generate an antitumor immune response and reduce immunosuppressive factors before the tumors cause clinical deterioration of the patient [3, 28].

Immunologic checkpoints are involved in limiting (or shutting down) the magnitude of an immune response by controlling the numbers and activation state of lymphocytes involved in an immune response. Signaling through binding of the PD-1 receptor to PD-L1 causes deactivation of lymphocytes, including CD8+ T-cells. PD-1 to PD-L1 binding is a significant component of peripheral tolerance and normally functions to protect tissues from "bystander" damage during an inflammatory event. However, when PD-L1 is expressed by tumor cells, it can prevent tumor-specific T-cells from killing malignant cells by shutting down their activity and sometimes triggering apoptosis of the CTLs.

While PD-1 blocking strategies have shown good clinical promise, there are still some shortcomings. In current PD-1 clinical trials, there is no study where more than 50% of patients can benefit from PD-1 binding inhibition, and in diseases where it works best, most response rates are the range of 20-40%, missing the majority of patients. One potential reason that PD-1 binding blockade might not be effective for a larger proportion of patients is that the needed tumor-specific cytotoxic cells were not generated in the first place. In this case, "opening up" the checkpoint will have no effect because there are no effector cells held-up at that checkpoint. Another, and potentially less "solvable", reason is that peripheral tolerance mediated by immune checkpoints is not the only mechanism of immunologic tolerance that can protect tumors from cellular immunity. Many solid tumors are also protected by mediators of central tolerance which include Tregs and myeloid derived suppressor cells (MDSCs). In this case, activated T-cells that make it past PD-L1 on the surface of tumors then infiltrate the tumor microenvironment only to be shut down by inhibitory exocrine factors from Tregs and MDSCs which include IL-10, IL-9, TGF beta, arginase, and inducible nitric oxide synthase, respectively. These factors result in anergy of the activated T-cells within the tumor microenvironment.

Essentially, the limited effectiveness of PD-1 treatment in the majority of cancer patients can be attributed to either the inability to generate tumor specific CTLs that do not already exist, and/or the inability for PD-1 blockade to have any impact on Tregs and MDSCs that reside within and protect the tumor microenvironment. However, if one could combine PD-1 blockade with a

treatment that ensures tumor reactive T-cells are generated and present, and also reduce or eliminate the effects of central tolerance mediated by Tregs and MDSCs in the tumor microenvironment, a significantly larger proportion of patients could be effectively treated in diseases where PD-1 blockade has shown weak or little activity. Additionally, by combining synergistically with an agent that reduces Tregs and MDSCs within tumors, PD-1 blockade could also contribute to activity in diseases which are currently protected solely by central tolerance and where PD-1 has not historically been active. These diseases may include prostate cancer, ovarian cancer and others. This combination could improve the activity of PD-1 where it has activity, and also create additional utility in diseases where PD-1 blockade appears to have little effect as a monotherapy.

The Advaxis *Lm*-LLO immunotherapy vectors are a unique technology that is proving to be effective as monotherapy in some notoriously resistant malignancies. Furthermore, this system is truly a platform and over 20 different tumor antigen-specific vectors have already been created. Unlike most therapeutic vaccines, this system generates a powerful and almost exclusive cellular immunity against the tumor target of interest in the setting of a systemic immune response to a potential pathogen. This response has been shown to increase the expression of PD-L1 on tumors as well as PD-1 expression on T-cells. These vectors shift the immunotope to a TH-1 phenotype and are associated with upregulation of chemokines and chemokine receptors thereby facilitating extravasation and infiltration of CD8+ T-cells into tumors. Perhaps the most significant aspect of ADXS31-142 treatment is the tumor microenvironment specific down-regulation of the relative number and function of both Tregs and MDSCs that mediate central tolerance, protecting the tumor microenvironment thereby allowing infiltrating CD8+ T-cells to kill tumor antigen expressing target cells in the tumors.

Simply stated, the Advaxis vector can ensure there is a fresh supply of tumor specific CTLs and at the same time, neutralize Tregs and MDSCs in the tumor microenvironment, enabling T-cells to kill tumor cells without restriction.

A recent publication from of the laboratory of Samir Khleif has demonstrated, in an animal model, the synergistic activity of combination Advaxis *Lm*-LLO-TAA treatment with a PD-1 blocking antibody active in both mouse and man [29]. His data demonstrate that these 2 treatments are complementary technologies. The Advaxis *Lm*-LLO immunotherapy generates TAA specific T-cells and neutralizes Tregs and MDSCs in the tumor microenvironment, and PD-1 antibody over-rides the inhibitory effects of PD-1 ligand binding which results in a significantly larger number of tumor antigen specific T-cells to fight against the cancer. This combination significantly improves the efficacy of the treatment over either monotherapy, resulting in significant improvement in survival.

Treatment of prostate cancer with a dendritic-cell based immunotherapy, Provenge (Dendreon) has been demonstrated to improve long-term survival in men with CRPC and has been approved by the United States (US) Food and Drug Administration (FDA). This suggests that immunotherapy can be effective against CRPC. Unfortunately, Provenge has not been associated with an objective tumor response and appears to slow progression of CRPC in some patients. ADXS31-142 has demonstrated significant PSA-specific antitumor activity in animal models including the clearance of existing tumors and preventing the progression of implanted

tumors. [redacted]

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 ADXS31-142 Dose Selection

ADXS31-142 has not been administered to any human subject prior to this clinical trial. [redacted]

ADXS31-142 is a live attenuated Gram Positive bacterial immunotherapy vector. Adverse events (AEs) with this class of agents seem to be directly related to innate immune effects associated with the infusion of the live attenuated bacteria. These typically consist of certain flu-like and CRS symptoms that are almost exclusively low grade, typically appear in 2-4 hours of infusion, and have not been either cumulative or associated with any delayed onset symptoms, including potential autoimmune symptoms. These symptoms typically self-resolve, or respond readily to symptomatic treatment. The symptoms appear to be related to the number of cfu infused over time. Pre-treatment with oral NSAIDs and antiemetics seems to reduce the incidence of these symptoms.

There is no specific target blood level that needs to be achieved in order for ADXS31-142 to be effective in order to compete with a target or bind to a receptor; therefore, maximum concentration (C_{max}), minimum concentration (C_{min}), and half-life of ADXS31-142 are not relevant beyond the clinical observation of a maximum tolerated cfu. In the current trial, the high dose limit of 1×10^{10} cfu was imposed.

[redacted]

[redacted]

4.2.2.2 Pembrolizumab (MK-3475) Dose Selection

The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W. The dose recently approved in the United States and several other countries for treatment of melanoma subjects is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

KEYNOTE-001 was an open-label Phase I study conducted to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD), and anti-tumor activity of pembrolizumab when administered as monotherapy. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg and 10 mg/kg, administered every 2 weeks (Q2W) and dose expansion cohorts evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no dose-limiting toxicities were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No maximum tolerated dose (MTD) has been identified. In addition, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and one randomized cohort evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg every 3 weeks (Q3W) is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.

A population pharmacokinetic (PK) model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. Pharmacokinetic properties of pembrolizumab, and specifically the weight-dependency in clearance and volume of distribution are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at tested doses among tumor types. Thus, the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate dose for pembrolizumab.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The efficacy endpoints to be used in this study [redacted] for prostate cancer, scans, and measurable and evaluable disease assessments) are those typically used to assess anti-tumor activity of mCRPC.

4.2.3.2 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of ADXS31-142 alone and in combination with pembrolizumab (MK-3475) in subjects with mCRPC. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received ADXS31-142 alone and in combination with pembrolizumab (MK-3475), including serious adverse events (SAEs) and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE v 4.03. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, laboratory changes and *Lm* Surveillance Monitoring.

[redacted]

5 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

The study will be conducted in male subjects with histologically confirmed mCRPC who have progressed or become resistant to no more than 2 prior systemic treatment regimens with chemotherapy, targeted therapies, radiopharmaceuticals, or immunotherapy in the metastatic setting. Hormonal treatment will not be considered when determining the number of prior regimens in the metastatic setting. Subjects cannot have had more than 1 prior chemotherapeutic regimen in the metastatic setting. Subjects with evidence of progressive bone or other metastases are acceptable. Subjects may remain on castration therapy (luteinizing-hormone-releasing hormone [LHRH] agonist or antagonist) during the trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent for the trial.

2. Be ≥18 years of age on day of signing informed consent.

3. Have progressive metastatic castration resistant prostate cancer, on androgen deprivation therapy, based on as least one of the following criteria:

   a. PSA progression defined as 25% increase over baseline value with an increase in the absolute value of at least 2 ng/mL that is confirmed by another PSA level with a minimum of a 1-week interval with a minimum PSA of 2 ng/ml.

   b. Progression of bi-dimensionally measurable soft tissue (nodal metastasis) assessed within 1 month prior to registration by a CT scan or MRI of the abdomen and pelvis (please refer to Section 7.1.2.5.1 for definitions of measurable disease).

c. Progression of bone disease (evaluable disease) (new bone lesion(s)) by bone scan. (Please refer to Section 7.1.2.5.1 for definitions of evaluable disease).

4. Has discontinued antiandrogens (bicalutamide, nilutamide) >6 weeks and enzalutamide or abiraterone >4 weeks prior to Day 1 of trial treatment

5. Have a performance status of 0 or 1 on the ECOG Performance Scale.

6. Demonstrate adequate organ function as defined in Table 3. All screening labs should be performed within 28 days of treatment initiation.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematologic	
Absolute neutrophil count (ANC)[a]	≥1000 /mcL
Platelets[a]	≥75,000 / mcL
Hemoglobin[a]	≥9 g/dL or ≥5.6 mmol/L
Lymphocytes	≥500 / mcL
Renal	
Serum creatinine **OR** Measured or calculated[b] creatinine clearance (CrCl) (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥50 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤2.5 X ULN **OR** ≤5 X ULN if liver metastases are present
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or INR is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as aPTT is within therapeutic range of intended use of anticoagulants

[a] ANC, Platelets and Hemoglobin requirements cannot be met by use of recent transfusion or growth factor support (G-CSF, erythropoietin, etc) within 2 weeks prior to treatment initiation
[b] Creatinine clearance should be calculated per institutional standard.

7. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days (approximately 4 months) after the last dose of study therapy.

5.1.3 Subject Exclusion Criteria

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

1. Received more than 2 prior systemic treatment regimens with chemotherapy, targeted therapy, radiopharmaceuticals, or immunotherapy in the metastatic setting or received more than 1 prior chemotherapeutic regimen in the metastatic setting.

2. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

3. Has a diagnosis of immunodeficiency or is receiving any systemic steroid therapy, abiraterone acetate, other androgen synthesis inhibitors or any form of immunosuppressive therapy within 7 days prior to Day 1 of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

4. Has had a prior monoclonal antibody or autologous cellular immunotherapy within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier.

   - Note: Subjects currently receiving denosumab are an exception and may qualify, however introduction of denosumab is not allowed while on study.

5. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤Grade 1 or at baseline) from AEs due to a previously administered agent.

   - Note: Subjects with ≤Grade 2 neuropathy are an exception to this criterion and may qualify for the study with Sponsor approval.

6. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin; squamous cell carcinoma of the skin or superficial urothelial cancer 2 years post therapy.

7. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

8. Has an active autoimmune disease requiring systemic treatment within the past 3 months (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

   - Note: Subjects with vitiligo or resolved childhood asthma/atopy may be allowed with Sponsor approval.

   - Note: Subjects who require intermittent use of inhaled steroids, bronchodilators or local steroid injections may be allowed with Sponsor approval.

   - Note: Subjects with hypothyroidism stable on hormone replacement or Sjogrens syndrome may be allowed with Sponsor approval.

9. Has evidence of interstitial lung disease or current pneumonitis or a history of (non-infectious) pneumonitis that required steroids.

10. Has an active infection requiring systemic therapy. Prior to dosing with ADXS31-142, the subject must be at least 5 half-lives from their last dose of antibiotic.

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

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

13. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or if the subject has previously participated in a Merck MK-3475 clinical trial. (Not applicable in enrollment to Part A)

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

15. Has a history of hepatitis B or hepatitis C.

16. Has received a live vaccine within 30 days prior to Day 1 of trial treatment.

17. 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.

18. Patients who are currently receiving or who have received any PI3K within 30 days prior to registration.

19. Any currently requiring or anticipated to require 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) during study therapy administration and within 30 days of the last dose of study therapy.

20. Has a contraindication to administration of trimethoprim/sulfamethoxazole **and** ampicillin.

21. Has contraindication to administration of NSAIDS.

22. Has undergone major surgery within 6 weeks prior to the initiation of ADXS31-142 treatment. NOTE: All toxicities and/or complications must have recovered to baseline or Grade 1 prior to the initiation of ADXS31-142 study therapy. Sponsor must be contacted prior to enrolling subjects on the study who recently had major surgery or have new artificial implant, and/or devices.

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

24. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

5.2 Trial Treatments

The treatments to be used in this trial are outlined below in Table 4. Trial treatment should begin within 5 days of eligibility confirmation.

Table 4 Trial Treatments

Drug	Dose	Route of Administration	Regimen
ADXS31-142	0.5 x 10^9, 1 x 10^9, 5 x 10^9, or 1 x 10^{10} cfu	IV infusion	Day 1 of Wks 1, 4 and 7, Q12W cycle
Pembrolizumab (MK-3475)	200 mg	IV infusion	Q3W

5.2.1 Dose Selection/Modification

The doses to be used in each part of the trial are described below.

5.2.1.1 Dose Selection

The rationale for the ADXS31-142 starting dose and the pembrolizumab (MK-3475) fixed dose are discussed in Section 4.2.2. In Part A of the trial, the study was originally designed to include

dose-escalation/de-escalation with the decisions based on interim safety data review or pre-defined DLT criteria (Section 5.2.1.1.1 – Dose Limiting Toxicity Criteria) and be based on 3 dosing intervals (below RP2D, at RP2D, or above RP2D) according to a mTPI with precalculated decisions that can easily be referred to (Table 5) [30, 31]. The TPI method would provide for exposure to fewer subjects to toxic doses above the MTD and yield similar probabilities in identifying the correct MTD, even when the sample size is matched [31]. A minimum of 3 subjects will be evaluated in each cohort before dose-escalation decisions are made. Table 5 consists of all the dose-escalation rules for the trial. If the toxicity rate of the currently used dose level is within the "under dosing" interval, the mTPI design recommended escalating the dose level; in the case of proper dosing, this design would recommend continuing at the current dose; for cases where toxicities indicate "over dosing", the mTPI design would recommend de-escalating the dose level. As dosing was not determined based on this study alone, it was decided that escalation to 5×10^9 cfu or 1×10^{10} cfu would no longer be included in this study design. This is based on overall review of the safety data across the *Lm*-based program of clinical trials which determined that the starting dose would be 1×10^9 cfu. At the RP2D level in Part A up to 10 subjects may be enrolled. The Sponsor reserves the right to add additional subjects in order to further evaluate safety and tolerability. All decisions on dose-escalation and dose de-escalation will be made by the Sponsor only after discussions between Sponsor and Investigators have occurred.

Table 5 Dose Decisions for ADXS31-142 Monotherapy (Targeted DLT Rate = 25%)

The table is based on a sample size of 21 subjects. Two parameters epsilon1 and epsilon2 are set at default values [30] of 0.05. X-axis is number of subjects treated at current dose; y-axis is number of toxicities.

mTPI Decision Table

Sample Size = 21 ; Target Toxicity Probability = 0.25 ; epsilon 1 = 0.05 ; epsilon 2 = 0.05

ESCALATE **STAY** **DE-ESCALATE** **UNACCEPTABLE**

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2		DU	D	D	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E
3			DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	E	E
4				DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S
5					DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S
6						DU	DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S
7							DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S
8								DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S
9									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
10										DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
11											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
12												DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
13													DU	DU	DU	DU	DU	DU	DU	DU	DU
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17																	DU	DU	DU	DU	DU
18																		DU	DU	DU	DU
19																			DU	DU	DU
20																				DU	DU
21																					DU

In the dose determining phase of Part B, dose-de-escalation will follow a modified 3+3 design as detailed in Section 5.2.1.1.3. At the RP2D level in Part B at least 6 subjects will be enrolled. All decisions on dose de-escalation will be made by the Sponsor only after discussions between Sponsor and Investigators have occurred.

5.2.1.1.1 Dose Limiting Toxicity Criteria

The same DLT criteria will be utilized for study Part A and Part B. All toxicities will be graded using CTCAE v 4.03. The DLT window of observation will begin at the administration of the initial dose of ADXS31-142 and end 1 week following the second dose of ADXS31-142. The occurrence of any of the following toxicities will be considered a DLT, if judged by the investigator to be possibly, probably or definitely related to study treatment administration. Treatment modifications for DLT are shown in Table 8 and Table 9.

General:

1. Prolonged delay (>2 weeks) in initiating the second dose due to treatment-related toxicity

2. Missing the second dose of ADXS31-142 or pembrolizumab (MK-3475) as a result of AE(s) during the first cycle.

Hematologic:

1. Grade 4 hematologic toxicity.

2. Febrile neutropenia, defined as absolute neutrophil count (ANC) < 1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour.

3. Grade 3 thrombocytopenia lasting >72 hours.

4. Grade 4 thrombocytopenia.

Non-Hematologic:

1. ≥ Grade 3 non-hematologic toxicity, (excluding nausea, vomiting and/or diarrhea lasting <3 days and reversible with medical intervention).

2. Grade 3 non-hematologic laboratory value that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management (excluding transient Grade 3 laboratory value abnormalities reversible within 5 days and without medical intervention).

3. Listeremia: positive blood culture(s) along with persistent (for 72 hours post dose) symptoms consistent with listeremia (e.g., fever and muscle aches, often preceded by diarrhea or other gastrointestinal symptoms).

4. ≥ Grade 3 flu-like or cytokine release symptoms that persist for >24 hours after ADXS31-142 administration despite symptomatic treatment (Refer to Section 7.2.3.2).

Subjects who experience a DLT at Dose Level -1 of 0.5 x 10^9 will be discontinued from study treatment. However, subjects who experience a DLT at DL 1 of 1 x 10^9 may be eligible to receive ADXS31-142 at a lower dose level for subsequent doses and cycles following discussion and agreement between the Investigator and Sponsor.

5.2.1.1.2 Part A – ADXS31-142 Monotherapy

Part A of the trial completed. The ADXS31-142 monotherapy doses that were to be used in this trial are outlined below in Table 6. The starting dose level of ADXS31-142 monotherapy in Part A is 1 x 10^9 cfu (DL 1). The dose was to be escalated, remain the same or be de-escalated based on interim safety data review from other Advaxis trials at a particular dose level or according to pre-defined DLT criteria (see Section 5.2.1.1.1) in accordance with the mTPI design (see Table 5), and after consultation with the Sponsor and Investigator, until the RP2D is selected. However, based on safety data from other Advaxis trials that use similar constructs, it was decided that escalation to 5 x 10^9 cfu or 1 x 10^{10} cfu would no longer be included in this study design. This is based on overall review of the safety data across the Lm-based program of clinical trials, which established that the starting dose of 1 x 10^9 cfu is more tolerable than higher doses.

Table 6 ADXS31-142 Monotherapy Doses to be used in Part A

Dose Level	Dose	Route of Administration	Regimen
1	1 x 10^9 cfu	IV infusion	Day 1 of Weeks 1, 4 and 7 of 12-week cycle
2	5 x 10^9 cfu	IV infusion	Day 1 of Weeks 1, 4 and 7 of 12-week cycle
3	1 x 10^{10} cfu	IV infusion	Day 1 of Weeks 1, 4 and 7 of 12-week cycle
-1	.5 x 10^9 cfu	IV infusion	Day 1 of Weeks 1, 4 and 7 of 12-week cycle

5.2.1.1.3 Part B – ADXS31-142 + Pembrolizumab (MK-3475) Combination Therapy

Part B consists of a modified 3+3 design to identify a recommended RP2D of the combination which will be used in the Part B expansion phase. The starting ADXS31-142 dose for Part B will be the RP2D determined in Part A. For example, if 1 x 10^9 cfu is determined to be the RP2D in Part A then that will be the starting dose. The ADXS31-142 dose will not be escalated in Part B. However, if the ADXS31-142 dose of 1 x 10^9 cfu (Dose Level 1) isn't tolerable in combination, then the dose of ADXS31-142 will be de-escalated to a dose of 0.5 x 10^9 cfu (Dose Level -1) in combination with pembrolizumab (MK-3475) 200 mg.

Interim safety data review and/or DLTs observed at the first dose level will be used to determine the need for de-escalation to the next lower dose level. Determination to dose de-escalate will be made according to a modified 3+3 design as follows:

An initial cohort of 3 subjects will be enrolled at doses of ADXS31-142 1 x 10^9 cfu in combination with pembrolizumab (MK-3475) 200 mg.

- If 0/3 subjects develop a DLT,
  - Another 3 subjects will be enrolled at this dose level.
    - If 0, 1 or 2 of the 3 new subjects develops a DLT (for a total of 0/6, 1/6 or 2/6 subjects with a DLT at this dose level), the current dose will be considered the RP2D and the trial will proceed to the dose expansion stage.
    - If 3 of the 3 new subjects develop a DLT (for a total of 3/6 subjects with a DLT at this dose level), the dose will be de-escalated to DL -1 and a dose of ADXS31-142 0.5 x 10^9 will be administered in combination with pembrolizumab (MK-3475) 200 mg.
- If 1/3 subjects develop a DLT,
  - Another 3 subjects will be enrolled at this dose level.
    - If 0 or 1 of the 3 new subjects develops a DLT (for a total of 1/6 or 2/6 subjects with a DLT at this dose level), the current dose will be considered

the recommended MTD, and the trial will proceed to the dose expansion stage.

- If >1 of the 3 new subjects develop a DLT (for a total of >2/6 subjects with a DLT at this dose level), the dose will be de-escalated to DL -1 of ADXS31-142 0.5 x 10^9 in combination with pembrolizumab (MK-3475) 200 mg.

- If 2/3 or 3/3 subjects develops a DLT the dose will be de-escalated.

If, following the rules above the dose is de-escalated, the 3 + 3 rules above will be repeated. Should additional de-escalation be required, a dose lower than 0.5 x 10^9 may be considered or the Sponsor may decide to take other action (e.g., stop the trial) based on a comprehensive review of the data from this trial as well as other trials.

This protocol will also allow de-escalation to an intermediate, not pre-defined and not previously-studied dose, if evaluation of toxicity at such a dose is desired in lieu of proceeding directly to the dose expansion stage of the trial.

Table 7 ADXS31-142 and Pembrolizumab (MK-3475) Combination Therapy Doses to be used in Trial Part B

Drug	Dose Level	Dose	Route of Administration	Regimen
ADXS31-142	11	1 x 10^9	IV infusion	Day 1 of Weeks 1, 4 and 7 of 12-week cycle
	-1	0.5 x 10^9	IV infusion	Day 1 of Weeks 1, 4 and 7 of 12-week cycle
Pembrolizumab (MK-3475)		200 mg	IV infusion	Day 1 Q3W of 12-week cycle

Cohort Expansion: Once the RP2D is decided, an additional cohort of subjects will be enrolled at the selected RP2D for combination therapy. The number of subjects will depend on the number of subjects previously treated in the dose-finding portion. It is planned to treat a total of approximately 30 subjects at the RP2D. Subjects will be enrolled on a rolling basis.

5.2.1.2 Treatment Delays and Modifications

5.2.1.2.1 Pembrolizumab (MK-3475)

Adverse events (both non-serious and serious) associated with pembrolizumab (MK-3475) exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab (MK-3475) must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 8 below.

Table 8 Dose Modification Guidelines for Drug-Related Adverse Events with Pembrolizumab (MK-3475)

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab (MK-3475) can be continued while endocrine replacement therapy is instituted.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (T1DM) (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab (MK3475) for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab (MK-3475) when subjects are clinically and metabolically stable.
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	1-4	Therapy with pembrolizumab (MK-3475) can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab (MK-3475) can be continued while thyroid replacement therapy is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4 or Recurrent 2	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs or any life-threatening event.

[1] For subjects with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then subjects should be discontinued.

[2] Subjects with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

If toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Sponsor. With Investigator and Sponsor agreement, subjects with a laboratory AE still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of AEs, see Section 5.6.1.

Subjects who experience a recurrence of the same severe or life-threatening (per CTCAE) event at the same grade or greater with re-challenge of pembrolizumab (MK-3475) should be discontinued from trial treatment.

5.2.1.2.2 ADXS31-142

The most likely anticipated AEs associated with ADXS31-142 are comprised primarily of individual flu-like symptoms (e.g., fatigue, lethargy and low grade fever) or cytokine release symptoms (e.g., constitutional symptoms such as fever, chills, rigors, headache, nausea, vomiting, tachycardia, shortness of breath, hypotension, and rash). These symptoms usually present within 2-4 hours after the completion of infusion 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 or delayed 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.

[redacted] ADXS31-142 has a tropism for the liver. Transient asymptomatic elevations of ALT and alkaline phosphatase were observed after dosing with ADXS11-001 in the Phase 1 trial without prophylactic medication administration. For that reason, subjects with significant liver disease are excluded, and particular attention is to be paid to hepatic abnormalities.

The dose of ADXS31-142 will not be modified (e.g., reduced or increased) unless if it is determined that the toxicities are clearly attributed to ADXS31-142 or the combination, the treatment modification guidelines for drug-related AEs in Table 9 shown below are to be followed.

Table 9 Treatment Delay/Discontinuation Guidelines for Drug-Related Adverse Events-ADXS31-142

Toxicity	Grade	Hold treatment	Timing for restarting treatment	Discontinue treatment
Hematologic	1-3	No	N/A	N/A
	4	Yes	Toxicity resolves to ≤Grade 1or baseline	Toxicity does not resolve to ≤Grade 1or baseline within 12 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 12 weeks of last infusion[a]
	4	N/A	Permanently discontinue treatment	Permanently discontinue treatment

[a] With Investigator and Sponsor agreement, subjects with a non-heme AE (e.g., alopecia, neuropathy) still at grade 2 after 12 weeks, may continue treatment if only asymptametic and controlled.

5.2.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of Week 1, 4 and 7 (for ADXS31-142) or Q3W (for pembrolizumab [MK-3475]) in each 12-week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6). Trial treatment may be administered up to 7 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Trial treatments will be administered as a 30 minute IV infusion for pembrolizumab (MK-3475) and [redacted] (treatment cycle intervals may be increased due to toxicity as described in Section 5.2.1.2). Sites should make every effort to target required infusion timing. However, given the variability of infusion pumps from site to site, a window of [redacted] is permitted.

Patients will receive either oral 80 mg trimethoprim/400 mg sulfamethoxazole once daily for 7 days or 160 mg trimethoprim / 800 mg sulfamethoxazole (DS) three times over the course of the 7 days. Subjects with known allergy to sulfa drugs may receive ampicillin 500 mg four times daily for 7 days beginning on Day 4 (approximately 72 hours) after each study treatment infusion.

During combination dosing in Part B, there should be approximately [redacted] between the end of the first infusion and the start of the second infusion. The pembrolizumab (MK-3475) infusion will be administered first, followed by the ADXS31-142 required prophylactic regimen at least [redacted] prior to the ADXS31-142 infusion.

The Pharmacy Manual contains specific instructions for ADXS31-142 dose preparation and administration, and pembrolizumab (MK-3475) reconstitution, preparation of the infusion fluid, and administration.

5.2.3 Administration of ADXS31-142

[redacted]

5.2.4 Pretreatment Prophylaxis Regimen

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 immunotherapy and often resolve within 12-24 hours. Prophylactic medications are intended to reduce the inflammatory response. Prior to administering any prophylactic medications (on Day 1 of Weeks 1, 4, and 7 of each 12-week cycle), place a [redacted]

Subjects should receive the following pretreatment prophylaxis regimen through a temporary IV:

- 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

Vital signs will be taken immediately before each study treatment infusion.

Pretreatment medication should be given on the day of dosing and completed at least 30 minutes prior to the start of the assigned 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.

5.2.5 Post-Treatment Monitoring

Vital signs will be taken every [redacted] following each study treatment infusion. Four hours after the study treatment, the Investigator must ensure the subject is in stable medical condition and in the Investigator's opinion can be safely discharged before being released. In the event that the subject is not stable, the Investigator must take action to provide appropriate medical care (Refer to Table 10).

5.2.6 Trial Blinding/Masking

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

5.3 Treatment Allocation

Subjects participating in this trial will be allocated by non-random assignment.

5.4 Stratification

Treatment groups will not be stratified.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or

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

5.5.1 Acceptable Concomitant Medication

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

All concomitant medications received within 28 days before informed consent is signed and through the 30-Day Follow-Up period should be recorded in the eCRF. Concomitant medications administered to treat SAEs and ECIs should be recorded as defined in Section 7.2

5.5.2 Prohibited Concomitant Medications

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

- Anti-cancer therapy including but not limited to hormonal, chemotherapy, radiation therapy, and treatment with targeting agents (e.g., tyrosine kinase inhibitors). However, occasional therapy for palliation of pain is allowed. Note: Radiation therapy to a symptomatic soft tissue lesion, bone lesions or to the brain may be allowed after consultation with Sponsor. Radiopharmaceuticals (radium, strontium, etc.) are not acceptable.

- Immunotherapy not specified in this protocol; unless approved by Investigator and Sponsor

- Bisphosphonates and denosumab

    - Note: Subjects already being treated with bisphosphonates or denosumab may continue treatment, however, introduction of either is not allowed while on study.

- Investigational agents other than ADXS31-142 and pembrolizumab (MK-3475)

- PI3K and TNFα inhibitors

- 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, *Bacille Calmette-*

Guerin (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.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology or to manage cytokine release symptoms. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. Intermittent use of inhaled steroids is allowed for management of asthma.

- Anti-infectives should be avoided. Note: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.

- Acetaminophen is not to be used for pre-medication because it does not have anti-inflammatory properties required for AE amelioration but may be used for supportive care measures; for subjects where naproxen and ibuprofen are contraindicated, an alternative anti-inflammatory should be used. Sponsor consultation is recommended.

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined below. Where appropriate, these measures include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab (MK-3475) or ADXS31-142.

Note: If after evaluation, the event is determined not to be related, the Investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 5.2.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

5.6.1.1 Pneumonitis:

- For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For Grade **3-4 events**, immediately treat with IV steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

5.6.1.2 Diarrhea:

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis** that persists > than 3 days, administer oral corticosteroids.
- For Grade **3 or 4 diarrhea/colitis** that persists > 1 week, treat with IV steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

5.6.1.3 Diabetes:

Type 1 diabetes mellitus (T1DM) (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

- For **T1DM** or **Grade 3-4** Hyperglycemia
  - Insulin replacement therapy is recommended for T1DM and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

- Evaluate subjects with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

5.6.1.4 Hypophysitis:

- For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

5.6.1.5 Hyperthyroidism or Hypothyroidism:

Thyroid disorders can occur at any time during treatment. Monitor subjects for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2** hyperthyroidism events (and **Grade 3-4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g., propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

5.6.1.6 Hepatic:

- For **Grade 2** events, monitor liver function tests more frequently until values return to baseline (consider weekly).
  - Treat with IV or oral corticosteroids
- For **Grade 3-4** events, treat with IV corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

5.6.1.7 Renal Failure or Nephritis:

- For **Grade 2** events, treat with corticosteroids.
- For **Grade 3-4** events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

5.6.1.8 Cytokine Release Symptoms:

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, headache, nausea, vomiting, rash, tachycardia, hypotension and shortness of breath, which usually presents several hours after the infusion and may last 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 immunotherapy administration, resulting from the body's immune response to the therapy. 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 required at baseline, and during the 4-hour 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 immunotherapy, 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 [33-35] and is 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 for subjects who have experienced these AEs are shown in Table 10.

Table 10 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)
Fever, Constitutional symptoms	1	• Supportive care	• No modification
Hypotension	2 Moderate	• Fluids • Increase monitoring of vital signs • If hypotension persists, consider low dose corticosteroids (e.g., hydrocortisone 100 mg IV over 30 seconds) • If hypotension persists despite fluids and low dose steroids administer 1 low dose of pressors (e.g., 0.3 mg epinephrine IM)	• 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 and administer corticosteriods • Increase monitoring of vital signs • If hypotension worsens or is unresponsive to the above measures, administer high dose pressors (e.g., dopamine 10 µg/kg/min) +/- 1 dose tocilizumab*(4 mg/kg over 1 hour) • If the subject's condition does not improve or stabilize despite the above measures, consider administration of a 2nd dose of tocilizumab per investigator's discretion when clinically indicated,	• Discuss with Sponsor

Toxicity	NCI CTCAE Grade or Severity	Treatment	Modification for Subsequent infusions
		please see ACTEMRA prescribing information (as above) +/- additional corticosteroids	
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/Organ toxicity, mechanical ventilation	4 Life threatening	• Vigilant supportive care • Fluids, high dose pressors • Tocilizumab per investigator's discretion when clinically indicated, please see ACTEMRA prescribing information (4mg/kg over 1 hour) +/- corticosteroids (hydrocortisone 100 mg IV infused over 30 seconds administered every 2 hours until symptoms resolve to <Grade 1)	• Permanently discontinue treatment

* Tocilizumab is a humanized, immunoglobulin G1k (IgG1k) anti-human IL-6R mAb approved for treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to Disease-Modifying Anti-Rheumatic Drugs (DMARDs), for the treatment of active polyarticular juvenile idiopathic arthritis (PJIA), and active systemic juvenile idiopathic arthritis (SJIA) in patients 2 years of age and older. 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.[32-35]

5.6.1.9 Listeriosis and Listeria Infection – Identification and Management

A person with wild-type (*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 [36]. 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 patients, 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. Listeria monocytogenes can be isolated readily on routine media, but care must be taken to distinguish this organism from other Gram-positive rods, particularly diphtheroids. Selective enrichment media improve rates of isolation from contaminated specimens. 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 [36].

Listeriosis is treated with a wide range of antibiotics. In preclinical studies, wt-*Lm* and ADXS31-142 are susceptible to the lowest tested concentration of the following antimicrobial agents: [redacted]

5.6.1.10 Management and Surveillance of Listeria during Study Participation

A subject who experiences a fever (CTCAE Grade 1 or greater) 24 hours following the completion of ADXS31-142 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 ADXS31-142 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. 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 ADXS31-142 treatment or at the time of study discontinuation. This additional safety measure is intended to eradicate *Lm* from the body. It is expected that a subject will participate in the study until the completion of the full 3-year *Lm* Surveillance Monitoring period. However, following the completion of the 6-month oral antibiotic treatment, a subject will be eligible to participate in other investigational clinical studies.

Lm Surveillance Monitoring will also be initiated following the completion of the last dose of ADXS31-142 treatment or at the time of study discontinuation. This monitoring will include obtaining a blood sample for CBC, comprehensive metabolic panel (CMP), including C-reactive protein (CRP) and Erythrocyte Sedimentation Rate (ESR), and blood cultures for the detection of listeria. Testing will be performed on all subjects who have received at least one dose of ADXS31-142 and occurs every 3 months (±2 weeks) 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 ADXS31-142 and the 6-month course of oral antibiotics is 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 ADXS31-142 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.

5.6.1.11 Nausea/vomiting

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

5.6.1.12 Management of Infusion Reactions

While there is some overlap between infusion reaction symptoms and cytokine release symptoms, infusion reaction 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.

Table 11 provides treatment guidelines for subjects who experience an infusion reaction associated with administration of ADXS31-142 or pembrolizumab (MK-3475).

Table 11 ADXS31-142 or Pembrolizumab (MK-3475) Infusion Reaction Treatment Guidelines

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. **Pembrolizumab (MK-3475) Related:** Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.
Grade 3: Prolonged (e.g., 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)	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids — NSAIDS Antihistamines — 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.
Grade 4: Life-threatening; pressor or ventilatory support indicated	Subjects who experience a Grade 4 reaction should be permanently discontinued from treatment. Subjects who experience a grade 3 reaction may be discontinued. Discussion with the Sponsor is recommended. **Pembrolizumab (MK-3475) Related:** If Grade 3 or Grade 4 infusion reaction to pembrolizumab (MK-3475), subject is permanently discontinued from further pembrolizumab (MK-3475) trial treatment administration

5.6.2 Diet

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

5.6.3 Use in Pregnancy

If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor, and followed as described in Section 7.2.2.

5.7 Subject Study Participation

Each subject may participate in the study for up to 5 years from the time informed consent is signed through the final study contact. This includes a study treatment phase (approximately 24 months), and a 3-year post-ADXS31-142 treatment *Lm* Surveillance Monitoring period. It is expected that a subject will participate in the study until the completion of the full 3-year *Lm* Surveillance Monitoring period. However, following the completion of the 6-month oral antibiotic treatment, subjects will be eligible to participate in other investigational clinical studies.

5.8 Major and Minor Surgeries and ADXS31-142 Treatment

No formal studies of the effect of ADXS31-142 on wound healing have been conducted. However, based on its mechanism of action it is not expected that administration of ADXS31-142 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.

5.9 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be discontinued from the trial at the discretion of the Investigator should any untoward effect occur. In addition, a subject may be withdrawn by the Investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 .

Subjects may be discontinued from the trial for any of the following reasons:

- The subject withdraws consent
- Documented disease progression (radiographic and/or clinical)
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Death
- Investigator's decision to withdraw the subject
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of study treatment with ADXS31-142/pembrolizumab (MK-3475). **Note:** 24 months of study medication is calculated from the date of first dose.
- Achieved irCR (complete response)
- Randomized/Registered but never received study drug
- Study terminated by Sponsor
- Other (specify)

The End of Treatment and Follow-up visit procedures are listed in Section 6 and Section 7.1.5. After the end of treatment, each subject will be followed for AE/SAE monitoring as described in Section 7.2.3.1. In addition to the *Lm* Surveillance Monitoring, subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up ([redacted] every 4 weeks and imaging every 12 weeks) until disease progression, initiating an anti-cancer therapy, withdrawing consent, becoming lost to follow-up, or the Sponsor ends the study.

5.10 Subject Replacement Strategy

Subjects will not be replaced.

5.11 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study treatment

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

6 TRIAL FLOW CHART

6.1 Part A Flow Chart – ADXS31-142 Monotherapy

	Screening	12 Week Treatment Cycle[1]								Follow up		
		Wk 1	Wk 3[2]	Wk 4	Wk 6[2]	Wk 7	Wk 9[2]	Wk 10	Wk 12[10]	End of Therapy procedures	30 & 90-Day Follow-up[3]	*Lm* Surveillance Monitoring Period[14]
Study Procedure	+ 28 days											
Administrative Procedures												
Informed consent[4]	X											
Inclusion/Exclusion criteria	X											
Demographics/Medical history	X											
Prior/Concomitant medication	X	X	X	X	X	X	X		X	X	X	X
NSAIDs & Antiemetic Administration[5]		X		X		X						
ADXS31-142 Administration[6]		X		X		X						
Dispense/Prescribe oral prophylactic antibiotics[7]		X		X		X				X		
Clinical Procedures/Assessments												
Review Adverse events[8]		X	X	X	X	X	X		X	X	X	X
Physical examination	X	X		X		X				X		
Vital signs[9]	X	X		X		X				X		
ECOG performance status	X	X		X		X				X		
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory												
CBC with Differential	X	X		X		X				X		X
Serum Chemistry Panel	X	X		X		X				X		X
PT/INR and aPTT	X											
Urinalysis	X	X		X		X				X		
CMP (including CRP, ESR) and Blood Cultures												X

Efficacy Measurements/Correlative Studies												
Tumor Imaging[10]	X							X	X			X
[redacted]												

1. Repeating 12-week treatment cycles
2. Week 3, Week 6 and Week 9 visits will be performed during Cycle 1 only. After Cycle 1, these visits are not required.
3. Safety follow-up will be conducted via a telephone call 30 days (± 5 days) and 90 days for SAE assessment after the last study treatment to confirm the resolution of any ongoing AEs. In addition, [redacted] testing every 4 weeks and imaging every 12 weeks (± 1 week) should continue for subjects who discontinue treatment for reasons other than progression (Refer to Section 7.1.5.3.).
4. Prior to conducting screening evaluations. Signing of consent does not start the 28 days screening window.
5. Prior to administering any prophylactic medications, place a "[redacted] The pre-treatment prophylactic regimen must be administered through a temporary IV and completed at least 30 minutes before each ADXS31-142 infusion.
6. Treatment may be administered [redacted] of each scheduled infusion. However, ADXS31-142 should not be administered less than 2 weeks apart without Sponsor approval.
7. All subjects will receive a 7-day course of oral antibiotic therapy starting 72 hours after administration of ADXS31-142. All subjects will also receive an additional 6-month oral antibiotic course to be initiated 72 hours following the last dose of study treatment or upon discontinuation (See Section 7.1.5.3.).
8. AEs and SAEs will be assessed from the time informed consent through the completion of the 30 Day and 90-Day Follow-Up periods.
9. Monitor vital signs (including weight) pre-dose for all infusions. Vital signs (excluding weight) will be monitored every [redacted] for the first [redacted] following the completion of the ADXS31-142 infusion. Height will be measured at screening only.
10. CT/MRI of the abdomen/pelvis and bone scan. Repeated at Week 10 during first cycle and every 12 weeks (± 1 week) during treatment. Evaluation should continue every 12 weeks (± 1 week) for subjects who discontinue treatment for reasons other than progression.
11. [redacted]
12. [redacted]
13. [redacted]
14. *Lm* Surveillance Monitoring will include routine monitoring of CBC (excluding LDH), CMP (including CRP, ESR) and blood cultures. Testing will be performed every 3 months (± 2 week) for 3 years beginning 3 months after the subject's last dose of study treatment or at time of discontinuation. During the 6-month post-treatment antibiotic period, AEs that occur, which are deemed by the Investigator to be related to *Lm* or antibiotic treatment, along with the concomitant medication(s) used to treat the AE(s), will be recorded on the eCRF.

6.2 Part B Flow Chart – ADXS31-142 Monotherapy + Pembrolizumab (MK-3475) Combination Therapy

	Screening[2]	12 Week Treatment Cycle[1]								Follow up		
		Wk 1	Wk 3[3]	Wk 4	Wk 6[3]	Wk 7	Wk 9[3]	Wk 10	Wk 12	End of Therapy procedures	30- & 90-Day Follow-up[4]	*Lm* Surveillance Monitoring Period[13]
Study Procedure	+ 28 days											
Administrative Procedures												
Informed consent[5]	X											
Inclusion/Exclusion criteria	X											
Demographics/Medical history	X											
Prior/Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Pembrolizumab (MK-3475) Administration[6]		X		X		X		X				
NSAIDs & Antiemetic Administration[7]		X		X		X						
ADXS31-142 Administration[8]		X		X		X						
Dispense/Prescribe oral prophylactic antibiotics[9]		X		X		X				X		
Clinical Procedures/Assessments												
Review Adverse events[10]		X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X		X		X		X		X		
Vital signs[11]	X	X		X		X		X		X		
ECOG performance status	X	X		X		X		X		X		
[redacted]												
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory												
CBC with Differential	X	X		X		X		X		X		X
Serum Chemistry Panel	X	X		X		X		X		X		X
PT/INR and aPTT	X											
Urinalysis	X	X		X		X		X		X		
TSH, T3, T4[12]		X		X		X		X				

CMP (including CRP, ESR) and Blood Cultures												X
Efficacy Measurements/Correlative Studies												
Tumor Imaging[14]	X							X	X			X
[redacted]												

1. Repeating 12-week treatment cycles
2. Baseline tumor evaluation will be performed 28 days prior to first dose.
3. Week 3, Week 6 and Week 9 visits will be performed during Cycle 1 only. After Cycle 1, these visits are not required.
4. Safety follow-up will be conducted via a telephone call 30 days (± 5 days) and 90 days for SAE assessment after the last study treatment to confirm the resolution of any ongoing AEs. In addition, [redacted] testing every 4 weeks and imaging every 12 weeks (± 1 week) should continue for subjects who discontinue treatment for reasons other than progression (Refer to Section 7.1.5.3. Post-Treatment Visits).
5. Prior to conducting screening evaluations. Signing of informed consent does not start the 28 days screening window.
6. Prior to administering any prophylactic medications, place a [redacted] Pembrolizumab (MK-3475) is to be administered before ADXS31-142 through a temporary IV with a [redacted] wait period between infusions.
7. Subjects will receive premedications at least 30 minutes before each ADXS31-142 infusion.
8. Study treatment may be administered [redacted] of each scheduled infusion. However, ADXS31-142 should not be administered less than 2 weeks apart without Sponsor approval.
9. All subjects will receive a 7-day course of oral antibiotic therapy starting 72 hours after each ADXS31-142 infusion. All subjects will also receive an additional 6-month oral antibiotic course to be initiated 72 hours following the last dose of study treatment or upon discontinuation (See Section 7.1.5.3).
10. AEs and SAEs will be assessed from the time Informed Consent through the completion of the *Lm* Surveillance Monitoring period. All AE/SAEs will be followed through resolution. All AEs/SAEs experienced during this period must be recorded on the eCRF.
11. Monitor vital signs (including weight) pre-dose for all infusions. Vital signs will be checked prior to pembrolizumab (MK-3475) administration, prior to the ADXS31-142 infusion and every [redacted] for the first [redacted] following the completion of the ADXS31-142 infusion. Weight will be collected once at every visit. Height will be measured at screening only.
12. Thyroid function tests will be monitored only during combination therapy.
13. *Lm* Surveillance Monitoring will include routine monitoring of CBC (excluding LDH), CMP (including CRP, ESR) and blood cultures. All testing will be performed every 3 months (±2 weeks) for 3 years beginning 3 months after the subject's last dose of study treatment or at the time of study discontinuation. During the 6-month post-treatment antibiotic period, AEs that occur, which are deemed by the Investigator to be related to *Lm* or antibiotic treatment, along with the concomitant medications used to treat the AE(s) will be recorded on the eCRF.
14. CT/MRI of the abdomen/pelvis and bone scan. Repeat every 10 weeks (± 1 week) during the first cycle and every 12 weeks (± 1 week) during treatment. Evaluation should continue every 12 weeks (± 1 week) for subjects who discontinue treatment for reasons other than progression.
15. [redacted]
16. [redacted]
17. [redacted]
18. [redacted]

7 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

7.1.1.4 Medical History

A medical history will be obtained by the Investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.5 Surgical History

A surgical history will be obtained by the investigator or qualified designee. Surgical history will include all clinically relevant surgeries including, but not limited to artificial (prosthetic) joints, implants and/or devices, such as ports or stents. Surgical procedures that occur after study enrollment will be documented separately.

7.1.1.6 Prior and Concomitant Medications Review

7.1.1.6.1 Prior Medications

The investigator or qualified designee will review and record prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before informed consent is signed. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication. In addition, all prescription and nonprescription medication (excluding vitamins and nutritional supplements) taken by the subject from 28 days prior to signing informed consent and up to and including 30 days after the last administration of ADXS31-142, if any, should be recorded in the eCRF. All medications related to reportable SAEs 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 and antibiotics should also be captured in the CRF along with any addition.

7.1.1.6.2 Concomitant Medications

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

7.1.1.6.3 Non-Drug Treatment/Procedures

The Investigator or qualified designee will document any non-drug treatment or surgical procedures. All treatments/procedures related to reportable AE/SAEs and ECIs should be recorded as defined in Section 7.2

7.1.1.7 Disease Details and Treatments

7.1.1.7.1 Prior Cancer History

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

7.1.1.7.2 Prior Cancer Treatment

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

7.1.1.7.3 Subsequent Anti-Cancer Therapy Status

The Investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into follow-up.

7.1.1.8 Assignment of Subject Identification Number

After giving signed informed consent, subjects will be assigned a unique number to be used as identification throughout the trial.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The Investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs/SAEs from the time written informed consent is obtained through the completion of the 30-Day follow-up. Adverse events and SAEs experienced during this period will be reported and recorded in the eCRF. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to

CTCAE v 4.03 (Refer to Section 12.2). Toxicities will be characterized in terms of seriousness, causality, toxicity grading, and action taken with regard to study treatment.

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

7.1.2.2 Physical Examination

The Investigator or qualified designee will perform a complete physical examination during the screening period. Clinically significant abnormal findings should be recorded as medical history. Clinically significant abnormal findings noted during the treatment period should be recorded as an AE. A physical examination should also be performed before each treatment administration and at the end of therapy as specified in the Trial Flow Chart (Section 6).

7.1.2.3 Vital Signs

The Investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment, every [redacted] for [redacted] following each ADXS31-142 dose, and at treatment discontinuation as specified in the Trial Flow Chart (Section 6). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only. During Part B, weight will be collected once at every visit.

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The Investigator or qualified designee will assess ECOG status (see Section 12.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart (Section 6).

[redacted]

[redacted]

7.1.2.6 Tumor Imaging and Assessment of Disease

Computed tomography (CT), magnetic resonance imaging (MRI) or bone scan will be considered the best currently available and reproducible methods to measure target lesions (as defined in Section 7.1.2.5.2) selected for response assessment. Conventional CT and MRI of the abdomen/pelvis should be performed with contiguous cuts of 10 mm or less. Spiral CT scan should be performed using a 5 mm contiguous reconstruction algorithm (as a general rule, lesion diameter should be no less than double the slice thickness). Lesions on chest x-rays will be acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable. Ultrasound will not be an acceptable method to measure disease. Bone scan response assessment will be primarily based on the PCWG2 criteria. [38]

7.1.2.6.1 Measurable and Non-measurable Lesions and Disease

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

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

7.1.2.6.2 Target/Non-Target Lesions

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

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

7.1.2.6.3 Response in Measurable Lesions (RECIST 1.1)

At baseline, the sum of the longest diameters (SumD) of all target lesions (up to 2 lesions per organ, up to total 5 lesions) is measured. At each subsequent tumor assessment (TA), the SumD of the target lesions and of new, measurable 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 (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 sum of diameter of target lesions, taking as reference the baseline sum diameter.

- 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.

- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

7.1.2.6.4 Immune-Related Response in Measurable Lesions (irRECIST)

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

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

- Subjects 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. Subjects will continue to receive study treatment until irPD is confirmed at this later time point.

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

TMTB = SumD target lesions + SumD new, measurable lesions

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

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

7.1.2.6.5 Response in Non-measurable lesions (RECIST 1.1)

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

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

When the subject also has measurable disease, to achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

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

7.1.2.6.6 Immune-Related Response in Non-measurable Lesions

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

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

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

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

7.1.2.6.7 Overall Response

Overall response will be determined based on RECIST 1.1 criteria and by irRECIST criteria. The differences are noted below in Table 12. Overall response according to irRECIST is derived from the responses in measurable lesions (based on TMTB) and the presence of any non-measurable lesions.

Table 12 Tumor Response Evaluation: Comparison of RECIST 1.1 and irRECIST

Criteria	RECIST1.1	irRECIST
New measurable lesions (≥ 10 mm)	Always represents PD	Incorporated into tumor burden

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

irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; BOR = best overall response; CR = complete response; irCR = immune-related complete response; PD = progressive disease; PR = partial response; SD = stable disease;
[a] Subjects 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. Subjects will continue to receive study treatment until irPD is confirmed at this later time point. 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).

7.1.2.6.8 Best Overall Response (RECIST 1.1)

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions Table 13.

Table 13 Best Overall Response (RECIST 1.1)

Target Lesions	Non-Target Lesions		
Baseline (Index) and New Measurable Lesions	Baseline Lesions	Unequivocal New Lesions	Overall Response
CR	CR	No	CR

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

The immune-related best overall response (irBOR) is the best irCR overall response 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 subject in the study (Table 14). 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 14 Immune-Related Best Overall Response (irBOR)

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

Target Lesions Baseline (Index) and New Measurable Lesions	Non-Target Lesions[a]		
Total Measurable Tumor Burden (TMTB)	**Baseline Lesions**	**Unequivocal New Lesions**	**irRC Overall Response**
Any	Any	Yes	irPD

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

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

7.1.2.6.9 Treatment after Initial Evidence of Radiologic Disease Progression

Immunotherapy may produce antitumor effects by potentiating endogenous cancer-specific immune response. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase on tumor burden or even the appearance of new lesions. If radiological imaging shows progressive disease (PD), subjects may continue on study with the option of continuing treatment, provided there is:

- No deterioration in ECOG performance status
- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Tumor assessment should be repeated ≥4 weeks later to confirm PD. If repeat imaging shows a reduction in the tumor burden demonstrating CR, partial response (PR) or stable disease (SD) compared to the initial scan, treatments may be continued or resumed. If repeat imaging shows continued progression of disease, subjects will be discontinued from study therapy, unless the basis for the PD assessment is enlarged tumor-draining lymph nodes in the presence of a target tumor reduction. In determining whether or not tumor burden has increased or decreased, Investigators should consider all target lesions as well as non-target lesions. If the repeat imaging confirms initially documented PD but shows no evidence of further tumor progression, subjects should be discontinued from the study treatment.

7.1.2.7 Correlative Studies Blood Sampling

[redacted]

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

7.1.3.1 Laboratory Safety Evaluations (Hematology and Chemistry)

Laboratory tests for hematology, chemistry, and others are specified in Table 15. The total amount of blood to be drawn over the course of the trial (from pre-trial to post-trial visits), including approximate blood by visit and by sample type per subject can be found in the Procedures Manual.

Table 15 Laboratory Tests

Hematology	Chemistry	Other
Hematocrit	Albumin	PT (INR) (screening only)
Hemoglobin	Alkaline phosphatase	aPTT (screening only)
Platelet count	Alanine aminotransferase (ALT)	Total triiodothyronine (T3)
WBC (total and differential)	Aspartate aminotransferase (AST)	Free thyroxine (T4)
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Thyroid stimulating hormone (TSH)
Absolute Neutrophil Count	Carbon Dioxide (CO_2 or bicarbonate)	[redacted]
	Calcium	Serum creatinine OR creatinine clearance
	Chloride	Blood for correlative studies
	Creatinine	
	Glucose	
	Potassium	
	Sodium	
	Total Bilirubin	
	Direct Bilirubin (If total bilirubin is above the upper limit of normal)	

Hematology	Chemistry	Other
	Total protein	
	Blood Urea Nitrogen	
	Erythrocyte Sedimentation Rate*	
	C-Reactive Protein*	

Laboratory tests should be performed within 3 days prior to dosing. Results must be reviewed by the Investigator or qualified designee and found to be acceptable per Inclusion Criteria (Refer to Table 3) prior to each dose of trial treatment.

* *Lm* Surveillance Monitoring will include routine monitoring of CBC, CMP (including CRP, ESR) and blood cultures. Following completion of study treatment or at the time of study discontinuation, if earlier, testing will be performed on all subjects who have received at least one dose of ADXS31-142. It will occur every 3 months (+ 2 weeks) for 3 years beginning 3 months after the last dose of study treatment. CRP, ESR, and blood cultures are only collected during the *Lm* Surveillance Monitoring period, and not during the main part of the study. Lactate dehydrogenase (LDH) is only collected during the main part of the study, and is not collected during the *Lm* Surveillance Monitoring period (it is not part of the standard CMP).

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any AEs which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2. Subjects who a) attain a CR or b) complete 24 months of treatment may discontinue treatment. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.3).

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6. Specific procedure-related details are provided above in Section 7.1.

7.1.5.1 Screening Period

Screening period – this 28-day period will start when the first screening evaluation is performed. This does not include signing of Informed Consent or wash-out periods.

Informed Consent - prior to conducting screening evaluations each subject must sign a copy of the most current Institutional Review Board/Independent Ethics Committee

(IRB/IEC) approved informed consent document. A copy of the signed document will be maintained with the subject's records.

Screening evaluations - will be performed after Informed Consent is signed and within 28 days prior to first dose of study treatment.

Laboratory Tests - must be performed no more than 28 days prior to first dose but may be used as Cycle 1 Day 1 safety labs if done within 3 days of first dose.

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

Medical History/Prior and Concomitant Medications - past or current medical conditions, past surgeries, current medications, medications taken within 28 days of study entry, histological confirmation of cancer, tumor staging (refer to the most current American Joint Committee on Cancer Staging Manual, the 5th edition or higher), and prior cancer therapies and best response(s), if applicable.

[redacted]

7.1.5.2 Treatment Period

Subjects will be treated for approximately 2 years. Subjects should arrive at the study center early on the days of their scheduled treatment in order to be evaluated, take study prophylactic medication at least 30 minutes prior to ADXS31-142 infusion, and have laboratory specimens collected before treatment commences. For Cycle 1 Day 1 pre-treatment laboratory specimens do not need to be collected if screening labs were collected within 3 days of first dose.

During the time the subjects are at the study site for ADXS31-142 or combination treatment (on Day 1 of Weeks 1, 4, and 7 of each 12-week cycle), all IV study medications must be administered through a temporary IV, which will be removed prior to discharge. Subjects will remain at the study center for a minimum of 4 hours after study treatment for safety observation, and if necessary, treatment of side effects. Additional doses of NSAIDs and antiemetics post ADXS31-142 infusion may be administered per label or package insert, as needed.

Adverse Event Monitoring - the Investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Schedule of Events and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the study and follow-up according to CTCAE v 4.03. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

[redacted]

Physical Examination - evaluation by body system.

Vital Signs - blood pressure, pulse rate, respiratory rate, and temperature will be checked and recorded prior to administration of ADXS31-142 and every [redacted] for the first [redacted] following the completion of the ADXS31-142 infusion. For combination treatment, vital signs will be checked prior to pembrolizumab (MK-3475) administration, prior to the ADXS31-142 infusion and every [redacted] for the first [redacted] following the completion of the ADXS31-142 infusion. Weight will be collected once at every visit.

ECOG Performance Status - ECOG should be assessed prior to administration of study treatment.

[redacted]

Laboratory Tests - must be performed no more than 3 days prior to dosing. Screening labs can be used for Cycle 1 Day 1 labs, if performed within 3 days of dosing.

- Hematology Profile - a complete blood count with differential, and platelet count.
- Chemistry Profile - glucose, total protein, albumin, blood urea nitrogen, ESR, CRP, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, phosphorus, sodium, potassium, bicarbonate, chloride, and calcium; thyroid function tests (TSH, T3, T4) during combination therapy only.
- Urinalysis - Routine dipstick measurements will be conducted as specified in the Study Flow Chart in Section 6

PO Antibiotics with Instructions - **(1) 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 ADXS31-142. Antibiotic therapy should consist of either 160 mg trimethoprim/800 mg sulfamethoxazole (DS) tablet administered three times during the 7 consecutive days or 80 mg trimethoprim/400 mg sulfamethoxazole administered daily for 7 consecutive days or for subjects with sulfa allergy ampicillin 500 mg four times daily for 7 consecutive days may be administered.

Correlative studies: Blood will be collected as indicated below for immunology studies.

- [redacted]

- [redacted]

Tumor Imaging/Disease Assessment - CT scan, MRI or bone scan for determination of unidimensional measurements and disease response. Baseline tumor imaging/disease assessment must be performed within 28 days prior to the first dose of ADXS31-142 and at Week 10 (± 1 week) for the first cycle and then every 12 weeks (± 1 week). Imaging areas will include the chest, abdomen, pelvis, and other areas as indicated by clinical presentation.

7.1.5.3 Post-Treatment Visits

End-of-Therapy is not a visit; assessments noted in Section 6 must be completed upon the decision to discontinue a subject from study treatment.

Safety follow-up will be conducted via a telephone call at 30 days (± 5 days) and 90 days (± 5 days) for SAEs after the last dose of trial treatment to confirm the resolution of any ongoing events. Additional unscheduled visits may be considered as needed and at the discretion of the investigator.

All subjects will receive a 6-month course of oral trimethoprim/sulfamethoxazole or ampicillin for subjects with sulfa allergy 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 three times a week or 80 mg trimethoprim/400 mg sulfamethoxazole administered daily. The dose of ampicillin consists of 500 mg four times daily for 6 months. Review the approved product labeling for trimethoprim/sulfamethoxazole and ampicillin, and monitor antibiotic tolerance as dosing adjustments may be necessary. During the 6-month post-treatment antibiotic period, AEs that occur, which are deemed by the Investigator to be related to *Lm* or antibiotic treatment along with the concomitant medications used to treat the AE(s), will be recorded on the eCRF.

Lm Surveillance Monitoring for the detection of *Lm* will be initiated at the completion of study treatment or at the time of study discontinuation, if earlier. The *Lm* Surveillance Monitoring period will consist of obtaining a blood sample to monitor CBC, CMP, including CRP and ESR, and blood cultures at regular intervals. This testing will be performed on all subjects who have received at least one dose of ADXS31-142. It will occur every 3 months (±2 weeks) for 3 years beginning 3 months after the last dose of study treatment.

During the 3-year *Lm* Surveillance Monitoring period, if a persistent increase in CRP and/or ESR is observed with negative blood cultures for listeria during this time the subject should be evaluated and treated, as appropriate, for another possible cause. In the event that a definite cause has not been identified then subjects must continue to be

monitored closely, including additional testing and blood culture(s), for possible listeriosis. This testing may be performed at the investigative site or at another acceptable location following consultation with the Sponsor. During the *Lm* Surveillance Monitoring period all related labs with positive blood cultures for Listeremia and all concomitant medications used to treat the infection will be captured as AEs.

Every effort should be made to collect information regarding disease status until the start of new anti-cancer treatment, disease progression, or end of the study. Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating an anti-cancer therapy, withdrawing consent or becoming lost to follow-up. After documented disease progression, each subject will be followed by telephone for safety. For subjects who discontinue treatment for reasons other than progression, [redacted] testing should continue every 4 weeks and imaging should continue every 12 weeks (± 1 week) until disease progression.

7.2 Assessing and Recording Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An 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 Advaxis' or Merck's product, is also an AE.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered AEs. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

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

Adverse events may occur during the course of the use of an Advaxis or Merck product in clinical trials or within the 30-Day Follow-Up period, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. All AEs will be recorded from the time the consent form is signed through the completion of the 30-Day Follow-Up period of the study or the initiation of a new anticancer therapy, whichever is

earlier. Adverse Events and SAEs experienced during this period will be reported and recorded in the eCRF. The reporting timeframe for AEs meeting any serious criteria is described in Section 7.2.3.1.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for ADXS31-142 or ≥1000 mg of pembrolizumab (MK-3475). No specific information is available on the treatment of overdose of ADXS31-142 or pembrolizumab (MK-3475). In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an AE(s) is associated with ("results from") an overdose, the AE(s) is reported as a SAE, even if no other seriousness criteria are met.

If an overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious ECI, using the terminology "accidental or intentional overdose without adverse effect."

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered AEs, it is the responsibility of Investigators or their designees to report any pregnancy or lactation in a subject's partner (spontaneously reported to them) that occurs during the trial or within 120 days of completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as SAEs (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A SAE is any AE occurring at any dose or during any use of Advaxis' or Merck's product that:

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

Refer to Table 16 for additional details regarding each of the above criteria.

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

Any SAE, or follow up to a SAE, including death due to any cause, that occurs to any subject from the time the consent is signed through the completion of the 90-Day Follow-Up period of the study, whether or not related to Advaxis' or Merck's product, must be reported within 24 hours of awareness to inVentiv Health Clinical Pharmacovigilance (Attn: iHC SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@inventivhealth.com).

Non-serious ECIs will be forwarded to inVentiv Health Clinical and will be handled in the same manner as SAEs. Concomitant medications administered to treat SAEs and ECIs should be recorded through the completion of the 30-Day Follow-Up period.

Additionally, any SAE, considered by an Investigator who is a qualified physician, to be related to the Advaxis' or Merck's product that is brought to the attention of the Investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to inVentiv Health Clinical Pharmacovigilance (Attn: iHC SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@inventivhealth.com).

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

Adverse Event reports meeting the requirements of a 7 Day Reports, 15 Day Reports, or the requirements for inclusion in the Annual Periodic Reports will be submitted as required to FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will be provided a copy of the submission and will utilize this for submission to local IRB/ECs as required. The submission will cross reference the Sponsor's Investigational Compound Number (IND, CSA, etc.).

All subjects with SAEs must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and SAEs are also known as ECIs and must be reported to the Sponsor. ECIs must be recorded as such on the Adverse Event CRFs/worksheets and reported within 24 hours to inVentiv Health Clinical Pharmacovigilance (Attn: iHC SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@inventivhealth.com).

ECIs for this trial include:

1. Overdose, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, which is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT value that is ≥3X the upper limit of normal and an elevated total bilirubin value that is ≥2X the upper limit of normal and, at the same time, an alkaline phosphatase value that is ≤2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

3. Cytokine release syndrome (CRS): Subjects presenting with all 6 symptoms of CRS that include nausea, headache, tachycardia, hypotension, rash, and shortness of breath.

4. Listeremia

5. Hypotension – ≥ Grade 2

6. Any AE ≥ Grade 3

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

ECIs that occur in any subject from the date of first dose through 30 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, must be reported within 24 hours of awareness to inVentiv Health Clinical Pharmacovigilance (Attn: iHC SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@inventivhealth.com).

7.2.4 Evaluating Adverse Events

An Investigator who is a qualified physician will evaluate all AEs according to the CTCAE v 4.03. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs according to Table 16. All AEs regardless of CTCAE grade must also be evaluated for seriousness. Symptoms associated with Cytokine Release Syndrome (CRS) which include *nausea, headache, tachycardia, hypotension, rash, and shortness of breath* MUST be reported as individual symptoms. If a subject manifest all five CRS symptoms, then CRS can be reported as a single event. Otherwise they must be reported individually as it is not a true CRS.

Table 16 Evaluating Adverse Events

V4.03 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A SAE is any AE occurring at any dose or during any use of Advaxis or Merck product that:	
	†**Results in death**; or	
	†**Is life threatening**; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an AE that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a SAE.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new cancer; (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any AE associated with an overdose is considered a SAE. An overdose that is not associated with an AE is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the AE. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the AE cause the Advaxis or Merck product to be discontinued?	

Relationship to test drug	Did the Advaxis or Merck product cause the AE? The determination of the likelihood that the Advaxis or Merck product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the AE based upon the available information. **The following components are to be used to assess the relationship between the Advaxis or Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Advaxis or Merck product caused the AE:	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Advaxis or Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
Relationship to Advaxis or Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Advaxis or Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Advaxis or Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Advaxis or Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Advaxis or Merck product(s) is/are used only one time).

		NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE ADVAXIS OR MERCK PRODUCT, OR IF REEXPOSURE TO THE ADVAXIS OR MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Advaxis or Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of an Advaxis or Merck product relationship).**
Definite:		The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug
Probable:		The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug AND the event cannot have been reasonably explained by an intercurrent medical condition or the event cannot be the effect of a concomitant medication
Possible		The event follows a reasonable temporal sequence from administration of the study drug or the event follows a known response pattern to the study drug BUT the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug or the event could be the effect of a concomitant medication
Unlikely		The event is clearly due to causes distinct from the use of the study drug, such as a documented pre-existing condition, the effect of a concomitant medication, a new condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug
Unrelated		The event does not follow a temporal relationship to the study treatment administration (too early, late, or study treatment(s) not taken) or there is a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

No inferential statistical analyses will be performed; however, the data will be summarized overall and by treatment dose. Discrete variables will be summarized with counts and percentages; continuous variables will be summarized with means, standard deviations, and ranges.

Data will be summarized for safety by evaluating physical examinations, serum chemistry values, and hematology values. Efficacy will be assessed by changes in PSA and tumor response, based upon CT/MRI scans and evaluations consistent with RECIST, irRECIST criteria and overall survival. [redacted]

8.2 Statistical Analysis Plan

8.2.1 Analysis Sets

The safety population will include all subjects who have been treated with at least one dose of ADXS31-142 or pembrolizumab (MK-3475).

All subjects who complete at least one cycle of study treatment will be included in the efficacy analyses. Characterization of the Study Population

Distributions of the following baseline data will be described by dose group:

- Demographics
- AJCC TNM prostate cancer stage
- Prior treatments and regimen for prostate cancer
- ECOG Performance Status
- Physical examination parameters

- Vital signs
- Baseline safety labs including hematology and serum chemistry
- Baseline immunology data
- [redacted]
- [redacted]

8.2.2 Study Conduct

Information about study conduct will be presented by treatment dose. Subject disposition at the end of the study will be tabulated including the number of subjects who completed the study as well as the reason for discontinuation for non-completers. The number of subjects in each of the analysis populations, the duration of time on study, and the number of injections will also be displayed. The number and type of protocol violations will be summarized.

8.2.3 Safety Endpoints

AEs will be coded using MedDRA and will be presented by System/Organ/Class and preferred term. Some AEs will be categorized and summarized by Grade as defined in CTCAE v 3.0. Concomitant medications will be coded using the CTCAE v 4.0 and summarized by drug class and generic name.

Tables and graphs will show changes from baseline through one year in:

- Physical examination
- Vital signs
- Safety labs, including hematology and serum chemistry

Other safety data that will be presented include:

- DLT
- Adverse events along with their severity and potential relationship to study treatment
- Injection site reactions
- Concomitant medications
- Prophylaxis treatment

8.2.4 Efficacy Endpoints

- Tumor response, time to tumor progression using RECIST, irRECIST or PCWG2 as appropriate
- Survival of subjects at timepoints up to 24 months
- PFS of subjects at timepoints up to 24 months
- [redacted]

[redacted]

Duration of response will be measured from the time the measurement criteria are met for irCR/irPR (whichever is first recorded) until the first date that progressive disease or death is objectively documented. Subjects who do not relapse will be censored at the day of their last tumor assessment.

Time to progression will be defined as the time from the first day of treatment until the date progressive disease or death is first reported. Subjects who die without a reported prior progression will be considered to have progressed on the day of their death. Subjects who did not progress will be censored at the day of their last tumor assessment.

Tumor response rate is the total number of CRs plus PRs divided by the number of treated subjects. Disease control rate is the number of subjects who have CR+PR+SD for a minimum of 12 weeks following the first day of treatment, divided by the number of response-evaluable subjects.

[redacted]

9 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 17.

[redacted]

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and handling Requirements

9.4.1 Storage Guidelines

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

[redacted]

MK-3475 is shipped at 2 – 8° C. It is imperative that all MK-3475 drug shipments be stored refrigerated at 2 – 8° C immediately after received.

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

Detailed storage and handling information can be found in the Pharmacy Manual. Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.4.2 Handling Requirements

ADXS31-142 is a live *Lm* that has been attenuated at least [redacted] logs more than wild-type *Lm* and is cleared by gamma interferon knock-out mice lacking adaptive immunity. It has also been altered by an irreversible deletion of the virulence gene which is essential for cell-to-cell spread of *Lm* infection. ADXS31-142 has not been administered to any human subject prior to this clinical trial. However, several clinical trials have been conducted with a similar *Lm*-LLO immunotherapy [redacted] including 2 studies in advanced cervical cancer, one study in CIN, one study in head and neck cancer, and one study in anal cancer. The external bacterial vector and elements regulating expression of the fusion proteins are identical in these immunotherapies. It has been administered intravenously over 500 times to over 200 subjects (at the time of this writing) with only mild-moderate side effects associated with infusion.

Wild-type *Lm* is gram-positive, non-spore-forming, facultative bacilli are hemolytic and catalase-positive. 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 ADXS31-142 is non-pathogenic, all *Lm* species are classified as [redacted] according to the Biosafety in Microbiological and Biomedical Laboratories (BMBL) 5th Edition [37]. In the US there currently is no method to reclassify Advaxis attenuated *Lm* strains in a manner that differentiates them from the more virulent wild type parent strain 10403S. Universal precautions and institutional guidelines should be used when handling investigational drugs and human specimens. Precautions as stated in the BMBL 5th Edition for wild-type *Lm* include:

> *Wild-type Lm 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 Lm may be 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 Lm 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: *Biosafety [redacted] 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 Listeria monocytogenes 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.*

[redacted]

Additional details regarding handling of both products can be found in the Pharmacy Manual.

9.5 Returns and Reconciliation

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

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

10 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

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

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

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

10.2 Compliance with Financial Disclosure Requirements

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

The Investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The Investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with law, Audit and Debarment

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

10.5 Quality Management System

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

10.6 Data Management

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

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

11 LIST OF REFERENCE

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Appendices

11.1 ECOG Performance Status

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

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

The descriptions and grading scales found in the revised CTCAE v 4.03 will be utilized for AE reporting (http://ctep.cancer.gov/reporting/ctc.html).

11.3 Immune Response Modification to Response Evaluation Criteria in Solid Tumors (irRECIST) for Evaluating Response in Solid Tumors

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

12 LIST OF ABBREVIATIONS

AE	Adverse event
AJCC TNM	American Joint Committee on Cancer tumor node metastasis staging
ALT	alanine transaminase
ANC	absolute neutrophil count
APC	antigen-presenting cells
AST	aspartate transaminase
BCG	Bacille Calmette-Guerin
BOR	best overall response
[redacted]	[redacted]
CBC	complete blood count
cfu	colony forming unit(s)
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CMP	Comprehensive metabolic panel
CNS	central nervous system
CR	complete response
CrCl	Creatinine clearance
CRF	case report form
CRP	C-reactive Protein
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic T lymphocytes
DKA	diabetic ketoacidosis or
DL	dose level
DLT	dose limiting toxicity
ECI	event(s) of clinical interest
ECOG	Eastern Cooperative Oncology Group
[redacted]	[redacted]
ERC	Ethical Review Committee
ESR	Erythrocyte sedimentation rate
EU	European Union
[redacted]	[redacted]
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
GFR	glomerular filtration rate
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HPV	human papillomavirus

IB	Investigator Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IND	Investigational new drug
INR	International normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
irBOR	immune-related best overall response
irCR	immune-related complete response
irECI	immune-related event of clinical interest
irPD	immune-related progressive disease
irPR	immune-related partial response
irRC	immune-related response criteria
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
irSD	immune-related stable disease
ITIM	immunoreceptor tyrosine-based inhibition motif
ITSM	immunoreceptor tyrosine-based switch motif
IV	intravenous
LDH	lactate dehydrogenase
LHRH	luteinizing hormone releasing hormone
LLO	listeriolysin O
Lm	*Listeria monocytogenes*
mAb	monoclonal antibody
mCRPC	metastatic castrate-resistant prostate cancer
MDSCs	myeloid-derived suppressor cells
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MTD/MAD	maximum tolerated dose/maximum allowable dose
mTPI	modified toxicity probability interval
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug(s)
OTC	over the counter
PAP	prostatic acid phosphatase
PBMCs	peripheral blood mononuclear cells
PCWG2	Prostate Cancer Working Group 2
PD	progressive disease; programmed death
PD-L	programmed death ligand
PFS	progression-free survival
PI3K	Phosphoinositide 3-kinase

PK	pharmacokinetic
PMDA	Pharmaceutical and Medical Devices Agency
PR	partial response
PSA	prostate specific antigen
PSCA	prostate stem cell antigen
PSMA	prostate-specific membrane antigen
PT	prothrombin time
PTT	partial thromboplastin time
[redacted]	[redacted]
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SD	stable disease
SOP	Standard Operating Procedure
SumD	sum of the longest diameters
TA	tumor assessment
TAAs	tumor-associated antigens
TFT	thyroid function test
TGF_{β}	transforming growth factor beta
tLLO	truncated listeriolysin O
T1DM	Type 1 Diabetes Mellitus
TMTB	total measurable tumor burden
TNF_{α}	tumor necrosis factor alpha
Treg	T regulatory cells
ULN	upper limit of normal
US(A)	United States (of America)
V-type	variable-type
WBC	white blood cell
wt	wild-type