Protocol J1L-AM-JZGC, AM0010-201

Study of Pegilodecakin (LY3500518) With Pembrolizumab Compared to Pembrolizumab Alone First-line Tx in Participants With Metastatic Non-Small Cell Lung Cancer (Cypress 1)

NCT03382899

Approval Date: 06-Nov-2018

CLINICAL TRIAL PROTOCOL

PROTOCOL TITLE:	An Open-Label, Randomized Phase 2 Trial of AM0010 in Combination with Pembrolizumab vs Pembrolizumab Alone as First-Line Therapy in Patients with Stage IV/Metastatic Non-Small Cell Lung Cancer and Tumors with High Expression of PD-L1 (≥50%)
PROTOCOL NUMBER:	AM0010-201; J1L-AM-JZGC
TRIAL NAME:	CYPRESS-1
TRIAL DRUG:	AM0010 (pegilodecakin; LY3500518) PEGylated Recombinant Human Interleukin 10 (PEG-rHuIL-10)
IND NUMBER:	131683
SPONSOR:	Eli Lilly and Company (Lilly) Indianapolis, Indiana USA 46285
ORIGINAL PROTOCOL:	06 December 2017
AMENDMENT 1	02 July 2018
AMENDMENT 2	See approval date stamp at the end of this page

Approval Date: 06-Nov-2018 GMT

PROTOCOL APPROVAL PAGE

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Approval of protocol by sponsor: See electronic signature on the last page of this document

PROTOCOL ACCEPTANCE PAGE

PROTOCOL TITLE:	An Open-Label, Randomized Phase 2 Trial of AM0010 in Combination with Pembrolizumab vs Pembrolizumab Alone as First-Line Therapy in Patients with Stage IV/Metastatic Non-Small Cell Lung Cancer and Tumors with High Expression of PD-L1 (≥50%)
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I have read the foregoing protocol and agree to conduct the trial as outlined. In addition, I agree to conduct the trial in compliance with the principles of Good Clinical Practice (GCP), as described in the United States Code of Federal Regulation (CFR) 21 Parts 11, 50, 54, 56, and 312 and the appropriate International Council for Harmonisation guidance documents and with all applicable regulations and guidelines as stated in the protocol and other information supplied to me.

INVESTIGATOR:

Printed Name	Institution
Signature	Date

SUMMARY OF CHANGES

Summary of Key Changes for Protocol AM0010-201 (J1L-AM-JZGC) Amendment 2

Section	Summary of Changes
Across the protocol	Sponsor name changed from ARMO Biosciences, Inc. to Eli Lilly and Company.
Synopsis; Sections 2.2, 2.3, 3.4	Duration of response was added as a secondary objective; disease control rate was moved from exploratory objective to secondary objective; characterization of pharmacokinetics in combination with pembrolizumab was added as an exploratory objective; corresponding changes were made to the endpoints description.
Synopsis; Sections 2.2, 3.0, 3.5, 7.1, 7.2, 7.10, 8.1	Tumor and overall survival assessment frequencies were revised.
Synopsis; Section 3.0, 4.1	Removed reference to echinoderm microtubule-associated protein-like 4 (EML4), as EML4 is not the only fusion partner with anaplastic lymphoma kinase (ALK).
Synopsis; Sections 3.0, 5.1, 10.1	Reference to tumor mutational burden (TMB) measurement was deleted.
Synopsis; Sections 3.0, 6.3, 7.2, 7.8	An option of receiving AM0010 alone as maintenance treatment for patients on Arm 1 who experienced pembrolizumab intolerance was deleted.
Synopsis; Section 3.0	Trial and treatment design schema were updated to reflect the changes in study design.
Synopsis; Section 4.1	Inclusion criterion about target population was updated to specify that the patients must not have had systemic treatment for incurable disease. If patients had chemotherapy as part of curative intent radical radiotherapy or surgery they should have completed the last dose of chemotherapy 6 months prior to randomization.
Synopsis; Section 4.1, 4.2	Inclusion criterion “patients without known epidermal growth factor receptor (EGFR) or EML4-anaplastic lymphoma kinase (ALK) mutation” was moved to exclusion criteria and revised as “Patients with non-squamous NSCLC with known EGFR mutation or ALK rearrangement.”
Synopsis; Section 4.1	Inclusion criteria about laboratory values were revised to delete approval of a patient with isolated increase by the Medical Monitor; exclusion criterion about prothrombin time was revised and moved under inclusion criteria.
Synopsis; Section 4.2	Criterion that required exclusion of patients with no history of tobacco use was deleted.
Synopsis; Section 4.2	Exclusion criterion “Patients that have received pembrolizumab” was deleted.
Synopsis; Sections 6.1, 6.2, 7.2, 7.7, 11.1	Reference to product concentration was deleted and reference to product label for full storage instructions was added.
Synopsis	Reticulocyte count and lactate dehydrogenase investigations were added to the laboratory panel.

Section	Summary of Changes
Synopsis; Sections 3.5, 7.2, 7.10, 8.1, 9.3, 10.5	Safety observation period was extended from 30 days to 90 days, including follow-up visits 60 and 90 days after the last dose of study treatment (±7 days).
Synopsis; Sections 3.7	Study design was updated to allow continued access of the study treatment to the patients remaining on study after study completion and continuing to experience clinical benefit.
Synopsis; Section 7.13, 7.14	Biomarker and immunogenicity sample collection requirement was updated to include collection on both the arms.
Synopsis; Section 10.3	Sample size justification was added.
Synopsis; Section 10.3	Schedule of analyses for key endpoints, including interim analysis, was added.
Synopsis	Clarified that all efficacy analyses will be based on the Intent-to-Treat population.
Synopsis; Sections 3.4, 6.4, 7.1, 8.1, 9.3, 10.5; and Appendix F	National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE) version was changed from 5.0 to 4.03.
Trial Glossary	Trial glossary was updated per changes made in the protocol.
Section 3.6	Study completion was defined.
Section 3.8	End of trial was defined.
Section 6.4	Terms Treatment Delay and Interruption were replaced by treatment Withhold; the section was updated to clarify the treatment withhold, discontinuation, and dose schedule reduction criteria.
Section 7.4; Appendix A	A requirement of mandatory tumor tissue sample for biomarker research was specified.
Section 7.12; Appendices A and B	Pharmacokinetic sample collection time points were revised; storage requirement for pharmacokinetic samples was added.
Section 7.13; Appendices A and B	Anti-drug antibody sample collection time points were revised; storage requirement for immunogenicity samples was added.
Section 7.14	Storage requirement for biomarker samples was added.
Section 9.0	Adverse event reporting requirement was updated to ensure accurate and effective reporting of safety information, including adverse events, serious adverse events, suspected unexpected serious adverse events, pregnancy, and complaint handling.
Appendix A	Updated per changes made in the protocol, including addition of extended safety observation period and addition of sample collection time points for pharmacokinetics, immunogenicity, and biomarkers.
Appendix B	Added schedule of assessment table for continued-access period.

Section	Summary of Changes
Appendix E	Added guidance on hepatic monitoring tests for treatment emergent abnormality.
Across the protocol	Other minor editorial changes were made to add clarity and to correct the inconsistencies.

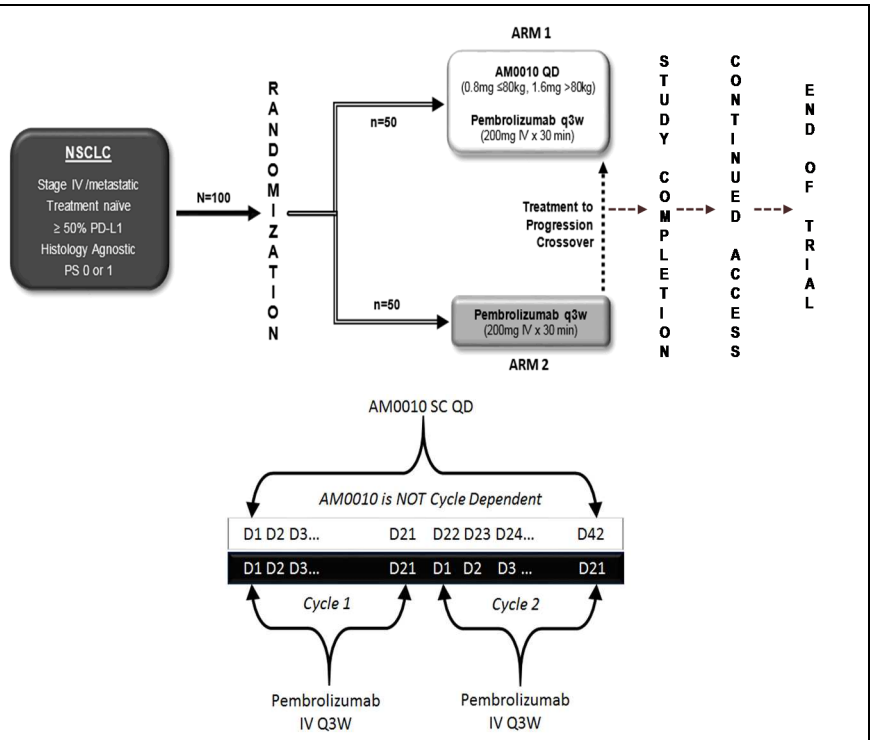
PROTOCOL SYNOPSIS

PROTOCOL TITLE:	An Open-Label Randomized Phase 2 Trial of AM0010 in Combination with Pembrolizumab vs Pembrolizumab Alone as First-Line (1L) Therapy in Patients with Stage IV/Metastatic Non-Small Cell Lung Cancer and Tumors with High Expression of PD-L1 (≥50%)
PROTOCOL NUMBER:	AM0010-201; J1L-AM-JZGC
CLINICAL PHASE:	2
INDICATION:	Wild type (without known specific driver mutations in epidermal growth factor receptor – EGFR or anaplastic lymphoma kinase [ALK]) non-small cell lung cancer (NSCLC).
NUMBER OF PATIENTS:	Approximately 100
INVESTIGATIONAL PRODUCT:	AM0010 (pegylated IL-10 [pegilodecakin]; LY3500518)
ACTIVE INGREDIENT:	PEG-rHuIL-10
OTHER DRUG:	Pembrolizumab
TRIAL LOCATION:	Multi-center, USA only
TRIAL DURATION:	Approximately 60 months
RESEARCH HYPOTHESIS:	In newly diagnosed metastatic NSCLC patients whose tumors have high PD-L1 expression, the administration of AM0010 in combination with pembrolizumab increases the objective response rate (ORR) when compared with the administration of pembrolizumab alone.
OBJECTIVES:	The trial objectives will be evaluated in adult patients with histologically or cytologically documented NSCLC that is metastatic or recurrent and whose tumor tissue PD-L1 expression ≥50%. PD-L1 IHC 22C3 assay is mandatory. To compare the efficacy of AM0010 in combination with pembrolizumab vs pembrolizumab alone as measured by: <u>Primary</u> ORR <u>Secondary</u> progression-free survival (PFS) overall survival (OS) disease control rate (DCR) duration of response (DoR) safety and tolerability profile <u>Exploratory</u> Characterize AM0010 pharmacokinetics in combination with pembrolizumab To explore biomarkers including immune activation markers that may correlate with efficacy outcome measures
TRIAL DESIGN:	This is an open-label, randomized, multicenter Phase 2 trial in adult patients with treatment-naïve, Stage IV/metastatic NSCLC whose tumors are not known to have EGFR mutation or ALK rearrangement, and have high expression (≥50%) of PD-L1. PD-L1 will be determined with an FDA-approved PD-L1 IHC 22C3 assay. Patients will be stratified according to tumor histology (squamous vs non-squamous).

PROTOCOL SYNOPSIS

	Patients will be randomized in a 1:1 ratio into 1 of 2 treatment arms. ***Arm 1:*** Patients will receive AM0010 as a subcutaneous (SQ) daily (QD) injection and pembrolizumab as intravenous (IV) infusion on Day 1 of a 21-day cycle. o ***AM0010 Dose*** ▪ ≤80 kg body weight = 0.8 mg ▪ >80 kg body weight = 1.6 mg o ***Pembrolizumab Dose*** ▪ 200 mg over approximately 30 minutes IV infusion ***Arm 2:*** Patients will receive pembrolizumab as IV infusion on Day 1 of a 21-day cycle. o ***Pembrolizumab Dose*** ▪ 200 mg over approximately 30 minutes IV infusion Trial sites will provide best supportive care per institution's standard of care, including concomitant medications. Arm 1 and 2 dosing (QD for AM0010 and Q3W for pembrolizumab) will continue in the absence of disease progression, unacceptable toxicity, or the patient withdraws consent, whichever is first. Patients will be treated with a maximum of 35 cycles of pembrolizumab every 3 weeks or 2 years, whichever is longer. At the time of documented disease progression (per Investigator assessment) patients in Arm 1 will be discontinued from the treatment period of the trial and patients in Arm 2 may crossover to receive treatment with AM0010 with pembrolizumab. All randomized patients will be followed for OS every 9 weeks (±7 days) during the first year from the 90-day follow-up visit, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter. The survival follow-up will be done until death or the study completion, whichever is first, whether or not trial drug was administered. For patients who were randomized, but withdraw consent, survival (date of death) will be obtained by use of publicly available information. Tumor assessment will be performed for all randomized patients every 9 weeks (±7 days) during the study treatment and during the first year from discontinuation of the study treatment, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter. Tumor assessment will be repeated until disease progression, death, or receipt of new anti-cancer therapy, or until study completion, whichever is first, whether or not study treatment was administered. All computed tomography (CT)/magnetic resonance imaging (MRI) scans for all randomized patients enrolled in the trial will be collected prospectively and submitted to a central imaging vendor for archiving. These scans may be independently reviewed at a later time at the request of Eli Lilly and Company (Lilly).

PROTOCOL SYNOPSIS

TRIAL and TREATMENT DESIGN SCHEMA:	

INCLUSION CRITERIA:	Patient will be eligible for trial participation as defined by the inclusion and exclusion criteria as follows: Eligible patients must meet the following criteria to be enrolled in the trial: 1. Signed Written Informed Consent (ICF). Patients must have signed and dated an IRB/IEC approved written ICF in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care. a. Patients must be willing and able to comply with scheduled visits, dosing schedule, laboratory tests, and other requirements of the trial. 2. **Target Population** a. Patients must have histologically or cytologically confirmed NSCLC that is Stage IV/metastatic. b. Patients must not have had systemic treatment for incurable disease. If patients had chemotherapy as part of curative intent radical radiotherapy or surgery they should have completed the last dose of chemotherapy 6 months prior to randomization. c. Patients with tumor tissue high expression of PD-L1 as defined by Tumor Proportion Score (TPS) ≥50% and as determined by an FDA-approved PD-L1 IHC 22C3 assay is mandatory. d. Patients ≥18 years of age. e. Patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. f. Patients with measurable disease by CT or MRI per Response Evaluation Criteria in Solid Tumor (RECIST) v.1.1 criteria. g. Patients with Radiographic Tumor Assessment performed within 30 days prior to randomization. i) Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression at that site. h. Patients that have completed prior radiotherapy or radiosurgery at least 2 weeks prior to randomization. i) Patients with brain metastases are eligible if they are asymptomatic, or are treated and are neurologically stable for at least 2 weeks without the use of steroids or on stable or decreasing dose of ≤10 mg daily prednisone (or equivalent). i. Patients with baseline laboratory values obtained 21 days prior to randomization meeting the following criteria: i) WBCs≥2000/μL. ii) Neutrophils ≥1500/μL. iii) Platelets ≥100×10^3/μL. iv) Hemoglobin ≥9.0 g/dL. v) Creatinine of ≤1.5×ULN or calculated creatinine clearance >60 mL/minute per institutional standard. For patients with a body mass index (BMI) >30 kg/m^2, lean body weight should be used instead of actual body weight. vi) AST≤1.5×ULN (<5×ULN for patients with liver metastasis). vii) ALT≤1.5×ULN (<5×ULN for patients with liver metastasis). viii) Total bilirubin ≤1.5×ULN (except patients with Gilbert Syndrome who must have total bilirubin <3.0 mg/dL). ix) Alkaline phosphatase <2.5×ULN (<5×ULN for patients with liver metastasis). x) Prothrombin Time (PT) <1.5×ULN, unless receiving anticoagulation therapy; activated Partial Thromboplastin Time (aPTT) <1.5×ULN, unless receiving anticoagulation therapy. 3. **Reproductive Status**

	a. Women of childbearing potential (WOCBP) must agree to use method(s) of contraception. b. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to the start of investigational product. c. Male or non-pregnant, non-lactating female, ≥18 years of age: • If sexually active, the subject must agree to use contraception considered adequate and appropriate by the Investigator during the period of trial drug administration. In addition, male and female patients must utilize contraception after the end of the treatment in the individual drugs product's Prescribing Information provided in the trial manual and the Clinical Trial Facilitation Group, provided in Appendix B
EXCLUSION CRITERIA:	Eligible patients **must not** have the following criteria (except where indicated) to be enrolled in the trial: 1. **Medical History and Concurrent Diseases** a. Patients with carcinomatous meningitis. b. Patients with active central nervous system (CNS) metastases. i) Patients are eligible if CNS metastases are adequately treated and neurologically stable at baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. In addition, patients must be either off corticosteroids or on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent) at the time of consent for the trial. c. Patients with life expectancy of <3 months. d. Patients with non-squamous NSCLC with known EGFR mutation or ALK rearrangement. e. Patients currently using medicinal or recreational cannabis. f. Patients with any serious or uncontrolled medical disorder or active infection with the hepatitis virus or the human immunodeficiency virus (HIV). g. Patients with other active malignancies requiring concurrent intervention other than hormone antagonists. h. Patients with previous malignancies (except non-melanoma skin cancers and the following in situ cancers: bladder, gastric, colon, cervical/dysplasia, endometrial, melanoma, or breast) are excluded, unless a complete remission was achieved at least 2 years prior to trial entry AND no additional therapy other than hormone antagonists is required or anticipated to be required during the trial period. i. Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications at the time of consent for the trial. Inhaled or topical steroids and adrenal replacement steroid doses >10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease. j. Patients with known prior history of hemophagocytic lymphohistiocytosis (HLH). k. Patients with active known or suspected autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression. Patients with vitiligo, Type I diabetes mellitus, residual hypothyroidism requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. l. Patients with >Grade 1 (NCI-CTCAE v.4.03) toxicities attributed to prior anti-cancer therapy (other than alopecia and fatigue) prior to randomization. m. Patients that have received therapy with anti-tumor vaccines or other

	immuno-stimulatory antitumor agents. Non-cancer vaccines (non-attenuated and non-live) are permitted. n. Patients that have received therapy with anti-PD-1, anti-PD-L1, anti-PD-L-2, anti-CD-137, and/or anti CTLA-4 antibodies (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways). o. Patients with a history of symptomatic interstitial lung disease. p. Patients not completely recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of trial treatment. 2. **Physical and Laboratory Test Findings** a. Patients with active Hepatitis B or C infections. b. Patients known to be HIV-positive. 3. **Allergies and Adverse Drug Reaction** a. Patients with a history of severe hypersensitivity reactions to monoclonal antibodies. b. Patients with a history of allergy or intolerance (unacceptable adverse event) to trial drug components, Polysorbate 80-containing infusions. 4. **Sex and Reproductive Status** a. WOCBP who are pregnant or breastfeeding. b. Women with a positive pregnancy test at enrollment or prior to administration of trial drug. 5. **Prohibited Treatments and/or Restricted Therapies** a. Patients requiring ongoing or planned administration of anti-cancer therapies other than those specified in this trial. b. Patients requiring the use of corticosteroids or other immunosuppressive medications (>10 mg daily prednisone equivalent for more than 14 sequential days). Corticosteroids or other immunosuppressive medications for more than 14 sequential days require approval of the Medical Monitor. c. Patients receiving any investigational agent within 28 days of first administration of trial treatment. 6. **Other Exclusion Criteria** a. Patients with any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the Investigator, would limit the individual's ability to comply with the trial requirements, substantially increase risk to their well-being, or impact the interpretability of trial results. Eligibility criteria for this trial have been carefully considered to ensure the safety of the trial patients and to ensure the integrity of the trial results. It is imperative that patients meet in full all eligibility criteria and requirements.
AM0010: DRUG and FORMULATION	AM0010 is provided as a sterile, single-use prefilled syringe, with a clear solution. AM0010 drug product is stored refrigerated. Refer to the product label for full storage instructions.
AM0010: DOSE/ROUTE/REGIMEN	Patients in Arm 1 (including crossover patients) will self-administer AM0010 as a QD SQ injection (abdomen, thigh, or back of upper arm) at weight-dependent dose. ≤80 kg body weight = 0.8 mg >80 kg body weight = 1.6 mg Doses will continue in the absence of disease progression, unacceptable toxicity, or subject's withdrawal of consent.

PEMBROLIZUMAB: DRUG and FORMULATION	Pembrolizumab is commercially available. Trial sites will be responsible for procurement, storage, and destruction. Pembrolizumab for injection (lyophilized powder): carton containing 1 50-mg single-dose vial (NDC 0006-3029-02). • Store vials refrigerated. Refer to the product label for full storage instructions. Pembrolizumab injection (solution): carton containing one 100-mg/4-mL (25 mg/mL), single-dose vial (NDC 0006-3026-02) • Store vials refrigerated. Refer to the product label for full storage instructions..
PEMBROLIZUMAB: DOSE/ROUTE/REGIMEN	Patients in trial Arm 1 or Arm 2 will be administered pembrolizumab as an IV infusion on Day 1 of a 21-day cycle. Patients on Arm 1 (including crossover patients) will be administered pembrolizumab at a fixed dose of 200 mg over approximately 30 minutes of IV infusion Patients on Arm 2 will be administered pembrolizumab at a fixed dose of 200 mg over approximately 30 minutes of IV infusion Treatment will continue every 3 weeks in the absence of disease progression, unacceptable toxicity, or subjects' withdrawal of consent.
TRIAL PROCEDURES:	The trial consists of the following procedures: **Screening Period:** The screening period must occur within 21 days prior to randomization (unless noted otherwise). Some screening assessment may be counted as Day 1 assessment (Baseline) if completed within 72 hours prior to dosing. • Baseline scans must include head, chest, abdomen, and pelvis. • **Clinical evaluation:** complete medical and cancer history, physical examination (Site/Organ System Status [includes: General appearance, skin, H/E/E/N/T – Thyroid, Pulmonary, Cardiovascular, Gastrointestinal, Musculoskeletal/Extremities, Genitourinary/Breast, Lymph Nodes, Neurological, and Psychiatric]), ECOG performance status, ECG, height (screening only), weight, vital signs, documentation of concomitant medications and obtaining pathology report of archival tissue. • **Laboratory studies:** hematology (WBC with differential, RBC count, hemoglobin, reticulocyte count, and platelet count); aPTT and International Normalized Ratio (INR) or PT; comprehensive chemistry panel (sodium, potassium, chloride, CO_2, creatinine, calcium, BUN, albumin, AST, ALT, alkaline phosphatase, lactate dehydrogenase, and total bilirubin); Thyroid Function Test (TSH, free T3, and free T4); urinalysis with microscopic examination; and serum or urine pregnancy test for women of childbearing potential. • **Clinical staging:** imaging for measurable disease by CT or MRI if allergic to contrast media must be performed within 30 days prior to randomization. Scan performed as part of standard practice may be used if conducted within 30 days prior to randomization. • A fresh tissue biopsy is only required if no archival tissue is available within 60 days of Informed Consent or unless approved by the Medical Monitor. Biopsy of prior radiation-treated areas is not preferred. • Most recent PD-L1 expression status $\geq$50% to determine eligibility. An FDA-approved PD-L1 IHC 22C3 assay is mandatory. **Randomization:** • Patients will be randomized within 21 days of their screening assessments. • Patients must begin treatment within 3 days after randomization. **Trial Treatment Period:** Patients may participate in this trial until they experience drug intolerance, disease progression, or withdraw consent.

	• **Clinical evaluation:** complete history, physical examination (Site/Organ System Status [includes: General appearance, skin, H/E/E/N/T – Thyroid, Pulmonary, Cardiovascular, Gastrointestinal, Musculoskeletal/Extremities, Genitourinary/Breast, Lymph Nodes, Neurological, and Psychiatric]), ECOG performance status, height, weight, vital signs, and documentation of concomitant medications. • **Laboratory studies:** hematology (WBC with differential, RBC count, reticulocyte count, and platelet count); aPTT and International Normalized Ratio (INR) or PT; comprehensive chemistry panel (sodium, potassium, chloride, CO_2, creatinine, calcium, BUN, albumin, AST, ALT, alkaline phosphatase, lactate dehydrogenase, and total bilirubin); Thyroid Function Test (TSH, free T3, and free T4); urinalysis with microscopic examination; and serum or urine pregnancy test for women of child bearing potential. • **Pharmacokinetic:** sparse sampling in all patients in Arm 1 and crossover and exploratory molecular biomarker sample collection in all patients. • **Tumor Assessment:** CT or MRI (if allergic to contrast media) scans will be performed every 9 weeks (±7 days) during the study treatment and during the first year from discontinuation of the study treatment, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter, to evaluate response to treatment by RECIST v.1.1. • Tumor assessment will be repeated until disease progression, death, or receipt of new anti-cancer therapy, or until study completion, whichever is first, whether or not study treatment was administered • The same radiographic procedure to define measurable lesions must be used throughout the trial for each patient. • Patients will continue the assigned trial treatments until tumor progression by RECIST v.1.1 criteria (per Investigator's assessment) by CT or MRI (if allergic to contrast media), withdrawal from the trial, or intolerance of therapy not manageable with dose modifications outlined in the protocol/package insert and/or supportive care. Note: Patients with suspected radiographic pseudoprogression, in the absence of clinical deterioration, should remain on trial treatments and be rescanned at 4 weeks or later. If progression is confirmed on follow-up scan, patients in Arm 1 will be discontinued from the treatment and patients in Arm 2 may crossover to receive treatment with AM0010 with pembrolizumab if they fulfill eligibility requirements. Refer to Section 7.6. • Patients who discontinue trial treatments with response of CR, PR, or SD will undergo CT or MRI scan evaluations per protocol until time of PD or death, or until study completion or initiation of subsequent anti-cancer therapy, whichever is first. • Patients who demonstrate clinical progression will have a scan conducted at the time to document disease status by RECIST v.1.1. • The first scheduled tumor response assessment will be performed at 9 weeks (±7 days), and responders (CR or PR per RECIST v1.1) will have a confirmatory scan at ≥4 weeks after response has been established using the same technique as baseline scans. • To mitigate the chance of detecting false progression (ie, pseudoprogression) early in the course of treatment with AM0010 in combination with pembrolizumab or the pembrolizumab-alone arm, patients whose scans show radiographic progression in the absence of clinical deterioration including worsening performance status as assessed by the Investigator may remain on trial treatments and an additional scan should be obtained at ≥4 weeks (±7 days) as outlined in Section 7.6. If this subsequent scan shows disease progression, patients in Arm 1 will be discontinued from the treatment period of the trial; patients in Arm 2 may cross over to receive treatment with AM0010 in combination with pembrolizumab if they fulfil the necessary eligibility criteria. • All screening and on-trial CT/MRI scans for all patients randomized on the

	trial will be collected prospectively and submitted to a central imaging vendor for archiving. These scans may be independently reviewed at a later time at the request of Lilly. **End of Treatment Visit and Extended Safety Observation Period:** All patients must have the end-of-treatment visit 28 days after the last dose of study treatment (±7 days) and extended safety observation period visits 60 and 90 days after the last dose of study treatment (±7 days). The procedures should be conducted as described in the protocol and schedule of events (Appendix A). **Long-Term Follow-Up Period:** All randomized patients will be followed for OS every 9 weeks (±7 days) during the first year from the 90-day follow-up visit, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter. The survival follow-up will be conducted until death or study completion, whichever is first, whether or not trial treatment was administered. For patients who were randomized, but withdrew consent, survival (date of death) will be obtained by use of publicly available information. Tumor assessment will be performed for all randomized patients every 9 weeks (±7 days) during the study treatment and during the first year from discontinuation of the study treatment, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter. Tumor assessment will be repeated until disease progression, death, or receipt of new anti-cancer therapy, or until study completion, whichever is first, whether or not study treatment was administered. Scans will include head and chest, abdomen, and pelvis (CAPs) and will be sent to the central imaging vendor for archiving and possible assessment at a later date. If clinical progression is suspected, all relevant clinical documentation is to be submitted to the central imaging vendor for archiving. All randomized patients will be followed after the end-of-treatment visit for treated patients or after randomization for patients not treated, until study completion or death, whichever is first. The Investigator (or designee) will acquire the following information from patients who were randomized: • Tumor assessment will be performed for all randomized patients every 9 weeks (±7 days) during the study treatment and during the first year from discontinuation of the study treatment, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter. Tumor assessment will be repeated until disease progression, death, or receipt of new anti-cancer therapy, or until study completion, whichever is first, whether or not study treatment was administered. • Subsequent cancer treatments (all randomized patients). • Any serious adverse events (SAEs) considered to be related to trial treatment >90 days post last day of trial treatment, follow until resolution. • Date and cause of death (all randomized patients). **Continued access:** All patients remaining on AM0010 without disease progression following study completion (see Section 3.7) will be able to enter the continued-access period of the study, in which patients on study treatment who continue to experience clinical benefit may continue to receive study treatment until disease progression, death, unacceptable toxicity, or end of trial.
SAFETY ASSESSMENTS:	Safety and tolerability will be monitored through continuous reporting of adverse events (AEs) and SAEs. Safety will be assessed by physical exam, standard clinical and laboratory tests (hematology, chemistry, coagulation tests, thyroid function, and urinalysis), and incidence of patients experiencing dose modifications, withholds, and/or discontinuation of trial drugs with reasons for trial drug discontinuation (refer Section 6.4). All AEs will be assessed regarding the relationship to trial treatments and the toxicity grade will be defined by National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE) v.4.03.

EFFICACY ASSESSMENTS:	Tumors responses will be assessed by RECIST v.1.1 criteria using CT or MRI scan (in patients who are known to be allergic to contrast media). Scans will be performed as described in Section 7.1 PFS and OS will be assessed from the date of randomization.
PHARMACOKINETICS:	Blood samples for pharmacokinetics (PK) with sparse sampling techniques will be obtained on all patients in Arm 1 (including crossover patients) to characterize PK of AM0010 in combination with pembrolizumab and to explore exposure-safety and exposure-efficacy relationships. Data from these investigations may be evaluated for correlations with response, survival, and safety data.
BIOMARKERS:	Blood samples for biomarker analysis will be obtained on all patients in Arms 1 and 2. A variety of factors that may impact the immunomodulatory properties and efficacy of AM0010 in combination with pembrolizumab will be investigated in peripheral blood. Data from these investigations may be evaluated for correlations with response, survival, and safety data.
IMMUNOGENICITY: (Anti-AM0010 Antibodies)	Blood samples for immunogenicity analysis will be obtained on all patients in Arms 1 and 2 according to the Schedule of Assessments. Samples will be evaluated for development of anti-drug antibodies (ADAs) by a validated immunoassay.
SAMPLE SIZE:	With 100 patients, this study has more than 80% power to detect a 25% improvement (ie, 45% vs 70%) in the ORR between AM0010 in combination with pembrolizumab and pembrolizumab alone at a 1-sided 5% type I error rate.
INTERIM ANALYSIS:	A planned interim analysis may be performed when the 50th randomized patient has been followed up for approximately 3 months. No statistical boundaries or alpha spending will be applied for this interim analysis as the primary purpose of this analysis is to assess safety and PK. At the time of interim data lock, all patients on study will continue on the study per protocol. See Table 6 for the schedule of analyses of key endpoints.
STATISTICAL METHODS: **EFFICACY ANALYSES**	All efficacy analyses will be based on the Intent-to-Treat (ITT) population, which includes all randomized patients regardless of whether the patient receives any study drugs or has any efficacy assessments. The primary efficacy endpoint is objective tumor response assessed according to RECIST v.1.1 criteria. The ORR will be summarized and compared using a Cochran-Mantel-Haenszel 2-sided test at a type I error rate of 10% stratified by tumor histology (squamous vs non-squamous.) Progression-free survival will be compared in the 2 randomized treatment arms using a 2-sided log-rank test, stratified by the tumor histology. Progression-free survival time will be summarized using the Kaplan-Meier method to estimate the median PFS and 95% confidence interval (CI). Overall survival will be summarized in the same manner as the PFS.
SAFETY ANALYSES	Safety Population includes all randomized patients who received any amount of study drug. Trial treatment exposure will be summarized. Adverse events will be summarized in terms of treatment-emergent events defined to be any event that begin or worsen in grade after first dose through 30 days after the last dose of trial drugs. Descriptive statistics of safety will be presented using NCI-CTCAE version 4.03 by treatment arm. All treatment-emergent AEs, due to any cause, treatment-related AEs, AEs leading to discontinuation from the trial treatments, SAEs, and drug-related SAEs will be tabulated using worst grade per NCI-CTCAE v4.03 criteria by system organ class and preferred term. On-trial lab parameters including hematology and chemistry will be summarized using the worst grade per NCI-CTCAE v4.03 criteria.

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TRIAL GLOSSARY

Abbreviation/Acronym	Definition
ADA	anti-drug antibody
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALK	anaplastic lymphoma kinase mutation
ALT	alanine transaminase
AM0010	PEGylated recombinant Human IL-10
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
AUC	area under the curve (pharmacological exposure)
BMI	body mass index
BUN	blood urea nitrogen
CAPs	chest, abdomen, and pelvis
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum drug concentration
CMH	Cochran-Mantel Haenszel
C_{min}	minimal drug concentration/serum trough concentration
CNS	central nervous system
Continued-access period	The continued-access period begins after study completion and ends at the end of trial.
CPK	creatine phosphokinase
CR	complete response (no measurable residual tumor)
CRF	case report form
CRP	Clinical Research Physician
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
EC_{10}	equivalent to 10% effective concentration
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EKG	electrocardiogram
End of trial	End of the trial is defined as the date of the last visit or last scheduled procedure for the last patient. The end of trial occurs after study completion after the continued-access period (if any).
FDA	US Food and Drug Administration
GCP	good clinical practice
G-CSF	granulocyte-colony-stimulating factor
GGT	gamma-glutamyl transferase
GLP	good laboratory practices
hCG	human chorionic gonadotropin
HCT	hematocrit
Hgb	hemoglobin
HIV	human immunodeficiency virus

HNSTD	highest non-severely toxic dose
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IFNγ	Interferon gamma
IL-10	interleukin 10
IND	Investigational New Drug Application
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous(ly)
LFT	liver function test
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NHP	non-human primate
NIMP	Non-investigational medicinal products
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung carcinoma
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death 1
PDAC	pancreatic ductal adenocarcinoma
PE	physical examination
PEG-rHuIL-10	PEGylated recombinant human interleukin 10
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PT	prothrombin time
qd	Latin: quaque die (once a day)
QT	QT interval
QTc	corrected QT interval
RCC	renal cell carcinoma
rHuIL-10	recombinant human interleukin 10
rMuIL-10	recombinant murine interleukin 10
SAE	serious adverse event
SD	stable disease
SQ	subcutaneous
Study completion	This study will be considered complete when the final analysis of the primary and secondary objectives is complete. This includes 3-year follow-up for OS after the last patient is randomized.
t½	half-life
TPS	tumor proportion score
TK	toxicokinetics
T_{max}	time of maximum concentration observed

TRAEs	treatment-related adverse events
ULN	upper limit of normal
vs	versus
WBC	white blood cell
WOCBP	women of childbearing potential

1.0 BACKGROUND AND RATIONALE

1.1 Non-Small Cell Lung Cancer

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide, accounting for approximately 18% of all cancer deaths (Jemal, Bray et al. 2011). Despite treatment with platinum and taxane-based chemotherapy, patients with metastatic NSCLC have a median survival of approximately 10 months, and a 5-year survival rate of approximately 15%. Despite the increased number of treatment options available for patients with both non-squamous and squamous histology NSCLC, there has been little overall survival (OS) improvement from several new agents, including pemetrexed, erlotinib, and bevacizumab, beyond very small subpopulations. Therapeutic options for mutation wild-type non-squamous and squamous NSCLC in the first-line setting are particularly limited. Docetaxel was approved as a second-line treatment for advanced NSCLC on the basis of longer survival than that with best supportive care (Fossella, DeVore et al. 2000); (Shepherd, Dancey et al. 2000). Newer agents, such as pemetrexed and erlotinib, which have a better side-effect profile than docetaxel, have either been shown to be non-inferior to docetaxel or have failed to show superiority to docetaxel with respect to OS when they are used as second-line therapy (Hanna, Shepherd et al. 2004); (Garassino, Martelli et al. 2013).

Immunotherapeutic approaches for the treatment of malignancies recently have demonstrated clinical efficacy in several cancer types. The programmed death 1 (PD-1) receptor expressed on activated T cells is engaged by the tumor-expressed ligands of PD-L1 and PD-L2 which are expressed on the tumor cell itself or on the tumor infiltrating cells, as well as on T cells. PD-1 activation down-regulates T cell activation and promote tumor immune escape (ie, the mechanism by which tumor cells escape recognition and elimination by the immune system) (Pardoll 2012).

Pembrolizumab is a humanized monoclonal antibody against PD-1 that in a recent phase 3 trial in advanced NSCLC was tested against chemotherapy. The patient population was previously untreated, with PD-L1 expression on at least 50% of the tumor cells. The median progression-free survival (PFS) was 10.3 months in the pembrolizumab group versus 6 months in the chemotherapy group. The survival at 6 months was 80.2% in the pembrolizumab versus 72% in the chemotherapy group. The objective response rate (ORR) was higher in the pembrolizumab group at 44.8% versus 27.8% in the chemotherapy group (Reck et al NEJM 375; 19 Nov 10, 2016). Recently, pembrolizumab in combination with platinum and pemetrexed received accelerated approval as first line of therapy for all non-squamous NSCLC patients based on PFS. The ORR with the combination was 55% as compared to 29% with chemotherapy alone and the median PFS was 13 months versus 8.9 months. The mOS was not established, but the OS was similar between both groups (Langer, Gadgeel et al. 2016). Due to insufficient data on the benefit of the combination, the most recent ASCO guidelines do not recommend the combination of immune checkpoint inhibitors with chemotherapy in first line treatment of NSCLC (Hanna, Johnson et al. 2017).

Pembrolizumab is FDA approved as a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression (tumor proportion score [TPS] ≥50%) as determined by an FDA-approved test, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations. Combining AM0010 with pembrolizumab may represent a promising therapeutic combination to address this unmet medical need in patients with advanced NSCLC.

1.2 AM0010 Background

AM0010 is a PEGylated recombinant form of human IL-10 (PEG-rHuIL-10). AM0010 is produced by prokaryotic fermentation, refolding, purification of rHuIL-10, followed by PEGylation and final purification of AM0010. AM0010 and PEG-rMuIL-10 bind and activate the murine IL-10 receptor in a comparable molar concentration, as shown in cell-based activity assays.

Preliminary evidence for the clinical activity of AM0010 was obtained in a first in human trial (Naing, Papadopoulos et al. 2016). Objective responses to AM0010 monotherapy were observed in 4 of 15 patients with renal cell cancer (RCC), one patient with ocular melanoma, and one patient with cutaneous T cell lymphoma. Combination of AM0010 with an anti-PD-1 immune checkpoint inhibitor lead to objective responses in 4 of 8 patients with RCC and in 2 of 5 patients with NSCLC. While a small number of patients were included in these cohorts, the rate of objective responses and the sustained duration of the observed responses appeared increased over what would be expected from monotherapy of either agent. This may indicate that a combination of AM0010 with anti-PD-1 is clinically beneficial for patients with refractory or resistant metastatic NSCLC. An additional 30 patients with NSCLC which progressed on or after platinum containing regimen are enrolled for the treatment with AM0010 (1.6 or 2 mg SQ qd based on weight of <80 kg or ≥ 80 kg, respectively) and nivolumab (240 mg IV, q2w). Preliminary results indicate that at least 38% of evaluable patients have an objective response, including one patient with a complete response.

1.2.1 AM0010 Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. Genetic mutations in tumor cells lead to the translation and presentation of mutant proteins on tumor and immune cells. Those are recognized by CD8+ T cells which in turn kill the tumor cells. As a consequence, tumors such as NSCLC and melanoma, which have a relatively high burden of somatic mutations, have a higher probability to respond to immune oncology drugs (Rizvi, Hellmann et al. 2015). Tumor progression may also be facilitated by the acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune response (Pardoll 2003); (Zitvogel, Tesniere et al. 2006); (Dunn, Bruce et al. 2002). The role of immunosurveillance in NSCLC and other cancers is supported by many studies, demonstrating a correlation between tumor infiltrating CD8+ T cells in

surgically resected specimens and patient survival (Fridman, Pages et al. 2012). AM0010 increases the infiltration of CD8+ T cells in preclinical models and in cancer patients. In addition, AM0010 induces a CD8+ T cell mediated immune activation in most treated patients, represented by elevation of activation markers on CD8+ T cells, elevation of CD8+ T cells stimulating cytokines in the serum, increase of the cytotoxic products of CD8+ T cells in the serum and the tumor and a de-novo expansion of CD8+ T cell clones in systemic circulation. Pembrolizumab releases the inhibition of CD8+ T cells by PD-1. This facilitates the stronger activation of CD8+ T cells recognizing foreign or novel mutated tumor antigens. Since the mechanisms of AM0010 and pembrolizumab are independent but activate the same target cell, it was postulated that the combination of AM0010 with an anti PD-1 immune checkpoint inhibitor could function synergistically.

1.2.2 AM0010 Nonclinical Experience

Nonclinical studies of AM0010 have demonstrated a favorable benefit-to-risk profile and strongly support its clinical investigation in solid tumors. An overview of AM0010 toxicology, pharmacology, and pharmacokinetics (PK) is provided below. Additional details can be found in the AM0010 Investigator's Brochure.

1.2.2.1 AM0010 Toxicology

Good laboratory practice (GLP) toxicology studies with AM0010 were performed in CD-1 mice (rodent species) and cynomolgus monkeys (non-human primate species [NHP]). These studies involved daily subcutaneous (SQ) administration for up to 28 days at doses up to 100 and 1000 µg/kg/day in monkeys and mice, respectively.

Effects seen in the studies with AM0010 were predominantly confined to NHP; the no observed adverse effect level (NOAEL) in the mouse was considered 1000 µg/kg/day. Changes in red blood cell parameters (decreased red blood cell [RBC] counts, hemoglobin (Hgb) and hematocrit (Hct), and increased reticulocyte counts) consistent with a regenerative anemia due to extravascular hemolysis was evident following 2 weeks of dosing at doses ≥20µg/kg/day. These changes resolved following the cessation of treatment (100 µg/kg/day) or continued dosing (doses > 20 µg/kg/day). Other findings consistent with previous experience with rHuIL 10 included a mild to moderate decrease in albumin and the albumin-to-globulin ratio. In monkeys, no effects upon cardiovascular, respiratory, or neurological parameters were noted at any dose. The NOAEL and highest non-severely toxic dose (HNSTD) in the monkey was 20 µg/kg/day.

The toxicology of AM0010 was evaluated in a 13-Week GLP toxicology study in cynomolgus monkeys.

No AM0010-related changes in PR interval, QRS duration, QT interval, corrected QT (QTc) interval, or heart rate were observed on Day 1 or 89 of the dosing phase in animals administered 5, 20, or 50 µg/kg/day. No rhythm abnormalities or qualitative ECG changes attributed to AM0010 were observed during qualitative assessment of the ECGs.

AM0010 administration had no effect on peripheral blood immunophenotyping (IPT) test results.

No AM0010-related organ weight or macroscopic or microscopic findings were present at the terminal or recovery sacrifice.

Clinical observations were limited to the 50 µg/kg/day treatment group and consisted of low food consumption in 3 males (Days 10-16) and squinting and potential bilateral uveitis in two males and two females given 50 µg/kg/day (the latter noted upon veterinary examination on Day 15 of the dosing phase). The latter animals were treated with topical atropine and intramuscular flunixin meglumine and the finding was not present from Day 18 onward. These findings are considered AM0010-related but not adverse.

Clinical pathology findings in animals were limited to dose-dependent hematological effects consisting of reductions in RBC parameters (decreased red blood cell mass, Hgb, and/or an increase in reticulocytes and platelets, the latter two reflecting a normal regenerative response) and transient increases in white blood cell (WBC) counts, predominantly lymphocytes. The hematological effects were transient and seen during Weeks 2-4 of the dosing phase with the effects resolving with continued dosing.

The results of toxicokinetic and anti-AM0010 antibody response analysis were generally in line with the findings in the 28 days toxicology study with AM0010 in cynomolgus monkeys. The median exposure levels between dosing groups were dose proportional between the dosing cohorts in weeks two through five, with an increased variability between individuals later in the study due to anti-drug antibodies (ADA) development. All animals developed ADAs, but several animals in each high dose cohort of both sexes maintained high serum trough levels throughout the study, suggesting that the overall interpretation of the study was not compromised by the ADA development.

The effects observed in this study were consistent with those obtained in the prior 4-week toxicology study in monkeys. The predominant finding was transient reductions in RBC parameters which resolved with continued dosing. As in the 4-week study, the NOEL was 5 µg/kg/day, the NOAEL and HNSTD was defined as 20 µg/kg/day.

1.2.2.2 AM0010 Pharmacology

The findings from the nonclinical studies suggest that a PEGylated rHuIL-10 may have strong anti-tumor effects in oncology by inducing cytotoxic activity and proliferation of tumor infiltrating and tumor specific CD8+ T cells. PEGylated IL-10 induces partial response (PR), complete response (CR), and curative effects in murine models of human late stage cancer, including animals with very large tumor burdens, animals with widespread metastatic dissemination, and in tumor types resistant to other therapeutic intervention, including chemotherapy and immunotherapy. Mice cured by treatment with PEGylated IL-10 remained tumor free and developed a protective immune memory against the tumor.

AM0010 stimulates the cytotoxic activity of murine or human peripheral CD8+ T cells and the expression of cytotoxic enzymes and Interferon gamma (IFNγ) in memory CD8+ T cells.

1.2.2.3 AM0010 Pharmacokinetics and Metabolism

1.2.2.3.1 Non-Clinical Pharmacokinetics

The pharmacokinetics/toxicokinetics (PK/TK) of AM0010 was evaluated in CD1 mice and cynomolgus monkeys in non-GLP pharmacokinetic studies and further evaluated in GLP toxicokinetic studies in both species.

In cynomolgus monkeys, the pharmacokinetics of AM0010 were linear over the dose range of 1 to 20 µg/kg/day administered SQ daily. No accumulation was observed in preclinical species, but based on extrapolation from pre-clinical species to humans, the predicted half-life (t½) of 14 hours upon SQ injections in humans would predict a mild accumulation of about 40% for the maximum drug concentration (Cmax) upon daily dosing. Low level ADAs developed in monkeys and high levels of ADAs were detected in mice. ADA positivity decreased AM0010 serum exposure in affected monkeys. Results of a 28 day daily SQ injection PK study conducted with AM0010 in cynomolgus monkeys showed a mean AM0010 half-life of approximately 9.94 hours after administration of the first dose. Volume of distribution of AM0010 was high, suggesting extravascular distribution and receptor mediated elimination.

The serum exposure of AM0010 in CD-1 mice (area-under-the-curve [AUC]0-∞ and Cmax) increased proportionally with dose after SQ administration of 1 and 20 µg/kg. Mean serum half-life of AM0010 was approximately 4.5 hours at 20 µg/kg. The trough serum AM0010 concentration of approximately 1 – 2 ng/mL was associated with a highly efficacious SQ dosing regimen of 0.1 mg/kg given daily in a murine syngeneic tumor model.

1.2.2.3.2 Human Pharmacokinetics

A summary of human PK is provided below. For the most current information on clinical PK, please refer to the current Investigator's Brochure.

Due to its PEGylation, AM0010 has a prolonged exposure compared to rHuIL-10 upon SQ delivery. The serum concentration of AM0010 was determined at 6 time points at Day 1 and Day 29, and the pre-dose concentration (Cmin) was determined weekly in patients in the dose escalation cohorts throughout the dosing period. The pretreatment serum level of IL 10 was found to be below the limit of detection (50 pg/mL) in all cancer patients analyzed.

At the starting dose (0.125 mg), patients had a serum concentration of AM0010 between 0.68 and 1 ng/mL or equivalent to 10% effective concentration (EC10). The average minimal AM0010 serum concentration at the 0.5 mg was 3.5 ng/mL or the equivalent to the EC25. The difference between Cmax and Cmin was approximately 33%, indicating a stable drug exposure with once daily dosing (Table 1).

Table 1. Clinical Pharmacokinetics of AM0010

Dose (mg) ≥80 kg / <80 kg*	C_{max} (ng/mL)	T_{max}	C_{min} (24 h)	AUC (ng/mL•24 h)
0.125 / (0.1)	0.85	7.3	0.68	18.4
0.25 / (0.2)	1.45	9.2	1.08	30.6
0.5 / (0.4)	5.30	14.4	3.54	106
1 / (0.8)	5.35	9.2	3.60	108
2 / (1.6)	13.9	9.2	11.7	307
4 / (3.2)	31.1	12.5	28.5	716

* Patient weight.

Serum concentrations of AM0010 remained stable throughout the duration of dosing. No significant accumulation or attenuation of AM0010 levels were observed after the first week of dosing. The absence of high titer ADAs was confirmed in all patients tested.

An interim pharmacokinetic analysis has been conducted on the data available from 155 subjects in AM0010-001. These patients received extended treatment with AM0010, and samples were obtained intermittently throughout their treatment course. The analysis is not complete and is ongoing. Results from this interim analysis support the following claims:

1. AM0010 is cumulative, reaching steady state conditions after approximately one week of daily dosing.
2. Apparent clearance (the sole determinant of -AUC) is proportional to weight, supporting a weight-normalized dosing regimen.
3. Apparent clearance (and, to a lesser extent, distribution volume) was smaller in subjects assigned to higher dose cohorts (values ranged from 1 to 40 µg/kg/dose).

None of the other covariates evaluated (age, gender, race, organ function, chemotherapy regimen) appears to influence the pharmacokinetic parameters. Preliminary analysis suggested a small decrease in apparent clearance with increasing serum albumin; however, the relationship was not statistically significant.

1.2.3 AM0010 Clinical Experience

1.2.3.1 Clinical Trial AM0010-001

In this First in Human trial, over 350 patients in 12 selected advanced solid malignancies were treated with AM0010 in a dose escalation 3+3 design, followed by several dose expansion cohorts in specific cancers and combinations with immune-oncology checkpoint inhibitors or chemotherapies that are standard of care for that tumor type.

A total of 33 patients were enrolled in monotherapy dose escalation cohorts. AM0010 was self-administered SC at doses of 1 to 40 µg/kg on a continuous daily (qd) dose schedule. Objectives of the trial were safety and tolerability, and early evidence of efficacy and immune activation. AM0010 monotherapy was well tolerated in this heavily pretreated advanced cancer patient population.

AM0010 led to systemic immune activation with elevated immune stimulatory cytokines and reduced TGF-beta in the serum. AM0010 induced an expansion of new T cell clones in the blood and CD8+ T cells with elevated checkpoint proteins such as PD-1 and Lag3 expression. PD-1 and Lag3 expression on CD8+ T cells isolated from the tumor or the blood of cancer patients, has been associated with tumor antigen reactivity (Gros, Robbins et al. 2014, Gros, Parkhurst et al. 2016). These data suggest an expansion of tumor directed CD8+ T cells in AM0010 treated patients.

In the NSCLC cohort 5 patients were treated with AM0010 at 10 µg/kg plus pembrolizumab 40% of the patients had at least 3 prior therapies, 20% had 2 prior therapies. The median number of prior therapies is 2 (range 0-5). Two patients had a best overall response of irPR (ORR=40%), and 3 patients had an irSD (disease control rate [DCR] = 100%).

The expected response rate of second-line NSCLC to anti-PD1 inhibitors is dependent on expression of PD-L1 in the tumor. The ORR to anti-PD1 therapy was 9.1-10.7% for patients with PD-L1 negative tumors (below 1% of tumor cells PD-L1 positive) and 45% for patients with ≥50% PD-L1 expressing tumor cells (Garon, Rizvi et al. 2015). The OS was 9.3 months for all patients and approximately 8.5 months for patients whose tumors were negative for PD-L1.

In this cohort, four of the five patients were evaluated for PD-L1 expression in the tumor, and all were negative for PD-L1 (<1% PD-L1 positive tumor cells), including both patients who had a PR.

Most patients enrolled in the escalation cohorts and expansion cohorts had previously progressed during or following multiple lines of therapy. Despite this fact, very encouraging objective tumor responses have been observed in most combination therapies with AM0010.

The median PFS was 10.9 months (range 4.7-19.3+), the mOS has not been reached; 80% of patients who received AM0010 at 1 mg (10 µg/kg) plus pembrolizumab were alive with a median follow-up of 25.2 months (range 24.5-26.9+).

1.2.3.2 Clinical Trial AM0010-301

Clinical trial AM0010-301 is an ongoing 566 patient randomized, open-label, global Phase 3 trial of AM0010 in combination with folinic acid, fluorouracil, and oxaliplatin (FOLFOX), compared with FOLFOX alone, as a second-line therapy in patients with metastatic pancreatic ductal adenocarcinoma (PDAC) that has progressed on a first-line gemcitabine-based regimen. The objectives of this trial are to assess safety and efficacy, as measured by OS, PFS, ORR by Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1, and other measures.

1.3 Trial Rationale and Design

In recent years, it has become apparent that cancers are recognized by human immune system and that under certain circumstances the immune system can obliterate tumors. Recently, the PD-1 pathway has emerged as a major immune checkpoint by which tumors suppress lymphocyte function. This pathway consists of PD-1, a protein expressed on activated immune cell types such as T cells and B cells, and its ligands, PD-L1 and PD-L2 which are expressed on many tumors. Cancer cells drive high expression levels of PD-L1 on their surface, allowing activation of the inhibitory PD-1 receptor on any T cells that infiltrate the tumor microenvironment, effectively switching those cells off. Indeed, up-regulation of PD-L1 expression levels has been demonstrated in many different cancer types (eg, melanoma [40%-100%], NSCLC [35%-95%], and multiple myeloma [93%]), and high levels of PD-L1 expression have been linked to poor clinical outcomes (Hino et al, 2010, Wang et al, 2011, Dong et al, 2002, Konishi et al, 2004, Liu et al, 2007, Patel et al, 2015).

Treatment of cancer patients with AM0010 alone in the Phase 1 trial led to an increase of CD8+ T cells positive for immune checkpoints, including PD-1 and Lag-3, suggesting the expansion of tumor reactive CD8+ T cells. Inhibition of those immune checkpoints with antibodies to PD-1 or Lag-3 should further enhance the anti-tumor activity. The treatment with AM0010 monotherapy lead to the expansion of T cell clones, which were previously not detected in the patient – “novel” T cell clones. The number of T cell clones which expand at least 10 fold during the treatment and their relative percentage in the patient’s T cell repertoire correlated with objective tumor response in patient treated with AM0010 monotherapy.

AM0010 and anti-PD-1 stimulate the same cell, the tumor infiltrating CD8+ T cells, which recognize tumor antigens and up-regulate the IL-10 receptor and the immune checkpoint. The molecular signaling pathways of both molecules are however different, opening the possibility that combination of the stimulation by AM0010 and the inhibition of PD-1 may act synergistically. Early results observed in the Phase 1 trial using pembrolizumab or nivolumab in combination with AM0010 indeed support this hypothesis. The response rate

of the combination of AM0010 with pembrolizumab in a small number of NSCLC and RCC (n=5 and 8, respectively) was two fold over the expected response rate of pembrolizumab alone, progression free and overall survival was increased even stronger. Preliminary results from a combination of nivolumab and AM0010 appear to support this observation.

AM0010 induces an expansion of novel T cell clones in patients. This expansion was similar in patients treated with pembrolizumab and AM0010 at 1 mg (10 µg/kg) and 2 mg (20 µg/kg), respectively. This and a comparable ORR on the cohorts treated with AM0010 at 1 mg (10 µg/kg) and 2 mg (20 µg/kg) provides a rationale for a threshold based fixed dose in Phase 2 and 3 trials.

AM0010 has an acceptable safety profile and encouraging clinical activity in RCC, NSCLC, and PDAC. In addition, the safety profile of anti-PD-1 and AM0010 show mostly non-overlapping treatment-related adverse events (TRAEs). In particular, immune checkpoint blockade frequently causes autoimmune toxicity, including colitis, gastritis or pneumonitis and endocrine disruptions, limiting the tolerability of combinations of immune checkpoint inhibitors. AM0010 monotherapy did not cause autoimmune toxicity. As a consequence, the combination of AM0010 with nivolumab (or another anti-PD-1 immune checkpoint inhibitor) was well tolerated (Section 1.2.3.1). The safety profile of AM0010 with PD-1 inhibitors, may be better tolerated than combinations of two or more immune checkpoint inhibitors. PEGylated IL-10 (AM0010) offers a potent novel and non-redundant mechanism adding to the arsenal of clinically active immune-oncology drugs. The direct activation of the CD8+ T cells by AM0010 in absence of immune related adverse events should enable combinations with other immune-therapies which block inhibitory mechanisms.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) designed to target the programmed death-1 receptor and thus directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection. Pembrolizumab only potentiates existing immune responses in the presence of antigen and does not non-specifically activate T cells. Evidence shows that PD-L1 expression levels correlate with increased response to pembrolizumab. For instance, in NSCLC phase 1 clinical trial data showed a correlation between PD-L1 expression and response to pembrolizumab, supporting the role of PD-L1 expression testing as a predictive biomarker (Garon et al, 2015).

In AM0010-001 Phase 1 trial, AM0010 in combination with pembrolizumab (and nivolumab) had substantially improved clinical efficacy compared to historical data with anti-PD-1 monotherapy in second line or greater metastatic NSCLC. Four of 5 NSCLC patients with high PD-L1 expression (≥ 50% of tumor cells positive for PD-L1) had a response and 100% had a durable clinical benefit (CR/PR or SD ≥ 6month).

Pembrolizumab is the only PD-1 inhibitor approved for use as first-line therapy of NSCLC in patients whose tumors have high PD-L1 expression (≥ 50% of tumor cells positive for PD-L1). It is the preferred treatment in the first line setting and has become the benchmark

comparator. Pembrolizumab was also chosen in this trial because its activity vs that of the AM0010 combination with pembrolizumab will show the contribution of components in this treatment setting.

2.0 TRIAL OBJECTIVES

2.1 Primary

- To evaluate the ORR

2.2 Secondary

- To evaluate PFS
- To evaluate OS
- To evaluate DCR
- To evaluate DoR
- To evaluate the safety and tolerability profile

2.3 Exploratory

- To characterize AM0010 LY3500518 PK in combination with pembrolizumab
- To further evaluate the biomarkers including immune activation markers that may correlate with efficacy outcome measures. These may include, but are not limited to:
  - FDA approved PD-L1 diagnostic assay
  - Immune cell infiltration
  - Tumor mutational burden test
  - Other assay, assessment, and test on residual tissue
  - to be conducted as part of exploratory analyses

3.0 TRIAL DESIGN

This is an open-label, randomized, multicenter, Phase 2 trial in 100 adult male and female patients with treatment-naïve, Stage IV/metastatic NSCLC whose tumors are not known to have EGFR mutations or ALK rearrangements, but have high expression (≥50%) PD-L1 as determined with an FDA-approved PD-L1 IHC 22C3 assay.

Patients will be stratified according to tumor histology (squamous vs non-squamous).

Patients will be randomized in a 1:1 ratio into 1 of 2 treatment arms (Figure 1).

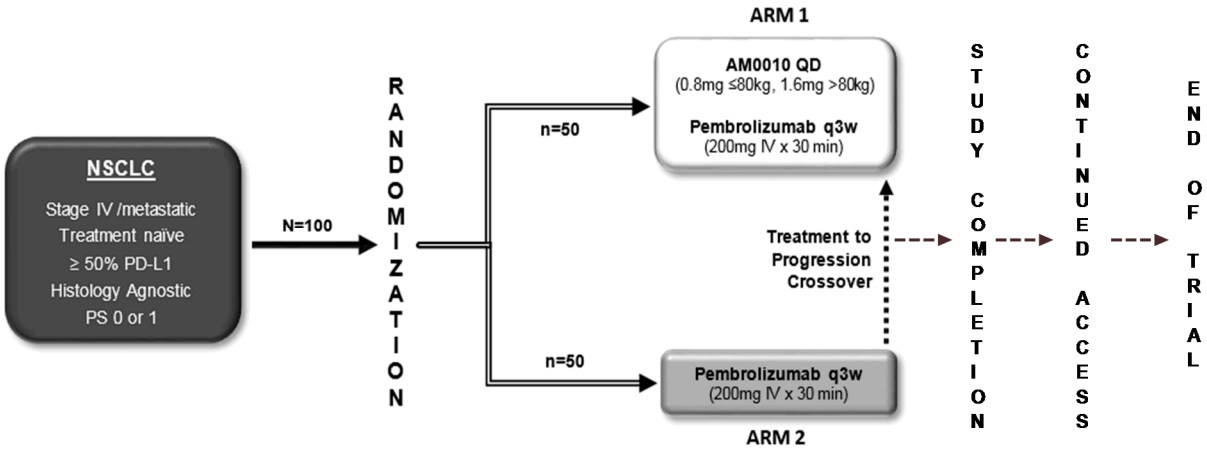

Figure 1. Trial Design

Trial sites will provide best supportive care per institution's standard of care including concomitant medications.

Arm 1 and 2 treatment will continue in the absence of disease progression, unacceptable toxicity, or patient's withdrawal of consent. Patients will be treated with a maximum of 35 cycles of pembrolizumab every 3 weeks or 2 years, whichever is longer.

All radiological assessments will include at minimum, scans of the head, chest, abdomen, and pelvis.

At the time of documented disease progression (by Investigator assessment) patients in Arm 1 will be discontinued from the treatment period of the trial and continue on the follow-up period. At the time of documented disease progression (by Investigator assessment), patients in Arm 2 may crossover to receive treatment with AM0010 and pembrolizumab.

Confirmation of complete response (CR) or partial response (PR) is required. Confirmatory scans will be performed as follows:

- CR and PR criteria per RECIST v1.1 must be met again at least 4 weeks after initial documentation.

Patients with suspected pseudoprogression on scans in the absence of clinical deterioration should remain on trial treatments and be rescanned at 4 weeks or later as outlined in Section 7.6.

If progression is confirmed on follow up scan, then discontinue treatments and follow trial procedures for end of treatment and survival follow-up or procedures for crossover patients.

Scans will include head and CAPs and will be sent to the central imaging vendor for archiving and possible assessment at a later date. If clinical progression is suspected, all relevant clinical documentation is to be submitted to the central imaging vendor.

For patients who were randomized, but withdraw consent, survival (date of death) will be obtained by use of publicly available information.

Tumor assessment will be performed for all randomized patients every 9 weeks (±7 days) during the study treatment and during the first year from discontinuation of the study treatment, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter. Tumor assessment will be repeated until disease progression, death, or receipt of new anti-cancer therapy, or until study completion, whichever is first, whether or not study treatment was administered.

All randomized patients will be followed for OS every 9 weeks (±7 days) during the first year from the 90-day follow-up visit, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter. The survival follow-up will be conducted until death or study completion, whichever is first, whether or not trial treatment was administered.

3.1 Number of Trial Centers

This trial will be conducted in multiple centers in the United States.

3.2 Number of Patients

Approximately 100 (50 within each treatment arm)

3.3 Estimated Trial Duration

The duration of patient accrual, treatment, and follow-up, is expected to last approximately enrollment +36 months.

3.4 Trial Endpoints

3.4.1 Primary

- The primary endpoint of this study is ORR defined as the proportion of patients who achieve a CR or PR as assessed by RECIST v.1.1.

3.4.2 Secondary

The secondary endpoints of the trial include:

- PFS, defined as the time from date of the first documented tumor progression as determined by the Investigator (per RECIST v.1.1 criteria or clinical progression) or death due to any cause whichever occurs first;

- OS, defined as the time from date of randomization to date of death due to any cause;
- DCR, defined as the proportion of patients who achieve a CR, PR, or SD as assessed by RECIST v.1.1;
- DoR, defined as the time from the date of the first documentation of objective tumor response (CR or PR) to the date of the first documentation of objective tumor progression or death due to any cause, whichever occurs first; and
- Evaluation of the safety and tolerability profile (serious adverse events [SAEs], treatment-emergent adverse events [TEAEs], electrocardiogram [ECG] parameters, vital signs, performance status, and laboratory parameters). TEAEs and laboratory findings will be graded according to the National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

3.4.3 Exploratory

- Characterize AM0010 PK in combination with pembrolizumab .
- Baseline and change from baseline in immune and molecular biomarkers and their relationship to clinical efficacy endpoints may be explored.

3.5 End of Treatment/Follow-Up Period

End of Treatment Visit

After patients receive their last dose of AM0010 and/or pembrolizumab, there will be a 28-day (±7 days) follow-up period, after which patients will return to the trial site to complete end of treatment assessments (Section 7.9). Then, follow-up will begin on Day 35 (±7 days) after the last dose of trial treatment.

Follow-Up Period

During the extended safety observation period, all randomized patients will be followed for safety 60 and 90 days (±7 days) after the last dose of study treatment and monitored according to the schedule of assessments (SOA; Appendix A).

During the long-term follow-up period, all randomized patients will be followed for OS every 9 weeks (±7 days) during the first year from the 90-day follow-up visit, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter. The survival follow-up will be conducted until death or study completion, whichever is first, whether or not trial treatment was administered.

3.6 Study Completion Definition

This study will be considered complete when the final analysis of the primary and secondary objectives is complete. This includes a 3-year follow-up for OS after the last patient is randomized. Investigators will continue to follow the study schedule for all patients until notified by Lilly that study completion has occurred. After study completion, the patients who are on treatment and continuing to receive clinical benefit may continue receiving study drugs during the continued-access period.

3.7 Continued-Access Period

All patients remaining on study treatment without disease progression following study completion will enter the continued-access period of the study. The continued-access period begins after study completion and ends at the end of trial. During the continued-access period, patients on AM0010 who continue to experience clinical benefit may continue to receive study treatment until disease progression, death, unacceptable toxicity, or end of trial. Patients who are in the follow–up, but have not yet completed the visits will complete the necessary follow-up visits when the continued-access period begins and then discontinue the study. The continued-access period includes 3 follow-up visits; 28, 60, and 90 days (±7 days) after the last dose of study treatment. If it is deemed to be in the best interest of the patient to start a new anti-cancer treatment prior to a scheduled follow-up visit, the follow-up visit duration may be shortened. In this case, the follow-up assessments should be completed prior to the initiation of the new therapy.

Lilly will notify investigators when the continued-access period begins.

During the continued-access period, all relevant assessments will be done according to Appendix B and recorded on the case report form (CRF).

Serious adverse events will also be reported to Lilly Global Patient Safety and collected in the pharmacovigilance system. In the event that an SAE occurs, additional information (such as local laboratory results, concomitant medications, and hospitalizations) may be requested by Lilly in order to evaluate the reported SAE.

Investigators may perform other standard procedures and tests needed to treat and evaluate patients; however, Lilly will not routinely collect the results of these assessments.

3.8 End of Trial Definition

End of the trial is defined as the date of the last visit or last scheduled procedure for the last patient. The end of trial occurs after study completion after the continued-access period (if any).

4.0 PATIENT ELIGIBILITY

Eligibility criteria for this trial have been carefully considered to ensure the safety of the trial patients and to ensure the integrity of the trial results. It is imperative that patients meet in full all eligibility criteria and requirements.

Confirmation of eligibility criteria is required for all potential trial patients PRIOR to randomization. A trial waiver will not be granted for study entry.

Patients will be eligible for trial participation as defined by the inclusion and exclusion criteria as follows.

4.1 Inclusion Criteria

Eligible patients must meet the following criteria to be enrolled in the trial:

1. Signed Written Informed Consent (ICF). Patients must have signed and dated an Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved written ICF in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal patient care.
    a. Patients must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, and other requirements of the trial.
2. **Target Population**
    a. Patients must have histologically or cytologically confirmed NSCLC that is stage IV / metastatic.
    b. Patients must not have had systemic treatment for incurable disease. If patients had chemotherapy as part of curative intent radical radiotherapy or surgery they should have completed the last dose of chemotherapy 6 months prior to randomization.
    c. Patients with tumor tissue high expression of PD-L1 as defined by Tumor Proportion Score (TPS) ≥ 50% and as determined by a FDA-approved PD-L1 IHC 22C3 assay is mandatory
    d. Patients ≥18 years of age.
    e. Patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
    f. Patients with measurable disease by CT or MRI per RECIST v.1.1 criteria.
    g. Patients with Radiographic Tumor Assessment performed within 30 days prior to randomization.
        i) Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression at that site.
    h. Patients that have completed prior radiotherapy or radiosurgery at <u>least</u> 2 weeks prior to randomization.
        i) Patients with brain metastases are eligible if they are asymptomatic, or are treated and are neurologically stable for at least 2 weeks without the use of steroids or on stable or decreasing dose of ≤10 mg daily prednisone (or equivalent).

i. Patients with baseline laboratory values obtained 21 days prior to randomization meeting the following criteria:

i) WBCs ≥ 2000/µL.

ii) Neutrophils ≥ 1500/µL.

iii) Platelets ≥ 100×10³/µL.

iv) Hemoglobin ≥ 9.0 g/dL.

v) Creatinine of ≤1.5× upper limit of normal (ULN) or calculated creatinine clearance >60 mL/minute per institutional standard. For patients with a body mass index (BMI) > 30 kg/m^2, lean body weight should be used instead of actual body weight.

vi) Aspartate transaminase (AST) ≤1.5×ULN (<5×ULN for patients with liver metastasis).

vii) Alanine transaminase (ALT) ≤1.5×ULN (<5×ULN for patients with liver metastasis).

viii) Total bilirubin ≤1.5×ULN (except Patients with Gilbert Syndrome who must have total bilirubin <3.0 mg/dL).

ix) Alkaline phosphatase <2.5×ULN (<5×ULN for patients with liver metastasis).

x) Prothrombin Time (PT) <1.5×ULN unless receiving anticoagulation therapy; activated Partial Thromboplastin Time (aPTT) <1.5×ULN unless receiving anticoagulation therapy.

3. **Reproductive Status**

a. Women of childbearing potential (WOCBP) must agree to use method(s) of contraception.

b. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) within 24 hours prior to the start of investigational product.

c. Male or non-pregnant, non-lactating female, ≥ 18 years of age:

i) If sexually active, the patients must agree to use contraception considered adequate and appropriate by the Investigator during the period of trial drug administration. In addition, male and female patients must utilize contraception after the end of the treatment in the individual drugs product's Prescribing Information provided in the trial manual and the Clinical Trial Facilitation Group, provided in Appendix B

4.2 Exclusion Criteria

Eligible patients must not have the following criteria (except where indicated) to be enrolled in the trial:

1. **Medical History and Concurrent Diseases**

a. Patients with carcinomatous meningitis.

b. Patients with active central nervous system (CNS) metastases.

i) Patients are eligible if CNS metastases are adequately treated and neurologically stable at baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. In addition, patients must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) at the time of consent for the trial.

c. Patients with life expectancy of < 3 months.

d. Patients with non-squamous NSCLC with known EGFR mutation or ALK rearrangement.

e. Patients currently using medicinal or recreational cannabis.

f. Patients with any serious or uncontrolled medical disorder or active infection with the hepatitis virus or the human immunodeficiency virus (HIV).

g. Patients with other active malignancies requiring concurrent intervention other than hormone antagonists.

h. Patients with previous malignancies (except non-melanoma skin cancers and the following in situ cancers: bladder, gastric, colon, cervical/dysplasia, endometrial, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to trial entry AND no additional therapy other than hormone antagonists is required or anticipated to be required during the trial period.

i. Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications at the time of consent for the trial. Inhaled or topical steroids and adrenal replacement steroid doses >10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.

j. Patients with known prior history of hemophagocytic lymphohistiocytosis (HLH).

k. Patients with active known or suspected autoimmune disease that required systemic therapy within 2 years of treatment, or a medical condition that required immunosuppression. Patients with vitiligo, Type I diabetes mellitus, residual hypothyroidism requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

l. Patients with Grade 1 (NCI-CTCAE v.4.03) toxicities attributed to prior anti-cancer therapy (other than alopecia and fatigue prior) to randomization.

m. Patients that have received therapy with anti-tumor vaccines or other immuno-stimulatory antitumor agents. Non-cancer vaccines (non-attenuated and non-live) are permitted.

n. Patients that have received therapy with anti-PD-1, anti-PD-L1, anti-PD-L-2, anti-CD-137, and/or anti CTLA-4 antibodies (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways).

o. Patients with a history of symptomatic interstitial lung disease.

p. Patients not completely recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of trial treatment.

2. **Physical and Laboratory Test Findings**

a. Patients with active Hepatitis B or C infections.

b. Patients known to be human immunodeficiency virus (HIV) positive.

3. **Allergies and Adverse Drug Reaction**

   a. Patients with a history of severe hypersensitivity reactions to monoclonal antibodies.

   b. Patients with a history of allergy or intolerance (unacceptable adverse event) to trial drug components, Polysorbate-80-containing infusions.

4. **Sex and Reproductive Status**

   a. WOCBP who are pregnant or breastfeeding.

   b. Women with a positive pregnancy test at enrollment or prior to administration of trial drug.

5. **Prohibited Treatments and/or Restricted Therapies**

   a. Patients requiring ongoing or planned administration of anti-cancer therapies other than those specified in this trial.

   b. Patients requiring the use of corticosteroids or other immunosuppressive medications (>10 mg daily prednisone equivalent for more than 14 sequential days). Corticosteroids or other immunosuppressive medications for more than 14 sequential days require approval of the Medical Monitor.

   c. Patients receiving any investigational agent within 28 days of first administration of trial treatment.

6. **Other Exclusion Criteria**

   a. Patients with any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the Investigator, would limit the individual's ability to comply with the trial requirements, substantially increase risk to their well-being, or impact the interpretability of trial results.

5.0 PATIENT ENROLLMENT

Before patients may be entered into the trial, all patients or legally acceptable representatives must personally sign and date, and receive a copy of the ICF before any trial-specific screening procedure is performed that is not part of standard medical practice.

All patients who enter into the screening period of the trial (defined as the point at which the patient signs the informed consent) will receive a patient identification number (PIN). This number will be used to identify the patient throughout the trial and must be used on all trial documentation related to that patient. The patient identification number (PIN) will remain constant throughout the entire trial; it will not be changed at the time of enrollment. A patient is considered enrolled on this trial when s/he signs the IRB approved informed consent (ICF). A patient will need to pass the screening assessments/procedures before they are randomized to one of two trial arms and then dosed accordingly.

5.1 Treatment Arms

Patients will be randomized in a 1:1 ratio into one of two arms according to histology type (squamous vs non-squamous) as follows:

- Arm 1: Patients will receive AM0010 and pembrolizumab
- Arm 2: Patients will receive pembrolizumab alone

6.0 TREATMENT PROCEDURES

AM0010 will be the only non-FDA approved drug used in this trial.

6.1 Investigational Product Dosage, Administration, and Schedule

AM0010 is provided by Lilly. AM0010 is provided as a sterile, single-use prefilled syringe, with a clear solution. AM0010 drug product is stored refrigerated. Refer to the product label for full storage instructions.

A pharmacy guide will be provided, which contains details regarding packaging, labeling, storage, (re)ordering and administration of AM0010.

A trial-defined AM0010 and pembrolizumab treatment will begin on trial day 1. Patients on Arm 1 will dose with AM0010 prior to initiation of pembrolizumab dosing. Patients' on Arm 1 will dose AM0010 according to their weight:

- ≤80 kg body weight = 0.8 mg
- >80 kg body weight = 1.6 mg

AM0010 dose recalculations are only required if a patient's body weight changed from ≤80 kg to >80 kg or vice versa. Change in bodyweight should be calculated based on change from baseline weight or last weight taken per protocol.

Patients will be trained to self-administer AM0010 and will self-administer the dose throughout the trial starting with the first dose. A patient's caregiver may also be trained to perform SQ injections. Both the patient's and caregiver's training must be recorded in the patient's medical records. The Investigator or a qualified designee must be present during administration of the first dose. An AM0010 administration diary must be kept for dosing compliance monitoring.

6.2 Pembrolizumab Administration

Pembrolizumab should be obtained by each site as per routine institutional practice. Sites will be responsible for storage and destruction of pembrolizumab. For preparation and complete prescribing information, refer to the most current prescribing information in the region. Investigators or designees will review the patient's hematology and chemistry panels, liver function tests (LFTs), and the incidence of hematologic and non-hematologic toxicities prior and during study treatment.

Pembrolizumab will be administered on Day 1 of each 21-day cycle. Patients will be treated for a maximum of 35 cycles of pembrolizumab every 3 weeks or 2 years, whichever is longer.

Medications used to treat pembrolizumab-related infusion reactions are (eg, diphenhydramine, acetaminophen/paracetamol, corticosteroids) considered non-investigational medicinal products (NIMPs) and will not be provided by the sponsor. These will be obtained by the investigational sites as marketed products, which should be stored in accordance to the package insert.

Pembrolizumab for injection (lyophilized powder): carton containing one 50-mg single-dose vial (NDC 0006-3029-02). Vials should be stored refrigerated. Refer to the product label for full storage instructions.

Pembrolizumab injection (solution): carton containing one 100-mg/4 mL (25 mg/mL), single-dose vial (NDC 0006-3026-02). Vials should be stored refrigerated. Refer to the product label for full storage instructions..

6.3 Dosing Schedule

Patients will be treated on an outpatient basis with AM0010 plus pembrolizumab or pembrolizumab alone (Figure 2).

Arm 1 consists of AM0010 at 0.8 mg for patients ≤80 kg body weight or 1.6 mg for patients >80 kg body weight, self-administered SQ QD (abdomen, thigh, or back of upper arm) plus pembrolizumab at 200 mg over approximately 30 minutes IV infusion on Day 1 of a 21-day cycle.

Arm 2 consists of pembrolizumab alone at 200 mg over approximately 30 minutes IV infusion on Day 1 of a 21-day cycle.

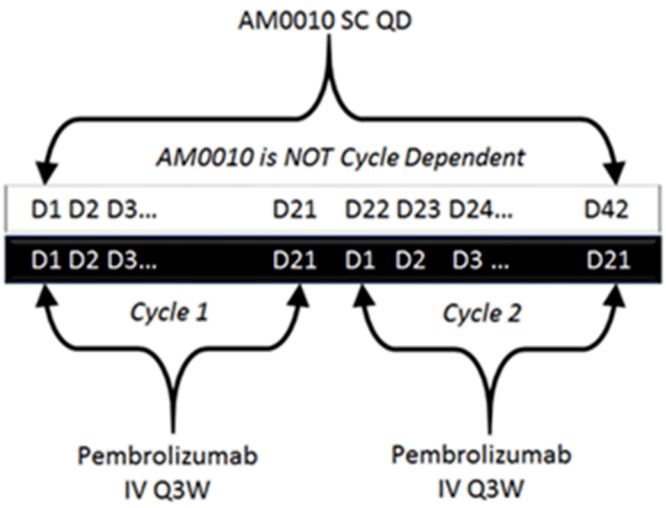

Figure 2. Dosing Schedule

Patients will continue on treatment until they experience progressive disease per Investigator assessment, unacceptable toxicity, require subsequent anticancer therapy, withdraw consent, or their physician feels it is no longer in their best interest to continue on treatment.

Crossover of patients from the pembrolizumab-only treatment arm (Arm 2) into the pembrolizumab plus AM0010 treatment arm (Arm 1) is permitted at the time of disease progression (as assessed by the Investigator). Supportive care per the institution's normal standard of care, including concomitant medications, can be provided at the Investigator's discretion.

The documentation of the investigational product administration (AM0010) will be noted on the case report form (CRF) page and in the source documentation/patient diary. The date,

dose volume, dose amount, and time of administration for each dose when the PK samples are collected (including the 2-day dosing history prior to a PK draw day), the first and last administered dose for the patient, doses withheld and missed, and dose schedule adjustments will be recorded on the respective CRF page. Details of preparing and administering AM0010 will be provided to the patient and are included in the Pharmacy Binder provided by the Lilly/designee.

6.4 Treatment Withhold, Dose or Schedule Reduction, or Discontinuation for Toxicity

If an adverse event (AE) occurs, the Investigator should determine if the AE could be attributed to either drug (AM0010 or pembrolizumab) or both, or if other factor(s) were the cause of the AE. Continued treatment with the study drugs is based on the Investigator's assessment of risk-benefit per the guidelines outlined below. Both the study drugs in Arm 1 should be discontinued if 1 study drug is discontinued.

6.4.1 Treatment Withhold and Discontinuation

6.4.1.1 AM0010

AM0010 dosing will be withheld or permanently discontinued based on the criteria provided in Table 2.

Table 2. Toxicity Management Guideline for AM0010

Toxicity/Adverse Event	Toxicity Grade (CTCAE) or Conditions	Action Taken to AM0010
Fatigue	Grade 3 or 4	Withhold
AST, ALT	Grade 3 or 4 >5-10×ULN for >2 weeks; drug-related >10×ULN; drug-related	Withhold Permanently discontinue Permanently discontinue
Total bilirubin	Grade 3 or 4 >5×ULN; drug-related	Withhold Permanently discontinue
Concurrent AST or ALT and total bilirubin elevation	AST or ALT>3×ULN and total bilirubin >2×ULN; drug-related	Permanently discontinue
Alkaline phosphatase	Grade 3 or 4	Withhold
Diarrhea, nausea, vomiting, abdominal pain, or bloating	Grade 3 or 4	Withhold
Other non-hematologic toxicities with an impact on organ function	Grade 3 or 4	Withhold
Skin drug-related AE	Grade 3 or 4	Withhold
Any adverse event, laboratory abnormality, or intercurrent illness	Presents a substantial clinical risk to the patient in the judgment of the Investigator	Permanently discontinue
Any adverse event including laboratory abnormalities, except • Grade 4 neutropenia ≤21 days • Grade 4 lymphopenia or leukopenia <21 days	Grade 4; drug-related	Permanently discontinue
Any event	Life-threatening and related	Permanently discontinue

Toxicity/Adverse Event	Toxicity Grade (CTCAE) or Conditions	Action Taken to AM0010
Any adverse event, laboratory abnormality, or inter-current illness that, in the judgment of the Investigator, warrants delaying the dose	Grade ≥2	Withhold
Any dosing delay	Lasting >12 weeks	Permanently discontinue
Thrombocytopenia	Grade 3 or 4 Grade 3 or 4 with Grade 3 or 4 bleeding; drug-related	Withhold Permanently discontinue
Anemia	Grade 3 or 4	Withhold

Notes:

- AM0010 doses may be withheld for ≤12 weeks (ie, up to 84 consecutive doses).
- AM0010 doses should be withheld until resolution to Grade 1 or pretreatment baseline.
- Withholding dose to allow prolonged steroid tapers to manage drug-related adverse events is allowed.
- Patients receiving AM0010 may receive growth factors (including G-CSF and erythropoietin) for febrile neutropenia or Grade 3 or greater anemia at the discretion of the Investigator.
- Anemia can be due to a direct effect of AM0010 on the scavenger receptor, leading to higher turnover of red blood cells. While this can be managed by withholding dose until resolution to Grade 1 or baseline, blood transfusion is permitted as well if the Investigator deems it necessary.
- Tumor assessments should continue as per protocol even if dosing is withheld.
- See Table 3 for dose schedule reduction criteria for AM0010.

For Grade 3 or 4 toxicities that are related to AM0010 and do not require dose discontinuation, dose schedule reduction will be performed according to Table 3.

Table 3. Dose and Dose Schedule Reduction of AM0010

Dose Schedule	Schedule Modification Criteria	AM0010
SC QD (continuous daily dosing)	-	Starting dose schedule
5 Days on/2 days off	First Grade 3 or 4 event(s)	First dose schedule reduction
4 Days on/3 days off	Second Grade 3 or 4 event(s)	Second dose schedule reduction
2 Days on/5 days off	Third Grade 3 or 4 event(s)	Third dose schedule reduction

Dosing will be withheld until return of the AE to Grade 1 or baseline. If Grade 3 or 4 toxicity occurs after 3 dose reductions of AM0010, patients will be discontinued from study. Once the dose schedule has been reduced, it should not be increased.

6.4.1.2 Pembrolizumab

Pembrolizumab dosing can be withheld up to 12 weeks according to Table 4, based on the most current package insert, dated July 2018. This document can be downloaded from the following Web sites:

FDA home page:
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=125514,

DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9333c79b-d487-4538-a9f0-71b91a02b287#S5.1,

Please ensure you are using the most current version of the package insert as updates by drug manufacturers are continuous.

Pembrolizumab infusion-related reactions should be managed according to Table 5.

Patients may resume treatment with pembrolizumab when drug-related AE(s) resolve(s) to Grade ≤1 or baseline value, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue.
- Patients who have not experienced a Grade 3 drug-related skin adverse event may resume treatment in the presence of Grade 2 skin toxicity.
- Patients with baseline AST/ALT or total bilirubin in the Grade 1 toxicity range who require dose withholds for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

Patients who do not meet the minimum re-treatment criteria on Day 21 of the cycle and do not meet the criteria for discontinuation will withhold treatment and be followed for resolution of toxicity to levels specified in package insert for resuming pembrolizumab.

Dose reduction is not permitted for pembrolizumab.

Table 4. Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Pembrolizumab

General instructions: Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks. For situations in which pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks. For severe and life-threatening immune-related AEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if immune-related AEs cannot be controlled by corticosteroids.				
Immune-related AEs	Toxicity grade or conditions (CTCAEv4.03)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis. Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. Add prophylactic antibiotics for opportunistic infections.
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST/ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable.
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin-replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
	Grade 3 or 4	Withhold or permanently discontinue		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue		
Hypothyroidism	Grades 2-4	Continue	Initiate thyroid-replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	Monitor changes of renal function.
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require		

		discontinuation include, and are not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Withholding or permanently discontinuing pembrolizumab is at the discretion of the investigator or treating physician.
NOTE:
For participants with Grade 3 or 4 immune-related endocrinopathy for whom withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤Grade 2 and is controlled with hormonal-replacement therapy or achieved metabolic control (in case of T1DM).

Abbreviations: AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; GI = gastrointestinal; irAE = immune-related adverse event; IV = intravenous; T1DM = Type 1 diabetes mellitus.

Note: Patients who have asymptomatic or clinically non-significant Grade 3 or 4 lipase or amylase elevations (that is, not associated with clinical symptoms or radiological signs of pancreatitis) that are transient as demonstrated by a decrease of at least 1 CTCAE Grade within 7 days ±3 days of onset will not require pembrolizumab discontinuation or modification. If the elevation has not decreased at least 1 CTCAE Grade within this time window, pembrolizumab treatment may only continue after consultation and discussion with the Sponsor.

Table 5. Pembrolizumab Infusion-Related Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None
Grade 2	**Stop infusion and monitor symptoms.** Additional appropriate medical therapy may include, but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hr of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Patient may be premedicated 1.5 hr (±30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

Pembrolizumab Infusion-Related Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion** Additional appropriate medical therapy may include, but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further trial treatment administration.**	No subsequent dosing.
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

Abbreviations: IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID = non-steroidal anti-inflammatory drug; po = by mouth.

6.4.2 Toxicity

Toxicities will be graded and reported according to the NCI-CTCAE version 4.03 (Appendix E). This document can also be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50.

6.4.3 Data Monitoring Committee (DMC)

No DMC will be formed for this trial. Safety will be evaluated on an ongoing basis.

6.5 Concomitant Medication

Throughout the trial, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for the following:

- Use of anti-cancer therapies (eg, chemotherapy, investigational agent) other than those specified in this protocol are not allowed. Palliative radiation is permitted.
- Immunomodulatory agents including but not limited to anti-CTLA4, anti-PD1, anti-PD-L1, sipuleucel-T, cyclosporine, and tacrolimus.
- Coumadin
- Patients on coumadin should be changed to SQ administered low-molecular weight heparin (LMWH) or oral Factor II or Xa inhibitors with a half-life of less than 24 hours.

- Factor II or Xa inhibitor with a half-life of greater than 24 hours.
- High dose steroids (eg, dexamethasone >10 mg/day for more than 14 sequential days).

6.6 Surgery During Trial Period

Patients should not schedule any elective surgeries during their participation in the trial, through 7 days after the last administration of AM0010 or pembrolizumab. If a patient undergoes any unexpected surgery during the course of the trial, that patient must discontinue trial treatment immediately, and Lilly or designee should be notified as soon as possible.

7.0 TRIAL ASSESSMENTS AND PROCEDURES

7.1 General Trial Procedures

Both trial Arm 1 and Arm 2 will follow the same schedule of assessment, unless otherwise noted.

A signed and dated IRB-approved ICF must be obtained before performing any trial-specific screening procedures that is not part of standard medical practice. All screening tests and assessments must be performed within 21 days of trial day 1, unless noted below.

During the trial, every effort should be made to keep the SOA on time for each patient (Appendix A). All visits should be performed on the visit specified ±3 days, unless otherwise noted.

Patients will continue to receive trial treatment until they experience progressive disease, unacceptable toxicity, require subsequent anticancer therapy, withdraw consent, or their physician feels it is no longer in their best interest to continue on treatment.

Tumor assessment will be performed for all randomized patients every 9 weeks (±7 days) during the study treatment and during the first year from discontinuation of the study treatment, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter. Tumor assessment will be repeated until disease progression, death, or receipt of new anti-cancer therapy, or until study completion, whichever is first, whether or not study treatment was administered.

Scans will include head and CAPs and will be sent be to the central imaging vendor for archiving and possible assessment at a later date and possible archiving at a later date. If clinical progression is suspected, all relevant clinical documentation is to be submitted to the central imaging vendor for archiving.

Tumor assessment of all sites of disease will follow RECIST v.1.1 (Appendix B): CT (or MRI if allergic to contrast). The same radiographic procedure used to define measurable lesions must be used throughout the study for each patient. Assessment should be obtained regardless of cycle number and regardless of any dose withholds until tumor progression. Patients with clinical progression must obtain an unscheduled scan to document disease status per RECIST v1.1. Patients with suspected radiographic pseudoprogression, in the absence of clinical deterioration should remain on trial treatments and be rescanned at 4 weeks or later. If progression is confirmed on follow-up scan per RECIST v1.1, then discontinue study treatments and follow study procedures for end of treatment and follow-ups. At the time of disease progression, patients randomized to trial Arm 2 may crossover to Arm 1 to receive AM0010 and pembrolizumab.

All randomized patients will be followed for OS every 9 weeks (±7 days) during the first year from the 90-day follow-up visit, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter. The survival follow-up will be conducted until death or study completion, whichever is first, whether or not trial drug was administered. For patients

who were randomized, but withdraw consent, survival (date of death) will be obtained by use of publicly available information.

Safety assessment will follow the guidelines provided in NCI-CTCAE v4.03 (Appendix E).

7.2 Overview

The trial consists of the following procedures:

(1) **Screening:** The screening period must occur within 21 days prior to dosing, unless otherwise stated. The screening visit may be counted as baseline (Day 1) if completed within 72 hours prior to dosing.

(2) **Treatment:** Patient will be randomized to either:

- Trial Arm 1: AM0010 self-administered as a SQ injection QD (≤80 kg body weight = 0.8 mg or >80 kg body weight = 1.6 mg). Pembrolizumab will be administered as intravenous (IV) infusion on Day 1 of a 21-day cycle (200 mg over approximately 30 minutes)

OR

- Trial Arm 2: Pembrolizumab will be administered as an IV infusion on Day 1 of a 21-day cycle (200 mg over approximately 30 minutes)

(3) **Clinical and Laboratory Assessments:**

Complete history, physical examination (Site/Organ System Status [includes: General appearance, skin, H/E/E/N/T – Thyroid, Pulmonary, Cardiovascular, Gastrointestinal, Musculoskeletal/ Extremities, Genitourinary/Breast, Lymph Nodes, Neurological and Psychiatric]), ECOG performance status, height (screening only), weight, vital signs, and documentation of concomitant medications.

Laboratory studies: see Section 7.11.

(4) **Continued Treatment:**

At the time of disease progression (as assessed by the Investigator), patients randomized to trial Arm 2 may crossover to Arm 1 receive AM0010 and pembrolizumab.

(5) **End of Treatment:** Patients will return to the trial site 28 days (±7 days) after the last dose of trial drug for end of treatment assessments.

(6) **Follow-Up Period:**

During the extended safety observation period, all randomized patients will be followed for safety 60 and 90 days (±7 days) after the last dose of study treatment and monitored according to the SOA (Appendix A).

During the long-term follow-up period, all randomized patients who discontinue trial treatment before disease progression or patients randomized but not treated will be followed for OS every 9 weeks (±7 days) during the first year from the 90-day follow-up visit, every

12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter. The survival follow-up will be conducted until death or study completion, whichever is first.

The Investigator (or designee) will acquire the following information from patients who were randomized:

- Tumor assessment for all randomized patients who discontinue the trial treatment before disease progression or patients randomized but not treated. Tumor assessment will be repeated every 9 weeks (±7 days) during the study treatment and during the first year from discontinuation of the study treatment, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter, until study completion, disease progression, death or receipt of new anti-cancer therapy, whichever is first.
- Subsequent cancer treatments (all randomized patients).
- Any SAEs considered to be related to trial treatment >90 days post last day of trial treatment, follow until resolution.
- Date and cause of death (all randomized patients).

Scans will include head and CAPs and will be sent to the central imaging vendor for archiving. If clinical progression is suspected, all relevant clinical documentation is to be submitted to the IRR for archiving and possible assessment at a later date. If clinical progression is suspected, all relevant clinical documentation is to be submitted to the central imaging vendor.

7.3 Screening

Informed consent must be obtained before any trial specific tests or evaluations are conducted.

The screening visit will occur within 21 days (unless otherwise stated) before administration of trial treatment and may be combined with baseline laboratory evaluations if both are done within 72 hours of initial dosing. Baseline scans for tumor assessment must be performed within 30 days prior to randomization. Trial eligibility will be based on fulfilling trial inclusion and exclusion criteria. The Investigator will use clinical judgment when determining the clinical significance of laboratory values at baseline and throughout the trial.

At the screening visit, information will be collected and patients will have clinical evaluations as follows:

- Informed consent
- Demographics
- Medical and Cancer history
- Physical examination (including pregnancy results, Site/Organ System Status [includes: General appearance, skin, H/E/E/N/T – Thyroid, Pulmonary, Cardiovascular, Gastrointestinal, Musculoskeletal/ Extremities, Genitourinary/Breast, Lymph Nodes, Neurological and Psychiatric]), including height and weight
- Vital signs (5-minute sitting blood pressure, pulse, respiratory rate, oxygen saturation, and oral temperature)

- ECOG performance status assessment
- Activated partial thromboplastin (aPTT) and International Normalized Ratio (INR) or Prothrombin (PT)
- Clinical laboratory tests (hematology, chemistry panel, thyroid function (TSH, T3, and T4), and urinalysis)
- 12-lead electrocardiogram (ECG)
- Pregnancy test (urine or serum) in women of childbearing potential
- Radiologic tumor assessment (within 30 days prior to randomization)
- PD-L1 expression as determined by FDA-approved PD-L1 IHC 22C3 PD-L1 assay.
- Concomitant medications
- Obtain pathology report of archival tissue.

If screening evaluations are not done within 72 hours of the initial dose of trial drug, the following evaluations will be repeated at a baseline visit:

- Physical examination (including pregnancy results, Site/Organ System Status [includes: General appearance, skin, H/E/E/N/T – Thyroid, Pulmonary, Cardiovascular, Gastrointestinal, Musculoskeletal/ Extremities, Genitourinary/Breast, Lymph Nodes, Neurological and Psychiatric]), including weight
- Vital signs (5-minute sitting blood pressure, pulse, respiratory rate, oral temperature)
- ECOG performance status assessment
- Clinical laboratory tests (hematology, chemistry panel, coagulation tests, and urinalysis)
- Non-radiologic tumor assessment (if applicable)

7.4 Clinical Visits

7.4.1 Clinic Evaluations

Once a patient is enrolled, a mandatory tumor tissue sample for biomarker research should be submitted (preferably from the same block used for PD-L1 testing).

Physical examination, vital signs, 12-lead ECG, ECOG performance status assessment, thyroid function, urinalysis, concomitant medications, and AEs will be assessed at Cycles 1, 3, 5, etc. Clinical laboratory tests (hematology, chemistry panel, and coagulation tests) will be assessed at every cycle.

- Physical examination (including pregnancy results, Site/Organ System Status [includes: General appearance, skin, H/E/E/N/T – Thyroid, Pulmonary, Cardiovascular, Gastrointestinal, Musculoskeletal/ Extremities, Genitourinary/Breast, Lymph Nodes, Neurological and Psychiatric]) including weight
- Vital signs (5-minute sitting blood pressure, pulse, respiratory rate, oxygen saturation, and oral temperature)
- 12-lead electrocardiogram (ECG)
- ECOG performance status assessment
- Clinical laboratory tests (hematology, chemistry panel, coagulation tests, thyroid function, and urinalysis)

- Concomitant medications
- Adverse Events

Note: The physical examination, weight measurement, and clinical laboratory tests may be performed up to 24 hours before dosing. Complete blood count (CBC) results must be available prior to infusion for every dose. If chemistry results are abnormal, assess again before dosing.

7.5 Tumor Assessments

- CT or MRI (if allergic to contrast media) scans will be performed every 9 weeks (±7 days) during the study treatment and during the first year from discontinuation of the study treatment, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter to evaluate response to treatment by RECIST v.1.1.
- The same radiographic procedure (includes head, chest, abdomen, and pelvis) to define measurable lesions must be used throughout the trial for each patient.
- Patients will continue the assigned trial treatments until tumor progression (by RECIST v.1.1 criteria) by CT or MRI (if allergic to contrast media), withdrawal from the trial, or intolerance of therapy not manageable with dose modifications outlined in the protocol/package insert and/or supportive care. Note: Patients with suspected radiographic pseudoprogression, in the absence of clinical deterioration, should remain on trial treatments and be rescanned at 4 weeks or later. If progression is confirmed on follow-up scan, study treatments will be discontinued or patients on Arm 2 may be eligible for crossover. Refer to Section 7.6.
- Patients who discontinue trial treatments with response of CR, PR, or SD will undergo CT or MRI scan evaluations per protocol until time of PD, or death, or until study completion, or initiation of subsequent anti-cancer therapy, whichever is first.
- Patients who demonstrate clinical progression before their scans are due will have an unscheduled scan conducted to document disease status by RECIST v.1.1.
- The first scheduled tumor response assessment will be performed at 9 weeks (±7 days), and responders (CR or PR per RECIST v1.1) will have a confirmatory scan at ≥4 weeks after response has been established using the same technique as baseline scans.
- All CT/MRI scans for all patients randomized on the trial will be collected prospectively and submitted to a central imaging vendor for archiving. These scans may be independently reviewed at a later time at the request of Lilly.

7.6 Pseudoprogression and Confirmation of Disease Progression

Accumulating evidence indicates a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of PD.

Patients will be permitted to continue treatment beyond initial RECIST 1.1 defined PD if they meet the following criteria:

- Investigator-assessed clinical benefit, and do not have rapid disease progression
- Continue to meet all other study protocol eligibility criteria
- Tolerance of study drug
- Stable performance status

Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases).

A radiographic assessment/scan should be performed 4 weeks (±7 days) after original PD to determine whether there has been a decrease in tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the patients is clinically deteriorating and unlikely to receive any benefit from continued treatment with AM0010 and/or pembrolizumab. A confirmatory scan will be required in the case of clinical deterioration suspected to be disease progression.

For patients who continue AM0010 and/or pembrolizumab beyond initial progression, confirmed progression is defined as an additional 10% increase in tumor burden volume from the time of initial PD. This includes an increase in the sum of all target lesions and/or the development of new measurable lesions. Treatment beyond confirmed progression is not allowed.

When assessing disease progression, the Investigator should use a new baseline tumor burden that includes new lesions that developed at the time of initial progression. New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm).

For patients in both treatment arms, global deterioration of health status (to ECOG Performance Status 2 for example) requiring discontinuation of study treatments without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression (ie, radiographic confirmation) even after discontinuation from study treatments.

7.7 Trial Drug Administration

AM0010 is provided as a sterile, single use prefilled syringe, with a clear solution formulated at a concentration of 4 mg/mL. A pharmacy guide will be provided, which contains details regarding packaging, labeling, storage, (re)ordering and administration of AM0010 as well as FDA approved labeling of pembrolizumab.

A trial-defined AM0010 and pembrolizumab treatment will begin on trial day 1. Patients on Arm 1 will dose AM0010 prior to initiation of pembrolizumab. Patients on Arm 1 will dose AM0010 according to their weight:

- ≤80 kg body weight = 0.8 mg
- >80 kg body weight = 1.6 mg

AM0010 dose recalculations are only required if a patient's body weight changed from ≤80 kg to >80 kg or vice versa. Change in body weight should be calculated based on change from baseline weight or last weight taken per protocol.

Patients will be trained to self-administer AM0010 and will self-administer the dose throughout the trial starting with the first dose. A patient's caregiver may also be trained to perform SQ injections. Both the patient's and caregiver's training must be recorded in the patient's medical records. The Investigator or a qualified designee must be present during administration of the first dose. An AM0010 administration diary must be kept for dosing compliance monitoring.

Pembrolizumab will be administered on Day 1 of each 21-day cycle;

- Patients on Arm 1 (including crossover patients) will be administered pembrolizumab at a fixed dose of 200mg over approximately 30 minutes IV infusion
- Patients on Arm 2 will be administered pembrolizumab at a fixed dose of 200mg over approximately 30 minutes IV infusion

Pembrolizumab should be obtained by each site as per routine institutional practice. For preparation and complete prescribing information, refer to the most current prescribing information in the region. Investigators or designees will review the patient's hematology and chemistry panels, liver function tests, and the incidence of hematologic and non-hematologic toxicities prior to and during immunotherapy regimens.

Medications used to treat pembrolizumab-related infusion reactions (eg, diphenhydramine, acetaminophen/paracetamol, corticosteroids) considered non-investigational medicinal products (NIMPs) and will not be provided by the sponsor. These will be obtained by the investigational sites as marketed product, which should be stored in accordance to the package insert.

7.8 Continued Treatment

7.8.1 Crossover

At the time of disease progression (as assessed by the Investigator) patients randomized to trial Arm 2 may crossover to study Arm 1 to receive AM0010 and pembrolizumab. When progressive disease is noted on the scan for an Arm 2 patient, no more than 21 days should pass before the patient crosses over to Arm 1. The scans and/or clinical assessment at crossover will be used as a new baseline to determine response or PD on Arm 1.

7.9 End of Treatment Visit

Twenty-eight (28) days (±7 days) after the last dose of trial treatment, patients are expected to return to the trial site to complete all end of treatment assessments as follows:

- Physical (including pregnancy results, Site/Organ System Status [includes: General appearance, skin, H/E/E/N/T – Thyroid, Pulmonary, Cardiovascular, Gastrointestinal, Musculoskeletal/ Extremities, Genitourinary/Breast, Lymph Nodes, Neurological and Psychiatric]), including weight

- Vital signs (5-minute sitting blood pressure, pulse, respiratory rate, oral temperature)
- 12-lead ECG
- Activated partial thromboplastin (aPTT) and International Normalized Ratio (INR) or Prothrombin (PT)
- ECOG performance status assessment
- Clinical laboratory tests (hematology, chemistry panel, thyroid function, and urinalysis)
- Biomarker blood sample
- Pregnancy test (urine or serum) in women of childbearing potential
- Concomitant medications
- Adverse events

7.10 Follow-Up Period

During the extended safety observation period, all randomized patients will be followed for safety 60 and 90 days (±7 days) after the last dose of study treatment and monitored according to the SOA (Appendix A).

During the long-term follow-up period, all randomized patients will be followed for OS every 9 weeks (±7 days) during the first year from the 90-day follow-up visit, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter. The survival follow-up will be conducted until death or study completion, whichever is first, whether or not trial treatment was administered.

For patients who were randomized, but withdrew consent, survival (date of death) will be obtained by use of publicly available information.

The Investigator (or designee) will acquire the following information from patients who were randomized:

- Tumor assessment will be repeated every 9 weeks (±7 days) during the study treatment and during the first year from discontinuation of the study treatment, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter. Tumor assessment will be repeated until study completion, disease progression, death, or receipt of new anti-cancer therapy for patients who were randomized, and not treated or discontinue treatment before disease progression, *and do not withdraw consent.*
- Subsequent cancer treatments (all randomized patients).
- Any SAEs considered to be related to trial treatment, follow until resolution.
- Date and cause of death (all randomized patients).

7.11 Laboratory Assessments

Local laboratories will perform the following laboratory tests, and results will be provided to the Investigator. Blood and urine samples for hematology, chemistry, activated partial thromboplastin (aPTT) and International Normalized Ratio (INR) or Prothrombin (PT), thyroid function, and urinalysis will be prepared using standard procedures. Laboratory panels are defined as follows:

Hematology	WBC count with differential, RBC count, hemoglobin, hematocrit, reticulocyte count, and platelet count
Chemistry	albumin, ALP, ALT, AST, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, potassium, sodium, total bilirubin, lactate dehydrogenase, and total protein
Coagulation Tests:	aPTT and International Normalized Ratio (INR) or PT
Thyroid Function Test	TSH, free T3, and free T4
Urinalysis	appearance, color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and occult blood (microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive)
Pregnancy Test	Serum or urine pregnancy test for women of child bearing potential

Abnormalities in clinical laboratory tests that lead to a change in patient management (ie, dose withhold or modification, requirement for additional medication or monitoring) are considered clinically significant for the purposes of this trial and will be recorded on the AE CRF page. If values meet criteria defining them as serious, they must be reported as SAEs (Section 9.1.2).

7.12 Pharmacokinetics

Blood samples for PK with sparse sampling techniques will be obtained on all patients on Arm 1 (including crossover patients). Serum samples will be collected to characterize PK of AM0010 in combination with pembrolizumab and to explore exposure-safety and exposure-efficacy relationships. Data from these investigations may be evaluated for correlations with response, survival, and safety data.

PK samples will be drawn pre-dose (AM0010 and pembrolizumab)

- Day 1 of Cycles 1, 2, 3, 4, and every fourth cycle thereafter (eg, 8, 12, 16, etc.)
- End of treatment visit
- Day-60 and -90 follow-up visits after the last dose of study treatment.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last participant visit for the study.

7.13 Immunogenicity (ADA [anti-drug antibodies])

Blood samples for immunogenicity analysis will be obtained on all patients on Arms 1 and 2 (including crossover patients). Samples will be evaluated for development of anti-drug antibodies (ADAs) by a validated immunoassay.

ADA samples will be drawn pre-dose at the following time points:

- Day 1 of Cycles 1, 2, 3, 4, and every fourth cycle thereafter (eg, 8, 12, 16, etc.)
- End of treatment visit

- Day-60 and -90 follow-up visits after the last dose of study treatment.

All immunogenicity samples will be retained for a maximum of 15 years after the last participant visit, or for a shorter period if local regulations and Ethical Review Boards (ERBs) allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the investigational product. Any samples remaining after 15 years will be destroyed.

7.14 Biomarkers

Blood samples for biomarker analysis will be obtained on all patients in Arms 1 and 2. A variety of factors that may impact the immunomodulatory properties and efficacy of AM0010 in combination with pembrolizumab will be investigated in peripheral blood. Data from these investigations may be evaluated for correlations with response, survival, and safety data.

- Biomarker samples will be drawn pre-dose (AM0010 and pembrolizumab) on Day 1 of Cycles 1, 2, 3, 5, 7, 9, 11, etc. and at the end of treatment visit.

All biomarker samples (both tissue and blood) will be retained for a maximum of 15 years after the last participant visit, or for a shorter period if local regulations and ERBs allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the investigational product. Any samples remaining after 15 years will be destroyed.

8.0 REMOVAL AND REPLACEMENT OF PATIENTS

8.1 Removal of Patients

Patients have the right to withdraw from the trial at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

Any patient who withdraws consent to participate in the trial will be removed from the trial immediately upon the date of request. The Investigator will make every effort to contact the patient and perform end-of-treatment procedures. Should a patient (or a legally acceptable representative) request or decide to withdraw from the trial, all efforts will be made to complete and report the observations as thoroughly as possible in addition to follow up for OS. All information should be reported on the applicable CRFs.

The patient who requests to stop trial treatment or has withdrawn from trial treatment because of the Investigator's or Sponsor's concern before completion of the protocol-specified treatment duration will be strongly encouraged to continue the schedule of trial observations, in addition to follow up for OS.

If the patient has withdrawn because of toxicities, the Investigator should arrange for the patient to be followed for a minimum of 90 days or until any drug-related toxicities resolve to grade 1 according to CTCAE Version 4.03, or return to the patients' baseline values, in addition to follow up for OS. All end-of-treatment procedures should be completed for such a patient.

Reasons for removal from investigational product or observation may include:

- Withdrawal of consent
- Administrative decision by the Investigator or Sponsor
- The patient's physician feels it is no longer in their best interest of the patient to continue on treatment.
- Require subsequent systemic anticancer therapy
- Pregnancy (report on Pregnancy Notification Worksheet/CRF)
- Ineligibility determined after enrollment
- Significant protocol deviation
- Patient noncompliance
- Adverse event (disease progression is not considered an AE)
- Progression of disease (clinical and/or radiological)
- Lost to follow-up

The reason for withdrawal, the date of administration of the final trial treatment, and the date of withdrawal should be recorded on the End-of-Treatment CRF.

All randomized patients will be followed for OS every 9 weeks (±7 days) during the first year from the 90-day follow-up visit, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter. The survival follow-up will be conducted until death or study completion, whichever is first, whether or not trial treatment was administered.

For patients who were randomized, but withdraw consent, survival (date of death) will be obtained by use of publicly available information.

All randomized patients who discontinue trial treatment before disease progression or patients randomized but not treated will be followed for PFS per protocol until study completion, disease progression, or death or receipt of new anti-cancer therapy, whichever is first. Scans will include head and CAPs and will be sent to the central imaging vendor for archiving and possible assessment at a later date. If clinical progression is suspected, all relevant clinical documentation is to be submitted to the central imaging vendor for archiving.

The Investigator (or designee) will acquire the following information from patients who were randomized:

- Tumor assessment for all randomized patients who discontinue the trial treatment before disease progression or patients randomized but not treated. Tumor assessment will be repeated until study completion, disease progression, death or receipt of new anti-cancer therapy, whichever is first.
- Subsequent cancer treatments (all randomized patients).
- Any SAEs considered to be related to trial treatment, follow until resolution.
- Date and cause of death (all randomized patients).

8.2 Replacement of Patients

Randomized patients who withdraw from the trial will not be replaced.

9.0 ADVERSE EVENT REPORTING

9.1 Definitions

9.1.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Investigators are responsible for:

- monitoring the safety of patients in this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient,
- the appropriate medical care of patients during the study,
- documenting their review of each laboratory safety report, and
- following, through an appropriate healthcare option, AEs that are serious or otherwise medically important, considered related to study treatment or the study, or that caused the patient to discontinue study treatment before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

A worsening of an existing medical condition occurs when a condition present at the time the informed consent form is signed (eg, diabetes, migraine headaches, gout) becomes more severe, more frequent, or increases in duration during investigational product treatment.

Abnormal laboratory values should not be reported as an AE, unless they are considered clinically significant by the Investigator; however, any clinical consequences of the abnormality should be reported as an AE. Abnormalities in clinical laboratory tests that lead to a change in patient management (ie, dose schedule reduction or withhold, requirement for additional medication or monitoring) are considered clinically significant for the purposes of this trial and will be recorded on the AE CRF page.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a study patient experiences elevated ALT≥5×ULN and elevated total bilirubin ≥2×ULN, or ALT≥8×ULN, liver tests (Appendix E), including ALT, AST, total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or

decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests (Appendix E) and in consultation with the Lilly Clinical Research Physician (CRP). Monitoring of ALT, AST, and total bilirubin should continue until levels normalize or return to approximate baseline levels.

9.1.2 Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (ie, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent 1 of the other outcomes listed in the definition above.

9.2 Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to study treatment or study procedure. United States 21 CFR 312.32 and Regulation (EU) No. 536/2014 and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

9.2.1 Pregnancy

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an AE, but should be reported. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

The Investigator will inform Lilly within 24 hours of awareness by any study personnel of any case of pregnancy and collect information on any exposure to the study drug(s) during pregnancy (female patient or male patient's partner). An exposure during pregnancy (also referred to as exposure in utero) occurs if a female is or has been found to be pregnant after being exposed to the study drug(s) directly, indirectly, or via her partner (paternal exposure). If any study subject becomes or is found to be pregnant and exposed to investigational product as described above, the Investigator must submit this information to Lilly on a

Pregnancy Report Form irrespective of whether an AE has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery. Follow-up is conducted to obtain pregnancy outcome information on all exposure during pregnancy reports with an unknown outcome. The Investigator will follow the pregnancy until completion or until pregnancy termination (ie, induced abortion) and then notify Lilly of the outcome. The Investigator will provide this information as a follow-up to the initial Pregnancy Report Form. The reason(s) for an induced abortion should be specified. A report is not created when an ectopic pregnancy report is received since this type of pregnancy is not usually viable. Rather, an SAE case is created with the event of ectopic pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, still birth, or neonatal death]), the Investigator should follow the procedures for reporting SAEs. In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (ie, no minimum follow-up period of a presumably normal infant is required before a Pregnancy Report Form can be completed), and birth information will be provided as a follow-up of the initial Pregnancy Report Form. Case processing at Lilly will be performed as described above for SAE reports. Additional information regarding the exposure during pregnancy may be requested from the Investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental withholds).

9.3 Reporting Procedures for All Adverse Events

After the ICF is signed, study site personnel will record via electronic case report form (eCRF) the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, study site personnel will record via eCRF any change in the preexisting conditions and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to study treatment via eCRF.

All AEs, regardless of grade and occurring after obtaining informed consent, observed by the Investigator or reported by the patient (whether or not attributed to investigational product), will be reported on the AE CRF. Please note that disease progression should not be considered an AE, but shall be documented on the appropriate CRF.

Medically significant AEs considered to be related to the investigational product by the Investigator or Sponsor will be followed until resolved or considered stable. The Investigator must assign the following attributes: description (concise diagnosis, if available); dates of onset and resolution; severity; assessment of relatedness to investigational product; and action taken. The Investigator may be asked to provide follow-up information, medical records, and extracts from medical records or CRFs.

The SAE reporting to Lilly or its designee begins after the patient has signed the ICF and has received study treatment. However, if an SAE occurs after signing the ICF, but prior to

receiving study treatment, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure. "Death" as an outcome of an AE may occur and should not be reported as an AE, but the cause of death should be reported on the AE eCRF.

For the purpose of this study, progression of underlying malignancy is not considered an (S)AE. Hospitalization, prolonged hospitalization, or death due solely to the progression of underlying malignancy will be captured on the AE CRF, but will NOT be reported as an SAE. Clinical symptoms of progression may be reported as AEs if they cannot be determined to be exclusively due to the progression, or if they do not fit the expected pattern of progression for late stage NSCLC cancer.

SAEs which are considered related to study drug occurring >90 days after last trial treatment must be reported on both a CRF and on a SAE Report Form (with an autopsy report if available).

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued (the patient summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discontinued from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly or its designee.

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

If it is deemed to be in the best interest of the patient to start a new anti-cancer treatment prior to the follow-up visit, the visit duration may be shortened. In this case, the follow-up assessments should be completed prior to the initiation of the new therapy. If an anti-tumor treatment is initiated within 90 days of the last dose of trial treatment, the start date of this treatment should be documented on the appropriate CRF.

The Investigator must notify the IRB of SAEs occurring at the site and other AE reports received from Lilly/designee in accordance with local procedures/site IRB policies.

It will be left to the Investigator's clinical judgment whether or not an AE is of sufficient severity to require the patient's removal from treatment. A patient may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the patient must undergo an end-of-treatment assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable. If the patient is permanently withdrawn from the trial or investigational product due to an SAE, this information must be included in either the initial or follow-up SAE Report Form or the End-of-Treatment CRF.

Study site personnel must report any treatment discontinuations that result from AEs to Lilly or its designee via eCRF, clarifying, if possible, the circumstances leading to the discontinuation of treatment.

The trial will use the Common Terminology Criteria for grading AEs that are experienced by research patients. If the AE is not specified in the NCI-CTCAE v4.03 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50) the severity will be assessed on the following scale with appropriate clinical definitions:

1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, 5 = fatal

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the disease, concomitant treatments, or pathologies.

The relationship of the AE to the investigational product will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the investigational product?' Answer Yes or No.

Determination of expectedness will be based on the contents of the Investigator's Brochure.

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to classify the events.

9.4 Serious Adverse Event Reporting Procedures

Study site personnel must notify Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a Lilly-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

9.5 Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, to monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

10.0 STATISTICAL CONSIDERATIONS

10.1 Trial Design

This is an open-label, randomized, multicenter Phase 2 trial in adult male and female patients with treatment-naïve, Stage IV/metastatic NSCLC whose tumors are not known to have EGFR mutation or ALK rearrangement, and have high expression (≥50%) of PD-L1 as determined by the FDA-approved PD-L1 IHC 22C3 assay.

Patients will be stratified according to tumor histology (squamous vs non-squamous).

Patients will be randomized in a 1:1 ratio into 1 of 2 treatment arms.

- **Arm 1:** Patients will receive AM0010 as a subcutaneous (SQ) daily (QD) injection plus pembrolizumab as IV infusion on Day 1 of a 21-day cycle.
- **Arm 2:** Patients will receive pembrolizumab as IV infusion on Day 1 of a 21-day cycle.

10.2 Trial Endpoints

10.2.1 Primary Endpoint

- **Objective Response Rate**

Objective response rate is defined as the proportion of patients with a confirmed CR or confirmed PR relative to the total analysis population. The ORR is determined by the best response designation per RECIST v1.1 recorded between the date of randomization and the date of objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first. For patient without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the ORR determination. Confirmed responses are those that persist on repeat imaging scan ≥4 weeks after initial documentation of response. For patients who continue treatment beyond progression due to suspected pseudoprogression as outlined in Section 7.6. The objective response should be determined based on response assessment recorded at the CT scan done no less than 4 weeks after suspected pseudoprogression. If the patient subsequently responds or returns to baseline, that assessment of objective tumor response is achieved after pseudoprogression as the true response per RECIST v.1.1.

10.2.2 Secondary Endpoints

- **Progression-Free Survival**

Progression-free survival is defined as the time from randomization to the date of the first documented tumor progression as determined by the Investigator (per RECIST v.1.1 criteria or clinical progression) or death due to any cause whichever occurs first. Patients who experience clinical disease progression should undergo scanning to document radiographic disease progression per RECIST v.1.1. In this case, the date of the confirmatory CT scan will be used as the date of disease progression. Patients who die without a reported prior progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last tumor assessment. Patients

who did not have any on-trial tumor assessment and did not die will be censored on the date they were randomized with a duration of 1 day. Patients who received any subsequent anti-cancer therapy without a prior documented progression will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy. Any additional censoring rules that may be needed will be specified in the statistical analysis plan.

- **Overall Survival**

Overall survival is defined as the time from the date of randomization to the date of death. Patients who are no longer on trial treatments should be followed for survival. A patient who is alive will be censored at the date last known to be alive.

- **Disease Control Rate (DCR)**

Disease control rate is defined as the proportion of patients who achieve Stable Disease (SD) ≥9 weeks (±7 days) plus confirmed CRs + confirmed PRs as determined by the Investigator using RECIST v.1.1.

- **Duration of Response (DoR)**

The DoR is defined as the time from the date of the first documentation of objective tumor response (CR or PR) to the date of the first documentation of objective tumor progression or death due to any cause, whichever occurs first.

10.3 Sample Size Considerations

Approximately 100 patients will be randomized to the 2 arms in a 1:1 ratio. With 100 patients, this study has more than 80% power to detect an absolute increase in ORR of 25% (ie 45% vs 70%) in the ORR between AM0010 in combination with pembrolizumab and pembrolizumab alone at a 1-sided 5% type I error rate.

10.4 Schedule of Analyses

Table 6 provides schedule of analyses for key endpoints.

Table 6. Schedule of Analyses

Type of Analysis	Key Endpoint(s)	Expected Timing of Analysis
Interim Analysis	PK, Safety	~3 months after the 50th patient randomized
Primary Analysis	ORR	~6 months after the 100th patient randomized

A planned interim analysis maybe performed when the 50th randomized patient has been followed up for approximately 3 months. No statistical boundaries or alpha spending will be applied for this interim analysis as the primary purpose of this analysis is to assess safety and PK. At the time of interim data lock, all patients on study will continue study per protocol.

10.5 Analysis Populations

- All Enrolled Patients: all patients who signed an informed consent form and were registered into the IWRS.

- ITT Population: All patients who are randomized. This is the primary population for analyses of efficacy and baseline characteristics.
- Safety Population: All randomized patients who received any amount of study drug. This is the primary population for exposure and safety.
- PK Population: All treated patients with available serum time-concentration data from randomized patients dosed with AM0010.
- Biomarker Population: All treated patients with available biomarker data from randomized patients.

10.6 Planned Method of Analysis

10.6.1 General Approach/Considerations

Unless otherwise stated, descriptive statistics will be provided for all endpoints for each treatment group and overall. Continuous measurements will be summarized using the mean, standard deviation, median, interquartile range, range, and number of patients.

All efficacy analyses will be stratified by the histology type at randomization.

10.6.2 Demographic and Baseline Characteristics

Demographics (age, sex, and race) and other baseline disease characteristics will be summarized using descriptive statistics.

10.6.3 Efficacy Analyses

10.6.3.1 Primary Efficacy Analyses

Objective response rate, defined as the proportion of patients who achieve confirmed CR+PR, will be summarized by treatment arm and compared using a Cochran-Mantel Haenszel (CMH) 2-sided test stratified by the histology type at a type I error rate of 10%. The odds ratio and 90% CI will also be provided.

10.6.3.2 Secondary Efficacy Analyses

PFS will be summarized by median PFS (including 95% CI) for each treatment arm along with the hazard ratio (including 95% CI). The Kaplan-Meier curve for PFS will be presented for each treatment arm and the difference in the curves will be tested using the stratified log-rank test.

Overall survival will be summarized by median survival time (including 95% CI) for each treatment arm along with the hazard ratio (including 95% CI). The Kaplan-Meier curve for survival will be presented for each treatment arm and the difference in the curves will be tested using the stratified log-rank test.

Disease control rate will be analyzed in the same manner as objective tumor response.

Duration of response is defined as the time from the date of the first documentation of objective tumor response (CR or PR), as determined by the Investigator using RECIST v.1.1, that is subsequently confirmed to the date of the first documentation of objective tumor progression or to death due to any cause, whichever occurs first. Duration of response will

be censored on the date of the last tumor assessment on trial for patients who do not have objective tumor progression and who do not die due to any cause while on trial. For patients who have an ongoing objective response but discontinued to have tumor scans assessments before disease progression, the duration of response will be censored at the date of the last tumor assessment.

Duration of response will be estimated for each treatment arm using the Kaplan-Meier product-limit method for patients who have CR or PR. Duration of SD will be summarized as well.

Time to response is defined as the time from date of randomization to the date of the first documentation of objective tumor response that is subsequently confirmed. Duration of response and time to response will only be evaluated in patients with objective response of CR or PR and will be summarized by trial treatment arm.

10.6.4 Safety Analyses

All safety summaries and analyses will be performed on the Safety Population.

Safety and tolerability will be measured by:

- Adverse events
- Physical examinations (including neurological examination)
- Vital Signs
- ECGs
- Laboratory assessments
  - Hematology
  - Chemistry
  - Coagulation Tests
  - Thyroid Function
  - Urinalysis

10.6.5 Extent of Exposure

Extent of exposure will be summarized, variables include duration of treatment, number of cycles, total dose administered, and relative dose intensity for the entire treatment duration as well as for each cycle. Number and percentage of patients experiencing dose modifications for each treatment arm, and reasons will be provided as well.

10.6.6 Adverse Events

Adverse events will be analyzed in terms of treatment-emergent AEs defined to be any AEs that begin or worsen in intensity after trial drug initiation through 90 days after the last dose of trial drug. All AEs will be coded based on MedDRA terms.

Descriptive statistics of safety will be presented using NCI-CTCAE v4.03 by treatment arm. All treatment emergent AEs due to any cause, treatment-related AEs, SAEs, treatment-related SAEs, and AEs leading to discontinuation from the trial treatments will be tabulated using the worst grade per NCI-CTCAE v4.03 criteria by system organ class and preferred

term. Additional summaries include AEs by intensity (Grade 1 to 4 or/and Grades 3 and 4). All AEs will be listed.

10.6.7 Clinical Laboratory Data

Summary and change in laboratory data will be provided over time for hematology, chemistry parameters and urinalysis.

The NCI-CTCAE v4.03 grade for selected hematology parameters will be summarized by the worst grade in each treatment cycle and the worst grade during the trial for each treatment arm. The number and percent of patients with NCI-CTCAE v4.03 hematology value of Grade 3 or 4 that occur after the first dose of trial drugs also will be presented. Shift tables may be provided.

Liver and renal function will be summarized using NCI-CTCAE v4.03 grade for selected chemistry parameters. The number and percent of patients with NCI-CTCAE v4.03 chemistry values of Grade 3 or 4 that occur after the first dose of trial drugs also will be presented. Shift tables may be provided.

10.6.8 ECOG Performance Status

Descriptive statistics will be provided for ECOG performance status at each assessment time.

10.6.9 Vital Signs

Vital signs (blood pressure, heart rate, temperature, and oxygen saturation), weight, and change from baseline will be summarized by treatment arm.

10.6.10 12-Lead ECG

ECG parameters including QTc and change from baseline will be summarized by visit and by treatment arm. Number and percent of patients for each QTc parameter for the following categories will be summarized:

- QTc <450, 450 to <480, 480 to 500, and >500 ms.
- QTc change from baseline 30 to <60 ms and ≥60 ms.

10.6.11 Immunologic Biomarkers

Associations between biomarkers and efficacy outcomes (OS, ORR, and PFS) may be analyzed on all patients with available biomarker data. Models to predict clinical activity based on combinations of biomarkers may also be investigated.

Additional post hoc statistical analyses not specified in the protocol or statistical analysis plan, such as alternative modeling approaches, may be conducted. All analyses are based on the availability of the data.

10.6.12 Pharmacokinetic Analyses

The concentration vs time will be collected for all patients treated with AM0010 in combination with pembrolizumab and used for exposure-response analyses (exposure-safety

and exposure-efficacy) of selected safety and efficacy endpoints. Results of PK and exposure-response analyses will be reported separately.

11.0 INVESTIGATIONAL PRODUCT

11.1 AM0010

AM0010 will be manufactured and packaged by a third-party under the direction of Lilly and distributed using Lilly's/designee clinical trial drug distribution procedures. AM0010 is provided as a sterile, single use prefilled syringe, with a clear solution formulated at a concentration of 4 mg/mL.

Each patient (Arm 1) will receive weight-based doses of single use prefilled syringes, instruction for self-administration and an AM0010 dosing diary.

AM0010 drug product is stored refrigerated. Refer to the product label for full storage instructions..

AM0010 should be stored in a secure location with limited access under controlled temperature conditions. Prefilled syringes should be stored in their original folding carton and should not be dispensed until patient is randomized or patient resupply is required.

The packaging lot number of AM0010 will be recorded on each patient's Drug Administration CRF.

Additional AM0010 details including labeling, storage, and preparation information are provided in the Pharmacy Guide. It should be noted that this manual may be updated/revised as additional information becomes available.

11.2 Compliance in Investigational Product Administration

When investigational product is dispensed for administration to the patient during a trial, the Investigator or responsible person will determine the extent to which the patient complies with the recommended administration of the investigational product. The patient's investigational product compliance will be recorded on the drug administration case report form. Because this trial involves the self-administration of an SQ drug product, patients will need to complete an AM0010 dosing diary.

12.0 ETHICAL CONSIDERATIONS

12.1 Local Regulations

The trial must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" (GCP) ICH E6 R2 Tripartite Guideline (June 2017). The Investigator will ensure that the conduct of the trial complies with the basic principles of GCP as outlined in the current version of 21 CFR, Subpart D, Part 312, "Responsibilities of Sponsors and Investigators," Part 50, "Protection of Human Subjects," and Part 56, "Institutional Review Boards."

12.2 Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator, to obtain written informed consent from each patient participating in this trial after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the trial. In the case where the patient is unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood.

If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated as necessary. All patients (including those already being treated) should be informed of the new information, should be given a copy of the revised form, and should give their consent to continue in the trial.

12.3 Institutional Review Board

A copy of the protocol and proposed informed consent form, other written patient information, and any proposed advertising material related to patient recruitment must be submitted to the IRB for written approval. A copy of the written IRB approval of the protocol and informed consent form must be received by Lilly or its designee before the recruitment of patients into the trial and the shipment of investigational product.

The Investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IRB of deviations from the protocol or SAEs occurring at the site and other AE reports received from Lilly in accordance with local procedures/IRB policies.

The Investigator will be responsible for obtaining annual IRB approval/renewal throughout the duration of the trial. Copies of the Investigator's reports and the IRB continuance of approval must be sent to Lilly or its designee.

12.4 Documentation Requirements

The Investigator is responsible for forwarding the following documents to Lilly or its designee for review before trial initiation can occur:

- Signed and dated protocol signature page (Investigator's Agreement)
- Copy of the IRB approval of the protocol, consent form, and patient information sheet
- Up-to-date curricula vitae of the Principal Investigator and all co/sub-investigators
- IRB composition and/or written statement that IRB is in compliance with regulations
- Laboratory normal ranges and documentation of laboratory certification (or equivalent)
- Current patient/Investigator indemnity insurance
- Signed trial contract
- Completed FDA form 1572 (Laboratories providing primary and secondary endpoint data and any central laboratories for the trial must be listed on the form.)
- Completed Financial Disclosure statements for the Principal Investigator, all co/sub-investigators, and their spouses or legal partners and dependent children.

12.5 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms or other documents submitted to Lilly or its designee, patients should be identified by their initials and/or a patient trial number only. Documents that are not for submission to Lilly (eg, signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal regulations/ICH GCP Guidelines, the Investigator and institution are required to permit authorized representatives of Lilly, of the regulatory agency(s), and the IRB direct access to review the patient's original medical records for verification of trial-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the trial. The Investigator is obligated to inform and obtain the consent of the patient to permit such representatives to have access to his/her trial-related records without violating the confidentiality of the patient.

13.0 ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 Protocol Amendments and Trial Termination

Protocol amendments, except where necessary to eliminate an immediate hazard to patients, must be made only with the prior approval of Lilly. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IRB must be informed of all amendments and give approval. The Investigator must send a copy of the approval letter from the IRB to Lilly.

Both Lilly and the Investigator reserve the right to terminate the trial according to the trial contract. The Investigator should notify the IRB in writing of the trial's completion or early termination and send a copy of the notification to Lilly.

13.2 Trial Documentation and Archive

The Investigator shall maintain a list of appropriately qualified persons to whom he/she has delegated trial duties. All persons authorized to make entries and/or corrections on case report forms will be included on a Site Signature Log.

Source documents are original documents, data, and records from which the patient's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The Investigator and trial staff are responsible for maintaining a comprehensive and centralized filing system of all trial-related (essential) documentation, suitable for inspection at any time by representatives from Lilly and/or applicable regulatory authorities. These elements should include:

- Patient files containing completed CRFs, ICFs, and patient identification list
- Trial files containing the protocol with all amendments, Investigator's Brochure, copies of pre-trial documentation (Section 12.4), and all correspondence to and from the IRB and Lilly
- Proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement, and all drug-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No trial document should be destroyed without prior written agreement between Lilly and the Investigator. Should the Investigator wish to assign the trial records to another party or move them to another location, he/she must notify Lilly in writing of the new responsible person and/or the new location.

13.3 Trial Monitoring and Data Collection

The Lilly representative and Regulatory Authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical trial (eg, CRFs and other pertinent data) provided that patient confidentiality is respected.

The Lilly monitor/designee is responsible for verifying the CRFs at regular intervals, approximately once per month, throughout the trial to verify adherence to the protocol, completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other trial-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this trial may be selected for audit by representatives from Lilly Clinical Quality Assurance Department (or designees). An inspection of site facilities (eg, pharmacy, drug storage areas, and laboratories) and a review of trial-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

If an anti-tumor treatment is initiated within 90 days of the last dose (AM0010/pembrolizumab), the start date of this treatment should be documented on the appropriate CRF, and no further recording of concomitant medications will occur unless it is to treat AM0010-related AEs.

To ensure the quality of clinical data across all patients and sites, a clinical data management review will be performed on patient data received at Lilly or its designee. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be sent to the site for completion and returned to Lilly or its designee.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the Principal Investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications, and agrees with the content.

13.4 Language

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

13.5 Publication Policy

To coordinate the dissemination of data from this trial, a publication committee may be formed consisting of both Principal Investigators and appropriate Lilly staff. The committee is expected to solicit input and assistance from other Investigators and Lilly staff as appropriate. Membership on the committee (both for Investigators and Lilly staff) does not guarantee authorship. The criteria described below should be met for every publication.

Authorship of any publications resulting from this trial will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2016), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- When a large, multi-center group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this trial must be submitted to Lilly for corporate review. The Clinical Trial Agreement between the institution, principal Investigator, and Lilly will detail the procedures for and timing of Lilly review of publications.

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15.0 APPENDICES

Appendix A – Schedule of Assessments

Assessments Both trial Arm 1 and Arm 2 will follow the same schedule of assessments unless otherwise noted.	**Screening**	**Clinic Visit (Cycle)**			**End of Treatment**	**Extended Safety Observation Period**	**Long-Term Follow-Up**
	Within 21 Days of Randomization	1, 3, 5, etc. ±3 Days	2 ±3 Days	4, 6, 8, etc. ±3 Days	28 Days ±7 Days from Last Dose	60 and 90 Days ±7 Days from Last Dose	
GENERAL and SAFETY AWARENESS							
Informed Consent	X						
Medical/Cancer History and Demographics	X						
Physical examination (include Ht [screening only] and Wt)	X	X			X		
Vital signs	X	X			X		
ECOG performance status	X	X			X		
12-Lead ECG	X	X			X		
Concomitant Medication	●	———	———	———	●		
Adverse Event	Post Randomization	●	———	———	———	●	
Survival[a] and Treatment Status							X
LABORATORY ASSESSMENTS							
Hematology, Chemistry	X	X	X	X	X		
aPTT and INR or PT	X	X	X	X	X		
Thyroid Function Test (TSH, T3, and T4)	X	X			X		
Pregnancy Test	X	X			X		
Urinalysis	X	X			X		
PD-L1 Status	X[b]						
Submission of tumor sample for biomarker research		X[c]					
TRIAL TREATMENT ARM 1 and ARM 2							
Arm 1 AM0010		Self-Administration QD SQ					
Arm 1 and Arm 2 Pembrolizumab		200 mg 30 min IV Q3W					
IMAGING ASSESSMENT							
Tumor Assessment[d]	Within 30 days of randomization	X				X	X
ADA, PK and Biomarker BLOOD SAMPLES							
ADA (required Arms 1 and 2)[e]		X	X	X	X	X	
PK (required Arm 1 and crossover)[e]		X	X	X	X	X	
Biomarkers (required Arms 1 and 2)[f]		X	X		**X**		

a All randomized patients will be followed for OS every 9 weeks (±7 days) during the first year from the 90-day follow-up visit, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter. The survival follow-up will be conducted until death or the study completion, whichever is first, whether or not trial drug was administered.

b A fresh tissue biopsy is only required if no archival tissue is available within 60 days of informed consent or unless approved by the Medical Monitor.

c Mandatory tumor tissue sample for biomarker research should be submitted once the patient is enrolled (preferably from the same block used for PD-L1 testing).

d Tumor assessment will be performed for all randomized patients every 9 weeks (±7 days) during the study treatment and during the first year from discontinuation of the study treatment, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter. Tumor assessment will be repeated until disease progression, death, or receipt of new anti-cancer therapy, or until study completion, whichever is first, whether or not study treatment was administered. A baseline tumor assessment is required at crossover.

e ADA and PK samples will be collected on Day 1 of Cycles 1, 2, 3, 4, every fourth cycle thereafter, and at end of treatment visit, and at the follow-up visits 60 and 90 days after the last dose of study treatment.

f Specific biomarker blood collection tubes may vary by time point. See the Lab Manual for details.

Appendix B – Continued-Access Period Assessments

	Continued-Access Treatment Visits ±3 Days	Continued-Access Follow-Up Visits 28, 60, and 90 days ±7 Days after the Last Dose of Study Treatment
Arm 1 AM0010	X	
Arm 1 and Arm 2 Pembrolizumab	X	
Adverse event	X	X
ADA[a]	X	X
PK[a]	X	X

[a] ADA and PK samples will be collected on Day 1 of every 4th cycle during the continued access treatment visits and at the continued access follow-up visits 28-, 60-, and 90-days after the last dose of study treatment.

Appendix C – Birth Control Methods that May Be Considered as Highly Effective

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation 1:

  oral
  intravaginal
  transdermal

- progestogen-only hormonal contraception associated with inhibition of ovulation 1:

  oral
  injectable
  implantable
  intrauterine device (IUD)
  intrauterine hormone-releasing system (IUS)
  bilateral tubal occlusion
  vasectomized partner
  sexual abstinence

Guidance on the acceptable contraception methods can be found here:

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

Appendix D – RECIST v.1.1 Criteria

The primary efficacy endpoint is ORR. Tumor response will be assessed by RECIST v.1.1 guidelines on images obtained with CT scans. CT scans will be performed at Baseline during Screening (within 4 weeks prior to Day 1), at Week 9 (±7 days) and every 9 weeks (±7 days) during the study treatment and during the first year from discontinuation of the study treatment, every 12 weeks (±7 days) during the second year, and every 16 weeks (±7 days) thereafter. Tumor assessment will be repeated until disease progression, death, or receipt of new anti-cancer therapy, or until study completion, whichever is first, whether or not study treatment was administered. Radiologic studies for antitumor response will be repeated at the end of treatment visit only if required per the defined study imaging schedule.

Definition of Measurable and Non-Measurable Lesions

Measurable Lesions at Baseline

The definition of a measurable lesion at Baseline is dependent on the technical factors of the imaging studies that were used to evaluate the patient. The recommendations for the imaging parameters are based on the American College of Radiology (ACR) Practice Guidelines and Technical Standards. The ACR Practice Guidelines and Technical Standards define principles and technical parameters of radiologic and radiation oncology practice, which should generally produce desired health care outcomes. They describe a range of acceptable approaches for the diagnosis and/or treatment of disease for most patients, in most circumstances. Given differences in training, experience, and local conditions, the ACR Practice Guidelines and Technical Standards acknowledge the need for health care providers to exercise their independent medical judgment in making decisions regarding the use and specific details of any procedure.

For CT scanning, the recommendation is for a slice thickness of 5 mm or less.

The RECIST v.1.1 guideline recommends CT images for chest, abdomen, and pelvis should be performed using 5 mm reconstructions, but it is not explicitly stated as a requirement (Eisenhauer, Therasse et al. 2009).

In preparing the technical specifications, we have followed the guidelines of the ACR, as 5 mm reconstructions are not the standard in the US or the rest of the world. Our proposal for modifying the size of measurable lesions at Baseline to 2 times the reconstruction interval of the Baseline/Screening studies is consistent with the RECIST definition for a measurable lesion.

- Conventional CT should be performed with contiguous cuts of 10 mm or less in reconstruction interval. CT should be performed by use of a 5–8 mm contiguous reconstruction interval or less, where the neck and brain CTs should be done at 5 mm or less.
- Lesions that can be accurately measured in at least 1 dimension with the longest diameter (LD) ≥20 mm with conventional techniques when the conventional scans are performed with a reconstruction interval of 10 mm or less are measurable lesions.

- Lesions that can be accurately measured in at least 1 dimension with the LD being 2 times the reconstruction interval (RI) of the CT scan. Depending on the RI of the CT (5–8 mm or less recommended) measurable lesion size may be ≥10–16 mm. For example, a CT scan done at 8 mm RI would have a minimum lesion size of 16 mm in the longest dimension. The minimum size of a measurable lesion is 10 mm.
- Although initially identified as measurable lesion ≥10 mm, target lesions may in time reduce to <5 mm in their LD. In those circumstances where the target lesion LD is less than the 5 mm minimum for measurability, the lesion LD should be recorded as 5 mm.
- In the instance where the reconstruction interval has changed from the Baseline to subsequent time points, it would be at the discretion of the radiologist whether this would affect interpretation. A note is made in the comment section of the source document, if applicable. The definition for target disease would not change and would be determined on the basis of the Baseline scan.

Non-Measurable Lesions

All other lesions that do not meet the criteria for measurable disease as well as other truly non-measurable lesions (eg, ascites, bone lesions, pleural effusion, etc.), are considered non-measurable.

Definition of Target, Non-Target and New Lesions (RECIST v1.1 Guidelines)

Target Lesions

Up to 5 target lesions, a maximum of 2 per organ, will be chosen for measurement over the course of the study. The distribution of these target lesions should be representative of the patient's overall disease. Target lesions should not be chosen from a previously irradiated area unless lesions in those areas have documented progression.

Target lesions must be measurable at Baseline. These lesions will generally be the largest lesions, most reliably measured, and most representative of the patient's sites of disease.

For any target lesion at any time point, measurements will be taken and recorded unidimensionally. The longest dimension of each target lesion will be measured and recorded. The longest dimension of the target lesions will be summed to obtain the Sum of the Longest Diameters (SLD). The Baseline SLD will be used as reference to further characterize the objective tumor response of the target lesions. For the consideration of progressive disease, the nadir of the SLD for the target lesions will be used as reference.

For cases where there is no target lesion identified, tumor assessment for progression should be done based on non-target lesion assessments or the development of new lesions. Response (PR or CR) and SD will not be assessed in patients where target lesions are not identified at Baseline. The following conventions will be applied in selecting target lesions in patients who have received prior radiation therapy:

- Intrathoracic measurable lesions in the periphery of the lung, just deep to the radiated chest wall concordant with the radiation portal cannot be selected as target lesions. However, if the lesions are more centrally located in the chest and do not appear in regions showing evidence of radiation injury (eg, scarring, radiation pneumonitis, etc.),

they can be selected as target lesions. The assigned radiologist will document descriptions of radiation damage in the comments field.

- Prior bone radiation (eg, vertebral, rib, pelvis, femur, etc., as stated on the Prior Radiation Therapy Form would not preclude the selection of measurable lesions in adjacent structures unless signs of radiation injury are evident (eg, scarring).
- Prior soft tissue radiation (eg, supraclavicular radiation, radiation of internal mammary lymph nodes, etc., as recorded on the Prior Radiation Therapy Form would preclude the selection of measurable disease in the site of radiation unless the site confirms on the Prior Radiation Therapy Form that the lesions are new since radiation was completed.

Non-Target Lesions

All of the sites of disease present at Baseline not classified as target lesions will be classified as non-target lesions. Non-target lesions must be qualitatively assessed at each subsequent time point. Examples of non-target lesions include:

- All bone lesions, irrespective of the modality used to assess them;
- Leptomeningeal disease;
- Lymphangitis of the skin or lung;
- Cystic lesions;
- Irradiated lesions that have not shown progression;
- Measurable lesions beyond the maximum number of 10;
- Groups of lesions that are small and numerous; and
- Pleural effusion/pericardial effusion/ascites.

New Lesions

Unequivocal new lesions are those that were not present at Baseline. At each time point, the presence of new lesions will be determined. New multi-focal or miliary disease of any size is considered a new lesion.

Lesions that are encountered (subsequent to the Baseline) in anatomic locations that were not scanned at Baseline will be considered new lesions and will represent progressive disease.

Lesions that were present which subsequently resolved and then recurred will be considered new lesions and will represent progressive disease.

Antitumor Response (RECIST v1.1 Guidelines)

Antitumor response will be defined as the percent of patients who achieve an objective confirmed response (complete or partial response). Disease control rate (SD for at least 16 weeks or confirmed CR or PR) also will be reported. Response will be determined according to RECIST guidelines. The original RECIST guidelines were developed and published in the Journal of the National Cancer Institute (Therasse, Arbuck et al. 2000).

Target Lesion Response (RECIST v1.1 Guidelines)

Percentage change in SLD will be evaluated by the following formulae:

1. When determining complete response or partial response:

   (Post value – Baseline value) / Baseline value)×100

2. When determining progressive disease:

   (Post value – Nadir value since treatment started) /
   (Nadir value since treatment started)×100

The following definitions will be used to evaluate response based on target lesions at each time point after Baseline:

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the SLD of target lesions, taking as reference the Baseline SLD.

Stable Disease (SD): Neither sufficient shrinkage of target lesions to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the nadir SLD since the treatment started.

Progressive Disease (PD): At least a 20% increase in the SLD of target lesions, taking as reference the nadir SLD recorded since the treatment started, or, the presence of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression. PET scans will not be used to determine target lesion progression or as a criterion for patient withdrawal from the study. Only CT scans or MRIs will be used for those purposes.

Not evaluable (NE): A target lesion present at Baseline which was not measured or which was unable to be evaluated leading to an inability to determine the status of that particular tumor for the time point in question. If the SLD cannot be determined at a time point and the rules for PD do not apply, a response of CR, PR, or SD cannot be assigned for that time point, and the time point response will be NE.

Not Applicable (NA): No target lesions were identified at Baseline. Patients with no target lesions identified at Baseline cannot be assessed for response. These patients will be assessed for progression only.

Not Done (ND): Scans were not performed at this time point to evaluate the target lesions.

Non-Target Lesion Response (RECIST v1.1 Guidelines)

Each non-target lesion will be qualitatively evaluated at each time point. Response of each lesion at each time point will be assessed with respect to the Baseline status. Progression will be assessed with respect to nadir size of the non-target lesions. The overall non-target lesion response for each time point will be assessed as the worst case for the non-target

lesions for that particular time point. If a non-target lesion is classified as NE/ND, the non-target response will be NE/ND unless progression is identified in the available non-target lesions. Response assessments are defined as follows:

Complete Response (CR): Disappearance of all non-target lesions, and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Non-CR / Non-PD: Persistence of one or more non-target lesions and or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): The "unequivocal progression" of existing non-target lesion(s) or appearance of one or more new lesion(s) is considered progressive disease.

Not Evaluable (NE): Any non-target lesion present at Baseline which was not measured or was unable to be evaluated leading to an inability to determine the status of that particular tumor for the time point in question.

Not Applicable (NA): No non-target lesions were identified at Baseline.

Not Done (ND): Scans were not performed at this time point to evaluate the non-target lesions.

Pseudoprogression: Patients whose scans show radiographic progression in the absence of clinical deterioration including worsening performance status as assessed by the Investigator may remain on study treatments and additional scan 4 weeks (±7 days) later. If this subsequent scan shows disease progression, the patient will be discontinued from study treatments.

Response Determination (RECIST v1.1 Guidelines)

Response at each time point will be assessed as a combination of the target and non-target responses as well as the presence of new lesions according to the table below:

Time Point Response / Target and Non-Target and Best Response

Target

Time Point Response: Patients With Target (± Non-Target) Disease			
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease,
PD = progressive disease, and NE = not evaluable

Non-Target

Time Point Response: Patients With Non-Target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = not evaluable
* "Non-CR/non-PD is preferred over "stable disease" for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Best Overall Response – Confirmation of CR and PR

Best Overall Response When Confirmation of CR and PR Required		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable

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

Source: (Eisenhauer, Therasse et al. 2009).

Appendix E - Hepatic Monitoring Tests for Treatment Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly CRP.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin (HGB)	
Hematocrit (HCT)	**Hepatic Coagulation[a]**
Erythrocytes (RBC)	Prothrombin time (PT)
Leukocytes (WBC)	Prothrombin time, INR
Neutrophils[b]	
Lymphocytes	**Hepatic Serologies[a,c]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets (PLT)	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
Alanine transaminase (ALT)	**Recommended Autoimmune Serology**
Aspartate aminotransferase (AST)	Anti-nuclear antibody[a]
Gamma-glutamyl transferase (GGT)	Anti-smooth muscle antibody[a]
Creatine phosphokinase (CPK)	Anti-actin antibody[a]

Abbreviations: CRF = case report form; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by laboratory.

[b] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. Whenever a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

[c] Confirmation dependent on regulatory requirements and/or testing availability.

Appendix F – NCI-CTCAE Version 4.03

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

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