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Title Page

A Phase 1/2, Open-Label Study of ADXS-503 Alone and in Combination with Pembrolizumab in Subjects with Metastatic Squamous or Non-Squamous Non-Small Cell Lung Cancer

Protocol Number: ADXS-503-101

Compound Number/ Name: ADXS-503

Sponsor Name and Legal Registered Address:

Advaxis, Inc.

9 Deer Park Drive, Suite K-1

Monmouth Junction, NJ 08852

Regulatory Agency Identifying Number(s): IND #: 018284

This study will be conducted under Food & Drug Administration IND regulations (CFR Part 312).

Protocol Version and Date:

Original Protocol, Version 1.0 dated 21-JUN-2018

Amendment # 1, Version 2.0 dated 06-AUG-2018

Amendment # 2, Version 3.0 dated 17-SEP-2018

Amendment # 3, Version 4.0 dated 14-OCT-2019

Amendment #4, Version 5.0, dated 19-JUN-2021
(see Section 13 for summary of protocol changes)

PROTOCOL APPROVAL

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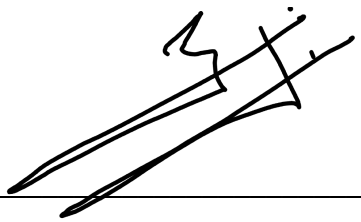

Signature

June 22, 2021

Date

Andres A Gutierrez, MD, PhD

Chief Medical Officer EVP- Advaxis, Inc.

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 (GCP), International Conference on Harmonisation (ICH) Guidelines, the Declaration of Helsinki, and local ethical and legal requirements.

Investigator Name:

_____ _____

Signature Date

_____ Site #: _____

Printed Name

Table of Contents

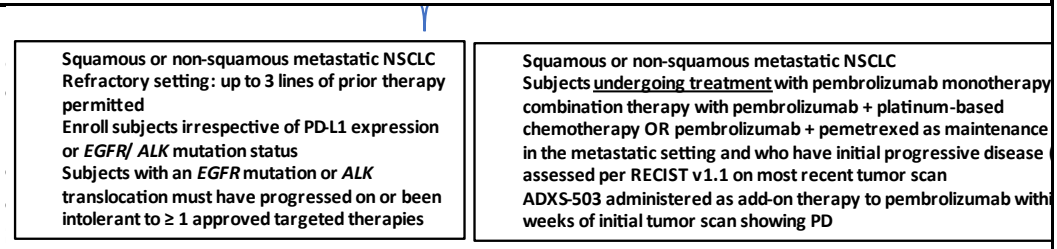
List of Appendices

List of In-Text Tables

List of In-Text Figures

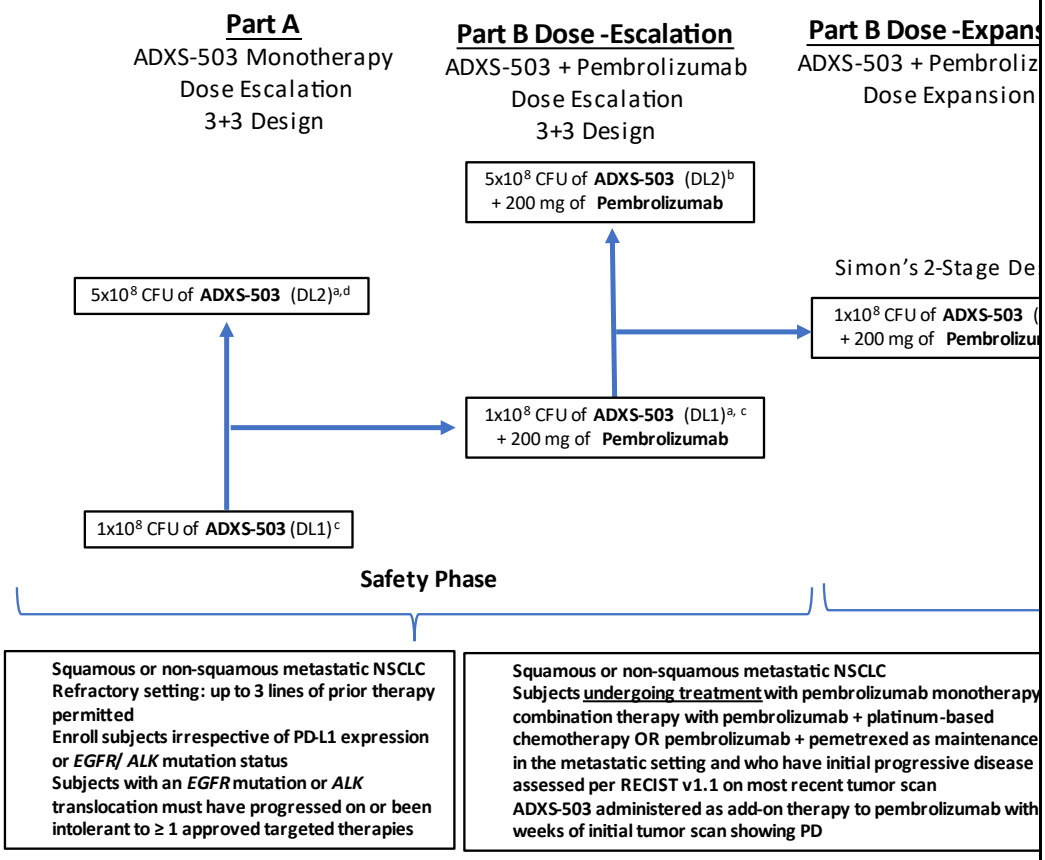
1. Trial Summary

1.1. Synopsis

Study Title	A Phase 1/2, Open-Label Study of ADXS-503 Alone and in Combination with Pembrolizumab in Subjects with Metastatic Squamous or Non-Squamous Non-Small Cell Lung Cancer
Trial Phase	Phase 1/2
Clinical Indication	Non-Small Cell Lung Cancer
Trial Type	Interventional, Simon's Two-stage design for Part B
Interventions	• **ADXS-503**: a live attenuated *Listeria monocytogenes (Lm)*-based immunotherapy bioengineered to elicit potent T cell responses against 22 tumor antigens that include 1) 11 peptide antigens derived from frequently occurring and commonly shared hotspot mutations in patients with squamous and non-squamous NSCLC and 2) 11 peptide antigens derived from sequence-optimized tumor-associated antigens (TAAs) that are differentially expressed or overexpressed in NSCLC tumors. • **Pembrolizumab**: a programed death receptor-1 (PD-1)- blocking antibody.
Type of control	None
Route of administration	Intravenous
Trial Blinding	Unblinded, Open-label
Estimated duration of trial	The sponsor estimates that for the duration of patient participation, the trial will require approximately 3 years from the time the first subject signs the informed consent until the last subject's last visit (which includes *therapy for up to 2 years*, plus *survival* and *Lm surveillance follow-up* for 1 year after subject's last visit or upon discontinuation from therapy with ADXS-503, whichever comes first). Approximate duration of trial: 4 years.
Study Phases/ Parts	 Figure 1 for a schematic of the study design.
Subject Population	**Safety phase (Part A and Part B):** **Part A** will enroll subjects with metastatic squamous or non-squamous NSCLC who have become refractory or intolerant to standard therapy. To be eligible for Part A, subjects must have previously received, and then progressed or been intolerant to up to 3 lines of prior therapy in the metastatic setting, including approved chemotherapy, targeted therapy, immunotherapy and antibody therapy, if eligible. Subjects will be eligible for Part A irrespective of PD-L1 expression or *EGFR* or *ALK* mutation status. However, subjects with an *EGFR* sensitizing mutation or *ALK* translocation must have received and then progressed or been intolerant to at least 1 prior line of approved targeted therapy to be eligible for Part A. **Part B** dose-escalation will enroll subjects with metastatic squamous or non-squamous NSCLC who meet the following criteria: • Are undergoing treatment with pembrolizumab monotherapy as last therapy for metastatic NSCLC

	OR • Are undergoing combination therapy with pembrolizumab plus platinum-based chemotherapy as last treatment OR • Are receiving pembrolizumab + pemetrexed as maintenance therapy, as last treatment after completing treatment with pembrolizumab plus platinum-based chemotherapy • The subject's most recent tumor assessment is consistent with progressive disease (PD) according to RECIST v1.1 • There is no evidence of rapid disease progression or clinical deterioration that would preclude continuation of pembrolizumab for up to 12 weeks before ADXS-503 is added-on. • In Part B, subjects must receive the first dose of ADXS-503 within 12 weeks of the initial tumor assessment showing PD (while on last treatment with pembrolizumab monotherapy or pembrolizumab + platinum-based chemotherapy or pembrolizumab + pemetrexed as maintenance therapy). ADXS-503 will be administered as add-on treatment to the ongoing pembrolizumab therapy. Subjects who are receiving pembrolizumab in combination with platinum-based chemotherapy or pembrolizumab with pemetrexed as maintenance therapy, will continue on pembrolizumab monotherapy every 3 weeks per schedule while other drugs are washed-out for 3 weeks. Subject must consent to allow the acquisition of fresh or archival formalin-fixed paraffin embedded (FFPE) tumor tissue, either a block or unstained slides along with a matching blood at baseline, for performance of sequencing analysis. **Efficacy phase (Part B expansion and Part C):** **Part B** expansion will enroll subjects with metastatic squamous or non-squamous NSCLC who meet the same criteria as Part B dose escalation mentioned above. Based on Stage I of Simon's Two-stage design, 18 patients will be accrued in this study arm. Sponsor may decide to accrue additional 25 subjects for a total of 43 patients in Stage II. Accrual of patients to Part B dose level 2 (ADXS-503 at $5x10^8$ CFU in combination with 200 mg pembrolizumab) is pending Sponsor decision to commence **Part C** will enroll subjects with metastatic squamous or non-squamous NSCLC who have received no prior systemic treatment in the metastatic setting, and who will be treated in accordance with the approved Product Label for pembrolizumab monotherapy for first-line treatment. Clinical site must provide documentation of tumor PD-L1 expression and EGFR mutation and/or ALK translocation status as evaluated by FDA-approved tests in all patients. Baseline tumor samples must express PD-L1 [TPS (Tumor Proportion Score) ≥1%] as determined by an FDA-approved test at a local laboratory facility, with no EGFR or ALK genomic tumor aberrations for subjects to be eligible for Part C. Subject must consent to allow the acquisition of fresh or archival FFPE tumor tissue, either a block or unstained slides along with a matching blood at baseline, for performance of sequencing analysis.
Study Objectives	**Primary** • To evaluate the safety and tolerability of ADXS-503 monotherapy in Part A and ADXS-503 + pembrolizumab in Part B, and to determine the MTD or MAD. • To characterize the preliminary anti-tumor activity of ADXS-503 + pembrolizumab in Part B and Part C per RECIST v1.1. **Secondary** • To characterize the preliminary anti-tumor activity of ADXS-503 monotherapy in dose escalation Part A and ADXS-503 + pembrolizumab in Part B per RECIST v1.1. • To determine PFS and PFS rate at 12 months per RECIST v1.1, for subjects treated with ADXS-503 monotherapy in Part A and ADXS-503 + pembrolizumab in Part B and Part C. • To determine OS and 6- and 12-month milestone OS rates for subjects treated with ADXS-

	503 monotherapy in Part A and ADXS-503 + pembrolizumab in Part B and Part C. • To evaluate the safety and tolerability of ADXS-503 + pembrolizumab in Part C. **Exploratory** • To characterize the preliminary anti-tumor activity, PFS and PFS rate at 12 months per iRECIST for subjects treated with ADXS-503 monotherapy in Part A, and ADXS-503 + pembrolizumab in Part B and Part C. • To evaluate correlates of immune response and biomarkers in peripheral blood and biopsy samples pre- and on-treatment in Part A, Part B and Part C.
Treatment Groups	**Safety Phase** • **Part A: ADXS-503 monotherapy dose escalation (3+3 design)** ADXS-503 monotherapy will be evaluated at 2 planned escalating dose levels: o Dose level 1: $1x10^8$ CFU of ADXS-503, IV, every 3 weeks until disease progression, unacceptable toxicity, or another treatment discontinuation criterion is met. o Dose level 2: $5x10^8$ CFU of ADXS-503, IV, every 3 weeks until disease progression, unacceptable toxicity, or another treatment discontinuation criterion is met. • **Part B: ADXS-503 + pembrolizumab dose escalation (3+3 design)** ADXS-503 will be evaluated at 2 planned escalating dose levels in combination with a fixed dose of pembrolizumab (with second dose level commencing upon Sponsor's decision): o Dose level 1: $1x10^8$ CFU of ADXS-503 + 200 mg of pembrolizumab, IV, every 3 weeks ***for up to 2 years*** or until disease progression, unacceptable toxicity, or another treatment discontinuation criterion is met. Upon Investigator assessment, Investigator could shift the schedule of therapy with $1x10^8$ CFU of ADXS-503 + 200 mg of pembrolizumab, IV, from every 3 weeks to every 6 weeks after the first year of study treatment. o Dose level 2: $5x10^8$ CFU of ADXS-503 + 200 mg of pembrolizumab, IV, every 3 weeks ***for up to 2 years*** or until disease progression, unacceptable toxicity, or another treatment discontinuation criterion is met. Upon Investigator assessment, Investigator could shift the schedule of therapy with $1x10^8$ CFU of ADXS-503 + 200 mg of pembrolizumab, IV, from every 3 weeks to every 6 weeks after the first year of study treatment. **Efficacy Phase** • **Part B-Expansion: ADXS-503 + pembrolizumab dose expansion (Simon's Two-stage design)** o Dose-expansion (DL-1): $1x10^8$ CFU of ADXS-503 + 200 mg of pembrolizumab, IV, every 3 weeks ***for up to 2 years*** or until disease progression, unacceptable toxicity, or another treatment discontinuation criterion is met. Upon Investigator assessment, Investigator could shift the schedule of therapy with $1x10^8$ CFU of ADXS-503 + 200 mg of pembrolizumab, IV, from every 3 weeks to every 6 weeks after the first year of study treatment. • **Part C: ADXS-503 + pembrolizumab** o $1x10^8$ CFU of ADXS-503 + 200 mg of pembrolizumab, IV, every 3 weeks ***for up to 2 years*** or until disease progression, unacceptable toxicity, or another treatment discontinuation criterion is met. Upon Investigator assessment, Investigator could shift the schedule of therapy with $1x10^8$ CFU of ADXS-503 + 200 mg of pembrolizumab, IV, from every 3 weeks to every 6 weeks after the first year of study treatment.
Number of trial subjects	**Safety phase:** Up to approximately 24 subjects will be enrolled in the safety phase; up to 12 subjects in Part A and up to 12 subjects in Part B based on a 3+3 dose escalation design at 2

	escalating dose levels. Up to approximately 25 subjects may also be enrolled in a Part A expansion cohort. **Efficacy phase:** Up to approximately 165 subjects may be enrolled in the efficacy phase (Part B-expansion and Part C combined). Up to 43 subjects may be enrolled in Part B expansion of DL1 in the Simon's Two-stage study cohort (S1 [n=18], and S2 [n= 25]) and up to a total of 140 thereafter. Approximately up to 25 subjects may be enrolled in Part C.
Study Design	This is a Phase 1/2, open-label, multi-center study of ADXS-503 administered alone and in combination with pembrolizumab in subjects with metastatic squamous or non-squamous NSCLC. This study will be performed in 2 phases, a safety phase and an efficacy phase, as described below. Refer to  Figure 1 for a schematic of the study design. Simon's Two-stage design has been incorporated for evaluation of subjects in Part B expansion Efficacy phase. **Safety Phase** The purpose of the safety phase is to evaluate the safety and tolerability of ADXS-503, administered as monotherapy (Part A) and in combination with pembrolizumab (Part B-dose escalation), and to determine the MTD or MAD. The preliminary clinical and immunological activity of ADXS-503 alone and in combination with pembrolizumab will also be characterized in the safety phase. The subject population to be enrolled in Part A and Part B is described above. In Part A, ADXS-503 will be administered as monotherapy at 2 planned escalating dose levels (dose level 1 [$1x10^8$ CFU] and dose level 2 [$5x10^8$ CFU]). In Part B, ADXS-503 will be

	administered at 2 planned escalating dose levels (dose level 1 [$1x10^8$ CFU] and upon Sponsor's decision, may be escalated to dose level 2 [$5x10^8$ CFU]) in combination with a fixed dose of 200 mg of pembrolizumab, as described above. Dose escalation in Part A and Part B will proceed according to a 3+3 dose escalation design. If treatment with ADXS-503 monotherapy is safe and tolerable at dose level 1 in Part A (based on DLT criteria), escalation to dose level 2 in Part A will proceed in parallel with accrual at dose level 1 in Part B-dose escalation. If treatment with ADXS-503 + pembrolizumab is safe and tolerable at dose level 1 in Part B (based on DLT criteria), this dose can be considered the recommended dose for use in Part B-expansion and Part C. In parallel, escalation to dose level 2 in Part B will proceed (upon Sponsor's decision) in parallel with accrual in Part C. Prior to declaring the MTD in Part A or Part B, dose level(s) previously established to be safe may be expanded or intermediate dose levels may be investigated. If a MTD is not established, a higher dose level may be evaluated with agreement between the Investigators and the Sponsor or study will continue with the recommended dose from Part B-escalation that is demonstrated to be safe and well tolerated. Dose escalation rules (cohort size, DLT evaluation interval, etc.) will apply to the expanded or additional cohorts. Upon completion of dose escalation in Part A, ADXS-503 monotherapy may be evaluated in an expansion cohort. This Part A expansion cohort may commence enrollment following consultation and agreement between study Investigators and the Sponsor. The expansion cohort may be restricted to the tumor type(s) found to be responsive to ADXS-503 monotherapy. The dose of ADXS-503 selected for the monotherapy expansion will not exceed the MTD established in Part A. However, the dose may be intermediate to those tested in Part A if recommended by the Investigators and the Sponsor. Up to approximately 25 subjects will be enrolled in this expansion cohort. **Efficacy Phase** Upon confirming treatment with ADXS-503 + pembrolizumab is safe and tolerable at dose level 1 in Part B-escalation (based on DLT criteria), accrual will be initiated in Part B expansion and Part C. Hence, the planned dose in Part B-expansion and in Part C will be ADXS-503 $1x10^8$ CFU in combination with 200 mg of pembrolizumab. Part B-dose expansion will evaluate preliminary efficacy using a Simon's Two-stage study design in subjects who have failed prior systemic treatment with 1) pembrolizumab monotherapy as last therapy or 2) while receiving combination therapy with pembrolizumab and platinum based-chemotherapy as last treatment or 3) while receiving pembrolizumab + pemetrexed maintenance therapy as last treatment in the metastatic setting. Part B dose-expansion may enroll up to 43 subjects in the Simon's Two-stage design (ie, S1 [n=18], and S2 [n=25]) and up to a total of 140 thereafter. The purpose of Part C is to evaluate the safety and preliminary clinical efficacy of ADXS-503 in combination with pembrolizumab in subjects who have received no prior systemic treatment in the metastatic setting, and whose tumors express PD-L1 [TPS (Tumor Proportion Score) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations. Toxicities will be evaluated on an ongoing basis in Part B-dose expansion and Part C. If the aggregate rate of treatment-related toxicities that meet the DLT criteria exceeds 33% at any time (across all subjects in Part B dose-expansion and Part C), the findings will be discussed between the Sponsor and study Investigators, and further enrollment may be interrupted. Depending on the nature and grade of the toxicities and after assessing the risk/ benefit, treatment may be adjusted to a lower dose of ADXS-503 or an alternative treatment schedule. In all cases, the dose of pembrolizumab will be fixed at 200 mg. Overall treatment and enrollment stopping rules for this study are described in **Section** 8.1.2.

Summary of study assessments/ procedures	• In Part B, subject must consent to allow the acquisition of fresh or archival FFPE tumor tissue, either a block or unstained slides along with matching blood at baseline, for performance of sequencing analysis. • At least 30 minutes prior to each ADXS-503 infusion, all subjects will receive a pre-infusion prophylactic regimen of adequate hydration, NSAIDs, antihistamines and antiemetics to mitigate the potential for "flu-like" symptoms during or after treatment infusion. Vital signs will be monitored every 30 minutes (±5 minutes) starting immediately prior to each ADXS-503 infusion, until 4 hours after the end of each ADXS-503 infusion. To ensure the clearance of *Lm*, subjects will receive a 7-day course of oral antibiotics starting approximately 48 hours after each ADXS-503 infusion. After the final dose of ADXS-503, a 3-week course of oral antibiotics will be administered to ensure the clearance of *Lm*, which will be confirmed by a blood culture. • Safety will be assessed throughout this study by AE monitoring, physical examination findings, vital sign measurements, monitoring of performance status, and clinical laboratory values. Adverse events will be graded in severity according CTCAE v4.03. • Tumor imaging will be performed by contrast-enhanced CT/MRI as follows: o Part A (ADXS-503 monotherapy): Screening (baseline), at Week 8 (±3 days), at Week 16 (± 7 days), followed by every 9 weeks (±7 days) thereafter, until confirmed disease progression or treatment discontinuation, whichever occurs later. o Part B dose-escalation and Part B dose-expansion (ADXS-503 + pembrolizumab): Screening (baseline) [which corresponds to the most recent tumor assessment that is consistent with PD (according to RECIST v1.1) while on treatment with pembrolizumab monotherapy, or while receiving combination therapy with pembrolizumab + platinum-based chemotherapy or while receiving pembrolizumab + pemetrexed maintenance therapy in the metastatic setting as the last systemic therapy] . Subsequent scans will be performed at Week 8 (±7 days), at Week 16 (± 7 days), followed by every 9 weeks (±7 days) thereafter, until confirmed disease progression or treatment discontinuation, whichever occurs later. As described above, the first dose of ADXS-503 added to pembrolizumab will be administered within 12 weeks of the initial assessment of PD. o Part C (ADXS-503 + pembrolizumab): Screening (baseline), at Week 8 (±7 days), at Week 16 (± 7 days), followed by every 9 weeks (±7 days), until confirmed disease progression or treatment discontinuation, whichever occurs later. • Tumor response will be evaluated by the Investigator (or designee) according to RECIST v1.1 as the basis for the primary analysis of tumor response-based endpoints. Exploratory analysis of tumor-response will be performed by the Sponsor (or designee) according to iRECIST. o In Part A and Part C, subjects may receive study treatment beyond initial Investigator-assessed, RECIST v1.1-defined disease progression, provided the subject is stable and is considered by the Investigator to be deriving clinical benefit. In Part B-dose-escalation and dose-expansion, all subjects will begin study treatment within 12 weeks of initial Investigator-assessed, RECIST v1.1-defined disease progression on treatment with last systemic therapy in metastatic setting (ie, pembrolizumab alone, or combination therapy with pembrolizumab + platinum-based chemotherapy, or pembrolizumab + pemetrexed as maintenance therapy) (if eligibility criteria are met). o In Parts A, B, and C, any apparent CR or PR must be confirmed ≥4 weeks after radiological imaging indicating CR or PR.

	○ Subjects who achieve a confirmed CR may receive up to 2 additional doses of study treatment after the date of confirmed CR but must subsequently discontinue treatment. ○ The following subjects may be eligible for re-treatment upon disease progression, with agreement between the Sponsor and Investigator: ▪ Subjects who achieve a confirmed CR during initial study treatment (Parts A, B, and C). ▪ Subjects in Part B and Part C who stop trial therapy after 2 years of treatment for reasons other than disease progression or intolerability. Note: Tumor response data collected during the re-retreatment period will not be used for the primary analysis of tumor response endpoints. • In Parts A, B and C, evaluable tumor biopsy tissue (fresh or archival) with matched peripheral blood samples must be collected at baseline. to evaluate biomarkers and correlates of immune response. Additional blood samples for correlative work will be collected during the treatment phase. • Following treatment discontinuation, all subjects will enter a 1-year survival/treatment and *Lm* surveillance (*Lm*S) follow-up period. Survival status will be confirmed remotely with the subject, their physician, or their legally authorized representative every 3 months (±2 weeks) for 1 year. In addition, during the *Lm*S Follow-up Period, subjects will be contacted remotely every 3 months (±2 week) for 1 year to determine whether they have experienced for several days, the following symptoms that could potentially be associated with delayed listeremia: fever or chills, headache, nausea, confusion, or changes in alertness (for over 72 hours). As part of the End of Therapy procedures, upon completing the *Lm*S Follow-up Period, site staff should instruct subjects to contact the site if they experience any of these symptoms, as applicable.

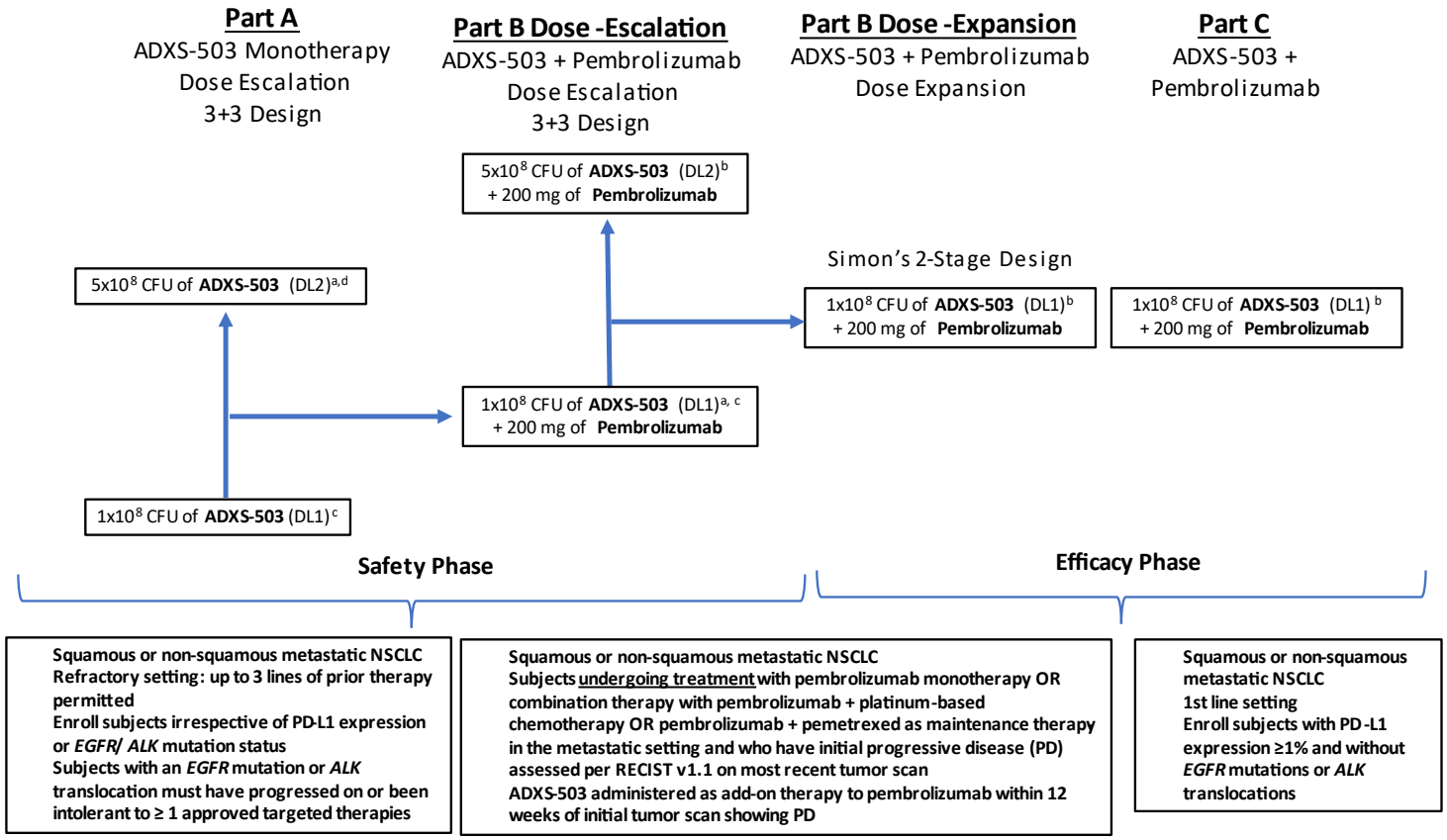


Figure 1. Study Design

a. Escalation to DL2 in Part A will occur in parallel with accrual at DL1 in Part B
b. Upon completion of DL1 in Part B, Dose-expansion of DL1 in Part B will occur in parallel with accrual in Part C. (Accrual in Part B Dose Level 2 may occur upon Sponsor's decision). Upon Investigators' assessment and decision, treatment schedule with $1x10^8$ CFU of ADXS-503 + 200 mg of pembrolizumab, IV, could shift from every 3 weeks to every 6 weeks after the first year of study therapy.

c. If treatment is not safe/tolerable at DL1 in Part A or Part B dose-escalation, a lower dose level (DL -1; $0.5x10^8$ CFU of ADXS-503) will be evaluated before proceeding with Part B and Part C, respectively.
d. Upon completion of dose escalation in Part A, ADXS-503 monotherapy may be evaluated in an expansion cohort.

Abbreviations: DL: dose level.

2. Schedule of Activities (SoA)

2.1. Safety Phase Part A: ADXS-503 Monotherapy

Procedure	Screening[1]	First 12 weeks of treatment [2]												Week 13 to EOT [3]	End of Therapy (EOT)[4]	Safety Follow-Up[21]	1-year Survival/ Treatment & *Lm*S Follow-up Period[22]
	Days -30 to -1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13 to EOT			
Administrative Procedures																	
Informed consent [5]	X																
Eligibility review [6]	X	X															
Issue subject ID card [7]	X																
Demographics	X																
Medical history [8]	X																
Surgical history [9]	X																
Prior cancer history [10]	X																
Prior/Concomitant medications [11]	X	<----------												>	X	X	X [22]
Non-drug treatment/Procedures [12]	X	<----------												>	X	X	
Clinical Procedures																	
Review adverse events [13]	X	<----------												>	X	X	
Physical examination [14]	X	X			X			X			X			X	X		
ECOG performance status [15]	X	X			X			X			X			X	X		
Vital signs [16]	X	X			X			X			X			X	X		
Tumor imaging/ assessments [17]	X								X					X	X		
Pre-infusion prophylaxis [18]		X			X			X			X			X			
Administer ADXS-503 [19]		X			X			X			X			X			
Administer/dispense prophylactic antibiotics [20]		X			X			X			X			X	X		
Safety follow-up phone call/ visit [21]																X	
Survival/*Lm*S remote monitoring [22]																	X
Laboratory Procedures																	
Virology [23]	X																
Coagulation profile [24]	X																
Complete Blood Count (CBC) with differential [25]	X	X			X			X			X			X	X		
Serum chemistry panel [25]	X	X			X			X			X			X	X		
Urinalysis [25]	X	X			X			X			X			X	X		
Pregnancy test [26]	X	X			X			X			X			X			

Procedure	Screening[1]	First 12 weeks of treatment [2]												Week 13 to EOT [3]	End of Therapy (EOT)[4]	Safety Follow-Up[21]	1-year Survival/ Treatment & *Lm*S Follow-up Period[22]
	Days -30 to -1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13 to EOT			
Tumor biopsy sample [27]	X								X						X		
Blood draw for cytokines/ chemokines [28]		X			X			X			X						
Blood draw for immune correlative studies [29]	X	X	X			X			X					X	X		
Blood sample for *Lm* culture [30]																X	

1 Screening procedures will be performed within 28 days (±2 days) prior to the first dose of study treatment to determine study eligibility.

2 Procedures noted here will be performed during the first 12 weeks of study treatment.

3 Procedures noted here will be performed from Week 13 up to the end of therapy (EOT). Refer to Table and indicated footnotes. Subjects will receive study treatment until a treatment discontinuation criterion is met (see **Section** 8.1).

4 EOT procedures noted here should be completed preferably within 7 days of when the decision is made for a subject to discontinue study treatment.

5 Informed Consent must be obtained prior to conducting Screening or baseline evaluations. Procedures conducted as part of the subject's routine clinical management and obtained before signing the Informed Consent Form, may be utilized for Screening or baseline purposes provided the procedures meet the protocol-specified criteria.

6 Subject eligibility (Inclusion/ Exclusion Criteria) must be reviewed during Screening and confirmed prior to the start of study treatment on Day 1 of the study.

7 Subject ID card will identify subject as a participant in this clinical trial and will be provided to subject after Informed Consent is provided. Subject ID card will contain trial site information to be used in case of an emergency and will specify that the subject is enrolled in a clinical trial of an experimental agent that may be associated with immune-mediated toxicity, induced by *Lm*.

8 Medical history will include all active conditions and any prior conditions that are considered by the Investigator to be clinically significant. Medical history will also include an assessment of smoking history.

9 Document any non-cancer surgeries, including, but not limited to the placement of artificial (prosthetic) joints, implants and/or devices, such as port/stent implant placed prior to study enrollment.

10 Document prior cancer history, including prior cancer treatments, surgeries and medications.

11 Prior/concomitant medications will be documented from 30 days prior to Screening until 30 days after the final dose of study treatment.

12 Document any non-drug treatment and surgical procedures including, but not limited to, artificial (prosthetic) joints, implants and/or devices.

13 AEs and SAEs will be assessed starting from the time Informed Consent is obtained through 30 days after the final dose of study treatment or the beginning of any anti-cancer treatment following the discontinuation of study treatment, whichever comes first. Reporting of ESIs will begin from the date of first dose of study treatment. ESIs will be reviewed as they are reported and will be discussed at the time of the dose escalation meetings, and periodically afterwards. All AEs/ECI/SAEs will be followed through resolution. All AEs/ESI/SAEs experienced during this period must be recorded on the eCRF. See **Section** 9.1.5 and Appendix 4**.**

14 A physical examination (PE) must be completed at Screening and within 72 hours prior to the start of each ADXS-503 infusion. Body height will be measured only at Screening. Body weight will be measured at all physical examination timepoints.

15 ECOG performance status to be evaluated at Screening and within 72 hours prior to the start of each ADXS-503 infusion (see Appendix 11).

16 Vital signs will be measured in a semi-supine position after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, pulse, oxygen saturation, and respiratory rate. Vital signs to be measured at Screening. Vital signs will also be measured every 30 minutes (± 5 minutes) starting immediately prior to each ADXS-503 infusion, until 4 hours after the end of each ADXS-503 infusion. Subsequent vital sign monitoring will be performed per institutional standard of care.

17 Tumor response will be evaluated by the Investigator (or designee) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Tumor imaging in Part A will be performed with CT/MRI during Screening (baseline), at Week 8 (±7 days), at Week 16 (±7 days), followed by every 9 weeks (±7 days) thereafter, until confirmed disease progression or treatment discontinuation, whichever occurs later. **Tumor imaging will occur at this schedule, independent of any adjustments to**

Procedure	Screening[1]	First 12 weeks of treatment [2]												Week 13 to EOT [3]	End of Therapy (EOT)[4]	Safety Follow-Up[21]	1-year Survival/ Treatment & *Lm*S Follow-up Period[22]
	Days -30 to -1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13 to EOT			

the treatment schedule. Note: The tumor scan at Week 8 must be performed before the scheduled tumor biopsy at Week 8 (see footnote # 27). See **Section** 9.4.1 and Appendix 10.

18 The pre-infusion prophylactic regimen of adequate hydration, NSAIDs, antihistamines and antiemetics will be administered prior to and will be completed at least 30 minutes before the start of each ADXS-503 infusion.

19 Administer ADXS-503 as a single IV infusion over 60 (±10) minutes, every 3 weeks until a treatment discontinuation criterion is met. See **Section** 7.1 for treatment administration instructions. Treatment with ADXS-503 must occur within **3 days** of the scheduled infusion day (every 3 weeks ±2 days) unless a delay in dosing is required to allow for the resolution of AEs as outlined in **Section** 7.6**.** The interval between each ADXS-503 dose should not be less than 2 weeks without Sponsor approval.

20 All subjects will receive a 7-day course of oral antibiotics after each ADXS-503 infusion to ensure clearance of *Lm.* The first dose of antibiotics will be administered approximately 72 hours after the ADXS-503 infusion. After the final dose of ADXS-503, a 3-week course of oral antibiotics will be administered to ensure the clearance of *Lm* (the first dose administered approximately 48 hours after the final ADXS-503 infusion). See **Section** 9.2.1.3 for the antibiotic regimen.

21 Safety follow-up phone call/ visit to be made 30 days (±5 days) after final dose of study treatment to confirm resolution of any new or ongoing AEs, ESI or SAEs.

22 Following treatment discontinuation, all subjects will enter a 1-year survival/treatment and *Lm* surveillance Follow-up Period.

- Survival status will be confirmed remotely with the subject, their physician, or their legally authorized representative every 3 months (±2 weeks) for up to 1 year.
- Any subsequent anti-cancer treatment received by the subject during this 1-year period will be recorded.
- During the *Lm* surveillance Follow-up Period, subjects will be contacted remotely every 3 months (±2 week) to determine whether they have experienced for several days, the following symptoms that could potentially be associated with delayed listeremia: fever or chills, headache, nausea, confusion or changes in alertness (for over 72 hours). As part of EOT procedures, upon completing the *Lm* Surveillance period, site staff should instruct subjects to contact the site if they experience any of these symptoms, as applicable.

23 HBsAg and HCV screening is required for subjects with a history of active hepatitis B or hepatitis C infection.

24 PT/INR and aPTT must be measured during Screening. Subsequent testing is to be performed only as clinically indicated.

25 All laboratory procedures are to be completed and assessed by the Investigator at Screening and within 72 hours prior to the start of each ADXS-503 infusion, to confirm that safety criteria for study treatment are met. If the Screening samples are obtained within 72 hours of the first dose of ADXS-503, only one set of samples will be required for both timepoints. See Appendix 2.

26 A pregnancy test must be performed at Screening and within 72 hours prior to the start of each ADXS-503 infusion for women of childbearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

27 During Screening, a fresh tumor biopsy must be obtained if clinically feasible, in the opinion of the Investigator for biomarker analysis. If a fresh biopsy cannot be obtained during Screening, the most recently acquired archived tumor biopsy sample may be used for analysis (date of biopsy within 3 years of Screening). For archived tumor biopsy samples, sufficient tumor samples should be acquired to allow biomarker testing (eg, at least 12-15 unstained slides). Tumors biopsied at screening will be designated as pretreatment biopsies. The baseline biopsy must be from a location that has not been radiated. In addition, a fresh on-treatment biopsy must be obtained from a suitable lesion, preferably from a non-target lesion, at Week 8 (± 7 days) or, if not possible, 1 week (±3 days) after next ADXS-503 infusion (Week 11). This on-treatment biopsy sample must be obtained after the scheduled tumor scan at Week 8 (see **Section** 9.4.1 and **Section** 9.5). Note: tumor biopsy samples may not be collected after the first 3 subjects in the dose escalation phase with evaluable samples at each dose level are biopsied, or during expansion cohorts. An EOT biopsy will be done only if the subject is discontinued before Week 7 (3rd dose) Additional matched biopsy tissue and blood samples at baseline and post treatment or End of treatment samples may be collected by sponsor when the Part A expansion cohort is opened.

28 Blood samples for cytokine/chemokine analysis will be collected for the **first 4** ADXS-503 infusions (Weeks 1, 4, 7, and 10) as follows:

- Within 30 minutes prior to the start of each ADXS-503 infusion and 2 hours after the end of each ADXS-503 infusion (± 15 minutes).

Procedure	Screening[1]	First 12 weeks of treatment [2]												Week 13 to EOT [3]	End of Therapy (EOT)[4]	Safety Follow-Up[21]	1-year Survival/ Treatment & *Lm*S Follow-up Period[22]
	Days -30 to -1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13 to EOT			

[29] Blood samples for immune correlative studies (eg, RNAseq, cfDNA, flow cytometry, and ELISpot analysis) will be collected during Screening, Week 1 (ie, right before the first infusion) and 7 days (± 2 days) after the end of each of the **first 3** ADXS-503 infusions (Weeks 2, 5, and 8). To monitor the durability of T cell responses, subsequent blood samples for PBMCs will be taken at Week 25 (±1 week) and/or at EOT.

[30] 7 days (±3 days) after the completion of the 3-week course of oral antibiotics following the final dose of ADXS-503, a blood sample will be collected to culture for *Lm*. If this blood test cultures positive for *Lm*, the subject should receive treatment as outlined in **Section** 9.2.1.3.

2.2. Part B (Safety & Efficacy Phases) and Part C: ADXS-503 + Pembrolizumab

Procedure	Screening[1]	First 12 weeks of treatment [2]												Week 13 to EOT [3]		End of Therapy (EOT)[4]	Safety Follow-Up[23]	1-year Survival/ Treatment & *Lm*S Follow-up Period [24]
	Days -42 to -1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13 to EOT	Wk 25			
Administrative Procedures																		
Informed consent [5]	X																	
Eligibility review [6]	X	X																
Issue subject ID card [7]	X																	
Demographics	X																	
Medical history [8]	X																	
Surgical history [9]	X																	
Prior cancer history [10]	X																	
Prior/Concomitant medications [11]	X	<----------												---------->		X	X	X [24]
Non-drug treatment/Procedures [12]	X	<----------												---------->		X	X	
Clinical Procedures																		
Review adverse events [13]	X	<----------												---------->		X	X	
Physical examination [14]	X	X			X			X			X			X		X		
ECOG performance status [15]	X	X			X			X			X			X		X		
Vital signs [16]	X	X			X			X			X			X		X		
Tumor imaging/ assessments [17]	X								X[17]					X		X		
Administer Pembrolizumab [18,19]		X[18]			X[18]			X[18]			X[18]			X[18]				
ADXS-503 Pre-infusion prophylaxis [20]		X			X			X			X			X				
Administer ADXS-503 [21]		X[18]			X[18]			X[18]			X[18]			X[18]				
Administer/dispense prophylactic antibiotics [22]		X			X			X			X			X		X		
Safety follow-up phone call/ visit [23]																	X	
Survival/follow up and *Lm*S remote monitoring[24]																		X
Laboratory Procedures																		
Virology [25]	X																	
Coagulation profile [26]	X																	

Procedure	Screening[1]	First 12 weeks of treatment [2]												Week 13 to EOT [3]		End of Therapy (EOT)[4]	Safety Follow-Up[23]	1-year Survival/ Treatment & *Lm*S Follow-up Period [24]
	Days -42 to -1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13 to EOT	Wk 25			
Complete Blood Count (CBC) with differential [27]	X	X			X			X			X			X		X		
Serum chemistry panel [27]	X	X			X			X			X			X		X		
Urinalysis [27]	X	X			X			X			X			X		X		
T3, FT4, TSH [27, 28]	X				X						X			X		X		
Pregnancy test [29]	X	X			X			X			X			X				
Tumor biopsy sample [30,]	X																	
PD-L1 expression and EGFR and ALK mutation testing [31]	X																	
Blood draw for immune correlative studies [32]	X	X	X			X			X						X	X		
Blood sample for *Lm* culture [33]																	X	

1 In Part B, screening procedures will be performed within 12 weeks of the most recent tumor assessment showing PD while on treatment with pembrolizumab monotherapy, to determine study eligibility. Subjects must receive the first dose of ADXS-503 within 12 weeks of this initial assessment of PD. ADXS-503 will be administered as add-on therapy to pembrolizumab for at least 4 weeks. In Part C, screening procedures will be performed within 28 days (±2 days) prior to the first dose of study treatment to determine study eligibility.

2 Procedures noted here will be performed during the first 12 weeks of study treatment for Part B andfor Part C.

3 Procedures noted here will be performed from Week 13 (Part Band Part C) up to the end of therapy (EOT). Refer to Table and indicated footnotes. Subjects will receive study treatment for up to 2 years or until a treatment discontinuation criterion is met (see **Section** 8.1).

4 EOT procedures noted here should be completed preferably within 7 days of when the decision is made for a subject to discontinue study treatment.

5 Informed Consent must be obtained prior to conducting Screening or baseline evaluations. Procedures conducted as part of the subject's routine clinical management and obtained before signing the Informed Consent Form, may be utilized for Screening or baseline purposes provided the procedures meet the protocol-specified criteria.

6 Subject eligibility (Inclusion/ Exclusion Criteria) must be reviewed during Screening and confirmed prior to the start of study treatment on Day 1 of the study.

7 Subject ID card will identify subject as a participant in this clinical trial and will be provided to subject after Informed Consent is provided. Subject ID card will contain trial site information to be used in case of an emergency and will specify that the subject is enrolled in a clinical trial of an experimental agent that may be associated with immune-mediated toxicity, induced by *Lm*.

8 Medical history will include all active conditions and any prior conditions that are considered by the Investigator to be clinically significant. Medical history will also include an assessment of smoking history.

9 Document any non-cancer surgeries, including, but not limited to the placement of artificial (prosthetic) joints, implants and/or devices, such as port/stent implant placed prior to study enrollment.

10 Document prior cancer history, including prior cancer treatments, surgeries and medications.

11 Prior/concomitant medications will be documented from 30 days prior to Screening until 30 days after the final dose of study treatment.

12 Document any non-drug treatment and surgical procedures including, but not limited to, artificial (prosthetic) joints, implants and/or devices.

[13] AEs and SAEs will be assessed starting from the time Informed Consent is obtained through 30 days after the final dose of study treatment or the beginning of any anti-cancer treatment following the discontinuation of study treatment, whichever comes first. Reporting of ESIs will begin from the date of first dose of study treatment. ESIs will be reviewed as they are reported and will be discussed at the time of the dose escalation meetings, and periodically afterwards. All AEs/ECI/SAEs will be followed through resolution. All AEs/ESI/SAEs experienced during this period must be recorded on the eCRF. See **Section** 9.1.5 and Appendix4. During the *Lm*S Follow-up Period, AEs and SAEs related to listeremia will be assessed.

[14] A physical examination (PE) must be completed at Screening and within 72 hours prior to the start of study treatment on each treatment day. Body height will be measured only at Screening. Body weight will be measured at all physical examination timepoints.

[15] ECOG performance status to be evaluated at Screening and within 72 hours prior to the start of study treatment on each treatment day (see Appendix 11).

[16] Vital signs will be measured in a semi-supine position after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, pulse, oxygen saturation, and respiratory rate. Vital signs to be measured at Screening. On treatment days, vital signs will be measured prior to the administration of pembrolizumab and subsequently as per institutional standard of care until the administration of ADXS-503. Vital sign monitoring for ADXS-503 will then occur every 30 minutes (± 5 minutes) starting immediately prior to each ADXS-503 infusion, until 4 hours after the end of each ADXS-503 infusion. Subsequent vital sign monitoring will be performed per institutional standard of care.

[17] Tumor response will be evaluated by the Investigator (or designee) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Tumor imaging in **Part B** will be performed with CT/MRI during Screening (baseline), which corresponds to the most recent tumor assessment that is consistent with PD (according to RECIST v1.1) while on treatment with pembrolizumab monotherapy as last therapy, while receiving combination therapy with pembrolizumab + platinum-based chemotherapy or while receiving pembrolizumab + pemetrexed as maintenance therapy, as last therapy in the metastatic setting. The first dose of ADXS-503 will be administered within 12 weeks of the initial assessment of PD. Subsequent scans will be performed at Week 8 (±7 days), at Week 16 (±7 days), followed by every 9 weeks (±7 days) thereafter, until confirmed disease progression or treatment discontinuation, whichever occurs later. Similarly, tumor imaging in Part C will be performed at Screening (baseline), at Week 8 (±7 days), at Week 16 (±7 days), followed by every 9 weeks (±7 days) thereafter, until confirmed disease progression or treatment discontinuation, whichever occurs later **Tumor imaging will occur at this schedule, independent of any adjustments to the treatment schedule**. Note: See **Section** 9.4.1 and Appendix 10.

[18] On each treatment day, pembrolizumab will be infused first, followed approximately 60 (± 15) minutes after the end of the pembrolizumab infusion by the ADXS-503 infusion (see footnote # 19 and footnote # 21). Treatment will continue every 3 weeks starting at Week 1 (±2 days) until the completion of 2 years of treatment, or until another treatment discontinuation criterion is met (see **Section** 8.1).

[19] Administer pembrolizumab as a single IV infusion over 30 (±5) minutes. See **Section** 7.1 for treatment administration instructions. Treatment with pembrolizumab must occur within **3 days** of the scheduled infusion (every 3 weeks ±2 days) day unless a delay in dosing is required to allow for the resolution of AEs as outlined in **Section** 7.6**.** The interval between each pembrolizumab dose should not be less than 2 weeks without Sponsor approval. Treatment will continue every 3 weeks (±2 days) for approximately the first year from the first dose on this study. Thereafter, the PI may decide to continue dosing at Q3W or change to Q6W schedule until the completion of 2 years of treatment on this study (see footnote 21), or until another treatment discontinuation criterion is met (see **Section** 8.1).

[20] The pre-infusion prophylactic regimen of adequate hydration, NSAIDs, antihistamines and antiemetics will be administered prior to and will be completed at least 30 minutes before the start of each ADXS-503 infusion.

[21] Administer ADXS-503 as a single IV infusion over 60 (±10) minutes, every 3 weeks starting at Week 1 (±2 days) until a treatment discontinuation criterion is met. See **Section** 7.1 for treatment administration instructions. Treatment with ADXS-503 must occur within **3 days** of the scheduled infusion day (every 3 weeks ±2 days) unless a delay in dosing is required to allow for the resolution of AEs as outlined in Section 7.6**.** The interval between each ADXS-503 dose should not be less than 2 weeks without Sponsor approval. Upon Investigator assessment and discretion, the treatment schedule of ADXS-503 ($1x10^8$ CFU) + 200 mg of pembrolizumab, IV, could shift from every 3 weeks to every 6 weeks after the first year of study treatment.

[22] All subjects will receive a 7-day course of oral antibiotics after each ADXS-503 infusion to ensure clearance of *Lm.* The first dose of antibiotics will be administered approximately 48 hours after the ADXS-503 infusion. After the final dose of ADXS-503, a 3-week course of oral antibiotics will be administered to ensure the clearance of *Lm* (the first dose administered approximately 48 hours after the final ADXS-503 infusion). See **Section** 9.2.1.3 for the antibiotic regimen.

[23] Safety follow-up phone call/ visit to be made 30 days (±5 days) after final dose of study treatment to confirm resolution of any new or ongoing AEs, ESI or SAEs.

[24] Following treatment discontinuation, all subjects will enter a 1-year survival/treatment Follow-up Period.

- Survival status will be confirmed remotely with the subject, their physician, or their legally authorized representative every 3 months (±2 weeks) for up to 1 year.
- Any subsequent anti-cancer treatment received by the subject during this 1-year period will be recorded.

- During the *Lm* surveillance Follow-up Period, subjects will also be contacted remotely every 3 months (±2 week) for 1 year to determine whether they have experienced for several days, the following symptoms that could potentially be associated with delayed listeremia: fever or chills, headache, nausea, confusion or changes in alertness (for over 72 hours). As part of EOT procedures, upon completing the *Lm* Surveillance period, site staff should instruct subjects to contact the site if they experience any of these symptoms, as applicable. See **Section** 9.2.1.4.

25 HBsAg and HCV screening is required for subjects with a history of active hepatitis B or hepatitis C infection.

26 PT/INR and aPTT must be measured during Screening only if clinically indicated.

27 All laboratory procedures are to be completed and assessed by the Investigator at Screening and within 72 hours prior to the start of study treatment on each treatment day, to confirm that safety criteria for study treatment are met. If the Screening samples are obtained within 72 hours of the first dose of treatment on Day 1, only one set of samples will be required for both timepoints. See Appendix 2.

28 Thyroid function tests to be performed at the local laboratory. Samples will be collected at Screening, followed by every 2 doses of pembrolizumab.

29 A pregnancy test must be performed at Screening and within 72 hours prior to the start of study treatment on each treatment day for women of childbearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Note: a pregnancy test will not be required prior to the first dose of pembrolizumab at Week 2 (it will be required prior to the first ADXS-503 dose at Week 1).

30 During Screening for subjects in Part B and Part C tumor tissue collection with matched blood at screening is **mandatory** for all patients in the study. A fresh tumor biopsy must be obtained if clinically feasible, in the opinion of the Investigator for biomarker analysis. If a fresh biopsy cannot be obtained during Screening, the most recently acquired archived tumor biopsy sample may be used for analysis (date of biopsy within 3 years of Screening). The baseline biopsy must be from a location that has not been radiated. (see **Section** 9.4.1 and **Section** 9.5). Sufficient tumor samples should be acquired to allow biomarker testing (eg, at least 12-15 unstained slides). Tumor tissue and matching blood samples collected during Screening will be used for sequencing analysis.

31 Clinical site must provide documentation of tumor PD-L1 expression and *EGFR* mutation and/or *ALK* translocation status as evaluated by FDA-approved tests in all patients from Part B and Part C. If the site is unable to provide this source documentation, PD-L1 expression and/or *EGFR*/*ALK* testing should be performed per institutional standard of care (see **Section** 9.5). Only subjects whose tumors express PD-L1 [Tumor Proportion Score (TPS)] ≥1% as determined by an FDA-approved test will be eligible for enrollment in Part C (see **Section** 9.4.1 and **Section** 9.5).

32 Blood samples for exploratory immune correlative studies (eg, RNAseq, cfDNA, flow cytometry and ELISPOT analysis) may be collected in up to 25 total patients from Part B and Part C during Screening, at Week 1 (ie, right before the first infusion), and 7 days (±2 days) after the end of each of the **first 3** ADXS-503 infusions (Weeks 2, 5, and 8) and EOT. Samples for cfDNA are only collected at week 1 if samples are not collected during screening. To monitor the durability of T cell responses, subsequent blood samples for PBMCs may be taken at Week 25 (±1 week) and/or at end of treatment.

33 7 days (±3 days) after the completion of the 3-week course of oral antibiotics following the final dose of ADXS-503, a blood sample will be collected to culture for *Lm*. If this blood test cultures positive for *Lm*, the subject should receive treatment as outlined in **Section** 9.2.1.3.

1 .

3. Introduction

3.1. Background on Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer death in the United States, with 154,000 deaths estimated in 2018. Lung cancer is also the second-leading cancer diagnosed in the United States with 234,000 new cases estimated in 2018. Globally, lung cancer is both the leading cause of cancer diagnoses (1.8 million) and cancer deaths (1.6 million) annually (American Cancer Society, 2019; Ferlay, 2015).

Lung cancers can be broadly divided into two histological groups: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Non-small cell lung cancer accounts for approximately 84% of lung cancers and can be subclassified according to squamous and non-squamous (including adenocarcinoma and large cell carcinoma) histological types (Luo, 2013).

Patients diagnosed with early-stage NSCLC may be cured with surgery and/or radiotherapy. However, more than 50% of patients are diagnosed with advanced or metastatic disease, for which systemic treatment is the standard of care (Ferlay, 2015; Luo 2013).

Traditionally, cytotoxic chemotherapy has been the mainstay of front-line treatment for patients with metastatic NSCLC. Multiple randomized clinical trials established platinum-based doublets as the most active regimens, because of a demonstrated improvement in overall survival (OS), when compared with best supportive care (Schiller, 2002). However, chemotherapy yields only a modest clinical benefit and is limited by toxicity and the development of resistance. Only 15-32% of patients treated with platinum-based chemotherapy achieve an objective tumor response, and most patients experience disease progression within 3-6 months (Kelly, 2001; Scagliotti, 2002; Scagliotti, 2008; Schiller 2002).

Over the past decade and a half, progress in characterizing the molecular biology of NSCLC, has provided the opportunity for a targeted therapeutic approach that has advanced the treatment landscape at a rapid pace (Luo 2013). Three key therapeutic milestones were the approval in 2003 and 2004 of the tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib, and the approval in 2006 of the angiogenesis inhibitor, bevacizumab, in combination with platinum-based chemotherapy (Nguyen-Ngoc, 2017; Sandler, 2006; Shepherd, 2005; Stinchcombe, 2007). Multiple TKIs were developed over the next decade for the limited subset of patients with activating mutations in the epidermal growth factor receptor (EGFR) and other mutated proteins that play key roles in cell growth and survival. TKIs are now an established option for front-line management of patients with NSCLC that harbor these mutations (Nguyen-Ngoc 2017; Zappa, 2016).

The next advancement was the development of immune checkpoint inhibitors, which took advantage of pre-existing immune responses to NSCLC, and provided a new treatment option for patients who were not candidates for TKI treatment. Multiple immune checkpoint inhibitors have now been approved for the front-line and later management of NSCLC, firmly establishing immunotherapy as a valid treatment strategy for this malignancy (Malhotra, 2017; Nguyen-Ngoc 2017; Zappa 2016).

A variety of treatment options are available for patients with NSCLC, based on factors that include histology (squamous or non-squamous), the presence of specific biomarkers, and the ability to tolerate treatment with regimens that incorporate bevacizumab (Malhotra 2017; Zappa 2016). However, despite considerable progress, outcomes remain poor for patients with advanced NSCLC. The estimated 5-year survival for all stages of NSCLC combined is approximately 18%, and for patients with metastatic disease, the 5-year survival estimate is less than 5% (American Cancer Society, 2019; Ferlay, 2015).

3.1.1. Mutational Burden in Non-Small Cell Lung Cancer

Genomic sequencing reveals that NSCLC, like other forms of cancer, develops as a consequence of accumulated mutations. These mutations trigger malignant transformation that results in cancer over the course of 2 to 3 decades (Massion, 2003). The concept of mutational burden has been introduced as a way to capture the number of mutations in the genome of a tumor (Alexandrov, 2013). Most mutations in NSCLC are somatically acquired as errors in DNA replication or as DNA damage caused by carcinogens such as tobacco smoke (Liu, 2012).

Some mutations, termed driver mutations, play a key role in oncogenesis and malignant progression. Up to 60% of lung adenocarcinomas and up to 80% of lung squamous cell carcinomas harbor at least one known driver mutation. The remaining tumor mutational burden consists of passenger mutations, which develop as a consequence of the genetic instability that develops in parallel with malignant progression (Alamgeer, 2013; Chan, 2015; Nguyen-Ngoc 2017; Savas, 2013).

Mutations in driver oncogenes or tumor suppressor genes encode for proteins (typically receptor or nonreceptor tyrosine kinases) with altered activity (gain-of-function/ loss-of-function) that stimulate a complex cascade of signaling pathways, such as RAS-RAF-MEK-ERK, PI3K-AKT-mTOR or JAK-STAT, ultimately leading to uncontrolled cell proliferation, evasion of apoptosis, and other oncogenic alterations (Chan 2015).

A notable aspect of mutational burden for most cancers, including NSCLC, is that several mutations occur in a limited set of genes, known as mutation hotspots. Hotspot mutations in NSCLC consist of certain driver mutations that appear with high frequency amongst patients with NSCLC and represent common or shared somatic mutations (Chang, 2016). For example, driver

mutations in *KRAS*, *EGFR* and *BRAF* genes are common in non-squamous NSCLC, and additional oncogenes have recently been documented (eg, *ERBB2*, *MET*, *HRAS* and *NRAS*: Figure 2A) (TCGA, 2014). In squamous cell NSCLC, driver mutations in *TP53*, *CDKN2A*, *PIK3CA*, *PTEN, MLL2* and *NOTCH* genes are common (Figure 2B) (TCGA, 2012).

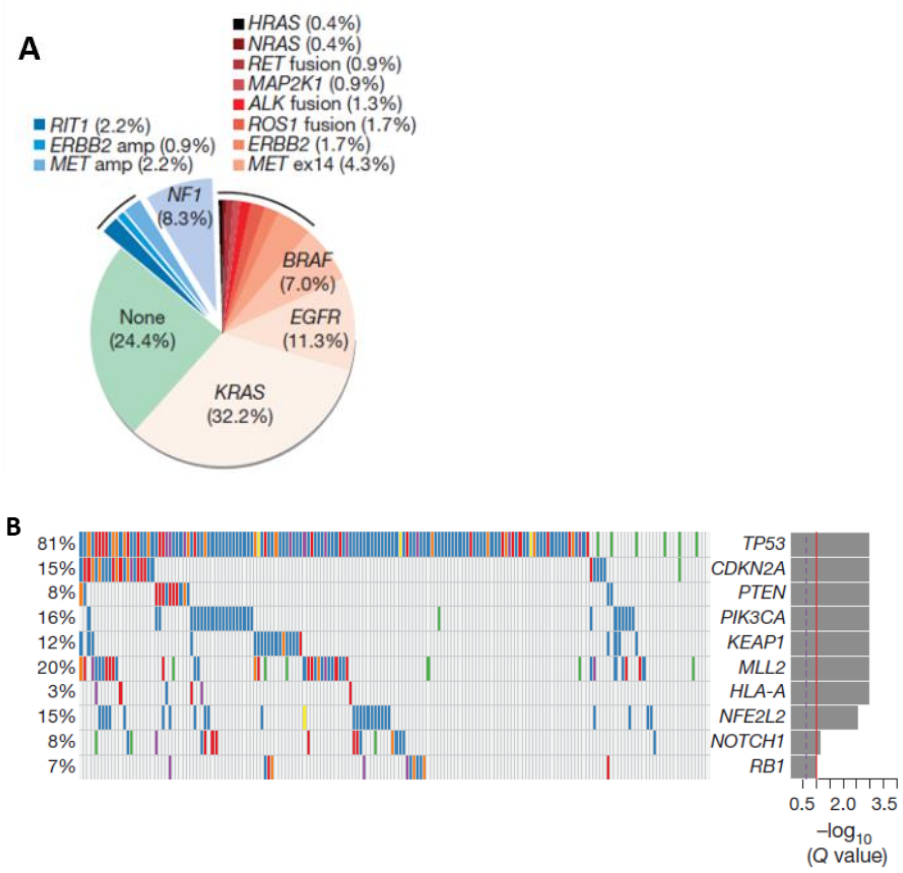


Figure 2. Driver mutations in non-small cell lung cancer.
(A) New candidate driver oncogenes (blue: 13% cases) and known somatically activated driver events (red: 63%) that activate the (RTK)/RAS/RAF pathway in 230 lung adenocarcinomas (TCGA, 2014); (B) Significant mutated genes in squamous cell NSCLC (TCGA, 2012).

In addition to accumulating mutations, tumor cells may abnormally express or overexpress non-mutated genes. Examples of these types of tumor-associated antigens (TAAs) are proteins normally expressed only during embryonic development (oncofetal antigens; OFAs) or cancer testis antigens (CTAs), which are proteins whose normal expression is restricted to male germ cells in the immune-privileged testis. Aberrant expression of OFAs (eg, CEACAM) or CTAs (eg, MAGE, NY-ESO-1) occurs in most patients with NSCLC (Reche, 2005).

3.2. Targeting Driver Mutations in Metastatic Non-Small Cell Lung Cancer

To date, several TKIs have been developed to target certain driver mutations found in NSCLC. These targeted therapies exert their anti-tumor activity by disrupting the molecular signaling pathways of specific mutated proteins, resulting in cancer cell death (Chan 2015; Hirsh, 2018; National Comprehensive Cancer Network (NCCN), 2018; Zappa 2016).

Unfortunately, currently approved TKIs are limited to the subset of patients (~20-25%) that harbor aberrations in *EGFR*, *ALK*, *ROS1* and *BRAF* genes. Other known driver mutations remain unactionable, most notably in squamous cell carcinoma (Chan 2015; NCCN, 2018).

Furthermore, despite objective response rates of up to approximately 80%, the long-term effectiveness of TKI treatment is limited by the inevitable development of acquired resistance, or the presence of resistant subsets of cancer cells from the time of treatment initiation. Most patients treated with currently approved TKIs ultimately experience disease progression within 10-19 months (Chan 2015; Hirsh 2018; Soria, 2018; Zappa 2016).

Therefore, existing targeted approaches with TKI agents are suboptimal, and new treatment strategies are needed.

3.3. Immunotherapy in Metastatic Non-Small Cell Lung Cancer

The recognition that NSCLC tumors harbor a high number of somatic mutations suggests the possibility of utilizing the power of the immune system to attack cancer cells by identifying tumor-specific mutated proteins as antigens. An important advantage of this strategy over TKI therapy, is that the immune system can target mutated proteins regardless of their role in driving malignancy. This means that the mutations that limit the duration of sensitivity to TKIs, will not limit the immune system. Furthermore, the immune system can elicit anti-tumor immunity by recognizing mutated proteins that are currently unactionable with available TKI options (eg, KRAS, TP53, and others).

In addition, the immune system can target TAAs (such as OFAs and CTAs), that are aberrantly expressed in NSCLC tumors, further extending the therapeutic potential of immunotherapy strategies.

Cancer immunotherapy rests on the premise that malignant cells can be recognized as foreign rather than as self and, as such, can be attacked by the immune system. An effective immune response in this setting relies on immune surveillance, where antigens expressed on cancer cells (such as somatic mutation-derived antigens or TAAs) are recognized by the immune system, resulting in an anti-tumor immune response and, ultimately, cancer cell death (Chen, 2013; Dunn, 2002; Zitvogel, 2006). However, tumor cells can employ multiple mechanisms to evade immune

detection. Programmed cell death protein 1 (PD-1) is a cell surface receptor expressed on activated T cells, and when bound to its ligand (PD-L1 or PD-L2) on tumor cells, functions as a checkpoint to halt or limit the anti-cancer T cell response. Aberrant expression of PD-L1 or PD-L2 has been observed in multiple tumor types; clear evidence of how tumors can exploit and co-opt this pathway to avoid immune-mediated eradication of cancerous cells (Carter, 2002; Freeman, 2000; Keir, 2008; Latchman, 2001). Alternatively, tumors may evade immune detection via tumor-mediated recruitment of immunosuppressive cells (including regulatory T cells [Tregs] and myeloid-derived suppressor cells [MDSCs]), which suppress the function of effector T cells (Chen 2013).

One approach to assist the immune system in overcoming these tactics is through the use of immune checkpoint inhibitors. Immune checkpoint inhibitors are a type of immunotherapy that release the brakes on the immune system, thereby improving the ability of tumor-specific T cells to function (Pardoll, 2012). The first immune checkpoint inhibitor, ipilimumab (targeting cytotoxic T-lymphocyte-associated protein 4 [CTLA-4]), was approved for advanced melanoma in 2011 (Hodi, 2010). It is worth noting that melanoma and NSCLC have of the highest mutational burden amongst cancers; a consequence of continual exposure to ultraviolet radiation from the sun, in the case of melanoma, and in large part to the numerous mutagens in cigarette smoke, in the case of NSCLC (Alexandrov 2013). Checkpoint inhibitors have now been successfully developed to treat patients with NSCLC.

To date, the immune checkpoint inhibitors pembrolizumab, nivolumab and atezolizumab have been approved to treat both squamous and non-squamous metastatic NSCLC (Borghaei, 2015; Brahmer, 2015; Herbst, 2016; Langer, 2016; Reck, 2016; Rittmeyer, 2017). These immunotherapies work by interrupting the suppression of pre-existing T cells by blocking the PD-1:PD-L1/PD-L2 checkpoint axis, which normally halts or limits a T cell response. All three checkpoint inhibitors (pembrolizumab, nivolumab and atezolizumab) have demonstrated meaningful clinical benefit over docetaxel as monotherapy in the second-line setting and are currently approved (Borghaei, 2015; Brahmer, 2015; Herbst, 2016; Rittmeyer, 2017). In the first-line setting, pembrolizumab has also been approved as monotherapy and in combination with chemotherapy (Brahmer, 2017; Langer 2016; Reck 2016). Additional studies are under evaluation with pembrolizumab, nivolumab, and atezolizumab in the first-line setting, as described below.

3.3.1. Immune Checkpoint Inhibitors in First-Line Metastatic Non-Small Cell Lung Cancer

Pembrolizumab is approved as monotherapy in the first-line setting, in patients with squamous or non-squamous metastatic NSCLC, with high PD-L1 expression (≥50%) and without an *EGFR* or *ALK* mutation. Pembrolizumab received approval in this setting based on the results from the Keynote 024 study, which evaluated pembrolizumab monotherapy compared with platinum-based

chemotherapy. Updated data with a median follow-up of 2 years, showed an improvement in OS (median of 30 months vs. 14.2 months; hazard ratio [HR]=0.63), progression-free survival (PFS) (median of 10.3 vs. 6 months; HR=0.50) and objective response rate (ORR) (45.5% vs. 29.8%) in favor of pembrolizumab (Brahmer 2017; Reck 2016).

Pembrolizumab has also received accelerated approval in the first-line setting in combination with pemetrexed and carboplatin chemotherapy, in patients with non-squamous metastatic NSCLC and without an *EGFR* or *ALK* mutation (irrespective of PD-L1 expression). Accelerated approval in this setting was based on the results from the Keynote 021 study. Updated data with a median follow-up of 23.9 months, showed a 14.7-month median increase in PFS (median of 24 months vs. 9.3 months; HR=0.53) and an improvement in ORR (57% vs. 30%) for the combination of pembrolizumab with pemetrexed-carboplatin compared with pemetrexed-carboplatin alone. The HR for OS was 0.56 in favor of the pembrolizumab combination (OS data are immature) (Gentzler, 2018; Langer 2016).

The confirmatory trial (Keynote 189) in subjects with treatment-naïve non-squamous metastatic NSCLC and without an *EGFR* or *ALK* mutation is ongoing. In this trial, subjects are randomized in a 2:1 ratio to receive pemetrexed-platinum chemotherapy in combination with pembrolizumab or placebo for 4 cycles, followed by pembrolizumab or placebo for up to 35 cycles with pemetrexed maintenance. Preliminary data, with a median follow-up of 10.5 months, showed a 3.9-month median increase in PFS (8.8 months vs. 4.9 months; HR=0.52), and a 12-month OS rate benefit (69.2% vs. 49.4%; HR=0.49) for the combination of pembrolizumab and chemotherapy compared with placebo and chemotherapy. The benefit in PFS and 12-month OS rate was observed irrespective of PD-L1 expression. The ORR and duration of response for each arm was 47.6% vs. 18.9% and 11.2 months vs. 7.8 months, respectively (Gandhi, 2018).

In subjects with metastatic squamous cell NSCLC, pembrolizumab has been evaluated in the first-line setting in combination with carboplatin-paclitaxel/nab-paclitaxel vs. placebo and carboplatin-paclitaxel/nab-paclitaxel (Keynote 407). In this trial, subjects are randomized in a 1:1 ratio to receive chemotherapy with pembrolizumab or placebo for 4 cycles, followed by pembrolizumab or placebo for up to 35 cycles. Preliminary data, with a median follow-up of 7.7 months, showed a 4.6-month improvement in median OS (median of 15.9 vs. 11.3 months; HR=0.64) with pembrolizumab in combination with chemotherapy compared with placebo and chemotherapy. The benefit in OS was observed irrespective of PD-L1 status. Progression-free survival (median of 6.4 months vs. 4.8 months; HR=0.56) and ORR (58.4% vs. 35%) also favored the combination of pembrolizumab with chemotherapy (Paz-Ares, 2018). Pembrolizumab in combination with chemotherapy in this setting, is yet to be approved.

Progression-free survival and OS have also been evaluated in the first-line setting with nivolumab in combination with ipilimumab vs. chemotherapy, in subjects with metastatic squamous or non-

squamous NSCLC, without *EGFR* or *ALK* mutations, and with a high tumor mutational burden (≥10 mutations per megabase). In this study (CheckMate 227), the PFS amongst subjects with high tumor mutational burden was improved with nivolumab + ipilimumab compared with chemotherapy. The 12-month PFS rate was 42.6% with nivolumab + ipilimumab vs. 13.2% with chemotherapy, and the median PFS was 7.2 vs. 5.5 months (HR=0.58). The ORR was 45.3% for nivolumab + ipilimumab and 26.9% with chemotherapy. The combination of nivolumab + ipilimumab in this setting, is yet to be approved (Hellmann, 2018).

Furthermore, atezolizumab has been evaluated in the first-line setting in combination with platinum-based chemotherapy and bevacizumab in subjects with metastatic non-squamous NSCLC (IMpower 150). Subjects were enrolled in this trial irrespective of PD-L1 expression, and without regard to *EGFR* or *ALK* mutation status. Updated data with a median follow-up of approximately 15 months, showed a 1.5-month median increase in PFS (median of 8.3 months vs. 6.8 months; HR=0.617) for the combination of atezolizumab with chemotherapy-bevacizumab compared with chemotherapy-bevacizumab alone. The improvement in PFS was observed across all PD-L1 subgroups (Socinski, 2018). Additionally, in subjects with metastatic squamous cell NSCLC, the combination of atezolizumab with carboplatin-paclitaxel or carboplatin-nab-paclitaxel vs. carboplatin-nab-paclitaxel is under evaluation in the IMpower 131 trial. Preliminary data, with a median follow-up of 17.1 months, showed a median PFS benefit of 0.7 months for atezolizumab in combination with carboplatin-nab-paclitaxel vs. carboplatin-nab-paclitaxel (6.3 months vs. 5.6 months; HR= 0.715). The PFS benefit was observed across all PD-L1 subgroups. The ORR was 49% and 41% for each group, respectively (Jotte, 2018).

3.3.2. The Unmet Need for New Immunotherapies to Treat Patients with Metastatic Non-Small Cell Lung Cancer

While PD-1/ PD-L1 checkpoint inhibitors have improved the treatment paradigm for metastatic NSCLC, the data described above shows that only approximately one-half of patients achieve an objective tumor response. Moreover, the PFS data in Keynote 189, Keynote 407, IMpower 150, IMpower 131 and CheckMate 227 show that approximately 50-60% of patients experience disease progression within one year of combination therapy with PD-1/ PD-L1 checkpoint inhibitors, regardless of the agents used (eg, VEGF inhibitor, ipilimumab and/or chemotherapy). This suggests that in metastatic NSCLC, the efficacy of immune checkpoint inhibitors requires the presence of another element of the immune response; a missing element.

Several insights suggest ways to optimize the anti-cancer activity of immune checkpoint inhibitors. The first insight is that pre-existing anti-cancer immunity is a pre-requisite for the activity of checkpoint inhibitors (Dammeijer, 2017). Secondly, the mutational burden, and thus number of mutation-derived tumor antigens, is an important determinant of the activity of checkpoint

inhibitors (Goodman, 2017; Rizvi, 2015). Furthermore, immunosuppressive factors (such as Tregs and MDSCs) in the tumor microenvironment (TME) are able to establish or maintain immune tolerance despite inhibition of immune checkpoints (Weber, 2018).

These observations suggest that an immunotherapeutic option that could directly 1) activate innate immunity to create an environment that supports anti-cancer immune system activation; 2) increase the number and breadth of T cells specific for NSCLC-associated tumor antigens and 3) reduce the immunosuppressive actions of MDSCs and Tregs within the TME, would be a promising approach to improve treatment outcomes.

3.4. Overview of ADXS-503

The first step of effective immunotherapy is to alert the immune system to the presence of cancer by delivering tumor-specific antigens to antigen-presenting cells (APCs). Since the immune system's raison d'être is to detect and eliminate infection, an infection or an apparent infection is the best method to engage the immune system.

ADXS-503 is a live attenuated *Listeria monocytogenes (Lm)*-based immunotherapy entering clinical development for the treatment of squamous and non-squamous NSCLC. ADXS-503 is bioengineered to secrete an antigen-adjuvant fusion protein consisting of a truncated nonhemolytic fragment of listeriolysin O (tLLO) fused to a total of 22 tumor antigens. Of these tumor antigens, 11 consist of peptides derived from tumor-specific somatic mutations that commonly occur in NSCLC patients ('hotspot mutation peptide antigens'), and 11 consist of sequence-optimized peptide antigens derived from commonly occurring tumor-associated antigens ('sequence-optimized TAA peptide antigens'), which include OFAs and CTAs. The *Lm* component of ADXS-503 serves as a delivery system for these tumor antigens, which are present in intra-bacterial plasmid constructs, the other component of ADXS-503. The proposed mechanism of action of ADXS-503 is to stimulate both the innate and adaptive immune systems to initiate a coordinated anti-tumor response culminating in the *de novo* generation of tumor antigen-specific T cells that are capable of infiltrating and destroying NSCLC tumors that express the targeted antigens.

ADXS-503 was designed so that 42% of patients with NSCLC will express at least one of the targeted hotspot mutation peptide antigens and that >90% will express at least one of the TAAs targeted by the sequence-optimized TAA peptide antigens. By combining these shared, commonly expressed antigen targets into a single *Lm*-based immunotherapy, ADXS-503 provides the potential for a potent, disease-specific approach to treating patients with NSCLC.

In addition to the generation of antigen-specific T cell responses, treatment with *Lm*-based immunotherapies has been shown to reprogram the TME, by reducing the frequencies and function of immunosuppressive Tregs and MDSCs within the TME, and upregulating PD-L1 expression (see **Section** 3.4.2).

ADXS-503 was developed to be used alone and in combination with standard of care agents in NSCLC, such as immune checkpoint inhibitors. In combination with immune checkpoint blockade, ADXS-503 has the potential to optimize immunotherapy, and even produce synergistic clinical activity, given complementary mechanisms of immune stimulation and reversal of immune tolerance (see **Section** 3.4.5 for clinical and nonclinical data supporting this approach).

Based on these properties, ADXS-503 is a promising cancer immunotherapy for treating patients with metastatic squamous or non-squamous NSCLC. Please refer to the ADXS-503 Investigator's Brochure (IB) for additional details.

3.4.1. Description of ADXS-503 Construct

ADXS-503 consists of LmddA, a highly attenuated strain of *Lm* bacteria, stably transformed with a DNA plasmid that expresses tLLO, an adjuvant (refer to **Section** 3.4.2), fused to 11 hotspot mutation peptide antigens and 11 sequence-optimized peptide antigens derived from TAAs. The TAA-derived peptide antigens expressed by the ADXS-503 construct were selected based on their binding affinity to 4 common HLA alleles, which cover >90% of patients with NSCLC in North America and Western Europe.

The 11 shared hotspot mutation peptide antigens are from 7 genes and represent the most frequent somatic alterations in a proprietary mutational database from over 600 patients with NSCLC. These hotspot mutations occur in oncogenic driver genes, such as *KRAS* and *PIK3CA*, and in tumor suppressor genes such as *TP53*. Approximately 42% of patients with squamous or non-squamous NSCLC have at least one hotspot mutation that is targeted by ADXS-503.

The 11 sequence-optimized TAA peptide antigens are derived from proteins, such as NY-ESO-1 and CEACAM5, that have been shown to be immunogenic in NSCLC patients. The sequence-optimized TAA-derived peptide antigens have been selected for wide expression across NSCLC tumors, with 7 of the selected TAA-derived peptide antigens expressed in all patients with NSCLC. These peptides have been sequence-optimized to increase binding affinity to the most common HLA types in North America and Western Europe. Enhancing peptide binding to a specific MHC class I allele increases the potential for recognition by tumor-specific T cells.

Please refer to the ADXS-503 IB for additional details on the ADXS-503 construct.

3.4.2. Mechanism of Action

As a live attenuated bacterium, the *Lm*-based vector is rapidly taken up by APCs that recognize the bacteria as foreign. The uptake of the *Lm*-based vector results in the activation and maturation of not only the **APC** but also other **innate immune cells** through their recognition of *Lm*-specific PAMPs (pathogen-associated molecular patterns) and DAMPs (damage-associated molecular patterns). Once inside the APC, ADXS-503 can escape the phagosome and enter the cytosol, where

it secretes fusion proteins consisting of tLLO attached to the selected hotspot mutation peptide antigens and sequence-optimized TAAs. These fusion proteins, along with other secreted *Lm* proteins, are transported to the proteasome and degraded into peptides that subsequently enter the **MHC class I antigen presentation pathway**. Not all bacteria, however, are able to escape the phagosome before phagosome-lysosome fusion. ADXS-503-derived proteins that are degraded into peptides in the phagolysosome gain access to the **MHC class II antigen presentation pathway**. The presentation of ADXS-503-derived peptides by MHC class I and class II molecules on the surface of activated APCs stimulates the **generation of hotspot mutation- and TAA-specific CD4$^+$ and CD8$^+$ T cells** and culminates in T cell infiltration and destruction of tumors expressing one or more of these antigens (Wood, 2014).

In addition to the generation of antigen-specific T cell responses, treatment with *Lm*-based immunotherapies has been shown to **reprogram the TME**. First, administration of an *Lm*-based immunotherapy triggers the expression of chemokines and chemokine receptors that recruit effector T cells from tumor-draining lymph nodes into the core of the tumor (Guirnalda, 2013). Second, administration of an *Lm*-based immunotherapy reduces the relative number and suppressive function of intratumoral Tregs and MDSCs (Wallecha, 2013). Overcoming the immunosuppressive TME that often characterizes solid tumors in patients with advanced cancers, such as metastatic NSCLC, is critical to enabling an effective immunologic response to the cancer. An increase in the ratio of CD8+ tumor-infiltrating leukocytes to Tregs, as a result of the administration of an *Lm*-based immunotherapy, has been observed in a variety of mouse tumor models (Chang, 2014). Finally, in preclinical studies, *Lm*-based immunotherapies induced the expression of PD-L1 on both tumor cells and tumor-infiltrating macrophages in a HPV+ murine tumor model that normally does not express PD-L1 (Figure 3). Therefore, *Lm*-based immunotherapies have been shown to reprogram the TME and to **convert a nonimmunogenic "cold" tumor to an immunogenic "hot tumor"**. This supports the combination of *Lm*-based immunotherapies with immune checkpoint inhibitors, as described in **Section** 3.4.5.1.

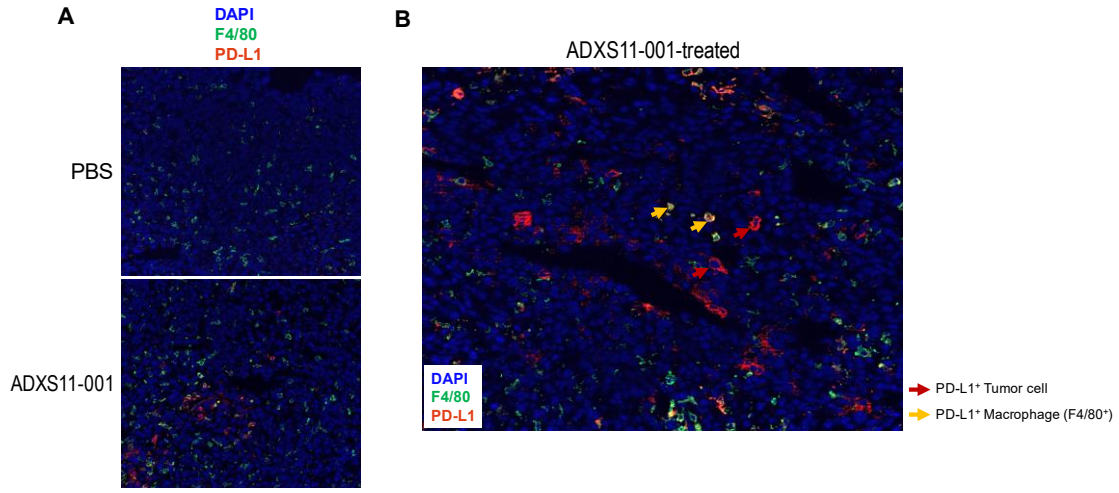


Figure 3. *Lm*-based immunotherapies induce expression of PD-L1 on tumor cells and tumor-infiltrating macrophages in a HPV+ murine tumor model.
C57BL/6 mice were implanted with $1x10^5$ HPV^+ TC-1 tumor cells in the hind flank. Tumor-bearing mice were then treated on Day 8 post-tumor implantation with phosphate buffered saline (PBS) or ADXS11-001 (*Lm* vector expressing the full length E7 protein of HPV 16) and at 7-day intervals thereafter for a total of 3 doses. Tumors were harvested on Day 24 post-implantation, embedded in OCT compound, sectioned, and then stained with antibodies against PD-L1 (red) and the macrophage marker F4/80 (green) for immunofluorescence microscopy. A) PD-L1 (red) expression is detected in tumors of ADXS11-001-treated mice but not in tumors of PBS-treated mice. B) In the tumors of ADXS11-001 treated mice, PD-L1 expression is detected on both TC-1 tumor cells (examples highlighted with red arrows) and tumor-infiltrating macrophages (examples highlighted with yellow arrows).

Please refer to the ADXS-503 IB for additional details on the mechanisms of action of Advaxis' *Lm*-based immunotherapies.

3.4.3. Nonclinical Studies with ADXS-503

The ability of ADXS-503 to inhibit tumor growth was evaluated in the CT26 mouse tumor model, which expresses the G12D hotspot mutation in Kras. Eight-week-old female BALB/c mice (n=40) were injected subcutaneously with $3x10^5$ CT26 tumor cells in the hind flank on Day 0. Mice (n=10 per group) subsequently received 1 of the following 4 treatments on Days 4, 11 and 18 post-tumor implantation:

- Phosphate buffered saline (PBS; vehicle control);
- $1x10^8$ colony forming units (CFU) of LmddA-274, a non-TAA expressing *Lm* vector;
- $1x10^8$ CFU of ADXS-503;
- $1x10^8$ CFU of ADXS-Kras G12D, an *Lm* vector expressing only the Kras G12D mutation, as a 21-mer, from the ADXS-503 construct.

Tumor growth was monitored by measuring tumor volume twice weekly for 24 days after tumor implantation. See Figure 4A for the experimental design.

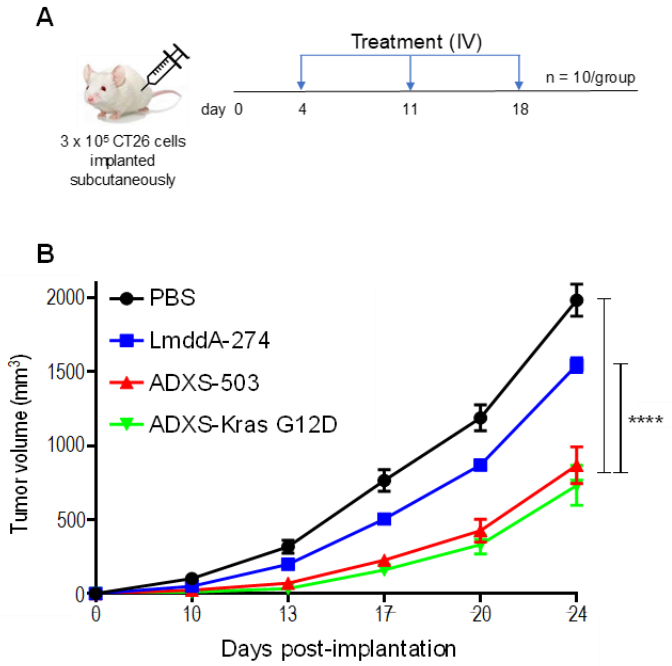


Figure 4. Both ADXS-503 and ADXS-Kras G12D, an *Lm*-based vector targeting a single Kras hotspot mutation, significantly inhibit the growth of CT26 tumors.
A) BALB/c mice were implanted with $3x10^5$ CT26 tumor cells in the hind flank. Tumor-bearing mice were then treated on Day 4 post-tumor implantation with PBS, LmddA-274 (empty *Lm* vector control), ADXS-503 or ADXS-Kras G12D (*Lm* vector expressing the Kras G12D mutation as a 21mer) and at 7-day intervals thereafter for a total of 3 doses. Tumor volume was measured twice a week. B) tumor growth curves for all treatment groups. ****P< .0001. Data are representative of 2 independent experiments.

As shown in **Figure 4B**, ADXS-503 significantly delayed tumor growth compared with control groups (PBS and LmddA-274), demonstrating the potential for ADXS-503 to prime an effective anti-tumor immune response against tumors that harbor at least 1 antigen expressed by the ADXS-503 construct. In addition, the anti-tumor activity of ADXS-Kras G12D was equivalent to that of ADXS-503, indicating that a peptide antigen derived from a single hotspot mutation and expressed by an *Lm*-based vector can inhibit tumor growth.

Please refer to the ADXS-503 IB for additional details on the anti-tumor activity of ADXS-503 in the CT26 tumor model experiments. The IB also describes other nonclinical studies with *Lm*-based immunotherapies that support the use of ADXS-503 in humans.

3.4.4. Clinical Experience with ADXS-503

3.4.4.1. Clinical Safety with ADXS-503

This is the first study of ADXS-503 in the clinic where humans were dosed, and therefore, clinical data are limited. However, because Advaxis *Lm*-based immunotherapies share a common platform and are bioengineered and manufactured in a similar manner, the clinical safety profile of

ADXS-503 is expected to be similar to that of other *Lm*-based immunotherapies. Therefore, the following clinical safety data across the Advaxis *Lm* immunotherapy platform is presented.

As of November 2020, clinical safety data are available for 540 subjects enrolled in 14 clinical studies with Advaxis *Lm*-based immunotherapies including ADXS-HPV (ADXS11-001), ADXS-PSA (ADXS31-142), and ADXS-NEO. These agents have been evaluated in subjects with human papillomavirus (HPV)-associated cancers, prostate cancer, metastatic solid tumors, and in personalized *Lm*-based cancer immunotherapy, respectively. A total of over 1,500 doses have been administered to subjects at doses ranging from $5x10^7$ to $1x10^{10}$ CFU every 3 or 4 weeks. Overall, Advaxis *Lm*-based immunotherapies have been safe and well-tolerated.

The toxicity induced by *Lm*-based immunotherapies is a consequence of activation of the innate immune system shortly after treatment infusion. The specific treatment-induced signs and symptoms are caused by the interaction of the innate immune system with the *Lm* bacteria. Since the core *Lm* structure of *Lm*-based immunotherapies is the same, these agents should produce the same pattern of toxicity. The adaptive immune response is not expected to be different because *Lm*-based immunotherapies will induce T cell responses against *Lm*- and tumor-specific antigens, but not against normal host tissue. In other words, since the antigenic peptides expressed by ADXS-503 are derived from hotspot mutations or OFAs/CTAs present in NSCLC cells, ADXS-503 is not expected to induce reactivity with normal tissue.

From clinical experience with *Lm*-based immunotherapies, a clear pattern of treatment-related AEs (TRAEs) has emerged, which is consistent with immune cell activation. The AEs typically consist of transient Grade 1-2 (mild-moderate) AEs such as chills, pyrexia, nausea, vomiting, fatigue, headache, tachycardia and hypotension, and appear during or shortly after treatment infusion. Grade 3 or Grade 4 hypotension is a manageable Event of Special Interest that occurs in ~7% of subjects treated with *Lm*-based immunotherapy. The symptoms usually resolve within 2 to 4 hours after infusion without specific intervention or respond rapidly to limited symptomatic treatment within 30 minutes to 1 hour. To date, there is no evidence of cumulative toxicity with subsequent dosing of *Lm*-based immunotherapy. Moreover, since incorporating a mandatory pre-infusion regimen into clinical trials, including adequate hydration, NSAIDs, antihistamines and antiemetics as key components, the incidence of acute signs and symptoms during or after treatment infusion, has been reduced.

The largest clinical experience with *Lm*-based immunotherapies is in 478 subjects treated with ADXS11-001, alone or in combination with other agents. Treatment-related AEs with ADXS11-001 monotherapy in Advaxis Sponsored clinical trials, are shown in Table 1. Refer to the ADXS-503 IB for safety data across the Advaxis *Lm*-based immunotherapy platform.

Table 1: Treatment-Related Adverse Events Reported ≥5% with ADXS11-001 Monotherapy in Advaxis Sponsored Trials

	n (%) Adverse Events (N=192)[a]	
System Organ Class Preferred Term	**All Grades**	**Grade 3 or 4**
Cardiac disorders		
Tachycardia	15 (7.8%)	0
Gastrointestinal disorders		
Diarrhoea	10 (5.2%)	1 (0.5%)
Nausea	54 (28.1%)	0
Vomiting	48 (25.0%)	1 (0.5%)
General disorders and administration site conditions		
Chills	91 (47.4%)	0
Influenza like illness	11 (5.7%)	0
Pain	10 (5.2%)	0
Pyrexia	70 (36.5%)	3 (1.6%)
Immune system disorders		
Cytokine release syndrome	15 (7.8%)	7 (3.6%)
Investigations		
Aspartate aminotransferase increased	13 (6.8%)	0
Blood alkaline phosphatase increased	11 (5.7%)	2 (1.0%)
Gamma-glutamyltransferase increased	15 (7.8%)	3 (1.6%)
Metabolism and nutrition disorders		
Decreased appetite	10 (5.2%)	0
Musculoskeletal and connective tissue disorders		
Back pain	12 (6.3%)	0
Myalgia	12 (6.3%)	0
Nervous system disorders		
Dizziness	14 (7.3%)	0
Headache	41 (21.4%)	0
Vascular disorders		
Hypotension	46 (24.0%)	12 (6.3%)

[a] Subjects who were dosed on or before 22 Dec 2017, including 24 subjects from study ADXS001-02 which had a 2:1 randomization between ADXS11-001 and placebo.
Note: Adverse events with onset on or before 22 Dec 2017 are included.

The Phase 1 study of ADXS-NEO (ADXS-NEO-02), a fully personalized *Lm*-based immunotherapy that expresses somatic mutation-derived neoantigens specific to each subject's tumor, is completed. Data are available for 2 subjects treated during the dose-escalation portion of the study at dose level 1 ($1x10^9$ CFU). Of these 2 subjects, as of August 2018, 1 subject with NSCLC experienced Grade 3 hypoxia and 1 subject with colorectal cancer experienced Grade 3 hypotension and Grade 3 hypoxia post-administration of the second dose. These events were

reported after the second dose of ADXS-NEO in both cases. The event of Grade 3 hypotension resolved within the first 24 hours, while both cases of Grade 3 hypoxia were more persistent, resolving in a few days. Prior medications and comorbidities were confounding factors in the genesis of hypoxia. Subsequently, 3 subjects completed ADXS-NEO therapy at 1×10^8 CFU dosing level; this dose was well-tolerated for subjects with advanced or metastatic solid tumors.

High-grade (≥ Grade 3) hypotension and/or hypoxia are considered Events of Special Interest with *Lm*-based immunotherapy treatment. An updated algorithm for the management of high-grade, acute toxicities during or after treatment infusion (including hypotension, hypoxia, encephalopathy, and organ toxicity) can be found in Appendix 7.

Although rare, there have been two (2) reported cases of listeremia, in which attenuated *Lm* was found to be growing on implanted medical devices after the completion of study treatment. As a key safety measure with *Lm*-based immunotherapies, a 7-day course of post-infusion antibiotics are administered to ensure the clearance of *Lm*. Additionally, following the final dose of treatment, a 3-week course of antibiotics is administered to ensure the clearance of *Lm* (see **Section** 9.2.1.3 for additional details). Furthermore, clinical trials with *Lm*-based immunotherapies prohibit the enrollment of subjects with implantable medical devices that can serve as a nidus of infection, further mitigating the risk of listeremia.

In the Phase 1 study for ADXS11-001 (n=15 subjects), *Lm* was not detected in the blood of any subject beyond 48 hours post dose. Additionally, in the absence of post-infusion antibiotic treatment, *Lm* was not shed in the urine or feces of any subject at the highest dose level tested ($1x10^{10}$ CFU) (Maciag, 2009). ADXS-503 is expected to have the same profile as ADXS11-001 in this regard.

Preliminary data from the ongoing ADXS-503-101study shows that ADXS-503 either alone (Part A) or in combination with Pembrolizumab (Part B-DL1 and Part C) appears to be safe and tolerable. Transient Grade 1–2 adverse events like fever, chills, and nausea were common after the infusion of ADXS-503. In 16 patients so far evaluated in the ongoing study, 7 treated with ADXS-monotherapy ($1x10^8$ and $5x10^8$ CFU) and 9 in combination with ADXS-503 ($1x10^8$ CFU) with pembrolizumab, there have been no dose-limiting toxicity events or events of high grade (eg, hypotension or hypoxia) as observed in the past at higher doses with other *Lm* constructs (Table 2).

Table 2: Treatment-Related Adverse Events, All Treated

	Part A		Part A DL1 + DL2 (N=7)	Part B Dose Level 1 (N= 7)	Part C Dose Level 1 (N=2)
	DL 1 (N=4)	D L 2 (N=3)			
≥ Grade 3 events					
Infusion related reaction	0	1 (33.33)	1 (14.28)	0	0
Grade 1 & 2					
Pyrexia	0	1 (33.33)	1 (14.28)	2 (28.57)	0
Chills	0	1 (33.33)	1 (14.28)	2 (28.57)	0
Influenza like illness	0	1 (33.33)	1 (14.28)	0	0
Nausea	0	1 (33.33)	1 (14.28)	0	0
Back pain	0	1 (33.33)	1 (14.28)	0	0
Neck pain	0	1 (33.33)	1 (14.28)	0	0
Rash	0			1 (14.28)	0
Acute kidney injury	0	1 (33.33)	1 (14.28)	0	0
Alanine aminotransferase increased	0	1 (33.33)	1 (14.28)	0	0
Aspartate aminotransferase increased	0	1 (33.33)	1 (14.28)	0	0

DL = Dose Levele. Comment about “Acute Kidney Injury” and elevation of liver enzymes were transient and in different patients and in all cases, patients recovered after brief hospitalization?

Please refer to the ADXS-503 IB for additional details on the clinical experience with *Lm*-based immunotherapies.

3.4.4.2. Clinical Efficacy with ADXS-503

ADXS-503 has not previously been administered to humans, and therefore, clinical efficacy data is not yet available.

3.4.5. Combination of *Lm*-Based Immunotherapy with an Immune Checkpoint Inhibitor

3.4.5.1. Rationale for Combining *Lm*-Based Immunotherapy with an Immune Checkpoint Inhibitor

ADXS-503 and immune checkpoint inhibitors have complementary mechanisms of immune activation and reversal of immune tolerance (see **Section** 3.3 and **Section** 3.4). ADXS-503 induces the generation of tumor-specific T cells, whereas pembrolizumab inhibits the PD-1/PD-L1 checkpoint, allowing the T cells to engage in a more sustained attack against the tumor. Therefore, combining both agents in a dual-treatment approach, has the potential to provide synergistic anti-cancer activity.

As described in **Section** 3.4.2, *Lm*-based immunotherapies elicit innate immunity, generate antigen-specific T cell responses and reprogram the TME. Specifically, *Lm*-based immunotherapies 1) trigger the expression of chemokines and chemokine receptors that recruit effector T cells from tumor-draining lymph nodes into the tumor core; 2) reduce the frequencies and function of immunosuppressive Tregs and MDSCs in the TME; and 3) induce the expression of PD-L1 in the TME (Chang 2014; Guirnalda 2013; Wallecha 2013). These are hallmark characteristics of an immunogenic or "hot" tumor and provide support for the combination of ADXS-503 with PD-1/PD-L1 checkpoint inhibitors (Sharma, 2015).

In a non-randomized clinical trial, the combination of ADXS-PSA with pembrolizumab in subjects with metastatic castrate-resistant prostate cancer (mCRPC) produced a 56.8% rate of disease control, whereas ADXS-PSA produced a 38.5% rate of disease control (Stein, 2018). These findings included stabilization of disease in subjects who presented with non-measurable disease (either soft tissue disease, bony disease, or both). Notably, *PDCD1* (PD-1) and *CD274* (PD-L1) expression were upregulated in PBMCs following a single dose of ADXS-PSA in this trial (Advaxis Internal Data). These results suggest that the upregulation of PD-L1 expression may be a key mechanism through which *Lm*-based immunotherapies can achieve clinical synergy when administered in combination with PD-1/PD-L1 checkpoint inhibitors. Furthermore, an optimal combination strategy may be to prime T cell immunity and induce the upregulation of PD-L1 expression before administering the first dose of a PD-1/ PD-L1 checkpoint inhibitor.

Please refer to the ADXS-503 IB for additional details.

3.4.5.2. Safety of *Lm*-Based Immunotherapy with an Immune Checkpoint Inhibitor

The known toxicity profile of *Lm*-based immunotherapies is generally non-overlapping with that of immune checkpoint inhibitors. In clinical trials combining *Lm*-based immunotherapies with immune checkpoint inhibitors, treatment has been generally well-tolerated. The toxicities observed

with *Lm*-based agents have been distinct from those observed with immune checkpoint inhibitors, both in terms of the timing of the onset of toxicity and the nature of the toxicity. For example, in a clinical trial combining ADXS-PSA with pembrolizumab in 37 subjects with mCRPC, the observed TRAEs were as expected relevant to each agent's individual safety profile, but no additive toxicities were observed as a result of the combination (Table 3). In this trial, ADXS-PSA was administered as monotherapy in Part A at escalating doses of $1x10^9$ CFU, $5x10^9$ CFU and $1x10^{10}$ CFU every 3 weeks. In Part B, ADXS-503 was administered at $1x10^9$ CFU in combination with 200 mg of pembrolizumab every 3 weeks for 3 doses, followed 3 weeks later by 200 mg of pembrolizumab alone, in a 12-week cycle. The 12-week cycle repeated until treatment discontinuation.

Table 3: Treatment-Related Adverse Events >10% with ADXS-PSA Alone (Part A) and in Combination with Pembrolizumab (Part B) in Metastatic Castrate-Resistant Prostate Cancer (mCRPC)

Treatment Related Adverse Event (TRAE) System Organ Class Preferred Term	Grade 1-2		Grade 3	
	Part A (N=13)	Part B (N=37)	Part A (N=13)	Part B (N=37)
Subjects with ≥1 TRAE; n (%)	13 (100%)	36 (97%)	5 (38.5%)	13 (35.1%)
TRAEs occurring in ≥10% of subjects (Part A + Part B)				
Chills	7 (53.8%)	25 (67.6%)	0	0
Rigors	6 (46.2%)	21 (56.8%)	1 (7.7%)	0
Fever	8 (61.5%)	19 (51.4%)	0	1 (2.7%)
Nausea	5 (38.5%)	14 (37.8%)	0	0
Fatigue	4 (30.8%)	10 (27.0%)	1 (7.7%)	3 (8.1%)
Hypertension	0	5 (13.5%)	2 (15.4%)	7 (18.9%)
Hypotension	4 (30.8%)	7 (18.9%)	1 (7.7%)	1 (2.7%)
Pain (all)	2 (15.4%)	11 (29.7%)	0	0
Anemia	0	4 (10.8%)	1 (7.7%)	3 (8.1%)
Vomiting	2 (15.4%)	4 (10.8%)	0	0
Sinus tachycardia	2 (15.4%)	3 (8.1%)	1 (7.7%)	0

Treatment Related Adverse Event (TRAE) System Organ Class Preferred Term	Grade 1-2		Grade 3	
	Part A (N=13)	Part B (N=37)	Part A (N=13)	Part B (N=37)
Subjects with ≥1 TRAE; n (%)	13 (100%)	36 (97%)	5 (38.5%)	13 (35.1%)
TRAEs occurring in ≥10% of subjects (Part A + Part B)				
Dyspnea	1 (7.7%)	4 (10.8%)	0	1 (2.7%)
Diarrhea	1 (7.7%)	3 (8.1%)	0	1 (2.7%)
Headache	1 (7.7%)	4 (10.8%)	0	0
Decreased appetite	0	5 (13.5%)	0	0
Hypothyroidism	0	5 (13.5%)	0	0

One Grade 5 toxicity has been reported following treatment with ADXS11-001 in combination with the PD-L1 inhibitor, durvalumab. Prior to the event, a 37 -year--old female subject with metastatic cervical cancer had been treated with 20 doses of durvalumab and 10 doses of ADXS11-001 over the course of approximately 9 months. The subject developed severe hypotension after the infusion of durvalumab and ADXS11-001 and subsequently died of acute respiratory failure secondary to pulmonary edema and diffuse cerebral edema with bilateral herniation of the uncus and cerebellar tonsils. The autopsy report indicated that the subject had areas of dense pulmonary fibrosis, but it is unknown whether the presence of fibrosis in the lung contributed to the event. An updated algorithm for the management of high-grade, acute toxicities during or after treatment infusion (including hypotension, hypoxia, encephalopathy, and organ toxicity), has been developed as a result of this event (see Appendix 7). Furthermore, the subject ID card provided to study subjects during Screening must specify that the subject is enrolled in a clinical trial of an experimental agent that may be associated with immune-mediated toxicity, induced by *Lm*.

Please refer to the ADXS-503 IB for additional details.

3.5. Study Rationale and Selected Patient Population

Over the past decade and a half, several TKIs and immune checkpoint inhibitors have been approved to treat patients with metastatic NSCLC, improving the overall therapeutic armamentarium (see **Section** 3.2 and **Section** 3.3). Unfortunately, the majority of known driver mutations are not targets for approved TKIs, and even in the subset of patients harboring an

actionable mutation, drug resistance ultimately develops, leading to disease progression in approximately 10-19 months Chan 2015; Hirsh 2018; NCCN, 2018; Soria, 2018; Zappa 2016). Furthermore, fewer than 20% of patients treated with immune checkpoint inhibitors derive long-term clinical benefit. For example, in patients with high PD-L1 expression who receive pembrolizumab as monotherapy in the first-line setting, the ORR is less than 50% and most patients experience disease progression in approximately 10-12 months (Brahmer 2017; Reck 2016). Furthermore, data from Keynote 189, Keynote 407, IMpower 150, IMpower 131 and CheckMate 227 clinical trials in the first-line setting show that approximately 50-60% of patients experience disease progression within one year of combination therapy with PD-1/ PD-L1 checkpoint inhibitors, regardless of the agents used (eg, VEGF inhibitor, ipilimumab and/or chemotherapy) (Gandhi 2018; Hellmann 2018; Jotte 2018; Paz-Ares 2018; Socinski 2018). Therefore, a clear unmet need remains for new treatment strategies for patients with metastatic NSCLC.

An important aspect of treatment with checkpoint inhibitors such as pembrolizumab, is the option to confirm apparent disease progression by repeating the tumor evaluation at originally scheduled approximately between 4 to 8 weeks after the first evidence of progression is expanded based on input from treating physicians. This is based on the observation that response patterns may be atypical in the context of immunotherapy. Apparent disease progression may not be confirmed after a subsequent assessment; therefore, it is appropriate to continue therapy while awaiting confirmation of disease progression. Stable subjects may be treated beyond confirmed progression in situations where the investigator determines that the subject is deriving clinical benefit. The iRECIST guidelines also provide a method for making treatment decisions in the context of confirmation of PD assessment.

This approach to managing checkpoint inhibitor treatment means that the introduction of a new treatment intervention may be able to delay the process of disease progression. The time interval prior to PD confirmation provides an opportunity to evaluate an investigational agent prior to the development of confirmed disease progression and allows the treating physician to independently assess the clinical status of the patient for possible benefit with treatment under this study.

ADXS-503 is a novel *Lm*-based immunotherapy, bioengineered to elicit potent T cell responses against 22 tumor antigens that include 1) 11 peptide antigens derived from frequently occurring and commonly shared hotspot mutations in patients with squamous and non-squamous NSCLC and 2) 11 peptide antigens derived from sequence-optimized TAAs that are differentially expressed or overexpressed in NSCLC tumors (see **Section** 3.4.1 and **Section** 3.4.2). ADXS-503 is designed to express multiple tumor antigen targets to which patients may generate a broad set of effector T cells for tumor control. Similar to other *Lm*-based immunotherapies, ADXS-503 has the potential to reduce immunosuppressive Treg and MDSC frequencies and function within the

TME and has the potential for clinical synergy when used in combination with immune checkpoint inhibitors (see **Section** 3.4.2 and **Section** 3.4.5). Furthermore, ADXS-503, which includes the KRAS G12D hotspot mutation peptide antigen, has demonstrated activity in a mouse Kras G12D tumor model (see **Section** 3.4.3). The multi-target ADXS-503 construct effectively suppressed tumor growth and demonstrated efficiency in eliciting anti-tumor activity. Therefore, ADXS-503 represents a new treatment approach for patients with metastatic NSCLC, with the potential for durable anti-tumor activity and long-term clinical benefit when used alone or in combination with standard of care agents such as immune checkpoint inhibitors.

The purpose of this first-in-human clinical study is to evaluate the safety, tolerability and clinical/immunological activity of ADXS-503 as monotherapy and in combination with pembrolizumab in subjects with metastatic squamous or non-squamous NSCLC. This study will be performed in 2 phases, a safety phase and an efficacy phase.

Safety Phase

In the **safety phase**, ADXS-503 will be administered as monotherapy in Part A and in combination with pembrolizumab in Part B.

Part A will enroll subjects in a refractory setting, who have previously received, and then progressed or been intolerant to up to 3 lines of prior therapy for metastatic NSCLC, including approved chemotherapy, targeted therapy, immunotherapy and antibody therapy, if eligible. Subjects will be enrolled in Part A irrespective of PD-L1 expression or *EGFR* or *ALK* mutation status. However, subjects with an *EGFR* sensitizing mutation or *ALK* translocation must have received and then progressed or been intolerant to at least 1 prior line of approved targeted therapy to be eligible for Part A. In this patient population, ADXS-503 monotherapy has the potential to provide clinical benefit when compared to salvage treatments such as single-agent docetaxel or pemetrexed.

Part B will enroll subjects with metastatic NSCLC who meet the following criteria:

- Are undergoing treatment with pembrolizumab monotherapy or combination therapy with pembrolizumab + platinum-based chemotherapy or are receiving pembrolizumab + pemetrexed as maintenance therapy, as last treatment for metastatic NSCLC
- The subject's most recent tumor assessment is consistent with PD according to RECIST v1.1
- There is no evidence of rapid disease progression or clinical deterioration that would preclude continuation of pembrolizumab treatment for up to 12 weeks before ADXS-503 is added-on
- Subjects must consent to allow the acquisition of fresh or archival formalin-fixed paraffin-embedded (FFPE) tumor tissue, either a block or unstained slides along with matching blood at

baseline for performance of sequencing analysis.

- In Part B, subjects must receive the first dose of ADXS-503 within 12 weeks of the initial tumor assessment showing PD (while on last treatment with pembrolizumab monotherapy or pembrolizumab + platinum-based chemotherapy or pembrolizumab + pemetrexed as maintenance therapy). ADXS-503 will be administered as add-on treatment to the ongoing pembrolizumab therapy.

- Subjects who are receiving pembrolizumab in combination with platinum-based chemotherapy or pembrolizumab with pemetrexed as maintenance therapy, will continue on pembrolizumab monotherapy every 3 weeks per schedule while other drugs are washed-out for 3 weeks.

Efficacy Phase

In the **efficacy phase (Part B)**, expansion of the Part B-dose level 1 cohort will enroll subjects with metastatic squamous or non-squamous NSCLC who meet the same criteria as Part B dose escalation mentioned above. Based on Stage I of Simon's Two-stage design, 18 patients will be accrued in this study arm. Sponsor may decide to accrue additional 25 subjects for a total of 43 patients in Stage II. Accrual of patients to Part B dose level 2 (ADXS-503 at $5x10^8$ CFU in combination with 200 mg pembrolizumab) is pending Sponsor decision to commence.

In the **efficacy phase (Part C)**, ADXS-503 will be administered in combination with pembrolizumab in subjects who have received no prior systemic treatment for metastatic NSCLC, and who will be treated in accordance with the approved Product Label for pembrolizumab monotherapy in the first-line setting. Clinical site must provide documentation of tumor PD-L1 expression and *EGFR* mutation and/or *ALK* translocation status as evaluated by FDA-approved tests in all patients in Part C. Baseline tumor samples must express PD-L1 [Tumor Proportion Score (TPS) ≥1% as determined by an FDA-approved test], with no EGFR or ALK genomic tumor aberrations for subjects to be eligible for Part C. The rationale for enrolling subjects in a first-line setting in Part C, is based on the principle of cancer immunotherapy that treatment may be less effective as a patient receives more lines of therapy. This would make detection of an efficacy signal more difficult. An earlier line of treatment makes sense because it provides an improved setting for detecting clinical activity.

Study objectives are described in **Section** 4. See **Section** 5.1 for a full description of the study design.

3.6. Overall Benefit/ Risk Assessment

3.6.1. Potential Benefits

ADXS-503 expresses a total of 22 NSCLC-associated tumor antigens, whose selection ensures that 42% of patients with NSCLC will express at least one of the targeted hotspot mutation peptide antigens and that >90% will express at least one of the TAAs targeted by the sequence-optimized TAA peptide antigens. The delivery of multiple tumor antigens increases the likelihood of immune recognition of tumor cells, leading to potential clinical efficacy. In addition to stimulating an anti-tumor immune response, Advaxis' *Lm* based immunotherapies reduce the frequencies and function of immunosuppressive Tregs and MDSCs within the TME, and upregulate the expression of PD-L1 (Advaxis Internal Data; Chang 2014; Guirnalda 2013; Wallecha 2013). This reprogramming of the TME increases the susceptibility of the tumor to immune attack and provides the potential for synergistic activity when ADXS-503 is used in combination with PD-1/PD-L1 immune checkpoint inhibitors. Based on these properties, ADXS-503 represents a new treatment approach for patients with metastatic NSCLC, with the potential for clinical benefit when used alone or in combination with an immune checkpoint inhibitor such as pembrolizumab.

3.6.2. Potential Risks

3.6.2.1. Potential Risks with ADXS-503

3.6.2.1.1. Risks Associated with Treatment Infusion

The clinical safety profile of ADXS-503 is expected to be similar to that of other *Lm*-based immunotherapies, as described in **Section** 3.4.4. The safety profile of these agents primarily consists of Grade 1-2 "flu-like" symptoms (eg, chills, pyrexia, nausea, vomiting, fatigue, headache, tachycardia and hypotension) that last 2 to 4 hours after treatment infusion and are consistent with immune cell activation, induced by *Lm*. These symptoms usually resolve without specific intervention or respond rapidly to limited symptomatic treatment within 30 minutes to 1 hour.

As a prophylaxis for acute symptoms which may occur during or after treatment infusion, a mandatory pre-infusion regimen of adequate hydration, NSAIDs, antihistamines and antiemetics, has been incorporated into *Lm*-based immunotherapy treatment regimens. In addition, a key aspect of risk mitigation is that following each ADXS-503 infusion, all subjects will be observed in the clinic and will have vital signs, including oxygen saturation, monitored for at least 4 hrs.

In some instances (<7%), Grade 3-4 hypotension has been observed following treatment with *Lm*-based immunotherapy, either as monotherapy or in combination with immune checkpoint inhibitors. Elevated IL-6 and other cytokine levels have been observed after infusion of *Lm*-based immunotherapy, with peak levels occurring 2 to 4 hours after infusion. Increased levels of IL-6

has been strongly associated with capillary leak, which manifests as hypotension. Emerging evidence indicates that IL-6 antagonists, such as tocilizumab, have demonstrated good results in treating IL-6-induced hypotension, and is therefore recommended for cases of severe hypotension refractory to supportive care (eg, fluids and/or pressors) early in the course of the event (Actemra®, 2020; Grupp, 2013; Herceptin®, 2020; Lee, 2014; Winkler, 1999).

Investigators will use their best judgement to appropriately code and treat individual AEs that occur during or after infusion, rather than grouping them into broad categories, such as "infusion reaction" or "cytokine release syndrome", so that specific management strategies can be applied, as appropriate. For example, a clinically suspected high-grade infusion reaction may only be related to anaphylaxis with hives and angioedema which can be treated with diphenhydramine/ steroids, while a high-grade hypotension may require tocilizumab ± steroids after failing to be controlled with saline boluses. Hypersensitivity/ anaphylactic events during or after the infusion, should be managed according to the guidelines provided in Appendix 6. An updated algorithm for the management of other acute AEs, including hypotension, hypoxia, encephalopathy, organ toxicity, fever and constitutional symptoms is provided in Appendix 7.

As described in **Section** 3.4.4.1, a subject with NSCLC experienced Grade 3 hypoxia and a subject with colorectal cancer experienced Grade 3 hypotension and Grade 3 hypoxia following the second dose of ADXS-NEO (dose of $1x10^9$ CFU). Furthermore, as described in **Section** 3.4.5.2, a Grade 5 acute respiratory failure event has been reported following treatment with ADXS11-001 and durvalumab. The algorithm in **Appendix 7** has subsequently been updated to provide management guidelines for high-grade toxicities considered Events of Special Interest, including Grade 3 or 4 hypotension, hypoxia, encephalopathy and organ toxicity (see **Section** 9.1.5). Furthermore, the subject ID card provided to study subjects during Screening must specify that the subject is enrolled in a clinical trial of an experimental agent that may be associated with immune-mediated toxicity induced by *Lm*.

As of April 2021, nineteen subjects have been treated with ADXS 503 in the ongoing ADXS_503-101 study: seven as monotherapy and 12 in combination with pembrolizumab or with ADXS-503 alone. TheADXS-503 in combination continues to be safe and tolerable without inducing high grade toxicity of added doses being administered. See Table 3.

3.6.2.1.2. Risks Associated with Immune-Related Adverse Events

While the hotspot mutation peptide antigens and TAAs expressed by the *Lm* construct are not expected to induce or exacerbate autoimmune toxicities, the potential for sub-acute or late-occurring immune-related AEs exists. Therefore, immune-related AEs will be closely monitored for in this study, with ADXS-503 as a single agent, and in combination with pembrolizumab. General guidance for treating immune-related AEs considered by the Investigator to be associated with ADXS-503, is provided in Appendix 8.

3.6.2.1.3. Risks Associated with Listeremia

ADXS-503 is a live attenuated *Lm*-based immunotherapy. A safety consideration is the administration of live attenuated *Lm* to potentially immunocompromised subjects who may have previously received heavy doses of radiation and chemotherapy. In preclinical studies, attenuated *Lm* strains from Advaxis were cleared within 48 hours in immunocompromised mouse models, such as SCID mice and IFNγ-deficient mice, in the absence of antibiotic treatment (Gunn, 2001).

As described in **Section** 3.4.4, listeremia, although rare, has been reported in two subjects with implanted medical devices, who were treated with *Lm*-based immunotherapy. The risk of *Lm* biofilm formation will be mitigated in this study through the prohibition of the enrollment of subjects with implanted devices with such a risk and which cannot be removed easily. Additionally, the risk of the persistence of *Lm* will be mitigated through the use of a 7-day course of prophylactic antibiotics after each ADXS-503 infusion. Following the final dose of ADXS-503, a 3-week course of oral antibiotics will be administered to ensure the clearance of *Lm* (see **Section** 9.2.1.3 for additional details).

Listeriosis (as opposed to listeremia with attenuated *Lm*) is a systemic organ infection caused by wild type, invasive *Lm* and is highly unlikely to occur during study treatment, because the method of attenuation used in the Advaxis *Lm* platform results in a greater than 4 log reduction in virulence compared to wild type *Lm*.

Lm-based immunotherapy is rapidly cleared from the blood and no shedding in urine or feces is observed. In the Phase 1 study for ADXS11-001 (n=15 subjects), *Lm* was not detected in the blood of any subject beyond 48 hours post dose. Additionally, in the absence of post-infusion antibiotic treatment, *Lm* was not shed in the urine or feces of any subject at the highest dose level tested ($1x10^{10}$ CFU) (Maciag 2009). Importantly, to date, no person-to-person transmission with *Lm*-based immunotherapies has been reported.

3.6.2.1.4. Other Risks

Although ADXS-503 is attenuated and nonpathogenic, all *Lm* strains are classified as biosafety level 2 (BSL-2) because the Centers for Disease Control and Prevention (CDC) do not provide differential classification for attenuated and wild-type bacterial agents. With proper PPE and hazardous waste disposal measures, nursing and pharmacy staff at over 50 global clinical research sites have handled *Lm* strains safely. Universal precautions and institutional guidelines should be used when handling investigational drugs and human specimens. While the administration of ADXS-503 is not expected to complicate wound healing, the effect of surgery itself may suppress the immune system and delay the healing process. Therefore, a subject may initiate or resume study treatment 2 weeks after minor surgery (ie, 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 (eg, return to baseline or Grade ≤1) from any toxicity and/or complication before the next dose of study treatment. Sponsor consultation is required prior to resuming study treatment for these subjects. If study treatment is delayed beyond 12 weeks due to concomitant surgery, the subject may be discontinued from study treatment.

As noted, ADXS-503 administration is safe, however, there may also be potential unknown risks and additional information about the known and expected risks of ADXS-503 can be found in the IB. Please refer to **Section** 9.2 for clinical safety management and supportive care guidelines for ADXS-503 treatment.

3.6.2.2. Potential Risks with Pembrolizumab

Please refer to the approved pembrolizumab Product Label for the known and expected risks of treatment with pembrolizumab.

A pattern of immune-related AEs has been defined for pembrolizumab, for which management guidelines have been developed. These immune-related AEs include: **pneumonitis**, **diarrhea/colitis**, **Type 1 diabetes mellitus (T1DM)**, **hypophysitis**, **hyperthyroidism** or **hypothyroidism**, **primary adrenal insufficiency, hepatic AEs**, **renal failure/ nephritis, skin reactions, infusion reactions**, **hemophagocytic lymphohistiocytosis, complications of allogeneic hematopoietic stem cell transplant (HSCT)**, and **hematological toxicity in patients with chronic Hodgkin lymphoma (cHL)**. Immune-mediated adverse reactions reported in less that 1% of patients treated with pembrolizumab include uveitis, myositis, Guillain-Barre syndrome, pancreatitis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis and myocarditis. Guidelines for the management of common immune-related AEs are provided in Appendix 9**.** Refer to Appendix 6 for guidelines to manage infusion reactions associated with pembrolizumab.

4. Study Objectives and Endpoints

The objectives and endpoints for this study are outlined in the Table below.

This study will enroll subjects with metastatic squamous or non-squamous NSCLC in a safety phase (Part A and Part B) and an efficacy phase (Part C). See **Section** 5.1 for details of the study design.

- Safety phase (Part A and Part B):
  - Part A: ADXS-503 monotherapy at 2 escalating dose levels; Refractory setting.
  - Part B: ADXS-503 at 2 escalating dose levels + pembrolizumab; Enroll subjects undergoing treatment with pembrolizumab monotherapy who have an initial assessment of PD per RECIST v1.1 on the most recent tumor scan, and are awaiting a confirmatory scan 4-8 weeks later. ADXS-503 administered as add-on therapy to pembrolizumab.
- Efficacy phase
  - Part B expansion: ADXS-503 at 1 x10^8 CFU+ pembrolizumab; Enroll subjects undergoing treatment with pembrolizumab monotherapy **or** receiving combination therapy with pembrolizumab + platinum-based chemotherapy **or** pembrolizumab + pemetrexed as maintenance therapy, as their last treatment in metastatic setting, and who have an initial assessment of PD per RECIST v1.1 on the most recent tumor scan. ADXS-503 administered as addon therapy to pembrolizumab. The administration of pembrolizumab is per the approved label and in the second year treating physicians can change dosing from Q3W to Q6W for both drugs.
  - Part C: ADXS-503 + pembrolizumab; Enroll subjects per the approved Product Label for pembrolizumab monotherapy in the first-line setting and in the second year treating physicians can change dosing from Q3W to Q6W for both drugs.

See **Section** 3.5 and **Section** 6 for a description of the subject populations in Parts A, B, and C.

Objectives	Endpoints
Primary 1. To evaluate the safety and tolerability of ADXS-503, administered as monotherapy in **Part A** and in combination with pembrolizumab in **Part B**, and to determine the maximum tolerated dose (MTD) or maximum administered dose (MAD).	1. Adverse events (AEs); dose-limiting toxicities (DLTs); physical examination findings; clinical laboratory values; vital sign measurements; and performance status monitoring.
2. To characterize the preliminary anti-tumor activity of ADXS-503, administered in combination with pembrolizumab in **Part B** dose-expansion and **Part C**, per RECIST v1.1.	2. Tumor response per RECIST v1.1, including: • Best overall response (BOR) • Objective response rate (ORR) • Disease control rate (DCR) • Duration of objective response (DOR)

Secondary 1. To characterize the preliminary anti-tumor activity of ADXS-503, administered as monotherapy in **Part A** and in combination with pembrolizumab in **Part B** dose-escalation, per RECIST v1.1.	1. Tumor response per RECIST v1.1, as described above.
2. To determine the progression-free survival (PFS) and PFS rate at 12 months per RECIST v1.1, for subjects treated with ADXS-503 monotherapy in **Part A** and ADXS-503 in combination with pembrolizumab in **Part B** and **Part C**.	2. PFS and PFS rate at 12 months per RECIST v1.1.
3. To determine overall survival (OS) and 6- and 12-month milestone OS rates for subjects treated with ADXS-503 monotherapy in **Part A** and ADXS-503 in combination with pembrolizumab in **Part B** and **Part C**.	3. OS; and 6- and 12-month milestone OS rates.
4. To evaluate the safety and tolerability of ADXS-503 in combination with pembrolizumab in **Part B** dose-expansion and **Part C**.	4. Safety and tolerability, as described above.
Exploratory 1. To characterize the preliminary anti-tumor activity of ADXS-503, administered as monotherapy in **Part A** and in combination with pembrolizumab in **Part B** and **Part C**, per iRECIST.	1. Tumor response per iRECIST, including BOR, ORR, DCR and DOR.
2. To determine PFS and PFS rate at 12 months per iRECIST, for subjects treated with ADXS-503 monotherapy in **Part A** and ADXS-503 in combination with pembrolizumab in **Part B** and **Part C**.	2. PFS and PFS rate at 12 months per iRECIST.
3. To characterize the immunological activity of ADXS-503, administered as monotherapy in **Part A** and in combination with pembrolizumab in **Part B**; and to characterize the genomic profiles of study subjects.	3. Immunological activity will be evaluated as follows: • In pre- and on-treatment blood samples: o Evaluate the changes in the states of activation and differentiation in various immune cells by flow cytometry, whole exome sequencing and profiling of gene expression.

	○ Evaluate changes in the peripheral T cell repertoire by immunosequencing. ○ Characterize subject-specific somatic mutations and neoantigens, microsatellite instability, tumor mutational burden, TCR analysis and haplotype.
4. To characterize changes in circulating free DNA (cfDNA) in **Part A**, **Part B**, and **Part C.**	4. Quantitate changes in cfDNA levels pre- and on treatment

5. Investigational Plan

5.1. Study Design

This is a Phase 1/2, open-label, multi-center study of ADXS-503 administered alone and in combination with pembrolizumab in subjects with metastatic squamous or non-squamous NSCLC. This study will be performed in 2 phases, a safety phase and an efficacy phase.

Safety Phase

In the safety phase, ADXS-503 will be administered as monotherapy in Part A and in combination with pembrolizumab in Part B. The subject population for Part A and Part B is as follows:

- **Part A** will enroll subjects with metastatic NSCLC who have become refractory or intolerant to standard therapy. To be eligible for Part A, subjects must have previously received, and then progressed or been intolerant to up to 3 lines of prior therapy in the metastatic setting, including approved chemotherapy, targeted therapy, immunotherapy and antibody therapy, if eligible. Subjects will be eligible for Part A irrespective of PD-L1 expression or *EGFR* or *ALK* mutation status. However, subjects with an *EGFR* sensitizing mutation or *ALK* translocation must have received and then progressed or been intolerant to at least 1 prior line of approved targeted therapy to be eligible for Part A.
- **Part B** will enroll subjects with metastatic NSCLC who meet the following criteria:
    - Are undergoing last treatment with pembrolizumab monotherapy for metastatic NSCLC **or** receiving combination therapy with pembrolizumab + platinum-based chemotherapy **or** pembrolizumab + pemetrexed as maintenance therapy in the metastatic setting.
    - The subject's most recent tumor assessment is consistent with PD according to RECIST v1.1

- There is no evidence of rapid disease progression or clinical deterioration that would preclude continuation of pembrolizumab for up to 12 weeks before ADXS-503 is added-on.
- Subjects who are receiving pembrolizumab in combination with platinum-based chemotherapy or pembrolizumab with pemetrexed as maintenance therapy, will continue on pembrolizumab monotherapy every 3 weeks per schedule while other drugs are washed-out for 3 weeks.
- Subject must consent to allow the acquisition of fresh or archival FFPE tumor tissue, either a block or unstained slides along with matching blood at baseline, for performance of sequencing analysis.

In Part B, subjects must receive the first dose of ADXS-503 within 12 weeks of the initial tumor assessment showing PD (while on treatment with pembrolizumab monotherapy or while receiving combination therapy with pembrolizumab + platinum-based chemotherapy or pembrolizumab + pemetrexed as maintenance therapy).

Efficacy Phase

In the efficacy phase Part B dose-expansion, subjects will be enrolled with metastatic squamous or non-squamous NSCLC who meet the same criteria as Part B dose-escalation mentioned above.

In the efficacy phase (**Part C**), ADXS-503 will be administered in combination with pembrolizumab in subjects who have received no prior systemic treatment in the metastatic setting, in accordance with the approved Product Label for pembrolizumab monotherapy for first-line treatment. Clinical site must provide documentation of tumor PD-L1 expression and *EGFR* mutation and/or *ALK* translocation status as evaluated by FDA-approved tests in all patients. Baseline tumor samples must express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations for subjects to be eligible for Part C. Subject must consent to allow the acquisition of fresh or archival FFPE tumor tissue, either a block or unstained slides along with matching blood at baseline, for performance of sequencing analysis (up to first 10 patients enrolled).

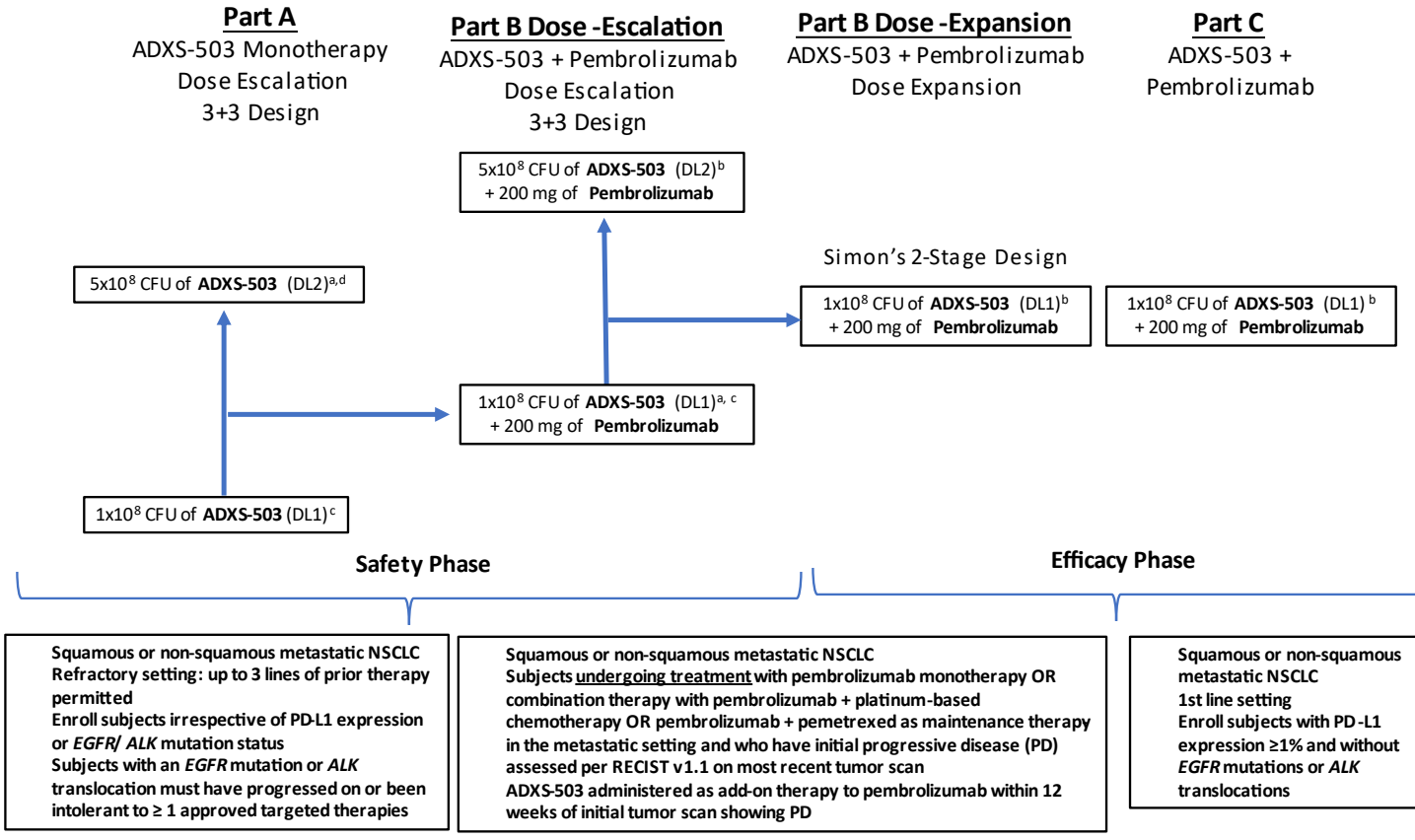


Figure **1** provides a schematic of the study design. Details of the study design are described in **Section** 5.1.1 (safety phase) and **Section** 5.1.2 (efficacy phase).

Additional cohorts or study parts may be added to the protocol based on emerging study data or the evolving treatment landscape. In this situation, the protocol will be amended accordingly.

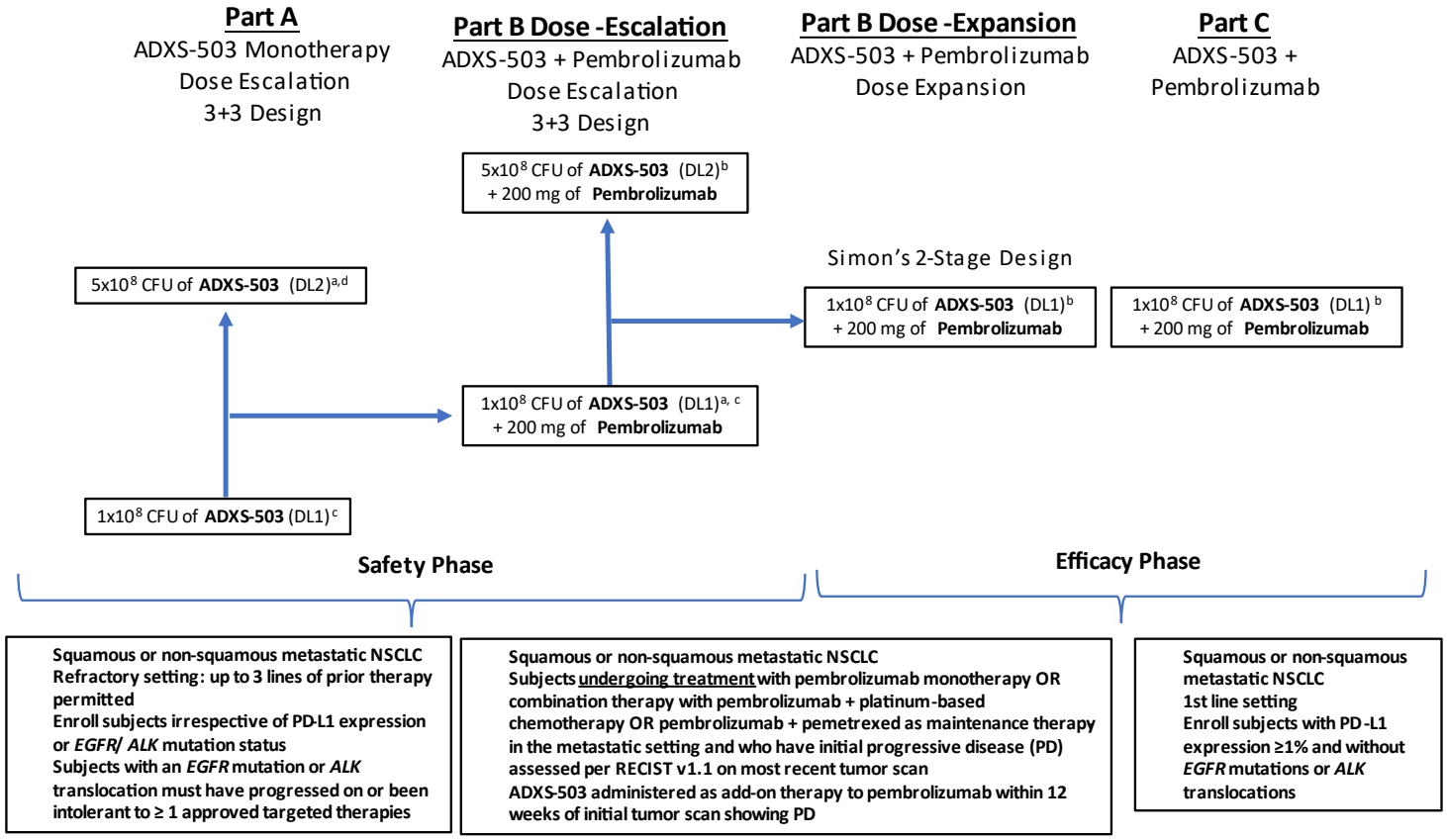


Figure 1 Figure 5. Study Design

a. Escalation to DL2 in Part A will occur in parallel with accrual at DL1 in Part B
b. Upon completion of DL1 in Part B, Dose-expansion of DL1 in Part B will occur in parallel with accrual in Part C. (Accrual in Part B Dose Level 2 may occur upon Sponsor's decision). Upon Investigators' assessment and decision, treatment schedule with $1x10^8$ CFU of ADXS-503 + 200 mg of pembrolizumab, IV, could shift from every 3 weeks to every 6 weeks after the first year of study therapy.
c. If treatment is not safe/tolerable at DL1 in Part A or Part B dose-escalation, a lower dose level (DL -1; $0.5x10^8$ CFU of ADXS-503) will be evaluated before proceeding with Part B and Part C, respectively.
d. Upon completion of dose escalation in Part A, ADXS-503 monotherapy may be evaluated in an expansion cohort.

5.1.1. Safety Phase

Up to approximately 24 subjects with metastatic NSCLC will be enrolled in the safety phase (subject population described in **Section** 5.1 above; see **Section** 6 for full eligibility criteria). The purpose of the safety phase is to evaluate the safety and tolerability of ADXS-503, administered as monotherapy and in combination with pembrolizumab, and to determine the MTD or MAD. The preliminary clinical and immunological activity of ADXS-503 alone and in combination with pembrolizumab, will also be characterized in the safety phase (see **Section** 4 for study objectives).

The safety phase will include 2 Parts (Parts A and B dose-escalation). In Part A, ADXS-503 will be administered as monotherapy at 2 planned escalating dose levels. In Part B, ADXS-503 will be administered at 2 planned escalating dose levels in combination with pembrolizumab. Treatment in Part A and Part B will be administered as follows:

- Part A (ADXS-503 monotherapy dose escalation)
    - Dose level 1 (DL1): $1x10^8$ CFU of ADXS-503 administered every 3 weeks (±2 days) until disease progression, unacceptable toxicity or another treatment discontinuation criterion is met (see **Section** 8.1).
    - Dose level 2 (DL2): $5x10^8$ CFU of ADXS-503 administered every 3 weeks (±2 days) until disease progression, unacceptable toxicity or another treatment discontinuation criterion is met (see **Section** 8.1).
- Part B (ADXS-503 + pembrolizumab dose escalation)
    - Dose level 1 (DL1): $1x10^8$ CFU of ADXS-503 + 200 mg of pembrolizumab administered every 3 weeks (±2 days) ***for up to 2 years*** or until disease progression, unacceptable toxicity or another treatment discontinuation criterion is met (see **Section** 8.1).
    - Dose level 2 (DL2) (To proceed upon Sponsor's decision): $5x10^8$ CFU of ADXS-503 + 200 mg of pembrolizumab administered every 3 weeks (±2 days) ***for up to 2 years*** or until disease progression, unacceptable toxicity or another treatment discontinuation criterion is met (see **Section** 8.1).

    Note for Part B:
    - The dose of pembrolizumab will be fixed at 200 mg for both dose levels.
    - ADXS-503 and pembrolizumab will be administered on the same day, every 3 weeks (±2 days), starting at Week 1 (±2 days). Upon Investigator assessment and discretion, the schedule of therapy with $1x10^8$ CFU of ADXS-503 + 200 mg of pembrolizumab, IV, could shift from every 3 weeks to every 6 weeks after the first year of study treatment.

See **Section** 7 for treatment administration instructions.

Part A (ADXS-503 Monotherapy Dose Escalation)

In Part A, a 3+3 dose escalation design will be used (rules described below). The first 3 subjects enrolled at DL1 will be designated as sentinel subjects and will start treatment at least 14 days apart. At DL2 in Part A, only the first 2 subjects will be designated as sentinel subjects and will start treatment at least 14 days apart. Dose-limiting toxicity (DLT) will be evaluated over the **first 28 days** of treatment for dose escalation purposes in Part A (see **Section** 9.1.6 for DLT criteria). If ADXS-503 is safe and tolerable at DL1 (based on DLT criteria), escalation to DL2 will proceed in parallel with accrual at DL1 in Part B (see below for description of Part B).

If based on DLT criteria, ADXS-503 monotherapy is not safe/tolerable at DL1 in Part A, a lower dose level (DL -1; $0.5x10^8$ CFU of ADXS-503) will be evaluated before proceeding with Part B.

Upon completion of dose escalation in Part A, ADXS-503 monotherapy may be evaluated in an expansion cohort. This expansion cohort may be enrolled following consultation and agreement between study Investigators and the Sponsor. This expansion cohort may be restricted to the tumor type(s) found to be responsive to ADXS-503 monotherapy. The dose of ADXS-503 selected for the monotherapy expansion will not exceed the MTD established in Part A. However, the dose may be intermediate to those tested in Part A if recommended by the Investigators and the Sponsor. Up to approximately 25 subjects will be enrolled in this expansion cohort.

Part B (ADXS-503 + Pembrolizumab Dose Escalation)

In Part B, a 3+3 dose escalation design will also be used (rules provided below). As described above, accrual at DL1 in Part B will proceed in parallel with escalation to DL2 in Part A (in accordance with dose escalation rules). The first 3 subjects enrolled at DL1 in Part B will be designated as sentinel subjects and will start treatment at least 14 days apart. At DL2 in Part B, only the first 2 subjects will be designated as sentinel subjects and will start treatment at least 14 days apart. Dose limiting toxicity will be evaluated over the **first 28 days** of treatment for dose escalation purposes in Part B (see **Section** 9.1.6 for DLT criteria). If ADXS-503 + pembrolizumab is safe and tolerable at DL1 in Part B (based on DLT criteria), DL1 will be expanded in parallel with accrual will occur in the efficacy phase (Part B-expansion and Part C). Part B-DL2 may occur upon Sponsor's decision.

If ADXS-503 + pembrolizumab is not safe/tolerable at DL1 in Part B, a lower dose level (DL -1; $0.5x10^8$ CFU of ADXS-503) will be evaluated before proceeding with Part C. The dose of pembrolizumab will remain fixed at 200 mg.

Note: Available safety data from DL2 in Part A will also be considered for escalation to DL2 in Part B.

Dose-Escalation Rules for Part A and Part B

Dose-limiting toxicity will be evaluated over the **first 28 days** of treatment in Part A and Part B (see **Section** 9.1.6 for DLT criteria). Note: The DLT window will end 7 days after the second dose of ADXS-503 monotherapy in Part A and 7 days after the second dose of ADXS-503 and pembrolizumab in Part B. If within the 28-day DLT period, a subject does not receive 2 doses of ADXS-503 monotherapy in Part A or 2 doses of ADXS-503 and pembrolizumab in Part B, the subject may be replaced for DLT assessment purposes.

Dose escalation in Part A and Part B will proceed as follows:

- An initial cohort of 3 subjects is enrolled.
- If 0 of 3 subjects develop DLT, escalation to the next dose level will occur.
- If 1 of 3 subjects develops DLT:
    - Another 3 subjects will be enrolled at this dose level.
        - If 0 of the 3 new subjects develops DLT (for a total of 1/6 subjects with DLT at this dose level), escalation to the next dose level will occur.
        - If ≥1 of the 3 new subjects develops DLT (for a total of ≥2/6 subjects with DLT at this dose level), dose escalation will stop and the dose directly below the current dose will be considered the MTD if <2/6 subjects experience DLT at this lower dose.
- If ≥2/3 subjects develop DLT, dose escalation will stop and the dose directly below the current dose will be considered the MTD if <2/6 subjects experience a DLT at this lower dose level.

Note: DL -1; $0.5x10^8$ CFU of ADXS-503 will be evaluated if DL1 is not safe and tolerable.

Prior to declaring the MTD in Part A or Part B, and in consultation with the study Investigators, the Sponsor has the option to expand any dose level(s) previously established to be safe, or to evaluate intermediate dose levels. In addition, if the MTD is not established, a higher dose level may be evaluated with agreement between the Investigators and the Sponsor. Dose escalation rules (cohort size, DLT evaluation interval, etc.) will apply to the expanded or additional cohorts.

No within-subject dose escalation will be permitted in Part A or Part B. If a dose level is found to exceed the MTD, subjects enrolled in that dose level may be treated at a lower dose level following consultation and agreement between the Investigator and the Sponsor. The dose of pembrolizumab in all cases will be fixed at 200 mg.

5.1.2. Efficacy Phase

Part B Dose Expansion (ADXS-503 + Pembrolizumab)

- Part B at Dose Level 1 (DL1): $1x10^8$ CFU of ADXS-503 + 200 mg of pembrolizumab administered every 3 weeks (±2 days) will be expanded using a Simon's Two-stage design prior to escalating to dose level 2.
- Upon Investigator assessment and discretion, the schedule of therapy with $1x10^8$ CFU of ADXS-503 + 200 mg of pembrolizumab, IV, could shift from every 3 weeks to every 6 weeks after the first year of study treatment.

In the Part B expansion cohort (at DL1), up to 43 subjects will be enrolled using a Simon's Two-stage design prior to escalating to DL2. In stage I, a total of 18 subjects will be accrued. If there are 2 or fewer responses among the 18 subjects, the study will be stopped early. Otherwise, an additional 25 subjects will be accrued in stage II, resulting in a total sample size of 43 subjects.

The purpose of Part B - dose expansion is to gather additional safety, tolerability, efficacy and pharmacodynamic information regarding the combination of ADXS-503 and pembrolizumab. The population in the dose expansion cohort will be restricted to the same population evaluated in Part B. Continuous evaluation of toxicity events in the dose-expansion cohort will be performed throughout enrollment. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across all subjects treated in the dose-expansion cohort, the finding will be discussed, and further enrollment may be interrupted. Depending on the nature and grade of toxicity and after assessing the risk:benefit ratio, a new lower dose may be initiated following consultation and agreement between the Investigators and the Sponsor.

If stage II completes enrollment of the 43 subjects, and the true response rate is ≥ 0.25, the cohort may be expanded up to 140 subjects to further evaluate efficacy, following consultation and agreement between the Investigators and the Sponsor.

Part C (ADXS-503 + Pembrolizumab)

In the efficacy phase (Part C), approximately 25 subjects with metastatic NSCLC who have received no prior systemic treatment in the metastatic setting, and whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, will be enrolled (see **Section** 6 for full eligibility criteria). Note: Subjects who have received adjuvant/neoadjuvant therapy are eligible for Part C if the adjuvant/neoadjuvant therapy was completed at least 6 months prior to the diagnosis of metastatic disease. The purpose of Part

C is to evaluate the safety and preliminary clinical efficacy of ADXS-503 in combination with pembrolizumab in this patient population. See **Section** 4 for study objectives.

The planned dose of ADXS-503 to be used in combination with pembrolizumab (200 mg) in Part C is $1x10^8$ CFU (dose evaluated at DL1 in Part B). This dose may be adjusted but will not exceed the MTD established in Part B. ADXS-503 + pembrolizumab will be administered every 3 weeks (±2 days) ***for up to 2 years*** or until disease progression, unacceptable toxicity or another treatment discontinuation criterion is met (see **Section** 8.1). Upon Investigator assessment and discretion, therapy with $1x10^8$ CFU of ADXS-503 + 200 mg of pembrolizumab, IV, could shift from every 3 weeks to every 6 weeks after the first year of study treatment.

Note for Part C: . Starting at Week 1, ADXS-503 and pembrolizumab will be administered on the same day, every 3 weeks (±2 days), as described above. See **Section 7** for treatment administration instructions.

In Part C, toxicities will be evaluated on an ongoing basis. If the aggregate rate of treatment-related toxicities that meet the DLT criteria (see **Section** 9.1.6**)** exceeds 33% at any time (across all subjects in Part C), the findings will be discussed between the Sponsor and study Investigators, and further enrollment may be interrupted. Depending on the nature and grade of the toxicities and after assessing the risk/ benefit, treatment may be adjusted to a lower dose of ADXS-503 or an alternative treatment schedule. In all cases, the dose of pembrolizumab will be fixed at 200 mg.

Overall treatment and enrollment stopping rules for this study are described in **Section** 8.1.2**.**

In total in the efficacy phase, up to approximately 165 subjects may be enrolled in Part B. Up to 43 subjects may be enrolled in Part B expansion of DL1 in the Simon's Two-stage study cohort (S1, n=18 and S2, n= 25) and up to a total of 140 thereafter. As described above, approximately up to 25 subjects may be enrolled in Part C.

5.1.3. Summary of Study Procedures/Assessments

Refer to the **SoA**, **Section** 9, and the sections referenced below for detailed information on study procedures and assessments.

- Subjects will be enrolled in this study according to the Inclusion/ Exclusion criteria outlined in **Section 6**. Clinical site must provide documentation of tumor PD-L1 expression and EGFR mutation and/or ALK translocation status as evaluated by FDA-approved tests in Part B and Part C patients. Participation in both parts will be dependent upon supplying tumor tissue (from fresh biopsy or archival) from a location that has not been radiated. Formalin-fixed specimens obtained either at the time of or after the diagnosis of metastatic disease will be required for performance of sequencing analysis. In Part C, biopsies

obtained PRIOR to receipt of neoadjuvant/adjuvant chemotherapy are NOT permitted. Only subjects whose tumors express PD-L1 (TPS ≥1%) as determined by as determined by an FDA-approved test, will be eligible for enrollment in Part C. Furthermore, documentation of *EGFR* mutation and/or *ALK* translocation status will be required for subjects with non-squamous NSCLC. If the clinical site is unable to provide this source documentation, PD-L1 expression and *EGFR*/ *ALK* testing should be performed in all Part C patients per institutional standard of care using FDA-approved tests before enrollment. See **Section** 9.5.

- Study treatment will be administered as described in **Section** 7.
- At least 30 minutes prior to each ADXS-503 infusion, all subjects will receive a pre-infusion prophylactic regimen of adequate hydration, NSAIDs, antihistamines and antiemetics to mitigate the potential for "flu-like" symptoms during or after treatment infusion. Vital signs will be monitored every 30 minutes (±5 minutes) starting immediately prior to each ADXS-503 infusion, until 4 hours after the end of each ADXS-503 infusion. To ensure the clearance of *Lm*, subjects will receive a 7-day course of oral antibiotics starting approximately 48 hours after each ADXS-503 infusion. After the final dose of ADXS-503, a 3-week course of oral antibiotics will be administered to ensure the clearance of *Lm*. A blood sample will also be collected at 7 days (±3 days) after the completion of the 3-week course of oral antibiotics to culture for *Lm*. See **Section 7** and **Section** 9.2 for details.
- Safety will be assessed throughout this study by AE monitoring, physical examination findings, vital sign measurements, monitoring of performance status, and clinical laboratory values. Adverse events will be graded in severity according CTCAE v4.03 (see **Section** 9.1).
- Tumor imaging will be performed by contrast-enhanced CT/MRI as follows:
    - Part A (ADXS-503 monotherapy): Screening (baseline), at Week 8 (±8 days), at Week 16 (±7 days), followed by every 9 weeks (±7 days) thereafter, until confirmed disease progression or treatment discontinuation, whichever occurs later.
    - Part B (ADXS-503 + pembrolizumab): Screening (baseline), which corresponds to the most recent tumor assessment that is consistent with PD (according to RECIST v1.1) while on treatment with pembrolizumab monotherapy as last treatment, **or** while receiving combination therapy with pembrolizumab + platinum-based chemotherapy **or** pembrolizumab + pemetrexed as maintenance therapy, as last treatment in the metastatic setting. As described above, the first dose of ADXS-503 will be administered within 12 weeks of the initial assessment of PD. Subsequent

scans will be performed at Week 8 (±7 days), at Week 16 (± 7 days), and every 9 weeks (±7 days) thereafter, until confirmed disease progression or treatment discontinuation, whichever occurs later.

- Part C (ADXS-503 + pembrolizumab): Screening (baseline), at Week 8 (±7 days), at Week 16 (± 7 days), followed by every 9 weeks (±7 days) thereafter, until confirmed disease progression or treatment discontinuation, whichever occurs later.

See **Section** 9.4.1 for details on tumor imaging.

- Tumor response will be evaluated by the Investigator (or designee) according to RECIST v1.1 as the basis for the primary analysis of tumor response-based endpoints. Exploratory analysis of tumor-response will be performed by the Sponsor (or designee) according to iRECIST (see **Section 9.4.1** for details).
  - In Part A and Part C, subjects may receive study treatment beyond initial Investigator-assessed, RECIST v1.1-defined disease progression, provided the criteria in **Section** 8.1.1 are met. In Part B, all subjects will begin study treatment within 12 weeks of initial Investigator-assessed, RECIST v1.1-defined disease progression on treatment with pembrolizumab monotherapy as last treatment **or** while receiving combination therapy with pembrolizumab + platinum-based chemotherapy **or** receiving pembrolizumab + pemetrexed as maintenance therapy, as last treatment in the metastatic setting (if eligibility criteria are met).
  - In Parts A, B and C, any apparent CR or PR must be confirmed ≥4 weeks after radiological imaging indicating CR or PR.
  - Subjects who achieve a confirmed CR may receive up to 2 additional doses of study treatment after the date of confirmed CR but must subsequently discontinue treatment (see **Section** 8.1).
  - The following subjects may be eligible for re-treatment upon disease progression, with agreement between the Sponsor and Investigator (see **Section** 8.1):
    - Subjects who achieve a confirmed CR during initial study treatment (Parts A, B and C)
    - Subjects in Part B and Part C who stop trial therapy after 2 years of treatment for reasons other than disease progression or intolerability.

    Note: Tumor response data collected during the re-retreatment period will not be used for the primary analysis of tumor response endpoints.

- In Part A, Part B and Part C, peripheral blood and tumor biopsy samples may be collected at baseline and/or during the treatment phase of this study to evaluate biomarkers and correlates of immune response. See **Section** 9.5.
    - Subject must consent to allow the acquisition of fresh or archival FFPE tumor tissue, either a block or unstained slides along with matching blood at baseline, for performance of sequencing analysis. A fresh tumor biopsy sample must be collected within 28 days prior to the first dose of study treatment (baseline) in Parts A, B, and C, where feasible, in the opinion of the Investigator. If a fresh tumor biopsy sample cannot be obtained, the most recently acquired archived tumor biopsy sample may be used for analysis. The archived sample must have been biopsied within 3 years of Screening. For archived tumor biopsy samples, sufficient tumor samples should be acquired to allow biomarker testing (eg, at least unstained 12-15 slides). The baseline tumor biopsy sample (fresh or archived) must be from a location that has not been radiated.
    - Blood samples for exploratory immune correlative studies (eg, RNAseq, cfDNA, flow cytometry and ELISPOT analysis) may be collected in up to 25 total patients from Part B and Part C during Screening, at Week 1 (ie, right before the first infusion) and 7 days (±2 days) after the end of each of the first 3 ADXS-503 infusions (Weeks 2, 5, and 8) and EOT. Samples for cfDNA are only collected at week 1 if samples are not collected during screening. To monitor the durability of T cell responses, subsequent blood samples for PBMCs may be taken at Week 25 (±1 week) and/or at end of treatment
- Following treatment discontinuation, all subjects will enter a 1-year survival/treatment and *Lm* surveillance (*Lm*S) Follow-up Period (see **Section** 9.2.1.4 - Management of Listeria during Follow-Up).
    - Survival status will be confirmed remotely with the subject, their physician, or their legally authorized representative every 3 months (±2 weeks) for up to 1 year. Any subsequent anti-cancer treatment received by the subject during this 1-year period will also be recorded.
    - During the *Lm*S Follow-up, subjects (or their legally authorized representative) will be contacted remotely every 3 months (±2 week) for up to 1 year to determine whether they have experienced for several days, the following symptoms that could potentially be associated with delayed listeremia and require prompt attention at the research site:
        - Fever or chills, headache, nausea, confusion or changes in alertness (for over 72 hours).

5.2. Scientific Rationale for Study Design

Section 3.5 describes the rationale for this study and the selected subject population.

5.2.1. Rationale for Starting Dose

The starting dose of ADXS-503 in this study is $1x10^8$ CFU, administered every 3 weeks. This dose is selected for three key reasons: (1) the *Lm*-based construct and attenuated bacterial platform are comparable across the entire Advaxis *Lm* program; (2) clinical data from approximately 540 subjects treated with Advaxis *Lm*-based immunotherapies, suggest that a higher dose of $1x10^9$ CFU is safe and well-tolerated. The AEs observed at $1x10^9$ CFU are primarily associated with infusion of the live attenuated *Lm* vector and are due to innate immune stimulation following phagocytosis of the bacteria by APCs. The incidence and severity of infusion-related signs and symptoms exhibit a dose-dependent relationship with the total number of CFUs infused (dose range of $1x10^9$ to $1x10^{10}$ CFU). These AEs have been well managed with a pre-infusion regimen of adequate hydration, NSAIDs, antihistamines and antiemetics; (3) however, as described in **Section** 3.4.4.1, 1 subject with NSCLC experienced Grade 3 hypoxia and 1 subject with colorectal cancer experienced Grade 3 hypotension and Grade 3 hypoxia following the second dose of the neoantigen-based *Lm* immunotherapy (ADXS-NEO) at $1x10^9$ CFU. Subsequently, 3 subjects completed ADXS-NEO therapy at 1×10^8 CFU dosing level; this dose was well-tolerated for subjects with advanced or metastatic solid tumors similarly to what has been observed in this study with ADXS-503 at dose level-1 ($1x10^8$ CFU).

Based on these factors, the starting dose of $1x10^8$ CFU of ADXS-503 is considered appropriate.

This study will use the approved dose of pembrolizumab for the treatment of metastatic NSCLC, 200 mg every 3 weeks. Refer to the approved pembrolizumab Product Label for additional information.

5.2.2. Rationale for 3+3 Dose Escalation/De-Escalation and Dose-Expansion Design

In this study, a standard 3+3 design will be used for dose escalation/de-escalation purposes. The 3+3 design is a widely used rule-based method for dose escalation/de-escalation in Phase 1 oncology clinical trials. This approach should allow for a sufficient number of subjects to be enrolled at each dose level to evaluate study endpoints, while limiting the number of subjects exposed to potential toxicity.

In Part B dose expansion, a Simon's Two-stage design will be used. The Simon's Two-stage design is one of the most common multi-stage designs used in Phase 2 oncology clinical trials. The Simon's Two-stage design is an exact design which allows flexibility regarding the null and alternative hypotheses, while also allowing stopping for futility (**Section** 10.1).

The rationale for combination of *Lm*-based immunotherapies in combination with PD-1/PD-L1 checkpoint inhibitors is described in **Section** 3.4.2 and **Section** 3.4.5.1.

5.3. Number of Subjects Enrolled

In the safety phase, up to approximately 24 subjects will be enrolled in either Part A (up to 12 subjects; ADXS-503 monotherapy; 2 planned dose levels) or Part B (up to 12 subjects; ADXS-503 + pembrolizumab; 2 possible dose levels). The actual number of subjects enrolled in Part A and Part B will depend upon potential toxicities observed during dose escalation according to the 3+3 design.

In the efficacy phase (Part B-dose expansion and Part C combined), up to approximately 165 subjects may be enrolled. In Part B dose expansion, up to 43 subjects will be enrolled in the Simon's Two-stage study cohort and up to a total of 140 thereafter; and approximately 25 subjects will be enrolled in the efficacy phase (Part C; ADXS-503 + pembrolizumab).

Up to approximately 25 subjects may be enrolled in the Part A expansion cohort. If additional cohorts or study parts are added, the protocol will be amended accordingly to reflect the number subjects enrolled.

Subjects may be replaced if they are enrolled in the study but discontinue prior to receiving a dose of ADXS-503. Furthermore, if a subject does not receive 2 doses of ADXS-503 monotherapy in Part A or 2 doses of ADXS-503 and pembrolizumab in Part B within the 28-day DLT period, the subject may be replaced for DLT assessment purposes.

5.4. End of Study Definition

The planned end of the study is defined as the scheduled date when the survival/treatment follow-up period ends for the final subject enrolled in this study.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Subjects are eligible for this study only if all the following criteria apply:

6.1. Inclusion Criteria

1. Subject and/or their legally authorized representative must be capable of understanding the investigational nature, potential risks, and benefits of the study. The subject and/or their legally authorized representative must sign a written informed consent;

2. Subject is ≥18 years of age upon signing the Informed Consent Form;

3. Subject has histologically or cytologically confirmed stage IV (metastatic) squamous or non-squamous NSCLC

   - **For Parts A and B:**
     - During Screening, a fresh tumor biopsy must be obtained if clinically feasible, in the opinion of the Investigator for biomarker analysis. If a fresh biopsy cannot be obtained during Screening, the most recently acquired archived tumor biopsy sample may be used for analysis (date of biopsy within 3 years of Screening). For archived tumor biopsy samples, sufficient tumor samples should be acquired to allow biomarker testing (eg, at least unstained12-15 slides). The baseline biopsy must be from a location that has not been radiated.
   - **Part A only:**
     - Subject has received, and then progressed or been intolerant to up to 3 lines of prior therapy in the metastatic setting, including approved chemotherapy, targeted therapy, immunotherapy and antibody therapy, if eligible. Subjects who have received >3 lines of prior therapy may be eligible for Part A, upon discussion with and approval by the Sponsor.
       - Subjects will be eligible for Part A irrespective of PD-L1 expression.
       - Subjects will be eligible for Part A irrespective of *EGFR* or *ALK* mutation status. However, subjects with an *EGFR* sensitizing mutation or *ALK* translocation must have received and then progressed or been intolerant to at least 1 prior line of approved targeted therapy to be eligible for Part A.

       Note: Subjects with tumors that harbour neuroendocrine or small cell components may be eligible for Part A upon discussion with and approval by the Sponsor.
   - **Part B only:**
     - Subject is undergoing treatment with pembrolizumab monotherapy for metastatic NSCLC as last therapy

     OR

     - Subject is undergoing combination therapy with pembrolizumab + platinum-based chemotherapy as the last treatment

     OR

     - Subject is receiving pembrolizumab + pemetrexed as maintenance therapy after completing treatment with pembrolizumab plus platinum-based chemotherapy as the last therapy in the metastatic setting

- Subject's most recent tumor assessment is consistent with progressive disease (PD) according to RECIST v1.1
- There is no evidence of rapid disease progression or clinical deterioration in the subject that would preclude continuation of pembrolizumab treatment for up to 12 weeks before ADXS-503 is added-on.
- Subjects who are receiving pembrolizumab in combination with platinum-based chemotherapy or with pemetrexed, will continue on pembrolizumab monotherapy every 3 weeks per schedule while other drugs are washed-out for 3 weeks
- Subject must consent to allow the acquisition of fresh or archival FFPE tumor tissue, either a block or unstained slides along with matching blood at baseline, for performance of sequencing analysis.

Note: In Part B, subjects must receive the first dose of ADXS-503 within 12 weeks of the initial tumor assessment showing PD (while on treatment with pembrolizumab monotherapy or the below referenced combination therapies with pembrolizumab). ADXS-503 will be administered as add-on treatment to the ongoing pembrolizumab therapy (whether as monotherapy, **or** while receiving combination therapy with pembrolizumab + platinum-based chemotherapy **or** pembrolizumab + pemetrexed as maintenance therapy, as their last treatment in metastatic setting, where subjects have had an initial assessment of PD per RECIST v1.1 on the most recent tumor scan).

- **Part C only:**
  - Subject has received no prior systemic treatment in the metastatic setting. Subjects previously treated with adjuvant or neoadjuvant therapy are eligible if the adjuvant/neoadjuvant therapy was completed at least 6 months prior to the diagnosis of metastatic disease.
  - Subject must consent to allow the acquisition of fresh or archival FFPE tumor tissue, either a block or unstained slides along with matching blood at baseline, for performance of sequencing analysis.
  - Subject has provided a formalin-fixed tumor sample from a biopsy of a tumor lesion either at the time of or after the diagnosis of metastatic disease AND from a site not previously irradiated, for correlative work. Biopsies obtained PRIOR to the administration of any systemic therapy to treat the subject's tumor (such as neoadjuvant/adjuvant therapy) will not be permitted for analysis. The tissue sample must be received by the specialty laboratory vendor for tumor testing prior to enrollment. Fine needle aspirates, Endobronchial Ultrasound (EBUS) or cell blocks are not acceptable. Needle or excisional biopsies, or resected tissue is required. If the tumor specimen has not been evaluated for PD-L1 expression, an additional tumor specimen must be submitted to the local laboratory facility for assessment following an FDA-approved test.

- Subject's tumor has PD-L1 expression (TPS≥1%) as determined by an FDA-approved test.
- Subject's tumor has no EGFR or ALK genomic tumor aberrations. *EGFR* sensitizing mutations are mutations that are amenable to treatment with TKIs (eg, erlotinib, gefitinib, afatanib, osimertinib). *ALK* translocations are amendable to treatment with TKIs such as crizotinib, alectinib and ceritinib. Investigators must produce the source documentation of the *EGFR* mutation and *ALK* translocation status in all subjects with non-squamous histology AND for subjects in whom testing is clinically indicated. If either an *EGFR* sensitizing mutation or *ALK* translocation is detected, additional information regarding the mutation status of the other molecule is not required. If the clinical site is unable to provide the source documentation, *EGFR* and *ALK* testing should be performed per institutional standard of care.
    - Subjects with non-squamous histology will not be eligible until the *EGFR* mutation and/or *ALK* translocation status is known.
    - *EGFR* and *ALK* testing will not be required for subjects with predominantly squamous histology, as this is not the standard of care.

4. Subject has measurable disease for response assessment as defined by RECIST v1.1 by the Investigator;

5. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (see Appendix 11);

6. Subject has a life expectancy of at least 3 months;

7. Subject has recovered to Grade ≤1 by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (NCI-CTCAE v4.03) of all clinically significant toxic effects of prior anti-cancer chemotherapy, immunotherapy, radiotherapy or surgery before entering this study, except for alopecia;

8. Subject has no major existing comorbidities or medical conditions that would preclude therapy in the opinion of the Investigator;

9. Subject has adequate organ function as described in Table 4 below.

Table 4: Organ Function Requirements for Study Inclusion

System	Laboratory Value
Hematologic	
Absolute neutrophil count (ANC) [a]	≥1 x 10^9/L (Parts A and B); ≥1.5 x 10^9/L (Part C)
Platelets [a]	≥75 x 10^9/L (Parts A and B); ≥100 x 10^9/L (Part C)
Hemoglobin [a]	≥9 g/dL or ≥5.6 mmol/L
WBC [a]	≥2000/ µL
Renal	
Serum creatinine **OR** Measured or calculated creatinine clearance (CrCl). Note: GFR can also be used in place of serum creatinine or CrCl	≤1.5 x upper limit of normal (ULN) **OR** ≥50 mL/min for subjects with serum creatinine levels >1.5 x institutional ULN [b]
Hepatic	
Serum total bilirubin	≤1.5 x ULN (except subjects with Gilbert Syndrome, who must have total bilirubin <3 x ULN)
AST (SGOT) and ALT (SGPT)	<3 x ULN (Parts A and B); <1.5 x ULN (Part C)
Endocrine	
Thyroid stimulating hormone (TSH)	Within normal limits (Parts B and C only). [c]

[a]ANC, platelets, hemoglobin, or WBC requirement cannot be met by the use of recent transfusions, or growth factor support (G-CSF, erythropoietin, etc.) within 2 weeks prior to treatment initiation.
[b]Creatinine clearance should be calculated per institutional standard.
[c]If TSH is not within normal limits, subject may still be eligible if T3 and free T4 are within normal limits.

Contraception

Female subjects

10. A female subject is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

    a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 5

    OR

    b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 120 days after the final dose of study treatment;

11. A female subject of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study treatment and throughout the study as defined in the **SoA**. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Male subjects

12. A male subject is eligible if he agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 120 days after the final dose of study treatment.

6.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Subject has an ongoing different primary malignancy. Exceptions include treated basal cell carcinoma of the skin or squamous cell carcinoma of the skin;

2. Subject has an active autoimmune disease requiring systemic treatment within the past 3 months, a documented history of clinically severe autoimmune disease, or a disorder that requires systemic corticosteroids or immunosuppressive agents. Subjects with vitiligo, psoriasis, alopecia or resolved childhood asthma/atopy not requiring systemic treatment would be an exception to this rule. Subjects with hypothyroidism who are stable on hormone replacement (>10 mg daily prednisone equivalent) or Sjögren's syndrome will not be excluded from the study;

3. Subject has a diagnosis of primary immunodeficiency, is dependent on or has received systemic corticosteroid therapy (>10 mg daily prednisone equivalent) or any other form of immunosuppressive therapy within 14 days prior to the first dose of study treatment. Inhaled or topical corticosteroids, and adrenal replacement corticosteroid doses >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease;

4. Subject has neuropathy (sensory or motor) ≥Grade 3 per CTCAE v4.03;

5. Subject has had an allogeneic tissue/solid organ transplant;

6. Subject has known history (past 5 years) or any evidence of interstitial lung disease (ILD) OR active, non-infectious pneumonitis that has required oral or IV steroids;

7. Subject has untreated central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (no new or enlarging brain metastases) by imaging for at least 2 weeks following treatment, and clinically stable with no symptoms due to CNS metastasis, and are not using corticosteroids for at least 14 days prior to the start of study treatment;

8. Subject has a concurrent unstable or uncontrolled medical condition (eg, active uncontrolled systemic infection, unstable angina, congestive heart failure, uncontrolled diabetes) or other chronic disease, which in the opinion of the Investigator could compromise the subject or the study;

9. Subject has a known history of human immunodeficiency virus (HIV) infection (HIV 1/2 antibodies);

10. Subject has a known active hepatitis B (eg, HBsAg reactive) or hepatitis C infection (eg, HCV RNA [qualitative] is detected) or tuberculosis;

11. Subject has an active infection requiring systemic therapy or is dependent on or currently receiving antibiotics that cannot be discontinued before dosing. (Note: Subjects who discontinue an antibiotic prior to dosing must wait at least 5 half-lives after the last dose of antibiotic before receiving any study treatment);

12. Subject has known psychiatric or substance abuse disorder(s) that would interfere with cooperation with the requirements of the study;

13. Subject has an implanted medical device that poses a high risk for bacterial colonization and/or that cannot be easily removed (eg, prosthetic joints, artificial heart valves, pacemakers, orthopedic screws, bone grafts, or other critical exogenous implants). NOTE: More common devices and prosthetics that include arterial and venous stents, hernia mesh, some metal plates, dental and breast implants and venous access devices (eg, Port-a-Cath or Mediport) are permitted. Sponsor must be contacted prior to consenting any subject who has any other device or implant;

14. Subject is pregnant or breastfeeding, or plans to become pregnant or to father children, from the Screening visit through at least 120 days after the final dose of study treatment;

15. Subject has a contraindication (eg, sensitivity/allergy) to trimethoprim/ sulfamethoxazole, ampicillin, and another antibiotic to which *Lm* is typically sensitive (eg, erythromycin, fluoroquinolones – see Section 9.2.1.3.1.1for further details);

16. Subject has a contraindication to non-steroidal anti-inflammatory drugs (NSAIDs);

    a. Subject has a known allergy to any component of the study formulation(s);

17. Subject has a history of listeriosis;

18. Subject has any other serious or uncontrolled physical or mental condition/disease that, as judged by the Investigator, could place the subject at higher risk derived from their participation in the study, could confound results of the study, or would be likely to prevent compliance with the requirements of the study;

Prior/Concomitant Therapy

19. Subject has received chemotherapy and/or radiation therapy (except palliative radiation therapy for disease-related pain) within 2 weeks of the first dose of study treatment;

20. Subject has received monoclonal antibody or other biologic therapy within 5 half-lives or 28 days prior to the first dose of study treatment, whichever is shorter. An exception to this exclusion criterion will be pembrolizumab monotherapy for subjects enrolled in Part B;

21. Subject has received prior treatment with an *Lm*-based immunotherapy;

    a. Subject is receiving or plans to receive future treatment with PI3K or TNFα inhibitors;

    b. Subject has received a live vaccine within 30 days prior to the first dose of study treatment;

    c. Subject has not recovered to baseline from AEs, with the exception of alopecia, due to previously administered agent(s);

22. Subject has had major surgery within 6 weeks prior to the initiation of study treatment. NOTE: All surgical complications must have recovered to baseline or Grade ≤1 prior to the initiation of study therapy. Sponsor must be consulted prior to enrolling subjects on the study who recently had a major surgery or have a new artificial implant, and/or devices;

Prior/Concurrent Clinical Study Experience

23. Subject is currently participating in or has participated in a study of an investigational agent(s) within 4 weeks of the first dose of study treatment;

24. Subject is or has an immediate family member (spouse or children) who, as investigational site or sponsor staff, is directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject;

Exclusion Criteria for Part C only

25. In Part C, subject has received systemic therapy for the treatment of their metastatic NSCLC. Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease;

26. In Part C, subject has an *EGFR* sensitizing mutation and/or an *ALK* translocation;

27. In Part C, baseline tumor specimen is not evaluable for PD-L1 expression. If an additional tumor specimen is submitted AND evaluable for PD-L1 expression, the subject will be eligible to participate if the tumor expresses PD-L1 (TPS ≥1%) as determined by an FDA-approved test with no EGFR or ALK genomic tumor aberrations;

28. In Part C, subject has received prior systemic chemotherapy, biological therapy, OR major surgery within 6 weeks of the first dose of study treatment; received thoracic radiation therapy of >30 Gy within 6 months of first dose of study treatment;

29. In Part C, subject has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug that specifically targets T cell co-stimulation or immune checkpoint pathways.

6.3. Lifestyle Restriction

No lifestyle restrictions are specified in this protocol. Subjects should maintain a normal diet unless modifications are required to manage an AE such as nausea, diarrhea or vomiting.

6.4. Screen Failures

Screen failures are defined as subjects who consent to undergo Screening for the clinical study but fail to meet the required entry criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

A subject who has laboratory test results, vital signs, or other findings that do not satisfy the eligibility criteria may have the test(s) repeated. These tests may be repeated as soon as the Investigator believes the re-test result to likely be within the acceptable range to satisfy the entry criteria but **must** be completed within the Screening period. The subject will not be required to sign another ICF, and the original subject identification number will be used. If the laboratory test(s) cannot be performed within the Screening period, if the re-test(s) does not meet the entry criteria or if the subject's medical condition has changed significantly during the Screening period so that inclusion/exclusion criteria are no longer met, then the subject is considered a Screen failure.

Individuals who do not meet the criteria for participation in this study (Screen failure) may be re-screened after consultation with the Sponsor and will require a new subject identification number.

Part C: If the tumor specimen has not been evaluated for PD-L1 expression, it may be tested at a local laboratory facility, so the subject can be eligible to participate if the tumor expresses PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

7. Treatments

The rationale for the starting dose of ADXS-503 ($1x10^8$ CFU) is described in **Section** 5.2.1. This study will use the approved dose of pembrolizumab for treating patients with metastatic NSCLC: 200 mg every 3 weeks. Upon Investigator assessment and discretion, the schedule of therapy with ADXS-503 plus 200 mg of pembrolizumab, IV, could shift from every 3 weeks to every 6 weeks after the first year of study treatment. Refer to the approved pembrolizumab Product Label for additional information.

7.1. Treatments Administered

7.1.1. ADXS-503 Monotherapy (Part A)

In Part A, ADXS-503 will be administered as monotherapy at 2 planned escalating dose levels ($1x10^8$ CFU and $5x10^8$ CFU). If treatment with ADXS-503 monotherapy at the starting dose of $1x10^8$ CFU (DL1) is not safe and tolerable (based on DLT criteria), a lower dose of $0.5x10^8$ CFU (DL -1) will be evaluated. Treatment in Part A will be administered as outlined in Table 5 and as described below.

Table 5: Treatment in Part A: ADXS-503 Monotherapy

Treatment	Dose Level (DL)	Dose	Dose Frequency	Route of Administration
ADXS-503	2	$5x10^8$ CFU	Q 3 weeks	Intravenous
	1 (starting dose)	$1x10^8$ CFU	Q 3 weeks	Intravenous
	-1	$0.5x10^8$ CFU	Q 3 weeks	Intravenous

In Part A, each subject will receive ADXS-503 monotherapy at their enrolled dose level, **every 3 weeks (±2 days)** until disease progression, unacceptable toxicity or another treatment discontinuation criterion is met (see **Section** 8.1). Treatment with ADXS-503 must occur within 3 days of the scheduled infusion day unless a delay in dosing is required to allow for the resolution of AEs as outlined in **Section** 7.6. The interval between each subsequent dose of ADXS-503 should not be less than 2 weeks without Sponsor approval. The following ***pre-infusion***, ***infusion*** and ***post-infusion*** procedures are required for each ADXS-503 treatment infusion.

Pre-infusion: A pre-infusion regimen of adequate hydration, NSAIDs, antihistamines and antiemetics as a prophylaxis for "flu-like" symptoms will be completed at least 30 minutes prior to each ADXS-503 infusion (see **Section** 9.2.1.1). Vital signs will be monitored every 30 minutes (±5 minutes) starting immediately prior to each ADXS-503 infusion, until 4 hours after the end of each ADXS-503 infusion (see **Section** 9.2.1.2).

Infusion: Administer ADXS-503 as a single IV infusion over 60 (±10) minutes through a dedicated infusion line. ADXS-503 **must not** be administered as an IV push or bolus injection. ADXS-503 **must not** be administered via an existing or newly placed central venous catheter or infusion port that is planned to be used for another purpose. In addition, the central venous catheter or infusion port **must not** be used for 72 hours following the completion of the ADXS-503 infusion

until after the subject's first post-infusion dose of oral antibiotics is administered. Refer to the **Pharmacy Manual** for treatment preparation and additional treatment administration instructions.

Vital signs will continue to be monitored every 30 minutes (±5 minutes) during each ADXS-503 infusion.

Post-infusion: Following each infusion of ADXS-503, vital signs will continue to be monitored every 30 minutes (±5 minutes) for 4 hours and a 7-day oral antibiotic regimen will be dispensed. The first antibiotic dose will be administered at approximately 48 hours after the completion of each ADXS-503 infusion. See **Section** 9.2.1.3 for additional information.

Refer to the **Pharmacy Manual** for treatment preparation and detailed treatment administration instructions.

Refer to **Section** 9.2.2 for supportive care guidelines for ADXS-503 treatment. Guidelines for the management of infusion reactions can be found in Appendix 6. Guidelines for the management of other acute events, including hypotension, hypoxia, encephalopathy, organ toxicity, fever and constitutional symptoms can be found in Appendix 7.

7.1.2. ADXS-503 + Pembrolizumab (Part B Dose-Escalation and Dose-Expansion)

In Part B dose escalation, ADXS-503 will be administered at 2 planned escalating dose levels ($1x10^8$ CFU and $5x10^8$ CFU) in combination with a fixed dose of pembrolizumab (200 mg). If treatment with ADXS-503 + pembrolizumab is not safe and tolerable at the starting dose of $1x10^8$ CFU (DL1) (based on DLT criteria), a lower dose of $0.5x10^8$ CFU (DL -1) will be evaluated. Treatment in Part B dose expansion, ADXS-503 will be administered at DL1 ($1x10^8$ CFU) in combination with a fixed dose of pembrolizumab (200 mg) as outlined in Table 6 and as described below.

Table 6: Treatment in Part B: ADXS-503 + Pembrolizumab

Treatment	Dose Level (DL)	Dose	Dose Frequency [a]	Route of Administration
ADXS-503	2	$5x10^8$ CFU	Q 3 weeks	Intravenous
	1 (starting/expansion dose)	$1x10^8$ CFU	Q 3 weeks	Intravenous
	-1	$0.5x10^8$ CFU	Q 3 weeks	Intravenous
PLUS				
Pembrolizumab	N/A	200 mg	Q 3 weeks	Intravenous

a: At each dose level in Part B, ADXS-503 and pembrolizumab will be administered on the same day, every 3 weeks, starting at Week 1 (±2 days).

In Part B, each subject will receive ADXS-503 at their enrolled dose level in combination with 200 mg of pembrolizumab, **every 3 weeks** (±2 days) until disease progression, unacceptable toxicity, the completion of 2 years of study treatment or another treatment discontinuation criterion is met (see **Section** 8.1). Upon Investigator assessment and discretion, the schedule of therapy with ADXS-503 + 200 mg of pembrolizumab, IV, could shift from every 3 weeks to every 6 weeks after the first year of study treatment. Treatment with ADXS-503 and pembrolizumab will start at Week 1 (±2 days). Treatment with ADXS-503 and pembrolizumab must occur within 3 days of the scheduled infusion day unless a delay in dosing is required to allow for the resolution of AEs as outlined in **Section** 7.6. The interval between each subsequent dose of ADXS-503 and each subsequent dose of pembrolizumab should not be less than 2 weeks without Sponsor approval.

Week 1 (±2 days) onwards: On each treatment day, pembrolizumab will be infused first over 30 (±5) minutes, followed approximately 60 (±15) minutes after the **end** of the pembrolizumab infusion by the ADXS-503 infusion. Treatment will be administered as follows:

1. Pembrolizumab Infusion: Administer pembrolizumab as a single IV infusion over 30 (±5) minutes through a dedicated infusion line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter. Pembrolizumab **must not** be administered as an IV push or bolus injection. Pembrolizumab **must not** be administered via an existing or newly placed central venous catheter or infusion port that is planned to be used for another purpose. A separate infusion line will be used to administer ADXS-503. For enrolled patients with difficulty to access veins, one infusion line for pembrolizumab may be used to administer ADXS-503 provided it is flushed after the pembrolizumab infusion, at pre-infusion and post-infusion of ADXS-503 regimen. If the infusion line is the same, the in-line filter used for the infusion of pembrolizumab

must be removed before infusing ADXS-503. See the approved pembrolizumab Product Label and **Pharmacy Manual** for treatment preparation and detailed treatment administration instructions.

2. ADXS-503 Infusion: Following the administration of pembrolizumab and before the administration of ADXS-503, the Investigator must confirm that the subject is in a stable medical condition and any ongoing AEs, if present, would not preclude the administration of ADXS-503. If ongoing AEs do preclude the administration of ADXS-503, ADXS-503 treatment must be delayed until the resolution of the AEs.

The following ***pre-infusion***, ***infusion*** and ***post-infusion*** procedures are required for each ADXS-503 treatment infusion.

Pre-infusion: A pre-infusion regimen of adequate hydration, NSAIDs, antihistamines and antiemetics as a prophylaxis for "flu-like" symptoms will be completed at least 30 minutes prior to each ADXS-503 infusion (see **Section** 9.2.1.1). Vital signs will be monitored every 30 minutes (±5 minutes) starting immediately prior to each ADXS-503 infusion, until 4 hours after the end of each ADXS-503 infusion (see **Section** 9.2.1.2).

Infusion: Administer ADXS-503 as a single IV infusion over 60 (±10) minutes through a dedicated infusion line, or through the same one used for pembrolizumab administration, if needed for subjects with vein access difficulties. Where one infusion line is used for the administration of both drugs, it must be flushed after each infusion, ie, after the pembrolizumab infusion and pre- and post-infusion of ADXS-503 infusion regimen (**Section** 7.1.1.). In addition, if the infusion line is the same, the in-line filter used for the infusion of pembrolizumab must be removed before infusing ADXS-503. ADXS-503 **must not** be administered as an IV push or bolus injection. ADXS-503 **must not** be administered via an existing or newly placed central venous catheter or infusion port that is planned to be used for another purpose. On the other hand, an existing central venous catheter or infusion port **may** be used to withdraw blood samples for correlative analysis in this trial. Refer to the **Pharmacy Manual** for treatment preparation and detailed treatment administration instructions.

Vital signs will continue to be monitored every 30 minutes (±5 minutes) during each ADXS-503 infusion.

Post-infusion: Following each infusion of ADXS-503, vital signs will continue to be monitored every 30 minutes (±5 minutes) for 4 hours and a 7-day oral antibiotic regimen will be dispensed. The first antibiotic dose will be administered at approximately 48 hours after the completion of each ADXS-503 infusion. See **Section** 9.2.1.3 for additional information.

Refer to **Section** 9.2.2 for clinical safety management and supportive care guidelines for ADXS-503 and pembrolizumab treatment. Guidelines for the management of infusion reactions can be found in Appendix 6. Guidelines for the management of other acute events, including hypotension, hypoxia, encephalopathy, organ toxicity, fever and constitutional symptoms can be found in Appendix 7.

Note: If any toxicity results in the discontinuation of either ADXS-503 or pembrolizumab but not both, treatment with the non-discontinued study drug may continue as monotherapy in Part B, unless the nature of the toxicity precludes administration of any treatment (see **Section** 7.6). **In such cases, the treatment administration instructions for the individual study drug administered as monotherapy are to be followed until treatment discontinuation**.

7.1.3. ADXS-503 + Pembrolizumab (Part C)

In Part C, ADXS-503 will be administered at a planned dose of $1x10^8$ CFU in combination with a fixed dose of pembrolizumab (200 mg). Treatment in Part C will be administered as outlined in Table 7, and as described below.

Table 7: Treatment in Part C: ADXS-503 + Pembrolizumab

Treatment	Dose	Dose Frequency [a]	Route of Administration
ADXS-503	$1x10^8$ CFU	Q 3 weeks	Intravenous
PLUS			
Pembrolizumab	200 mg	Q 3 weeks	Intravenous

a: In Part C, ADXS-503 and Pembrolizumab will be administered on the same day, every 3 weeks starting on Week 1 (±2 days). However, after first year of treatment, the dosing schedule could be changed to every 6 weeks, upon investigator assessment and discretion.

In Part C, starting at Week 1 (±2 days), ADXS-503 and pembrolizumab will be administered on the same day, **every 3 weeks** (±2 days) until disease progression, unacceptable toxicity, the completion of 2 years of study treatment, or another treatment discontinuation criterion is met (see **Section** 8.1). Upon Investigator assessment and discretion, the schedule of therapy with ADXS-503 + 200 mg of pembrolizumab, IV, could shift from every 3 weeks to every 6 weeks after the first year of study treatment. Treatment with ADXS-503 and pembrolizumab must occur within 3 days of the scheduled infusion day unless a delay in dosing is required to allow for the resolution of AEs as outlined in **Section** 7.6. The interval between each subsequent dose of ADXS-503 and each subsequent dose of pembrolizumab should not be less than 2 weeks without Sponsor approval.

Follow the treatment administration instructions outlined below for each respective agent.

1. Pembrolizumab Infusion: Administer pembrolizumab as a single IV infusion over 30 (±5) minutes through a dedicated infusion line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter. Pembrolizumab **must not** be administered as an IV push or bolus injection. Pembrolizumab **must not** be administered via an existing or newly placed central venous catheter or infusion port that is planned to be used for another purpose. The same infusion line may be used to administer ADXS-503. For example, enrolled patients who present with difficulty to accessing their vein, could use one infusion line to administer both drugs if it is flushed after the pembrolizumab infusion and pre- and post-ADXS-503 infusion regimen (**Section** 7.1.1.). If the infusion line is the same, the in-line filter used for the infusion of pembrolizumab **must** be removed before infusing ADXS-503. See the approved pembrolizumab Product Label and **Pharmacy Manual** for treatment preparation and detailed treatment administration instructions.

2. ADXS-503 Infusion: Following the administration of pembrolizumab and before the administration of ADXS-503, the Investigator must confirm that the subject is in a stable medical condition and any ongoing AEs, if present, would not preclude the administration of ADXS-503. If ongoing AEs do preclude the administration of ADXS-503, ADXS-503 treatment must be delayed until the resolution of the AEs.

The following ***pre-infusion***, ***infusion*** and ***post-infusion*** procedures are required for each ADXS-503 treatment infusion.

Pre-infusion: A pre-infusion regimen of adequate hydration, NSAIDs, antihistamines and antiemetics as a prophylaxis for "flu-like" symptoms will be completed at least 30 minutes prior to each ADXS-503 infusion (see **Section** 9.2.1.1). Vital signs will be monitored every 30 minutes (±5 minutes) starting immediately prior to each ADXS-503 infusion, until 4 hours after the end of each ADXS-503 infusion (see **Section** 9.2.1.2).

Infusion: Administer ADXS-503 as a single IV infusion over 60 (±10) minutes through a dedicated infusion line or through the same one used for pembrolizumab administration, if needed for subjects with vein access difficulties. Where one infusion line is used to administer both drugs, it must be flushed after each infusion, ie, after the pembrolizumab infusion, pre- and post-infusion of ADXS-503 regimen (**Section** 7.1.1). In addition, if the infusion line is the same, the filter used for the infusion of pembrolizumab must be removed before infusing ADXS-503. ADXS-503 **must not** be administered as an IV push or bolus injection. ADXS-503 **must not** be administered via an existing or newly placed central venous catheter or infusion port that is planned to be used for another purpose. The central venous catheter or infusion port may be used to withdraw blood

samples for correlative analysis. Refer to the **Pharmacy Manual** for treatment preparation and detailed treatment administration instructions.

Vital signs will continue to be monitored every 30 minutes (±5 minutes) during each ADXS-503 infusion.

Post-infusion: Following each infusion of ADXS-503, vital signs will continue to be monitored every 30 minutes (±5 minutes) for 4 hours and a 7-day oral antibiotic regimen will be dispensed. The first antibiotic dose will be administered at approximately 48 hours after the completion of each ADXS-503 infusion. See **Section** 9.2.1.3 for additional information.

Refer to **Section** 9.2.2 for clinical safety management and supportive care guidelines for ADXS-503 and pembrolizumab treatment. Guidelines for the management of infusion reactions can be found in Appendix 6. Guidelines for the management of other acute events, including hypotension, hypoxia, encephalopathy, organ toxicity, fever and constitutional symptoms can be found in Appendix 7.

Note: If any toxicity results in the discontinuation of either ADXS-503 or pembrolizumab but not both, treatment with the non-discontinued study drug may continue as monotherapy in Part C, unless the nature of the toxicity precludes administration of any treatment (see **Section** 7.6). **In such cases, the treatment administration instructions for the individual study drug administered as monotherapy are to be followed until treatment discontinuation**.

7.2. Preparation/ Handling/ Storage/ Accountability

1. **ADXS-503** is shipped at **minus (-)80°C** with a temperature monitor included in the box that will be retrieved by the courier. It is imperative that all ADXS-503 drug shipments be stored at **minus (-)80°C** (±10°C**)** immediately after being removed from the shipping container. Recommended safety measures for preparation and handling of ADXS-503 include laboratory coats and gloves.
2. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
3. Only subjects enrolled in the study may receive study treatment and only authorized site staff may administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
4. Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site or by a third party outside of 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.

5. Further guidance is provided in the **Pharmacy Manual**.

ADXS-503 will be supplied by the Sponsor. Pembrolizumab may be provided by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements. For any commercially available product (including pembrolizumab) that is provided by the trial site, subsidiary or designee, every attempt will be made to source these supplies from a single lot/batch number. The trial site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased 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 trial treatments in accordance with the protocol and any applicable laws and regulations.

7.3. Treatment Compliance

Treatment compliance is not applicable to this study because ADXS-503 and pembrolizumab will be administered by the Investigator or designee in a clinical setting.

7.4. Method of Treatment Assignment

Each subject who has signed Informed Consent and has been screened for entry into the study, will be assigned a unique, sequential number that also includes the subject's study site.

In Part A, ADXS-503 will be administered as monotherapy at 2 planned escalating dose levels. In Part B, ADXS-503 will be administered at 2 planned escalating dose levels in combination with a fixed dose of pembrolizumab (200 mg). The dose of ADXS-503 administered to each subject will depend on the point at which the subject enrolls in the study during the dose escalation phase for Part A and Part B.

In Part C, all subjects will receive ADXS-503 + pembrolizumab. The planned dose of ADXS-503 in Part C is $1x10^8$ CFU in combination with a fixed dose of pembrolizumab (200 mg).

See **Section** 5.1 for a description of the study design.

7.5. Blinding

This is an open-label study. Therefore, the Sponsor, Investigator and subject will be aware of the treatment and dose administered.

7.6. Treatment Modification and Discontinuation Guidelines for Toxicity

Treatment will be delayed, or treatment will be discontinued due to specific toxicities as outlined in **Section** 7.6.1 for ADXS-503 and **Section** 7.6.2 for pembrolizumab.

For subjects treated with ADXS-503 in combination with pembrolizumab (Part B and Part C), the following guidance should be followed:

- Treatment modifications and treatment discontinuation as a result of toxicity should be based on the causal agent. Toxicity that was assessed as being caused by ADXS-503 should be managed according to the criteria for dose delays and treatment discontinuation for ADXS-503 (see **Section** 7.6.1), whereas toxicity that was assessed as being caused by pembrolizumab should be managed according to the criteria for dose delays and treatment discontinuation for pembrolizumab (see **Section** 7.6.2). This means that when administration of one agent has been delayed for toxicity, the other agent may be administered as scheduled, unless the nature of the toxicity precludes administration of any treatment. Similarly, treatment with either ADXS-503 or pembrolizumab may be discontinued when either drug is considered to be the cause of the toxicity.
- If any toxicity results in the discontinuation of either ADXS-503 or pembrolizumab but not both, treatment with the non-discontinued study drug may continue as monotherapy, unless the nature of the toxicity precludes administration of any treatment.
- On the day of dosing (from Week 1 [± 2 days] onwards in Part B and Part C), following the administration of pembrolizumab and before the administration of ADXS-503, the Investigator must confirm that the subject is in a stable medical condition and any ongoing AEs, if present, would not preclude the administration of ADXS-503. If ongoing AEs do preclude the administration of ADXS-503, ADXS-503 treatment must be delayed until the resolution of the AEs.

7.6.1. ADXS-503: Treatment Modification and Discontinuation Guidelines

Treatment modification and discontinuation guidelines for ADXS-503-related toxicities are outlined in Table 8 below.

Table 8: Treatment Modifications/Discontinuation for ADXS-503-Related Toxicity

Toxicity	Grade	Interrupt or Hold Treatment?	Timing for Restarting Treatment	Discontinue Treatment
Hematologic	1, 2, 3	No	N/A	N/A
	4	Yes	Toxicity resolves to Grade ≤ 1 or baseline within 12 weeks of previous dose of ADXS-503	Toxicity does not resolve to Grade ≤ 1 or baseline within 12 weeks of previous dose of ADXS-503
Non-hematologic (excluding AEs described in footnote b) [b]	1	No	N/A	N/A
	2-3	Yes	Toxicity resolves to Grade ≤ 1 or baseline within 12 weeks of previous dose of ADXS-503 [a]	Toxicity does not resolve to Grade ≤ 1 or baseline within 12 weeks of previous dose of ADXS-503 [a]
	4	N/A	Permanently discontinue treatment	Permanently discontinue treatment

[a] With Investigator and Sponsor agreement, subjects with a non-hematologic AE (eg, alopecia, vitiligo) still at Grade 2 after 12 weeks, may continue treatment only if asymptomatic and controlled.
[b] Refer to Appendix 6 for recommended management guidelines for AEs associated with infusion reactions; Appendix 7 for recommended management guidelines for other acute events, including hypotension, hypoxia, encephalopathy, organ toxicity, fever and constitutional symptoms; and Appendix 8 for guidelines to manage immune-related AEs.

Treatment with ADXS-503 must occur within 3 days of the scheduled infusion day (every 3 weeks ±2 days) unless a delay in dosing is required to allow for the resolution of AEs (see Table 8 above). Subjects who require a delay of ADXS-503 dosing should be re-evaluated weekly or more frequently if clinically indicated and resume ADXS-503 dosing when re-treatment criteria are met as outlined in Table 8 above. If treatment with ADXS-503 is delayed by >12 weeks from the previous dose of ADXS-503 for toxicities as outlined in Table 8, treatment should be discontinued after consultation with the Sponsor.

Dosing delays lasting >12 weeks from the previous dose of ADXS-503 that occur for non-drug-related reasons may be allowed if approved by the Medical Monitor. Prior to re-initiating treatment, the Medical Monitor must be consulted. Periodic study visits to assess safety should also continue every 6 weeks or more frequently if clinically indicated during dosing delays lasting >12 weeks.

If a subject discontinues treatment at their enrolled dose level due to toxicity, but is otherwise experiencing clinical benefit, he/she may be eligible to receive ADXS-503 at a lower dose level. This dose reduction may only take place upon discussion and agreement between the Investigator and the Sponsor, and once toxicities have returned to baseline or resolved. Only one dose reduction for ADXS-503 is allowed per subject. No other reason for dose reduction will be considered. All study-related procedures will apply for subsequent doses at the reduced dose.

7.6.2. Pembrolizumab: Treatment Modification and Discontinuation Guidelines

Treatment modification and discontinuation guidelines for pembrolizumab-related toxicities are outlined in Table 9 below.

Table 9: Treatment Modifications/ Discontinuation for Pembrolizumab-Related Toxicity

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject [d]
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 can be continued while hormone 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). [a]	Permanently discontinue.
Type 1 diabetes mellitus (T1DM) (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab 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 can be continued while thyroid replacement therapy is instituted.	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.
Infusion Reaction	2 [b]	Toxicity resolves to Grade 0-1.	Permanently discontinue if toxicity develops despite adequate premedication.
	3-4	Permanently discontinue.	Permanently discontinue.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject [d]
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.
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 [c]	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.

[a] 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.

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. See Appendix 6 for additional details.

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

[d] With Investigator and Sponsor agreement, subjects with certain non-hematologic AEs (eg, alopecia, vitiligo) still at Grade 2 after 12 weeks, may continue treatment only if asymptomatic and controlled.

Treatment with pembrolizumab must occur within 3 days of the scheduled infusion day (every 3 weeks ±2 days) unless a delay in dosing is required to allow for the resolution of AEs (see Table 9 above). Subjects who require a delay of pembrolizumab dosing should be re-evaluated weekly or more frequently if clinically indicated and resume pembrolizumab dosing when re-treatment criteria are met as outlined in Table 8 above. If treatment with pembrolizumab is delayed by >12 weeks from the previous dose of pembrolizumab for toxicities as outlined in Table 8, treatment should be discontinued after consultation with the Sponsor.

Dosing delays lasting >12 weeks from the previous dose of pembrolizumab that occur for non-drug-related reasons may be allowed if approved by the Medical Monitor. Prior to re-initiating treatment, the Medical Monitor must be consulted. Periodic study visits to assess safety should also continue every 6 weeks or more frequently if clinically indicated during dosing delays lasting >12 weeks.

The dose of pembrolizumab cannot be reduced in this study.

Guidelines for the management of immune-related AEs considered by the Investigator to be related to pembrolizumab, are provided in Appendix 9**.**

7.7. Concomitant Therapy

7.7.1. Concomitant Medications

All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant prescription and nonprescription medications or vaccines received by the subject from 30 days prior to screening until 30 days after the final dose of study treatment, will be recorded in the electronic case report form (eCRF) along with:

- generic name of the medication
- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

Any addition, deletion, or change in the dose of these medications will also be recorded.

If a subject develops intolerance or an AE to ampicillin and/or trimethoprim/sulfamethoxazole on study for *Lm* prophylaxis, another antibiotic to which *Lm* is typically sensitive may be substituted upon discussion with and approval from the Sponsor (eg, erythromycin or fluoroquinolone).

In addition, any anti-cancer treatment received by the subject for 1 year following the final dose of study treatment (during the survival/treatment follow-up period), will be recorded in the eCRF, along with the information listed above.

Medications specifically prohibited in the exclusion criteria (**Section** 6.2) and **Section** 7.7.2 are not allowed during the ongoing study. If there is a clinical indication for a medication specifically prohibited during the trial, discontinuation from study treatment may be required.

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery or radiotherapy for tumor control is not permitted during the study; however, radiotherapy or procedures for symptom management is allowed.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.7.2. Prohibited Medications/ Therapy

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

- Anti-cancer systemic chemotherapy, immunotherapy, targeted therapy (eg, tyrosine kinase inhibitors), or other biological therapy (eg, anti-VEGF agents) not specified as study treatment in this protocol. Note: Ongoing pembrolizumab therapy will be permitted for subjects enrolled in Part B.
- Surgical treatment as per consultation with the Sponsor.
- Immunosuppressive agents (except as stated in **Section** 6.2).
- Immunosuppressive doses of systemic corticosteroids (ie, >10 mg daily prednisone equivalent), except as stated in **Section** 6.2.
- PI3K and TNFα inhibitors.
- Any Investigational agent(s) other than that/those to be administered to the subject per protocol in this study.
- Radiation therapy (except palliative radiation therapy for disease-related pain with a consult with the Sponsor's Medical Monitor).
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines and are not allowed.
- Acetaminophen cannot be substituted for NSAIDs as pre-medication for ADXS-503.

Subjects who, in the Investigator's judgement, require the use of any of the aforementioned treatments for clinical management, should be discontinued from study treatment. Subjects may receive other medications that the Investigator deems to be medically necessary.

In addition, please note the following:

- Anti-infectives should be avoided. However, subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.
- Medications described in Appendix 6, Appendix 7, or Appendix 8, Appendix 9 for the management of infusion reactions; acute hypotension, hypoxia, encephalopathy, organ toxicity, fever and constitutional symptoms; and immune-related AEs, respectively, should be administered as described in these guidelines.

7.7.3. Major and Minor Surgeries and ADXS-503 Treatment

No formal studies of the effect of ADXS-503 on wound healing have been conducted. However, based on the mechanism of action of ADXS-503, it is not expected that administration of the agent would complicate wound healing. Therefore, a subject may initiate or resume study treatment 2 weeks after minor surgery (ie, 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 (eg, return to baseline or Grade ≤1) from any toxicity and/or complication before the next dose of study treatment. Sponsor consultation is required prior to resuming study treatment for these subjects. If study treatment is delayed beyond 12 weeks due to concomitant surgery, the subject may be discontinued from study treatment.

7.8. Treatment after the End of the Study

There is no mandated treatment following the end of the study.

8. Discontinuation/ Withdrawal Criteria

8.1. Discontinuation of Study Treatment

Each subject will receive study treatment until a treatment discontinuation criterion is met.
Treatment discontinuation criteria include:

- Documented disease progression (radiographical per RECIST v1.1 or clinical, as determined by the Investigator).
- Unacceptable toxicity. See **Section** 7.6.
- Intercurrent illness that prevents the further administration of study treatment.
- Physician determines that it is in the subject's best interest.
- Noncompliance with study treatment or procedure requirements.
- Subject requires treatment with prohibited medication(s)/ therapy (see **Section** 7.7.2).
- Pregnancy or breastfeeding (see Appendix 5).
- Withdrawal of consent.
- Death.

- Sponsor's decision to terminate treatment or the study.
- Part B and Part C: subject completes 2 years of treatment with ADXS-503 + pembrolizumab. Note: 2 years of study treatment is calculated from the first dose of pembrolizumab.
- Subject achieves a confirmed CR, as described below.

If a subject achieves a confirmed Investigator-assessed, RECIST v1.1-defined CR, the subject may receive up to 2 additional doses of study treatment after the date of confirmed CR but must subsequently discontinue treatment. Confirmation of CR should be performed ≥4 weeks after initial CR assessment.

Subjects who achieve a confirmed CR (Parts A, B and C), as well as those subjects in Part B or Part C who stop trial therapy after 2 years of treatment for reasons other than disease progression or intolerability, may be eligible for re-treatment upon disease progression (with discussion and agreement between the Investigator and Sponsor).

Section 8.1.1 provides guidelines for treating subjects beyond initial Investigator-assessed RECIST v1.1-defined disease progression. **Section** 8.1.1 also provides guidelines for confirmatory tumor imaging upon initial progression.

8.1.1. Treatment after Initial Evidence of Radiologic Disease Progression

Immunotherapy may produce anti-tumor effects by potentiating an 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 in tumor burden or even the appearance of new lesions. Therefore, if initial radiological imaging on study in Part A, Part B and Part C indicates disease progression per RECIST v1.1, subjects may continue to receive study treatment provided the following criteria are met:

- 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 (eg, spinal cord compression) requiring urgent alternative medical intervention
- The subject is tolerating treatment
- Continued treatment is in the best interest of the subject, in the opinion of the Investigator

To mitigate against the possibility of pseudo-progression, tumor imaging must be repeated ≥4 weeks after initial Investigator-assessed RECIST v1.1-defined disease progression in Parts A, B, and C to confirm PD, when the subject's clinical condition warrants. If repeat imaging does not confirm PD, then treatment may continue or resume. If repeat imaging confirms initially documented PD and shows further progression of disease, the subject should be discontinued from study treatment, unless the basis for the PD assessment is enlarged tumor-draining lymph nodes in the presence of a target tumor reduction. In determining whether 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, the subject should be discontinued from study treatment, unless the Investigator considers the subject to be deriving clinical benefit, the Investigator considers continued treatment to be in the best interest of the subject, and the other criteria listed above are met. In this situation, treatment may continue after consultation with the Sponsor.

Additional information, including iRECIST assessments may be provided to the Investigator to assist in treatment-related decisions at the time of RECIST v1.1-defined progression.

8.1.2. Treatment/ Enrollment Stopping Rules

Continuous medical oversight will be performed in this study. The purpose of the medical oversight is to identify potential safety signals that indicate continued treatment and/or further study enrollment may present a risk to study subjects. Observed safety signals will be discussed between the Sponsor and study Investigators during scheduled teleconferences.

Treatment and/or study enrollment may be stopped based on the nature, frequency, or reversibility of observed toxicity. The following are examples of safety events that may require stopping study treatment and/or study enrollment for further Investigation by the Sponsor:

- A rate of dose-limiting toxicity at dose level 1 in Part A or Part B that exceeds 33%
- Evidence of invasive infection with study treatment
- Delayed listeremia in subjects without risk factors such as implanted medical devices or hardware
- A rate of toxicity or type of toxicity that is unanticipated based on prior experience with *Lm*-based immunotherapy and or/ pembrolizumab

Study treatment and/or study enrollment may resume if deemed appropriate by the Sponsor and study Investigators, based on the review of cumulative study data and an evaluation of risk/ benefit.

In dose-escalation Part A and Part B, safety data, including dose-limiting toxicities (see **Section** 9.1.6) will be discussed between the Sponsor and study Investigators for dose escalation/ de-escalation purposes during scheduled meetings. In Part B dose-expansion and Part C, toxicities

will be evaluated on an ongoing basis. If the aggregate rate of treatment-related toxicities that meet the DLT criteria (see **Section** 9.1.6**)** exceeds 33% at any time (across all subjects in Part B dose-expansion and Part C), the findings will be discussed between the Sponsor and study Investigators, and further enrollment may be interrupted. Depending on the nature and grade of the toxicities and after assessing the risk/benefit, treatment may be adjusted to a lower dose of ADXS-503 or an alternative treatment schedule.

See **Section** 5.1 for dose escalation rules for Part A and Part B.

8.2. Discontinuation from the Study

A subject may be discontinued from the study for any of the following reasons:

- A subject may withdraw from the study at any time at the subject's own request or that of the subject's legally authorized representative or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or administrative reasons.
    - If a subject is withdrawn from the study, the Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal including the date of last treatment and the reason for withdrawal.
    - Refer to the **SoA** for procedures to be completed at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- Eligibility (subject doesn't meet key eligibility criteria).
- Study closure or termination.
- Death.
- Lost to follow-up.

8.2.1. Withdrawal from the Study

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw consent from study participation at any time and for any reason without prejudice to his/her future medical care by the Investigator or at the Study Center.

Only subjects who refuse **all of** the following methods of follow-up will be considered to have withdrawn consent from study participation:

- Attendance at study visits per protocol.
- Study personnel contacting the subject by telephone.
- Study personnel contacting an alternative person (eg, family member, spouse, partner, legal representative, physician, or other healthcare provider).

- Trial personnel accessing and reviewing the subject's medical information from alternative sources (eg, doctor's notes, hospital records).

If the subject and/or their legally authorized representative refuses all of the above methods of follow-up, the Investigator should personally speak to the subject and/or their legally authorized representative to ensure the subject and/or their legally authorized representative understands all of the potential methods of follow-up. If the subject and/or their legally authorized representative continues to refuse all potential methods of follow-up, the Investigator will document this as a withdrawal of consent in the medical record and in the eCRF.

For a subject and/or their legally authorized representative who withdraws consent as defined above, study personnel may use local, regional, and national public records (in accordance with local law) to monitor vital status.

8.2.2. Lost to Follow-Up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases in which the subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA**.**
- As protocol waivers or exemptions are not allowed with the exception of immediate safety concerns, these should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

- Adherence to the study design requirements, including those specified in the **SoA**, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management and obtained before signing the Informed Consent Form, may be utilized for Screening or baseline purposes provided the procedure meets the protocol-specified criteria.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (**Section** 2). Safety assessments may be performed more frequently than the timepoints specified in the **SoA**, as clinically indicated. An "Unscheduled Visit" form will be used to record this additional information in the eCRF.

9.1.1. Physical Examinations

A complete physical examination will include, at a minimum, assessment of the body systems. Height will be measured at Screening only. Weight will be measured at all physical examination timepoints.

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

9.1.2. Vital Sign Measurements

Vital signs will be measured in a semi-supine position after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, pulse, oxygen saturation, and respiratory rate.

In Part A, vital signs will be monitored every 30 minutes (±5 minutes) starting immediately prior to each ADXS-503 infusion, until 4 hours after the end of each ADXS-503 infusion. Subsequent vital sign monitoring will be performed per institutional standard of care.

In Part B and Part C, vital signs will be monitored prior to the administration of pembrolizumab and subsequently as per institutional standard of care until the administration of ADXS-503. Vital sign monitoring for ADXS-503 will then occur every 30 minutes (±5 minutes) starting

immediately prior to each ADXS-503 infusion, until 4 hours after the end of each ADXS-503 infusion. Subsequent vital sign monitoring will be performed per institutional standard of care.

9.1.3. Performance Status Monitoring

The Eastern Cooperative Oncology Group (ECOG) Performance Scale will be used to monitor performance status. Refer to Appendix 11 for a description of the ECOG scale.

9.1.4. Clinical Safety Laboratory Assessments

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the **SoA**.
- The volume of blood to be collected at each timepoint for clinical safety laboratory assessments, can be found in the Laboratory Manual.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in the subject's clinical management or are considered clinically significant by the Investigator (eg, SAE or AE or treatment modification), then the results must be recorded in the eCRF.
- A pregnancy test will be performed for all WOCBP. All WOCBP must have a negative pregnancy test within 72 hours prior to receiving each dose of ADXS-503 in Part A, or each dose of ADXS-503 or pembrolizumab in Parts B and C. Note: the only exception will be Week 2 in Part C, where a pregnancy test will not be required prior to the first pembrolizumab dose (pregnancy test performed prior to the first ADXS-503 dose at Week 1). A positive urine pregnancy test must be confirmed by a serum pregnancy test (minimum sensitivity of 25 IU/L or equivalent units of βHCG). If the pregnancy test is positive, the subject must not receive study treatment and must not be enrolled in the study.

9.1.5. Assessment and Reporting of Adverse Events

The definition of an AE, Event of Special Interest (ESI), and SAE can be found in Appendix 4.

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, ESI, or SAE and remain responsible for follow-up of AEs that are serious, considered related to the study treatment or study procedures, or that caused the subject to discontinue the study treatment or the study (see **Section** 8).

9.1.5.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until 30 days after the final dose of study treatment or the beginning of any subsequent anti-cancer treatment, whichever occurs first. Reporting of ESI will begin from the date of first dose of study treatment. In Part A and Part B, ESI will be reviewed as they are reported and will be discussed at the time of the dose escalation meetings, and periodically afterwards. In Part C, ESI will be reviewed and discussed on an ongoing basis.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section.

All SAEs and ESI will be recorded and reported to the Sponsor or designee within **24 hours**, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study subjects. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor (ie, within 24 hours). Furthermore, if the Investigator becomes aware of any instances (eg, blood tests performed at another medical facility) in which a subject has *Lm* isolated from a blood culture or develops an illness consistent with an *Lm* infection, the Sponsor must be notified within 24 hours of the Investigator becoming aware of the event.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

Adverse reactions will be reported to FDA according to 21 CFR 312.32.

Toxicity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

9.1.5.2. Method of Detecting AEs, ESIs, and SAEs

Care will be taken not to introduce bias when detecting AEs, ESIs, and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

9.1.5.3. Follow-Up of AEs, ESI and SAEs

After the initial AE/SAE report, the Investigator is required to follow each subject at subsequent visits/contacts. All AEs, SAEs, and ESI (as defined in Appendix 4), will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in **Section** 8.2.2). See Appendix 4 for additional information on follow-up procedures.

9.1.5.4. Regulatory Reporting Requirements for SAEs

- Prompt notification (ie, within 24 hours) by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review the information and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.1.5.5. Pregnancy and Breastfeeding

- Prior to enrollment, study candidates who are WOCBP must be advised of the importance of avoiding pregnancy and lactation/breastfeeding during trial participation and the potential risk factors for an unintentional pregnancy.
- All WOCBP must have a negative pregnancy test within 72 hours prior to receiving each dose of ADXS-503 in Part A, or each dose of ADXS-503 or pembrolizumab in Parts B and C. Note: the only exception will be Week 2 in Part C, where a pregnancy

test will not be required prior to the first pembrolizumab dose (pregnancy test performed prior to the first ADXS-503 dose at Week 1). A positive urine pregnancy test must be confirmed by a serum pregnancy test (minimum sensitivity of 25 IU/L or equivalent units of βHCG). If the pregnancy test is positive, the subject must not receive study treatment and must not be enrolled in the study.

- A highly effective method of birth control must be used during study treatment and for at least 120 days after the final dose of study treatment (see Appendix 5).
- Details of all pregnancies and lactation/breastfeeding cases in female subjects or female partners of male subjects, will be collected during the treatment period and for at least 120 days after the final dose of study treatment.
- If a pregnancy or lactation/breastfeeding case is reported, the Investigator should inform Advaxis within 24 hours of learning of the pregnancy or lactation/breastfeeding case and should follow the procedures outlined in Appendix 5.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.
- In the case of pregnancy or a subject breastfeeds while taking protocol-required therapy, study treatment will be discontinued.

9.1.6. Dose Limiting Toxicity Criteria

Dose-limiting toxicity will be assessed over the **initial 28 days of treatment in Part A** and **Part B** for dose escalation/de-escalation decisions. Note: the DLT window will end 7 days after the second dose of ADXS-503 in Part A and 7 days after the second dose of ADXS-503 and pembrolizumab in Part B. Refer to **Section** 5.1 for the study design.

The same DLT criteria will be used in both Part A and Part B. A DLT is defined as any of the following AEs that is judged by the Investigator to be possibly, probably, or definitely related to study treatment, and occurs during the DLT evaluation period described above (according to CTCAE v4.03).

Grade 5 fatal adverse event

Hematologic:

1. Grade 4 neutropenia that lasts ≥72 hours
2. Grade 4 febrile neutropenia of any duration
3. Grade 3 febrile neutropenia that lasts more than 48 hours

4. Grade 4 thrombocytopenia

5. Grade 3 thrombocytopenia associated with clinically significant bleeding

6. Grade 3 hemolysis

7. Grade 3 anemia that does not resolve to Grade ≤1 within 72 hours with supportive treatment, including transfusions

Hepatic:

1. ALT or AST >8 x ULN, regardless of duration

2. ALT or AST >5 x and ≤8 x ULN, that fails to return to Grade ≤1 within 2 weeks despite medical intervention

3. Total bilirubin >5 x ULN

4. ALT or AST >3 x ULN and concurrent total bilirubin >2 x ULN

Non-hematologic:

1. Grade 4 anaphylaxis, hypotension, hypoxia, or acute respiratory distress

2. Grade ≥3 non-hepatic or non-hematologic toxicity that cannot be controlled within 24 hours, with the exceptions below:

The following Grade 3 non-hematologic toxicities **will not** be considered DLTs:

   a. Grade 3 nausea, vomiting and/or diarrhea lasting <3 days and reversible with medical intervention

   b. Grade 3 or 4 increase in amylase or lipase that persists <3 weeks and it is not associated with clinical or radiographic evidence of pancreatitis

   c. Grade 3 electrolyte abnormality that lasts <72 hours, is not clinically complicated and resolves spontaneously or responds to conventional medical intervention

   d. Grade 3 fever that lasts <72 hours, and it is not associated with hemodynamic compromise (including hypotension, or clinical or laboratory evidence of end organ perfusion impairment)

   e. Grade 3 endocrinopathy that is well controlled by hormone replacement

   f. Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to the sites of known or suspected tumor)

   g. Grade 3 fatigue for less than 7 days

3. Delay of >12 weeks in treatment administration (ADXS-503 or pembrolizumab) due to unresolved toxicities that are possibly, probably, or definitely related to study treatment

The occurrence of toxicities that meet the criteria listed above but occur outside of the DLT evaluation period, will be assessed on a continual basis and may be taken into consideration for future dose escalation/de-escalation decisions in Part A and Part B. Subjects in Part A and Part B who discontinue prior to the end of the DLT evaluation period for any reason other than toxicity will be replaced. Furthermore, if within the 28-day DLT period, a subject does not receive 2 doses of ADXS-503 monotherapy in Part A or 2 doses of ADXS-503 and pembrolizumab in Part B, the subject may be replaced for DLT assessment purposes.

In Part C, toxicities will be evaluated on an ongoing basis. If the aggregate rate of treatment-related toxicities that meet the DLT criteria listed above exceeds 33% at any time (across all subjects in Part C), the findings will be discussed between the Sponsor and study Investigators, and further enrollment may be interrupted. See **Section** 5.1.

Treatment modifications for specific toxicities are described in **Section** 7.6.

Overall treatment and enrollment stopping rules for this study are described in **Section** 8.1.2**.**

9.2. Clinical Safety Management

9.2.1. ADXS-503 Treatment and *Lm* Management Guidelines

9.2.1.1. ADXS-503 Pre-Infusion Prophylactic Regimen

From the previous clinical experience with *Lm*-based immunotherapies, it is anticipated that mild to moderate “flu-like” symptoms (eg, chills, pyrexia, nausea, vomiting, fatigue, headache, tachycardia and hypotension) may occur during or shortly after treatment infusion. The symptoms usually resolve within 2 to 4 hours after infusion without specific intervention or respond rapidly to limited symptomatic treatment within 30 minutes to 1 hour.

Prophylactic medications are intended to reduce the inflammatory response. The incorporation of pre-medication and hydration has reduced the apparent incidence and severity of infusion-related symptoms. Therefore, subjects should receive the following pre-infusion regimen prior to each ADXS-503 infusion:

IV Fluid Hydration:

- Normal saline (eg, 500 mL over 30 minutes).

Pre-Medication Regimen:

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

Pre-infusion treatment should be administered on the day of dosing and be completed at least 30 minutes prior to the start of the ADXS-503 infusion. Additional NSAID and antiemetic treatment should be given per the approved Product Label after the initial administration, 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.

9.2.1.2. ADXS-503 Infusion and Post-Infusion Monitoring

Vital signs will be monitored every 30 minutes (±5 minutes) starting immediately prior to each ADXS-503 infusion, until 4 hours after the end of each ADXS-503 infusion. Vital signs will be measured in a semi-supine position after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, pulse, oxygen saturation, and respiratory rate (see **Section** 9.1.2). At 4 hours after the ADXS-503 infusion, the Investigator must ensure that the subject is in a stable medical condition. If the subject is not stable, the Investigator must take action to provide appropriate medical care (see Appendix 6 and Appendix 7).

In Part B and Part C, ADXS-503 will be administered approximately 60 (±15) minutes after the end of the pembrolizumab infusion. Before administering ADXS-503, the Investigator must confirm that the subject is in a stable medical condition and any ongoing AEs, if present, would not preclude the administration of ADXS-503. If ongoing AEs do preclude the administration of ADXS-503, ADXS-503 treatment must be delayed until the resolution of the AEs.

9.2.1.3. Management of Listeria during Study Participation

Following the completion of each ADXS-503 infusion, subjects will receive a 7-day course of either **oral 80 mg trimethoprim / 400 mg sulfamethoxazole** once daily or **160 mg trimethoprim/ 800 mg sulfamethoxazole (DS)** 3 times over the course of the 7 days, starting approximately 48 hours after each ADXS-503 infusion. Subjects with a known allergy to sulfa drugs may receive **ampicillin 500 mg** 4 times daily for 7 days starting approximately 48 hours after each ADXS-503 infusion. Subjects with dual hypersensitivity to ampicillin and sulfa drugs may be treated with erythromycin or fluoroquinolones, after agreement between the Investigator and the medical monitor (**Section** 9.2.1.3.1.1). Post-infusion antibiotics are administered to ensure the clearance of

Lm. A subject who experiences a fever (Grade 1 or greater) 24 hours following the completion of the ADXS-503 infusion should be started on NSAIDs, hydration and other appropriate measures to treat the fever (see Appendix 7). If the fever persists or worsens 48 hours following the ADXS-503 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 ADXS-503 infusion, then a blood culture should be obtained to evaluate for listeremia and to determine the appropriate treatment course.

If symptoms consistent with sepsis occur at any time after ADXS-503 administration, immediate medical attention must be sought. A microbial culture will be collected to identify the agent of sepsis and antibiotic sensitivity testing should be performed to confirm susceptibility. An infectious disease consult should be obtained for further management of these events.

As an additional precautionary measure to ensure the clearance of *Lm*, a 3-week course of oral antibiotics (regimen as described above but for 21 days rather than 7 days) will be administered after the final dose of ADXS-503. The first dose will be administered at approximately 48 hours after the final dose of ADXS-503.

Seven days (±3 days) after the completion of the 3-week course of oral antibiotics, a blood sample will be collected to culture for *Lm*. If this blood test cultures positive for *Lm*, immediate and intensive IV antibiotic treatment (ampicillin +/- gentamycin or other IV antibiotic regimen as indicated) is required. The Sponsor must be notified within 24 hours. An infectious disease consult should also 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 the initiation of ADXS-503 treatment may be warranted.

Furthermore, if the Investigator becomes aware of any instances (eg, blood tests performed at another medical facility) in which a subject has *Lm* isolated from a blood culture or develops an illness consistent with an *Lm* infection, the Sponsor must be notified within 24 hours of the Investigator becoming aware of the event.

9.2.1.3.1.1. Listeremia – Identification and Management

ADXS-503 listeremia is confirmed only after isolation of *Lm* from a normally sterile site, such as blood or spinal fluid (in the setting of nervous system involvement). Stool samples are of limited use as Advaxis *Lm* strains are not shed and Advaxis *Lm*-based immunotherapies are administered intravenously. In addition, genotyping of the isolated *Lm* strain may be performed to confirm the isolate as ADXS-503.

ADXS-503 listeremia can be treated with antibiotics. In preclinical studies, wild-type *Lm* and Advaxis *Lm* strains were susceptible to the lowest tested concentration of the following antimicrobial agents: ampicillin, amoxicillin, ciprofloxacin, erythromycin, gentamicin, penicillin,

tetracycline, trimethoprim/sulfamethoxazole, and vancomycin (IV). ADXS-503 is resistant to streptomycin and nalidixic acid.

9.2.1.3.1.2. Biofilm-Associated Listeremia

Wild-type *Lm* is capable of forming and persisting within biofilms, including on medical devices, despite antibiotic treatment. Although rare, medical device-related infections such as ventriculo-peritoneal shunt infection, peritoneovenous shunt infection, and prosthetic joint infection have been reported after systemic listeriosis (Charlier, 2012; Dominguez, 1994; Le Monnier, 2011; Winslow, 1984). ADXS-503 is expected to be highly sensitive to antibiotics such as trimethoprim/sulfamethoxazole, amoxicillin and ampicillin, erythromycin and fluoroquinolones which can be effective treatment regimens for listeremia.

Therefore, subjects with implanted medical device(s) that pose a high risk for biofilm colonization and/or that cannot be easily removed, are excluded from this study. In addition, all subjects will receive a 7-day course of oral antibiotics beginning approximately 48 hours after each dose of ADXS-503 and for 3 weeks following the final dose of ADXS-503 to ensure clearance of *Lm*.

The use of PI3K or TNFα inhibitors will be prohibited in this study. As the PI3K signaling pathway may be directly involved in the regulation of TNFα production, PI3K inhibitors could reduce TNFα production and increase subject susceptibility to bacterial infections (Smith, 2007). The absence of TNFα-mediated signaling may also enhance the potential virulence of attenuated *Lm* in subjects taking PI3K or TNFα inhibitors (Sonje, 2010).

9.2.1.3.1.3. Antibiotic-Related Complications

Subjects who develop complications during antibiotic administration, including but not limited to hypersensitivity reactions and *Clostridium difficile*-related diarrhea, may be appropriately managed with alternative antibiotics following discussion with the Sponsor.

9.2.1.4. Management of Listeria During Follow-Up

After completion of the treatment period that can last for 2 year, or discontinuation from study treatment, subjects enter the Follow-up Period. During Follow-up, subjects will be contacted remotely every 3 months (±2 week) for 1 year to determine whether they have experienced for several days the following symptoms that could potentially be associated with delayed listeremia and require prompt attention at the research site:

- Fever or chills, headache, nausea, confusion or changes in alertness (for over 72 hours).

As part of the End of Therapy procedures, upon completing the *Lm* surveillance period, site staff should instruct subjects to contact the site if they experience any of these symptoms, as applicable.

9.2.2. Supportive Care Guidelines for ADXS-503 and Pembrolizumab

Immunotherapies are associated with AEs that may differ in severity and duration compared to treatments such as chemotherapy or TKIs. Early recognition and management of AEs associated with immunotherapies may mitigate severe toxicity.

Subjects should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Suggested supportive care measures for the management of AEs associated with the administration of ADXS-503 or pembrolizumab are outlined below. Where appropriate, these measures include the use of oral or intravenous treatment with corticosteroids and additional anti-inflammatory agents if symptoms do not improve with the 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 AE, attempts should be made to rule out other causes, such as bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines an AE to be related to ADXS-503 or pembrolizumab.

Note: If after evaluation, the event is determined not to be related to a specific study treatment, the Investigator does not need to follow the treatment guidance (as outlined below).

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

9.2.2.1. Infusion Reactions

Pembrolizumab and *Lm*-based immunotherapies have each been associated with infusion reactions following treatment administration (see **Section** 3.6.2). ADXS-503 is expected to have the same profile as *Lm*-based immunotherapies in this regard. Infusion reaction signs/symptoms typically occur during the treatment infusion, or shortly thereafter. Signs/symptoms of infusion reactions may include: allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritic/itching; rash/ desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); and vomiting.

The management guidelines for subjects who experience infusion reactions associated with the administration of ADXS-503 or pembrolizumab are provided in Appendix 6.

9.2.2.2. Acute, High-Grade Hypotension, Hypoxia, Encephalopathy and Organ Toxicity

Guidelines for the management of acute, high-grade hypotension, hypoxia, encephalopathy, and organ toxicity, can be found in Appendix 7. Additional information is provided in **Section** 3.6.2.1.1.

9.2.2.3. Management of Immune-Related Adverse Events

9.2.2.3.1. ADXS-503

While the hotspot mutation peptide antigens and TAAs expressed in the *Lm* construct are not expected to induce or exacerbate autoimmune toxicities, the potential for sub-acute or late-occurring immune-related AEs exists. Therefore, immune-related AEs will be closely monitored for in this study, with ADXS-503 as a single agent, and in combination with pembrolizumab. General guidance for treating immune-related AEs considered by the Investigator to be related to ADXS-503, is provided in Appendix 8.

9.2.2.3.2. Pembrolizumab

A pattern of immune-related AEs has been defined for pembrolizumab, for which management guidelines have been developed. These immune-related AEs include: **pneumonitis**, **diarrhea/colitis**, **Type 1 diabetes mellitus (T1DM)**, **hypophysitis**, **hyperthyroidism** or **hypothyroidism**, **primary adrenal insufficiency, hepatic AEs**, **renal failure/ nephritis, skin reactions, infusion reactions** (as described above), **hemophagocytic lymphohistiocytosis**, **complications of allogeneic hematopoietic stem cell transplant (HSCT)**, and **hematological toxicity in patients with chronic Hodgkin lymphoma (cHL)**. Immune-mediated adverse reactions reported in less that 1% of patients treated with pembrolizumab include uveitis, myositis, Guillain-Barre syndrome, pancreatitis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis and myocarditis. Guidelines for the management of common immune-related AEs are provided in Appendix 9**.** Refer to Appendix 6 for guidelines to manage infusion reactions associated with pembrolizumab.

9.2.2.4. Nausea and Vomiting

Nausea and vomiting should be treated aggressively. Following treatment, subjects should receive antiemetic therapy as needed, according to standard institutional practice. Subjects should also be strongly encouraged to maintain liberal oral fluid intake.

9.3. Treatment of Overdose

For this study, any dose of ADXS-503 and/or pembrolizumab greater than the prescribed dose will be considered an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Sponsor's Medical Monitor immediately
2. Closely monitor the subject
3. Document the quantity of the administered dose as well as the duration of the dosing in the eCRF

Appropriate supportive treatment should be provided if clinically indicated.

9.4. Efficacy Assessments

9.4.1. Tumor Response-Based Assessments

Tumor imaging will be performed by contrast-enhanced CT/MRI. Baseline tumor imaging will be performed within 28 days prior to the first dose of study treatment and will include CT/MRI of the chest, abdomen, pelvis and any additional known sites of disease. Subjects with known CNS metastases and subjects with signs or symptoms suggestive of brain metastasis should be evaluated with a CT/MRI of the brain at baseline. Subsequent tumor assessments should include CT/MRI of the head (for subjects with known CNS metastases), chest, abdomen, pelvis and any additional known sites of disease using the same imaging method used for the baseline scan.

In **Part A** (ADXS-503 monotherapy), tumor imaging will be performed during Screening (baseline), at Week 8 (±7 days), at Week 16 (±7 days), followed by every 9 weeks (±7 days) thereafter, until confirmed disease progression or treatment discontinuation, whichever occurs later.

In **Part B** dose-escalation and dose-expansion (ADXS-503 + pembrolizumab), tumor imaging will be performed during Screening (baseline), which corresponds to the most recent tumor assessment that is consistent with PD (according to RECIST v1.1) while on treatment with pembrolizumab monotherapy **or** while receiving combination therapy with pembrolizumab + platinum-based chemotherapy **or** while receiving pembrolizumab + pemetrexed as maintenance therapy, as the last therapy in the metastatic setting. As described above, the first dose of ADXS-503 will be administered within 12 weeks of the initial assessment of PD. Subsequent scans will be performed at Week 8 (±7 days), at Week 16 (±7 days), every 9 weeks (±7 days) after dosing with ADXS-503 + pembrolizumab in all Part B subjects, until confirmed disease progression or treatment discontinuation, whichever occurs later.

In **Part C** (ADXS-503 + pembrolizumab), tumor imaging will be performed during Screening (baseline), at Week 8 (±7 days), at Week 16 (± 7 days), followed by every 9 weeks (±7 days)

thereafter, until confirmed disease progression or treatment discontinuation, whichever occurs later.

Tumor imaging will occur at the schedule above, independent of any adjustments to the treatment schedule.

Tumor response will be evaluated by the Investigator (or designee) according to RECIST v1.1 as the basis for the primary analysis of tumor response-based endpoints. Exploratory analysis of tumor-response will be performed by the Sponsor (or designee) according to iRECIST.

- In Part A and Part C, subjects may receive study treatment beyond initial Investigator-assessed, RECIST v1.1-defined disease progression, provided the criteria in **Section** 8.1.1 are met. Additional information, including iRECIST assessments may be provided to the Investigator to assist in treatment-related decisions at the time of RECIST v1.1-defined progression. In Part B, all subjects will begin study treatment within 12 weeks of initial Investigator-assessed, RECIST v1.1-defined disease progression on treatment with pembrolizumab monotherapy **or** while receiving combination therapy with pembrolizumab + platinum-based chemotherapy **or** while receiving pembrolizumab + pemetrexed as maintenance therapy, as the last therapy in the metastatic setting (if eligibility criteria are met).

- For all subjects in Parts A, B and C, any apparent CR or PR must be confirmed ≥4 weeks after radiological imaging indicating CR or PR.

- Subjects who achieve a confirmed CR may receive up to 2 additional doses of study treatment after the date of confirmed CR but must subsequently discontinue treatment (see **Section** 8.1).

- Subjects who achieve a confirmed CR (Parts A, B and C), and subjects in Part B or Part C who stop trial therapy after 2 years of treatment for reasons other than disease progression or intolerability, may be eligible for re-treatment upon disease progression (with agreement between the Investigator and Sponsor) [see **Section** 8.1]. Tumor response data collected during the re-retreatment period will not be used for the primary analysis of tumor response endpoints.

- All subjects who complete the first tumor scan after the first dose of study treatment, will be considered evaluable for tumor response.

The following efficacy endpoints will be evaluated from the tumor response data in Part A, Part B and Part C, according to RECIST v1.1 (primary analysis) and selectively, as deemed appropriate by iRECIST (exploratory analysis) (see **Section** 10.3 and Appendix 10):

- **Best overall response (BOR)**
- **Objective response rate (ORR)**
- **Duration of objective response (DOR)**
- **Disease control rate (DCR)**
- **Progression-free survival (PFS)**
- **PFS rate at 12 months**

Please refer to **Section** 10.3 for the definition of tumor response-based endpoints and their analysis.

9.4.2. Survival Assessments

All subjects will be assessed for survival status from study enrollment until approximately 1 year after the final dose of study treatment. Following treatment discontinuation, survival status will be confirmed remotely with the subject, their physician, or their legally authorized representative every 3 months (±2 weeks) for up to 1 year.

The following efficacy endpoints will be evaluated from the survival data in Part A, Part B and Part C:

- **Overall survival (OS)**
- **6- and 12-month overall survival rates**

Please refer to **Section** 10.3 for the definition of survival endpoints and their analysis.

9.5. Biomarker Assessments

- Blood and tumor tissue samples for biomarker research will be collected at the time points specified in the **SoA**.
- The volume of blood and tissue to be collected for biomarker analysis, and processing and shipping instructions, can be found in the Laboratory Manual.
- Blood and tumor tissue samples may be stored for a maximum of 5 years following the last subject's last study visit at a facility selected by the Sponsor to enable further analysis of the samples.
- **Blood Sampling for Exploratory Correlates of Immune Response in Parts A, B and C**
    - In Part A, Part B and Part C, peripheral blood may be collected at Screening and during the treatment phase of the study at the time points specified in the **SoA**.

Peripheral blood mononuclear cells (PBMCs) and sera will be prepared for the planned immune correlative analyses, as outlined in **Section** 9.5.1 below.

- **Tumor Biopsy Sampling**
  - **Exploratory Biomarker Evaluation in Part A, Part B & Part C**
    - **Baseline biopsy sample:** All subjects must consent to allow the acquisition of fresh or archival FFPE tumor tissue, either a block or unstained slides along with matching blood at baseline, for performance of sequencing analysis. A fresh tumor biopsy sample must be collected within 28 days (±2 days) prior to the first dose of study treatment (baseline) in Part A and within 6 weeks in Part B, where feasible, in the opinion of the Investigator. If a fresh tumor biopsy sample cannot be obtained, the most recently acquired archived tumor biopsy sample may be used for analysis. For archived tumor biopsy samples, sufficient tumor samples should be acquired to allow sequencing analysis (eg, at least unstained 12-15 slides). The archived sample must have been biopsied within 3 years of Screening. The baseline tumor biopsy sample (fresh or archived) must be from a location that has not been radiated.
    - Baseline tumor biopsy samples and matching blood for sequencing analysis will be evaluated in all patients in the study as outlined in **Section** 9.5.1 below.
  - **Required Specimen Evaluation for Eligibility in Part C**
    - Participation in Part C of this trial will be dependent upon supplying tumor tissue from a location that has not been radiated. Subject must consent to allow the acquisition of fresh or archival FFPE tumor tissue, either a block or unstained slides along with matching blood at baseline, for performance of sequencing analysis. Biopsies obtained PRIOR to receipt of neoadjuvant/adjuvant chemotherapy are NOT permitted. The tumor tissue must have been previously evaluated for expression status of PD-L1 at a local laboratory facility using FDA-approved tests. Fine needle aspirates, Endobronchial Ultrasound (EBUS) or cell blocks are not acceptable. Needle or excisional biopsies, or resected tissue is required. If the tumor specimen is not evaluable for PD-L1 expression, an additional tumor specimen must be submitted to the local laboratory facility for testing with FDA approved assays before enrolling. Only subjects whose tumors express PD-L1 (TPS

≥1%), as determined by an FDA-approved test will be eligible for enrollment.

- In Part C, documentation of *EGFR* mutation and/or *ALK* translocation status will be required for subjects with non-squamous NSCLC AND if clinically indicated. If the site is unable to provide this source documentation, *EGFR*/ *ALK* testing should be performed per institutional standard of care using FDA-approved tests.

9.5.1. Biomarker Evaluation in Part A and Part B

In Part A and in up to a total of 25 patients from Part B and Part C, peripheral blood will be collected at Screening and during the treatment phase of the study for correlative work at the time points specified in the **SoA (Section 2)**. Peripheral blood mononuclear cells (PBMCs) and sera will be prepared for the planned immune correlative analyses.

Immune Cell Phenotype

Flow cytometry will be performed on isolated PBMCs to examine the states of activation,differentiation and cytotoxicity of various immune cells in Patients from Part A and in up to a total of 25 patients from Part B and/or Part C.

Monitoring of T Cell Responses

At baseline and during treatment in in up to 25 patients from dose-escalation Part A and Part B and Part C, the frequency of functional tumor antigen-specific T cells will be quantified by FluoroSpot in peripheral blood samples.

Genetic Alterations in Tumor Cells, Tumor Microenvironment and T cells

DNA and RNA from FFPE specimens and matching blood samples will be analyzed by whole exome sequencing and RNA sequencing in Parts A, B and C at baseline. These assays will determine the expression pattern of the hotspot mutations and the tumor-associated antigens, which are included in ADXS-503, in each subject's tumor, to identify subject-specific mutation-derived antigens, and to determine the subject's tumor mutational burden, microsatellite status, TCR repertoire, and haplotypes.

9.6. Pharmacokinetic Assessments

Blood samples for pharmacokinetic analysis will not be taken in this study. Pharmacokinetic parameters will not be evaluated.

9.7. Pharmacodynamic Assessments

Pharmacodynamic parameters other than biomarkers described in **Section** 9.5, will not be evaluated in this study.

9.8. Pharmacogenomic Assessments

Pharmacogenomic parameters will not be evaluated in this study.

9.9. Health Economics OR Medical Resource Utilization and Health Economic Assessments

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

10. Statistical Considerations

10.1. Sample Size Determination

Safety Phase

Up to approximately 24 subjects will be enrolled in the safety phase in either Part A or Part B dose-escalation.

In Part A, up to approximately 12 subjects will receive treatment with ADXS-503 monotherapy at 1 of 2 planned escalating dose levels. In Part B dose-escalation, up to approximately 12 subjects will receive treatment with ADXS-503 at 1 of 2 planned escalating dose levels in combination with a fixed dose of pembrolizumab. A 3+3 design will be used for dose escalation/ de-escalation purposes in Part A and Part B.

The sample size in Part A and Part B dose-escalation/de-escalation is not based on statistical considerations and will be determined by safety data and DLTs observed at each dose level evaluated.

Upon completion of dose escalation in Part A, ADXS-503 monotherapy may be evaluated in an expansion cohort. Up to approximately 25 subjects may be enrolled in this expansion cohort.

Efficacy Phase

In the efficacy phase (Part B dose-expansion and Part C), up to approximately 165 subjects may be enrolled. Up to 43 subjects may be enrolled in Part B expansion of DL1 in the Simon's Two-stage study cohort and up to a total of 140 thereafter. In addition, approximately up to 25 subjects may be enrolled in Part C.

The sample size in Part B dose-expansion at dose level 1 (DL-1) will use Simon's optimal Two-stage design (Simon, 1989). The null hypothesis is that the true response rate is 0.1, and the alternative hypothesis is that the true response rate is 0.25. The Part B dose-expansion will be carried out in 2 stages. In stage I, a total number of 18 subjects is accrued. If there are 2 or fewer responses among these 18 patients, the study will be stopped early. Otherwise, an additional 25 patients will be accrued in stage II, resulting in a total sample size of 43 subjects. If there are 8 or more responses among these 43 subjects, we reject the null hypothesis and claim that the treatment is promising. The design controls the type I error rate at 0.05 and yields a power of 0.8.

	r1	n1	r	n	Type I error	Power	PET(p0)	EN(p0)
Optimal	2	18	7	43	0.48	0.8003	0.7338	24.7

Note: r1 = the first stage threshold to stop the trial for futility; n1 = number of accrual subjects for stage I; n = total number of subjects; r = overall threshold to stop the trial for futility; EN(p0) = expected sample size for the cohort when the true response rate is p0; PET(p0) = probability of early termination when the true response rate is p0.

In Part C, approximately 25 subjects will be enrolled and will receive treatment with ADXS-503 in combination with pembrolizumab. The sample size in Part C is not based on statistical considerations but is considered sufficient to evaluate the preliminary clinical efficacy of the treatment combination.

Additional subjects may be enrolled in the study based on emerging study data or the evolving treatment landscape. In this situation, the protocol will be amended accordingly to reflect the sample size and relevant statistical analyses.

10.2. Populations for Statistical Analyses

For purposes of statistical analysis, the following populations are defined (see Table 10):

Table 10: Populations for Statistical Analysis

Population	Description
All Enrolled Subjects	All subjects who sign the ICF, meet entry criteria and are allocated a slot in the study.
All Treated Subjects	All subjects enrolled in the study who receive at least one dose of study treatment.
Tumor Response Evaluable Subjects	All subjects in the All Treated Subjects population with at least one post-baseline evaluable tumor scan.

10.3. Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock to provide full details on the study populations, endpoint definitions, analyses and methods.

Summary statistics for continuous variables will include mean, standard deviation, median and range. Categorical variables will be presented as frequency counts and percentages; and time-to-event variables will be summarized by Kaplan-Meier (KM) medians and survival plots. Data listings will be created to support tables and figures and to present data.

Below is a summary of the planned statistical analyses to support the endpoints of this study.

10.3.1. Analysis of Safety

All safety analyses will be performed on All Treated Subjects and summarized by dose level and study part.

Adverse events will be summarized (incidence) and listed by the System Organ Class (SOC), preferred term, toxicity/severity grade, and Investigator-assigned relationship to study treatment. In addition, separate summaries of SAEs, ESIs and Grade 3 and 4 AEs will be presented. Tabulations will be limited to treatment emergent events – ie, those with onset anytime during study treatment through 30 days after the final dose of study treatment or the beginning of subsequent any anti-cancer treatment, whichever occurs first; or if they were present prior to the first dose of study treatment and worsened during study treatment as specified above.

Hematological and chemistry laboratory parameters will be graded according to the CTCAE v.4.03, where applicable. Shifts from baseline in severity grade will be tabulated. Absolute values and changes from baseline will be summarized.

Vital sign measurements and the corresponding changes from baseline will be summarized using descriptive statistics.

Results of performance status and physical examinations will be presented in the subject data listings.

10.3.2. Analysis of Efficacy

All efficacy analyses will be performed on All Treated Subjects and summarized by dose level and study part.

Efficacy endpoints will be descriptively summarized by dose level and study part. Tumor response will be summarized according to response category. Objective response rate (ORR) and disease control rate (DCR) will be summarized by frequency tables. The KM method will be used to estimate progression-free survival (PFS), PFS rate at 12 months, overall survival (OS) and

milestone OS rates at 6 and 12 months. Descriptive statistics and KM curves will also be presented. Actual tumor response results may render exploratory evaluation by the iRECIST criterion unnecessary or superfluous, such as when the difference between results using RECIST v1.1 and iRECIST criteria is small or insignificant. In such a case, selected efficacy endpoints by iRECIST as stated below may not be conducted.

10.3.2.1. Best Overall Response

Best overall response (BOR) will be evaluated for All Treated Subjects, and if warranted, for Tumor Response Evaluable Subjects according to RECIST v1.1 and iRECIST.

Best overall response is determined based on tumor assessments recorded between the first dose of study treatment and the date of first objectively confirmed disease progression, or the date of subsequent anti-cancer treatment, whichever occurs first. For subjects without confirmed disease progression or subsequent anti-cancer treatment, all available response designations will contribute to the BOR assessment.

10.3.2.2. Objective Response Rate

Objective response rate will be evaluated for All Treated Subjects, and if warranted, for Tumor Response Evaluable Subjects according to RECIST v1.1 and iRECIST. Objective response rate is defined as the proportion of subjects who achieve a CR/iCR or PR/iPR as BOR.

CR or PR determinations included in the BOR assessment must be confirmed by a confirmatory scan ≥4 weeks after the criteria for response are first met.

10.3.2.3. Duration of Objective Response

Duration of objective response will be evaluated for subjects who have a BOR of CR or PR per RECIST v1.1, or a BOR of iCR or iPR per iRECIST. Duration of objective response is defined as the time from the date when the criteria are first met for a CR/iCR or PR/iPR to the first date that disease progression is objectively documented, or death regardless of cause, whichever occurs first.

For subjects who neither progress nor die, the duration of objective response will be censored at the same time as the primary definition of PFS.

10.3.2.4. Disease Control Rate

Disease control rate will be evaluated for All Treated Subjects, and if warranted, for Tumor Response Evaluable Subjects according to RECIST v1.1 and iRECIST. Disease control rate is defined as the proportion of subjects who achieve a CR/iCR, PR/iPR or SD/iSD ≥24 weeks as BOR (as defined above).

10.3.2.5. Progression-Free Survival

Progression-free survival will be evaluated for All Treated Subjects according to RECIST v1.1 and iRECIST. Progression-free survival is defined as the time from the date of the first dose of study treatment to the date of the first objectively confirmed radiographic disease progression, or death regardless of cause, whichever occurs first.

Clinical deterioration in the absence of objectively confirmed progression is not considered progression for the purpose of determining radiographic PFS. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who do not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who do not have any on-study tumor assessments and do not die will be censored on the date of the first dose of study treatment. Subjects who start any subsequent anti-cancer therapy, without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy.

10.3.2.6. Progression-Free Survival Rate at 12 Months

Progression-free survival rate at 12 months will be evaluated for All Treated Subjects according to RECIST v1.1 and iRECIST. Progression-free survival rate at 12 months is defined as the KM probability of PFS at 12 months.

10.3.2.7. Overall Survival

Overall survival will be evaluated for All Treated Subjects. Overall survival is defined as the time from the date of the first dose of study treatment to the date of death, regardless of cause. If no death date is known for a subject, OS will be censored at the date the subject is last confirmed to be alive.

10.3.2.8. Milestone Overall Survival Rate at 6 and 12 Months

Milestone survival will be evaluated for All Treated Subjects. Milestone survival is defined as the KM survival probability at 6 and 12 months after the date of the first dose of study treatment.

10.3.3. Biomarker Analyses

The analysis of biomarker endpoints will be described in the SAP that is finalized before database lock. The results of biomarker data may be presented separately from the main clinical study report (CSR).

10.3.4. Interim Analyses

No formal interim analysis is planned for this study. Administrative interim analyses on safety and efficacy may be conducted prior to the completion of the study in order to facilitate program decisions and to support study presentations or publications.

11. Regulatory

See Appendix 3 for information regarding regulatory and ethical considerations, including financial disclosure, informed consent process, data protection, publication policy, dissemination of clinical study data, data quality assurance, source documents, and study and site closure.

12. References

Actemra®. (2020). (tocilizumab) [prescribing information]. South San Francisco, CA: Genentech, Inc.

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Advaxis Internal Data.

Alamgeer, M., Ganju, V., & Watkins, D. N. (2013). Novel therapeutic targets in non-small cell lung cancer. *Curr Opin Pharmacol, 13*(3), 394-401. doi:10.1016/j.coph.2013.03.010

Alexandrov, L. B., Nik-Zainal, S., Wedge, D. C., et al. (2013). Signatures of mutational processes in human cancer. *Nature, 500*(7463), 415-421. doi:10.1038/nature12477

American Cancer Society. (2019). Cancer Facts & Figures. Retrieved from https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf

Borghaei, H., Paz-Ares, L., Horn, L., et al. (2015). Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med, 373*(17), 1627-1639. doi:10.1056/NEJMoa1507643

Brahmer, J., Reckamp, K. L., Baas, P., et al. (2015). Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med, 373*(2), 123-135. doi:10.1056/NEJMoa1504627

Brahmer, J., Rodriguez, A., Robinson, A., et al. (2017). *Updated Analysis of KEYNOTE-024: Pembrolizumab vs Platinum-Based Chemotherapy for Advanced NSCLC With PD-L1 TPS ≥50%.* Paper presented at the IASLC 18th World Conference on Lung Cancer; October 15-18, 2017, Yokohama, Japan. Abstract OA 17.06 (ID 9582).

Carter, L., Fouser, L. A., Jussif, J., et al. (2002). PD-1:PD-L inhibitory pathway affects both CD4(+) and CD8(+) T cells and is overcome by IL-2. *Eur J Immunol, 32*(3), 634-643. doi:10.1002/1521-4141(200203)32:3<634::AID-IMMU634>3.0.CO;2-9

Chan, B. A., & Hughes, B. G. (2015). Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. *Transl Lung Cancer Res, 4*(1), 36-54. doi:10.3978/j.issn.2218-6751.2014.05.01

Chang, J. T., Wherry, E. J., & Goldrath, A. W. (2014). Molecular regulation of effector and memory T cell differentiation. *Nat Immunol, 15*(12), 1104-1115. doi:10.1038/ni.3031

Chang, M. T., Asthana, S., Gao, S. P., et al. (2016). Identifying recurrent mutations in cancer reveals widespread lineage diversity and mutational specificity. *Nat Biotechnol, 34*(2), 155-163. doi:10.1038/nbt.3391

Charlier, C., Leclercq, A., Cazenave, B., et al. (2012). Listeria monocytogenes-associated joint and bone infections: a study of 43 consecutive cases. *Clin Infect Dis, 54*(2), 240-248. doi:10.1093/cid/cir803

Chen, D. S., & Mellman, I. (2013). Oncology meets immunology: the cancer-immunity cycle. *Immunity, 39*(1), 1-10. doi:10.1016/j.immuni.2013.07.012

Dammeijer, F., Lau, S. P., van Eijck, C. H. J., et al. (2017). Rationally combining immunotherapies to improve efficacy of immune checkpoint blockade in solid tumors. *Cytokine Growth Factor Rev, 36*, 5-15. doi:10.1016/j.cytogfr.2017.06.011

Dominguez, E. A., Patil, A. A., & Johnson, W. M. (1994). Ventriculoperitoneal shunt infection due to Listeria monocytogenes. *Clin Infect Dis, 19*(1), 223-224.

Dunn, G. P., Bruce, A. T., Ikeda, H., et al. (2002). Cancer immunoediting: from immunosurveillance to tumor escape. *Nat Immunol, 3*(11), 991-998. doi:10.1038/ni1102-991

Eisenhauer, E. A., Therasse, P., Bogaerts, J., et al. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer, 45*(2), 228-247. doi:10.1016/j.ejca.2008.10.026

Ferlay, J., et al. (2015). Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer, 136*, E359-E386.

Freeman, G. J., Long, A. J., Iwai, Y., et al. (2000). Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med, 192*(7), 1027-1034. doi:10.1084/jem.192.7.1027

Gandhi, L., Rodriguez-Abreu, D., Gadgeel, S., et al. (2018). Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med, 378*(22), 2078-2092. doi:10.1056/NEJMoa1801005

Gentzler, R. D., Langer, C. J., Borghaei, H., et al. (2018). 24-month overall survival from KEYNOTE-021 cohort G: Pemetrexed-carboplatin plus pembrolizumab as first-line therapy for advanced nonsquamous NSCLC. *Journal of Clinical Oncology, 36*(15_suppl), 9026-9026. doi:10.1200/JCO.2018.36.15_suppl.9026

Goodman, A. M., Kato, S., Bazhenova, L., et al. (2017). Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers. *Mol Cancer Ther, 16*(11), 2598-2608. doi:10.1158/1535-7163.MCT-17-0386

Grupp, S. A., Kalos, M., Barrett, D., et al. (2013). Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N Engl J Med, 368*(16), 1509-1518. doi:10.1056/NEJMoa1215134

Guirnalda, P., Wood, L., Goenka, R., et al. (2013). Interferon gamma-induced intratumoral expression of CXCL9 alters the local distribution of T cells following immunotherapy with Listeria monocytogenes. *Oncoimmunology, 2*(8), e25752. doi:10.4161/onci.25752

Gunn, R. G. (2001). Recombinant Listeria monocytogenes as a tumor therapeutic (Doctoral dissertation). *Dissertations available from ProQuest*(Paper), AAJ3O15316.

Hellmann, M. D., Ciuleanu, T. E., Pluzanski, A., et al. (2018). Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. *N Engl J Med, 378*(22), 2093-2104. doi:10.1056/NEJMoa1801946

Herbst, R. S., Baas, P., Kim, D. W., et al. (2016). Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet, 387*(10027), 1540-1550. doi:10.1016/S0140-6736(15)01281-7

Herceptin®. (2020). (trastuzumab) [prescribing information]. South San Francisco, CA. Genentech, Inc.

Hirsh, V., & Melosky, B., eds. (2018). *Update on the Treatment of Metastatic Non-small Cell Lung Cancer (NSCLC) in New Era of Personalised Medicine*: Lausanne: Frontiers Media.

Hodi, F. S., O'Day, S. J., McDermott, D. F., et al. (2010). Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med, 363*(8), 711-723. doi:10.1056/NEJMoa1003466

Jotte, R. M., Cappuzzo, F., Vynnychenko, I., et al. (2018). IMpower131: Primary PFS and safety analysis of a randomized phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. *Journal of Clinical Oncology, 36*(18_suppl), LBA9000-LBA9000. doi:10.1200/JCO.2018.36.18_suppl.LBA9000

Keir, M. E., Butte, M. J., Freeman, G. J., et al. (2008). PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol, 26*, 677-704. doi:10.1146/annurev.immunol.26.021607.090331

Kelly, K., Crowley, J., Bunn, P. A., Jr., et al. (2001). Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non--small-cell lung cancer: a Southwest Oncology Group trial. *J Clin Oncol, 19*(13), 3210-3218. doi:10.1200/JCO.2001.19.13.3210

Keytruda®. (pembrolizumab) [prescribing information]. Whitehouse Station, NJ: Merck & Co, Inc; 2020.

Langer, C. J., Gadgeel, S. M., Borghaei, H., et al. (2016). Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol, 17*(11), 1497-1508. doi:10.1016/S1470-2045(16)30498-3

Latchman, Y., Wood, C. R., Chernova, T., et al. (2001). PD-L2 is a second ligand for PD-1 and inhibits T cell activation. *Nat Immunol, 2*(3), 261-268. doi:10.1038/85330

Le Monnier, A., Blanot, S., Abachin, E., et al. (2011). Listeria monocytogenes: a rare complication of ventriculoperitoneal shunt in children. *J Clin Microbiol, 49*(11), 3924-3927. doi:10.1128/JCM.01083-11

Lee, D. W., Gardner, R., Porter, D. L., et al. (2014). Current concepts in the diagnosis and management of cytokine release syndrome. *Blood, 124*(2), 188-195. doi:10.1182/blood-2014-05-552729

Liu, P., Morrison, C., Wang, L., et al. (2012). Identification of somatic mutations in non-small cell lung carcinomas using whole-exome sequencing. *Carcinogenesis, 33*(7), 1270-1276. doi:10.1093/carcin/bgs148

Luo, S. Y., & Lam, D. C. (2013). Oncogenic driver mutations in lung cancer. *Transl Respir Med, 1*(1), 6. doi:10.1186/2213-0802-1-6

Maciag, P. C., Radulovic, S., & Rothman, J. (2009). The first clinical use of a live-attenuated Listeria monocytogenes vaccine: a Phase I safety study of Lm-LLO-E7 in patients with advanced carcinoma of the cervix. *Vaccine, 27*(30), 3975-3983. doi:10.1016/j.vaccine.2009.04.041

Malhotra, J., Jabbour, S. K., & Aisner, J. (2017). Current state of immunotherapy for non-small cell lung cancer. *Transl Lung Cancer Res, 6*(2), 196-211. doi:10.21037/tlcr.2017.03.01

Massion, P. P., & Carbone, D. P. (2003). The molecular basis of lung cancer: molecular abnormalities and therapeutic implications. *Respir Res, 4*, 12. doi:10.1186/1465-9921-4-12

National Comprehensive Cancer Network (NCCN). (2018). Non-Small Cell Lung Cancer. *Version 3.2008.* Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/nscl

Nguyen-Ngoc, T., Reck, M., Tan, D., et al. (2017). Immunotherapy and Targeted Therapies in the Treatment of Non-small Cell Lung Cancer. *European Oncology & Haematology*. doi:https://doi.org/10.17925/EOH.2017.13.01.35

Oken, M. M., Creech, R. H., Tormey, D. C., et al. (1982). Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol, 5*(6), 649-655.

Pardoll, D. M. (2012). The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer, 12*(4), 252-264. doi:10.1038/nrc3239

Paz-Ares, L. G., Luft, A., Tafreshi, A., et al. (2018). Phase 3 study of carboplatin-paclitaxel/nab-paclitaxel (Chemo) with or without pembrolizumab (Pembro) for patients (Pts) with metastatic squamous (Sq) non-small cell lung cancer (NSCLC). *Journal of Clinical Oncology, 36*(15_suppl), 105-105. doi:10.1200/JCO.2018.36.15_suppl.105

Reche, P. A., & Reinherz, E. L. (2005). PEPVAC: a web server for multi-epitope vaccine development based on the prediction of supertypic MHC ligands. *TCGAbiolinks: an R/Bioconductor package for integrative analysis of TCGA data, 33*(suppl_2), W138-W142. doi:10.1093/nar/gki357

Reck, M., Rodriguez-Abreu, D., Robinson, A. G., et al. (2016). Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med, 375*(19), 1823-1833. doi:10.1056/NEJMoa1606774

Rittmeyer, A., Barlesi, F., Waterkamp, D., et al. (2017). Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet, 389*(10066), 255-265. doi:10.1016/S0140-6736(16)32517-X

Rizvi, N. A., Hellmann, M. D., Snyder, A., et al. (2015). Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science (New York, NY), 348*(6230), 124-128. doi:10.1126/science.aaa1348

Sandler, A., Gray, R., Perry, M. C., et al. (2006). Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med, 355*(24), 2542-2550. doi:10.1056/NEJMoa061884

Savas, P., Hughes, B., & Solomon, B. (2013). Targeted therapy in lung cancer: IPASS and beyond, keeping abreast of the explosion of targeted therapies for lung cancer. *J Thorac Dis, 5 Suppl 5*, S579-592. doi:10.3978/j.issn.2072-1439.2013.08.52

Scagliotti, G. V., De Marinis, F., Rinaldi, M., et al. (2002). Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. *J Clin Oncol, 20*(21), 4285-4291. doi:10.1200/JCO.2002.02.068

Scagliotti, G. V., Parikh, P., von Pawel, J., et al. (2008). Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol, 26*(21), 3543-3551. doi:10.1200/JCO.2007.15.0375

Schiller, J. H., Harrington, D., Belani, C. P., et al. (2002). Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med, 346*(2), 92-98. doi:10.1056/NEJMoa011954

Seymour, L., Bogaerts, J., Perrone, A., et al. (2017). iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol, 18*(3), e143-e152. doi:10.1016/s1470-2045(17)30074-8

Sharma, P., & Allison, J. P. (2015). The future of immune checkpoint therapy. *Science, 348*(6230), 56-61. doi:10.1126/science.aaa8172

Shepherd, F. A., Rodrigues Pereira, J., Ciuleanu, T., et al. (2005). Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med, 353*(2), 123-132. doi:10.1056/NEJMoa050753

Simon, R. (1989). Optimal two-stage designs for phase II clinical trials. *Control Clin Trials, 10*(1), 1-10. doi:10.1016/0197-2456(89)90015-9

Smith, M. V., Lee, M. J., Islam, A. S., et al. (2007). Inhibition of the PI3K-Akt signaling pathway reduces tumor necrosis factor-alpha production in response to titanium particles in vitro. *J Bone Joint Surg Am, 89*(5), 1019-1027. doi:10.2106/JBJS.F.00615

Socinski, M., & Kowanetz, M. (2018). *IMPower150: efficacy of atezolizumab plus bevacizumab and chemotherapy in 1L metastatic nonsquamous NSCLC across key subgroups*. Paper presented at the AACR 2018 Annual Meeting; April 14-18, 2018, Chicago, Illinois, USA.

Sonje, M. B., Abram, M., Stenzel, W., et al. (2010). Listeria monocytogenes (delta-actA mutant) infection in tumor necrosis factor receptor p55-deficient neonatal mice. *Microb Pathog, 49*(4), 186-195. doi:10.1016/j.micpath.2010.05.012

Soria, J. C. (2018). Osimertinib in Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer. *N Engl J Med, 378*(2), 113-125. doi:10.1056/NEJMoa1713137

Stein, M., Fong, L., Tutrone, R., et al. (2018). KEYNOTE-046: ADXS-PSA plus pembrolizumab (pembro) in metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol, 36*(15), 5019. doi:10.1200/JCO.2018.36.15_suppl.5019

Stinchcombe, T. E. (2007). Targeted therapy of advanced non-small cell lung cancer: the role of bevacizumab. *Biologics, 1*(3), 185-194.

The Cancer Genome Atlas [TCGA]. (2012). Comprehensive genomic characterization of squamous cell lung cancers. *Nature, 489*(7417), 519-525. doi:10.1038/nature11404

The Cancer Genome Atlas [TCGA]. (2014). Comprehensive molecular profiling of lung adenocarcinoma. *Nature, 511*(7511), 543-550. doi:10.1038/nature13385

Wallecha, A., Singh, R., & Malinina, I. (2013). Listeria monocytogenes (Lm)-LLO immunotherapies reduce the immunosuppressive activity of myeloid-derived suppressor cells and regulatory T cells in the tumor microenvironment. *J Immunother, 36*(9), 468-476. doi:10.1097/CJI.0000000000000000

Weber, R., Fleming, V., Hu, X., et al. (2018). Myeloid-Derived Suppressor Cells Hinder the Anti-Cancer Activity of Immune Checkpoint Inhibitors. *Front Immunol, 9*, 1-9. doi:10.3389/fimmu.2018.01310

Winkler, U., Jensen, M., Manzke, O., et al. (1999). Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). *Blood, 94*(7), 2217-2224.

Winslow, D. L., & Steele, M. L. (1984). Listeria bacteremia and peritonitis associated with a peritoneovenous shunt: successful treatment with sulfamethoxazole and trimethoprim. *J Infect Dis, 149*(5), 820.

Wood, L. M., & Paterson, Y. (2014). Attenuated Listeria monocytogenes: a powerful and versatile vector for the future of tumor immunotherapy. *Front Cell Infect Microbiol, 4*(51). doi:10.3389/fcimb.2014.00051

Zappa, C., & Mousa, S. A. (2016). Non-small cell lung cancer: current treatment and future advances. *Transl Lung Cancer Res, 5*(3), 288-300. doi:10.21037/tlcr.2016.06.07

Zitvogel, L., Tesniere, A., & Kroemer, G. (2006). Cancer despite immunosurveillance: immunoselection and immunosubversion. *Nat Rev Immunol, 6*(10), 715-727. doi:10.1038/nri1936

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13. Summary of Changes Within Protocol Amendment 4

#	Section	Revision	Rationale
1	Throughout	• Editorial changes and corrections • **Part B:** includes 2 parts: dose-escalation (part of Safety Phase) and dose-expansion of dose level 1 (part of Efficacy Phase). Part B-escalation to DL2 is contingent upon sponsor's decision to commence this segment of the study. • Revised text and Figure 1 to reflect updated expansion phase of Part B DL1 • Part B and Part C: Clarification of eligibility criteria and use of same timepoints for tumor scans and biomarkers in both parts, as priming with ADXS-503 before pembrolizumab is no longer needed in Part C. • Part B and Part C: Reduced biomarker plan with reduced collection of blood samples, mandatory tumor tissue at baseline (archival or fresh) and no on-therapy biopsies	• To provide additional clarity • To expand on prior plans of extending investigations of the efficacy signals seen in Part B safety phase in a dose-expansion efficacy phase, with further details added for clarity in this regard. Accrual in Part B DL2 may occur pending Sponsor decision, however, accrual is ongoing in the efficacy portions of the study. • Confirmatory scans of progression are mainly used in research studies to characterize primary and secondary resistance in pts failing checkpoint inhibitor (CPI) therapy. But, in the clinic, it is not always feasible or practical to wait for another scan to start rescue therapy just to try to document "pseudoprogression", which happens in 5% of pts.
2	Trial Summary/ 2.2/Figure 1/ 4/5.1/5.1.3/6.1/ 9.4.1 Appendix 2	**Part B :** Revised dose-expansion eligibility criteria: • Screening (baseline), which corresponds to the most recent tumor assessment that is consistent with PD (according to RECIST v1.1) while on treatment with pembrolizumab monotherapy as last treatment, **or** while receiving combination therapy with pembrolizumab + platinum-based chemotherapy as last treatment **or** pembrolizumab + pemetrexed as maintenance therapy, as last treatment in the metastatic setting. • Subjects receiving pembrolizumab + platinum-based chemotherapy or pembrolizumab + pemetrexed, will continue pembrolizumab monotherapy every 3 weeks; other drugs	• Clarification of patient population enrolled, especially given recent changes in treatment standard landscape and pembrolizumab's approvals/PI updates. Thus, allowing subjects undergoing or completed pembrolizumab

#	Section	Revision	Rationale
		washed-out for 3 weeks. • No evidence of rapid disease progression/clinical deterioration that would preclude continuation of pembrolizumab monotherapy for up to 12 weeks before ADXS-503 is added-on. Expansion of the eligibility window from 4 to 12 weeks for refractory patients that progress on pembrolizumab as last treatment **Part B** and **Part C**: • Added: Mandatory fresh or archival formalin-fixed paraffin embedded (FFPE) tumor tissue, either a block or unstained slides along with a matching blood at baseline, for performance of sequencing analysis. • Blood samples for exploratory immune correlative studies (eg, RNAseq, cfDNA, flow cytometry and ELISPOT analysis) may be collected in up to 25 total patients from Part B and Part C during Screening, at Week 1, 2, 5, and 8. To monitor the durability of T cell responses, subsequent blood samples for PBMCs may be taken at Week 25 (±1 week) and/or at end of treatment. • Language removed from inclusion criteria Table 3 for coagulation testing: "PT/INR and aPTT must be measured during Screening. Subsequent testing is to be performed only as if clinically indicated". **Part C**: PD-L1 expression in baseline tumor samples changed from ≥50% to Tumor Proportion Score (TPS) ≥1% as determined by an FDA-approved test	+ platinum-based chemotherapy or currently receiving pembrolizumab + pemetrexed as their last therapy • Coagulation times will not be part of eligibility criteria. There have been no reports of coagulation abnormalities associated with administration of *Lm* constructs in legacy studies nor in the safety phase of this study. However, the coagulation times can be evaluated at any timepoint by the Investigator, as clinically indicated. • PD-L1 TPS ≥1% is FDA approved for the use of pembrolizumab in first line therapy of NSCLC
3	Trial Summary/ 2.2/ 3.5/5.1/5.1.3/6.1/ 9.4.1	In Part B, administer ADXS-503 first dose within **12 weeks** of initial tumor assessment showing PD (on pembrolizumab monotherapy, pembrolizumab + platinum-based chemotherapy and/or pembrolizumab + pemetrexed).	Consistent with current clinical practice.
4	Trial Summary/ Figure 1/5.1.1	**Part B:** Accrual in DL1 dose-expansion and **Part C** will occur in parallel, and updating Figure with changes related to Part B dose-escalation and expansion	Clarification
5	Trial Summary/2.2/4	**Part C:** Included in Exploratory objectives of correlative studies.	Clarification

#	Section	Revision	Rationale
6	Trial Summary/ 2.1/2.2/ 5.1.2/7.1.1/ 7.1.2/7.1.3/9.2.1.3/ 9.2.1.3.1.2	Oral antibiotics will be administered starting approximately **48 hours** after each ADXS-503 infusion instead of 72 hours.	To further decrease the risk of formation of listeria biofilms on allowed medical devices and/or in the development of delayed listeremia. ADXS-503 is an *Lm*-based immunotherapy that is rapidly cleared from the blood and not detectable beyond 48 hours post dose, even without the use of antibiotics. There is evidence to suggest immunogenicity can be elicited within this period of time and it is not necessary to wait 72 hours to start antibiotics.
7	Trial Summary/ 5.1/5.1.3/6.1/9.4.1	**Part B:** (dose-escalation and dose-expansion) screening/ baseline tumor imaging is most recent tumor assessment consistent with progressive disease (PD) according to RECIST v1.1 while receiving pembrolizumab alone, pembrolizumab + platinum-based chemotherapy or pembrolizumab + pemetrexed as maintenance therapy, after platinum-based chemotherapy in the metastatic setting.	To confirm PD while on therapy with pembrolizumab monotherapy or in combination therapies. Definition of PD by RECIST v1.1 is standard clinical practice
8	Trial Summary/ 9.4.1	**Part B:** Screening (baseline), which corresponds to the most recent tumor assessment that is consistent with PD (according to RECIST v1.1) while on treatment with pembrolizumab monotherapy as last treatment, **or** while receiving combination therapy with pembrolizumab + platinum-based chemotherapy **or** pembrolizumab + pemetrexed as maintenance therapy, as last treatment in the metastatic setting. Subsequent scans will be performed in all subjects at Week 8 (±7 days), at Week 16 (± 7 days), followed by every 9 weeks (±7 days) after the start of ADXS-503 + pembrolizumab until confirmed PD or treatment discontinuation, whichever occurs later. **Part C:** After Screening, at Week 8 (±7 days), at Week 16 (± 7 days), followed by every 9 weeks (±7 days) after the start of ADXS-503 + pembrolizumab until confirmed PD or treatment discontinuation, whichever occurs later.	Standard of clinical practice Scans are now conducted at similar timepoints in Part B and Part C. Data from Part B suggests that there is no need to prime Part C patients with ADXS-503 one week in advance of the first dose of pembrolizumab. Hence, both drugs will start on Week 1 in patients from Part C as it has been done for Part B patients.

#	Section	Revision	Rationale
9	Trial Summary/2.2/ 5.1.3/6.1/8.1.1/9.4.1	• **Parts A**, **B**, and **C: Deleted** Tumor imaging must be repeated ≥4 weeks after initial PD while on therapy. • Removed: In Part A and Part C, tumor imaging must be repeated ≥4 weeks after initial Investigator-assessed, RECIST v1.1-defined disease progression, to confirm PD, when the subject's clinical condition warrants (see Section 8.1.1 and Section 9.4.1). In Part B, a confirmatory scan will be performed between 4-8 weeks after the initial assessment of PD on treatment with pembrolizumab monotherapy (to confirm PD or determine CR, PR or SD), as described above. **Part B: Deleted requirement for confirmatory scan 4-8 weeks after the initial assessment of PD on pembrolizumab monotherapy. Following language was removed**: • "Only subjects who have progressed within 6 months of starting pembrolizumab monotherapy may require a confirmatory scan within 4-8 weeks after the initial scan showing PD before starting ADXS-503, if the Investigator considers it necessary. …." • Subjects will receive at least four weeks of treatment with ADXS 503 plus pembrolizumab before the new confirmatory scan is done. Based on the computer scan the decision is made to continue study treatment" Under eligibility criteria, "Only subjects who have progressed within six months of starting pembrolizumab monotherapy may require a confirmatory scan within four - eight weeks after the initial scan showing PD and before starting advances 503, if the investigator considers it necessary ", has been removed	Confirmatory scans of PD are not mandatory in patients progressing while on checkpoint point inhibitor (CPI) as last therapy. Confirmatory scans are used in clinical research to characterize primary and secondary resistance to CPIs (Kluger H et.al.. Journal for ImmunoTherapy of Cancer 2020). The scans can define "pseudo progression" in the former category, which is an event that only happens in 5% of patients. And it is unlikely that pts with secondary resistance - who have had a response to CPIs for more than 6 months and which is the case for most of our patients in Part B- will now have
10	Trial Summary 2/2.2/5.1.3/6.1/9.5	**Parts A**, **B**, and **C:** Blood and biopsy samples **may** be collected for correlative studies. For all Part B and Part C patients: Mandatory fresh or archival formalin-fixed paraffin embedded (FFPE) tumor tissue, either a block or unstained slides along with a matching blood at baseline, for performance of sequencing analysis. Added, "During Screening for subjects in Part B and Part C tumor tissue collection with matched blood at screening is **mandatory** for all patients in the study. A fresh tumor biopsy must be obtained if clinically feasible, in the opinion of the Investigator for biomarker analysis. If a fresh biopsy cannot be obtained during Screening, the most recently acquired archived tumor biopsy sample may be used for analysis (date of biopsy within 3 years of Screening). The baseline biopsy must be from a location that has not been radiated. Sufficient tumor samples should be acquired to allow biomarker testing (eg, at least unstained 12-15 unstained slides). Tumor tissue and matching blood samples collected during Screening will be used for sequencing analysis". On-therapy tumor tissues biopsies will no longer be collected between weeks 5-9 in Part B or C.	Selection of most informative biomarker assessments/ correlative work for exploratory objectives, and clarifications of current text. It has been challenging to collect on-therapy biopsies due to the nature and localization of the tumors and the benefit/risk ratio is low. Age of archival biopsy accepted for eligibility has been extended from 2 to 3 years to provide flexibility.

#	Section	Revision	Rationale
		Blood samples for exploratory immune correlative studies (eg, RNAseq, cfDNA, flow cytometry and ELISPOT analysis) may be collected in up to 25 total patients from Part B and Part C during Screening, at Week 1, 2, 5, and 8. To monitor the durability of T cell responses, subsequent blood samples for PBMCs may be taken at Week 25 (±1 week) and/or at end of treatment.	Evaluation of cytokines, FluoroSpot, immunohistochemistry of PD-L1 at a central lab and multiplex immunofluorescence will no longer be performed.
11	Trial Summary 2.2/6.1	**Part B and Part C:** Clinical site must provide documentation of tumor PD-L1 expression and EGFR mutation and/or ALK translocation status as evaluated by FDA-approved tests in all patients. Baseline tumor samples must express PD-L1 [TPS (Tumor Proportion Score) ≥1%] as determined by an FDA-approved test at a local laboratory facility, with no EGFR or ALK genomic tumor aberrations for subjects to be eligible for Part C. If the site is unable to provide this source documentation, PD-L1 expression and/or *EGFR*/*ALK* testing should be performed per institutional standard of care (see Section 9.4.1 and Section 9.5).	Clarification that PD-L1 expression can be documented from the medical records and-if not available- to do so by running the test in baseline tumor samples at a local laboratory facility using FDA approved tests. No central laboratory is currently needed to test PD-L1, because it is standard of care.
12	2.2/9.5	**Part C**: Clinical site must provide documentation of tumor EGFR mutation and/or ALK translocation status for subjects with non-squamous NSCLC, AND if clinically indicated. If the site is unable to provide this source documentation, *EGFR*/*ALK* testing should be performed per institutional standard of care.	Clarification
13	2.2/9.5	**Part B:** dose-expansion: removed Blood samples for cytokine/chemokine and FluoroSpot analyses at Screening and on-therapy.	Cytokines were relevant to evaluate safety during dose escalation.FluoroSpot assays in dose escalation and -in some pts in Part B dose expansion- further documented MOA. Collection of blood for FluoroSpot and cytokines/ chemokines are therefore no longer needed, reducing blood collection by ~ 160 mL during the course of therapy. Exploratory objectives

#	Section	Revision	Rationale
14	2.2/ 9.5	**Part B** dose-expansion and **Part C:** Blood samples for exploratory immune correlative studies (eg, RNAseq, cfDNA, flow cytometry) may be collected in up to 25 total patients from Part B and Part C during Screening, at Week 1 (ie, right before the first infusion) and 7 days (±2 days) after the end of each of the **first 3** ADXS-503 infusions (Weeks 2, 5, and 8) and EOT. Samples for cfDNA are only collected at week 1 if samples are not collected during screening. To monitor the durability of T cell responses, subsequent blood samples for PBMCs may be taken at Week 25 (±1 week) and/or at end of treatment	Optimized exploratory objectives focusing in sequencing and flow cytometry analyses of peripheral blood at baseline and on-therapy. These will be correlated with sequencing analysis of the matching tumor tissue at baseline
15	2.3	Deleted as Combined SoA of Part B and Part C	Evaluation of Scans and Biomarkers is now conducted at the same timepoints as there is no longer priming with ADXS-503 one week in advance of dosing pembrolizumab in Part C patients.
16	3.4.4/3.5	Updated clinical experience and safety data from the ADXS-503-001 Trial	To ensure availability of up-to-date data
17	4	**Part B:** Added “dose escalation” to safety objectives	Clarification
18	4/5.1.1	**Part B:** Added “dose expansion” to efficacy objectives.	Clarification
19	4	**Part C:** Added to objective to characterize subject immunological activity and genomic profiles	Exploratory objectives
20	5.1.2/ 10.1	**Part B: Added Part B** dose-expansion to Efficacy Phase Part B expansion – Expanding the patient population and enrollment based on Simon’s Two-stage design, where at Stage I of Simon’s design, 18 subjects will be accrued in this study arm. Sponsor may decide to accrue additional 25 subjects for a total of 43 patients in Stage II. Part B study objectives - Include evaluation of preliminary antitumor activity of ADXS- 503 plus pembrolizumab as a primary objective In the efficacy phase (Part B-dose expansion and Part C combined), up to approximately 165 subjects may be enrolled. In Part B dose expansion, up to 43 subjects will be enrolled in the Simon’s Two-stage study cohort and up to a total of 140 thereafter. Approximately up to 25 subjects may be enrolled in Part C	Clarification To better characterize the safety, tolerability and early clinical activity of the combination therapy in patients failing pembrolizumab as last therapy at Stage 1. Then, depending on the results, the combination could be further evaluated in Stage 2 and beyond, if pre-established GO criteria is met

#	Section	Revision	Rationale
21	5.1.3	Added: In "**Part B** dose-expansion and" **Part C**, ... "Clinical site must provide documentation of tumor PD-L1 expression and EGFR mutation and/or ALK translocation status as evaluated by FDA-approved tests in Part B and Part C patients. Participation in both parts will be dependent upon supplying tumor tissue (from fresh biopsy or archival) from a location that has not been radiated. Formalin-fixed specimens obtained either at the time of or after the diagnosis of metastatic disease will be required for performance of sequencing analysis. In Part C, biopsies obtained PRIOR to receipt of neoadjuvant/adjuvant chemotherapy are NOT permitted. Only subjects whose tumors express PD-L1 (TPS ≥1%) as determined by as determined by an FDA-approved test, will be eligible for enrollment in Part C. Furthermore, documentation of EGFR mutation and/or ALK translocation status will be required for subjects with non-squamous NSCLC. If the clinical site is unable to provide this source documentation, PD-L1 expression and *EGFR*/*ALK* testing should be performed in all Part C patients per institutional standard of care using FDA-approved tests before enrollment. See Section 9.5.	Clarification and addition of correlative work PD-L1 expression with FDA-approved tests can now be conducted at local laboratory facilities as it is standard of care. No need for central lab testing PD-L1 expression in baseline tumor samples changed from ≥50% to Tumor Proportion Score (TPS) ≥1% as determined by an FDA-approved test
22	5.2.2	**Part B** dose-expansion: Added rationale for design	Clarification
23	5.2.3	Deleted rationale for priming in Part C	No need for priming with ADXS-503 1st before addition of pembro based on results from Part B
24	5.3	Increased number of subjects enrolled	Part B expansion following a Simon's Two-stage design
25	7.1.2/ 7.1.3	**Part C**: Starting at Week 1 (±2 days), ADXS-503 and pembrolizumab will be administered on the same day	Not necessary to prime with ADXS-503 (see 18 above)

#	Section	Revision	Rationale
26	7.1.2/ 7.1.3	**Part B and Part C** Infusion of ADXS-503 can be through the infusion line used for pembrolizumab. A single infusion line can be used for pembrolizumab and ADXS-503. Language added in Section 7.1.2. "For enrolled patients with difficulty to access veins, one infusion line for pembrolizumab may be used provided it is flushed after the pembrolizumab infusion, at pre-infusion and post-infusion of ADXS-503 regimen. If the infusion line is the same, the in-line filter used for the infusion of pembrolizumab must be removed before infusing ADXS-503". The central port or central venous catheter can be used to withdraw blood for correlative analysis.	There is no reason to have 2 independent IV lines for drug infusion every 3 weeks. The risks of an intravenous catheter include pain, bruising, clotting, bleeding, leakage of drug solution, and possibly infection at the catheter site can be prevented for patients with vein access difficulty. And patients in Part B can be with disease control on therapy for over a year, which prompts the clinicians to preserve IV access as much as possible.
27	Trial Summary/2.2/ 5.1/5.1.3/7.1.2	Dosing scheme for Part B and Part C: Upon Investigator assessment and discretion, the schedule of therapy with $1x10^8$ CFU of ADXS-503 + 200 mg of pembrolizumab, IV, could shift from every 3 weeks to every 6 weeks after the first year of study treatment.	The use of pembrolizumab Q6W has been approved by FDA in the US. Current data in this study has shown that memory T cells are activated around week 8 of combination therapy with ADXS-503 and pembrolizumab and that they persist at week 25 on therapy. Hence, we assume that T cell activation with the combo in the first year of therapy Q3W will be enough to keep immunogenicity if we reduce the frequency of administration of the two drugs during the second year.
28	7.7.1/6.2 9.2.1.3/9.2.1.3.1.1 9.2.1.3.1.2	Added erythromycin and fluoroquinolones as an alternative antibiotic treatments in subjects with known intolerance and/or allergy to Bactrim and ampicillin. The exclusion criteria has been modified accordingly.	Refer to IB Section 4.2.1; based on documenting dual hypersensitivity to ampicilin and TMP/SMZ and the activity of other antibiotics with anti-*Listeria* effect.

#	Section	Revision	Rationale
29	6.2 Exclusion Criteria #13	Hernia mesh, and some metal plates are now listed under more common devices permitted.	To provide flexibility at enrollment without compromising safety
30	2.1, 9.4.2	Added: "•During the *Lm* surveillance Follow-up Period, subjects will be contacted remotely every 3 months (±2 week) for 1 year to determine whether they have experienced for several days, the following symptoms that could potentially be associated with delayed listeremia and require prompt attention at the research site: fever or chills, headache, nausea, confusion or changes in alertness (for over 72 hours). As part of EOT procedures, upon completing the *Lm* Surveillance period, site staff should instruct subjects to contact the site if they experience any of these symptoms, as applicable.	Clarification that the follow-up period will also include *Lm* monitoring to continue assessments for potential listeremia during the telephone calls or text messages or an app inquiring survival status, in addition to instructions provided to patients following the 1-year follow-up period. To provide instructions for Lm surveillance (*Lm*S) monitoring addressing FDA request (emailed August 10, 2018). This for *Lm* surveillance strategy is consistent with the agreement between FDA and Advaxis of a 1-year *Lm*S being sufficient, per the FDA written responses (dated 10 November 2020) to the questions in a Type C Meeting (meeting information package submitted in SN0177 to IND 13,712).
31	10.1	Added sample size calculation for **Part B** dose-expansion: The sample size in Part B dose-expansion at dose level 1 (DL-1) will use Simon's optimal Two-stage design (Simon, 1989). The Part B dose-expansion will be carried out in 2 stages. In stage I, a total number of 18 subjects is accrued. If there are 2 or fewer responses among these 18 patients, the study will be stopped early. Otherwise, an additional 25 patients will be accrued in stage II, resulting in a total sample size of 43 subjects. If there are 8 or more responses among these 43 subjects, we reject the null hypothesis and claim that the treatment is promising. The design controls the type I error rate at 0.05 and yields a power of 0.8.	Part B expansion following a Simon's Two-stage design based on a target response rate of 25%

#	Section	Revision	Rationale
		r1 n1 r n Type I error Power PET(p0) EN(p0) Optimal 2 18 7 43 0.48 0.8003 0.7338 24.7 Note: r1 = the first stage threshold to stop the trial for futility; n1 = number of accrual subjects for stage I; n = total number of subjects; r = overall threshold to stop the trial for futility; EN(p0) = expected sample size for the cohort when the true response rate is p0; PET(p0) = probability of early termination when the true response rate is p0.	
32	Appendix 4	Added: "Any SAE that occurs within the follow-up period, that is associated with a case of confirmed delayed listeremia during this *Lm* surveillance study, once becoming aware of any blood culture that is positive for *Lm* during the *Lm* surveillance monitoring period, must be reported within 24 hours to the Sponsor, so that the Sponsor can promptly send a notification via email and/or voicemail to both FDA and Centers for Disease Control and Prevention (CDC) concurrently, whether or not it fulfills expedited reporting requirements."	Increased SAE monitoring during *Lm* Surveillance

14. Appendices

Appendix 1 Abbreviations and Terms

AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT/SGPT	Alanine aminotransferase
ANC	Absolute neutrophil count
APC	Antigen presenting cell
aPTT	Activated partial thromboplastin time
AST/SGOT	Aspartate transaminase
β-HCG	Beta human chorionic gonadotropin
BRAF	B-Raf proto-oncogene
BCG	Bacillus Calmette–Guérin vaccine
BSL-2	Biosafety level 2
BOR	Best overall response
°C	Degrees Celsius
CBC	Complete blood count
cfDNA	Cell free DNA
CFU	Colony forming units
cHL	chronic Hodgkin lymphoma
CMP	Complete Metabolic Panel
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CR	Complete response
eCRF	Electronic case report form
CrCl	Creatinine clearance
CRP	C-Reactive Protein
CRS	Cytokine release syndrome
CSR	Clinical study report
CT	Computed tomography

CTA	Cancer testis antigen
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DAMP	Damage-associated molecular pattern
DCR	Disease control rate
DL	Dose level
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of objective tumor response
DS	Double strength
EBUS	Endobronchial ultrasound
ECOG	Eastern Cooperative Oncology Group
ESI	Events of special interest
EGFR	Epidermal growth factor receptor
ESR	Erythrocyte Sedimentation Rate
FDA	US Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl-transferase
HBsAg	Hepatitis B virus surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPV	Human papillomavirus
HR	Hazard ratio
HRT	Hormone replacement therapy
HSCT	Hematopoietic stem cell transplant
IB	Investigator’s Brochure
ICF	Informed consent form

ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFNγ	Interferon gamma
IHC	Immunohistochemistry
IL	Interleukin
ILD	Interstitial lung disease
INR	International normalized ratio
ir	Immune-related
IRB	Institutional Review Board
iBOR	Immune best overall response
iCR	Immune complete response
iUPD	Immune unconfirmed progressive disease
iCPD	Immune confirmed progressive disease
iPR	Immune partial response
iRC	Immune response criteria
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
iSD	Immune stable disease
IV	Intravenous
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma viral oncogene homolog
LDH	Lactate dehydrogenase
LLO	Listeriolysin O
Lm	*Listeria monocytogenes*
*Lm*S	*Lm* surveillance
MAb	Monoclonal antibody
MAD	Maximum administered dose
mCRPC	Metastatic castrate-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MDSC	Myeloid-derived suppressor cells
MHC	Major histocompatibility complex

MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No-observed-adverse-effect-level
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
OFA	Oncofetal antigen
ORR	Objective response rate
OS	Overall survival
PAMP	Pathogen-associated molecular pattern
PBMC	Peripheral blood mononuclear cell
PBS	Phosphate buffered saline
PD	Progressive disease
PD-1	Programmed death receptor-1
PD-L1/ PD-L2	Programmed death-ligand 1 / Programmed death-ligand 2
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetic
PR	Partial response
prn	pro re nata; when necessary
PT	Prothrombin time
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	ROS proto-oncogene-1
RNA	Ribonucleic acid
SAE	Serious adverse event
SAER	Serious adverse event report
SAP	Statistical Analysis Plan
SCID	Severe combined immune deficiency
SCLC	Small cell lung cancer
SD	Stable disease

SoA	Schedule of Activities
SOC	System Organ Class
SOP	Standard operating procedure
SumD	Sum of longest diameters
T1DM	Type 1 diabetes mellitus
t1/2	Elimination half-life
TA	Tumor assessment
TAA	Tumor associated antigen
TCR	T cell receptor
TSH	Thyroid stimulating hormone
TKI	Tyrosine kinase inhibitor
TME	Tumor microenvironment
TRAE	Treatment-related adverse event
tLLO	Truncated Listeriolysin O
TMTB	Total measurable tumor burden
TNF	Tumor necrosis factor
TPS	Tumor Proportion Score
Tregs	Regulatory T cells
ULN	Upper limit of normal
US, USA	United States of America
USP	United State Pharmacopeia
VEGF	Vascular endothelial growth factor
WBC	White blood cell count
WHO	World Health Organization
WOCBP	Women of Child-Bearing Potential

Appendix 2 Clinical Laboratory Tests

- The tests detailed in Table 2.1 and Table 2.2 will be performed by the local laboratory
- Laboratory values for subject inclusion in the study are detailed in Table 2.1
- Safety laboratory assessments to be performed during the study are detailed in Table 2.2
- Additional tests may be performed at any time during the study as deemed necessary by the Investigator or Sponsor or required by local regulations
- Investigators must document their review of each laboratory report.

Table 2.1: Organ Function Requirements for Study Inclusion

System	Laboratory Value
Hematologic	
Absolute neutrophil count (ANC) [a]	≥1 x 10^9/L (Parts A and B); ≥1.5 x 10^9/L (Part C)
Platelets [a]	≥75 x 10^9/L (Parts A and B); ≥100 x 10^9/L (Part C)
Hemoglobin [a]	≥9 g/dL or ≥ 5.6 mmol/L
WBC [a]	≥2000/ µL
Renal	
Serum creatinine **OR** Measured or calculated creatinine clearance (CrCl). Note: GFR can also be used in place of serum creatinine or CrCl	≤1.5 x upper limit of normal (ULN) **OR** ≥50 mL/min for subjects with serum creatinine levels >1.5 x institutional ULN [b]
Hepatic	
Serum total bilirubin	≤1.5 x ULN (except subjects with Gilbert Syndrome, who must have total bilirubin <3 x ULN)
AST (SGOT) and ALT (SGPT)	<3 x ULN (Parts A and B); <1.5 x ULN (Part C)
Endocrine	
Thyroid stimulating hormone (TSH)	Within normal limits (Parts B and C only). [c]
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

[a]ANC, platelets, hemoglobin, or WBC requirement cannot be met by the use of recent transfusions, or growth factor support (G-CSF, erythropoietin, etc.) within 2 weeks prior to treatment initiation.
[b]Creatinine clearance should be calculated per institutional standard.
[c]If TSH is not within normal limits, subject may still be eligible if T3 and free T4 are within normal limits.

Table 2.2: Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red Blood Count (RBC) Hemoglobin Hematocrit	RBC Indices: Mean Corpuscular Volume (MCV) Mean Corpuscular Hemoglobin (MCH) % Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils Absolute Neutrophil Count (ANC)	
Clinical Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin and direct bilirubin *(if total bilirubin is elevated above the upper limit of normal)*
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Lactate dehydrogenase (LDH)
	Carbon dioxide (*CO_2 or bicarbonate)*	Chloride		
Routine Urinalysis	• Specific gravity • Glucose, protein, blood • Microscopic examination (if blood or protein is abnormal)			
Other Tests	• Follicle-stimulating hormone and estradiol (as needed for WOCBP only) • Urine (confirmed by serum if urine is positive) human chorionic gonadotropin (βHCG) pregnancy test (as needed for WOCBP only) • Coagulation profile (PT/INR and aPTT) is required only at Screening and subsequently as clinically indicated • Part B and Part C: Total Triiodothyronine (T3) or Free T3 (FT3); Free T4, Thyroid stimulating hormone (TSH)			
Lm blood culture:	• A blood sample will be collected at 7 days (±3 days) after completion of the 3-week course of oral antibiotics to culture for *Lm*.			
The results of each test must be entered into the eCRF.				

Appendix 3 Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Overall conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

If participants will be asked to consent to optional exploratory research using the remainder of mandatory samples, include text that addresses the use of remaining mandatory samples for optional exploratory research.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in optional exploratory research will not provide this separate signature.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

This study will be registered and results posted on **www.clinicaltrials.gov**. The sponsor has proprietary interest in the study. Authorship and manuscript composition will reflect joint

cooperation between study investigator(s) and sponsor personnel. Authorship will be established prior to the writing of the manuscript. As this study may be multicenter, no individual publication will be allowed prior to completion of the final report of the multicenter study, except as agreed with the sponsor.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator after study completion for the maximum period required by applicable regulations and guidelines, institution procedures, or the period specified by the sponsor, whichever is longer. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

The sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Events Meeting the ESI Definition for this Trial
• Signs and symptoms during or after treatment infusion: Any of the following events, if they were considered to be treatment-related and began within 24 hours after study treatment, and were ≥Grade 3: hypotension, hypoxia, encephalopathy or organ toxicity. • Immune-related adverse events (irAE): ≥Grade 3 treatment-induced events (acute, sub-acute or late occurring) that involve inflammatory reactions that were mediated through the action of T cells on the subject's tissues or organs. • Delayed listeremia: The presence of *Lm* in a blood culture after treatment with ADXS-503. Once becoming aware of any blood culture that is positive for *Lm* **during the *Lm* surveillance monitoring period**, the Sponsor must be notified within 24 hours so that the Sponsor can promptly send a notification via email and/or voicemail to both FDA and Centers for Disease Control and Prevention (CDC) concurrently, whether or not it fulfills expedited reporting requirements. Additional testing may be performed by CDC to evaluate the bacteria for the presence of genetic elements that are consistent with an *Lm*-based immunotherapy drug. **NOTE: this does not include the presence of *Lm* in a blood culture within the first 48 hours after treatment with ADXS-503.**

Reporting of ESI will begin from the date of first dose of study treatment must be reported within 24 hours of awareness to the sponsor appointed Pharmacovigilance service provider. ESIs will be reviewed in order to identify notable safety trends. In Part A and Part B, ESI will be reviewed as they are reported and will be discussed at the time of the dose escalation meetings, and periodically afterwards. In Part C, ESI will be reviewed and discussed on an ongoing basis.

Definition of SAE

Any SAE, or follow-up to an SAE, including death due to any cause, that occurs to any participant within 24 hours of receipt of the information from the time the Informed Consent Form is signed through 30 days following cessation of treatment, or the initiation of a new anti-cancer therapy, whichever is earlier, whether or not related to study product, must be reported within 24 hours to the EDC tool.

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that

would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial and persistent disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Considerations for reporting treatment-related toxicity

- Investigators must use their best judgement to appropriately code and treat individual AEs that occur during or after treatment infusion. In particular, it's important to record individual components of AEs that occur on the day of dosing. Instead of grouping signs and symptoms into broad categories, such as "infusion reaction" or "cytokine release syndrome", each term must be reported as a verbatim AE term with an assessment of severity, seriousness, and relationship to study treatment. This reporting is important, because it provides essential information regarding the nature of observed toxicity, and facilitates the application of appropriate and specific management strategies.

Assessment of Intensity

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.03) will be used to evaluate AEs and SAEs.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1: Mild; asymptomatic or mild 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 of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4: Life-threatening consequences; urgent intervention indicated.
Grade 5: Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the IB/ Product Label (if applicable) in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the EDC tool. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the EDC tool.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor appointed Pharmacovigilance provider to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide a certificate of death, if available.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the EDC tool within 24 hours of receipt of the information from the time the consent/assent is signed through 30 days after the last dose of study treatment, regardless of relatedness.

Reporting of SAE to the Sponsor or Designee

SAE Reporting to Sponsor

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE, the site can report this information to the sponsor appointed Pharmacovigilance service provider. Detailed instructions for such reporting will be provided separately to sites.
- Adverse reactions will be reported to FDA according to 21 CFR 312.32.

Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

1. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: (1) review of participant's medical records; (2) medical examination; or (3) medical history interview.
2. Premenarchal
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

- Male participants with female partners of child-bearing potential are eligible to participate in this study if they agree to use a highly effective method of contraception during the treatment period and for at least 120 days after the last dose of study treatment.

- Women of childbearing potential are eligible to participate in this study if they agree to use 2 highly effective methods of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods That Are User Dependent [b] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • oral • injectable
Highly Effective Methods That Are User Independent [b]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for clinical study participants. b) Two highly effective methods of contraception should be utilized during the treatment period and for at least 120 days after the last dose of study treatment.

Pregnancy Testing

- WOCBP will only be included in the study after a negative highly sensitive pregnancy test.
- Additional pregnancy testing should be performed as described in the **SoA** and as required locally. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
- Pregnancy testing, with a minimum sensitivity of 25 IU/L or equivalent units of βHCG will be performed locally.

Collection of Pregnancy and Lactation Information

- The Investigator will collect pregnancy/lactation information on any female participant or female partner of a male participant who becomes pregnant or breastfeeds while participating in this study and for at least 120 days after the last dose of study treatment.

- Information will be recorded on the appropriate form and submitted to the Sponsor appointed Pharmacovigilance provider within 24 hours of learning of a participant's pregnancy or lactation case.
- The pregnancy will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and neonate, which will be forwarded to the Sponsor appointed Pharmacovigilance provider. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy and lactation itself are not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to the EDC tool as described in Appendix 4. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant or breastfeeds while participating in this study will discontinue study treatment.

Appendix 6 Recommended Management Guidelines for Infusion Reactions

NCI CTCAE v4.03 Grade	Management
Grade 1 Mild transient 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 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	1. Stop Infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics 2. 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 pre-medicated for the next scheduled dose. **ADXS-503-Related**: continue with protocol-described pre-medication for next infusion**.** **Pembrolizumab-Related:** Subject may be pre-medicated 1.5 h (+/- 30 mins) prior to the next infusion with: • Diphenhydramine 50 mg orally (or equivalent dose of antihistamine) • Acetaminophen 500-1000 mg orally (or equivalent dose of antipyretic) If despite adequate pre-medication the subject developments recurrent Grade 2 infusion-related toxicity that is considered by the Investigator to be related to pembrolizumab, the subject should be permanently discontinued from pembrolizumab treatment.
Grade 3 Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	1. Stop Infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine 2. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. 3. Hospitalization may be indicated. **ADXS-503-Related**: Subjects who experience a Grade 3 infusion-related toxicity that is considered by the Investigator to be related to ADXS-503, may be discontinued from study treatment. Discussion with the Sponsor is recommended. **Pembrolizumab-Related:** Subjects who experience a Grade 3 infusion-related toxicity that is considered by the Investigator to be related to pembrolizumab, should be permanently discontinued from pembrolizumab treatment.
Grade 4 Life-threatening consequences; urgent intervention indicated.	Subjects who experience a Grade 4 infusion reaction should be permanently discontinued from study treatment. Follow institutional standard of care. Sponsor should be contacted.
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.	

Appendix 7 Grading and Management Guidelines for Acute Hypotension, Hypoxia, Encephalopathy, Organ Toxicity, Fever and Constitutional Symptoms

The grading scale and toxicity management criteria below are adapted from criteria proposed by *MD Anderson Cancer Center: Chimeric Antigen Receptor (CAR) Cell Therapy Toxicity Assessment and Management - Adult* (10/31/2017)

Table 7.1. Grading Scale for Hypoxia, Hypotension, and Organ Toxicity

Grade	Description of Severity
1	Fever (temperature $\geq$ 38°C) or Grade 1 organ toxicity
2	Symptoms require and respond to moderate intervention Oxygen requirement FiO_2 < 40%, and/or subject requires intermittent supplemental oxygen, OR Hypotension responsive to IV fluids or low-dose of one vasopressor to maintain systolic blood pressure > 90 mmHg, OR Grade 2 organ toxicity
3	Needs oxygen to maintain O_2 saturation > 90% Oxygen requirement $FiO_2 \geq$ 40% and/or requiring BiPAP, OR Hypotension refractory to management for Grade 2 or where hospitalization is required, OR Grade 3 organ toxicity or Grade 4 transaminitis per CTCAE v4.03 criteria
4	Life-threatening signs and symptoms OR Requirement for ventilator support to maintain O_2 saturation > 90% OR Grade 4 organ toxicity (excluding Grade 4 transaminitis) per CTCAE v4.03 criteria

Table 7.2. Management Guidelines for Acute Hypotension, Hypoxia, Organ Toxicity, Fever and Constitutional Symptoms

Toxicity Grade	Sign/Symptom	Treatment	Instructions for Interruption of ADXS-503	Modification for Subsequent infusions
1	Hypotension	• Supportive care	Not applicable	• Increase pretreatment IV fluids (eg, 500 ml -1L normal saline)
1	Fever; Constitutional symptoms; Grade 1 organ toxicity	• Symptomatic management of constitutional symptoms and organ toxicity • Acetaminophen and hypothermia blanket as needed for fever • Ibuprofen if fever is not controlled with above, use with caution or avoid if thrombocytopenic • IV fluids as needed • Consider the IL-6 antagonist tocilizumab for persistent (>3 days) or refractory fever	Not applicable	• No modification

Toxicity Grade	Sign/Symptom	Treatment	Instructions for Interruption of ADXS-503	Modification for Subsequent infusions
2	Hypotension	• Fluids (500 – 1000 mL normal saline to keep systolic blood pressure > 90 mmHg) • If hypotension persists despite IV fluid bolus and a low dose pressor, administer the IL-6 antagonist tocilizumab (8 mg/kg IV over 1 hour) • If hypotension persists after IV fluid bolus, administer a vasopressor (eg, epinephrine 0.5 mg IM), and consider transfer to ICU • If hypotension persists despite these measures, treat with a high-dose corticosteroid. • If there are signs of hypo-perfusion or if there is rapid deterioration in the opinion of the clinician, may use dexamethasone 10 mg IV every 6 hours • Increase frequency of monitoring vital signs	• Immediately interrupt ADXS-503 until AE(s) resolve to Grade ≤ 1 but for no less than 72 hours • Permanently discontinue ADXS-503 if there is no improvement of AE(s) to ≤ Grade 1 within 7 days.	• Extend infusion time to 2 hours • Increase pretreatment IV fluids (eg, 500 mL – 1L normal saline) • Incorporate Glucocorticoid-Hydrocortisone or equivalent- 50 mg, IV, as premedication
2	Hypoxia	• Use supplemental oxygen as needed		• No modifications

Toxicity Grade	Sign/Symptom	Treatment	Instructions for Interruption of ADXS-503	Modification for Subsequent infusions
		• Use tocilizumab 8 mg/kg IV with or without corticosteroids as with Grade 2 hypotension (described above) • Increase frequency of monitoring vital signs • Restrict the administration of IV fluid if possible	See above	• Discussion with Sponsor recommended
2	Fever, Constitutional symptoms; Grade 2 organ toxicity	• Appropriate supportive care • Manage organ toxicity as per standard guidelines • Use tocilizumab 8 mg/kg IV with or without corticosteroids as described above for Grade 2 hypotension • Manage fever and constitutional symptoms as noted above for Grade 1 toxicity		• Extend infusion time to 2 hours • Consider increasing doses of prophylactic medications • Discussion with Sponsor recommended, but not required
3	Hypotension	• IV fluid bolus (as for Grade 2 hypotension) and tocilizumab (8mg/kg IV over 1 hour)	• Immediately interrupt ADXS-503	• Discuss with Sponsor

Toxicity Grade	Sign/Symptom	Treatment	Instructions for Interruption of ADXS-503	Modification for Subsequent infusions
		○ If an IV fluid bolus was previously administered it may be repeated, depending on the subject's hemodynamic status. However, IV fluid administration in the presence of hypoxia may lead to increased pulmonary edema (see guidance for hypoxia above) ○ Tocilizumab IV may not be administered if it was used within the previous 8 hours • Transfer subject for inpatient management • High dose vasopressors (eg, Dopamine 10 µg/kg/min) • If hypotension worsens or is unresponsive to above measures, administer high dose corticosteroids (methylprednisolone or dexamethasone) • Monitor for neurologic signs and symptoms. **Consult neurology to assess for signs of elevated intracranial pressure** (eg, papilledema) /cerebral involvement. See **Tables 7.3** and **7.4** below for grading and management of encephalopathy • Increase frequency of monitoring vital signs	• Permanently discontinue ADXS-503 if there is no improvement in AE(s) to ≤ Grade 2 within 5 days or AE ≤ Grade 1 within 7 days	

Toxicity Grade	Sign/Symptom	Treatment	Instructions for Interruption of ADXS-503	Modification for Subsequent infusions
3	Hypoxia	• Use supplemental oxygen • Use tocilizumab 8 mg/kg IV with or without corticosteroids as in hypotension • Increase frequency of monitoring vital signs • Restrict the administration of IV fluid if possible	• Immediately interrupt ADXS-503	• Discuss with Sponsor
3	Fever, Constitutional symptoms; Grade 3 organ toxicity	• Appropriate supportive care • Manage organ toxicity as per standard guidelines • Use tocilizumab 8 mg/kg IV, corticosteroids • Manage fever and constitutional symptoms above for Grade 1 toxicity	• Immediately interrupt ADXS-503	• Discuss with Sponsor
4	Hypotension	• IV fluid bolus (as for Grade 2 hypotension) and tocilizumab • High-dose methylprednisolone	• Immediately interrupt ADXS-503	• Permanently discontinue ADXS-503
4	Hypoxia	• Mechanical ventilation • Tocilizumab, high-dose methylprednisolone, and supportive care	• Immediately interrupt ADXS-503	• Permanently discontinue ADXS-503
4	Fever, Constitutional symptoms; Grade 4 organ toxicity	• Appropriate supportive care • Manage organ toxicity as per standard guidelines	• Immediately interrupt ADXS-503	• Permanently discontinue ADXS-503

Toxicity Grade	Sign/Symptom	Treatment	Instructions for Interruption of ADXS-503	Modification for Subsequent infusions
		• Tocilizumab, high-dose methylprednisolone, and supportive care • Manage fever and constitutional symptoms as noted for Grade 1 above • Increase frequency of monitoring vital signs		

* 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, and for the treatment of adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome.

Tocilizumab works by preventing IL-6 binding to both cell-associated and soluble IL-6 receptors (Actemra®, 2020; Grupp 2013; Lee 2014; Winkler 1999).

Dosing guidelines for tocilizumab are provided below.

Tocilizumab Dosing Guidelines (Actemra®, 2020)

- 8 mg/kg IV; maximum dose/infusion = 800 mg.
- If the subject's condition does not improve or stabilize within 8 hours of the tocilizumab dose, administration of a second dose of tocilizumab should be considered. A total of three doses can be administered in a 24-hour period (maximum 800 mg/dose), and a maximum of 4 doses total can be administered.
- Tocilizumab may be administered with corticosteroids.

Table 7.3. Grading Scale for Encephalopathy

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

CARTOX 10-point neurological assessment (Assign one point for each task performed correctly; score of 10 = normal)
- Orientation to year, month, city, hospital, President: 5 points
- Name 3 objects (point to clock, pen, button): 3 points
- Ability to write a standard sentence (eg, Our national bird is the bald eagle): 1 point
- Count backwards from 100 by ten: 1 point

[1] Papilledema grading is performed according to Modified Frisén scale
CSF = cerebrospinal fluid

Table 7.4. Management Guidelines for Encephalopathy

Toxicity Grade	Treatment	Instructions for Interruption of ADXS-503	Modification for Subsequent Infusions
1	● Vigilant supportive care; aspiration precautions; IV hydration ● Withhold oral intake of food/medicines/fluids and assess swallowing ● Convert all oral medications and/or nutrition to IV if swallowing is impaired ● Avoid medications that cause CNS depression ● Low doses of lorazepam (0.25-0.5 mg IV every 8 hours) or haloperidol (0.5 mg IV every 6 hours) may be used for agitated patients with careful monitoring ● Neurology consultation ● Daily CARTOX 10-point neurological assessment as in **Table 7.3** ● Fundoscopic exam to assess for papilledema ● MRI brain with and without contrast; diagnostic lumbar puncture with OP; MRI spine if focal signs exist; CT of brain may be performed if MRI brain is not feasible	Not applicable	Discuss with Sponsor

Toxicity Grade	Treatment	Instructions for Interruption of ADXS-503	Modification for Subsequent Infusions
2	● Supportive care and neurological workup as per Grade 1 ● IL-6 antagonist (tocilizumab[1]), if associated with other events such as refractory hypotension and/or hypoxia ● Dexamethasone or methylprednisolone if refractory to tocilizumab[1] therapy, when it is administered ● Consider ICU transfer if associated with other events such as hypotension or hypoxia	• Immediately interrupt ADXS-503	Discuss with Sponsor
3	● Supportive care and neurological workup as per Grade 1 ● ICU transfer is recommended ● Tocilizumab[1], if associated with concurrent refractory hypotension and/or hypoxia and if not administered previously ● Dexamethasone or methylprednisolone around the clock, if symptoms worsen despite tocilizumab therapy. Continue corticosteroids until improvement to Grade 1 and then taper or stop. ● Low grade (Stage 1 or 2) papilledema with CSF OP less than 20 mmHg, acetazolamide as per Institutional guidelines ● Consider repeat neuro-imaging (CT or MRI) every 2-3 days if persistent event greater than or equal to Grade 3	• Immediately interrupt ADXS-503 • Permanently discontinue ADXS-503	Not applicable
4	● Supportive care and neurological workup as per Grade 1	• Immediately interrupt	Not applicable

Toxicity Grade	Treatment	Instructions for Interruption of ADXS-503	Modification for Subsequent Infusions
	● ICU monitoring; consider mechanical ventilation for airway protection ● Tocilizumab[1] and repeat neuro-imaging as per Grade 3 ● High dose methylprednisolone ● For high-grade (Stage 3, 4, or 5) papilledema, CSF OP greater than or equal to 20 mmHg, or cerebral edema, follow Institutional guidelines for high dose steroids, hyperventilation, hyperosmolar therapy, metabolic profile; CT scan daily.	ADXS-503 • Permanently discontinue ADXS-503	
[1] IL-6 antagonist (tocilizumab) administration- See Table 7.2			

Appendix 8 General Approach for Managing Immune-Related Adverse Events Associated with ADXS-503

Immune-Related AE	Withhold/Discontinue ADXS-503?	Supportive Care
Grade 1	• No action.	• Provide symptomatic treatment.
Grade 2	• May withhold ADXS-503.	• Consider topical or systemic corticosteroid in addition to appropriate symptomatic treatment.
Grade 3 and Grade 4	• Withhold ADXS-503. • Discontinue if unable to reduce corticosteroid dose to <10 mg per day prednisone equivalent within 12 weeks of toxicity.	• Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. • Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

Appendix 9 Guidelines to Manage Immune-Related Adverse Events Associated with Pembrolizumab

The following guidance is according to the Product Label (Keytruda®) for pembrolizumab and can be found on the Keytruda® website at **https://www.keytruda.com/**

Table 2: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold†
	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold†
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver For liver enzyme elevations in patients treated with combination therapy with axitinib, see Table 3.	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold†
	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver‡	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold†
	ALT or AST increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold†
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold†
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold†

Adverse Reaction	Severity*	Dosage Modification
	Grade 3 or 4	Permanently discontinue
Hematologic toxicity in patients with cHL or PMBCL	Grade 4	Withhold until resolution to Grades 0 or 1
Other Adverse Reactions		
Infusion-related reactions *[see Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

* Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0
† Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.
‡ If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue KEYTRUDA based on recommendations for hepatitis with no liver involvement.
ALT = alanine aminotransferase, AST = aspartate aminotransferase, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson Syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit normal

No dose reduction for KEYTRUDA is recommended. In general, withhold KEYTRUDA for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue KEYTRUDA for Life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

Dosage modifications for KEYTRUDA for adverse reactions that require management different from these general guidelines are summarized in Table 2.

Appendix 10 Assessment of Disease

Tumor response will be evaluated at the tumor imaging timepoints specified in the **SoA**. Tumor response will be evaluated by the Investigator (or designee) according to RECIST v1.1 as the basis for the primary analysis of tumor response-based endpoints (Eisenhauer, 2009). Exploratory analysis of tumor-response will be performed by the Sponsor (or designee) according to iRECIST (Seymour, 2017). See **Section** 9.4.1.

Baseline Tumor Assessment

The baseline tumor burden (unidimensionally measured or evaluable disease) will be assessed during the pre-treatment Screening evaluations. The Investigator will identify prospectively, the lesions to be followed in order to evaluate the subject's response to therapy (see **Target/Non-target Lesions**). Baseline imaging areas will include the chest, abdomen, pelvis and any additional known sites of disease. Subjects with known CNS metastases and subjects with signs or symptoms suggestive of brain metastasis should be evaluated with imaging of the brain at baseline.

Tumor Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) will be considered the best currently available and reproducible methods to measure target lesions selected for response assessment. Lesions on chest x-rays will be acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable. Ultrasound is not an acceptable method to measure disease.

Target/Non-Target Lesions

All measurable lesions, up to a maximum of 2 lesions per organ and up to 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 (lesions with the longest diameters) 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.

One exception to the above escribed approach is related to pathological lymph nodes. Pathological lymph nodes are defined as measurable lesions and may be identified as target lesions if the criterion of a short axis of ≥15 mm by CT is met. Only the short axis of these nodes will contribute to the baseline sum. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

Measurable lesions other than the target lesions (including pathologic lymph nodes) 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 assessment timepoints as target lesions.

Measurable and Non-Measurable Lesions and Disease

Measurable lesions will be those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm for lesions other than lymph nodes and assessed by CT/MRI scan - (CT/MRI scan slice thickness no greater than 5 mm)
- 10 mm for lesions assessed clinically by caliper measurement (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm for lesions assessed by chest x-ray

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

Non-measurable lesions/disease will be all other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with a ≥10 mm but <15 mm short axis), as well as truly non-measurable lesions. Truly non-measurable lesions include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam and not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone Lesions

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions

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

Lesions with Prior Local Treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Response in Target Lesions (RECIST v1.1)

At baseline, the sum of the longest diameters (SumD) of all target lesions (up to 2 lesions per organ, up to 5 lesions total) is measured. At each subsequent tumor assessment, the response in target and new measurable lesions is defined 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 the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Response in Non-Target Lesions (RECIST v1.1)

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).

Tumor-Response According to iRECIST

For a description of tumor-response evaluation according to iRECIST, and the differences between iRECIST and RECIST v1.1, refer to:

Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol*. 2017; 18:e143-52.[75]

Appendix 11 ECOG Performance Status

ECOG Performance Status	
Grade	**Status**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Reference: (Oken, 1982)