Janssen Research & Development *

Clinical Protocol

An Open-label Randomized Phase 1b/2 Study of the Efficacy and Safety of JNJ-64041757, a Live Attenuated Listeria monocytogenes Immunotherapy, in Combination with Nivolumab Versus Nivolumab Monotherapy in Subjects With Advanced Adenocarcinoma of the Lung

Protocol 64041757LUC2002; Phase 1b/2
Amendment 2

JNJ-64041757

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JNJ-64041757 is being investigated in Phase 1 and Phase 2 clinical studies.
Nivolumab is approved for marketing.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	02 August 2016
Amendment 1	02 June 2017
Amendment 2	04 January 2018

Amendments below are listed beginning with the most recent amendment.

Amendment 2 (04 January 2018)
This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: To limit Phase 1b enrollment to subjects with mesothelin-positive status at screening, to modify the assessment schedules for biomarkers and core needle biopsy, and to add biomarker measurements.

The rationale for and description of the changes are listed below, and representative revisions are sometimes provided; when revisions are provided verbatim, bold font denotes new text and strikethrough denotes deleted text.

Applicable Section(s)	Description of Change(s)
Rationale: Mesothelin-positive status at screening will be required for all subjects enrolled (Phase 1b and Phase 2), not just those in Phase 2, to ensure that each enrolled subject has improved potential to benefit from both innate and adaptive immune responses elicited by JNJ-757.	
Synopsis (Subject Population); Synopsis (Biomarker Evaluations); 3.2. Study Design Rationale (Rationale for Biomarker Assessments); 4. Subject Population; 4.1. Inclusion Criteria (Criterion 2); 9.1.2.1. Determination of Mesothelin and PD-L1 Level; 9.6.3. Primary Biomarker Assessment	Added mesothelin-positive status (>0% positive tumor cells) as an inclusion criterion for subjects in Phase 1b.

Applicable Section(s)	Description of Change(s)
Rationale: Additional subjects may be enrolled in Phase 1b, as determined by the Safety Evaluation Team (SET), to further explore safety and translational data before the decision to initiate the randomized Phase 2 portion of the study.	
Synopsis (Overview of Study Design); Synopsis (Statistical Methods); 1.5. Overall Rationale for the Study; 3.1.1. Phase 1b (Safety Run-in Phase); 3.1.1. Phase 1b (Safety Run-in Phase; Safety Evaluation Team [SET]) Figure 7 (Study Flowchart); 11.2. Sample Size Determination	Information (including an upper limit on the number of subjects) has been provided on additional subjects to be enrolled in Phase 1b as determined by the SET. Enrollment in Phase 2 will not begin until the SET has recommended proceeding, following the evaluation of safety and translational data from Phase 1b. Determination on tolerability of the regimen by the SET have been added. Phase 1b will be a safety run-in phase of at least 6 subjects to evaluate the incidence of dose limiting toxicities (DLTs) and demonstrate the tolerability of the combination ~~before initiation of the randomized Phase 2~~. **Additional subjects (up to 30 in total) may be enrolled, as determined by the Safety Evaluation Team (SET), to further explore safety and translational data before the decision to initiate the randomized Phase 2.**
Rationale: Core needle tumor biopsy sample collection was made mandatory for subjects in Phase 1b. Removed the soluble mesothelin and single nucleotide polymorphism from the biomarker assessments; added pentamer staining. These and other modifications were made to help evaluate the drug-clinical response relationship to improve translational data collected for the SET before initiating the Phase 2 portion of the study.	
Synopsis (Biomarker Evaluations); 3.1.2. Phase 2 (Randomized Phase)	**Mandatory c**ore needle **on-study** tumor biopsy samples will be collected from ~~approximately 20 subjects who consent separately to an optional translational substudy (where local regulations permit), and correlated with mesothelin-directed peripheral adaptive immune response~~ **subjects in Phase 1b, with core needle tumor biopsy samples being required from subjects at selected sites in Phase 2 who consent separately to an optional tumor biopsy substudy (where local regulations permit)**.
Table 1 (Time and Events Schedule - Assessments and Procedures for Phase 1b and Phase 2)	Several revisions and modifications were made to timing and assessments in Table 1.
9.6.1. Sample Collection	Details for sample collection have been revised and updated based on changes to biomarker assessments.

Applicable Section(s)	Description of Change(s)
9.6.2. Pharmacodynamic and Predictive Biomarker Evaluations	The revisions shown below have been made, and some bullets have been separated or combined. Pharmacodynamic (PD) biomarkers **and translational data** will be informed by available Phase 1 results, will be assessed before, during, and after treatment with JNJ-757, and may include the following: 3. NK**, CD4, and CD8 T** cell ~~number~~ **enumeration** and activation status using standard activation markers (such as CD69) by flow cytometry in PBMCs. ~~4. Soluble mesothelin levels, using appropriate techniques such as ELISA.~~ ~~6. Single nucleotide polymorphism of genes associated with the PD-1/PD-L1 pathway and activated T-cell phenotype.~~ **9. Infiltration and activation status of several immune cells subsets using appropriate techniques such as single color or multiplex immunocytochemistry of formalin fixed paraffin embedded (FFPE) tumor biopsies.**
Rationale: Revisions were made to inclusion and exclusion criteria to clarify eligibility.	
4.1 Inclusion Criteria (Criterion 2)	• ~~(In Phase 2 only)~~ Mesothelin-positive status (>0% positive tumor cells), determined at a central laboratory using mesothelin immunohistochemistry (IHC) assay
4.1 Inclusion Criteria (Criterion 6)	Adequate hepatic function, defined as: • Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) ≤1.5 times the upper limit of normal (ULN) **if no liver metastases, and ≤3×ULN with documented liver metastases** • Total serum bilirubin ≤1.5xULN (unless due to Gilbert~~'s~~ syndrome**; if so, direct bilirubin ≤3xULN**)
4.1 Inclusion Criteria (Criterion 9)	Before **Cycle 1 Day 1 (Phase 1b) o**r randomization **(Phase 2)**, a woman must be either:
4.2 Exclusion Criteria (Criterion 1)	Subjects with a history of brain metastasis must have completed treatment for brain metastasis for at least 28 days, and be neurologically stable and off steroids before ~~enrollment~~ **Cycle 1 Day 1** (Phase 1b) or randomization (Phase 2).
4.2 Exclusion Criteria (Criterion 2)	Tumor with activating EGFR mutation or ALK translocation (EGFR and ALK results must be confirmed in the Screening Period for all non-smokers**. A positive KRAS result may be used in lieu of an EGFR or ALK result**).
4.2 Exclusion Criteria (Criterion 3)	More than 1 prior line of chemotherapy for metastatic disease (not including therapy given in the maintenance setting, or neoadjuvant or adjuvant therapy for locally advanced disease) **(Phase 2)**.
4.2 Exclusion Criteria (Criterion 10)	Concurrent treatment with anti-TNFα therapies, systemic corticosteroids (prednisone dose >10 mg per day or equivalent), or other immunosuppressive drugs <14 days before **Cycle 1 Day 1 (Phase 1b) or** randomization **(Phase 2)**.
4.2 Exclusion Criteria (Criterion 11)	**A p**ositive test result **by medical history** for human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS).
4.2 Exclusion Criteria (Criterion 13)	History of clinically significant cardiovascular disease within 6 months of **Cycle 1 Day 1 (Phase 1b) or** randomization **(Phase 2)** including, but not limited to:

Applicable Section(s)	Description of Change(s)
4.2 Exclusion Criteria (Criterion 15)	Active second malignancy within 2 years prior to **Cycle 1 Day 1 (Phase 1b) or** randomization **(Phase 2)**.
4.2 Exclusion Criteria (Criterion 19)	Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 28 days before ~~enrollment~~ **Cycle 1 Day 1** (Phase 1b) or randomization (Phase 2).
Rationale: The timing of disease response using computed tomography (CT) scans with IV contrast (or if necessary, magnetic resonance imaging [MRI] scans) of the chest, abdomen, and pelvis has been revised to allow the first assessment to occur at the same time as the on-treatment biopsy.	
Synopsis (Overview of Study Design); Table 1 (CT or MRI of chest, abdomen, and pelvis); 3.1.2. Phase 2 (Randomized Phase); 9.2.1. Evaluations	Disease response will be assessed with Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria, using computed tomography (CT) scans with IV contrast (or if necessary, magnetic resonance imaging [MRI] scans) of the chest, abdomen, and pelvis at Week 8 (±7 days), then every 8 weeks (±7 days) during the first year, and then every 12 weeks (±7 days) thereafter **until disease progression, subsequent therapy, or completion of therapy**. **For subjects receiving on-treatment biopsy, the first assessment will be at Cycle 3 Day 8 (+3 days).**
Rationale: Follow-up visits may be conducted by telephone after the first year, to reduce the burden for subjects not requiring follow-up blood cultures. The window for the visits is (±7 days).	
Synopsis (Overview of Study Design); 3.1.2. Phase 2 (Randomized Phase); Figure 7 (Study Flowchart); 9.1.4. Posttreatment Follow-up Phase	Follow-up visits ~~(after the first year, these visits can be conducted by telephone contact or an alternative contact method per institution policy/practice)~~ will be made every 3 months (±~~14~~ **7** days) after the last dose of study agent to obtain blood cultures (up to 1 year **for subjects who receive JNJ-757**) and to determine survival, unless the subject has died, is lost to follow-up, or has withdrawn consent. **For subjects in Group B and after the first year for subjects in Phase 1b and Group A, these visits may be conducted by telephone contact or an alternative contact method per institution policy/practice.**
Rationale: Revisions and modifications were made throughout the protocol to increase clarity, to update the protocol based on revisions made during this amendment, or to correct omissions and errors.	
Synopsis (Objectives, Endpoints, and Hypothesis);	Disease control rate (stable disease for **at least** 16 weeks, complete response, or partial response)
2.1. Objectives and Endpoints; 9.2.2. Efficacy Endpoints	To evaluate the safety of JNJ-757 **in combination with nivolumab**
Table 1 (multiple places);	Clarified that for Day 1 assessments, predose refers to before nivolumab and postdose refers to after the last study drug.
Table 1 (Brain MRI; required only for subjects with known brain metastasis); 9.2.1. Evaluations	Brain MRI to be done only as clinically indicated after the Screening Phase.

Applicable Section(s)	Description of Change(s)
3.1.1. Phase 1b (Safety Run-in Phase); 3.1.2. Phase 2 (Randomized Phase); 9.2.1.3. Discontinuation of Study Agent After Complete Response; 10.2. Discontinuation of Study Treatment	The maximum allowed duration of nivolumab **or JNJ-757** treatment is 2 years.
3.1.1. Phase 1b (Safety Run-in Phase; Safety Evaluation Team [SET])	The following rules will be applied to determine that the combination of JNJ-757 and nivolumab is safe and tolerable: • If <2 of 6 (or <33%) evaluable subjects in Phase 1b experience a DLT during the first treatment cycle (ie, 28 days), then the selected doses and dose regimens for JNJ-757 + nivolumab combination therapy will be considered tolerable in subjects with advanced or metastatic NSCLC~~, and the study will proceed to Phase 2~~. • If ≥2 **of 6** evaluable subjects (or ≥33%) experience a DLT in the first treatment cycle, then the SET will examine the totality of available safety**, translational,** and pharmacokinetic/PD data, and may recommend either stopping the study or expanding the Phase 1b population ~~to a maximum of 12 subjects total~~ to evaluate alternate doses and dose regimens.
Figure 7 (Study Flowchart)	Deleted the box for eligibility in Phase 2 (Randomized Phase).
3.2. Study Design Rationale (Rationale for Study Population)	Therefore, subjects with activating EGFR mutations or ALK translocations are excluded from participation in this study (EGFR and ALK results must be confirmed in the Screening Period for all non-smokers). **KRAS mutations are mutually exclusive from EGFR and ALK translocations; therefore, a positive KRAS mutation does not require ALK testing.**
6.3.2. Cycle Delay	Revised “autoimmune” to “immune-mediated”.
Table 4	Revised “Hepatitis” to “Hepatic toxicity”.
8.3.2. Nivolumab; Table 7; Table 8; 8.3.2.4. Rash (Including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis)	Revised “immune-related” to “immune-mediated”.

Applicable Section(s)	Description of Change(s)
Synopsis (Safety Evaluations); 3.1.2. Phase 2 (Randomized Phase); 8. Prestudy and Concomitant Therapy; 9.1.3. Treatment Phase; 12.3.1. All Adverse Events	Any new or worsening adverse events that occur and all concomitant medications that are administered between when the informed consent form (ICF) is signed and 100 days after the last dose of study agent will be recorded **for subjects who enter the Screening Phase**.
9.1.2.1. Determination of Mesothelin and PD-L1 Level	Before ~~enrollment~~ **proceeding** ~~in~~to the Treatment Phase of the study, tumor tissue samples for each subject must be provided for assessment of tumor mesothelin ~~positive~~ status and PD-L1 level. The results must be reported by the central laboratory before **Cycle 1 Day 1 (Phase 1b) or** randomization **(Phase 2)**.
9.1.4. Posttreatment Follow-up Phase	Subjects who have a treatment-related Grade ≥3 toxicity at the End-of-Treatment Visit will continue follow-up until recovery to Grade ≤1 or baseline, the AE is deemed irreversible, ~~or for a maximum of 6 months after the last dose of study agent~~ **or the subject starts subsequent anticancer therapy**. Subjects with treatment-related adverse events leading to discontinuation will continue follow-up until resolution or return to baseline, **the AE is deemed irreversible,** or end of study, whichever occurs first.
9.2.1. Evaluations	**For Phase 2, r**adiographic scans may be submitted to a third-party core imaging laboratory for quality assessment and for audit purposes.
9.5. Nivolumab Immunogenicity Evaluations	~~Analysis will be performed by a central laboratory.~~ **Analysis will be performed under the supervision of the sponsor.**
12.4.1. Adverse Events of Special Interest	~~Transient~~ **Persistent** bacteremia will be followed as part of standard safety monitoring activities by the sponsor and will include both serial blood cultures after dosing in Cycle 1, and subsequent predose surveillance blood cultures during the treatment phase, at the End-of-Treatment visit, and during the follow-up phase, for 1 year after the completion of dosing with JNJ-757.
12.4.2. Pregnancy	All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form **beginning at the time a signed and dated ICF is obtained until 5 months (female subjects) or 7 months (male subjects) after the last dose of study agent**.
14.2. Packaging	JNJ-757 drug product will be shipped and stored frozen at –60ºC or colder. It consists of attenuated *Lm* suspended in ~~either 1.5 mL or 1.2 mL of~~ Dulbecco's phosphate-buffered saline and 9% volume concentration glycerol.
Throughout the protocol	Revised "before enrollment (Phase 1b)" to "before Cycle 1 Day 1 (Phase 1b)".
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (02 June 2017)

The overall reason for the amendment: To add a Phase 1b run-in Phase to assess the safety of the combination of JNJ-64041757 (JNJ-757) with nivolumab; to limit Phase 2 randomization to subjects with mesothelin-positive status at screening; to change the stratification for randomization to 3 levels of PD-L1; to modify the assessment schedules for biomarkers, disease evaluation, blood cultures, nivolumab pharmacokinetics, and nivolumab immunogenicity; to add measurements of patient-reported outcomes; and to update the nivolumab dosing schedule and safety evaluations based on revisions to product labeling for nivolumab.

The rationale for and description of the changes are listed below, and representative revisions are sometimes provided; when revisions are provided verbatim, bold font denotes new text and strikethrough denotes deleted text.

Applicable Section(s)	Description of Change(s)
Rationale: A Phase 1b Safety Run-in was added to the protocol to assess the safety of the combination of JNJ-757 with nivolumab in subjects with advanced adenocarcinoma of the lung.	
Throughout the protocol	Clarified that all subjects will receive nivolumab treatment, and that subjects in Phase 1b and Group A of Phase 2 will receive JNJ-757.
Title	Changed "Phase 2" to "Phase **1b/**2."
Cover Page	Clarified that JNJ-757 "is being investigated in **Phase 1 and** Phase 2 clinical studies."
Time and Events Schedule	Clarified that biomarker assessments are required in Phase 2.
Synopsis (Overview of Study Design); Synopsis (Statistical Methods)	Added descriptions of dose limiting toxicities (DLTs) and the Safety Evaluation Team (SET) in Phase 1b.
1.5. Overall Rationale for the Study	Added a description of the role of the Safety Evaluation Team (SET) to analyze the safety of the combination of JNJ-757 and nivolumab after the last subject dosed in Phase 1b has been observed for at least 28 days.
3.1. Overview of Study Design	Added Section 3.1.1. Phase 1b (Safety Run-in Phase) to describe the SET, DLTs, and the DLT rules. Added Phase 1b to the Study Flowchart figure (Figure 7).
3.2. Study Design Rationale; 5. TREATMENT ALLOCATION AND BLINDING	Clarified that the randomization will occur in Phase 2, after the safety run-in phase.
4. SUBJECT POPULATION; 9.1.2. Screening Phase	Changed inclusion criteria, exclusion criteria, and screening phase methods to the following: "28 days before **enrollment (Phase 1b) or** randomization **(Phase 2)**."
Time and Events Schedule; 9.3. Blood Culture and Bacterial Shedding Assessments for JNJ-757	Clarified that the shedding profile of JNJ-757 will be studied for at least 20 subjects who receive JNJ-757 plus nivolumab "**(in Phase 1b or in Phase 2 Group A**)."

Applicable Section(s)	Description of Change(s)
11.1. Subject Information	Added this sentence: "**The subjects in the safety run-in cohort will also be included in disposition and appropriate efficacy analyses and listed separately.**"
Rationale: The Data Monitoring Committee (DMC) for Phase 2 was modified from an independent DMC to a Janssen DMC and the schedule and purpose of the DMC assessments were modified to improve monitoring of the benefits and risks of the combination of JNJ-757 with nivolumab.	
Synopsis (Statistical Methods); 1.5. Overall Rationale for the Study; 3.1.2. Phase 2 (Randomized Phase); 11.3. Statistical Model for Probability of ORR; 11.11. Data Monitoring Committee	Changed the independent DMC to a Janssen DMC. Changed the DMC schedule for Phase 2: • From: 20 subjects (safety) and 60 subjects (futility) • To: randomization of 40, 60, 80, 100, and 120 subjects (for ORR), every 3 months (for safety), and as needed (based on the accumulating data)
Rationale: Revised the statistical analysis plan to use a Bayesian hierarchical logistic regression model, such that more subjects can be enrolled in a PD-L1 subgroup where the combination therapy is more effective. If the combination therapy is not effective in any PD-L1 level, then the study could be stopped early.	
Throughout the protocol	Clarified that PD-L1 levels for stratification in Phase 2 will be assessed centrally during the Screening Phase using submitted tumor material and the DAKO PD-L1 IHC 28-8 pharmDx Assay.
Synopsis (Objectives, Endpoints, and Hypothesis; Overview of Study Design); 2.1. Objectives and Endpoints	Added PD-L1 subgroups to the primary endpoint: "To evaluate whether the efficacy of JNJ-757 combined with nivolumab is better than the efficacy of nivolumab monotherapy for subjects with **mesothelin-positive** relapsed/refractory Stage IIIB or **Stage** IV adenocarcinoma of the lung**, by PD-L1 level**"
Synopsis (Hypothesis); 2.2. Hypothesis	"The primary hypothesis of the study is that the addition of JNJ-757 to nivolumab will result in a higher ORR compared with nivolumab monotherapy **in at least one of the PD-L1 subgroups (<1%, 1-49%, or ≥50%)** in subjects with relapsed or refractory Stage IIIB or **Stage** IV adenocarcinoma of the lung."
Synopsis (Overview of Study Design); 3.1.2. Phase 2 (Randomized Phase)	"~~Approximately 174~~ **In Phase 2, a maximum of 140** subjects who meet all of the inclusion criteria and none of the exclusion criteria will be stratified in subgroups according to ~~mesothelin status (>0% vs 0%) and programmed death receptor ligand 1 (PD-L1) status (≥1% vs <1%),~~ **PD-L1 level (<1%, 1–49%, or ≥50%), using the DAKO PD-L1 IHC 28-8 pharmDx Assay,** and then be assigned randomly (1:1) to receive JNJ-757 plus nivolumab (Group A) or nivolumab monotherapy (Group B). **Throughout randomization, ORR will be monitored using a Bayesian hierarchical logistic regression model, such that more subjects may be enrolled in a PD-L1 subgroup where the combination therapy is more effective. However, in such cases subjects will always be randomized to Group A or Group B at 1:1 ratio within that subgroup. If the combination therapy is not effective in any PD-L1 subgroup, then the study could be stopped early.**"
Figure 7	Updated the stratification categories in the study flowchart.

Applicable Section(s)	Description of Change(s)
5. TREATMENT ALLOCATION AND BLINDING	"Central randomization will be implemented in **Phase 2 of** this study. **Upon entry, eligible** subjects will be randomly assigned 1:1 to treatment Groups A and B based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified ~~by mesothelin status (>0% vs 0%) and PD-L1 status (≥1% vs <1%), which will be assessed during the Screening Phase using submitted tumor material~~. **according to PD-L1 level (<1%, 1–49%, or ≥50%).**"
11.2. Sample Size Determination	Updated to reflect the changes to the randomization and stratification.
Synopsis (Statistical Methods); [New section] 11.3. Statistical Model for Probability of ORR	Added a description of the Bayesian hierarchical logistic regression model that will be used to estimate the posterior probability of observing an objective response (complete response or partial response) for each treatment group within each PD-L1 level.
Rationale: Study eligibility criteria, prohibitions, and prophylaxis against *Listeria* infection were modified based on emerging efficacy and safety data from the Phase 1 study of JNJ-757 in lung cancer.	
Synopsis (Overview of Study Design); Time and Events Schedule; 3.1.2. Phase 2 (Randomized Phase)	Added assessments of blood cultures with a disease assessment or as clinically indicated during study treatment; as well as at 3, 6, 9, and 12 months after the last dose of JNJ-757.
3.2. Study Design Rationale	Added the rationale for blood culture and bacterial shedding surveillance, including data from clinical experience with CRS-207 and from the Phase 1 study (64041757LUC1001) of JNJ-757 in lung cancer.
Synopsis (Study Population); 4.2. Exclusion Criteria	Added to Exclusion Criteria 8 and 10 anti-TNFα therapies or history of any other condition that may require the initiation of anti-TNFα therapies or other immunosuppressant medications during the study. Added to Exclusion Criterion 12 any history of cardiac pacemakers, orthopedic screws, or metal plates. Clarified in Exclusion Criterion 12 that subjects with venous access devices (eg, Port-a-Cath or Mediport), arterial and venous stents, dental implants, or breast implants are permitted on the study.
4.3. Prohibitions and Restrictions	Added prohibitions and restrictions for subjects with indwelling venous access devices.
8.2. Prohibited Medications	Added anti-TNFα therapies or other immunosuppressants. Added systemic antibiotics during the treatment phase (except the required antibiotic prophylaxis for *Listeria* infection after the last dose of JNJ-757).
8.3.1.1. Prophylaxis Against *Listeria* Infection After the Last Dose of JNJ-757; 10.2. Discontinuation of Study Treatment	Detailed instructions were added regarding antibiotic prophylaxis against *Listeria* infection in all subjects after the last dose of JNJ-757
8.3.1.2. Treatment for *Listeria* Infection	Added details regarding treatment for *Listeria* infection among subjects requiring an emergent placement of a prohibited implanted device, or in a subject with surveillance blood cultures positive for listeriosis.

Applicable Section(s)	Description of Change(s)
9.1.3. Treatment Phase	Added a description of the schedule for surveillance blood cultures and the appropriate management of a subject with a positive surveillance blood culture. Added a description of the mandatory prophylactic antibiotic therapy after the last dose of JNJ-757.
9.3. Blood Culture and Bacterial Shedding Assessments for JNJ-757	Added details to the description of blood culture assessments.
10.2. Discontinuation of Study Treatment	Clarified that JNJ-757 treatment should be discontinued if predose peripheral surveillance cultures are positive for listeriosis or if the subject requires an emergent placement of a prohibited implanted device.
12.3.3. Adverse Events of Special Interest	Added a description of monitoring for bacteremia and positive surveillance blood cultures as adverse events of special interest.
Rationale: The schedule for disease evaluations was modified to reduce patient burden.	
Synopsis (throughout); Time and Events Schedule; 3.1.2. Phase 2 (Randomized Phase); Figure 7; 9.1.4. Posttreatment Follow-up Phase;9.2.1. Evaluations	Reduced frequency of disease evaluations after the first year from every 8 weeks to every 12 weeks. Reduced frequency of survival follow-up from every 2 months to every 3 months. Removed the requirement for confirmation of response 4 weeks after initial response.
Throughout the protocol	Changed the windows for disease assessments from "+7 days" to "±7 days."
Time and Events Schedule (footnotes); 9.1.3. Treatment Phase	Clarified that if nivolumab is permanently discontinued but the subject continues to receive treatment with JNJ-757, then the Day 15 visits of subsequent cycles will be optional.
9.1.4. Posttreatment Follow-up Phase	Clarified that for subjects who withdraw from treatment before disease progression, the results of subsequent tumor assessments should also be collected according to the study schedule until disease progression is radiographically documented or until subsequent therapy begins.
Rationale: The schedule for biomarker assessments was modified to strengthen the analyses of these endpoints.	
Synopsis (Biomarker Evaluations)	Clarified that markers of innate immune response will be measured in subjects treated with JNJ-757.
Time and Events Schedule	Cytokines: clarified that they will be collected in 3 separate tubes (Cytokines LADD, Cytokines Nivolumab, and Clinical) and modified the assessment schedule. NK panel: modified the assessment schedule. Immune profile: changed from 3 tubes to 1 tube and modified the assessment schedule. T-Cell proliferation/ICS, IFN-γ ELISpot, and TCR sequencing: modified the assessment schedule. SNP, MDSC: removed assessments of these biomarkers.

Applicable Section(s)	Description of Change(s)
Rationale: In Phase 2, mesothelin positivity in the tumor was changed from a stratification factor to an eligibility criterion to ensure that subjects have the potential to benefit from both innate and adaptive immune responses elicited by JNJ-757.	
3.2. Study Design Rationale	Added this sentence: "**Mesothelin selection will ensure that each enrolled subject has the potential to benefit from both innate and adaptive responses elicited by JNJ-757.**"
4.1. Inclusion Criteria	Added mesothelin-positive status for Phase 2 to inclusion criterion 2.
9.1.2.1. Determination of Mesothelin and PD-L1 Level	Clarified that mesothelin positive status (>0% positive tumor cells) is defined as tumor cells exhibiting positive membrane or cytoplasmic staining at any intensity.
9.6.3. Primary Biomarker Assessment	Clarified that positive mesothelin status will now be used as a study eligibility criterion in Phase 2.
Rationale: The assessment schedules for nivolumab pharmacokinetics and nivolumab immunogenicity were modified to strengthen the analyses of these endpoints.	
Synopsis (Objectives, Endpoints, and Hypothesis); 2.1. Objectives and Endpoints	Added nivolumab pharmacokinetics (serum concentrations of nivolumab) and nivolumab immunogenicity (incidence of anti-nivolumab antibodies) to the secondary study objectives, and endpoints/assessments.
Time and Events Schedule	Rescheduled nivolumab pharmacokinetics assessments to the following study days: Cycle 1 Day 15; Cycle 2 Day 1; Day 1 of Cycles 3, 8, 12, 18, and 24; and End of Treatment. Rescheduled nivolumab immunogenicity assessments to the following days: Cycle 1 Day 1; Day 1 of Cycles 3, 8, 12, 18, and 24; and End of Treatment.
3.2. Study Design Rationale	Added a rationale for the pharmacokinetics and immunogenicity assessments.
Rationale: In Phase 2, an exploratory objective and an exploratory endpoint were added to understand the effect of JNJ-757 combined with nivolumab treatment on patient-reported outcomes, including cancer symptoms and functional status, over time in subjects with NSCLC.	
Synopsis (Objectives, Endpoints, and Hypothesis); 2.1. Objectives and Endpoints	Objectives: added "**To assess patient-reported outcomes**" as an exploratory objective. Endpoints: added "**NSCLC-SAQ and EORTC QLQ**" as an exploratory endpoint.
Time and Events Schedule	Added assessments of patient-reported outcomes on Day 1 of each cycle and at the End-of-Treatment Visit.
3.2. Study Design Rationale	Added a rationale for including patient-reported outcomes assessments.
9.1.1. Overview	Clarified that PRO assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing subject perceptions.

Applicable Section(s)	Description of Change(s)
9.2. Efficacy Evaluations	In Section 9.2.1 Evaluations, added descriptions of the instruments that will be used for patient-reported outcomes. In Section 9.2.2 Efficacy Endpoints. Added NSCLC-SAQ and EORTC QLQ to Efficacy Endpoints.
11.9. Patient-reported Outcomes Analyses	Added a description of the planned analysis of patient-reported outcomes.
Rationale: The nivolumab dosing schedule, pregnancy restrictions, and safety evaluations were modified to be consistent with revised product labeling for nivolumab.	
Throughout the protocol	Changed nivolumab dose for all subjects from weight-based doses (3 mg/kg) to a fixed dose (240 mg), based on the approved dosage in the USPI for nivolumab. Changed contraception and sperm/egg donation requirements: "~~at least 31 weeks after the last dose of study agent~~" **5 months (female subjects) or 7 months (male subjects) after the last dose of study agent**."
Synopsis (Safety Evaluations); Time and Events Schedule; 3.1.2. Phase 2 (Randomized Phase); 8. PRESTUDY AND CONCOMITANT THERAPY; 9.1.3. Treatment Phase; 12.3.1. All Adverse Events	Clarified that adverse events and concomitant medications should be recorded until 100 days after the last dose of study agent.
Table 4; 8.3.2.4. Rash (Including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis)	Added Stevens-Johnson Syndrome and toxic epidermal necrolysis to possible adverse events of rash.
6.3.2. Cycle Delay; Table 4	Updated the criteria to resume nivolumab treatment, based on revisions to product labeling for nivolumab and additional information from ongoing studies of nivolumab.
8.3.2.10. Treatment of Nivolumab Related Infusion Reactions	Added this statement: "**If a nivolumab related infusion reaction occurs on Day 1 of a treatment cycle, then the scheduled dose of JNJ-757 should be withheld on that day. The subject can resume JNJ-757 treatment with the next scheduled dose of JNJ-757 on Day 1 of the next cycle of nivolumab treatment.**"
Attachment 4: Anticipated Events	Updated the lists of disease-related and nivolumab-related adverse events based on currently available safety data.
Rationale: The background descriptions for JNJ-757 and nivolumab were updated with newer information.	
1.2.1. Clinical Experience with LADD *Lm-based* Immunotherapeutics	Modified to include information from the STELLAR study of CRS-207 with GVAX vaccine and cyclophosphamide, with or without nivolumab, in patients with pancreatic cancer.
1.3.2. Clinical Experience with JNJ-757	Modified to include updated safety and biomarker information from an ongoing Phase 1 study of JNJ-757 in subjects with lung cancer (Study 64041757LUC1001).

Applicable Section(s)	Description of Change(s)
1.4. Nivolumab	Updated to include additional information about the mechanism and action and safety of nivolumab.
1.5. Overall Rationale for the Study	Updated to include survival curves for the combination of JNJ-757 and a PD-1 inhibitor from mouse models of lung cancer. Clarified that based on currently available nonclinical and clinical data, the toxicity profiles of JNJ-757 and nivolumab are not anticipated to overlap.
Rationale: The role of continued study agent administration after suspected tumor flare was clarified.	
9.2.1.2. Treatment Beyond Progression; 10.2. Discontinuation of Study Treatment	Clarified that subjects with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (ie, tumor flare), and that subsequent responses will be reported in the eCRF. Clarified the conditions under which a subject with suspected tumor flare may be permitted to remain on study therapy.
Rationale: The exclusion criterion for EGFR mutation or ALK translocation in nonsmokers was clarified.	
3.2. Study Design Rationale; 4.2. Exclusion Criteria	Updated Criterion 2 to clarify that EGFR and ALK results must be confirmed in the Screening Period for all non-smokers.
Rationale: Revision to reflect the formulations that may be used in this study.	
14.2 Packaging	Clarified that the JNJ-757 attenuated *Lm* is suspended in [redacted] and that primary packaging consists of single-use 2 mL glass vial(s) with gray butyl **or bromobutyl** stoppers.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

An Open-label Randomized Phase 1b/2 Study of the Efficacy and Safety of JNJ-64041757, a Live Attenuated Listeria monocytogenes Immunotherapy, in Combination with Nivolumab Versus Nivolumab Monotherapy in Subjects With Advanced Adenocarcinoma of the Lung

JNJ-64041757 (formerly known as ADU-214 and henceforth referred to as JNJ-757) is a live-attenuated, double-deleted (LADD) *Listeria monocytogenes* (*Lm*)-based immunotherapy containing an ActAN100-EGFRvIII (ActANE)-human mesothelin (hMeso) fusion expression vector. After infection and intracellular processing, JNJ-757 elicits a proinflammatory immune response resulting in recruitment and activation of innate and adaptive effector cells, ultimately leading to systemic mesothelin-specific $CD4^+$ and $CD8^+$ T-cell immunity. In patients with adenocarcinoma of the lung, the combination of JNJ-757 with nivolumab, a programmed death receptor-1 (PD-1) immune checkpoint inhibitor, has the potential to improve efficacy compared with nivolumab monotherapy, which is approved for treatment of non–small-cell lung cancer (NSCLC).

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives	Endpoints/Assessments
Primary	
• To evaluate whether the efficacy of JNJ-757 combined with nivolumab is better than the efficacy of nivolumab monotherapy for subjects with mesothelin-positive relapsed/refractory Stage IIIB or Stage IV adenocarcinoma of the lung, by PD-L1 level	• Objective response rate (complete response plus partial response, based on RECIST 1.1 criteria)
Secondary	
• To compare the clinical benefit of JNJ-757 combined with nivolumab versus nivolumab monotherapy	• Disease control rate (stable disease for at least 16 weeks, complete response, or partial response) • Duration of objective response • Progression-free survival • Overall survival
• To evaluate the safety of JNJ-757 in combination with nivolumab	• Incidence of adverse events
• To correlate PD-L1 level with clinical activity	• Disease control rate, duration of response, progression-free survival, and overall survival in biomarker subpopulations defined by PD-L1 level
• To assess the blood culture and shedding profile of JNJ-757	• Blood cultures • Bacterial shedding samples
• To assess the pharmacokinetics and immunogenicity of nivolumab	• Serum concentrations of nivolumab • Incidence of anti-nivolumab antibodies
Exploratory	
• To monitor markers of innate and adaptive immune responses	• Biologic markers of immune system activation
• To evaluate other biomarkers that may be predictive of a response	• Objective response rate in other biomarker subpopulations
• To assess patient-reported outcomes	• NSCLC-SAQ and EORTC QLQ

EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; NSCLC-SAQ=non–small-cell lung cancer self-administered questionnaire; PD-L1=programmed death receptor ligand 1; RECIST=Response Evaluation Criteria in Solid Tumors.

Hypothesis

The primary hypothesis of the study is that the addition of JNJ-757 to nivolumab will result in a higher objective response rate (ORR) compared with nivolumab monotherapy in at least one of the programmed death receptor ligand 1 (PD-L1) subgroups (<1%, 1-49%, or ≥50%) in subjects with relapsed or refractory Stage IIIB or Stage IV adenocarcinoma of the lung.

OVERVIEW OF STUDY DESIGN

This is a multicenter, open-label, randomized Phase 1b/2 study to determine if subjects with advanced relapsed/refractory adenocarcinoma of the lung will derive greater clinical benefit from the addition of JNJ-757 to nivolumab.

Phase 1b will be a safety run-in phase of at least 6 subjects to evaluate the incidence of dose limiting toxicities (DLTs) and demonstrate the tolerability of the combination. Additional subjects (up to 30 in total) may be enrolled, as determined by the Safety Evaluation Team (SET), to further explore safety and translational data before the decision to initiate the randomized Phase 2. All subjects in Phase 1b will receive nivolumab, administered at 240 mg IV over approximately 60 minutes, every 2 weeks, in 28-day cycles. After completion of the nivolumab infusion on Day 1 of each 28-day cycle, JNJ-757 will be administered at a dose of 1×10^9 colony-forming units (CFU) IV over approximately 60 minutes. The SET will be responsible for reviewing the safety and translational data during Phase 1b and for making a formal determination of whether the study will expand the Phase 1b cohort, modify the dosing regimen, or proceed to the randomized phase (Phase 2) after the last subject dosed has been observed for at least 28 days.

In Phase 2, a maximum of 140 subjects who meet all of the inclusion criteria and none of the exclusion criteria will be stratified in subgroups according to PD-L1 level (<1%, 1–49%, or ≥50%), using the DAKO PD-L1 IHC 28-8 pharmDx Assay, and then be assigned randomly (1:1) to receive JNJ-757 plus nivolumab (Group A) or nivolumab monotherapy (Group B). Throughout randomization, ORR will be monitored using a Bayesian hierarchical logistic regression model, such that more subjects may be enrolled in a PD-L1 subgroup where the combination therapy is more effective. However, subjects will always be randomized to Group A or Group B in a 1:1 ratio within that subgroup. If the combination therapy is not effective in any PD-L1 subgroup, then the study could be stopped early. In both groups, subjects will receive nivolumab, administered at 240 mg intravenously (IV) over approximately 60 minutes, every 2 weeks, in 28-day cycles. In Group A, after completion of the nivolumab infusion on Day 1 of each 28-day cycle, JNJ-757 will be administered at a dose of 1×10^9 CFU IV over approximately 60 minutes.

Disease response will be assessed with Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria, using computed tomography (CT) scans with IV contrast (or if necessary, magnetic resonance imaging [MRI] scans) of the chest, abdomen, and pelvis at Week 8 (±7 days), then every 8 weeks (±7 days) during the first year, and then every 12 weeks (±7 days) thereafter until disease progression, subsequent therapy, or completion of therapy. For subjects receiving on-treatment biopsy, the first assessment will be at Cycle 3 Day 8 (+3 days).

In both phases of the study, treatment will continue until disease progression, unacceptable toxicity, protocol violation requiring discontinuation of study treatment, withdrawal of consent, noncompliance with study procedures, or the sponsor terminates the study. After discontinuing study treatment, subjects will be contacted by clinic visit or telephone every 3 months (±7 days) for survival follow-up until the subject withdraws consent or dies, or the sponsor terminates the study. Information on subsequent therapies (regimen, initiation dates, and stop dates) and best response (if available) will also be collected. Among subjects who receive JNJ-757, surveillance blood cultures will be collected as follows: at the first 4 visits of the Treatment Phase; on Day 1 of any subsequent cycle with a disease assessment, or as clinically indicated; at the End of Treatment visit (before prophylactic antibiotic therapy); and 3, 6, 9, and 12 months after the last dose of JNJ-757. The end of the study will occur when 80% of the randomized

subjects have died, or approximately 3 years after the last subject is randomized, or the sponsor terminates the study.

SUBJECT POPULATION

Subjects must be ≥18 years of age and have histologically documented adenocarcinoma of the lung, Stage IIIB or Stage IV disease, tumor biopsy positive for mesothelin and tumor biopsy material available for PD-L1 assessment in Phase 2, and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Subjects must have progressive disease during or after platinum-based doublet chemotherapy. Subjects must have adequate bone marrow function, adequate hepatic function, and adequate renal function. Subjects are excluded from eligibility for the following: untreated brain metastases, activating epidermal growth factor receptor (EGFR) mutation or ALK translocation, history of symptomatic interstitial lung disease, history of major implants or devices, or history of any other condition that may require the use of immunosuppressant medications such as anti-tumor necrosis factor alpha (TNFα) therapy.

BIOMARKER EVALUATIONS

Pharmacodynamic biomarkers will be assessed before, during, and after treatment with JNJ-757. Biomarker analyses performed as part of the screening activities will include central assessment of mesothelin-positive status and PD-L1 level in tumor tissues. Tumor mesothelin status will be used as a study eligibility criterion and in Phase 2, subjects with mesothelin-positive tumors will be stratified based on PD-L1 level (<1%, 1-49%, or ≥50%). The primary endpoint of ORR will be assessed by PD-L1 level.

Markers of innate immune response, including changes in lymphocyte cell count and activation, and serum cytokines, will be measured as pharmacodynamic markers before, during, and after treatment with JNJ-757 when given in combination with nivolumab. Mandatory core needle on-study tumor biopsy samples will be collected from subjects in Phase 1b, with core needle tumor biopsy samples being required from subjects at selected sites in Phase 2 who consent separately to an optional tumor biopsy substudy (where local regulations permit).

SAFETY EVALUATIONS

Safety evaluations will include adverse event monitoring, clinical laboratory tests, symptom-directed physical examinations, vital signs, and ECOG performance status. Any new or worsening adverse events occurring any time after signing the informed consent form (ICF) and up to 100 days after the last dose of study agent (JNJ-757 or nivolumab), as well as concomitant medications used throughout this time period, will be recorded for subjects who enter the Screening Phase. The severity of adverse events will be assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. Adverse events indicative of inflammatory cytokine release will be followed as part of standard safety monitoring activities by the sponsor.

STATISTICAL METHODS

Phase 1b will be a safety run-in phase of at least 6 subjects to evaluate the incidence of DLTs and demonstrate the tolerability of the combination. Additional subjects (up to 30 in total) may be enrolled, as determined by the SET, to further explore safety and translational data before the decision to initiate the randomized Phase 2. The SET will be responsible for reviewing the safety and translational data during Phase 1b.

In Phase 2, a maximum of 140 subjects will be randomized. Based on preliminary data, it is estimated that 60%, 25%, and 15% of mesothelin-positive subjects have a PD-L1 level of <1%, 1-49%, or ≥50%, respectively. The projected ORRs are as follows:

	PD-L1 (<1%)	PD-L1 (1-49%)	PD-L1 (≥50%)	Overall
Group A (JNJ-757 plus nivolumab)	0.30	0.40	0.80	0.40
Group B (nivolumab)	0.10	0.20	0.40	0.17

Using frequentist methods, a sample size of 140 subjects will provide at least 90% power to test a difference of 17% versus 40% in the overall population, using a 2-sided alpha of 10%.

A Janssen Data Monitoring Committee (DMC) will review the ORR data after approximately 40, 60, 80, 100, and 120 subjects have been randomized in Phase 2. The DMC may request additional ad-hoc reviews based on the accumulating data. Enrollment of subjects may be stopped during the DMC reviews.

The accumulated ORR data from the eligible subjects will be used to estimate the posterior probability of observing an objective response (complete response or partial response) for each treatment group within each PD-L1 level. A Bayesian hierarchical logistic regression model will be used to calculate this probability. The details of the statistical model including specifications for prior distributions, decision rules to suspend accrual within a PD-L1 subgroup, hypothetical data scenarios, and operating characteristics will be provided in the Statistical Analysis Plan.

If accrual is stopped permanently in all PD-L1 subgroups, then the study is considered complete; otherwise, accrual will continued until a total of 140 subjects are randomized in Phase 2. The DMC may decide to expand any subgroup in which benefit of the combination has been demonstrated, to collect additional data within this subgroup.

The DMC will review safety data every 3 months. Enrollment of subjects may be stopped during the DMC reviews.

TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule - Assessments and Procedures for Phase 1b and Phase 2

Subjects	Assessments	Notes	Screening Phase	Treatment Phase (28d Cycle)										End of Adverse Event Evaluation Period	Posttreatment Follow-up Phase
				Cycle 1			Cycle 2 and Cycle 3			Subsequent Cycles[a]			EOT	100 days after the last dose of nivolumab (+7d)	
			Day -28 to -1	D1	D2	D15	D1	D8	D15[c]	D1	D8[b]	D15[c]	+30d (+7d)		Every 3 Months (±7d)
Subjects in Phase 1b and Group A of Phase 2 will receive JNJ-757 + nivolumab. Subjects in Group B of Phase 2 will receive nivolumab.															
Screening/Administrative															
All	Informed consent		X												
All	Eligibility criteria		X												
All	Weight, height	Height at screening only	X	X			X			X					
All	Tumor sample for mesothelin and PD-L1 testing	Archival[d] or fresh sample required; may be collected in Screening Phase or in optional Prescreening Phase with separate ICF (Section 9.1.2.2)	X												
Ph2	Stratification	Mesothelin and PD-L1 results required before stratification and randomization	X												
Study Agent Administration															
All	Nivolumab infusion	240 mg IV over ~60 min		X		X	X		X	X		X			
Ph1b + Ph2 Group A	Pre- and post- JNJ-757 infusion medications	See Section 8.1		X			X			X					

Subjects	Assessments	Notes	Screening Phase	Treatment Phase (28d Cycle)										End of Adverse Event Evaluation Period	Posttreatment Follow-up Phase
				Cycle 1			Cycle 2 and Cycle 3			Subsequent Cycles[a]			EOT	100 days after the last dose of nivolumab (+7d)	
			Day -28 to -1	D1	D2	D15	D1	D8	D15[c]	D1	D8[b]	D15[c]	+30d (+7d)		Every 3 Months (±7d)
Ph1b + Ph2 Group A	JNJ-757 infusion	1×10^9 CFU over ~60 min Administer after nivolumab infusion Peripheral IV only Observe for ~5 hr after infusion on C1D1		X			X			X					
Ph1b + Ph2 Group A	Required prophylactic antibiotic therapy	See Section 8.3.1.1											X		
Disease Evaluations															
All	CT or MRI of chest, abdomen, and pelvis	CT with IV contrast preferred The same method should be used throughout the study	X	Week 8 (±7d), then every 8 weeks (±7d) during the first year, and then every 12 weeks (±7d) thereafter until disease progression, subsequent therapy, or completion of therapy. For subjects receiving on-treatment biopsy, the first assessment will be at C3D8 (+3d).											
All	Brain MRI	Required only for subjects with known brain metastasis	X	As clinically indicated.											
Ph2	Patient-reported outcomes	NSCLC-SAQ, EORTC QLQ, PGIC, PGIS		X			X			X			X	X	
All	Survival status														X

Subjects	Assessments	Notes	Screening Phase	Treatment Phase (28d Cycle)										End of Adverse Event Evaluation Period	Posttreatment Follow-up Phase
				Cycle 1			Cycle 2 and Cycle 3			Subsequent Cycles[a]			EOT	100 days after the last dose of nivolumab (+7d)	Every 3 Months (±7d)
			Day -28 to -1	D1	D2	D15	D1	D8	D15[c]	D1	D8[b]	D15[c]	+30d (+7d)		
Safety Assessments															
All	Physical examination	Full physical exam at Screening Symptom/disease-directed at subsequent visits, with clinically relevant abnormalities reported as adverse events	X	X	X[b]	X	X		X	X		X	X	X	
All	ECOG performance status score		X	X			X			X				X	
All	Heart rate, blood pressure, temperature, respiratory rate, and O_2 saturation by pulse oximetry	On dosing days, record before nivolumab infusion, before JNJ-757 infusion, and at end of JNJ-757 infusion	X	X	X	X	X		X	X		X	X	X	
All	12-lead ECG		X	As clinically indicated											
Ongoing Subject Review															
All	Adverse events	See Section 12		Record all adverse events from signing of ICF until 100d after the last dose of study agent											
All	Concomitant therapies	See Section 8		Record all concomitant therapies from signing of ICF until 100d after the last dose of study agent											

Subjects	Assessments	Notes	Screening Phase	Treatment Phase (28d Cycle)										End of Adverse Event Evaluation Period	Posttreatment Follow-up Phase
				Cycle 1			Cycle 2 and Cycle 3			Subsequent Cycles[a]			EOT	100 days after the last dose of nivolumab (+7d)	Every 3 Months (±7d)
			Day -28 to -1	D1	D2	D15	D1	D8	D15[c]	D1	D8[b]	D15[c]	+30d (+7d)		
Laboratory Assessments															
All	Hematology Serum chemistry	C1D1: no need to repeat test(s) if performed ≤7d before first dose After C1D1: may be performed up to 3d before infusion For parameters, see Section 9.7	X	X		X	X		X	X		X		X	
All	Thyroid-stimulating hormone	Reflex to free T3, T4 if abnormal	X				X			Every other cycle					
All	Serum or urine pregnancy test (β-hCG)	Women of childbearing potential only; first test <14d before C1D1, second test <24hr before first dose	X	X			X			X				X	

Subjects	Assessments	Notes	Screening Phase	Treatment Phase (28d Cycle)										End of Adverse Event Evaluation Period	Posttreatment Follow-up Phase
				Cycle 1			Cycle 2 and Cycle 3			Subsequent Cycles[a]			EOT	100 days after the last dose of nivolumab (+7d)	Every 3 Months (±7d)
			Day -28 to -1	D1	D2	D15	D1	D8	D15[c]	D1	D8[b]	D15[c]	+30d (+7d)		
Blood Cultures															
Ph1b + Ph2 Group A	Blood cultures	Peripheral blood samples for aerobic and anaerobic cultures. If venous access device is in place, blood cultures at EOT and follow-up visits will be drawn through the device.		Predose nivo	X	Predose	Predose nivo			On Day 1 of each cycle with a disease assessment, or as clinically indicated			Before prophylactic antibiotic therapy		3, 6, 9, and 12 months after the last dose of JNJ-757
Bacterial Shedding Assessments															
All subjects in Ph1b + Ph2 Group A (substudy only)	Fecal (stool or rectal swab), urine, and saliva (aerobic and anaerobic)	Subjects with a positive shedding result will be tested every 2-4d until a negative shedding result		4hr after JNJ-757 infusion	X	Predose	Predose nivo						X		
Nivolumab Pharmacokinetics and Immunogenicity															
All	Nivolumab pharmacokinetics					Predose and ≤0.5hr postdose	Predose nivo			(C8, 12, 18, and 24) Predose nivo			X	X	
All	Nivolumab immunogenicity			Predose nivo		Predose and ≤0.5hr postdose	Predose nivo			(C8, 12, 18, and 24) Predose nivo			X	X	

Subjects	Assessments	Notes	Screening Phase	Treatment Phase (28d Cycle)										End of Adverse Event Evaluation Period	Posttreatment Follow-up Phase
				Cycle 1			Cycle 2 and Cycle 3			Subsequent Cycles[a]			EOT	100 days after the last dose of nivolumab (+7d)	Every 3 Months (±7d)
			Day -28 to -1	D1	D2	D15	D1	D8	D15[c]	D1	D8[b]	D15[c]	+30d (+7d)		
Biomarkers															
All	Cytokines	One tube - "Cytokines LADD"	X	Predose nivo and 2-4hr postdose last study drug	X	Predose	Predose nivo and 2-4hr postdose last study drug	X		(C8, 12, 18, and 24) Predose nivo	(C8, 12, 18, and 24)				
		One tube - "Cytokines Nivolumab"	X	Predose nivo and 2-4hr postdose last study drug	X	Predose and 2-4hr postdose	Predose nivo and 2-4hr postdose last study drug	X	Predose and 2-4hr postdose	(C8, 12, 18, and 24) Predose nivo	(C8, 12, 18, and 24)		X		
		One tube - "Clinical"	X	Predose nivo and 2-4hr postdose last study drug	X		Predose nivo and 2-4hr postdose last study drug	X							
		Unscheduled[e]													
All	NK panel	One tube - "NK Panel"		Predose nivo	X	Predose	Predose nivo	X	Predose	Predose nivo	X		X		
All	Immune profile	One tube - "Immune Profile"		Predose nivo	X	Predose	Predose nivo	X	Predose	Predose nivo	X		X		
All	HLA typing	One tube - "HLA"	X												

Subjects	Assessments	Notes	Screening Phase	Treatment Phase (28d Cycle)										End of Adverse Event Evaluation Period	Posttreatment Follow-up Phase
				Cycle 1			Cycle 2 and Cycle 3			Subsequent Cycles[a]			EOT	100 days after the last dose of nivolumab (+7d)	Every 3 Months (±7d)
			Day -28 to -1	D1	D2	D15	D1	D8	D15[c]	D1	D8[b]	D15[c]	+30d (+7d)		
All[b]	T-Cell proliferation/ICS/Pentamer staining, IFN-γ ELISpot	Ten tubes - "PBMC" Collection may cease or timepoints modified based on emerging data		Predose nivo		X	X	X			X		X		
All	TCR sequencing	One tube - "TCR Sequence" Samples will be collected and stored. Analysis will be triggered retrospectively based on emerging data.	X			X		C2 and should coincide with CT or MRI imaging at C3D8 only Predose			X		X		
Tumor Biopsy															
All[b]	CT- or FDG-PET/CT-guided core needle tumor biopsy	Requires separate ICF Screening biopsy ≥4 weeks after the last chemotherapy	X	Should coincide with CT or MRI imaging at Cycle 3 Day 8. If a biopsy sample is collected during the study as part of standard care, a sample should be submitted for biomarker analysis.											

β-hCG=β-human chorionic gonadotropin; CFU=colony-forming unit; C=Cycle; CT=computed tomography; d/D=day(s); ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ELISpot=enzyme-linked immunospot assay; EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EOT=end-of-treatment; FDG-PET=fluorodeoxyglucose positron emission tomography; hr=hour; HLA=human leukocyte antigen; ICF=informed consent form; ICS=intracellular cytokine staining; IFN-γ=interferon gamma; IV=intravenous; MRI=magnetic resonance imaging; nivo=nivolumab; NK=natural killer; NSCLC-SAQ=non–small-cell lung cancer self-administered questionnaire; O_2=oxygen; PD-L1=programmed death receptor ligand 1; PET=positron emission tomography; PGIC=patient global impression of change; Ph1b=Phase 1b; Ph2=Phase 2; PGIS=patient global impression of severity; TCR=T-cell receptor.

a. The start of each subsequent cycle may occur ±3 days of the scheduled day to accommodate the schedule of the site or subject.

b. All subjects in Phase 1b and required for subjects participating in the tumor biopsy substudy at selected sites approved by the sponsor in Phase 2.

c. If nivolumab is permanently discontinued but the subject continues to receive treatment with JNJ-757, then the Day 15 visits and evaluations will be optional in Cycle 3 or later.

d. Tumor samples (block or unstained tumor slides) may be either from archival tissue or newly obtained (if archival tissue is insufficient). Unstained slides must be made within 4 months prior to central laboratory assessment and stored in the dark at 2°–8°C.

e. Based on emerging data, adjustments to the planned schedule of assessments may be made by the sponsor to protect subject safety. One or more serum samples for selected cytokines (including but not limited to IFN gamma, TNF alpha, and IL-6) may be drawn after a suspected infusion-related reaction, and submitted to a central laboratory. The sponsor will closely monitor and evaluate the collection of cytokine samples and will notify the participating centers of any change to the collection requirements.

ABBREVIATIONS

β-hCG	β-human chorionic gonadotropin
actA	actin assembly protein
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
ANOVA	analysis of variance
APC	antigen presenting cells
AST	aspartate aminotransferase
BSC	best supportive care
CD4	cluster of differentiation 4
CD69	cluster of differentiation 69
CD8	cluster of differentiation 8
CFU	colony-forming unit
CNS	central nervous system
CR	complete response
CRF	case report form(s) (paper or electronic as appropriate for this study)
CRO	contract research organization
CT	computed tomography
CTLA-4	cytotoxic T lymphocyte associated antigen 4
DCR	disease control rate
DILI	drug-induced liver injury
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EGFR	epidermal growth factor receptor
EGFRvIII	epidermal growth factor receptor variant III
ELISpot	enzyme-linked immunospot assay
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
FDG-PET/CT	fluorodeoxyglucose positron emission tomography/computed tomography
FFPE	formalin fixed paraffin embedded
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HRQOL	health-related quality of life
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	hazard ratio
HTA	Health Technology Assessment
ICF	informed consent form
ICH	International Conference on Harmonisation
ICS	intracellular cytokine staining
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
IHC	immunohistochemistry
IPPI	Investigational Product Preparation Instructions
IRB	Institutional Review Board
ITT	intent to treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous

IWRS	interactive web response system
LADD	live-attenuated, double-deleted
LD_{50}	median lethal dose
LFT	liver function test
Lm	*Listeria monocytogenes*
MDSC	myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NSCLC	non–small-cell lung cancer
NSCLC-SAQ	Non-Small Cell Lung Cancer Symptom Assessment Questionnaire
ORR	objective response rate
PAP	Papanicolaou
PBMC	peripheral blood mononuclear cells
PD-1	programmed death receptor-1
PD-L1	programmed death receptor ligand 1
PD-L2	programmed death receptor ligand 2
PGIC	patient global impression of change
PGIS	patient global impression of severity
PET	positron emissions tomography
PFS	progression-free survival
PQC	Product Quality Complaint
PR	partial response
PRO	patient-reported outcome(s)
RECIST	Response Evaluation Criteria in Solid Tumors
SAQ	self-administered questionnaire
SET	Safety Evaluation Team
SIPPM	Site Investigational Product Procedures Manual
SUSAR	suspected unexpected serious adverse reaction
TCR	T-cell receptor
TNFα	tumor necrosis factor alpha
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
USP	United States Pharmacopeia

1. INTRODUCTION

JNJ-64041757 (formerly known as ADU-214 and henceforth referred to as JNJ-757) is a live-attenuated, double-deleted (LADD) *Listeria monocytogenes* (*Lm*)-based immunotherapy. JNJ-757 is engineered to encode and express human mesothelin and to efficiently deliver this tumor-associated antigen into major histocompatibility complex (MHC) Class I and Class II antigen-processing pathways. JNJ-757 is expected to be taken up specifically by phagocytic cells in the liver and spleen upon intravenous (IV) infusion. After infection and intracellular processing, JNJ-757 elicits a proinflammatory immune response resulting in the recruitment and activation of innate and adaptive effector cells, ultimately leading to systemic mesothelin-specific $CD4^+$ and $CD8^+$ T-cell immunity. In patients with adenocarcinoma of the lung, the combination of JNJ-757 with nivolumab, a programmed death receptor-1 (PD-1) immune checkpoint inhibitor, may provide a synergistic effect to improve efficacy compared with nivolumab monotherapy, which is approved for treatment of non–small-cell lung cancer (NSCLC).

For the most comprehensive nonclinical and clinical information regarding JNJ-757, refer to the latest version and addenda of the Investigator's Brochure for JNJ-757. The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

1.1.1. Current Treatment Standards and Unmet Medical Need in Advanced or Metastatic Non–Small-Cell Lung Cancer

Lung cancer is the leading cause of cancer mortality globally (WHO 2015).[43] In the United States, lung cancer is the second most commonly diagnosed cancer with more than 200,000 people diagnosed annually. It is the leading cause of cancer-related deaths and approximately 160,000 people are estimated to succumb to the disease each year (Am Cancer Society 2014).[2] Approximately 80% to 85% of the newly diagnosed cases of lung cancer are NSCLC (adenocarcinoma, squamous carcinoma, or large cell carcinoma) and 15% to 20% are small cell lung carcinoma (Molina 2008).[24]

Recently, a better understanding of the biology of NSCLC has translated into the incorporation of molecular testing and the introduction of targeted agents, including tyrosine kinase inhibitors and immunomodulatory agents that can provide significantly improved response rates and duration of response (DOR) in molecularly defined subsets of patients. However, the overall prognosis of patients diagnosed with lung cancer has not improved significantly; the 5-year survival rate remains below 18% overall and below 5% among patients with metastatic disease at diagnosis (SEER 2015).[34]

The anti-PD-1 checkpoint inhibitor nivolumab has been approved for use as monotherapy in patients with metastatic lung cancer, after failure of first-line platinum doublet therapies. The approval was based on Phase 3 results demonstrating improved overall survival compared with single-agent docetaxel in squamous NSCLC (Brahmer 2015)[6] and nonsquamous NSCLC (Borghaei 2015).[5] While nivolumab has demonstrated impressive DOR in patients with NSCLC, a majority of patients will not respond to nivolumab when it is given as monotherapy (Section 1.4). For patients with nonimmunogenic tumors, or in whom the immune system has not mounted effective anti-tumor T cell responses, the combination of nivolumab with a tumor vaccine may improve response rates, based on the complementary mechanisms of action of these agents.

1.1.2. Clinical Experience With Cancer Vaccines for Non–Small-Cell Lung Cancer

Cancer vaccines are intended to induce or increase an adaptive immune response against malignant tumor cells (Rodriguez 2013).[31] These vaccines can be divided into whole-cancer cell preparations that have been rendered replication incompetent and antigen-specific (glyco) peptides or antigen-specific recombinant proteins (Forde 2014; Mostafa 2014; Ruiz 2014).[11,25,32]

Whole-cell based vaccination approaches may be derived from individual patient tumors or allogeneic tumor cells, as in the NSCLC vaccine belagenpumatecel-1 (Lucanix®), and thus trigger adaptive immune responses against a variety of tumor-specific antigens (De Pas 2012).[8] In contrast, antigen-specific peptide or protein immunotherapies, which are frequently augmented by immunoadjuvants or immunostimulants, are designed to induce adaptive immune responses against a specific antigen overexpressed in NSCLC.

The current lack of clinical success with vaccines for NSCLC, despite multiple attempts, is believed to be caused by "immune evasion" (De Pas 2012).[8] Data derived from nonclinical disease models and clinical studies indicate that NSCLC cells are able to generate a hostile immune environment in the tumor stroma through the secretion of immunosuppressive factors and the recruitment of suppressive immune cells of myeloid origin (myeloid-derived suppressor cells [MDSC]) or lymphoid origin (ie, regulatory T cells [Treg cells]). Defects in the processing and presentation of antigens in the NSCLC microenvironment may also contribute to the limited efficacy observed with the cancer vaccines investigated thus far (Rodriguez 2013).[31]

New approaches are needed that address the mechanisms of immune evasion in NSCLC. Antigen processing and presentation defects may be overcome by more effectively engaging and activating dendritic cells and macrophages; tolerance to tumor antigens may be overcome by triggering a more robust and sustained adaptive immune response; and reducing Treg cells and MDSC may modulate the immune-suppressive tumor microenvironment (Wood 2014).[42] In addition, the induction of immune responses against unmutated tumor antigens may overcome the requirement for neoantigen burden (Wood 2014).[42]

1.2. LADD: An Immunotherapeutic Platform

LADD *Lm*-based immunotherapeutics have the potential to address the immune evasion mechanisms described in NSCLC (Wood 2014).[42] The LADD *Lm*-based platform features a deletion of 2 virulence genes (actin assembly protein [*actA*] and internalin B [*inlB*]) from the *Lm* chromosome, which leads to a >1000-fold attenuation in virulence without loss of its ability to induce potent innate and adaptive cellular immunity (Brockstedt 2004).[7] *Lm*-based immunotherapy takes advantage of the unique ability of the Gram-positive bacterium *Lm* to induce a powerful innate immune response, as well as a strong adaptive immune response, upon direct infection of antigen presenting cells (APC), with subsequent expression of the desired (multiple) tumor antigens (Wolf 2013).[41]

Within hours after IV infusion, the LADD *Lm*-based immunotherapeutic induces an inflammatory reaction reflecting activation of the innate immune response. This immediate reaction is followed over the next 7 to 10 days by an adaptive response as the T cells and B cells are activated by the dendritic cells and macrophages (ie, APC) in the liver and spleen. The direct and selective targeting of APCs by the LADD *Lm*-based platform stands in contrast to previous vaccine-based approaches, and delivers the antigen(s) encoded in its expression cassette directly to the high-efficiency MHC Class I and II antigen-presenting machinery (Wolf 2013).[41] This mechanism of action may enhance antigen processing and presentation, as well as improve T-cell priming. Using repeated infusions, a more robust and sustained cytotoxic T-cell-mediated, antigen-specific immune response may be achieved (Wolf 2013).[41] Emerging data indicate that its efficacy may be increased by the ability of *Lm* to directly reduce tumor-associated immunosuppression by inhibiting the expansion of Treg cells and MDSC in the tumor microenvironment, as well as downregulating their immunosuppressive ability (Wallecha 2013).[38] Thus, LADD *Lm*-based immunotherapeutics offer the potential to 1) repeatedly deliver tumor-specific antigens with superior efficiency, 2) enhance the emerging adaptive antitumor immune response, and 3) suppress the immune resistance of the tumor microenvironment. Several LADD *Lm*-based therapies, all derived from the ANZ-100 parental strain, are currently in development in multiple disease types, including CRS-207 (mesothelioma [NCT01675765], pancreatic cancer [NCT02004262, NCT01417000], and ovarian cancer [NCT02575807]), ADU-623 (astrocytoma [NCT01967758]), JNJ-64041809, hereafter referred to as JNJ-809 (prostate cancer [NCT02625857]), and JNJ-757 (lung cancer [NCT02592967]).

1.2.1. Clinical Experience with LADD *Lm*-based Immunotherapeutics

The most studied LADD *Lm*-based immunotherapeutic is CRS-207, which was engineered to express human mesothelin. The safety and immunogenicity of CRS-207 was first assessed in a Phase 1 study of 17 patients with mesothelin-overexpressing tumors, including NSCLC, mesothelioma, pancreatic cancer, and ovarian-cancer (Le 2012).[20] Treatment-related adverse events occurred predominantly within 4 hours from the start of the study treatment, and were indicative of a systemic innate immune response: fever, rigors/chills, nausea, dehydration, headache, and hypotension, mostly of Grade 1 or 2 severity, were reported. Transient and self-limiting laboratory abnormalities (lymphopenia, hypophosphatemia, and transaminitis) were noted and were thought to represent a temporary shift of lymphocytes and electrolytes out of the blood compartment.

Induction of proinflammatory chemokines and interferon gamma (IFN-γ), consistent with activation of innate immunity, as well as specific T-cell responses, were detected with minor differences in magnitude across all CRS-207 dose levels. Of the 3 subjects with NSCLC who were treated with CRS-207, all had tumors that expressed mesothelin in at least 50% of tumor cells. Two of 3 subjects were evaluated for listeriolysin O (an *Lm*-secreted virulence factor)-specific T-cell responses. A statistically significant increase in IFN-γ $CD8^+$ clones detected by enzyme-linked immunospot assay (ELISpot) demonstrated the subjects' ability to mount an immune response to the *Lm* platform. One subject, who received 1×10^9 colony-forming units (CFU) of CRS-207, showed a statistically significant increase in IFN-γ–producing $CD8^+$ clones by ELISpot and mesothelin staining in 100% of tumor cells. This subject had stable disease by Response Evaluation Criteria in Solid Tumors (RECIST) at 91 days and long-term survival of 26+ months (Le 2012).[20] Based on the emerging safety profile and the immunologic activity, a CRS-207 dose of 1×10^9 CFU was selected as the recommended Phase 2 dose (Le 2012).[20]

The overall safety and efficacy results obtained from the Phase 1 and Phase 2 studies conducted with CRS-207 indicate that: (1) LADD *Lm*-based immunotherapeutics are generally well tolerated at a dose of 1×10^9 CFU and have a predictable and manageable safety profile that is consistent with activation of an innate immune response; (2) LADD *Lm*-based immunotherapeutics containing a mesothelin expression cassette induce a robust and sustainable mesothelin-specific adaptive immune response; and (3) LADD *Lm*-based immunotherapeutics may extend overall survival, even in the absence of classical tumor responses (as defined by RECIST 1.1).

The STELLAR study (Safety and Therapeutic Efficacy of Live-attenuated *Listeria*/GVAX with Anti-PD1 Regimen – NCT02243371) is an ongoing Phase 2 study to evaluate survival, safety, and immune response following treatment with CRS-207, GVAX vaccine, and cyclophosphamide, with or without nivolumab, in patients with pancreatic cancer. Enrollment in this study is complete. Scheduled reviews of safety data by a Data Monitoring Committee (DMC) communicated no concerns regarding increased immunologic toxicities in the combination CRS-207 and nivolumab arm.

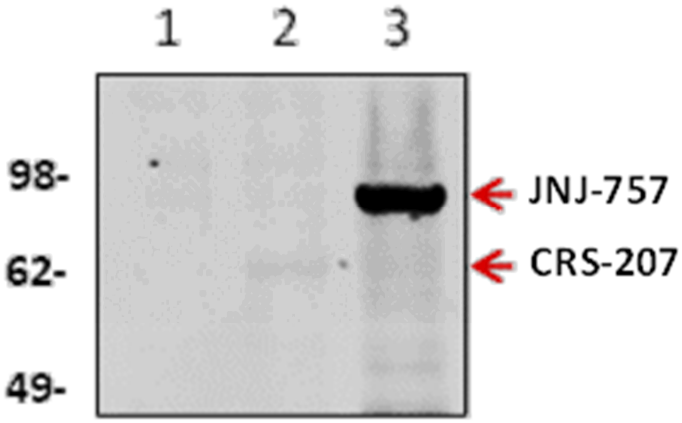
Additional studies are investigating CRS-207 in combination with chemotherapy (mesothelioma; NCT02575807) and in combination with other immunotherapies such as epacadostat (ovarian cancer; NCT02291055). Refer to the JNJ-757 Investigator's Brochure for updated data regarding CRS-207 monotherapy and combination studies. Two other combination approaches are being pursued with another *Listeria*-based platform, investigating combinations of ADXS31-142 with pembrolizumab (prostate cancer; NCT02325557) or ADXS11-001 with MEDI4736 (head and neck cancer; NCT02291055).

1.3. JNJ-757: A Lung Cancer Directed Tumor Vaccine

JNJ-757, similar to CRS-207, was engineered from the parent LADD *Lm* strain ANZ-100 to contain an ActANE-human mesothelin (hMeso) fusion expression vector. Mesothelin is fused in-frame with portions of the *actA* and epidermal growth factor receptor variant III (EGFRvIII)

proteins (ActANE), which have been shown to augment expression and secretion of the antigen proteins, and may therefore lead to improved antigen presentation by the APC (Figure 1).

Figure 1: Expression of Mesothelin by JNJ-757 Compared With CRS-207



Lane	Strain	Antigen Cassette	ActA	P60	Ratio
1	Lm11	None	-	13.67	-
2	CRS-207	Mesothelin	0.56	8.6	0.07
3	JNJ-757	EGFRvIIIx5-Mesothelin	32.23	10.9	2.96

Mesothelin, a glycosylphosphatidylinositol-linked cell surface glycoprotein, is an established target in lung cancer drug development. Mesothelin has limited expression on the surface of normal tissues, including mesothelial cells lining the pleura, peritoneum, and pericardium, but is highly expressed in several human tumors, including 50% to 70% of lung adenocarcinomas (Hassan 2008; Thomas 2016).[15,37] Based on this expression pattern, mesothelin has been targeted by numerous immune-directed approaches, including blocking antibodies (Hassan 2010),[14] antibody-drug conjugates moieties (Ordóñez 2003),[29] and immunotherapeutics (Le 2012).[20] Evolving data show mesothelin expression in lung cancer is largely cytoplasmic and thus may not be amenable to therapies targeting membrane expression (Hassan 2008; Kachala 2014).[15,19] However, this pattern of expression is not expected to impede an immune-based approach such as that elicited by JNJ-757.

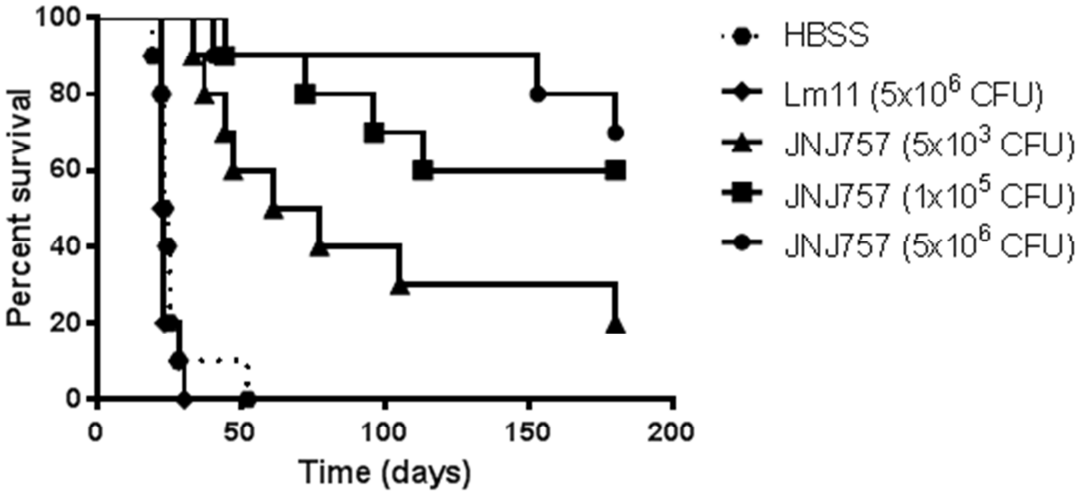
Being derived from ANZ-100, JNJ-757 has the same genetic background as CRS-207, as well as 2 other LADD *Lm*-based investigational agents, ADU-623 and JNJ-809. Emerging clinical safety data available from studies with ANZ-100, CRS-207, JNJ-809, and ADU-623 suggest that strains derived from the ANZ-100 platform share common clinical safety characteristics that appear to be unaffected by the specific antigen cassette. It is anticipated that the clinical safety characteristics described for ANZ-100 and derived strains, particularly CRS-207, which targets the same mesothelin tumor antigen, will also apply to JNJ-757. The recommended Phase 2 doses for CRS-207, JNJ-809, and JNJ-757 have all been confirmed as 1×10^9 CFU.

1.3.1. Nonclinical Experience with JNJ-757

1.3.1.1. Nonclinical in Vivo Efficacy of JNJ-757

The efficacy of JNJ-757 has been investigated in a pulmonary metastatic model of colorectal cancer-bearing mice. CT26 colon carcinoma cells engineered to express human mesothelin (CT26-hMeso; 2×10^6) injected into the tail vein of female BALB/c mice efficiently metastasize to the lungs (Francia 2011).[12] In this model, infusion of JNJ-757 three days after tumor implantation resulted in a significant dose dependent survival benefit compared with vehicle or the control LADD *Lm*-based immunotherapeutic, *Lm*11 (Figure 2).

Figure 2: Dose-dependent Therapeutic Antitumor Efficacy of JNJ-757 in Mice



CT26-hMeso-bearing mice were treated with vehicle (HBBS), empty LADD platform (*Lm*11), or JNJ-757 at the indicated doses.
HBSS=Hank's balanced salt solution.

1.3.1.2. Nonclinical Biodistribution Studies with JNJ-757

Nonclinical studies were performed to determine the biodistribution of JNJ-757 and to compare it with that of CRS-207 in the blood, spleen, liver, kidney, gall bladder, heart, lung, brain, and ovaries in BALB/c mice after IV administration. These studies determined that the highest number of JNJ-757 CFUs was observed in the liver and spleen within 24 hours after a single IV administration. This is consistent with previous studies examining the biodistribution of ANZ-100, which is the platform strain from which both JNJ-757 and CRS-207 are derived. Both CRS-207 and ANZ-100 were cleared from most tissues within 7 days after dosing. Similarly, JNJ-757 was cleared from all tissues by 7 days postinfusion. Based on these results, expression of the EGFRvIII-h Mesothelin fusion antigen by JNJ-757 does not alter the biodistribution of LADD *Lm* compared with CRS-207.

1.3.1.3. Nonclinical Toxicology Profile of JNJ-757

In vivo studies in BALB/c mice indicated that IV administration of 5×10^6 CFU of JNJ-757 (known to elicit immune responses) leads to transient alterations in hematology comparable to those seen with CRS-207. All transient changes, including lymphopenia, thrombocytopenia (nadir on Day 2), and anemia (nadir on Day 4) resolved within 7 days after dosing. Transient changes in clinical chemistry parameters after JNJ-757 infusion (ie, decreases in albumin, alkaline phosphatase, glucose, and triglycerides) were comparable in magnitude and duration to those observed with CRS-207. Based on these results, expression of the EGFRvIII-hMesothelin fusion protein by JNJ-757 does not appear to alter the hematology profile or the clinical chemistry parameters of JNJ-757 compared with the mesothelin-expressing CRS-207.

The median lethal dose (LD_{50}) of JNJ-757 is comparable to the LD_{50} of CRS-207 (4.6×10^7 CFU for JNJ-757 and 3.0×10^7 CFU for CRS-207). The results were also consistent with previous analysis done with ANZ-100.

Together these studies indicate that expression of the EGFRvIII-hMeso fusion antigen by JNJ-757 does not alter the biodistribution, hematologic parameters, clinical chemistry parameters, or the median lethality in BALB/c mice compared with CRS-207. The results support the hypothesis that changes resulting from exposure to the LADD *Lm* bacteria are independent of the expression of different fusion antigens.

1.3.2. Clinical Experience with JNJ-757

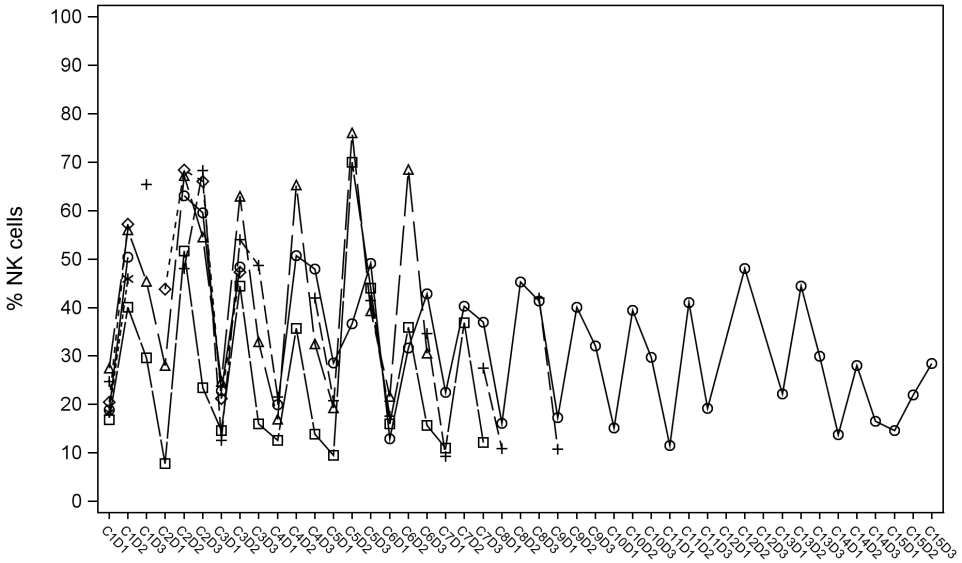
A first-in-human study (64041757LUC1001) of JNJ-757 was initiated to identify the recommended Phase 2 dose, and to evaluate the safety and immunogenicity of JNJ-757 in subjects with advanced (Stage IIIb) or metastatic (Stage IV) NSCLC (adenocarcinoma). This dose-escalation study began enrolling on 10 December 2015; enrollment is complete in the dose escalation cohorts (Part 1), with the first dose cohort (1×10^8 CFU) enrolling 6 subjects, and the second dose cohort (1×10^9 CFU) enrolling 3 subjects. With no dose-limiting toxicities (DLTs) identified in either the 1×10^8 CFU dose cohort or the 1×10^9 CFU dose cohort, the Safety Evaluation Team (SET) confirmed the safety of JNJ-757 at both doses, and identified the 1×10^9 CFU dose level as the recommended Phase 2 dose. At the time of the SET meeting data cutoff (13 October 2016), 4 subjects were still undergoing therapy, and the maximum number of cycles administered to a single subject was 14.

Preliminary safety data from the ongoing Phase 1 study of JNJ-757 were consistent with the safety profile of CRS-207. Infusions of JNJ-757 were uncomplicated, with subjects typically experiencing low-grade fevers, chills/rigors, fatigue, and nausea and vomiting, beginning approximately 1.5 hours to 3 hours after completion of the JNJ-757 infusion. These symptoms were transient, typically resolving after 24 hours, and were effectively managed with supportive measures outlined in the protocol, allowing for repeated dosing.

Preliminary biomarker data for the 6 subjects who received JNJ-757 at a dose of 1×10^8 CFU on Day 1 of each 21-day cycle in Study 64041757LUC1001 were consistent with those reported for the other LADD *Lm*-based agents ANZ-100 and CRS-207 (Le 2012),[20] confirming activation of

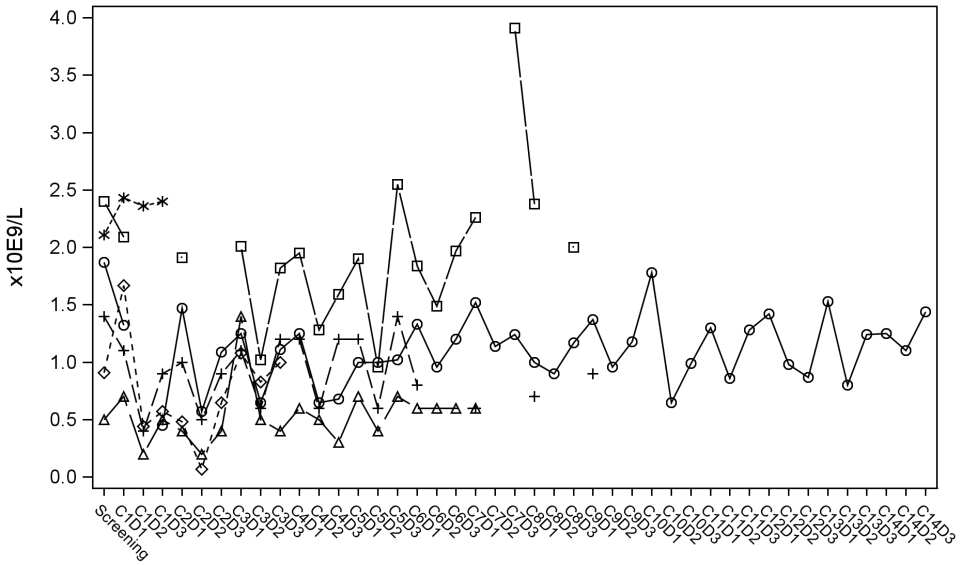
both innate and adaptive immune responses with JNJ-757 administration. Activation of the innate immune response was demonstrated by transient increases in serum cytokine levels and expression of markers of natural killer (NK) cell activation (eg, CD69) after JNJ-757 administration, even with repeated dosing (Figure 3). These increases in NK-cell activation corresponded with transient decreases in peripheral absolute lymphocyte counts, consistent with margination of activated lymphocytes out of the peripheral circulation (Figure 4), which returned to baseline by Day 3 of each cycle. Finally, preliminary ELISpot assay analyses have confirmed the potential for JNJ-757 treatment to initiate antigen-specific T-cell responses, even at the 1×10^8 CFU dose, targeting the *Lm* antigen listeriolysin O (LLO), and the tumor antigens mesothelin and EGFRvIII (Figure 5). Refer to the Investigator's Brochure for the most recent updates of safety and translational data from the Phase 1 study.

Figure 3: Natural Killer (NK) Cell Activation (CD69 Positivity) Over Time in Individual Subjects who Received JNJ-757 at a Dose of 1×10^8 Colony Forming Units on Day 1 of Each 21-Day Cycle (Study 64041757LUC1001)



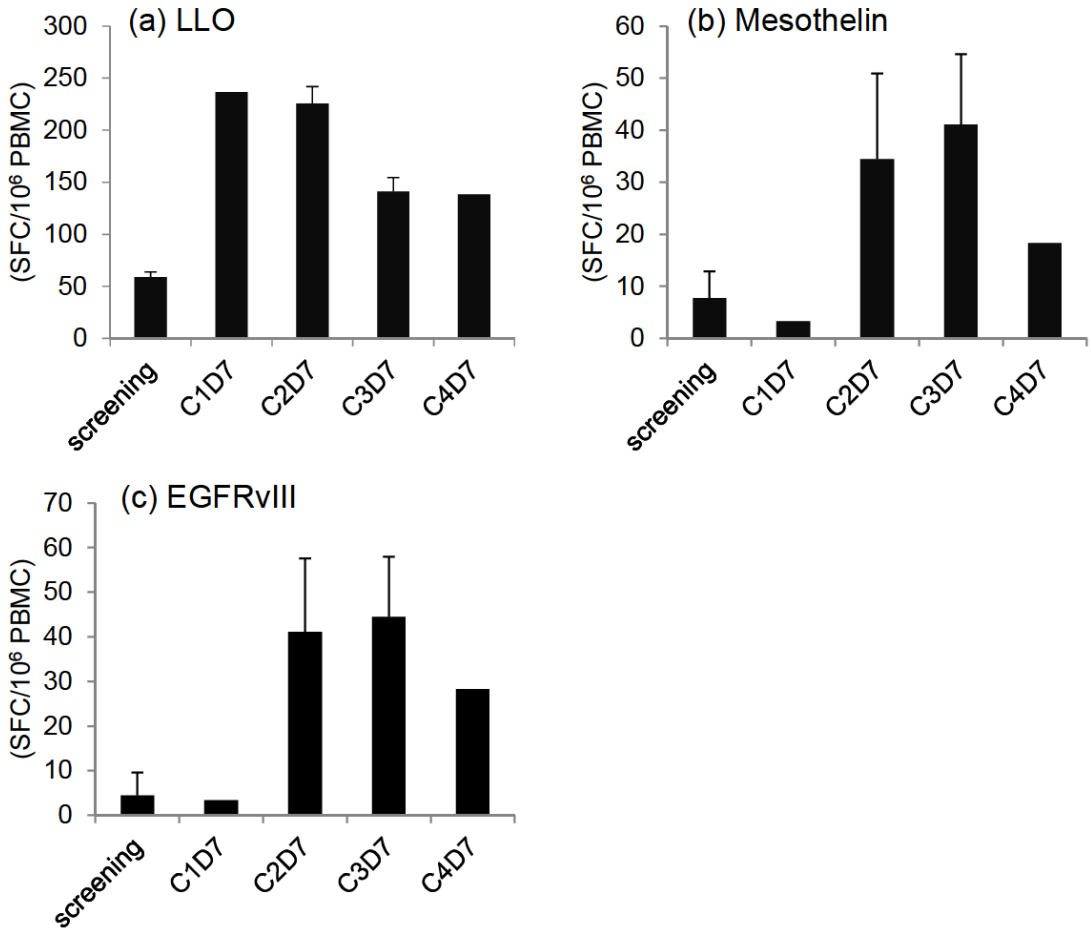
CxDy=Cycle x Day y.

Figure 4: Absolute Lymphocyte Count Over Time in Individual Subjects who Received JNJ-757 at a Dose of 1×10^8 Colony Forming Units on Day 1 of Each 21-Day Cycle (Study 64041757LUC1001)



CxDy=Cycle x Day y.

Figure 5: Preliminary Data for Adaptive Immune Response by ELISpot Over Time in a Subject who Received JNJ-757 at a Dose of 1×10^8 Colony Forming Units on Day 1 of Each 21-Day Cycle (Study 64041757LUC1001)



CxDy=Cycle x Day y; EGFRvIII=epidermal growth factor receptor variant III; LLO=listeriolysin O; PBMC=peripheral blood mononuclear cells; SFC=spot forming colonies.

1.4. Nivolumab

Nivolumab (OPDIVO®) is a fully human IgG4 PD-1 immune checkpoint inhibitor that disrupts PD-1–mediated signaling and restores antitumor immunity. Cancer immunotherapy rests on the premise that tumors may be recognized as foreign rather than as self and may be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses (Dunn 2002; Jemal 2011; Pardoll 2003; Zitvogel 2006).[9,17,30,44] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system.

T-cell stimulation is a complex process involving the integration of numerous positive as well as negative costimulatory signals in addition to antigen recognition by the T-cell receptor (Greenwald 2005).[13] Collectively, these signals govern the balance between T-cell activation and tolerance. PD-1 is a member of the CD28 family of T-cell costimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA (Nishimura 2001).[26] PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression has also been noted to inhibit T-cell activation and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice, which develop a variety of autoimmune phenotypes (Sharpe 2007).[35] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self antigens.

In vitro, nivolumab binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands programmed death receptor ligand 1 (PD-L1) and programmed death receptor ligand 2 (PD-L2) (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction. Using a cytomegalovirus re-stimulation assay with human peripheral blood mononuclear cells (PBMCs), the effect of nivolumab on antigen-specific recall response indicates that nivolumab augmented IFN-γ secretion from cytomegalovirus-specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02) (Wolchok 2009).[40]

As a single agent, the mean elimination half-life of nivolumab is approximately 25 days, with steady-state concentrations occurring by 12 weeks when 3 mg/kg is dosed every 2 weeks. The systemic accumulation is approximately 3.7-fold. In 2022 patients treated with single-agent nivolumab dosed at 3 mg/kg every 2 weeks, 11.4% patients tested positive for anti-nivolumab antibodies and 0.7% had neutralizing antibodies against nivolumab. These did not appear to affect the pharmacokinetics or incidence of infusion reactions (OPDIVO 2017).[28]

Nivolumab has been approved for the treatment of patients with NSCLC with progression during or after platinum-based chemotherapy, based on the results of Phase 3 studies in patients with squamous NSCLC (Brahmer 2015)[6] and nonsquamous NSCLC (Borghaei 2015).[5]

In the Phase 3 study of patients with nonsquamous NSCLC (Borghaei 2015),[5] nivolumab treatment improved overall survival compared with docetaxel treatment (hazard ratio [HR]=0.73; 95% CI, 0.59-0.89; p=0.002). This improvement in overall survival was associated with an increased objective response rate (ORR) in the nivolumab arm (19% vs 12%; p=0.02). Despite the improved ORR, median progression-free survival (PFS) was not improved in the nivolumab arm compared with the docetaxel arm (2.3 vs 4.2 months). The rate of PFS at 1 year, however, was higher with nivolumab treatment (19% vs 8%), which may in part reflect the greatly improved DOR observed in the nivolumab arm compared with the docetaxel arm (median, 17.2 vs 5.6 months).

The incidence of treatment-related adverse events was reduced in the nivolumab arm of each study, relative to their respective docetaxel control arm, with the greatest discrepancy observed in Grade 3-4 toxicities (≤10% in the nivolumab arm in both studies, compared with 54% and 55%, respectively, in the docetaxel control arm) (Brahmer 2015, Borghaei 2015).[5,6] The incidence of serious adverse events was reduced in the nivolumab treatment arms (7% in both nivolumab treatment arms, versus 20% and 24%, respectively, in the docetaxel arms). The most frequently experienced adverse events (≥10%) in the nivolumab arms of both studies were fatigue (16%), decreased appetite (11%), and asthenia (10%) in the squamous population, and fatigue (16%), nausea (12%), decreased appetite (10%), and asthenia (10%) in the nonsquamous population, all of which occurred more frequently in the respective control arms. Selected adverse events (those with potential immunologic causes) occurred in <10% of subjects treated with nivolumab in either study and, with the exception of infusion reactions (which occurred in ≤3% of subjects), the median time to onset was a few weeks after treatment.

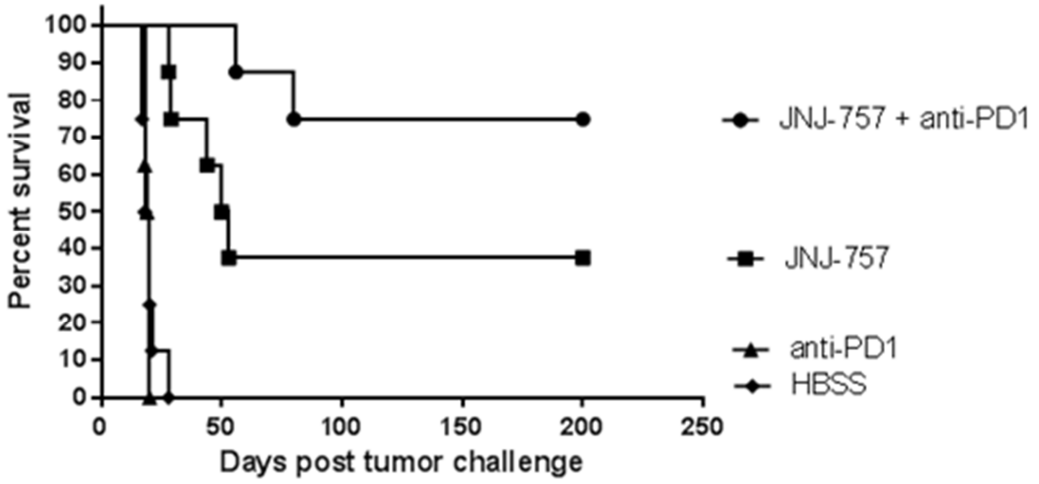
The safety profile of nivolumab monotherapy as well as combination therapy is manageable and generally consistent across completed and ongoing clinical studies with no maximum tolerated dose reached at any dose tested up to 10 mg/kg. There was no pattern in the incidence, severity, or causality of adverse events to nivolumab dose level. Most adverse events were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) adverse events. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in the management algorithms provided in Section 6.3.2. In this study, nivolumab will be administered to all subjects at the dose and schedule approved for use in patients with NSCLC. For further information regarding nivolumab refer to the locally approved label applicable to the country in which the study is being conducted.

1.5. Overall Rationale for the Study

The clinical activity of nivolumab has demonstrated the potential of immunologic approaches to provide clinical benefit to patients with lung cancer. Although nivolumab has demonstrated improved overall survival in 2 Phase 3 studies, with an ORR of 19% in each study, the majority of treated subjects do not respond to nivolumab monotherapy. There is an ongoing effort to investigate combinations that can build upon the established clinical efficacy of nivolumab and broaden the population of NSCLC patients that benefit from immunology-based therapy.

The addition of JNJ-757 may enhance the activity of nivolumab by inducing a new population of mesothelin-directed T cells. In mouse models of lung cancer, the combination of JNJ-757 and a PD-1 inhibitor prolonged survival beyond the survival seen with either agent alone (Figure 6).

Figure 6: Prolongation of Survival with the Addition of JNJ-757 to a PD-1 Inhibitor in a Nonclinical Mouse Model of Lung Cancer



HBSS=Hank's balanced salt solution.

The potential ability of JNJ-757 to promote activation of both innate and adaptive immune responses provides a strong rationale to investigate the potential clinical synergy of the combination of JNJ-757 and nivolumab. Given their complementary mechanisms of action, it is hypothesized that the combination of JNJ-757 and nivolumab will provide increased efficacy relative to either agent alone in patients with adenocarcinoma of the lung.

All subjects in this study will receive nivolumab at 240 mg over approximately 60 minutes, every 2 weeks (Day 1 and Day 15 of each 28-day cycle). For those subjects in Phase 1b and those subjects randomized to the combination arm in Phase 2, JNJ-757 will be administered after completion of each Day 1 nivolumab infusion, to ensure that transient adverse events anticipated after JNJ-757 infusion will not interfere with nivolumab administration. Based on currently available clinical data, the safety profiles for LADD *Lm*-based immunotherapy and nivolumab appear to be non-overlapping: adverse events associated with LADD *Lm*-based immunotherapy reflect proximal activation of the innate immune response (Section 1.2.1), while those associated with nivolumab are more consistent with delayed development of autoimmunity in a minority of patients (Section 1.4).

This study will monitor safety closely to ensure that subjects in both assigned treatment arms have the potential to achieve benefit from nivolumab. Safety will be assessed throughout study treatment to ensure resolution of the anticipated JNJ-757 toxicities. Surveillance cultures will be obtained during the treatment and follow-up phases, to confirm the clearance of JNJ-757 after repeated dosing, and up to 1 year after prophylactic antibiotics.

In Phase 1b, to ensure that the combination is tolerable without unanticipated toxicity, the SET will analyze the toxicity after the last subject dosed has been observed for at least 28 days. Enrollment in Phase 2 will not begin until the SET has recommended proceeding, following the evaluation of safety and translational data from Phase 1b.

In Phase 2, a Janssen DMC (see Section 11.11) will review the ORR data after approximately 40, 60, 80, 100, and 120 subjects are randomized. The DMC may request additional ad-hoc reviews based on the accumulating data. It is anticipated the first ORR analysis will occur approximately 24 weeks after the first subject in Phase 2 has been randomized. Safety data will be reviewed every 3 months. Enrollment of subjects may be stopped during the DMC reviews.

Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction. JNJ-757 elicits an innate immune response capable of activating peripheral lymphocytes, and an adaptive immune response targeting the mesothelin tumor antigen. Therefore, the hypothesis is that a combination of the agents will be more effective than nivolumab alone. As seen in Figure 6, an improvement in survival when JNJ-757 was added to an anti-PD1 was demonstrated in nonclinical models; these data provide the rationale for testing the combination in patients with lung cancer.

Based on currently available clinical data, the safety profiles for LADD *Lm*-based immunotherapy and nivolumab are anticipated to be non-overlapping. All subjects will receive active therapy with nivolumab, which has been demonstrated to improve survival in the target population. Efficacy in the 2 arms will be compared on an ongoing basis, allowing for the potential closing of PD-L1 strata in which increased efficacy of the combination is not observed. These considerations strongly support the conduct of this study in an effort to improve treatment outcomes for eligible patients with mesothelin-expressing adenocarcinoma of the lung.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESES

2.1. Objectives and Endpoints

Objectives	Endpoints/Assessments
Primary	
• To evaluate whether the efficacy of JNJ-757 combined with nivolumab is better than the efficacy of nivolumab monotherapy for subjects with mesothelin-positive relapsed/refractory Stage IIIB or Stage IV adenocarcinoma of the lung, by PD-L1 level	• Objective response rate (complete response plus partial response, based on RECIST 1.1 criteria)
Secondary	
• To compare the clinical benefit of JNJ-757 combined with nivolumab versus nivolumab monotherapy	• Disease control rate (stable disease for at least 16 weeks, complete response, or partial response) • Duration of objective response • Progression-free survival • Overall survival
• To evaluate the safety of JNJ-757 in combination with nivolumab	• Incidence of adverse events
• To correlate PD-L1 levels with clinical activity	• Disease control rate, duration of response, progression-free survival, and overall survival in biomarker subpopulations defined by PD-L1 level
• To assess the blood culture and shedding profile of JNJ-757	• Blood cultures • Bacterial shedding samples
• To assess the pharmacokinetics and immunogenicity of nivolumab	• Serum concentrations of nivolumab • Incidence of anti-nivolumab antibodies
Exploratory	
• To monitor markers of innate and adaptive immune responses	• Biologic markers of immune system activation
• To evaluate other biomarkers that may be predictive of a response	• Objective response rate in other biomarker subpopulations
• To assess patient-reported outcomes	• NSCLC-SAQ and EORTC QLQ

EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; NSCLC-SAQ=non–small-cell lung cancer self-administered questionnaire; PD-L1=programmed death receptor ligand 1; RECIST=Response Evaluation Criteria in Solid Tumors.

Refer to Section 9, Study Evaluations for evaluations related to endpoints.

2.2. Hypothesis

The primary hypothesis of the study is that the addition of JNJ-757 to nivolumab will result in a higher ORR compared with nivolumab monotherapy in at least one of the PD-L1 subgroups (<1%, 1-49%, or ≥50%) in subjects with relapsed or refractory Stage IIIB or Stage IV adenocarcinoma of the lung.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a multicenter, open-label, randomized Phase 1b/2 study to determine if subjects with advanced relapsed/refractory adenocarcinoma of the lung will derive greater clinical benefit from the addition of JNJ-757 to nivolumab.

3.1.1. Phase 1b (Safety Run-in Phase)

Phase 1b will be a safety run-in of at least 6 subjects to evaluate the incidence of dose limiting toxicities (DLTs) and demonstrate the tolerability of JNJ-757 administered in combination with nivolumab. Additional subjects (up to 30 in total) may be enrolled, as determined by the SET, to further explore safety and translational data before the decision to initiate the randomized Phase 2. All subjects in Phase 1b will receive nivolumab, administered at 240 mg IV over approximately 60 minutes, every 2 weeks, in 28-day cycles. After completion of the nivolumab infusion on Day 1 of each 28-day cycle, JNJ-757 will be administered at a dose of 1×10^9 CFU IV over approximately 60 minutes. Treatment will continue until disease progression, unacceptable toxicity, protocol violation requiring discontinuation of study treatment, withdrawal of consent, noncompliance with study procedures, or the sponsor terminates the study. The maximum allowed duration of nivolumab or JNJ-757 treatment is 2 years.

Dose-Limiting Toxicity (DLT)

To be evaluable for a DLT, a subject must receive ≥1 infusion of JNJ-757 in combination with nivolumab and either experience a DLT after initiation of JNJ-757 or be followed for ≥4 weeks without experiencing a DLT. Enrollment into Phase 1b will be staggered, with at least 72 hours between subjects for initiation of study treatment. Tolerability of the first dose should be confirmed after 72 hours and prior to treating the next subject.

A DLT includes any toxicity requiring permanent discontinuation of nivolumab (see Section 6.3.2), or a toxicity that meets any criterion for a DLT in Table 2. Toxicities will be graded for severity according to NCI-CTCAE Version 4.03. During the safety run-in phase, the DLT evaluation period is 28 days starting from the day of the first dose of study agent. Only toxicities that occur during the 28-day DLT evaluation period will be considered for DLT assessment. If for any reason, the safety of a subject is deemed not evaluable for DLT, the subject may be replaced.

Table 2: Criteria for Dose-limiting Toxicity in Phase 1b

	DLT Criteria for Non-hematologic Toxicity[a]
Fever, chills, hypotension, or dyspnea	Grade ≥3 persisting >24 hours despite best supportive care
Fatigue	Grade 3 persisting ≥7 days despite best supportive care
Nausea/vomiting	Grade ≥3 persisting >72 hours days despite best supportive care
Hypertension	Grade 4
	DLT Criteria for Hematologic Toxicity[a]
Neutropenia	Grade 3 with fever >38.5°C, or Grade 3 persisting ≥7 days despite best supportive care, or Grade 4
Thrombocytopenia	Grade 4
Anemia	Grade 4

DLT=dose-limiting toxicity.
a. Toxicity graded according to the NCI-CTCAE, Version 4.03.

Safety Evaluation Team (SET)

In Phase 1b, the SET will be responsible for reviewing the safety and translational data and for making a formal determination of whether the study will expand the Phase 1b cohort, modify the dosing regimen, or proceed to the randomized phase (Phase 2). The SET will be chaired by the sponsor study-responsible physician. Membership will include a sponsor clinical scientist, statistician, clinical pharmacologist, and the Safety Management Team chair, along with additional sponsor staff as appropriate. Additionally, the investigators who have enrolled the safety run-in subjects will participate. Documentation of meeting outcomes will be maintained by the sponsor in the Study Master File.

The following rules will be applied to determine that the combination of JNJ-757 and nivolumab is safe and tolerable:

- If <2 of 6 (or <33%) evaluable subjects in Phase 1b experience a DLT during the first treatment cycle (ie, 28 days), then the selected doses and dose regimens for JNJ-757 + nivolumab combination therapy will be considered tolerable in subjects with advanced or metastatic NSCLC.
- If ≥2 of 6 evaluable subjects (or ≥33%) experience a DLT in the first treatment cycle, then the SET will examine the totality of available safety, translational, and pharmacokinetic/PD data, and may recommend either stopping the study or expanding the Phase 1b population to evaluate alternate doses and dose regimens.

3.1.2. Phase 2 (Randomized Phase)

In Phase 2, a maximum of 140 subjects who meet all of the inclusion criteria and none of the exclusion criteria will be stratified in subgroups according to PD-L1 level (<1%, 1–49%, or ≥50%), using the DAKO PD-L1 IHC 28-8 pharmDx Assay, and then be assigned randomly (1:1) to receive JNJ-757 plus nivolumab (Group A) or nivolumab monotherapy (Group B). Throughout randomization, ORR will be monitored using a Bayesian hierarchical logistic regression model, such that more subjects may be enrolled in a PD-L1 subgroup where the combination therapy is more effective. However, subjects will always be randomized to Group A or Group B in a 1:1 ratio within that subgroup. If the combination therapy is not effective in any PD-L1 subgroup, then the study could be stopped early. In both groups, subjects will receive nivolumab, administered at 240 mg IV over approximately 60 minutes, every 2 weeks, in 28-day cycles. In Group A, after completion of the nivolumab infusion on Day 1 of each 28-day cycle, JNJ-757 will be administered at a dose of 1×10^9 CFU IV over approximately 60 minutes.

A treatment cycle will be 28 days. Disease response will be assessed with RECIST 1.1 criteria, using computed tomography (CT) scans with IV contrast (or if necessary, magnetic resonance imaging [MRI] scans) of the chest, abdomen, and pelvis at Week 8 (±7 days), then every 8 weeks (±7 days) during the first year, and then every 12 weeks (±7 days) thereafter until disease progression, subsequent therapy, or completion of therapy. For subjects receiving on-treatment biopsy, the first assessment will be at Cycle 3 Day 8 (+3 days). Mandatory core needle on-study tumor biopsy samples will be collected from subjects in Phase 1b, with core needle tumor biopsy samples being required from subjects at selected sites in Phase 2 who consent separately to an optional tumor biopsy substudy (where local regulations permit). Treatment will continue until disease progression, unacceptable toxicity, protocol violation requiring discontinuation of study treatment, withdrawal of consent, noncompliance with study procedures, or the sponsor terminates the study. However, the maximum allowed duration of nivolumab or JNJ-757 treatment is 2 years.

After discontinuing study treatment, subjects will be contacted by clinic visit or telephone every 3 months (±7 days) for survival follow-up. Among subjects who receive JNJ-757, surveillance blood cultures will be collected as follows: at the first 4 visits of the Treatment Phase; on Day 1 of any subsequent cycle with a disease assessment, or as clinically indicated; at the End of Treatment visit (before prophylactic antibiotic therapy); and 3, 6, 9, and 12 months after the last dose of JNJ-757. In the event that a subject cannot return to the study site, posttreatment surveillance blood cultures should be performed at a local laboratory and the results recorded in the subject source documentation and reported in the eCRF. After the first year, follow-up visits may be conducted by telephone contact or an alternative contact method per institution policy/practice. Information on subsequent therapies (regimen, initiation dates, and stop dates) and best response (if available) will be collected. Any new or worsening adverse events that occur and all concomitant medications that are administered between when the informed consent form (ICF) is signed and 100 days after the last dose of study agent will be recorded for subjects who enter the Screening Phase. Any subject with an ongoing adverse event will be followed beyond 100 days after the last dose of study agent, subjects will be followed for ongoing treatment-related adverse events and associated medications until all adverse events are resolved,

return to baseline, are deemed irreversible, or the subject starts subsequent anticancer therapy. Adverse events, including those reflecting laboratory abnormalities, will be graded and summarized using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03.

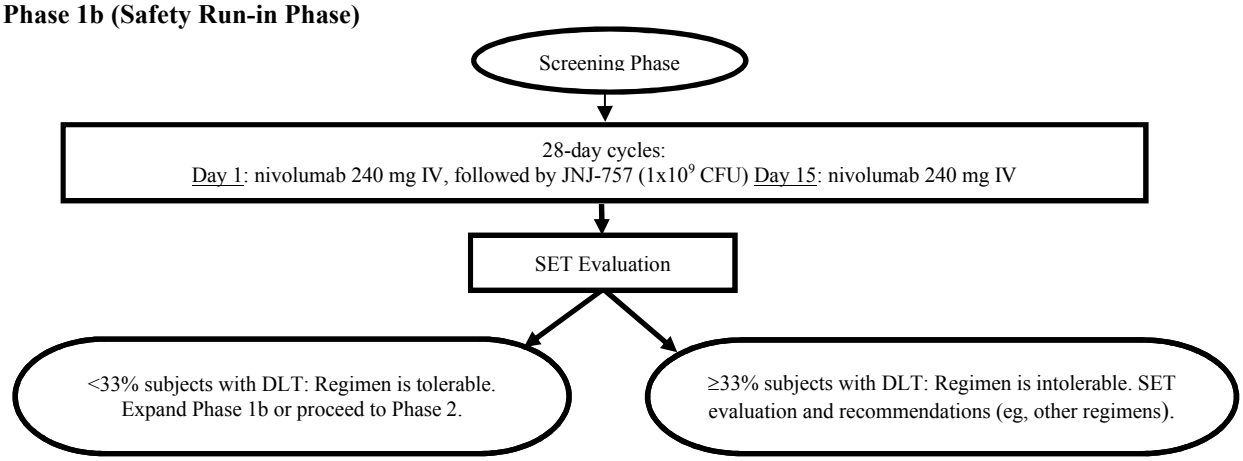
The study will consist of a Screening Phase, a Treatment Phase, and a Posttreatment Follow-up Phase. The clinical cutoff for the primary endpoint will occur 16 weeks after the last subject has been randomized. The end of the study will occur when 80% of the randomized subjects have died, or approximately 3 years after the last subject has been randomized, or the sponsor terminates the study. A study design scheme is provided in Figure 7.

Data Monitoring Committee (DMC)

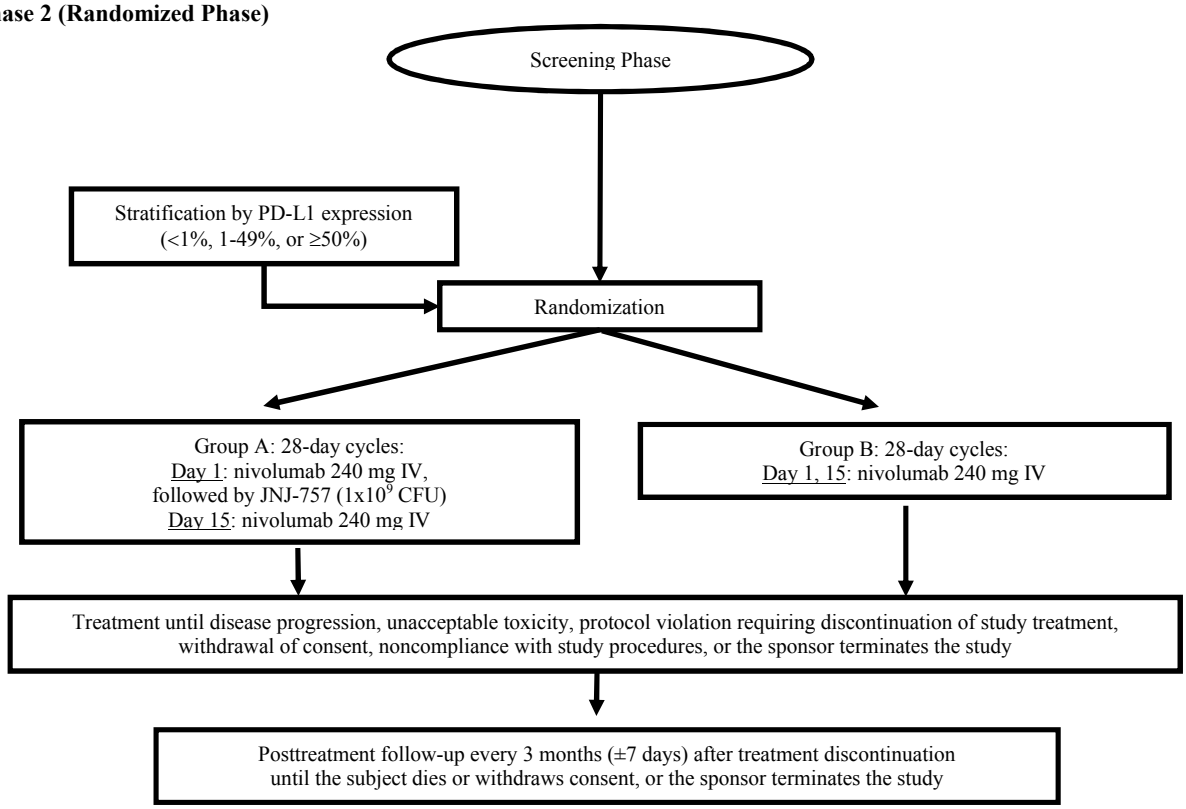
In Phase 2, a Janssen DMC (see Section 11.11) will review the ORR data after approximately 40, 60, 80, 100, and 120 subjects are randomized. The DMC may request additional ad-hoc reviews based on the accumulating data. It is anticipated the first ORR analysis will occur approximately 24 weeks after the first subject in Phase 2 has been randomized. The DMC will review safety data every 3 months. Enrollment of subjects may be stopped during the DMC reviews.

Figure 7: Study Flowchart

Phase 1b (Safety Run-in Phase)



Phase 2 (Randomized Phase)



CFU=colony-forming units; DLT = dose-limiting toxicity; PD-L1= programmed death receptor ligand 1; SET = Safety Evaluation Team.

3.2. Study Design Rationale

Rationale for Study Population

Subjects with advanced (Stage IIIb) or metastatic (Stage IV) lung adenocarcinoma who have completed treatment with platinum-based double therapy have limited treatment options. Among the most effective agents available to these subjects is nivolumab, a treatment that has been approved for use in this population and has previously demonstrated a response rate of 19% in patients with nonsquamous NSCLC (Borghaei 2015).[5] Although this response rate led to improved overall survival in patients with nonsquamous NSCLC, the majority of treated subjects do not respond to nivolumab when given as a monotherapy. Participation in a clinical study to evaluate the potential of JNJ-757 to increase the proportion of subjects receiving clinical benefit from nivolumab is a reasonable option for these patients.

Patients with adenocarcinoma of the lung that is characterized by epidermal growth factor receptor (EGFR) mutations and ALK translocation have not demonstrated similar clinical benefit with nivolumab, and they have alternative, more effective, treatment options directed toward these driver mutations. Therefore, subjects with activating EGFR mutations or ALK translocations are excluded from participation in this study (EGFR and ALK results must be confirmed in the Screening Period for all non-smokers). KRAS mutations are mutually exclusive from EGFR and ALK translocations; therefore, a positive KRAS mutation does not require ALK testing.

Rationale for Randomized Controlled Design and Dose Selection

In Phase 2, randomization will be used to minimize bias in the assignment of subjects to treatment groups. Nivolumab will be administered to all subjects at 240 mg IV every 2 weeks, in 28-day cycles. Subjects in Group A will also receive JNJ-757 1×10^9 CFU IV on Day 1 of each cycle (ie, every 28 days), after completion of the nivolumab infusion, to correspond with the schedule for nivolumab administration.

Rationale for Blood Culture and Bacterial Shedding Surveillance

As of February 2017, clinical experience with CRS-207 has identified 3 cases in which CRS-207 has been cultured from patients after the completion of their prophylactic antibiotics. The persistence of CRS-207 in all cases was identified in patients with venous access devices that were in place during their therapy with CRS-207, and therefore these cases are consistent with colonization of the venous access device. In each case the subject was successfully treated with antibiotics, without requiring the removal of the venous access device, in keeping with ASCO guidelines (Schiffer 2013).[32]

In the ongoing Phase 1 study of JNJ-757 (64041757LUC1001), shedding samples (from feces, urine, and saliva) were collected into *Listeria*-specific culture medium from subjects administered JNJ-757 at several timepoints. All assessed shedding samples tested have been negative for growth of *Lm*. Blood samples also were collected into *Listeria*-specific culture medium at several timepoints. To date, 2 subjects have had blood cultures reported as positive for *Listeria* growth on the day of the first infusion, but in both cases subsequent blood cultures

were all negative for bacterial growth, consistent with previously reported results showing rapid clearance of CRS-207 from peripheral blood after IV administration (Le 2012).[20]

Surveillance cultures will therefore be obtained in this study during the treatment and follow-up phases, to confirm the clearance of JNJ-757 after repeated dosing, and up to 1 year after prophylactic antibiotics. In those subjects with indwelling venous access devices that are present during JNJ-757 dosing, additional blood cultures will be drawn through the venous access device, to document any evidence of colonization and allow for early treatment in accordance with ASCO guidelines (Schiffer 2013).[32]

Rationale for Pharmacokinetics and Immunogenicity Assessments

This is the first study where nivolumab and LADD *Lm*-based immunotherapy will be used concomitantly. LADD *Lm*-based immunotherapy may affect the pharmacokinetics and immunogenicity of nivolumab through modulation of immune response. Hence, it is important to characterize the pharmacokinetics and immunogenicity of nivolumab with and without JNJ-757.

Rationale for Biomarker Assessments

Mesothelin-positive status in tumor samples will be assessed prospectively. Mesothelin selection will ensure that each enrolled subject has the potential to benefit from both innate and adaptive responses elicited by JNJ-757. In Phase 2, PD-L1 levels will be used to ensure equal distribution of patients exhibiting tumor characteristics that may be associated with clinical outcomes with nivolumab treatment, and to ensure that JNJ-757 is adequately assessed in each of the PD-L1 subgroups. The goal of the biomarker analyses is to evaluate the pharmacodynamics of JNJ-757 and nivolumab and aid in evaluating the drug-clinical response relationship. Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

Rationale for Patient-reported Outcomes Assessments

The patient-reported outcomes (PRO) instruments in this study are the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 and EORTC QLQ-LC13). The NSCLC-SAQ was developed in accordance with US FDA PRO Guidance and scientific best practices for use in clinical trials of NSCLC. This study will support validation efforts for this PRO. The EORTC-QLQ-C30 will be included to meet requirements for Health Technology Assessment (HTA) in Europe.

4. SUBJECT POPULATION

Adult subjects age 18 and older with advanced (Stage IIIB) or metastatic (Stage IV) adenocarcinoma of the lung are eligible for the study. Screening for eligible subjects will be performed within 28 days before Cycle 1 Day 1 (Phase 1b) or randomization (Phase 2). Central confirmation of tumor mesothelin-positive status and PD-L1 level is required in all subjects and will use samples collected either in the Screening Phase or in the optional Prescreening Phase described in Section 9.1.2.2.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. ≥18 years of age

2. Criterion modified per Amendment 2

   2.1. Disease-related criteria:

   - Histologically documented adenocarcinoma of the lung
   - Stage IIIB or Stage IV disease
   - Biopsy material available for central assessment of PD-L1 and mesothelin, consisting of either tumor block or unstained slides of tumor sample (archival tissue, or fresh biopsy if archival tissue is insufficient)
   - Mesothelin-positive status (>0% positive tumor cells), determined at a central laboratory using mesothelin immunohistochemistry (IHC) assay

3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

4. Progressive disease during or after platinum-based doublet chemotherapy, administered in the metastatic setting (continuation or switch maintenance therapy is permitted)

5. Adequate bone marrow function, defined as:

   - Absolute neutrophil count (ANC) ≥1500/μL (or 1.5×10^9/L)
   - Platelets ≥100,000/μL (or 100×10^9/L)
   - Hemoglobin ≥10.0 g/dL

   Administration of transfusions or growth factors will not be allowed within 7 days before collection of these hematology laboratory values

6. Criterion modified per Amendment 2

6.1. Adequate hepatic function, defined as:

- Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) ≤1.5 times the upper limit of normal (ULN) if no liver metastases, and ≤3×ULN with documented liver metastases
- Total serum bilirubin ≤1.5xULN (unless due to Gilbert syndrome; if so, direct bilirubin ≤3xULN)

7. Adequate renal function, defined as:

- Calculated creatinine clearance ≥40 mL/min using the Cockcroft-Gault equation

8. A woman of childbearing potential must have a negative serum (β-human chorionic gonadotropin [β-hCG]) or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of hCG) within 14 days before the first dose of nivolumab and a second negative test within 24 hours before the first dose of nivolumab.

9. Criterion modified per Amendment 2

9.1. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies.

Before Cycle 1 Day 1 (Phase 1b) or randomization (Phase 2), a woman must be either:

a. Not of childbearing potential defined as:
   - postmenopausal
     A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - permanently sterile
     Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

b. Of childbearing potential and
   - practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly)

     Examples of highly effective contraceptives include
     - user-independent methods:
       implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (s*exual abstinence is considered a highly effective method*

only *if defined as refraining from heterosexual intercourse during the entire period of risk associated with JNJ-757 or nivolumab. 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 subject.*)

- user-dependent methods:
  combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable

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 subjects participating in clinical studies. Hormonal contraception may be susceptible to interaction with the study agent, which may reduce the efficacy of the contraceptive method.

- agrees to remain on a highly effective method while on the study agent and for 5 months (female subjects) or 7 months (male subjects) after the last dose of study agent.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active,) a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

10. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction while on the study agent and for 5 months after the last dose of study agent

11. To avoid risk of drug exposure through the ejaculate (even men with vasectomies), subjects must use a condom during sexual activity while on the study agent and for 5 months (female subjects) or 7 months (male subjects) after the last dose of study agent. If the subject or their partner is a woman of childbearing potential, a condom is required along with another effective contraceptive method consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies and their partners. Donation of sperm is not allowed while on the study agent and for 7 months after the last dose of the study agent.

12. Willing and able to adhere to the prohibitions and restrictions specified in this protocol

13. Must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Criterion modified per Amendment 2

   1.1. Untreated brain metastases or other active central nervous system (CNS) metastases. Subjects with a history of brain metastasis must have completed treatment for brain metastasis for at least 28 days, and be neurologically stable and off steroids before Cycle 1 Day 1 (Phase 1b) or randomization (Phase 2).

2. Criterion modified per Amendment 2

   2.1. Tumor with activating EGFR mutation or ALK translocation (EGFR and ALK results must be confirmed in the Screening Period for all non-smokers. A positive KRAS result may be used in lieu of an EGFR or ALK result).

3. Criterion modified per Amendment 2

   3.1. More than 1 prior line of chemotherapy for metastatic disease (not including therapy given in the maintenance setting, or neoadjuvant or adjuvant therapy for locally advanced disease) (Phase 2).

4. History of symptomatic interstitial lung disease.

5. History of disallowed therapies, as follows:

   - In Phase 1b only: Prior exposure to anti-PD1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) antibody within 28 days before the first dose of study agent
   - In Phase 2 only: Prior exposure to anti-PD1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) antibody
   - History of listeriosis or vaccination with a *Listeria*-based vaccine or prophylactic vaccine (eg, influenza, pneumococcal, diphtheria, tetanus, and pertussis [dTP/dTAP]) within 28 days before the first dose of study agent
   - Chemotherapy within 28 days before the first dose of study agent
   - Radiation within 14 days before the first dose of study agent (exception: palliative radiotherapy for pain can be used ≥7 days before or after study agent)

6. Any uncontrolled active systemic infection, active noninfectious pneumonitis, or any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.

7. Any active autoimmune disease or a documented history of autoimmune disease (excluded/exception to the rule: subjects with vitiligo or resolved childhood asthma/atopy, type 1 diabetes mellitus, subjects with hypothyroidism stable on hormone

replacement, Sjorgen's syndrome, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger).

8. History of any other condition that may require the initiation of anti-tumor necrosis factor alpha (TNFα) therapies or other immunosuppressant medications during the study.

9. Known allergy to both penicillin/amoxicillin and trimethoprim/sulfamethoxazole. Subjects who are only allergic to 1 of these antibiotics are allowed to enroll.

10. Criterion modified per Amendment 2

10.1. Concurrent treatment with anti-TNFα therapies, systemic corticosteroids (prednisone dose >10 mg per day or equivalent), or other immunosuppressive drugs <14 days before Cycle 1 Day 1 (Phase 1b) or randomization (Phase 2). Steroids that are topical, inhaled, nasal (spray), or ophthalmic solution are permitted.

11. Criterion modified per Amendment 2

11.1. A positive test result by medical history for human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS).

12. History of major implant(s) or device(s), including but not limited to:

- Prosthetic heart valve(s)
- Cardiac pacemakers
- Orthopedic screws
- Metal plates
- Artificial joints and prosthetics
- Subjects with venous access devices (eg, Port-a-Cath or Mediport), arterial and venous stents, dental implants, or breast implants are permitted on the study.

13. Criterion modified per Amendment 2

13.1. History of clinically significant cardiovascular disease within 6 months of Cycle 1 Day 1 (Phase 1b) or randomization (Phase 2) including, but not limited to:

- Myocardial infarction or unstable angina
- Clinically significant ventricular arrhythmia
- Uncontrolled (persistent) hypertension: systolic blood pressure >160 mmHg; diastolic blood pressure >100 mmHg
- Deep vein thrombosis, pulmonary embolism, stroke or transient ischemic attack before the first dose of the study agent
- Congestive heart failure (New York Heart Association class III-IV [Attachment 1])
- Pericarditis/clinically significant pericardial effusion
- Myocarditis
- Endocarditis

14. Known active or chronic hepatitis B or hepatitis C as demonstrated by hepatitis B surface antigen (HBsAg) positivity and/or anti-hepatitis C virus (HCV) positivity, respectively. Subjects with clinically active or chronic liver disease, including liver cirrhosis, are also excluded.

15. Criterion modified per Amendment 2

    15.1. Active second malignancy within 2 years prior to Cycle 1 Day 1 (Phase 1b) or randomization (Phase 2). Exceptions that do not require a 2-year remission include: nonmelanoma skin cancer; cervical carcinoma in situ on biopsy; squamous intraepithelial lesion on Papanicolaou (PAP) smear; localized prostate cancer (Gleason score <6); resected melanoma in situ; or ductal carcinoma in situ.

16. Evidence of active viral, bacterial, or systemic fungal infection requiring systemic treatment within 7 days before the first dose of the study agent. Subjects requiring any systemic antiviral, antifungal, or antibacterial therapy for active infection must have completed treatment no less than 7 days before the first dose of the study agent.

17. Known allergies, hypersensitivity, or intolerance to JNJ-757 or its excipients (refer to Investigator's Brochure).

18. Known allergies, hypersensitivity, or intolerance to nivolumab or its excipients (refer to locally approved label).

19. Criterion modified per Amendment 2

    19.1. Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 28 days before Cycle 1 Day 1 (Phase 1b) or randomization (Phase 2).

20. Currently enrolled in another interventional study.

21. Pregnant, breast-feeding, or planning to become pregnant while enrolled in this study, within 5 months after the last dose of study agent.

22. Plans to father a child while enrolled in this study, within 7 months after the last dose of study agent.

23. Any serious underlying medical or psychiatric condition (eg, alcohol or drug abuse), dementia or altered mental status or any issue that would impair the ability of the subject to receive or tolerate the planned treatment, to understand informed consent or that in the opinion of the investigator would contraindicate the subject’s participation in the study or that would confound the results of the study.

24. Major surgery (eg, requiring general anesthesia) within 2 weeks before screening, not fully recovered from surgery, or surgery planned during the time the subject is expected to participate in the study. Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate after consultation with the medical monitor.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation: Subject must agree to avoid intimate contact with individuals known to be at high risk of complications from listeriosis (eg, newborn infants, pregnant women, immunocompromised individuals) during the course of study treatment until completion of the mandatory antibiotic regimen.

Subjects with indwelling venous access devices in Phase 1b and Group A of Phase 2 must not have their device accessed for at least the first 4 days at the beginning of each cycle, must consent to blood cultures through the device at the End-of-Treatment visit and follow-up visits, and must have their first dose of posttreatment prophylactic antibiotic at the End-of-Treatment visit administered intravenously through the device.

If the subject is engaged in sexual activity, a condom is required. If the subject or their partner is a woman of childbearing potential, a condom and an additional highly effective contraceptive method should be used. The additional method of contraception should be consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies. Highly effective forms of contraception include:

- established use of oral, injected, or implanted hormonal methods of contraception;
- placement of an IUD or IUS;
- barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; or
- vasectomy

These precautions are required during the Treatment Phase and for 5 months (female subjects) or 7 months (male subjects) after the last dose of study agent.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Central randomization will be implemented in Phase 2 of this study. Upon entry, eligible subjects will be randomly assigned 1:1 to treatment Groups A and B based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified according to PD-L1 level (<1%, 1–49%, or ≥50%).

The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study agent kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Blinding

As this is an open-label study, blinding procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

6.1. Study Agent Administration

For the purposes of this study, "study agent" refers to JNJ-757 and nivolumab, and a treatment cycle refers to 28 days. After Cycle 2, the start of each subsequent cycle may occur ±3 days of the scheduled day to accommodate the schedule of the site or subject.

All subjects will receive nivolumab at 240 mg as an IV infusion over approximately 60 minutes, on Day 1 and Day 15 of each 28-day cycle. Normal saline (0.9% sodium chloride) should be used to flush the peripheral IV line after administration of nivolumab.

Subjects in Phase 1b and in Group A of Phase 2 will receive JNJ-757 at a dose of 1×10^9 CFU, administered as an IV infusion, after completion of the nivolumab infusion on Day 1 of each 28-day cycle. The JNJ-757 infusion will be administered over approximately 60 minutes, with the option to increase the duration of the infusion if clinically indicated. Normal saline (0.9% sodium chloride) should be used to flush the peripheral IV line to ensure that the entire amount of JNJ-757 is delivered to the subject. Additional details are provided in the Site Investigational Product Procedures Manual (SIPPM) and the Investigational Product Preparation Instructions (IPPI).

On Day 1 of each cycle, nivolumab and JNJ-757 must be administered through a peripheral vein catheter; administration through a central venous catheter is prohibited. On Day 15 of each cycle, nivolumab may be administered through a peripheral or central venous catheter.

6.2. JNJ-757 Dose Modifications

Any change to the JNJ-757 infusion (dose interruption or change in infusion rate) and the reason for the change must be recorded in the subject's electronic case report form (eCRF). For a dose interruption, the duration of the interruption is to be recorded.

6.2.1. Cycle Delay

On the first day of each new cycle and before administration of nivolumab/JNJ-757, the investigator will evaluate the subject for any toxicity at least possibly related to JNJ-757 that would preclude/delay retreatment with JNJ-757. At a minimum, the laboratory parameters in Table 3 must be met before administration of JNJ-757.

Table 3: Laboratory Criteria for JNJ-757 Treatment After Cycle 1

Hematology	
Absolute neutrophil count	≥1000/μL (or ≥1.0×10^9/L) with or without hematopoietic growth factors
Platelet count	≥75,000/ μL (or ≥75×10^9/L) with or without transfusion

JNJ-757 should be administered on Day 1 of each 28-day treatment cycle, after completion of the nivolumab infusion. A subject who skips a dose of JNJ-757 should continue to receive nivolumab as scheduled and restart JNJ-757 administration on Day 1 of the next nivolumab treatment cycle. Doses of JNJ-757 may be skipped as many times as needed until any toxicity that is at least possibly related to JNJ-757 recovers to a level that allows administration of JNJ-757 on Day 1 of the next nivolumab treatment cycle.

If a delay in nivolumab treatment is needed for one of the reasons described in Section 6.3.2, then JNJ-757 should be delayed until the next Day 1 dose of nivolumab is administered. If JNJ-757 treatment is stopped completely, then the subject may continue to receive nivolumab treatment after consultation with the medical monitor if, in the investigator's opinion, the subject may benefit from nivolumab monotherapy without JNJ-757.

6.2.2. Monitoring During and After JNJ-757 Administration

Monitoring During JNJ-757 Administration

Subjects must remain at the infusion center for monitoring for 5 hours after the end of the first infusion of JNJ-757. The 5-hour observation period may be reduced to a minimum of 2 hours starting with Cycle 2 if, in the opinion of the investigator, 1) the previous infusion was well tolerated without dose interruption or additional supportive measures; and 2) the subject's expected toxicities can be managed as an outpatient.

Although not anticipated, if a subject experiences signs and symptoms consistent with inflammatory cytokine release (eg, Grade 2 or 3 fever, chills/rigor, nausea, vomiting, hypotension) during JNJ-757 administration, the infusion should be stopped immediately and best supportive care (BSC) should be initiated.

- In the event that these acute, adverse events occurring during JNJ-757 administration resolve within ≤2 hours with BSC, the infusion may be restarted at a 50% reduced flow rate. The subject should be monitored for approximately 5 hours after the end of the infusion. Hospitalization for additional monitoring may be considered.
- In the event that these acute, adverse events occurring during JNJ-757 administration are prolonged (lasting >2 hours to resolve despite BSC), the infusion must not be restarted. Hospitalization for additional monitoring should be considered.
- In the event of a second acute adverse event after a previous stop and restart, the JNJ-757 infusion cannot be restarted a second time. The subject should be monitored for at least 5 hours after the discontinuation of the infusion. Hospitalization for additional monitoring may be considered.

Monitoring After JNJ-757 Infusion

After the observation period is completed, or if the observation period exceeds the clinic hours, hospitalization may be considered, at the investigator's discretion, to facilitate continued safety monitoring. These admissions for observation should not be reported as serious adverse events.

6.3. Nivolumab Dose Modifications

Each dose interruption for nivolumab, the reason for the interruption, and the duration of the interruption must be recorded in the eCRF.

6.3.1. Dose Change

No dose reductions or dose escalations are permitted for nivolumab.

6.3.2. Cycle Delay

Subjects in both groups will receive nivolumab at the dose and schedule approved for single-agent treatment of patients with adenocarcinoma of the lung. Adverse events involving immune-mediated toxicities have been reported with nivolumab (see Section 8.3.2); subjects should be monitored for these toxicities, which may be indications for cycle delays as well as treatment discontinuation. Guidelines for withholding nivolumab doses or permanent discontinuation of nivolumab, based on the approved labeling, are described in Table 4.

Criteria to Resume Treatment

A subject for whom nivolumab treatment is delayed should be assessed at least weekly for resolution of toxicity. Nivolumab treatment may be restarted at the same dose and schedule (240 mg by IV infusion every 2 weeks) when the adverse event returns to Grade 0 or 1 (or to Grade 2 for drug-related fatigue). Drug-related pulmonary toxicity, diarrhea, or colitis must resolve to baseline before nivolumab treatment is resumed. Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the medical monitor. If nivolumab administration is delayed for >6 weeks due to toxicity, the subject must permanently discontinue nivolumab treatment.

If nivolumab treatment is delayed, then JNJ-757 should be delayed until the next Day 1 dose of nivolumab is administered, unless an additional delay in JNJ-757 treatment is needed for one of the reasons described in Section 6.2.1. If nivolumab treatment is stopped completely, then the subject may continue to receive JNJ-757 treatment after consultation with the medical monitor if, in the investigator's opinion, the subject may benefit from JNJ-757 monotherapy without nivolumab.

Table 4: Nivolumab Cycle Delay or Discontinuation for Adverse Events

Adverse Event	Severity	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose[a]
	Grade 3 or 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 1 or 2 pneumonitis	Withhold dose[a,b]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatic toxicity	AST or ALT >3 and ≤5xULN, or total bilirubin >1.5 and ≤3xULN	Withhold dose[a]
	AST or ALT >5xULN, or total bilirubin >3xULN Concurrent Grade 2 AST/ALT and total bilirubin	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 diabetes mellitus	Grade 3 hyperglycemia	Withhold dose[a]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and renal dysfunction	Serum creatinine >1.5 and ≤6xULN	Withhold dose[a]
	Serum creatinine >6xULN	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[a]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Pancreatitis	Grade 3 pancreatitis	Withhold dose[a,c]
	Grade 4 pancreatitis	Permanently discontinue
Uveitis	Grade 1 or 2 uveitis	Withhold dose[a,d]
	Grade 3 or 4 uveitis	Permanently discontinue[d]
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse event[e] First occurrence Recurrence of same Grade 3 adverse event	 Withhold dose[a] Permanently discontinue
	Life-threatening or Grade 4 adverse event[f]	Permanently discontinue
	Requirement for prednisone ≥10 mg per day or equivalent for >12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse event lasting ≥12 weeks	Permanently discontinue
	Any adverse event, laboratory abnormality, or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication	Withhold dose
	Any Grade 3 non-skin, drug-related adverse event lasting >7 days[g]	Permanently discontinue

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.

[a] Resume treatment when adverse event returns to Grade 0 or 1 (treatment can be resumed if AE is Grade 2 drug-related fatigue). Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before nivolumab treatment is resumed. Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the medical monitor.

[b] Any Grade ≥ 2 drug-related pneumonitis or interstitial lung disease that does not resolve following dose delay and systemic steroids

[c] Any Grade 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The medical monitor should be consulted for such Grade 3 amylase or lipase abnormalities.
[d] Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment should result in discontinuation of nivolumab.
[e] Grade 3 lymphopenia does not require dose delay.
[f] With the exception of Grade 4 neutropenia ≤ 7 days, Grade 4 lymphopenia or leukopenia, and isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
[g] Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation. Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation. Grade 3 drug-related thrombocytopenia > 7 days associated with clinically significant bleeding requires discontinuation; other Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation.

Toxicity grades are per NCI-CTCAE Version 4.0.3.
Source: Table based on OPDIVO (nivolumab) package insert (Revised February 2017).[28]

7. TREATMENT COMPLIANCE

Nivolumab and JNJ-757 will be administered as IV infusions by qualified staff. The details of each administration will be recorded in the eCRF.

8. PRESTUDY AND CONCOMITANT THERAPY

All concomitant therapies will be recorded in the eCRF and in source documents throughout the study beginning with signing of the ICF and continuing until 100 days after the last dose of study agent for subjects who enter the Screening Phase. Beyond 100 days, concomitant therapies will be collected if the subject is being followed for treatment-related adverse events (see Section 3.1.2).

8.1. Permitted Medications

8.1.1. JNJ-757 Preinfusion Medications

Mandatory and optional medications to be administered before the JNJ-757 infusion are outlined in Table 5. If symptoms consistent with a systemic innate immune response to bacterial infection (eg, fever, chills/rigor, nausea, vomiting, hypotension) are observed in Cycle 1 or Cycle 2, the premedication regimen may be modified at the investigator's discretion. As outlined in Table 5, premedication with H_2-antagonists and antiemetics may be introduced in the case of specific, severe, or prolonged toxicities.

Table 5: Mandatory and Optional Concomitant Medications to be Administered with JNJ-757

Premedication	Dose	Administration	Cycle 1	Cycle 2	Subsequent Cycles
Mandatory Premedications					
Saline	500 to 1000 mL[a]	IV: bolus starting ~1 hour before JNJ-757	X	X	X
Antihistamine	Diphenhydramine 50 mg	Oral: ≥1 hour before study JNJ-757 or IV: start ≥30 minutes before JNJ-757	Not recommended	X[b]	X[b]
Antipyretic	Acetaminophen 650 to 1000 mg	Oral: ≥30 minutes before JNJ-757	X	X	X
Optional Premedications					
H_2-antagonist	Ranitidine 50 mg	IV: start ~30 minutes before JNJ-757	Not allowed	Optional[c]	Optional[c]
Antiemetic	Ondansetron 16 mg	IV: start ~30 minutes before JNJ-757	Not allowed	Optional[c]	Optional[c]

IV=intravenous.

[a] If the nivolumab infusion is administered with saline, the volume of that infusion may be included in the calculation of total saline to be infused before JNJ-757 administration.

[b] If clinical signs and symptoms indicative of a systemic innate immune response to bacterial infection are observed in Cycle 1, prophylactic antihistamine treatment should be introduced in subsequent cycles.

[c] In the absence of nausea and vomiting in Cycle 1 requiring supportive care during or after study agent administration, the prophylactic use of H_2-antagonists and antiemetics in Cycle 2 and subsequent cycles is not recommended.

8.1.2. JNJ-757 Postinfusion Medications

The anticipated symptoms associated with JNJ-757 treatment are thought to arise from the release of cytokines occurring within hours of the infusion, and typically resolve within 24 hours. At the discretion of the investigator, postinfusion medications (Table 6 should be used during or immediately (ie, within 24 hours) after JNJ-757 administration for subjects experiencing symptoms consistent with systemic innate immune response to bacterial infection. Postinfusion medications may be continued for up to 48 hours after the infusion, as needed. Hospitalization for monitoring after JNJ-757 administration may be considered, if clinically indicated.

Table 6: Postinfusion Medications for Systemic Innate Immune Response to Bacterial Infection

Adverse Event[a]	Supportive Therapy
Allergic reaction Grade 1 Grade ≥2	 Diphenhydramine 50 mg orally or IV Dexamethasone 4 mg orally or IV twice daily
Fever (≥38°C or ≥100.4°F)	Ibuprofen 400 to 800 mg orally, alternated with acetaminophen 650 to 1000 mg orally, every 4 hours
Rigors	Warming blanket, nonsteroidal anti-inflammatory drug (eg, ibuprofen, aspirin, naproxen), or narcotic (eg, morphine, meperidine) according to institutional standards
Hypotension	Saline 500 to 1000 mL IV bolus during the postinfusion observation period
Nausea/vomiting	Ondansetron 8 mg, according to institutional standards

IV=intravenous.
[a] Adverse event during or after the JNJ-757 administration.

8.1.3. Palliative Radiation

Only non-target bone lesions without lung tissue included in the planned radiation field may receive palliative radiotherapy. There should be a 1-week window between study agent administration and any palliative radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and adverse events should resolve to Grade ≤1 prior to resuming study agent. Details of palliative radiotherapy should be documented in the source records and eCRF. Details in the source records should include the following: dates of treatment, anatomical site, dose administered and fractionation schedule, and adverse events. If warranted, symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression.

8.2. Prohibited Medications

During the clinical study, subjects are anticipated to continue the use of prescribed medications documented during the screening procedures, consistent with study inclusion and exclusion criteria (Section 4.1 and Section 4.2). The following therapies are prohibited during the Treatment Phase (if administered, the subject may be removed from the study). The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered, to discuss the indication for these agents, and the suitability of the subject for further study treatment:

- Anti-TNFα therapies or other immunosuppressants (including prednisone doses >10 mg/day or equivalent) (see Section 8.3.1.1)
- Any anticancer chemotherapy or nonstudy immunotherapy (approved or investigational)
- Another investigational product
- Vaccinations (exception: killed vaccine for seasonal influenza is allowed)

In addition, the following therapies should not be administered during the Treatment Phase unless medically necessary. Approval must be obtained from the sponsor's medical monitor for a subject to continue dosing if therapy is given concurrently with the study agent:

- Surgical procedure or intervention requiring general anesthesia or deep sedation

- Systemic antibiotics (except the required antibiotic prophylaxis for *Listeria* infection after the last dose of JNJ-757 [Section 8.3.1.1])

The use of systemic antibiotics and conditions that require surgical intervention may put the subject at increased risk from further study therapy. If these interventions are medically required during the study, the study investigator must notify the sponsor's medical monitor immediately to discuss the appropriateness and timing of any further study treatment.

8.3. Guidelines for the Prevention and Management of Toxicities

8.3.1. JNJ-757

A majority of subjects receiving treatment with the LADD *Lm*-based immunotherapeutic CRS-207 (Phase 1: ~80%; Phase 2: ~60%), experienced clinical symptoms of a systemic innate immune response to bacterial infection including fever, chills/rigors, nausea, vomiting, and hypotension (Le 2012; Le 2015).[20,21] Results from the Phase 1 study of JNJ-757 (64041757LUC1001) are consistent with those from the CRS-207 studies. Clinical safety data derived from Phase 1 and 2 studies of CRS-207 indicate that timely initiation of supportive therapeutic measures ensured efficient clinical management of the symptoms. Moreover, a reduction of both the frequency and severity of these specific treatment-related adverse events was achieved when supportive care was provided before CRS-207 administration that was also used in the Phase 1 study of JNJ-757 and will be used in this study (Section 8.1.1).

8.3.1.1. Prophylaxis Against *Listeria* Infection After the Last Dose of JNJ-757

After the last JNJ-757 infusion, mandatory prophylactic antibiotic therapy must be administered for 7 days with amoxicillin [redacted] (or trimethoprim/sulfamethoxazole [redacted] for subjects with penicillin allergy). The antibiotics should be initiated on the day of the End-of-Treatment visit, after collection of End-of-Treatment blood cultures (through peripheral vein and indwelling venous access device, if applicable) have been collected. Subjects who have a venous access device should have their first dose of antibiotic administered as an intravenous dose through the venous access device ([redacted] ampicillin or [redacted] trimethoprim/sulfamethoxazole [based on trimethoprim component] for subjects with penicillin allergy), followed by 6 days of oral antibiotic prophylaxis.

Immunosuppressants such as anti-TNFα therapies or high-dose prednisone (>10 mg/day) are prohibited concomitant medications. If use of immunosuppressants is clinically indicated during therapy with JNJ-757 or nivolumab, hold further dosing with study treatment, and initiate oral antibiotic prophylaxis for listeriosis for the duration of the immunosuppressant therapy (recommended: oral [redacted] a week). Prophylactic antibiotics should be initiated even when immunosuppressants are utilized after JNJ-757 therapy has been completed.

In addition, subjects requiring an emergent placement of a prohibited implanted device (see Section 4.2) while on therapy will discontinue JNJ-757 treatment and will receive an intravenous antibiotic course appropriate for the treatment of listeriosis for 14 days (see Section 8.3.1.2) as prophylaxis against colonization of the implant.

8.3.1.2. Treatment for *Listeria* Infection

Appropriate bacterial cultures, including blood cultures, should be performed when a *Listeria* infection is suspected. Specifically, culture of cerebrospinal fluid should be obtained for subjects with suspected CNS infection. In such instances, analysis of cerebrospinal fluid should also include cell count, protein, glucose, Gram staining, and polymerase chain reaction analysis to determine the strain involved. In subjects who meet the following criteria while on study, antibiotic therapy should be initiated:

- Fever Grade ≥4 (>40.0ºC [104ºF] for >24 hours)
- Persistent fever >39ºC (102.2ºF) for ≥48 hours
- Infection Grade ≥3
- Evidence of abscess
- Hypotension Grade ≥3
- JNJ-757 isolation in culture from any site (other than blood) that is normally sterile (eg, cerebrospinal fluid, joint fluid)
- Clinical signs or symptoms (eg, meningeal symptoms) or unexpected positive blood culture that in the judgment of the investigator necessitates starting antibiotics.
- Subjects requiring an emergent placement of a prohibited implanted device (see Section 4.2)

In addition, the identification of any predose, end-of-treatment, or post-therapy surveillance cultures (peripheral collections only) as positive for listeriosis, should result in the initiation of an IV antibiotic treatment with a regimen appropriate for the treatment of (wild-type) listeriosis for 14 days. If, however, cultures obtained from venous access devices are positive after prophylactic antibiotic therapy, consistent with device colonization, the treating physician can consider administering IV antibiotics, through the device in accordance with ASCO guidelines, in an effort to salvage the venous access device (see Section 8.3.1.1).

If a *Listeria* infection is suspected or confirmed, 1 of the following IV antibiotic regimens is preferred for a minimum of 7 consecutive days. The regimen is determined according to whether the subject has a penicillin/amoxicillin allergy.

- In subjects **without** a penicillin/amoxicillin allergy, initial doses of systemic (IV) ampicillin should be approximately [redacted] with gentamicin [redacted] in divided doses every [redacted] (with adjustments according to renal function and serum levels of gentamicin).
- In subjects **with** a penicillin/amoxicillin allergy, initial IV doses of trimethoprim/ sulfamethoxazole should be [redacted] based on trimethoprim component) divided [redacted] per day, with gentamicin [redacted] in divided doses every [redacted] (with adjustments according to renal function and serum levels of gentamicin).

If clinically indicated, use of broader-spectrum antibiotic treatment should be implemented, as appropriate for the clinical situation, in accordance with standard institutional practice.

8.3.2. Nivolumab

Therapy with immuno-oncology agents such as nivolumab may lead to specific immune-mediated adverse events that differ in nature, severity, and duration compared with adverse events caused by agents with a different mode of action. Early recognition and management of these events may mitigate more severe toxicity. However, differential diagnoses including noninflammatory etiologies, as well as the effects of the underlying malignant disease or concomitant medication, should be evaluated according to standard medical practice. Management algorithms have been developed to assist investigators in assessing and managing specific immune-mediated adverse events, as summarized above in Table 4 and in the following sections. Guidelines for nivolumab dose delays are provided in Section 6.3.2.

8.3.2.1. Gastrointestinal Adverse Events

Diarrhea and colitis have been observed in subjects receiving nivolumab (Table 7). Early recognition and treatment of diarrhea and colitis are critical to their management. Subjects should be advised to seek immediate medical evaluation if they develop new-onset diarrhea, blood in stool, or severe abdominal pain or if they have worsening of baseline diarrhea. In subjects with pre-existing diverticulosis and/or diverticulitis receiving concomitant medication with corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioid analgesics together with nivolumab, diverticular perforation has been observed.

Table 7: Management and Follow-up of Immune-mediated Gastrointestinal Adverse Events

Grade 1	Symptomatic treatment according to institutional standards Close monitoring; instruct subject to report worsening immediately and treat as Grade ≥2
Grade 2	**≤5 days:** Symptomatic treatment according to institutional standards **>5 days or recurrence:** 0.5–1.0 mg/kg/d methylprednisolone.; consider prophylactic antibiotics; **Persistence or worsening despite steroids >3 days:** treat as Grade 3/4 **Improvement to ≤Grade 1:** taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, resume study therapy per protocol
Grade 3	**Immediately:** 1.0–2.0 mg/kg/d methylprednisolone IV; consider prophylactic antibiotics and lower endoscopy **Persistence >3 days or recurrence:** add infliximab 5 mg/kg (if no contraindication such as perforation or sepsis) **Improvement to ≤Grade 2 within ≤3 days:** taper steroids over at least 1 month
Grade 4	The oral corticosteroid equivalent of the recommended IV dose may be considered for ambulatory subjects; the lower bioavailability of oral corticosteroids need to be considered. Clinical caution should be exercised, for subjects receiving concomitant medications of corticosteroids, NSAID, or opioid analgesics. In addition, be vigilant for signs and symptoms of potential perforation, especially in subjects with known diverticular disease. Narcotics should be used with caution as pain medicines may mask the signs of colonic perforation.

For nivolumab dose modification guidelines, refer to Table 4.

8.3.2.2. Hepatic Adverse Events

Hepatic AEs, including elevated liver function tests (LFTs) and, infrequently, drug-induced liver injury (DILI) have been observed after treatment with nivolumab (Table 8). Early recognition and treatment of elevated LFTs and DILI are critical to their management. Subjects should be advised to seek medical evaluation if they notice jaundice (yellow appearance of skin or sclera) or if they develop bruising, bleeding, or right-sided abdominal pain. Physicians should monitor LFTs prior to each nivolumab treatment.

Table 8: Management and Follow-up of Immune-mediated Hepatic Adverse Events

Grade 1	Monitor LFTs as outlined in the protocol **Worsening:** treat as Grade ≥2
Grade 2	Monitor every 3 days **Returning to baseline:** resume per protocol monitoring **LFT elevation >5 days or worsening:** 0.5 – 1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics **LFT return to ≤Grade 1 or baseline:** taper steroids over at least 1 month; resume routine monitoring and resume study treatment per protocol
Grade 3-4	Monitor every ≤2 days; **Immediately:** 1. –2.0 mg/kg/d methylprednisolone IV or IV equivalent; start prophylactic antibiotics; consult gastroenterologist **Persistence >3 days or recurrence:** add mycophenolate mofetil 1g twice daily; if no response within ≤5 days consider other immunosuppressants per local guidelines **LFT return to Grade 2:** stop immunosuppressants **LFT return to ≤Grade 1:** taper steroids over at least 1 month

For nivolumab dose modification guidelines, refer to Table 4.

8.3.2.3. Endocrinopathies

Endocrinopathies have been observed after treatment with nivolumab (Table 9). The events are typically identified through either routine periodic monitoring of specific laboratories values (eg, thyroid-stimulating hormone [TSH]) or as part of a work-up for associated symptoms (eg, fatigue). Events may occur within weeks of starting treatment, but also have been noted to occur after many months (while still on treatment). More than 1 endocrine organ may be involved (eg, hypophysitis [pituitary inflammation] may need to be evaluated at the time adrenal insufficiency or thyroid disorder is suspected). Subjects should be advised to seek medical evaluation if they notice new-onset fatigue (or if baseline fatigue worsens), lightheadedness, or difficulty with vision.

Table 9: Management and Follow-up of Endocrinopathies

Asymptomatic TSH abnormality	**TSH <0.5xLLN** or **TSH >2xULN** or **TSH >ULN in 2 subsequent measurements:** include free T4 assessment prior/after subsequent cycles of nivolumab; consider endocrinology consult
Symptomatic endocrinopathy	Assess endocrine function with appropriate laboratory testing; consider pituitary MRI scan **With abnormal lab and pituitary scan:** 1.0–2.0 mg/kg/d methylprednisolone IV or oral equivalent; initiate appropriate hormone therapy; consider prophylactic antibiotics **Clinical and laboratory improvement:** taper steroids over at least 1 month; subjects with adrenal insufficiency may need to continue steroids with mineralcorticoid component **Without abnormal lab and pituitary scan but symptoms persist:** repeat laboratory assessments in ≤3 weeks and MRI in 4 weeks
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	Rule out sepsis **Immediately:** initiate/stress dose of IV steroids with mineralocorticoid activity; fluids IV; consult endocrinologist **Adrenal crisis ruled out:** treat as symptomatic endocrinopathy
General	Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered

For nivolumab dose modification guidelines, refer to Table 4.

8.3.2.4. Rash (Including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis)

Rash and pruritus are the most common skin immune-mediated adverse events observed after treatment with nivolumab (Table 10). The rash is typically focal with a maculopapular appearance, occurring on the trunk, back, or extremities. Most cases are of low or moderate grade. In some cases, rash and pruritus resolve without intervention. Stevens-Johnson Syndrome and toxic epidermal necrolysis have also been reported, including cases with a fatal outcome. Subjects should be advised to seek medical evaluation if they notice new-onset rash. Early consultation with a dermatology specialist and a biopsy should be considered if there is uncertainty as to the cause of the rash, or if there is any unusual appearance or clinical feature associated with it.

Table 10: Management and Follow-up of Rash

Grade 1-2	**Immediately:** Symptomatic therapy (eg, anti-histamines, topical steroids) **Persistence ≤2 weeks or recurrence:** consider skin biopsy; consider 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics **Improvement to ≤Grade 1:** taper steroids over at least 1 month **Worsening to >Grade 2:** treat as Grade 3-4
Grade 3-4	**Immediately:** consult dermatologist; consider skin biopsy; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; add prophylactic antibiotics **Improvement to ≤Grade 1:** taper steroids over at least 1 month
General	Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered

For nivolumab dose modification guidelines, refer to Table 4.

8.3.2.5. Renal Adverse Events

Elevated creatinine and biopsy-confirmed tubulointerstitial nephritis and allergic nephritis are infrequently observed after treatment with nivolumab (Table 11). Physicians should monitor creatinine regularly.

Table 11: Management and Follow-up of Renal Adverse Events

Grade 1	Monitor creatinine weekly **Creatinine returns to baseline:** continue monitoring per protocol **Creatinine increases:** treat as Grade ≥2
Grade 2-3	Monitor creatinine every ≤3 days **Immediately:** start 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics; consider renal biopsy **Improvement to ≤Grade 1:** taper steroids over at least 1 month **Persistence >7 days or worsening:** treat as Grade 4
Grade 4	Monitor creatinine daily **Immediately:** consult nephrologist; consider renal biopsy; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; add prophylactic antibiotics **Improvement to ≤Grade 1:** taper steroids over at least 1 month
General	Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered

For nivolumab dose modification guidelines, refer to Table 4.

8.3.2.6. Neurologic Adverse Events

Neurologic adverse events have been uncommonly observed after treatment with nivolumab (Table 12). Neurologic adverse events may be central abnormalities (eg, aseptic meningitis or encephalitis) or peripheral sensory/motor neuropathies (eg, Guillain-Barre Syndrome). The onset has been observed as early as after a single treatment. Early recognition and treatment of neurologic adverse events is critical to their management. Subjects should be advised to seek medical evaluation if they notice impairment in motor function (eg, weakness), changes in sensation (eg, numbness), or symptoms suggestive of possible CNS abnormalities such as new headache or mental status changes.

Table 12: Management and Follow-up of Neurologic Adverse Events

Grade 1	Monitor per protocol **Worsening:** treat as ≥Grade 2
Grade 2	**Immediately:** treat symptoms according to institutional standards; consider 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent **Worsening:** treat as Grade 3-4
Grade 3-4	**Immediately:** consult neurologist; treat symptoms according to institutional standards; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; prophylactic antibiotics **Worsening or atypical presentation:** consider IV immunoglobulins or other immunosuppressive therapies according to institutional standards **Improvement to ≤Grade 2:** taper steroids over at least 1 month
General	Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered.

For nivolumab dose modification guidelines, refer to Table 4.

8.3.2.7. Pulmonary Adverse Events

Pulmonary adverse events, including radiographic changes (eg, focal ground glass opacities and patchy infiltrates), indicative of drug-related pneumonitis have been observed in subjects receiving nivolumab (Table 13). These pulmonary adverse events are either asymptomatic or associated with symptoms such as dyspnea, cough, or fever. The initial occurrence of pulmonary adverse events may be as early as after a single dose of nivolumab or delayed after prolonged therapy. Early recognition and treatment of pneumonitis is critical to its management. Subjects should be advised to seek medical evaluation promptly if they develop new-onset dyspnea, cough, or fever or if they have worsening of these baseline symptoms.

Table 13: Management and Follow-up of Pulmonary Adverse Events

Grade 1	Monitor for symptoms every 2-3 days; consider pulmonary and infectious-disease consult; re-image every 3 weeks **Worsening:** treat as ≥Grade 2
Grade 2	Monitor symptoms daily; re-image every 1-3 days; pulmonary and infectious-disease consultation; consider bronchoscopy and lung biopsy; consider hospitalization **Immediately:** start 1.0 mg/kg/d methylprednisolone IV or oral equivalent; prophylactic antibiotics **Persistence for 2 weeks or worsening:** treat as Grade 3-4 **Improvement to ≤Grade 1 or baseline:** taper steroids over at least 1 month
Grade 3-4	Hospitalize; pulmonary and infectious-disease consult; consider bronchoscopy and lung biopsy **Immediately:** 2-4 mg/kg/d methylprednisolone or IV equivalent; add prophylactic antibiotics; **Persistence for 2 days or worsening:** add immunosuppression (eg, infliximab, cyclophosphamide, IV immunoglobulins, or mycophenolate mofetil) **Improvement to ≤Grade 2:** taper steroids over at least 6 weeks
General	Subjects on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered

For nivolumab dose modification guidelines, refer to Table 4.

8.3.2.8. Uveitis and Visual Complaints

Immune therapies have been uncommonly associated with visual complaints (Table 14). Inflammation of components within the eye (eg, uveitis) is an uncommon, but clinically important, event. An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers, and retina. Complaints of double vision should also prompt medical evaluation. The differential diagnosis should include pituitary inflammation.

Table 14: Management and Follow-up of Uveitis and Visual Complaints

Grade 1-2	Thorough eye examination Topical corticosteroids should be considered Persisting despite topical steroids, treat as Grade 3-4
Grade 3-4	Thorough eye examination Systemic corticosteroids

For nivolumab dose modification guidelines, refer to Table 4.

8.3.2.9. Lipase/Amylase Elevations

Asymptomatic elevations in lipase and amylase have been reported in nivolumab studies. Very few subjects have associated symptoms (eg, abdominal pain) or radiographic findings (eg, stranding) consistent with pancreatitis. Given that most events are asymptomatic, the recommended management is close observation. Physicians should ensure that subjects have no associated symptoms consistent with pancreatitis, such as abdominal pain. Corticosteroids do not seem to alter the natural history of lipase/amylase elevations. Laboratory values tend to fluctuate on a day-to-day basis and eventually return to baseline or low grade levels over the course of weeks, whether or not subjects receive corticosteroids. Asymptomatic elevations should be monitored approximately weekly.

8.3.2.10. Treatment of Nivolumab Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce an infusion or hypersensitivity reaction. However, if such a reaction were to occur, it might be associated with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other symptoms (Table 15).

If a nivolumab related infusion reaction occurs on Day 1 of a treatment cycle, then the scheduled dose of JNJ-757 should be withheld on that day. The subject can resume JNJ-757 treatment with the next scheduled dose of JNJ-757 on Day 1 of the next cycle of nivolumab treatment.

Table 15: Management and Follow-up of Nivolumab Infusion Reactions

Grade 1	No intervention indicated; remain at bedside and monitor subject until recovery from symptoms, Consider diphenhydramine 50 mg or equivalent and or paracetamol (acetaminophen) 325 to 1000 mg at least 30 minutes before additional nivolumab administration
Grade 2	**Stop nivolumab infusion**; start IV saline infusion; give diphenhydramine 50 mg (or equivalent) IV and/or paracetamol 325 to 1000 mg (acetaminophen); consider corticosteroids and bronchodilator therapy; remain at bedside and monitor subject until recovery from symptoms **Re-start infusion at 50% of initial rate:** if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate; monitor subject closely. **Symptoms recur:** stop and discontinue further nivolumab treatment at that visit; administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of nivolumab infused must be recorded in the eCRF.
Grade 3-4	**Stop nivolumab infusion**; start IV saline infusion; recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).
General	**Prophylactic medications (after initial event):** diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations; if necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used Appropriate resuscitation equipment should be available in the room and a physician readily available during the infusion of nivolumab.

For nivolumab dose modification guidelines, refer to Table 4.

8.4. Subsequent Therapies

Any subsequent anticancer therapy administered after the study agent should be recorded in the eCRF. The start and end date and best response should be documented in the eCRF, if available.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule (Table 1) summarizes the frequency and timing of measurements applicable to this study. The study is divided into 3 phases: a Screening Phase (with an optional Prescreening Phase to collect tumor tissue), a Treatment Phase, and a Posttreatment Follow-up Phase. All subjects will continue follow-up for survival and subsequent anticancer therapy in the Posttreatment Follow-up Phase, except for those who additionally withdraw consent for continued study participation.

After Cycle 2, the start of each cycle may occur ±3 days of the scheduled day to accommodate the schedule of the site or subject. The End-of-Treatment Visit may occur +7 days after the scheduled day. Assessments/procedures should be completed on the day indicated; if this is not possible because of a weekend, holiday, or emergency, the assessment/procedure should be completed within the timeframe noted in Table 1. Imaging studies should be completed within ±7 days of the scheduled assessment.

All PRO assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing subject perceptions. Blood collections for pharmacodynamic/biomarker assessments should be kept as close to the specified time as possible. Actual dates and times of assessments will be recorded in the source documentation and on the laboratory requisition form or eCRF. Blood samples must be taken from a peripheral vein from the arm contralateral to the arm into which JNJ-757 is infused. Use of a central catheter to administer JNJ-757 is prohibited for the duration of the study.

Clinical laboratory results must be reviewed by the investigator before any study agent is administered. Repeat or unscheduled samples may be collected for safety reasons or for technical issues with the samples. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, during the subject's participation in the study.

The blood volume will vary by treatment cycle. See Table 1 for details on sample collections and the laboratory manual for details on blood volumes.

9.1.2. Screening Phase

The Screening Phase will include a review of medical history to determine eligibility for the study. All subjects must sign an ICF before the conduct of any study-specific procedures. Screening procedures, including radiographic imaging and 12-lead electrocardiogram (ECG), are to be performed up to 28 days before Cycle 1 Day 1 (Phase 1b) or randomization (Phase 2). Study assessments performed as part of the subject’s routine clinical evaluation within the 28-day screening period can be used prior to signed informed consent. Retesting of abnormal laboratory screening values is allowed during the Screening Phase (to reassess eligibility). The last result obtained before Cycle 1 Day 1 (Phase 1b) or randomization (Phase 2) will be used to determine eligibility. An optional prescreening phase to minimize delay for central confirmation of tumor status is described in Section 9.1.2.2.

9.1.2.1. Determination of Mesothelin and PD-L1 Level

Before proceeding to the Treatment Phase of the study, tumor tissue samples for each subject must be provided for assessment of tumor mesothelin status and PD-L1 level. The results must be reported by the central laboratory before Cycle 1 Day 1 (Phase 1b) or randomization (Phase 2). Tumor samples (block or unstained tumor slides) may be either from archival tissue or newly obtained (if archival tissue is insufficient). For the evaluation of mesothelin in tumor tissues, a validated assay will be used at the central lab. Mesothelin positive status (>0% positive tumor cells) is defined as tumor cells exhibiting positive membrane or cytoplasmic staining at any intensity. Tumor tissue will be assessed for PD-L1 staining, by the sponsor or sponsor's designee using the DAKO PD-L1 IHC 28-8 pharmDx Assay, for which excisional, incisional, punch, or core biopsies are required. Fine needle aspirates or other cytology specimens are insufficient for PD-L1 analysis. Unstained slides must be made within 4 months prior to central laboratory assessment and stored in the dark at 2°–8°C.

9.1.2.2. Optional Prescreening Phase

Subjects must have available tumor material for testing of mesothelin and PD-L1 to be eligible for the study. The purpose of the optional Prescreening Phase is to provide adequate time for the collection of archived formalin-fixed paraffin-embedded tumor tissue (block or unstained tumor slides) from primary or metastatic tumor material to be submitted to the laboratory along with the associated pathology reports. The tumor samples will be studied for mesothelin and PD-L1 before the formal screening process for the study. A separate informed consent for this optional Prescreening Phase will permit collection of archival tumor material from the subject and testing of the mesothelin required for eligibility and PD-L1 levels required for stratification purposes in Phase 2.

9.1.3. Treatment Phase

The Treatment Phase begins on Cycle 1, Day 1 with the administration of the first dose of nivolumab and continues until the completion of the End-of-Treatment Visit. Nivolumab should be administered within 3 days of randomization. The measurements collected at the time closest to, but before, the start of nivolumab administration will be defined as the baseline values for safety assessment and treatment decisions. Any new or worsening adverse events that occur and all concomitant medications that are administered between when the informed consent form (ICF) is signed and 100 days after the last dose of study agent will be recorded for subjects who enter the Screening Phase. Any subject with an ongoing adverse event will be followed beyond 100 days after the last dose of study agent, subjects will be followed for ongoing treatment-related adverse events and associated medications until all adverse events are resolved, return to baseline, are deemed irreversible, or the subject starts subsequent anticancer therapy. See Section 12 for complete details on adverse event reporting.

The study will be conducted in an outpatient setting. Subjects must remain at the infusion center for monitoring for 5 hours after the end of the first infusion of JNJ-757. At the investigator's discretion, hospitalization after any study agent infusion may be considered, if clinically indicated, to facilitate safety monitoring. Subjects who have symptoms indicative of a systemic innate immune response to bacterial infection within 5 hours of the end of any infusion may be considered for hospitalization for continued observation, at the investigator's discretion. These admissions for observation should not be reported as serious adverse events. Physician visits will be conducted on Days 1, 2, and 15 of Cycle 1, and Days 1 and 15 of subsequent cycles (if nivolumab is permanently discontinued but the subject continues to receive treatment with JNJ-757, then the Day 15 visits of subsequent cycles will be optional). Subjects who undergo ELISpot assessments will be scheduled for additional physician visits at Day 8 of Cycles 2 and 3.

Required study procedures and assessments to be conducted during the Treatment Phase are outlined in Table 1. A focused medical history and symptom-directed physical exam will be conducted. Subjects will be evaluated throughout the Treatment Phase for possible toxicities and adverse events. Adverse event information will be collected using the NCI-CTCAE, Version 4.03. All new concomitant medications or changes to concomitant medications will be recorded. Clinical laboratory assessments will be reviewed before the administration of study agent. After Cycle 1, Day 1, laboratory tests may be performed up to 3 days before the scheduled infusion day.

On Day 1 of each cycle with a scheduled disease assessment (ie, every 8 weeks in the first year and then every 12 weeks), predose peripheral surveillance blood cultures will be performed as described in the Time and Events Schedule. If the results of the peripheral blood cultures are positive for listeriosis after receiving JNJ-757, the subject must discontinue subsequent therapy with JNJ-757 and be treated with an intravenous antibiotic therapy appropriate for the treatment of listeriosis (See Section 8.3.1.2).

The investigator will assess each subject's response to therapy using the efficacy measurements and RECIST 1.1 disease response criteria outlined in Attachment 2, according to the schedule in Table 1. If progressive disease is diagnosed or if a subject discontinues study treatment for reasons other than withdrawal of consent, the subject should complete the End-of-Treatment Visit within 30 days (+7 days) and then enter the Posttreatment Follow-up Phase. For subjects who discontinue treatment before disease progression (for reasons such as an adverse event or investigator decision) radiologic assessments should be performed according to the protocol schedule until disease progression, initiation of subsequent therapy, withdrawal of consent from study participation, or study end.

End-of-Treatment/Early Withdrawal

The End-of-Treatment Visit should be performed within 30 days (+7 days) after the last dose of study agent (JNJ-757 or nivolumab) for each subject, including those discontinuing treatment for any reason, except for withdrawal of consent for study participation. Subjects who discontinue treatment (due to progression of disease or unacceptable toxicity) and who are entering the Posttreatment Follow-up Phase should have the End-of-Treatment Visit completed before starting any new anticancer treatment to collect safety information, draw the required blood cultures, and initiate the required prophylactic antibiotics. If the subject is scheduled to start subsequent therapy, this visit should be performed as soon as possible after the last administration of study agent.

After the last JNJ-757 infusion, mandatory prophylactic antibiotic therapy must be administered (refer to Section 8.3.1.1). Study subjects who wish to withdraw from the study are required to complete the planned administration of antibiotics. End-of-Treatment assessments, including blood culture sample collection, should be performed prior to the initiation of the mandatory prophylactic antibiotics. All subjects who receive JNJ-757, including those withdrawing consent for further participation, should receive the full 7-day course of mandatory prophylactic antibiotics.

9.1.4. Posttreatment Follow-up Phase

The Posttreatment Follow-up Phase starts after the End-of-Treatment Visit and ends with the end of study participation or end of study. Subjects who withdraw from treatment due to disease progression, unacceptable toxicity, or subject or investigator decision will enter the Posttreatment Follow-up Phase.

Follow-up visits will be made every 3 months (±7 days) after the last dose of study agent to obtain blood cultures (up to 1 year for subjects who receive JNJ-757) and to determine survival, unless the subject has died, is lost to follow-up, or has withdrawn consent. For subjects in Group B and after the first year for subjects in Phase 1b and Group A, these visits may be conducted by telephone contact or an alternative contact method per institution policy/practice. Assessments that will occur at the Posttreatment Follow-up visits are summarized in Table 1. The first Posttreatment Follow-up visit should occur 100 days after the last dose of study agent. Additional information on reporting of adverse events can be found in Section 12.

If the subject has died, the date and cause of death will be collected and documented in the eCRF. For subjects who withdrew from treatment before disease progression, the results of subsequent tumor assessments, conducted according to the study schedule, should also be collected until disease progression is radiographically documented, or until the subject initiates subsequent therapy.

Subjects who have a treatment-related Grade ≥3 toxicity at the End-of-Treatment Visit will continue follow-up until recovery to Grade ≤1 or baseline, the AE is deemed irreversible, or the subject starts subsequent anticancer therapy. Subjects with treatment-related adverse events leading to discontinuation will continue follow-up until resolution or return to baseline, the AE is deemed irreversible, or end of study, whichever occurs first.

9.1.5. End of Study

The end of the study will occur when 80% of the randomized subjects have died, or approximately 3 years after the last subject is randomized, or the sponsor terminates the study.

9.2. Efficacy Evaluations

9.2.1. Evaluations

Disease response will be assessed using CT scans with IV contrast (or if necessary, MRI scans) of the chest, abdomen, and pelvis. The scans will be performed at Week 8 (±7 days), then every 8 weeks (±7 days) during the first year, and then every 12 weeks (±7 days) thereafter, in accordance with the schedule outlined in Table 1 until disease progression, subsequent therapy, or completion of therapy. For subjects receiving on-treatment biopsy, the first assessment will be at Cycle 3 Day 8 (+3 days). Tumor measurements will occur as recommended by the RECIST 1.1 criteria (Attachment 2).

Magnetic resonance imaging may be used to evaluate sites of disease that cannot be adequately imaged using CT. If MRI is used to assess a site of disease at baseline, then it must be the imaging technique for that site of disease at all subsequent response evaluations.

For subjects with known brain metastasis, brain MRI scans are required at baseline and as clinically indicated. Survival status will be assessed according to the schedule in Table 1.

All efficacy evaluations, including other sites of disease by radiologic imaging, physical examination, or other procedures as necessary, will be performed at the site. These assessments should be performed throughout the study at each timepoint using the same method of assessment used to assess disease at baseline. Response to treatment will be assessed by the investigator at the site and the results will be recorded in the eCRF. The results of radiologic assessments performed after treatment discontinuation, as part of the standard of care at the site, should be recorded in the eCRF. Copies of the images must be retained at the site. For Phase 2, radiographic scans may be submitted to a third-party core imaging laboratory for quality assessment and for audit purposes. Further details regarding submission of these materials will be provided in the Imaging Manual.

The PRO instruments in this study are NSCLC-SAQ, EORTC QLQ-C30, and EORTC QLQ-LC13. Validation of the NSCLC-SAQ is ongoing. It contains 7 items that assess cough, pain, dyspnea, fatigue, and poor appetite over a 7-day recall period. Three items (assessing cough and pain) assess peak intensity, and use response options range from "no [symptom]" to "very severe [symptom]," while the remaining items assess the frequency of symptoms (dyspnea, fatigue, and poor appetite) and use a rating scale from "never" to "always" (McCarrier 2016).[22] A Patient Global Impression of Change (PGIC) and a Patient Global Impression of Severity (PGIS) will also be included at follow-up visits to provide anchor-based comparisons for the NSCLC-SAQ and support validation efforts for this PRO. The single-question PGIC and PGIS should be administered prior to other PRO assessments.

The EORTC QLQ-C30 includes 30 items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The recall period is 1 week (the past week). The EORTC QLQ-C30 has been widely used among patients with cancer. Scores are transformed to a 0 to 100 scale (Aaronson 1993).[1] The EORTC QLQ-LC13 is a 13-item lung cancer-specific module of the EORTC QLQ-C30. It incorporates 1 multiple-item scale to assess specific lung cancer symptoms including dyspnea and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis (Bergman 1994).[4]

9.2.1.1. Assessment of Disease Response and Progressive Disease

Assessments of disease response are to be conducted until disease progression, withdrawal of consent from study participation, or the end of study. For subjects who discontinue study agent before disease progression is documented, disease assessments should continue during the Posttreatment Follow-up Phase according to the study schedule until disease progression is documented or subsequent therapy is initiated.

9.2.1.2. Treatment Beyond Progression

Antitumor response patterns seen with immunotherapeutic agents may extend beyond the typical time course of responses seen with cytotoxic agents (Melosky 2016).[23] Accumulating evidence indicates that a minority of patients with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of disease progression (ie, tumor flare). At the time of response assessment, subjects who meet the criteria for progressive disease per RECIST 1.1 but whose progression is attributed to tumor flare may be permitted to remain on study therapy, based on the investigator's assessment of clinical benefit, if the subject is clinically stable, meets all other study protocol eligibility criteria, and is tolerating the study agent(s). All decisions to continue treatment beyond suspected tumor flare must be discussed with the sponsor's medical monitor. An assessment of the benefit-risk of continuing with study therapy, as well as the subject's agreement to continue study therapy, must be documented in the study records. Subsequent disease assessments will continue as scheduled, and results of these assessments will be reported in the eCRF.

9.2.1.3. Discontinuation of Study Agent After Complete Response

Subjects with a confirmed complete response (CR) at the next regularly scheduled scan may continue study agent at the discretion of the investigator. The maximum allowed duration of nivolumab or JNJ-757 treatment is 2 years. Study agent discontinuation may be considered for a subject with a CR if the subject has received at least 2 cycles of study treatment beyond the date when the initial CR was documented. The reason for discontinuation must be documented in the eCRF.

9.2.2. Efficacy Endpoints

The efficacy endpoints are as follows:

- ORR is defined as the proportion of subjects who achieve CR or partial response (PR), as assessed by the investigator, using RECIST 1.1 criteria (Attachment 2).
- Disease control rate (DCR) is defined as the proportion of subjects with stable disease lasting for at least 16 weeks, PR, or CR.
- DOR is defined as the time from the date of initial documentation of a response (CR or PR) to the date of first documented evidence of progressive disease or death from any cause.
- PFS is defined as the time from the date of randomization until the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death from any cause, whichever comes first.
- Overall survival is defined as the time from the date of randomization to the date of the subject's death.
- Change from baseline in PRO subscale scores as assessed by NSCLC-SAQ and EORTC QLQ30+LC13.

9.3. Blood Culture and Bacterial Shedding Assessments for JNJ-757

Blood Cultures

Blood cultures should be performed for all subjects during the Treatment Phase, at the End-of-Treatment visit, and during the Posttreatment Follow-up Phase, as outlined in Table 1. Refer to the laboratory manual for details. Every effort should be made to collect surveillance cultures at the site, using sponsor-supplied kits. However, in the event that a subject cannot return to the study site, posttreatment surveillance blood cultures should be performed at a local laboratory and the results recorded in the subject source documentation and reported in the eCRF. Surveillance cultures positive for listeriosis will be reported to the sponsor's medical monitor within 24 hours of awareness irrespective of seriousness (ie, serious and nonserious adverse events) and will require enhanced data collection.

Bacterial Shedding

The shedding profile of JNJ-757 will be studied for all subjects who receive JNJ-757 plus nivolumab in Phase 1b, and in Phase 2 Group A (tumor biopsy substudy only). The shedding of JNJ-757 will be studied in (1) feces by stool or rectal swab, (2) urine, and (3) saliva. Any subject

with a positive shedding result will be tested every 2 to 4 days until a negative shedding result. Samples will be obtained as specified in Table 1. Refer to the laboratory manual for details.

9.4. Nivolumab Pharmacokinetic Evaluations

Blood samples will be collected from subjects in both phases for determination of serum concentrations of nivolumab as specified in Table 1. Nivolumab concentration data will be summarized using descriptive statistics. Serum samples will be analyzed for nivolumab by a validated method.

9.5. Nivolumab Immunogenicity Evaluations

Subjects in Phase 2 will be monitored for anti-nivolumab antibodies. Blood for serum anti-nivolumab antibody testing will be collected as specified in Table 1. Analysis will be performed under the supervision of the sponsor. Details on blood sample collection, processing, storage and shipping procedures are provided in the laboratory manual.

9.6. Biomarkers

Biopsy and blood biomarker analyses are dependent upon the availability of appropriate biomarker assays and may be deferred or not performed if either during or at the end of the study it becomes clear that the analysis will have no scientific value. If the study is terminated early, completion of biomarker assessments will be based on justification and intended utility of the data.

9.6.1. Sample Collection

Collection of blood samples will occur at the times specified in Table 1. Biomarker analyses indicated below will be performed in subjects in the tumor biopsy substudy, which includes all subjects in Phase 1b and subjects at selected sites approved by the sponsor in Phase 2. Subjects in the tumor biopsy substudy will undergo collection of samples for T-cell proliferation, intracellular cytokine staining, IFN-γ ELISpot, and pentamer staining. Mandatory core needle on-study tumor biopsy samples will be collected as specified in Table 1 from subjects who consent separately to participate in the tumor biopsy substudy (where local regulations permit). Deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein may be isolated from tumor biopsies for evaluation of tumor-associated biomarkers to better understand their correlation with clinical response. No pharmacogenomic analyses will be conducted on the biomarker samples. Samples of resected tissue from unscheduled diagnostic or surgical interventions may also be submitted and evaluated for further biomarker investigations of potential mechanisms of tumor response or resistance. Analyses from the tumor biopsy substudy will be reported separately.

9.6.2. Pharmacodynamic and Predictive Biomarker Evaluations

Pharmacodynamic (PD) biomarkers and translational data will be informed by available Phase 1 results, will be assessed before, during, and after treatment with JNJ-757, and may include the following:

1. Differential absolute lymphocyte count in peripheral blood.
2. Cytokine release in plasma as analyzed using appropriate techniques such as electrochemiluminescence-based bridging immunogenicity assay (Meso Scale Discovery).
3. NK, CD4, and CD8 T cell enumeration and activation status using standard activation markers (such as CD69) by flow cytometry in PBMCs.
4. Lymphocyte subsets and expression levels of T cell costimulatory markers (by flow cytometry). Analyses may include, but not be limited to, the proportion of T-, B-, and NK-cells, proportion of memory- and effector T-cell subsets, and expression levels of PD-1, PD-L1, PD-L2, ICOS, and Ki67.
5. Analysis of the diversity of the T-cell repertoire in correlation to clinical efficacy.
6. Adaptive T-cell responses. The magnitude, breadth, and duration of antigen-specific responses to the tumor associated antigen mesothelin, as well as recall and de novo responses to control human leukocyte antigen (HLA) class II-restricted T-cell epitopes (cytomegalovirus, Epstein-Barr virus, influenza and tetanus toxoid), the *Listeria* antigen listeriolysin O, and the *ActANE* sequences will be evaluated using appropriate assays such as IFN-γ ELISpot and flow cytometric analysis of intracellular cytokine staining, markers of T-cell activation, and markers of proliferation.
7. Infiltration and activation status of several immune cells subsets using appropriate techniques such as single color or multiplex immunocytochemistry of formalin fixed paraffin embedded (FFPE) tumor biopsies.

9.6.3. Primary Biomarker Assessment

Tumor sample collection and analyses will be performed before Cycle 1 Day 1 (Phase 1b) or randomization (Phase 2) as part of the screening activities, and will include central assessment of mesothelin status and PD-L1 level (Section 9.1.2.1). Tumor mesothelin status will be used as a study eligibility criterion and in Phase 2, subjects with mesothelin-positive tumors will be stratified based on PD-L1 level (<1%, 1-49%, or ≥50%). The primary endpoint of ORR will be assessed by PD-L1 level.

9.6.4. Exploratory Biomarker Evaluations

Additional analyses may be carried out to assess immunosuppression in the blood and tumor microenvironment after treatment with JNJ-757. These analyses may include, but are not limited to, checkpoint expression in the tumor and blood, and expression of lung cancer and immune gene signatures (including, but not limited to, expansion of the T-cell or B-cell immune repertoire and tumor immune phenotyping) in the blood and tumor tissue that may be predictive of response or prognosis. Additionally, tumor genetics may be assessed on tumor tissues or from circulating DNA. The list of exploratory biomarkers to be evaluated will be informed by available results of JNJ-757 Phase 1 biomarker assessments or results arising from other LADD *Lm*-based clinical studies or PD-1 inhibitor clinical studies. Other biomarker analyses are dependent upon the availability of appropriate biomarker assays. In the event that the study is terminated early, completion of biomarker assessments will be based on justification and intended utility of the data.

9.6.5. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. Refer to the Time and Events Schedule (Table 1) for the timing and frequency of biomarker sample collections. Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

If it is determined at any time before study completion that additional material is needed from a formalin-fixed, paraffin-embedded tumor sample for the successful completion of the protocol-specified analyses, the sponsor may request that additional material be retrieved from existing samples. In this case, such analyses would be specific to research related to the study agent or diseases being investigated.

9.7. Safety Evaluations

The study will include evaluations of safety and tolerability outlined in the following sections according to the timepoints provided in Table 1. All subjects who receive at least 1 dose of study agent will be considered evaluable for safety. Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF. Adverse events will be graded according to NCI-CTCAE, Version 4.03.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will continue follow-up by the investigator until resolution or until a clinically stable endpoint is reached (see also Section 9.1.4).

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected before each study agent infusion, with the exception of TSH (with reflex testing), which will be collected on Day 1 of every other cycle. More frequent clinical laboratory tests may be performed if indicated by the clinical condition of the subject or by laboratory abnormalities that warrant more frequent monitoring. Screening laboratory results must be available to the investigator for evaluation before Cycle 1 Day 1 (Phase 1b) or randomization (Phase 2), and before each study agent administration thereafter. The investigator must review the laboratory report(s), document this review, and ensure that any clinically relevant changes occurring during the study are recorded in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents.

The following tests will be performed:

- Hematology

  -hemoglobin
  -white blood cell count
  -absolute neutrophil count (ANC)
  -absolute lymphocyte count (ALC)
  -platelet count

- Serum Chemistry Panel

  -sodium
  -potassium
  -creatinine
  -glucose
  -AST
  -ALT
  -total bilirubin
  -alkaline phosphatase
  -lactate dehydrogenase
  -calcium
  -albumin
  -total protein

- Thyroid function tests

  -TSH, with reflex to free T3, T4 if abnormal

- Serum pregnancy testing for women of childbearing potential only (urine, when serum is not available)

Electrocardiogram

The ECG must be reported locally for all subjects at Screening. Additional cardiovascular assessments should be performed as clinically appropriate to ensure subject safety. The clinical investigator will review the printout, including ECG morphology. Clinically relevant abnormalities noted at the time of Screening should be documented in the subject's medical history and recorded on the eCRF.

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. Hypokalemia should be corrected before ECG collection.

Vital Signs

Vital signs include temperature, pulse rate, respiratory rate, SaO_2 by pulse oximetry, and blood pressure (see Table 1 for frequency). Blood pressure and pulse rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available, or to confirm abnormal results. Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Physical Examination

A full physical examination must be performed at Screening. Subsequently, symptom-directed and disease-directed physical examinations (includes all organ systems that were previously abnormal or involved with disease and documentation of any clinically relevant abnormalities in any organ) will be performed at the timepoints specified in Table 1. Height and weight will be measured at screening. Weight will also be measured at the start of each cycle, before study agent administration. Abnormal physical findings should be reported as adverse event if clinically indicated.

ECOG Performance Status

The ECOG performance status scale, provided in Attachment 3, will be used to grade changes in the subject's daily living activities. The frequency of ECOG performance status assessment is provided in Table 1.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will complete the study if he or she has completed all protocol-specified procedures, has not been lost to follow-up, and has not withdrawn consent for study participation before the end of the study. In addition, subjects who die before the end of the study will be considered to have completed the study.

10.2. Discontinuation of Study Treatment

If study treatment must be discontinued, this will not result in automatic withdrawal of the subject from the study. In Group A, if the discontinuation of one study agent is indicated, the subject may continue the other agent as monotherapy at the same dose and schedule after consultation with the medical monitor if, in the investigator's opinion, the subject may benefit from monotherapy.

Study treatment should be discontinued if:

- Occurrence of toxicity as noted in Section 8.3 or unacceptable toxicity
- The investigator believes that for safety reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- Documented disease progression (see Section 9.2.1.2)
- The subject receives concurrent (nonprotocol) anticancer treatment
- Intercurrent illness prevents further administration of treatment
- The subject refuses further treatment with study agent
- Noncompliance with study treatment or procedure requirements that, in the opinion of the investigator or sponsor, preclude participation in the study for reasons of subject safety

JNJ-757 treatment should be discontinued if predose peripheral surveillance cultures are positive for listeriosis or if the subject requires an emergent placement of a prohibited implanted device (refer to Section 8.3.1.2 for mandatory antibiotic treatment).

Study agent discontinuation may be considered for a subject with a CR if the next disease assessment confirms CR and the subject has received at least 2 courses of JNJ-757 beyond the date when the initial CR was documented (see Section 9.2.1.3). The maximum allowed duration of nivolumab or JNJ-757 treatment is 2 years. If a subject discontinues study agent for any reason before the onset of disease progression, end-of-treatment and posttreatment assessments should be obtained and follow-up of scheduled disease assessments should be continued. The reason(s) a subject discontinues treatment should be recorded on the eCRF.

At the time of response assessment, subjects who meet the criteria for progressive disease per RECIST 1.1 but whose progression is attributed to tumor flare may be permitted to remain on study therapy, based on the investigator's assessment of clinical benefit, if the subject is clinically stable, meets all other study protocol eligibility criteria, and is tolerating the study agent(s) (see Section 9.2.1.2).

10.3. Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent

If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study agent assigned to the withdrawn subject may not be assigned to another subject. If a subject withdraws from the study before the end of treatment, the End-of-Treatment Visit and Posttreatment assessments should be obtained.

10.4. Withdrawal From the Use of Research Samples

A subject who withdraws from the study will have the following options regarding the optional research samples:

- The collected samples will be retained and used in accordance with the subject's original separate informed consent for optional research samples.

- The subject may withdraw consent for optional research samples, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The subject may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for future research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

11.1. Subject Information

Intent to treat (ITT) Population: The ITT population will include all randomized subjects classified according to their assigned treatment group, regardless of the actual treatment received. Subject disposition and efficacy analyses will be performed on data from the ITT population. The subjects in the safety run-in cohort will also be included in disposition and appropriate efficacy analyses and listed separately.

Safety Population (As Treated): The safety population will include all subjects who receive ≥1 dose of either of the study agents.

Biomarker Population: The biomarker population will include all subjects who receive ≥1 dose of study agent and have pretreatment and ≥1 posttreatment biomarker measurement.

11.2. Sample Size Determination

Phase 1b will be a safety run-in phase of at least 6 subjects to evaluate the incidence of DLTs and demonstrate the tolerability of the combination. Additional subjects (up to 30 in total) may be enrolled, as determined by the SET, to further explore safety and translational data before the decision to initiate the randomized Phase 2. A SET will be responsible for reviewing the safety and translational data during Phase 1b.

In Phase 2, a maximum of 140 subjects will be randomized. Based on preliminary data, it is estimated that 60%, 25%, and 15% of mesothelin-positive subjects will have a PD-L1 level of <1%, 1-49%, or ≥50%, respectively. The projected ORRs are as follows:

	PD-L1 (<1%)	PD-L1 (1-49%)	PD-L1 (≥50%)	Overall
Group A (JNJ-757 plus nivolumab)	0.30	0.40	0.80	0.40
Group B (nivolumab)	0.10	0.20	0.40	0.17

Using frequentist methods, a sample size of 140 subjects will provide at least 90% power to test a difference of 17% versus 40% in the overall population, using a 2-sided alpha of 10%.

Throughout randomization, ORR will be monitored using a Bayesian hierarchical logistic regression model, such that more subjects may be enrolled in a PD-L1 subgroup where the combination therapy is more effective. However, subjects will always be randomized to Group A or Group B in a 1:1 ratio within that subgroup. If the combination therapy is not effective in any PD-L1 subgroup, then the study could be stopped early.

11.3. Statistical Model for Probability of ORR

The DMC (see Section 11.11) will review the ORR data after approximately 40, 60, 80, 100, and 120 subjects have been randomized in Phase 2. The DMC may request additional ad-hoc reviews based on the accumulating data. Enrollment of subjects may be stopped during the DMC reviews.

The accumulated ORR data from the eligible subjects will be used to estimate the posterior probability of observing an objective response (CR or PR) for each treatment group within each PD-L1 level. A Bayesian hierarchical logistic regression model will be used to calculate this probability. The details of the statistical model including specifications for prior distributions, decision rules to suspend accrual within a PD-L1 subgroup, hypothetical data scenarios, and operating characteristics will be provided in the Statistical Analysis Plan.

If accrual is stopped permanently in all PD-L1 subgroups, then the study is considered complete; otherwise, accrual will continue until a total of 140 subjects are randomized in Phase 2. The DMC may decide to expand any subgroup in which benefit of the combination has been demonstrated, to collect additional data within this subgroup.

11.4. Efficacy Analyses

Continuous variables will be summarized using number of subjects (n), mean, standard deviation, median, minimum, and maximum. Discrete variables will be summarized with n and percent. Efficacy endpoints will be analyzed using the ITT population.

Primary Endpoint

The number and percentage of subjects who have either CR or PR according to RECIST 1.1 criteria as their best response will be calculated and compared between the 2 treatment groups using a chi-square test.

Secondary Endpoints

Time to response and DOR will be summarized for subjects who have a best response of CR or PR. No formal statistical test will be performed for DOR. Subgroup analysis will be performed for ORR, DCR, PFS, and overall survival to assess the consistency of treatment effects in subpopulations by PD-L1 level.

Kaplan-Meier product limit methods will be used to estimate the distribution of time-to-event variables. Cox proportional hazards model will be used to obtain the HR along with the associated 95% confidence intervals, and log-rank test will be used to test the treatment effect for PFS and overall survival. A subject without an event at the time of analysis will be censored. Detailed censoring rules will be provided in the statistical analysis plan. DCR will be analyzed using the same method as ORR.

11.5. Blood Culture and Bacterial Shedding Analyses

Descriptive statistics will be used to summarize blood cultures and bacterial shedding as appropriate.

11.6. Nivolumab Pharmacokinetic Analyses

Nivolumab concentration data will be listed by visit and timepoint for subjects who receive at least 1 dose of nivolumab and have available serum concentrations. Descriptive statistics will be used to summarize nivolumab serum concentrations. Based on data, population PK analyses may be performed and summarized in a separate report.

11.7. Nivolumab Immunogenicity Analyses

Immunogenicity analyses will be descriptive in nature and will include the number and percentage of subjects with anti-nivolumab antibodies at baseline and who develop anti-nivolumab antibodies. A listing of subjects with anti-nivolumab antibodies will be provided.

11.8. Biomarker Analyses

Descriptive statistics and graphical procedures will be used to summarize each biomarker. The associations of PD-L1 level with disease response or time-to-event endpoints will be assessed using the appropriate statistical methods (analysis of variance [ANOVA], Poisson regression, Fisher's exact test, or Kaplan-Meier curve and Cox proportional hazards model, depending on the endpoint and biomarker). Correlation of baseline expression levels or changes in expression levels with response or time-to-event endpoints will identify responsive (or resistant) subgroups. Generalized linear models or other appropriate parametric or nonparametric models will be explored to identify treatment effect and time trends of biomarkers.

Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information. Any biomarker samples received by the contract vendor or sponsor after the cutoff date will not be analyzed, and therefore, excluded from the biomarker analysis.

Changes in pharmacodynamic biomarkers over time will be summarized by treatment group. Associations between biomarker baseline levels and changes from baseline in such biomarkers and clinical response may be explored.

11.9. Patient-reported Outcomes Analyses

PRO subscale scores will be descriptively summarized by treatment group at each timepoint and change from baseline will be compared between treatment groups.

11.10. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset during the Treatment Phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Summaries, listings, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled timepoint. Changes from baseline results will be presented in pretreatment versus posttreatment cross-tabulations. A listing of subjects with any laboratory results outside the reference ranges will be provided.

Parameters with predefined NCI-CTCAE toxicity grades will be summarized. Change from baseline to the worst toxicity grade experienced by the subject during the study treatment will be provided as shift tables.

Electrocardiogram (ECG)

Electrocardiograms are included at screening only. Any other ECGs will be performed as clinically indicated and abnormalities will be reported as adverse events.

Vital Signs

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled timepoint.

Physical Examination

Physical examination findings will be listed as appropriate.

11.11. Data Monitoring Committee

For Phase 2, a Janssen DMC will be established to review the ORR and safety data on a regular basis. The DMC will consist of a minimum of 3 members with at least 1 clinician and a statistician, one of whom will chair the committee.

The DMC will review the ORR data after approximately 40, 60, 80, 100, and 120 subjects have been randomized, and will formulate recommended decisions/actions in accordance with the statistical decision rule of the ORR analysis. The DMC also will review safety data every 3 months. The DMC may request additional ad-hoc reviews based on the accumulating data. It is anticipated the first ORR analysis will occur approximately 24 weeks after the first subject in Phase 2 has been randomized. Enrollment of subjects may be stopped during the DMC reviews.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or noninvestigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or noninvestigational) product, whether or not related to that medicinal (investigational or noninvestigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-757, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For nivolumab, the expectedness of an adverse event will be determined by whether or not it is listed in the locally approved labeling.

Adverse Event Associated With the Use of a Drug

An adverse event is considered associated with the use of a drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

The NCI-CTCAE (Version 4.03) will be used to grade the severity of adverse events.

Any adverse event not listed in the NCI-CTCAE will be graded according to the investigator's clinical judgment using the standard grades as follows:

- Grade 1 (Mild): Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.
- Grade 2 (Moderate): Sufficient discomfort is present to cause interference with normal activity.
- Grade 3 (Severe): Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.
- Grade 4 (Life-threatening): Urgent intervention indicated.
- Grade 5 (Death): Death.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study agent that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study agent
- Suspected abuse/misuse of a sponsor study agent
- Accidental or occupational exposure to a sponsor study agent
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study agent, eg, name confusion)
- Exposure to a sponsor study agent from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until 100 days after the last dose of study agent for subjects who enter the Screening Phase. Any subject with an ongoing adverse event will be followed beyond 100 days after the last dose of study agent, subjects will be followed for ongoing treatment-related adverse events and associated medications until all adverse events are resolved, return to baseline, are deemed irreversible, or the subject starts subsequent anticancer therapy. Serious adverse events must be reported using the Serious

Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 4.

All adverse events, regardless of seriousness, severity, or presumed relationship to study agent, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual serious adverse events the sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, the sponsor will submit a safety report in narrative format to the investigators (and the head of the investigational institute where required).

The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.4. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be transmitted electronically or by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study agent or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- A standard procedure for protocol therapy administration will not be reported as a serious adverse event. Hospitalization for a complication of therapy administration will be reported as a serious adverse event.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, sampling for laboratory tests, or biomarker blood sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of

efficacy will be reported if they fulfill the serious adverse event definition (refer to Section 12.1.1, Adverse Event Definitions and Classifications).

12.4.1. Adverse Events of Special Interest

Adverse events indicative of inflammatory cytokine release are expected after infusion of JNJ-757 and will be followed as part of standard safety monitoring activities by the sponsor, and managed in accordance with the guidelines in Section 8.3. Any inflammatory cytokine-related events considered to be serious should be reported to the sponsor's medical monitor within 24 hours of awareness according to the procedure described above for serious adverse events and will require enhanced data collection.

Persistent bacteremia will be followed as part of standard safety monitoring activities by the sponsor and will include both serial blood cultures after dosing in Cycle 1, and subsequent predose surveillance blood cultures during the treatment phase, at the End-of-Treatment visit, and during the follow-up phase, for 1 year after the completion of dosing with JNJ-757. Positive surveillance cultures will be reported to the sponsor's medical monitor within 24 hours of awareness irrespective of seriousness (ie, serious and nonserious adverse events) following the procedure described above for serious adverse events, and will require enhanced data collection.

12.4.2. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form beginning at the time a signed and dated ICF is obtained until 5 months (female subjects) or 7 months (male subjects) after the last dose of study agent. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment. Because the effect of the study agent on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.5. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.4, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY AGENT INFORMATION

14.1. Physical Description of Study Agent(s)

JNJ-757

The JNJ-757 supplied for this study is formulated as: liquid in vial, translucent white suspension, formulated in phosphate-buffered saline + 9% glycerol, at a concentration/strength by viable cell count (colony count assay) of 1.0×10^9 CFU/mL. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

Nivolumab

Nivolumab is a sterile, preservative-free, nonpyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. Nivolumab injection for IV infusion is supplied in single-dose vials. Each mL of solution contains nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, United States Pharmacopeia (USP). The formulation may contain hydrochloric acid or sodium hydroxide to adjust the pH to 6.

14.2. Packaging

JNJ-757

JNJ-757 drug product will be shipped and stored frozen at –60ºC or colder. It consists of attenuated *Lm* suspended in Dulbecco's phosphate-buffered saline and 9% volume concentration glycerol. Primary packaging consists of single-use 2 mL glass vial(s) with gray butyl or bromobutyl stoppers and aluminum crimp seals with flip-off caps. The study agent is supplied in glass vials containing JNJ-757 at a concentration/strength by viable cell count (colony count assay) of 1.0×10^9 CFU/mL. It will be supplied to the site/pharmacy as bulk supply.

Nivolumab

Nivolumab will be shipped and stored under refrigeration at 2°C to 8°C (36°F to 46°F). Protect nivolumab from light by storing in the original package until time of use. Do not freeze or shake. Primary packaging consists of single-use 100 mg/10 mL single-dose vials.

14.3. Labeling

JNJ-757

Study agent labels will contain information to meet the applicable regulatory requirements. Each vial will contain a study-specific label with a unique identification number.

Nivolumab

Nivolumab labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study agent preparation, handling, and storage, as well as handling of reconstituted and diluted solutions.

JNJ-757 is a live-attenuated double-deleted version of *Lm* that exhibits greatly reduced virulence by deletion of 2 genes encoding *actA* and *inlB*. JNJ-757 has been classified as a Risk Group 1 agent. Individuals who prepare JNJ-757 for injection must take standard precautions (eg, use of gloves, laboratory coat, face protection, needle stick or sharps precautions) to avoid contamination or direct contact with the study agent (Siegel 2007).[36] During the storage, preparation, and administration of individual study doses and for the disposal of materials used in the preparation and administration of this product, the study will adhere to applicable institutional infection-control procedures for Risk Group 1 agents (Wilson 2009).[39]

Environmental Precautions

Although shedding of LADD-based products has not been observed in previous studies, precautions should be exercised to avoid intimate contact (ie, exchange of bodily fluids) between subjects and individuals who are at high risk of complications of listeriosis (eg, newborn infants, pregnant women, immunocompromised individuals) from first infusion of JNJ-757 until completion of study-prescribed antibiotic regimen.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study agent received at the site is inventoried and accounted for throughout the study. The study agent administered to the subject must be documented on the drug accountability form. All study agent will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study agent containers.

Study agent must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study agent must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study agent will be documented on the drug return form. When the study site is an authorized destruction unit and study agent supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study agent should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study agent will be supplied only to subjects participating in the study. Returned study agent must not be dispensed again, even to the same subject. Study agent may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study agent from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Recruitment tools
- Study binder with all other necessary documentation (eg, protocol, Investigator's Brochure for JNJ-757, locally approved label for nivolumab, sample ICF, Clinical Trial Agreement, Contact Information sheet[s])
- Investigational Product Preparation Instructions (IPPI)
- Pharmacy manual/SIPPM
- Laboratory manual, laboratory operations manual, requisition forms, sampling supplies, and equipment, if necessary
- Link to NCI-CTCAE Version 4.03: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
- RECIST guidelines Version 1.1
- IWRS manual and worksheets
- Electronic data capture (eDC) manual

- Materials for PRO collection

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

In this study, nivolumab will be administered to all subjects at the dose and schedule approved for use in patients with NSCLC. For those subjects randomized to the combination arm, JNJ-757 will be administered after completion of each Day 1 nivolumab infusion, to ensure that the anticipated adverse events associated with JNJ-757 activation of the innate immune response will not interfere with nivolumab administration.

Thorough scientific evaluation of any promising treatment before market authorization is an ethical requirement. A discussion of the safety and efficacy of JNJ-757 is provided in Section 1.3. This is the first efficacy evaluation of the combination of JNJ-757 with nivolumab; hence, the benefits and risks of the combination are unknown. A DMC will review evolving safety data from this study and the Phase 1 study of JNJ-757. Other LADD *Lm*-based immunotherapeutics such as CRS-207, ADU-623, and JNJ-809 are being studied in combination with immunotherapies including PD-L1 inhibitors. A discussion of the safety and efficacy of CRS-207 is provided in Section 1.2.1.

As with all clinical and pharmacology studies, there are risks associated with venipuncture and multiple blood sample collection. The blood sample collection scheme was designed to collect the minimum number of blood samples that accurately and completely describe the pharmacology of the study agent. This minimizes the number of venipunctures and the total volume of blood collected from each subject during the study. The volume of blood to be drawn is considered to be customary and acceptable for subjects participating in a cancer clinical study and is deemed reasonable for the time frame of the study, based upon the standard of the American Red Cross (2014).[3] Blood cultures and shedding samples will also be collected in Group A, in accordance with established regulatory guidance.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- JNJ-757 Investigator's Brochure (or equivalent information) and amendments/addenda
- Locally approved label for nivolumab
- Sponsor-approved subject recruiting materials
- Sponsor-approved wallet study card
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study agent
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

Subjects will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the subject or his or her legally acceptable representative will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the subject.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject is obtained.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original

medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory pharmacodynamic and biomarker research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand JNJ-757 and nivolumab, to understand adenocarcinoma of the lung, to understand differential drug responders, and to develop tests/assays related to JNJ-757 and nivolumab. The research may begin at any time during the study or the poststudy storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research.

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for nonacceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study agent to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be

obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.

- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: eligibility and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study agent administration information; and date of study completion and reason for early discontinuation of study agent or withdrawal from the study, if applicable. The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct. The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documents. Data must be entered into the eCRF in English. The eCRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The importance of timely disease assessments will be stressed. The sponsor will review the eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will use a combination of monitoring techniques to monitor this study.

The contract research organization (CRO) designated by the sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first postinitiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last scheduled study assessment shown in the Time and Events Schedule (Table 1) for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study agent development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding JNJ-757 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-757, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication.

Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence and the results of clinical studies as required by law.

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Attachment 1: New York Heart Association Criteria

The following table presents the New York Heart Association classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Classification of Functional Capacity and Objective Assessment. Available at http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp. Accessed 22 January 2015.

Attachment 2: Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference

RECIST Version 1.1	
Measurable Tumor Burden	A maximum of 5 target lesions in total (and up to 2 per organ) can be identified at baseline and measured through the course of therapy.
Minimum Size of Measurable Lesions	≥10 mm in longest diameter (LD) by CT scan of which slice is thickness no greater than 5 mm ≥15 mm in short axis (SA) for nodal lesions by CT scan of which slice is thickness no greater than 5 mm ≥10 mm in LD for clinical lesions (must be measured using electronic calipers) ≥20 mm in LD for chest X-ray (if clearly defined and surrounded by aerated lung); CT is preferable Ultrasound (US) cannot be used to measure lesions
Lymph Nodes	Lymph nodes are considered pathologically enlarged if >10 mm in SA. To be measurable, nodal lesions must be ≥15 mm in SA by CT scan of which slice is thickness no greater than 5 mm. Nodal lesions with SA >10 mm and <15 mm are non- measurable. The sum of the diameters (LD for non-nodal target lesions, SA for nodal lesions) is followed through the course of therapy.
Bone Lesions	A lytic or mixed lytic-blastic bone lesion with a soft tissue component assessed on CT/MRI can be measurable if the minimum size criteria are met. Blastic bone lesions and bone lesions assessed on bone scan, positron emission therapy (PET) or plain films are non-measurable.
Cystic Lesions	Lesions that meet the criteria for radiographically defined simple cysts are not malignant. Cystic lesions thought to be metastases can be measurable if they meet the minimum size criteria. If noncystic lesions are present in the same patient, they are preferred for selection as target lesions.
Lesions with Prior Local Treatment	Lesions in previously irradiated areas (or areas treated with local therapy) are not measurable unless the lesion has progressed since therapy.
Too Small To Measure	If a target lesion becomes too small to measure, a default value of 5 mm is assigned. If the lesion disappears, the measurement is recorded as 0 mm.
Lesions which split or Coalesce	If non-nodal target lesions fragment, the LDs of the fragmented portions are added to calculate the sum. If target lesions coalesce and cannot be distinguished, the LD of the coalesced lesion is added to the sum.
Definition of Complete Response (CR)	CR requires: • The disappearance of all lesions. • All lymph nodes must be non-pathological in size (<10 mm SA). • Normalization of tumor marker level.
Definition of Partial Response (PR)	≥30% decrease in the sum of the diameters of all target lesions compared with baseline, in absence of new lesions or unequivocal progression of nontarget lesions
Definition of Stable Disease (SD)	<30% decrease in sum of diameters of all target lesions compared with baseline and < 20% increase compared with nadir, in the absence of new lesions or unequivocal progression of nontarget lesions

Definition of Progressive Disease (PD)	PD is assessed if the sum of the diameters has increased by ≥20% and ≥5 mm from nadir (including baseline if it is the smallest sum). Patients with measurable disease: for "unequivocal progression" based on non-target disease, there must be an overall level of substantial worsening that merits discontinuation of therapy (if target disease is SD/PR). Patients without measurable disease: for "unequivocal progression" of non-target disease, the increase in overall tumor burden must be comparable to the increase required for PD of measurable disease. Furthermore, the appearance of 1 or more new lesions or unequivocal progression of a non-target lesion is also considered as PD.
Assessment of New Lesions	New lesions should be unequivocal and not attributable to differences in scanning technique or findings which may not be tumor (ie, 'new' bone lesions may be healing or flare of pre-existing lesions). If one is equivocal, repeat scans are needed to confirm. If confirmed, PD is assessed at the date of the initial scan. Lesions identified in anatomic locations not scanned at baseline are considered new. New lesions on US should be confirmed on CT/MRI.
FDG-PET	New lesions can be assessed using FDG-PET: (-) PET at baseline and (+) PET at follow-up is PD based on a new lesion. No PET at baseline and (+) PET at follow-up is PD if the new lesion is confirmed on CT. If a subsequent CT confirms the new lesion, the date of the PD is the date of the initial PET scan. No PET at baseline and (+) PET at follow-up corresponding to pre-existing lesion on CT that is not progressing; not PD.
Recurrence of lesions	For a patient with SD/PR, a lesion which disappears and then reappears will continue to be measured and added to the sum. Response will depend upon the status of the other lesions. For a patient with CR, reappearance of a lesion would be considered PD.
Overall Response	One overall response table integrates target, non-target and new lesions for subjects with measurable disease; and another table integrates non-target and new lesions for subjects without measurable disease.
Confirmation of Response	In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. In these trials, subsequent confirmation of PR with one interim time point of SD is acceptable. In randomized trials, confirmation of response is not required.

Source: Eisenhauer 2009 [10]

Attachment 3: Eastern Cooperative Oncology Group Performance Status Score

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all predisease 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 house work, 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

Source: Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair (Oken, 1982).[27]

Attachment 4: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (serious or nonserious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

Disease-Related	Nivolumab Background Therapy
Local respiratory events	Alanine aminotransferase increased
Bronchitis	Arthralgia
Chest pain	Aspartate aminotransferase increased
Cough	Asthenia
Dyspneoa	Blood alkaline phosphatase increased
Hemoptysis	Blood creatinine increased
Plural effusion	Blood thyroid stimulating hormone increased
Pneumonia	Constipation
Wheezing	Cough
CNS metastasis events	Decreased appetite
Altered mental status	Diabetes mellitus
Ataxia	Diarrhoea
Bone pain	Dry mouth
Headache	Hyperglycaemia
Meningismus	Hyponatremia
Seizures	Immune mediated colitis
Spinal cord depression	Immune mediated encephalitis
Paraneoplastic syndromes	Immune mediated endocrinopathy
Cushing syndrome	Immune mediated hepatitis
Hypercalcaemia	Immune mediated nephritis
Syndrome of inappropriate ADH production	Immune mediated pneumonitis
	Immune mediated rash
	Immune mediated renal dysfunction
	Infusion reaction
	Myalgia
	Nausea/vomiting
	Pruritus
	Rash

ADH=antidiuretic hormone.

Reporting of Anticipated Events

All adverse events will be recorded in the eCRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described in Section 12.4, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review it is determined that an anticipated event is possibly related to study agent, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

An Anticipated Event Review Committee (ARC) will be established to perform reviews of prespecified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study agent.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

INVESTIGATOR AGREEMENT

JNJ-64041757
Clinical Protocol 64041757LUC2002 Amendment 2

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Roland Knoblauch

Institution: Janssen Research & Development, LLC

Signature: [redacted] Date: 4-Jan-2018
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Status: Approved, Date: 4 January 2018