Protocol Amendment J1L-AM-JZGA (10)

A Phase 1, Open-Label Dose Escalation First-in-Human Study to Evaluate the Tolerability, Safety, Maximum Tolerated Dose, Preliminary Clinical Activity, and Pharmacokinetics of AM0010 in Patients with Advanced Solid Tumors

NCT02009449

Approval Date: 25-Feb-2019

CLINICAL STUDY PROTOCOL

STUDY TITLE:	A Phase 1, Open-Label Dose Escalation First-in-Human Study to Evaluate the Tolerability, Safety, Maximum Tolerated Dose, Preliminary Clinical Activity, and Pharmacokinetics of AM0010 in Patients with Advanced Solid Tumors
INVESTIGATIONAL PRODUCT:	AM0010 (Pegilodecakin; LY3500518) Pegylated Recombinant Human Interleukin 10 (PEG-rHuIL-10)
PROTOCOL NUMBER:	AM0010-001; J1L-AM-JZGA
EudraCT	2014-005184-33
FINAL PROTOCOL DATE	09 August 2013
AMENDMENT 1	25OCT2013
AMENDMENT 2	30OCT2013
AMENDMENT 3	24JAN2014
LETTER OF AMENDMENT TO 3	15MAY2014
AMENDMENT 4	23MAY2014
AMENDMENT 5	09JUN2014
AMENDMENT 6	19JUN2014
AMENDMENT 7	20DEC2014
AMENDMENT 8	19AUG2015
AMENDMENT 9	02MAR2016
AMENDMENT 10	See approval date stamp at the end of this page
SPONSOR:	Eli Lilly and Company (Lilly) Indianapolis, Indiana, USA 46285

Approval Date: 25-Feb-2019 GMT

SUMMARY OF CHANGES

Summary of Changes from Protocol AM0010-001 Amendment 9

Section	Summary of Changes
Throughout the protocol	Sponsor name changed from ARMO Biosciences, Inc. to Eli Lilly and Company.
Appendix B	Added Continued Access table and procedures.
Section 8.1	Details of product packaging and references to 8 mg/mL removed.
Section 11.3	Updated SAE reporting process to match Lilly standards.
Section 11.4	Section added to include instructions for product complaint handling.
Synopsis, Section 5.4.3	Removed European sites language
Section 5.4.5.1	Included specification of when end of treatment occurs.
Section 5.4.6, 5.4.7, 5.4.8	Sections added to include definitions of study completion, continued access period, and end of trial.
Section 9.3.6	Added referral to Continued Access definition and procedures in Study Procedures list
Section 4.5.3.2	Updated IB date with date of most recent revision
Throughout the protocol	Minor editorial and formatting changes

Summary of Change from Protocol AM0010-001 Amendment 8

Section	Summary of Changes
Synopsis, Section 5.4.3	Update number of sites, number of subjects planned
Synopsis, Section 8.3.9	Update Gemcitabine dose in Group J: Gemcitabine 500 mg/m^2 IV over 30 minutes

Section	Summary of Changes
Synopsis, Section 6.1	Inclusion criterion #4 update for progressive metastatic disease according to PCWG2 criteria: Transaxial imaging needs to show new measurable disease GnRH analog or antagonist treatment for the duration of the study (or orchiectomy) and serum testosterone < 50 ng/mL Inclusion criterion #11 inserted for patient in cohort C1: Patients must provide an archival tumor tissue specimen and/or fresh biopsies to be taken during the study.
Section 4.2.1.1	Update of pharmacology information PEG-IL-10 and chemotherapeutic agents combination therapy
Section 5.4	Update of Study Design and Rationale
Section 5.4.2.2	Update of FOLFOX (ORR) research data and the FDA approval of liposomal irinotecan (Onivyde) plus fluoruracil/leucovorin combination therapy.
Sections 5.4.2.3, 5.4.2.4	Update Part I study rationale
Section 5.4.4	Update of number of patients
Section 8.4.3	Updating of number of transfusions allowed in a given period to three transfusions in a one-month period for immune related adverse events and dose limiting toxicity (DLT). Updating of the occurrence of hematological toxicity to be monitored by the investigator to Parts B, C, D, E, G, and J of the protocol.
Section 8.5.1	Updating of dose modification guideline for the number of transfusions allowed in a given period to three transfusions in a one-month period due to AM0010 related toxicity.
Section 12.1.2	Update of FOLFOX (ORR) research data in the statistical considerations section
Section 12.1.4	Introduce statistical considerations for Part I expansion Cohort 1 – NSCLC Patients
Section 12.1.5	Introduce statistical considerations for Part I expansion Cohort 2 – RCC Patients
Throughout the protocol	Various administrative changes

Summary of Change from Protocol AM0010-001 Amendment 7

Section	Summary of Changes
Synopsis, Sections 8.3, 8.5, 9.2, Appendices	Introduce combination therapy arms for 1 additional chemotherapy regimen and 1 immune therapy (Part I, J)
Section 8.5	Add dose modification guideline for all arms
Synopsis, Section 5.4, 12.1	Introduce 3 cohorts to assess preliminary clinical activity in specific target populations
Synopsis, Sections 5.2, 5.3, 9.14.3	Allow additional response criteria in addition to irRC or PCWG2
Throughout the protocol	Various administrative changes

Summary of Change from Protocol AM0010-001 Amendment 6

Section	Summary of Changes
Synopsis, Sections 8.3, 8.5, Appendices	Introduce combination therapy arms for 3 additional chemotherapy regimens, 1 targeted therapy, and 1 immune therapy (Part D – H)
Synopsis, Section 8.3.2	Allow FOLFOX6 for FOLFOX4
Exclusion criteria 10 (Synopsis, Section 6.2)	Allow short half live anticoagulation in PDA and Cholangiocarcinoma
Section 8.4.3	Refine definition of non-DLT immune related toxicity
Synopsis, Section 8.6	Refined definition of non-study therapies
Throughout the protocol	Various administrative changes

Summary of Change from Protocol AM0010-001 Amendment 5

Section	Summary of Changes
Section 8.4	Allow intra-patient dose escalation after 91 days

Summary of Change from Protocol AM0010-001 Amendment 4

Section	Summary of Changes
Synopsis, Section 6.2 Exclusion Criteria	Exclude anticoagulation therapy
Section 5.4. and 8.3	Clarify Chemotherapy administration
Section 11.2	Clarify relatedness of AE to study drug
Throughout the protocol	Various administrative changes

Summary of Change from Protocol AM0010-001 Amendment 3

Section	Summary of Changes
Synopsis, Sections 6.2 Exclusion Criteria, and 8.7 Excluded Therapy	Allow anticoagulation therapy
Section 8.3, Chemotherapy	Introduce combination therapy with AM0010 Part B: Platinum / Taxane and Part C: FOLFOX4
Section 5.4.1 Dose Escalation, and 9.3.1 Continued Treatment	Allow patient who derive clinical benefit to continue with treatment
Section 8.4.3 Immune Related Adverse Events	Adjust the grading of injection site reactions to CTCAE 4.03 guidelines
Synopsis, Section 6.1 Inclusion criteria	Admit patients with all tumor types
Section 8.4.3 Immune Related AEs and DLT	Transient hematological adverse events, definition and clinical care
Throughout the protocol	Various administrative changes

Summary of Change from Protocol AM0010-001 Amendment 2

Section	Summary of Changes
Synopsis, 6.2 Exclusion Criteria, Section 8.7 Excluded Therapy	Allow anticoagulation therapy for the treatment of thrombotic events occurring during the treatment period due to the underlying metastatic disease
Section 9.2.21, SOE	Cycle 3 and 4: Dispense of AM0010 kit every two weeks (as documented Drug Product stability is at least 2 months)
Section 9.16 Exploratory Biomarker Analysis	Allow collection and analysis of body fluids, pending informed consent (ascites)
Throughout the protocol	Various administrative changes

Summary of Change from Protocol AM0010-001 Amendment 1

Section	Summary of Changes
Section 9.2 Treatment	Additional PK sampling time points on Day 1 (8h, 12h) and on Day 29 (2h, 6h, 8h, 12h, 24h)
Section 9.3.3	Additional immunogenicity sampling at the 30 day follow up visit
Throughout the protocol	Various administrative changes

Summary of Change from Protocol AM0010-001

Section	Summary of Changes
Synopsis, Section 4.4 and 5.4	Lowering the starting dose to 1 μg/kg and introducing additional cohort, change exposure calculations
Synopsis and Section 8.1	CCI [redacted]
Synopsis and Section 6.2 Exclusion Criteria #4 #6	Clarification of the exclusion of MS, Guillain-Barre, CNS/PNS disorders Allowing prior hospitalization
Synopsis Statistical Methods; Section 12.4	Response Population definition for statistical purposes
Section 5.4.1 and 8.4.2	Clarification that DLTs in Cycle 2, 3, and 4 are used to determine the MTD for 2, 3, and 4 cycles, respectively
Section 8.4.3	Clarification that dose interruption are indicated in case of Grade 3 anemia / thrombocytopenia; supportive treatment allowed, excluding transfusions
Section 8.4.3	Introduction of a grading schedule for injection site reactions
Section 8.5.1	Allowance of dose reduction only to previously explored dose levels
Section 8.5.1	Clarification: Maximally allowed dose interruption: 21 days
Throughout the protocol	Various administrative changes

1 SYNOPSIS

Name of Sponsor	**Eli Lilly and Company (Lilly)**
Investigational Product	**AM0010**
Indication	Part A Escalation: Solid tumors (MEL, NSCLC, CRC, OvCa, RCC, CRPC, PanC) Patients with any tumor type may be enrolled in combination therapy escalation cohorts if there is evidence that the regimen combined with AM0010 represents an acceptable treatment for the patient. Advanced solid tumor types eligible for Escalation and Expansion Cohorts may be restricted by Lilly prior to enrolment start.
Title of Study	A Phase 1, Open-Label Dose Escalation First-in-Human Study to Evaluate the Tolerability, Safety, Maximum Tolerated Dose, Preliminary Clinical Activity, and Pharmacokinetics of AM0010 in Patients with Advanced Solid Tumors
Number of Centers	Approximately 8 – 25 centers in the US
STUDY OBJECTIVES	
Primary	To characterize the safety, tolerability, maximal tolerated dose (MTD), and pharmacokinetic (PK) of AM0010 after daily subcutaneous (SC) administrations in patients with advanced solid tumors as monotherapy or in combination with chemotherapy or immunotherapy.
Secondary	To measure the tumor response • in radiographically measurable disease by immune related Response Criteria (irRC). • progression in bone in patients with metastatic castration-resistant prostate cancer (CRPC) using Prostate Cancer Working Group 2 (PCWG2) criteria. • or according to tumor evaluation criteria best suitable and accepted for the tumor type evaluated To evaluate the formation of anti-AM0010 antibodies
Exploratory	To investigate biomarkers for patient stratification and treatment response, including genetic analysis, serum chemokines, and tumor antigen specific immune responses such as antibody and T cell responses as surrogates for anti-tumor activity of AM0010.
METHODOLOGY	
Study Design	This is a first-in-human, open-label, dose escalation study to evaluate the safety, tolerability, and preliminary clinical activity of AM0010 in patients with advanced solid tumors, dosed daily SC. This study will be done in 10 parts, each part will have 2 phases as follows. In some parts showing preliminary evidence for clinical activity of AM0010 in the primary escalation and expansion cohorts, the clinical activity of AM0010 will be further evaluated in selected patient populations. Part A: In the Dose Escalation Phase the dose of AM0010 will be escalated to evaluate the safety, tolerability, pharmacokinetics, MTD for patients with advanced solid tumors. In the Expansion Phase at least one cohort of 10-15 patients will be enrolled at a previously evaluated safe dose to expand the number of patients for additional safety, pharmacokinetic and pharmacodynamic analysis, and to establish a

Name of Sponsor	Eli Lilly and Company (Lilly)
Investigational Product	**AM0010**
	recommended dose for Phase 2. Part B: In the Dose Escalation Phase the dose of AM0010 will be escalated in combination with Carboplatin or Cisplatin and Paclitaxel or Docetaxel chemotherapy to evaluate the safety, tolerability, pharmacokinetics, and MTD for patients with advanced solid tumors. In the Expansion Phase at least one cohort of 10 – 15 patients will be enrolled at a previously evaluated safe dose to expand the number of patients for additional safety, pharmacokinetic and pharmacodynamic analysis, and to establish a recommended dose for Phase 2. Part C: In the Dose Escalation Phase the dose of AM0010 will be escalated in combination with FOLFOX chemotherapy to evaluate the safety, tolerability, pharmacokinetics, MTD for patients with advanced solid tumors. In the Expansion Phase at least one Cohort of 10 – 15 patients will be enrolled at a previously evaluated safe dose of AM0010 in combination with FOLFOX to expand the number of patients for additional safety, pharmacokinetic and pharmacodynamic analysis, and to establish a recommended dose for Phase 2. Part D: In the Dose Escalation Phase the dose of AM0010 will be escalated in combination with gemcitabine and nab-paclitaxel chemotherapy to evaluate the safety, tolerability, pharmacokinetics, MTD for patients with advanced solid tumors. In the Expansion Phase, Cohorts of 10 – 15 patients may be enrolled at a previously evaluated safe dose of AM0010 in combination with gemcitabine and nab-paclitaxel to expand the number of patients for additional safety, pharmacokinetic and pharmacodynamic analysis and to establish a recommended dose for Phase 2. Part E: In the Dose Escalation Phase the dose of AM0010 will be escalated in combination with capecitabine chemotherapy to evaluate the safety, tolerability, pharmacokinetics, MTD for patients with advanced solid tumors. In the Expansion Phase, Cohorts of 10 – 15 patients may be enrolled at a previously evaluated safe dose of AM0010 in combination with capecitabine to expand the number of patients for additional safety, pharmacokinetic and pharmacodynamic analysis, and to establish a recommended dose for Phase 2. Part F: In the Dose Escalation Phase the dose of AM0010 will be escalated in combination with paclitaxel chemotherapy to evaluate the safety, tolerability, pharmacokinetics, MTD for patients with advanced solid tumors. In the Expansion Phase, Cohorts of 10 – 15 patients may be enrolled at a previously evaluated safe dose of AM0010 in combination with paclitaxel to expand the number of patients for additional safety, pharmacokinetic and pharmacodynamic analysis, and to establish a recommended dose for Phase 2. Part G: In the Dose Escalation Phase the dose of AM0010 will be escalated in combination with pazopanib to evaluate the safety, tolerability, pharmacokinetics, MTD for patients with advanced solid tumors. In the Expansion Phase at least one Cohort of 10 – 15 patients will be enrolled at a previously evaluated safe dose to expand the number of patients for additional safety, pharmacokinetic and pharmacodynamic analysis, and to establish a recommended dose for Phase 2. Part H: In the Dose Escalation Phase the dose of AM0010 will be escalated in combination with pembrolizumab to evaluate the safety, tolerability, pharmacokinetics, MTD for patients with immune sensitive advanced solid tumors. In the Expansion Phase, at least one Cohort of 10 – 20 patients will be enrolled at a previously evaluated safe dose of AM0010 in combination with pembrolizumab to expand the number of patients for additional safety, pharmacokinetic and pharmacodynamic analysis, and to establish a recommended dose for Phase 2. Part I: In the Dose Escalation Phase, the dose of AM0010 will be escalated in

Name of Sponsor	Eli Lilly and Company (Lilly)
Investigational Product	AM0010

combination with nivolumab to evaluate the safety, tolerability, pharmacokinetics, and MTD for patients with immune sensitive advanced solid tumors. In the Expansion Phase, two cohorts, one of NSCLC patients and another one of RCC patients will be enrolled. 30 patients each will be enrolled at a previously evaluated safe dose of AM0010 in combination with nivolumab to expand the number of patients for additional safety, pharmacokinetic, and pharmacodynamic analysis, and to establish a recommended dose for Phase 2.

Part J: In the Dose Escalation Phase, the dose of AM0010 will be escalated in combination with gemcitabine and carboplatin to evaluate the safety, tolerability, pharmacokinetics, and MTD for patients with advanced solid tumors. In the Expansion Phase, at least one Cohort of 10 – 20 patients will be enrolled at a previously evaluated safe dose of AM0010 in combination with gemcitabine and carboplatin to expand the number of patients for additional safety, pharmacokinetic and pharmacodynamic analysis, and to establish a recommended dose for Phase 2.

If preliminary evidence for clinical activity of AM0010 is observed in the primary escalation or expansion cohorts, the clinical activity of AM0010 will be further evaluated dedicated expansion cohorts in selected patient populations.

Part A AM0010 Dose Escalation Phase – Monotherapy

Dose Cohort	Number of Patients	AM0010 Dose (μg/kg), daily	AM0010 qd (until irPD)
1	3 – 6	1	No additional therapy
2	3 – 6	2.5	
3	3 – 6	5	
4	3 – 6	10	
5	3 – 6	20	
Optional*	3 – 6	40	
Expansion**	10 – 15	Previously evaluated, safe dose in combination therapy	

Part B AM0010 Dose Escalation Phase + Platinum / Taxane

Dose Cohort	Number of Patients	AM0010 Dose (μg/kg) daily	Platinum Taxane q21d x 6 AM0010 qd (until irPD)
1	3 – 6	2.5	Day 1 of every 21 day cycle Carboplatin or Cisplatin and Paclitaxel or Docetaxel See Section 8.3 for detailed dosing and scheduling instructions
2	3 – 6	5	
3	3 – 6	10	
4	3 – 6	20	
Optional*	3 – 6	40	
Expansion**	10 –15	Previously evaluated, safe dose in combination therapy	

Name of Sponsor	**Eli Lilly and Company (Lilly)**
Investigational Product	**AM0010**

Part C AM0010 Dose Escalation Phase + FOLFOX

Dose Cohort	Number of Patients	AM0010 Dose (μg/kg) daily	FOLFOX q14d x 12 AM0010 qd (until irPD)
1	3 – 6	2.5	Day 1, 2 of every 14 day cycle See Section 8.3 for detailed dosing and scheduling instructions
2	3 – 6	5	
3	3 – 6	10	
4	3 – 6	20	
Optional*	3 – 6	40	
Expansion**	10 – 20	Previously evaluated, safe dose in combination therapy	

Part D AM0010 Dose Escalation Phase + Gemcitabine / nab-paclitaxel

Dose Cohort	Number of Patients	AM0010 Dose (μg/kg) daily	Gemcitabine / nab-paclitaxel q7d x 3 / 28 day cycle (until irPD) AM0010 qd (until irPD)
1	3 – 6	5	Day 1, 8, 15 of each 28 day cycle Section 8.3 for detailed dosing and scheduling instructions
2	3 – 6	10	
3*	3 – 6	20	
Expansion**	10 – 15	Previously evaluated, safe dose in combination therapy	

Part E AM0010 Dose Escalation Phase + Capecitabine

Dose Cohort	Number of Patients	AM0010 Dose (μg/kg) daily	Capecitabine bid x 2 weeks (until irPD) AM0010 qd (until irPD)
1	3 – 6	10	Day 1 – 14 of every 21 day cycle See Section 8.3 for detailed dosing and scheduling instructions
2*	3 – 6	20	
Expansion**	10 – 15	Previously evaluated, safe dose in combination therapy	

Part F AM0010 Dose Escalation Phase + Paclitaxel

Dose Cohort	Number of Patients	AM0010 Dose (μg/kg) daily	Paclitaxel q7d x 3 / 28 day cycle (until irPD) AM0010 qd (until irPD)
1	3 – 6	10	Day 1, 8, 15 of every 28 day cycle See Section 8.3 for detailed dosing and scheduling instructions
2	3 – 6	20	
Expansion**	10 – 15	Previously evaluated, safe dose in combination therapy	

Name of Sponsor	**Eli Lilly and Company (Lilly)**
Investigational Product	**AM0010**

Part G AM0010 Dose Escalation Phase + Pazopanib

Dose Cohort	Number of Patients	AM0010 Dose (μg/kg) daily	Pazopanib qd (until irPD) AM0010 qd (until irPD)
1	3 – 6	10	Daily See Section 8.3 for detailed dosing and scheduling instructions
2	3 – 6	20	
Expansion**	10 – 15	Previously evaluated, safe dose in combination therapy	

Part H AM0010 Dose Escalation Phase + anti PD-1 (Pembrolizumab)

Dose Cohort	Number of Patients	AM0010 Dose (μg/kg), daily	Pembrolizumab q3w (until irPD) AM0010 qd (until irPD)
1	3 – 6	10	Day 1 of every 21 day cycle See Section 8.3 for detailed dosing and scheduling instructions
2	3 – 6	20	
3	3 – 6	40	
Expansion**	10 – 20	Previously evaluated, safe dose in combination therapy	

Part I AM0010 Dose Escalation Phase + anti PD-1 (Nivolumab)

Dose Cohort	Number of Patients	AM0010 Dose (μg/kg), daily	Nivolumab q2w (until irPD) AM0010 qd (until irPD)
1	3-6	20	Day 1 of every 14 day cycle See Section 8.3 for detailed dosing and scheduling instructions
2	3-6	40	
Expansion**	10 - 20	Previously evaluated, safe dose in combination therapy	

Part J AM0010 Dose Escalation Phase + Gemcitabine & Carboplatin

Dose Cohort	Number of Patients	AM0010 Dose (μg/kg), daily	Gemcitabine / Carboplatin q7d x 2 / 21 day cycle (until irPD) AM0010 qd (until irPD)
1	3 – 6	10	Day 1 and 8 of every 21 day cycle See Section 8.3 for detailed dosing and scheduling instructions
2	3 – 6	20	
Expansion**	10 – 20	Previously evaluated, safe dose in combination therapy	

*In the absence of dose limiting toxicities (DLTs) and continued benefit, the dose may be further escalated, following a two-fold increase.

**Additional Expansion Cohorts may be enrolled based on emerging efficacy, safety,

Name of Sponsor	**Eli Lilly and Company (Lilly)**
Investigational Product	**AM0010**
	or PK data from the Dose Escalation Phase and Expansion Phase.

Name of Sponsor	**Eli Lilly and Company (Lilly)**
Investigational Product	**AM0010**
Treatments	**Part A –** Daily SC injection with AM0010 until disease progression (irPD). Patients may continue to receive AM0010 after confirmed irPD in the absence of clinical deterioration and if the investigator considers that the patient continues to receive benefit from the treatment. **Part B –** Daily SC injection of AM0010 and **Platinum / Taxane doublet** Every 21 days, (21 days = 1 cycle), Day 1 • Paclitaxel 200/175 mg/m^2 IV, or • Docetaxel 75/65 mg/m^2 IV And • Carboplatin AUC 6/5/4 (max. 6 x 150 mg) IV or • Cisplatin 75 mg/m^2 IV. After 5 or 6 cycles of chemotherapy, patients may continue with AM0010 monotherapy until confirmed irPD. Patients may continue to receive AM0010 after confirmed irPD in the absence of clinical deterioration and if the investigator considers that the patient continues to receive benefit from the treatment. **Part C**- Daily SC injection of AM0010 and **FOLFOX** regimen Every 14 days FOLFOX4 or FOLFOX6 (14 days = 1 cycle); FOLFOX4, Day 1 • Oxaliplatin 85 mg/m^2 IV over 2 hours • Leucovorin 200 mg/m^2 IV over 2 hours followed by • 5-FU 400 mg/m^2 IV bolus and • 5-FU 600 mg/m^2/day IV over 22 hours • Leucovorin 200 mg/m^2 IV over 2 hours on Day 2 followed by • 5-FU 400 mg/m^2 IV bolus and • 5-FU 600 mg/m^2/day IV over 22 hours or FOLFOX6, Day 1 • Oxaliplatin 85 mg/m^2 IV over 2 hours • Leucovorin 400 mg/m^2 IV over 2 hours followed by • 5-FU 400 mg/m^2 IV bolus and • 5-FU 2400 mg/m^2/day IV over 46 hours After discontinuation of the chemotherapy, patients may continue with AM0010 monotherapy until confirmed irPD. Patients may continue to receive AM0010 after confirmed irPD in the absence of clinical deterioration and if the investigator considers that the patient continues to receive benefit from the treatment.

Name of Sponsor	Eli Lilly and Company (Lilly)
Investigational Product	**AM0010**
	Part D - Daily injection with AM0010 and **Gemcitabine / nab-paclitaxel** Gemcitabine and nab-paclitaxel on Days 1, 8, 15 of each cycle (28 days = 1 cycle). • Nab-paclitaxel 125 mg/m^2 IV over 30 minutes followed by • Gemcitabine 1000 mg/m^2 IV. After discontinuation of the chemotherapy, patients may continue with AM0010 monotherapy until confirmed irPD. Patients may continue to receive AM0010 after confirmed irPD in the absence of clinical deterioration and if the investigator considers that the patient continues to receive benefit from the treatment. **Part E** - Daily injection with AM0010 and **Capecitabine** Capecitabine BID daily for 14 days of each cycle (21 days= 1 cycle) • Capecitabine 1000 mg/m^2 po BID After discontinuation of the capecitabine, patients may continue with AM0010 monotherapy until confirmed irPD. Patients may continue to receive AM0010 after confirmed irPD in the absence of clinical deterioration and if the investigator considers that the patient continues to receive benefit from the treatment. **Part F** - Daily injection with AM0010 and **Paclitaxel weekly** Paclitaxel. weekly on Days 1, 8, 15 of each cycle (28 days= 1 cycle) • Paclitaxel 80 mg/ m^2 IV After discontinuation of the paclitaxel, patients may continue with AM0010 monotherapy until confirmed irPD. Patients may continue to receive AM0010 after confirmed irPD in the absence of clinical deterioration and if the investigator considers that the patient continues to receive benefit from the treatment. **Part G** - Daily injection with AM0010 and **Pazopanib** Pazopanib orally given daily of each cycle (28 days= 1 cycle) • Pazopanib 800 mg po QD In the case of discontinuation of pazopanib due to pazopanib related toxicity, patients may continue with AM0010 monotherapy until confirmed irPD. Patients may continue to receive AM0010 after confirmed irPD in the absence of clinical deterioration and if the investigator considers that the patient continues to receive benefit from the treatment. **Part H** - Daily injection with AM0010 and **Pembrolizumab** Pembrolizumab on Day 1 of each cycle (21 days= 1 cycle) until disease progression. • Pembrolizumab 2 mg/kg IV over 30 min Patients may continue with AM0010 and PD-1 blocking combination therapy until confirmed irPD. Patients may continue to receive combination therapy or AM0010 mono-therapy after confirmed irPD in the absence of clinical deterioration and if the

Name of Sponsor	**Eli Lilly and Company (Lilly)**
Investigational Product	**AM0010**
	investigator considers that the patient continues to receive benefit from the treatment. **Part I** - Daily injection with AM0010 and **Nivolumab** Nivolumab on Day 1 of each cycle (14 days= 1 cycle) until disease progression. • Nivolumab 3 mg/kg IV over 60 min Patients may continue with AM0010 and PD-1 blocking combination therapy until confirmed irPD. Patients may continue to receive combination therapy or AM0010 mono-therapy after confirmed irPD in the absence of clinical deterioration and if the investigator considers that the patient continues to receive benefit from the treatment. **Part J** - Daily injection with AM0010 and **Gemcitabine / Carboplatin** Gemcitabine and Carboplatin on Days 1, 8 of each cycle (21 days = 1 cycle) until disease progression. • Gemcitabine 500 mg/m^2 IV over 30 minutes followed by • Carboplatin AUC2 over 60 minutes After discontinuation of the chemotherapy, patients may continue with AM0010 monotherapy until confirmed irPD. Patients may continue to receive AM0010 after confirmed irPD in the absence of clinical deterioration and if the investigator considers that the patient continues to receive benefit from the treatment.
Treatment Duration	The patient participation time is planned to be maximally 24 months consisting of a screening period of up to 28 days, up to 22 months of treatment, and a 30-day follow-up period. Patients may continue to receive treatment longer than 22 months at the sponsor and investigator's discretion or until progressive disease, toxicity, or patient or physician decision. All patients will be followed for survival after the 30-day follow-up period until study completion.
Study Drug and Formulation	AM0010 is provided as a sterile clear solution CCI [redacted]. AM0010 study drug kits will be dispensed weekly, then bi-weekly or monthly. CCI [redacted]
Dose and Route of Administration	**Part A:** The starting dose of AM0010 is 1 μg/kg, with an escalation to 20 μg/kg or until an MTD is reached. AM0010 is administered by daily SC injection. **Part B and C:** The starting dose of AM0010 is 2.5 μg/kg, with an escalation to 20 μg/kg or until an MTD is reached. AM0010 is administered by daily SC injection. **Part D:** The starting dose of AM0010 is 5 μg/kg, with an escalation to 20 μg/kg. AM0010 is administered by daily SC injection. **Parts E – H and J:** The starting dose of AM0010 is 10 μg/kg with an escalation to 20 μg/kg. AM0010 is administered by daily SC injection. **Part I:** The starting dose of AM0010 is 20 μg/kg with an escalation to 40 μg/kg. AM0010 is administered by daily SC injection Dose and route of the administration of the additional therapy regimens are following standard clinical practice and are outlined in Section 8.

Name of Sponsor	**Eli Lilly and Company (Lilly)**
Investigational Product	**AM0010**
Concomitant and Excluded Therapy	Patients with metastatic CRPC should continue androgen deprivation therapy (GnRH analogs or antagonists); patients may receive steroid hormone replacement doses, 20 mg/m^2/day hydrocortisone equivalent. No non study chemo-, targeted or immune therapy, no use of another investigational product; no concurrent radiation on study.
SUBJECT POPULATION	
Number Planned	Part A through J will enroll up to 392 patients. Parts A through J will enroll each 6 – 30 patients during the dose escalation phase and at least 1 cohort of 15 – 30 patients during the expansion phase.
Major Inclusion Criteria	1. Provide signed written informed consent 2. Part A Escalation Cohorts: o Histologically or cytologically confirmed advanced malignant solid tumor, limited to melanoma, castrate resistant prostate cancer (CRPC), ovarian cancer (OvCa), renal cell carcinoma, colorectal carcinoma (CRC), pancreatic carcinoma or non-small cell lung carcinoma (NSCLC) that is refractory to, intolerant of, for which no standard of therapy is available, or where the patient refuses existing therapies Part A Expansion Cohorts, Part B through J Escalation and Expansion Cohorts: o Tumors with all histological diagnosis or tissue origin may be enrolled o Patients must have failed prior standard curative chemotherapy for their disease OR refuse existing therapies OR the proposed regimen to which AM0010 is added represents an acceptable standard treatment for their disease. 3. Measurable or evaluable disease according to irRC or for patients with CRPC and bone-only metastases, disease detectable on bone scintigraphy following PCWG2 recommendations or according to tumor evaluation criteria best suitable and accepted for the tumor type evaluated. 4. Metastatic prostate cancer must also meet any of the following criteria for progressive metastatic disease according to PCWG2 criteria (Section 9.14.2): o a rise in PSA, (minimal value 2 ng/mL; ≥ three consecutive rising values) o transaxial imaging showing new measurable disease, or o radionuclide bone scan (≥ 2 new metastases) And o GnRH analog or antagonist treatment for the duration of the study (or orchiectomy) and o serum testosterone < 50 ng/mL o Metastatic CRPC patients who are receiving an anti-androgen as part of their first-line hormonal therapy must have shown progression of disease off the anti-androgen prior to enrollment 5. At least 18 years of age 6. ECOG Performance Status of 0 or 1 7. Life expectancy of > 16 weeks, in the opinion of the Investigator 8. Women of childbearing age must have a negative pregnancy test at study entry and bi-weekly thereafter. All patients of childbearing potential must practice an

Name of Sponsor	Eli Lilly and Company (Lilly)
Investigational Product	**AM0010**
	acceptable form of contraception (e.g., condom, diaphragm plus spermicide, or oral contraceptive) and have their partners agree to an additional barrier method of contraception for the duration of the study 9. Willingness and ability to comply with study requirements 10. Adequate organ function defined as follows: **Hematologic** o Platelets ≥ 100 × 10^9/L, patients with platelets < 150 × 10^9/L on Day 1 should confirm platelet levels ≥ 60× 10^9/L on Day 4 or 5, prior continued dosing o Hemoglobin ≥ 9.0 g/dL (Parts A, H, I); HGB ≥ 10.0 g/dL (Parts B–G and J) o Absolute Neutrophil Count (ANC) ≥ 1.5 × 10^9/L o PT/INR and PTT ≤ 1.5 × clinical laboratory upper limit of normal (clULN) and ≤ 2.5 × clULN if patient receives anti-coagulants **Hepatic** o AST/ALT ≤ 2.5 × clULN (if liver metastases are present, ≤ 5 × clULN) o Alkaline phosphatase ≤ 2.0 × clULN (if liver or bone metastases are present, ≤ 5 × clULN) o Total bilirubin ≤ 1.5 × clULN **Renal** o Serum creatinine < 2.0 mg/dL 11. Patients in expansion Cohort C must consent to providing: i) Archival tumor tissue specimen and/or a fresh tumor biopsy to be collected prior to first dose (up to 10 days prior) AND ii) Fresh tumor biopsy at 8 weeks after the first study treatment (± 10 days of Cycle 4, Day 1)
Major Exclusion Criteria	1. History or evidence of clinically significant disorder, condition, or disease that, in the opinion of the Investigator and Lilly study team, would pose a risk to patient safety or interfere with the study evaluations, procedures, or completion. 2. Hematologic malignancies (Part A Escalation cohorts only). 3. Pregnant or lactating. 4. Present or history of immune mediated neurological disorders such as Multiple Sclerosis and Guillain-Barré or inflammatory CNS/PNS disorders. 5. Myocardial infarction within the last 6 months prior to study Day 1, symptomatic congestive heart failure (New York Heart Association Classification > Class II), unstable angina, or unstable cardiac arrhythmia requiring medication. 6. History of surgery within 28 days prior to study Day 1 or anticipated surgery during the study period. 7. Systemic fungal, bacterial, viral, or other infection that is not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement) despite appropriate antibiotics or other treatment. 8. Non study anti-tumor therapy (antibodies, chemotherapy, molecular targeted therapy, retinoid therapy, hormonal therapy) within 14 days prior to study Day 1 (six weeks for nitrosoureas, mitomycin C, or four weeks for molecular agents with $t_{½}$ > 10 days); (concurrent use of hormone therapy for prostate cancer with GnRH

Name of Sponsor	Eli Lilly and Company (Lilly)
Investigational Product	**AM0010**
	analog or antagonist is permitted and required). Patients on anti-PD-1, continuing anti-PD-1 treatment in combination with AM0010 (Part H) can start receiving AM0010 anti-PD-1 combination without washout of the prior anti-PD-1 antibody. 9. Treatment with non-study immune modulators including, but not limited to, anti-CTLA4, anti-PD1, anti-PDL1, sipuleucel-T, cyclosporine and tacrolimus within 14 days prior to study Day 1 (four weeks for molecular agents with $t_{½}$ > 10 days). Patients on anti-PD-1, continuing anti-PD-1 treatment in combination with AM0010 (Part H, I) can start receiving the AM0010 anti-PD-1 combination without washout of the prior anti-PD-1 antibody. 10. Concurrent or prior anticoagulation therapy (allow at least 5 days and at least 5 half-lives between the last anticoagulation and AM0010 treatment); low-dose warfarin (< 2 mg/day) or equivalent for prophylaxis against central venous catheter thrombosis is allowed; patients with pancreatic or advanced biliary cancer are allowed to use short lived injectable or oral anticoagulants (half-life < 24 h) for the prevention or treatment of thrombosis. 11. History of bleeding diathesis within the last 6 months prior to study Day 1 12. Patient with tumor that is infiltrating or invading a major blood vessel 13. Patients known to be positive for human immunodeficiency virus (HIV), hepatitis C, or hepatitis B virus; patients with hepatocellular cancer may be positive for HBV or HCV. 14. Participation in an investigational drug or device trial within 30 days prior to study Day 1 or within 5 times the half-life of the investigational drug in the other clinical study, whichever is shorter, if known. Patients on anti-PD-1, continuing anti-PD-1 treatment in combination with AM0010 (Part H, I) can start receiving AM0010 anti-PD-1 combination without washout of the prior anti-PD-1 antibody. 15. Unavailable for follow-up assessment or concerns for patient's compliance with the protocol procedures. 16. Any other condition that might reduce the chance of obtaining data required by the protocol or renders the patient at high risk for treatment complications.
ASSESSMENTS	
Efficacy	Tumor assessment for disease progression is measured at Weeks 8, 16, and every eight weeks afterwards • according to irRC until progressive disease (irPD). • Patients with CRPC and bone metastases will be assessed per PCWG2. • or according to tumor evaluation criteria best suitable and accepted for the tumor type evaluated.
Pharmaco-kinetics and Pharmaco-dynamics	Serum samples for drug concentration and anti-drug antibodies are drawn on Day 1 and weekly, then bi-weekly or monthly, at EOT and at the Follow-up visit. 24h PK analysis is required in Part A, B, and C escalation cohort. Biomarkers of Pharmacodynamics are measured every 4 – 8 weeks as shown in the SOE.
Safety	Safety is evaluated during the study to understand potential cumulative immune toxicities. Physical examination, hematology, serum chemistry, urinalysis, vital signs, AE monitoring, and concomitant medications are examined on Day 1, 2 and 3, weekly,

Name of Sponsor	**Eli Lilly and Company (Lilly)**
Investigational Product	**AM0010**
	then biweekly and at EOT.
For the Schedule of Events, see Table 29 through Table 38	
STATISTICAL METHODS AND ANALYSIS	
Efficacy	The Response Population will be comprised of all patients who have a baseline and a post baseline tumor measurement.
Pharmaco-kinetics and Pharmaco-dynamics	Summary statistics (mean, standard deviation, minimum, maximum, n, and coefficient of variation) will be calculated for serum concentrations of AM0010 at each time point.
Safety	Adverse event (AE) monitoring, including toxicity grade rating, concomitant medications, electrocardiogram (ECG), hematology, physical examination, serum chemistry, urinalysis, and vital signs.

2 TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

5-FU	5 Fluorouracil
5-HT3	5-hydroxytryptamine-3
ADA	Anti-Drug Antibodies
ADL	Activities of Daily Living
AE	Adverse Event
ALT	Alanine Transaminase
AM0010	PEGylated Recombinant Human IL-10
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST	Aspartate Transaminase
AUC	Area Under the Curve (pharmacological exposure)
BID	twice daily
BUN	Blood Urea Nitrogen
CA 19-9	Cancer antigen 19-9
CA-125	Cancer antigen 125
CEA	Carcinoembryonic Antigen
CFR	Code of Federal Regulations
Cl	Clearance
clULN	Clinical Laboratory Upper Limit of Normal
C_{max}	Maximum Drug Concentration
C_{min}	Minimal Drug Concentration / Serum trough concentration
CNS	Central Nervous System
CPT	Cell Preparation Tube
CR	Complete Response (No Measurable Residual Tumor)
CRC	Colorectal Cancer
CRF	Case Report Form
CRPC	Castration-Resistant Prostate Cancer
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DEC	Dose Expansion Cohort
DLT	Dose Limiting Toxicity
EC_{50}	Half Maximal Effective Concentration
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
end of trial	defined as the date of the last visit or last scheduled procedure for the last patient, including the continued access follow-up visit.
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of Study Treatment
FDA	Food and Drug Administration
FDG	18F-Fludeoxyglucose
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony-stimulating factor
GFR	Glomerular filtration rate
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practices
GNRH	Gonadotropin Releasing Hormone
HBV	Hepatitis B virus

HCV	Hepatitis C virus
HDL-C	High-Density Lipoprotein
HED	Human equivalent dose
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non-Severely Toxic Dose
HuIL-10	Human Interleukin 10
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMS	Isotope dilution mass spectrometry
IEC	Independent Ethics committee
IFNγ	Interferon gamma
IL-10	Interleukin 10
IL-10R	Interleukin 10 receptor
IND	Investigational New Drug Application
irAE	Immune-related Adverse Events
IRB	Institutional Review Board
irCR	Immune-related Complete Response
irPD	Immune-related Progressive Disease
irPR	Immune-related Partial Response
irRC	Immune related Response Criteria
irSD	Immune-related Stable Disease
irSPD	Immune Response Sum of the Product of the Diameters
IV	Intravenous
LDL-C	Low-density Lipoprotein
LFT	Liver function Test
LOT	Line of treatment
LV	Leucovorin
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MS	Multiple sclerosis
MTD	Maximum Tolerated Dose
NHP	Non-human Primate
NOEL	No effect level
NSCLC	Non-small cell lung carcinoma
ORR	Overall Response Rate
OvCa	Ovarian Cancer
PanC	Pancreatic Cancer
PCWG2	Prostate Cancer Working Group 2
PD	Progressive Disease
PEG-rHuIL-10	Pegylated Recombinant Human Interleukin 10
PERCIST	PET Response Criteria in Solid Tumors
PET	Positron emission tomography
PK	Pharmacokinetics
PNS	Peripheral nervous system
PR	Partial Response
PSA	Prostate Specific Antigen
PT/INR	Prothrombin Time International Normalized ratio
qd	Latin: quaque die (once a day

QRS	QRS interval
QT	QT interval
QTc	Corrected QT Interval
RBC	Red Blood Cell
RCC	Renal Cell Carcinoma
rHuIL-10	Recombinant Human Interleukin 10
rMuIL-10	Recombinant Murine Interleukin 10
RP2D	Recommended Phase 2 dose
RS	Reference Standard
SAE	Serious Adverse Event
SAER	Serious Adverse Event Report
SC	Subcutaneous
SOE	Schedule of Events
SOP	Standard Operating Procedure
SPD	Sum of the products of the two largest perpendicular diameters of all lesions
study completion	This study will be considered complete when the final analysis of the primary and secondary objectives is complete
$t_{½}$	Half Life
TAA	Tumor Associated Antigen
TCR	T cell receptor
TK	Toxicokinetics
TKI	Tyrosine kinase inhibitors
TNBC	Triple Negative Breast Cancer
WBC	Whites Blood Cell
WHO	World Health Organization

4 BACKGROUND AND RATIONALE

4.1 Rationale for PEG-rHuIL-10 Treatment in Cancer

Cancer immune therapy has sparked the renewed interest of clinicians and scientists due to recently developed exciting new treatments (Wolchok, Hoos et al. 2009, Hodi, O'Day et al. 2010). Cancer infiltrating memory and cytotoxic CD8+ T cells protect cancer patients from tumor progression (Fridman, Pages et al. 2012). One of the most promising new therapeutic entities in this biology is IL-10, which induces the cytotoxic activity of tumor specific CD8+ T cells towards tumor cells *in vitro* (Mumm, Emmerich et al. 2011). *In vivo*, the treatment of tumor bearing mice with PEGylated recombinant murine IL-10 (PEG-rMuIL-10) results in tumor rejection and tumor cures, including control of advanced and metastatic cancers (Mumm, Emmerich et al. 2011). More importantly, animals that reject their tumors following PEG-rMuIL-10 treatment are capable of rejecting the same type of tumors upon second exposure several months later without any further PEG-rMuIL-10 treatment (Mumm, Emmerich et al. 2011). This indicates that, in addition to tumor rejection, PEG-IL-10 induces an immunological memory against tumors resulting in vaccination against the tumor.

PEG-rMuIL-10 directly induces profound activation of CD8+ T cells and expansion of CD8+ T cell mediated immune surveillance against tumor cells in animals. The preclinical data suggests that PEGylated IL-10 can induce a lasting anti-tumor effect *in vivo*. The murine cancer models which are regressing under PEG-IL-10 therapy share many similarities with late stage human cancers, such as a high degree of metastasis and a low infiltration of T cells into the tumor tissue. Furthermore, PEG-rMuIL-10 treatment induces tumor regressions of aggressive and very progressed cancer models, whereas other experimental or approved cancer therapies tested in parallel and reported in literature failed to significantly inhibit tumor growth.

CD8+ T cell produced granzymes and IFNγ mediate the anti-tumor efficacy of PEG-rMuIL-10 in murine models of human cancer. While studies in healthy volunteers and patients showed that higher doses of rHuIL-10 up-regulate the serum levels of IFNγ and granzymes (Fedorak, Gangl et al. 2000), these studies also indicated that rHuIL-10 has a very short half-life in human plasma ($t_{½}$ of 3.5 – 4 hours upon SC injection). Hence, it is expected that similar to the studies in mice, rHuIL-10 is unable via bolus parenteral administration to maintain exposures necessary for the required sustained stimulation of tumor infiltrating

CD8+ T cells and their subsequent anti-tumor effect in humans. AM0010 has an optimized serum retention time for daily dosing while preserving a high in-tissue bio-availability.

4.2 Background on AM0010

AM0010 is a PEGylated recombinant form of human IL-10 (PEG-rHuIL-10). AM0010 is produced in prokaryotic fermentation. 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. AM0010 is active in human, mouse, and cynomolgus monkeys, but AM0010 is recognized by the murine immune system, inducing anti AM0010 antibodies. Due to the immunogenicity of AM0010 in mice, long term efficacy studies were performed with PEG-rMuIL-10.

4.2.1 Pharmacology

A number of preclinical *in vitro* and *in vivo* studies were conducted to evaluate the effects of AM0010 and PEG-rMuIL-10 in models of human disease.

PEG-rMuIL-10 was shown to inhibit growth and induce tumor rejection in *in vivo* murine models of human cancer. The rejection of tumors was associated with increased infiltration of CD8+ T cells in the tumor and was dependent on the presence of CD8+ T cells in the host.

In vitro cell-based studies have shown that rHuIL-10 or rMuIL-10 strongly activated the cytotoxicity of CD8+ T cells. Concentrations of AM0010 inducing CD8 T cell activation are approximately equivalent to the concentrations projected for the first dosing cohorts in human cancer patients.

Similar to its effect on mouse CD8+ T cells, PEG-rHuIL-10 induced IFNγ synthesis in human CD8+ T cells, as tested in T cells from more than 91 human donors. This *in vitro* effect was observed at concentrations of 1 ng/mL or greater. In line with this result, a minimum concentration of 1 ng/mL (serum trough) or greater of PEG-IL-10 is required to induce tumor rejection in mice. More importantly, while rMuIL-10 induces many of the same effector molecules as PEG-rMuIL-10, tumor cures can only be reproducibly achieved using PEG-rMuIL-10. This implies that the continuous exposure to IL-10 serum is essential to elicit the maximal anti-tumor effect.

In addition to its effects on primary tumors, PEG-rMuIL-10 has a strong impact on metastatic disease. PEG-rMuIL-10 treatment suppressed the numbers of lung metastases in a metastatic mouse model of breast cancer by several orders of magnitude.

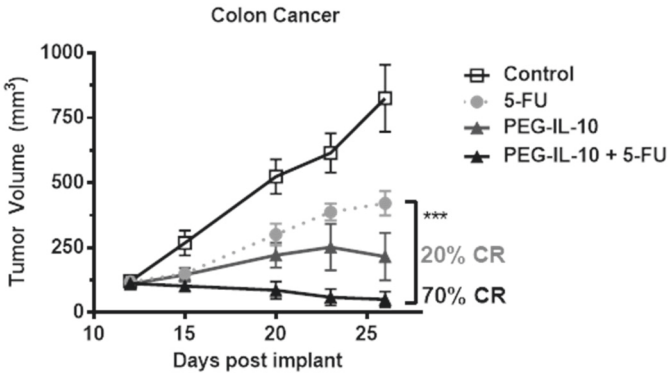
Mice cured upon treatment with PEG-rMuIL-10 stayed tumor-free for observation periods up to 8 months. Re-challenge of such mice with the original tumor cell line led to rejection of the re-injected tumor cells, without the requirement for further PEG-rMuIL-10 treatment, indicating an active immune memory protecting the host against the tumor cells.

4.2.1.1 Combination Therapy of PEG-IL-10 and Chemotherapeutic Agents

Preclinical exploration of combination therapy of PEG-rMuIL-10 with various chemotherapies has shown synergistic tumor inhibition and rejections. For those studies a sub-optimal concentration of PEG-rMuIL-10 (0.1 mg/kg) was used, since optimal doses of PEG-rMuIL-10 (1 mg/kg) result in a high percentage of tumor rejections. Mechanistically, PEG-IL-10, stimulates anti-apoptotic signals (STAT3) in CD8 T cells and increases tumor infiltration with cytotoxic CD8+ T cells. This leads to an upregulation of antigen presentation in the tumor. The combination of AM0010 immune therapy with cytoreductive chemotherapy also leads to increased tumor cell apoptosis (due to the secretion of pro-apoptotic Granzymes by CD8 T cells) (Mumm, Emmerich et al. 2011). The combination also stimulates the immune response against tumor cells which undergo apoptosis in response to the cytoreductive chemotherapy, as antigen presentation in the tumor is upregulated.

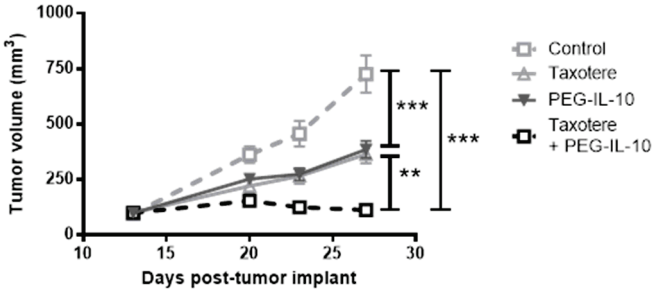
Synergy of PEG-IL-10 with 5 Fluorouracil (5-FU) was explored in a murine model for colorectal cancer (CT-26). PEG-rMuIL-10 and 5-FU both showed single agent activity reducing the tumor growth, with the combination of both therapies inducing complete responses in 70% of the animals.

Figure 1: Combination of PEG-IL-10 with 5-FU



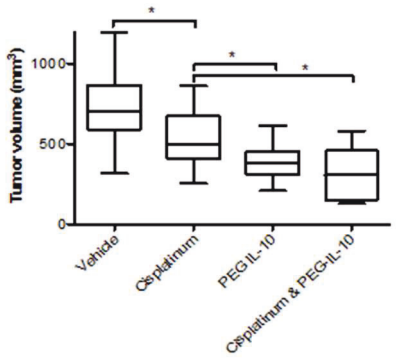
Synergy with Taxanes was explored in a very aggressive and metastasizing murine breast cancer model (4T1). Both Taxotere and PEG-rMuIL-10 (0.1 mg/kg) showed single agent activity reducing tumor growth, with the combination inducing synergistic tumor size reduction (Figure 2).

Figure 2: Combination Therapy of PEG-IL-10 with Taxotere



Combination therapy with platinum compounds was also tested in a breast cancer model (4T1). Mice with firmly established 4T1 tumors were treated with Cisplatin and PEG-IL-10. Both molecules reduced tumor growth as single agents and with the combination inducing synergistic tumor size reduction.

Figure 3: Combination Therapy with Cisplatin



Collectively, the findings from the preclinical studies described above suggest that AM0010 may exhibit strong anti-tumor effects in human cancer patients and may synergize with chemotherapeutic agents.

In particular, combinations of Carboplatin and Paclitaxel for the treatment of Non-small cell lung carcinoma (NSCLC) or ovarian cancers (Burger, Brady et al. 2011) and FOLFOX for the treatment of colon cancer (Douillard, Oliner et al. 2013) are successful clinical regimens which may be further improved on by the addition of AM0010.

Further details on the pharmacology of AM0010 and PEG-rMuIL-10 can be found in the Investigator's Brochure.

4.2.2 Toxicology

Mice and cynomolgus monkeys were chosen as relevant toxicology species on the basis of the demonstrated cross reactivity of AM0010 with mouse and cynomolgus monkey IL-10R and activity of AM0010 in mice and cynomolgus monkeys. The GLP animal toxicology studies include: i) a 4-week (daily dosing) SC study in mice with toxicokinetic (TK) and an 8-week recovery period; ii) an 4-week (daily dosing) SC injection study in cynomolgus monkeys with TK and an 8-week recovery period.

A non-GLP 28 days study in cynomolgus monkeys, which included IV and daily SC dose arms, was conducted to support design of the GLP 4-week toxicity study.

In mouse GLP toxicology studies with AM0010 doses of 100 μg/kg, 300 μg/kg, and 1000 μg/kg were studied and no obvious systemic toxicity was identified. Mice in the

highest dose cohort showed moderately increased spleen weights at the end of the dosing period.

In GLP toxicology studies in cynomolgus monkeys, AM0010 was studied at 3 dose levels, (5 μg/kg, 20 μg/kg, and 100 μg/kg). There were no adverse events observed in the low dose group. A moderate transient regenerative anemia was observed in the medium dose group, reverting to normal within one week and with continued dosing. At 100 μg/kg, 3 of 10 animals experienced a marked reduction of RBC numbers and Hemoglobin. Two monkeys were euthanized with a general lack of activity. Dosing was stopped in the remaining monkeys of the high dose group, with all hematologic parameters returning to normal within one week in all animals. Subsequently, the animals in the high dose group received AM0010 at 100 μg/kg for an additional week, with all hematopoietic values remaining within normal boundaries.

A qualitatively similar transient anemia was also observed in GLP toxicity studies with rHuIL-10 in non-human primates and in clinical studies.

Histologic analysis of the NHP tissues from both GLP toxicology studies with PEG-rHuIL-10 and rHuIL-10 revealed signs of an extravascular hemolysis with increased iron deposition in Kupffer cells in the liver and spleen macrophages.

While the high dose in cynomolgus monkeys is approximately 40 x above the starting dose in humans, this protocol recommends dose reduction or dose interruption in case of treatment induced anemia Grade 2 or above.

Preliminary data from the Phase 1 study with AM0010 confirms a similar regulation in humans (Section 4.5).

Further details on the toxicology evaluation performed with AM0010 can be found in the Investigator's Brochure.

4.2.3 Pharmacokinetics

The PK/TK of AM0010 and PEG-rMuIL-10 was evaluated in CD1 mice and cynomolgus monkeys in non GLP studies and is further explored as part of the GLP toxicology studies. In both species, the PK of AM0010 was linear over the dose range of 0.1 to 100 μg/kg/day administered. No significant accumulation was observed throughout the studies. At a daily

dose of 20 μg/kg, an average C_{max} of 43.7 ng/mL and an AUC_{0-24h} of 458 ng•h/mL was observed in mice and a C_{max} of up to 71.9 ng/mL and an AUC_{0-24h} of up to 939 ng•h/mL was observed in monkeys. ADAs developed in monkeys and ADA positivity may have affected AM0010 serum exposure in the third and fourth week of the study. The non-GLP PK studies with AM0010 in cynomolgus monkeys showed an average half-life of 9.94 hours after a single administration. Volume of distribution of AM0010 upon the application of a 20 μg/kg dose was 282 mL/kg in mice and 366 mL/kg in cynomolgus monkeys, suggesting extravascular distribution.

Further details on the PK of AM0010 can be found in the Investigator's Brochure.

4.3 Anticipated Risk

rHuIL-10 has been safely dosed in multiple Phase 1, 2, and 3 stage clinical trials and in more than 3000 human subjects. rHuIL-10 was continuously dosed at daily SC doses up to 20 μg/kg and was generally well tolerated. Based on its well documented anti-inflammatory properties, rHuIL-10 was clinically tested by Schering-Plough for the treatment of a variety of inflammatory diseases, including rheumatoid arthritis, psoriasis, colitis, and HCV associated hepatitis. In addition, Renovo (UK) studied local injection of rHuIL-10 (Prevascar) in the treatment of scar formation.

4.3.1 Clinical Experience with rHuIL-10

Early clinical trials conducted by Schering-Plough demonstrated objective responses in inflammatory diseases, most prominently in Psoriasis, HCV hepatitis, and Crohn's disease (Asadullah, Sterry et al. 2003). However, the disease course altering capabilities of the chosen treatment schedules of rHuIL-10 in pivotal Phase 3 clinical studies in Crohn's disease and rheumatoid arthritis were not prominent and reproducible enough to justify further development of rHuIL-10. Furthermore, around the same time more potent anti-inflammatory molecules such as TNFα antagonists were in a later stage of their development. Studies conducted by Renovo to prevent scar tissue formation by local injection of rHuIL-10 in the surrounding of a surgical wound failed to provide statistical significant inhibition in the amount of scar formation.

rHuIL-10 was generally well tolerated and most side effects were mild to moderate. The core safety database contains more than 1600 patients. The most common side effects with chronic rHuIL-10 administration (> 10% incidence in at least one of the treatment groups)

were headache, fatigue, nausea, fever, arthralgia, myalgia, abdominal pain, viral infection, diarrhea, back pain, aggravated Crohn's disease, and pharyngitis. There was no indication of increased susceptibility to bacterial or viral infections. The side effects were rarely severe and comparable in frequency to placebo controls where present. Dose dependent reduction in some laboratory values (hemoglobin, platelets, cholesterol, albumin, and calcium) were observed and were reversible upon cessation of rHuIL-10 or only transiently observed in the first weeks of a study. In six patients, neurological serious adverse events were observed, including the aggravation of multiple sclerosis (MS), Guillain-Barré like syndrome, or dizziness. While the etiology and causality for those adverse events is unclear, precautions will be taken by including appropriate information in the Investigators Brochure and assuring the attention of clinical investigators to the early detection of polyneuropathies.

4.3.2 Preclinical Safety of AM0010 and PEG-rMuIL-10

In a mouse 1 month non-GLP toxicology study using the murine homologue of AM0010 (PEG-rMuIL-10), an accumulation of immune cells was detected in several epithelial organs including the exocrine pancreas. The immune reaction affected the acini of the exocrine pancreas without diminishing endocrine functions or causing systemic toxicity or weight loss. In this study, exposures to PEG-rMuIL-10 (AUC 4550 ng•h/mL) were significantly higher than anticipated in any dose group in humans and 47 fold higher than the starting dose group of the planned clinical safety studies. No indication of a similar process has been reported from the clinical trials evaluating rHuIL-10 in humans or in the GLP toxicology studies in mice and monkeys using AM0010. Determination of serum pancreatic enzymes will be included in the routine patient monitoring as a measure of additional precaution. The protocol recommends dose reductions and dose interruptions in case of immune mediated toxicologies.

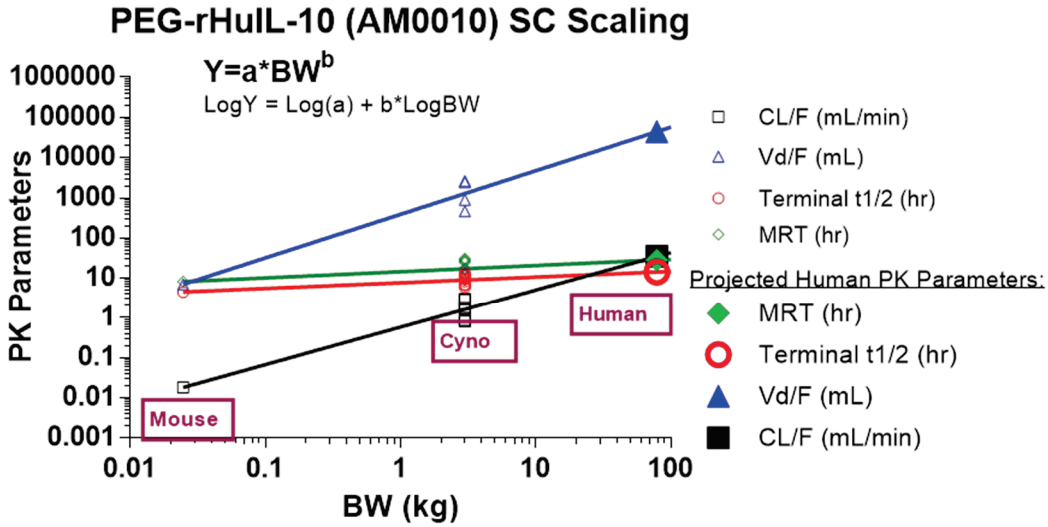
All biologic agents have a potential for development of anti-drug antibodies. In animal studies, anti-AM0010 antibodies affected the concentration of AM0010 in systemic circulation but did not induce adverse reaction. Very limited anti-drug antibodies against rHuIL-10 were detected in previous clinical studies. The development of antibodies will be monitored throughout the study.

4.4 Dose Rationale

4.4.1 Predicted AM0010 Concentrations in Humans

The pharmacokinetic profile of AM0010 follows an absorption driven two compartmental model. Species scaling from mice and monkeys was used to predict the PK parameters in humans. The average weight in humans was assumed to be 79 kg. Allometric scaling based on body weight predicts Cl of 34.548 mL/kg/h, V_d of 44213 mL/kg, and a serum half-life in humans of 14 h, see Figure 4. The clinical starting dose of 1 μg/kg is expected to achieve an AUC of 47.7 ng•h/mL. Accumulation of AM0010 was not observed in mice or monkeys, but the projected half-life of 14 hours might lead to a minimal accumulation of AM0010 by approximately 41% over the first dose during the treatment. However, clinical PK analysis for rHuIL-10 also showed a 40% reduction in serum levels after one week of daily dosing, possibly due to an increased pre-systemic clearance mechanism.

Figure 4: Predicted PK Parameters of AM0010 in Humans Scaled from Monkey and Mouse



Linear regression for mouse and cyno PK parameters.

	CL/F (mL/min)	Vd/F (mL)	Terminal t1/2 (hr)	MRT (hr)
Slope	0.9365 ± 0.1140	1.085 ± 0.1941	0.1420 ± 0.05755	0.1544 ± 0.1022
Y-intercept when X=0.0	-0.2387 ± 0.07578	2.587 ± 0.1623	0.8796 ± 0.03826	1.156 ± 0.06794
X-intercept when Y=0.0	0.2549	-2.384	-6.196	-7.487

	CL/F (mL/min)	Vd/F (mL)	Terminal t1/2 (hr)	MRT (hr)
R square	0.8824	0.9124	0.4034	0.2024

	CL/F (mL/min)	Vd/F (mL)	Terminal t1/2 (hr)	MRT (hr)
Deviation from zero?	Significant	Significant	Significant	Not Significant

Expected human PK parameters based on interspecies scaling:

BW (kg)	CL/F (mL/min)	Vd/F (mL)	Terminal t1/2 (hr)	MRT (hr)
79.000	34.548	44213.130	14.092	28.144

The PK parameters in human were scaled based on AM0010 PK experiments in mice and monkeys.

4.4.1.1 Exposure Margins in Humans

Based on allometric scaling, the human exposures after the first dose at the currently proposed clinical doses range between 48 and 762 ng•h/mL) (Table 1).

Table 1: Predicted Human Exposure after the First SC Dose Administered Scaled from Preclinical Species

Cohort	1	2	3	4	5
Clinical Dose (μg/kg)	1	2.5	5	10	20
Projected Human AUC (ng•h/mL)	47.7	95.3	190.6	381.1	762.2

Preclinical pharmacokinetic and pharmacological studies did find a marked, though transient, regenerative anemia at a dose of 100 μg/kg. This dose was therefore set as a severely toxic dose. The medium dose evaluated in the 4-week GLP toxicology study in monkeys (20 μg/kg) showed transient anemia that was reversible with continued dosing and was therefore used as the highest non severely toxic dose (HNSTD) in preclinical species. Following the ICH S9 guideline, we propose a human starting dose of less than 1/6 of human equivalent dose (HED) of the HNSTD in monkeys.

$$Human\ starting\ dose < \frac{HNSTD\ (HED)}{6} = \frac{20}{6}\ \frac{\text{ug}}{\text{kg}} / 3.1 = 1.07 \frac{\text{ug}}{\text{kg}}$$

The GLP toxicology studies in mice explored the toxicology margins further. Mice have been exposed to the PEG-rHuIL-10 up to 1000 μg/kg without signs of systemic toxicity. However, cynomolgus monkeys were determined to represent the more appropriate model species for toxicology evaluations of AM0010.

The predicted safety margins for the exposures (AUC) for the starting dose and four first dose escalations of AM0010 in this study are summarized in Table 2. The predicted exposure margin (AUC) based on human PK derived through allometric scaling (Table 2) is 19.7-fold at the proposed starting dose of 1 μg/kg after the first dose. At the highest proposed dose of 20 μg/kg, the exposure margin based on PK scaled (Table 2) is 1.23-fold after the first injection.

Table 2: Projected Human Exposure Margins at the Proposed Clinical Doses after Daily Injections of AM0010

Cohort	1	2	3	4	5
Clinical Dose (μg/kg)	1	2.5	5	10	20
Projected Human AUC (ng•h/mL)	47.7	95.3	190.6	381.1	762.2
Exposure Margin (AUC)	19.7	9.85	4.93	2.46	1.23

Exposure margins were derived from the predicted human $AUC_{0\text{-}24}$ values at each clinical dose compared to the $AUC_{0\text{-}24}$ achieved in cynomolgus monkeys at the highest dose of 20 μg/kg (939 ng•hr/mL).

4.4.2 Dose Rational for Part B and C

Preliminary clinical experience with AM0010 was accumulated in Part A of the study. The data indicate that the AM0010 exposures explored in the first 6 dose cohorts were very well tolerated (Section 4.5).

In the starting dose cohort of Part A (1 μg/kg), AM0010 serum concentrations at both, the peak and the trough concentrations were less than 10% of the EC_{50} of AM0010 in cell based assays (Table 4) and only very limited biological activity of AM0010 was observed (Table 5, Table 7). In the second dose cohort (2.5 μg/kg), AM0010 serum concentrations were between 10 and 20% of the EC_{50} in cell based assays and below the exposures at NOEL in toxicology species.

AM0010 was very well tolerated at this dose, and only very mild biological activity of AM0010 was observed. To explore the safety and tolerability of AM0010 in combination with chemotherapeutic agents, the starting dose in Part B and C will be 2.5 μg/kg.

4.4.3 Dose Rational for Part D, E, and F

AM0010 was well tolerated in monotherapy dose escalation up to 20 and 40 μg/kg. In combinations with two different chemotherapy regimens (Part B and C), AM0010 was well tolerated at doses of 2.5 and 5 μg/kg. Preliminary efficacy such as stabilization of tumor growth, reduction of tumor burden, and the reduction of the tumor markers CA19.9 or CEA has been experienced by several patients with pancreatic cancer and gastro-esophageal cancers.

To explore chemotherapeutic regimens best suited to treat patients with these tumor types, additional chemotherapeutic regimens are introduced in this protocol (Parts D, E, F).

AM0010 was well tolerated at 5 μg/kg in combination with two different chemotherapeutic regimens used in first line cancer therapy (Part B, C). Both regimens have substantial hematopoietic adverse effects in the absence of AM0010. Dose escalation cohorts of Part D will be started at 5 μg/kg, since this regimen has comparable adverse effects as regimens in Part B and C.

Part E and F comprise therapeutic regimens with a lesser degree of hematological adverse events and are generally well tolerated. Dose escalation in Part E and F will start at 10 μg/kg.

4.4.4 Dose Rational for Part G, H, and I

Patients with renal cell cancers (RCC) treated with AM0010 monotherapy experienced disease stabilization, and 3 patients with RCC experienced a reduction of tumor burden of more than 50% (19% ORR for RCC patients).

RCC patients also experience tumor response when treated with tyrosine kinase inhibitors (TKI) or immune checkpoint inhibitors.

Part G will explore tolerability of pazopanib (TKI) in combination with AM0010. Part H will explore tolerability of pembrolizumab (immune checkpoint inhibition) in combination with AM0010. Part I will explore the tolerability of Nivolumab with AM0010. The adverse event profile of those agents is dissimilar to the adverse event profile of AM0010. Dose escalation in Part G and H will therefore start at 10 μg/kg.

The combination of AM0010 (20 mcg/kg) with Pembrolizumab was deemed safe by the investigators of AM0010-001. The dose escalation of Part I (Nivolumab), which has the same mechanism of action and a comparable side effect profile, will therefore start at 20 mcg/kg.

4.4.5 Dose Rational for Part J

Tolerability of AM0010 has been explored in combination with carboplatin (at AUC6 with taxane), with oxaliplatin (combined with 5-fluorouracil), and in combination with gemcitabine and nab-paclitaxel. Patients with triple negative breast cancer had deep partial responses when treated with AM0010 / platinum / taxane combination. Triple negative breast cancer (TNBC) patients frequently receive a combination of gemcitabine and carboplatin, which includes 2 doses of carboplatin at AUC2 per cycle.

AM0010 was tolerated at 10 mcg/kg in combination with carboplatin and paclitaxel or in combination with oxaliplatin and 5FU. The starting dose for the combination with carboplatin/ gemcitabine is therefore 10 mcg/kg.

4.5 Preliminary Clinical Experience with AM0010

In Part A of this First in Human study, preliminary exposure and safety data have been collected, which may be important in the further progression into Expansion cohorts and Part B through J.

4.5.1 Preliminary Clinical Experience

The objective of this dose escalating study is to define the safety profile, maximum tolerated dose, recommended Phase 2 dose, pharmacokinetics, and tumor response in patients with advanced malignant tumors.

In Part A dose escalation, 33 patients with advanced malignant tumors across several indications (melanoma, ovarian, pancreatic, prostate, renal cell, colorectal, NSCLC) have been exposed to AM0010 as a single agent. Patients received doses from 1 µg/kg up to 40 µg/kg daily. Cohorts 1 through 6 (1 through 40 µg/kg) were found safe and tolerable.

Table 3: Preliminary Clinical Experience

Part	Regimen (AM0010, qd)	Highest Daily Dose of AM0010 Administered	G3/4 AEs Related to Study Drugs	DCR/ORR (evaluable patients **)
A	Monotherapy	40 µg/kg *	thrombocytopenia, anemia, LFT, nausea (1 patient)	38/7 (29)
B	Platinum / Taxane	10 µg/kg *	thrombocytopenia, anemia, fatigue neutropenia	64/45 (11)
C	FOLFOX	5 µg/kg * 10 µg/kg	neutropenia, leukopenia, anemia, fatigue, hyperbilirubinemia	77/8 (13)
D	Gemcitabine / nab-Paclitaxel	5 µg/kg	anemia, neutropenia, thrombocytopenia, nausea, emesis	100/33 (3)
E	Capecitabine	10 µg/kg	NA	100/0 (4***)
F	Paclitaxel (weekly)	10 µg/kg	NA	NA
G	Pazopanib	10 µg/kg	fatigue	100/20 (5)
H	Pembrolizumab	20 µg/kg *	thrombocytopenia, anemia, hyponatremia, rash	82/45 (11)

* found well tolerated by AM0010-001 investigators;
** escalation cohorts only;
*** pancreatic cancer patients only

Most patients enrolled in the escalation cohorts and first expansion cohort had previously progressed on multiple lines of therapy. Despite this fact, very encouraging anti-tumor responses have been observed in most combination arms. Refer to AM0010-001 Investigator's Brochure for more information.

4.5.2 Preliminary AM0010 Exposures

The serum concentrations of AM0010 have been monitored at 0, 2, 6, 8, 12, and 24 hours after dose administration on Day 1 and 29. The 24 hour serum trough has been monitored weekly and after two months biweekly throughout the study.

Preliminary AM0010 serum exposures are shown in Table 4. The preliminary analysis shows stable exposures to AM0010 with less than 2 fold C_{max}/C_{min} differences and with a stable 24 hour serum trough (C_{min}) for at least 29 days upon daily dosing. The serum levels observed at Day 15 and Day 29 are generally dose proportional. Analysis of patients dosed for more than six months shows very consistent exposures throughout the dosing period. A quantitatively significant molecular antagonism to the drug such as anti-drug antibodies is therefore less likely. A validated assay to further investigate anti-drug antibodies has been developed and will be applied in 2015.

Consistent with prior clinical experience with SCH52000 and preclinical experience with AM0010, inter-individual differences in absorption and C_{max} were observed. Several patients in Cohort 4 (10 μg/kg) presented a lower serum concentration than expected from this dose, resulting in a lower median C_{max} and C_{min} on Day 1 for this cohort. This may be due to the prevalence of inflammatory cells expressing the interleukin 10 receptor (IL-10R) on the surface. IL-10R is the molecular target for AM0010 and could mediate target mediated clearance of AM0010.

Table 4: Preliminary Median Serum Concentrations of AM0010

Dose Cohort	C_{max} Day 1 (ng/mL)	T_{max} (Hours post dose)	C_{min} Day 1 24h (ng/mL)	C_{min} Day 15 (ng/mL)	C_{min} Day 29 (ng/mL)
1 μg/kg	0.36	5.50	0.22	0.40	0.77
2.5 μg/kg	1.12	19.20	1.08	1.41	1.27
5 μg/kg	2.27	14.00	2.29	2.39	2.63
10 μg/kg	3.37	12.77	2.31	4.11	4.46
20 μg/kg	16.05	20.00	13.56	18.08	14.03

Dose Cohort	C_{max} Day 1 (ng/mL)	T_{max} (Hours post dose)	C_{min} Day 1 24h (ng/mL)	C_{min} Day 15 (ng/mL)	C_{min} Day 29 (ng/mL)
40 µg/kg*	20.67	18.00	16.32	N/A	N/A

* Exposures from two patients were available at the time of this amendment

4.5.3 Preliminary Blood Parameters

The safety and efficacy of rHuIL-10 was previously studied in normal subjects and patients with inflammatory diseases (Fedorak, Gangl et al. 2000). rHuIL-10 was well tolerated. In those clinical studies, rHuIL-10 induced a transient reduction of blood thrombocytes and a reduction in blood erythrocytes, resulting in lower blood hemoglobin (HGB) levels. The transient reduction in thrombocyte numbers did not lead to an increased frequency of bleedings.

In the dose escalation of Part A of AM0010-001, a reduction of red blood cells / hemoglobin and thrombocytes was observed, which was qualitatively and quantitatively similar to that seen during the previous clinical experience with rHuIL-10.

4.5.3.1 Anemia

A mild to moderate reduction of red blood cells and HGB was observed within two weeks of exposure to AM0010 in most patients. HGB remained at the reduced level throughout the dosing period. The reduction in red blood cells and hemoglobin occurred within the first four weeks of dosing. The reduction of hemoglobin was observed at doses above 2.5 µg/kg, with a further decrease at doses above 5 µg/kg.

A reproductive compensation with increases in reticulocytes was detectable throughout the study. This may limit a further reduction in HGB with continued AM0010 dosing (Table 5). However, reduction in HGB lead to the discontinuation of one patient in Cohort 5 (20 µg/kg), who had reduced red blood cell count at the dosing start.

In non-human primates, hemosiderin positive macrophages have been observed in several organs, indicating the phagocytosis of erythrocytes by macrophages. This mechanism had been previously described during the development of rHuIL-10 (SCH52000). The reduction of red blood cells in response to AM0010 may be mediated by the up-regulation of scavenger receptors on macrophages in the spleen and the liver, resulting in increased elimination of aging erythrocytes. This type of anemia has been described as anemia of

inflammation and chronic disease and may be counteracted by iron supplement and erythropoietin (Weiss and Goodnough 2005).

Many chemotherapy regimens are known to cause a reduction in hemoglobin, thrombocytes, and white blood cells. The safety of a combination of AM0010 with two different chemotherapy regimens was therefore investigated. The combined treatment of AM0010 with chemotherapy regimens lead to a mild increase of the reduction of hemoglobin and red blood cells. The reductions in hemoglobin reverted with dose interruptions or supportive treatment.

For further information, consult the Investigator Brochure for AM0010 (20 December 2014).

Table 5: Preliminary Mean Hemoglobin Values in Cohorts 1 – 6

Dose Cohort (μg/kg)	Hemoglobin prior (g/dL)	Hemoglobin Day 8 (g/dL)	Change Day 8 (%)	Hemoglobin Day 15 (g/dL)	Change Day 15 (%)	Hemoglobin Day 22 (g/dL)	Change Day 22 (%)	Hemoglobin Day 29 (g/dL)	Change Day 29 (%)
1.0	11.8	10.7	-8.7	12.3	4.4	11.2	-4.7	11.0	-6.7
2.5	12.1	11.8	-2.8	10.9	-10.5	10.9	-10.0	10.8	-10.9
5.0	11.3	10.2	-10.0	9.6	-15.4	9.7	-14.2	9.8	-13.6
10.0	11.5	10.9	-5.2	9.3	-19.7	10.1	-12.5	9.4	-18.2
20.0	11.8	11.0	-6.9	10.3	-13.0	10.0	-15.2	10.5	-11.1
40.0	13.5	12.2	-9.9	11.4	-15.8	11.2	-16.8	10.6	-21.5

Table 6: Preliminary Mean Hemoglobin Values in Chemotherapy Cohorts

Dose Cohort (μg/kg)	Hemoglobin prior (g/dL)	Hemoglobin Day 8 (g/dL)	Change Day 8 (%)	Hemoglobin Day 15 (g/dL)	Change Day 15 (%)	Hemoglobin Day 22 (g/dL)	Change Day 22 (%)	Hemoglobin Day 29 (g/dL)	Change Day 29 (%)
Part B Platinum / Taxane + AM0010									
2.5	12.2	11.0	-9.8	10.3	-16.1	10.4	-14.7	9.7	-21.0
5	11.3	9.7	-14.4	9.4	-16.8	9.6	-15.3	9.1	-19.4
Part C FOLFOX + AM0010									
2.5	11.8	11.2	-4.8	9.8	-16.7	9.5	-19.5	9.2	-21.8
5	13.1	12.2	-6.6	12.1	-7.4	11.8	-9.9	11.1	-15.1

4.5.3.2 Thrombocyte Reduction

The reduction of thrombocytes was most pronounced at Day 8 in all Part A cohorts receiving AM0010. The reduction of thrombocytes was partially or completely reversible on Day 15 through Day 29 with continued dosing. In the 40 g/kg/day AM0010 cohort remained reduced by 35% from baseline on Day 29 (Table 7). One patient in the 20 μg/kg/day AM0010 cohort experienced a transient Grade 3 thrombocytopenia, possibly due to a low thrombocyte count at enrollment. In 33 patients enrolled in Part A, two incidences of bleeding occurred, one each in Cohort 2 and 4; both were deemed not related to AM0010 by the investigator. For further information, consult the Investigator Brochure for AM0010.

Table 7: Mean Thrombocyte Numbers in AM0010 Monotherapy Escalation Cohorts

Dose Cohort (μg/kg)	Thrombocytes Prior (x 10^3)	Thrombocytes Day 8 (x 10^3)	Change Day 8 (%)	Thrombocytes Day 15 (x 10^3)	Change Day 15 (%)	Thrombocytes Day 22 (x 10^3)	Change Day 22 (%)	Thrombocytes Day 29 (x 10^3)	Change Day 29 (%)
1	270	289	6.9	294	8.8	245	-9.3	269	-0.4
2.5	251	215	-14.0	231	-7.7	270	7.8	263	4.9
5	333	158	-52.6	212	-36.2	225	-32.3	244	-26.7
10	222	99	-55.4	160	-27.7	191	-13.7	181	-18.2
20	199	77	-61.6	104	-47.8	97	-51.4	108	-46.0
40	221	88	-60.2	105	-52.6	114	-48.6	143	-35.2

Table 8: Mean Thrombocyte Numbers in AM0010 Chemotherapy Cohorts 1 and 2

Dose Cohort (μg/kg)	Thrombocytes Prior (x 10^3)	Thrombocytes Day 8 (x 10^3)	Change Day 8 (%)	Thrombocytes Day 15 (x 10^3)	Change Day 15 (%)	Thrombocytes Day 22 (x 10^3)	Change Day 22 (%)	Thrombocytes Day 29 (x 10^3)	Change Day 29 (%)
Part B Platinum / Taxane + AM0010									
2.5	261.0	146.8	-43.8	171.5	-34.3	186.0	-28.7	157.3	-39.8
5	254.0	97.0	-61.8	175.5	-30.9	113.0	-55.5	93.0	-63.4
Part C FOLFOX + AM0010									
2.5	151.7	93.3	-38.5	111.7	-26.4	173.7	14.5	103.7	-31.6
5	207.5	90.0	-56.6	109.5	-47.2	93.3	-55.0	94.3	-54.5

With the addition of AM0010 to chemotherapy regimen in Part B and C, the reduction in thrombocytes appeared more prolonged (Table 8). Grade 3 thrombocytopenia was not observed in Cohort 1 and 2 of Part B and C. One Grade 1 CCI was reported in Part B Cohort 1, deemed not related to AM0010, and no incidence of bleeding occurred in Part C.

In summary, these data indicate that AM0010 reduces the number of thrombocytes in patients with advanced solid tumors. Dose interruptions lead in all cases to the return of thrombocyte counts to baseline or Grade 1 within days. It is therefore less likely that thrombocyte reduction by AM0010 would be the result of the inhibition of thrombocyte progenitors in the bone marrow. It is possible that the increase of inflammatory cytokines by AM0010 stimulates the production of prostaglandins and thromboxane, leading to the activation of platelets in patients. The reduction of thrombocytes did not lead to increased bleeding in patients with advanced solid tumors treated with AM0010. It is important to note that treatment of several thousand patients with rHuIL-10 did not result in an increase incidence of bleeding.

5 EXPERIMENTAL PLAN

5.1 Hypothesis

Safety, tolerability, and pharmacokinetics of AM0010 established in preclinical species can be transferred to humans; AM0010 will reduce disease associated biomarkers and possibly provide preliminary information about its use in cancer therapy.

5.2 Objectives

5.2.1 Primary

- To characterize the safety, tolerability, MTD, and PK of AM0010 after daily subcutaneous (SC) administrations in patients with advanced solid tumors as monotherapy or in combination with chemotherapy or immunotherapy.

5.2.2 Secondary

- To measure the tumor response
    - by immune related Response Criteria (irRC)
    - by Prostate Cancer Working Group 2 (PCWG2) criteria for prostate cancer metastatic to bone
    - or according to tumor evaluation criteria best suitable and accepted for the tumor type evaluated
- To evaluate the formation of anti-AM0010 antibodies

5.2.3 Exploratory

- To investigate biomarkers for patient stratification and treatment response, including genetic analysis, serum chemokines, and tumor antigen specific immune responses such as antibody and T cell responses as surrogates for anti-tumor activity of AM0010

5.3 Endpoints

5.3.1 Primary

- Incidence of adverse events, clinically relevant changes in laboratory values, electrocardiograms (ECGs), and vital signs

- PK parameters including the serum trough concentration (C_{min}), the maximal drug concentration (C_{max}), area under the curve of serum concentration over time (AUC), and half-life ($t_{½}$).

5.3.2 Secondary

- Change in tumor burden measured by volumetric CT or MRI according to irRC
- Progression in bone by bone scintigraphy according to PCWG2 for patients with metastatic CRPC
- or change in tumor burden according to tumor evaluation criteria best suitable and accepted for the tumor type evaluated
- Anti-AM0010 antibody formation.

5.3.3 Exploratory

- Biomarker analysis, including but not limited to whole blood DNA analysis for genetic predisposition, serum cyto- and chemokines, and antibodies directed against tumor associated antigens (TAA)
- Prevalence and expansion of TAA reactive T cells.

5.4 Study Design and Rationale

This is a first-in-human, open-label, dose escalation study to evaluate the safety and tolerability of AM0010 in patients with advanced solid tumors dosed daily SC.

The primary objective of this study is to characterize the safety, tolerability, MTD, and the PK of AM0010 after daily SC injections in patients with advanced solid tumors. The secondary objectives are to measure clinical activity, the tumor response and to evaluate the formation of anti-AM0010 antibodies.

- Rationale for Part I – Nivolumab and AM0010:

  PD-1 and the IL10R is upregulated on CD8+ T cells upon stimulation of the T cell receptor (TCR). PD1 activation inhibits the TCR signal, while IL-10 stimulates survival and activation of CD8 T cells. Anti PD-1 antibodies have anti-tumor activity in a wide spectrum of cancer patients. Pembrolizumab is approved for the treatment on patients with melanoma or PDL-1 high NSCLC. Nivolumab is approved for the treatment of

patients with melanoma, RCC, or NSCLC. AM0010 monotherapy has demonstrated single agent activity in patients with RCC (ORR 27%) and melanoma. A combination of AM0010 with pembrolizumab lead to durable responses in 4 of 8 RCC patients and durable tumor control (> 6 months) in 6 of 8 RCC patients. To further test the hypothesis that a combination of PD1 inhibition and IL-10R activation leads improved benefit of patients, a combination of AM0010 with nivolumab will be explored in patients with RCC or NSCLC in Part I.

- Rationale for Part J Gemcitabine/Carboplatin and AM0010

  Patient with triple negative breast cancer have limited therapeutic options. Immune checkpoint inhibitors provide benefit to only a small subset of patients. A combination of carboplatin and paclitaxel with AM0010, lead to 100% tumor control and 3 PRs in 7 patients (Part B). The combination of Gemcitabine and Carboplatin provides an acceptable first or second line treatment option for patients with metastatic TNBC. The hypothesis that the combination of Gemcitabine/Carboplatin / AM0010 is tolerable and may provide additional and durable benefit to patients with TNBC will be tested in dose escalation and expansion cohorts in Part J

All treatments are to be given in an outpatient setting.

This study will be done in 10 parts, each part will have 2 phases (Table 9).

It is anticipated that 5 dose cohorts in the Dose Escalation Phase will be evaluated as monotherapy in Part A. In Part B and C, it is anticipated that 4 dose cohorts in the Dose Escalation Phase will be evaluated with chemotherapy and immunotherapy. The starting dose of AM0010 in Part B and C will be 2.5 µg/kg, since AM0010 alone was well tolerated at this dose and at significantly higher doses. The dose escalation of Part D (Gemcitabine/nab-paclitaxel) will comprise of 3 dose cohorts. The escalation phases of Parts F–G and I–J will comprise of only 2 dose escalation cohorts. Part H will have 3 escalation cohorts. Part I is anticipated to have one dose escalation cohort (following the recommended dose of Part H). Part J is anticipated to have not more than 2 escalation cohorts (following information from Cohorts B–E). See Section 4.4, Dose Rationale, for further information.

Table 9: AM0010 Dose Schedule for Part A – J

Part A AM0010 Dose Escalation Phase – Monotherapy			
Dose Cohort	**Number of Patients**	**AM0010 Dose (μg/kg), daily**	**AM0010 until irPD**
1	3 – 6	1	No additional therapy
2	3 – 6	2.5	
3	3 – 6	5	
4	3 – 6	10	
5	3 – 6	20	
Optional*	3 – 6	40	
Expansion**	10 – 15	Previously evaluated, safe dose in combination therapy	
Part B AM0010 Dose Escalation Phase + Platinum / Taxane			
Dose Cohort	**Number of Patients**	**AM0010 Dose (μg/kg) daily**	**Chemotherapy q21d x 5 (or x6) AM0010 until irPD**
1	3 – 6	2.5	Day 1 of every 21 day cycle Carboplatin or Cisplatin and Paclitaxel or Docetaxel See Section 8.3 for detailed dosing and scheduling instructions
2	3 – 6	5	
3	3 – 6	10	
4	3 – 6	20	
Optional*	3 – 6	40	
Expansion**	10 – 15	Previously evaluated, safe dose in combination therapy	
Part C AM0010 Dose Escalation Phase + FOLFOX			
Dose Cohort	**Number of Patients**	**AM0010 Dose (μg/kg) daily**	**FOLFOX q14d x 12 AM0010 until irPD**
1	3 – 6	2.5	Day 1, 2 of every 14 day cycle See Section 8.3 for detailed dosing and scheduling instructions
2	3 – 6	5	
3	3 – 6	10	
4	3 – 6	20	
Optional*	3 – 6	40	
Expansion**	10 – 20	Previously evaluated, safe dose in combination therapy	

Part D AM0010 Dose Escalation Phase + Gemcitabine / nab-paclitaxel			
Dose Cohort	**Number of Patients**	**AM0010 Dose (μg/kg) daily**	**Gemcitabine / nab-paclitaxel q7d x 3 / 28 day cycle (until irPD) AM0010 until irPD**
1	3 – 6	5	Day 1, 8, 15 of each 28 day cycle Section 8.3 for detailed dosing and scheduling instructions
2	3 – 6	10	
3*	3 – 6	20	
Expansion**	15	Previously evaluated, safe dose in combination therapy	
Part E AM0010 Dose Escalation Phase + Capecitabine			
Dose Cohort	**Number of Patients**	**AM0010 Dose (μg/kg) daily**	**Capecitabine bid x 2 weeks (until irPD) AM0010 until irPD**
1	3 – 6	10	Day 1-14 of every 21 day cycle See Section 8.3 for detailed dosing and scheduling instructions
2*	3 – 6	20	
Expansion**	10 – 15	Previously evaluated, safe dose in combination therapy	
Part F AM0010 Dose Escalation Phase + Paclitaxel			
Dose Cohort	**Number of Patients**	**AM0010 Dose (μg/kg) daily**	**Paclitaxel q7d x 3 / 28 day cycle (until irPD) AM0010 (until irPD)**
1	3 – 6	10	Day 1, 8, 15 of every 28 day cycle See Section 8.3 for detailed dosing and scheduling instructions
2	3 – 6	20	
Expansion**	15	Previously evaluated, safe dose in combination therapy	
Part G AM0010 Dose Escalation Phase + Pazopanib			
Dose Cohort	**Number of Patients**	**AM0010 Dose (μg/kg) daily**	**Pazopanib qd (until irPD) AM0010 (until irPD)**
1	3 – 6	10	Daily See Section 8.3 for detailed dosing and scheduling instructions
2	3 – 6	20	
Expansion**	10 – 15	Previously evaluated, safe dose in combination therapy	

Part H AM0010 Dose Escalation Phase + anti PD-1 (Pembrolizumab)			
Dose Cohort	**Number of Patients**	**AM0010 Dose (μg/kg), daily**	**Pembrolizumab q3w (until irPD) AM0010 (until irPD)**
1	3 – 6	10	Day 1 of every 21 day cycle See Section 8.3 for detailed dosing and scheduling instructions
2	3 – 6	20	
3*	3	40	
Expansion**	10 – 15	Previously evaluated, safe dose in combination therapy	
Part I AM0010 Dose Escalation Phase + anti PD-1 (Nivolumab)			
Dose Cohort	**Number of Patients**	**AM0010 Dose (μg/kg), daily**	**Nivolumab q2w (until irPD) AM0010 qd (until irPD)**
1	3 – 6	20	Day 1 of every 14 day cycle See Section 8.3 for detailed dosing and scheduling instructions
2	3 – 6	40	
Expansion**	10 – 20	Previously evaluated, safe dose in combination therapy	
Part J AM0010 Dose Escalation Phase + Gemcitabine & Carboplatin			
Dose Cohort	**Number of Patients**	**AM0010 Dose (μg/kg), daily**	**Gemcitabine / Carboplatin q7d x 2 / 21 day cycle (until irPD) AM0010 qd (until irPD)**
1	3 – 6	10	Day 1, 8 of every 21 day cycle See Section 8.3 for detailed dosing and scheduling instructions
2	3 – 6	20	
Expansion**	10 – 20	Previously evaluated, safe dose in combination therapy	

* In the absence of DLTs and continued benefit, the dose may be further escalated, following a two-fold increase.
**Additional Cohorts may be enrolled based on emerging safety or PK data from the Dose Escalation Phase and Expansion Phase.

5.4.1 Dose Escalation

The AM0010 starting dose for Part A of the Dose Escalation will be 1 μg/kg. The AM0010 starting dose for Part B and C of the Dose Escalation will be 2.5 μg/kg. The starting dose for Part D will be 5 μg/kg; for Parts E – H and J will be 10 μg/kg, Part I will start at 20 μg/kg. Subsequent doses of up to 20 μg/kg and 40 μg/kg are planned. Investigators and the Sponsor may consider intermediate doses if toxicity or other data support this decision. Three to 6 patients will be enrolled using a 3 + 3 design. Biological activity including immunological stimulation and modulation of cholesterol was observed in the first dose

cohort. To assure the collection of safety information regarding potential cumulative, immune mediated toxicity, up to 6 patients may be enrolled at the start of each cohort.

Doses of AM0010 will be administered SC daily to characterize the safety, tolerability, MTD, and PK. Part A will be AM0010 monotherapy and Part B and C will be AM0010 combined with chemotherapy.

On the first day of the first cohort in Part A, only one patient will be dosed. Additional patients of the first cohort can be enrolled after 24 hours, once the first patient of the first cohort is successfully dosed for one day in the absence of acute toxicity. Tolerability and safety parameters will be evaluated on the first two days and weekly/biweekly thereafter.

The DLT assessment window is 28 days. Cohort dose escalation will occur upon dosing of at least three patients of a cohort without DLTs for 28 days or dosing of at least six patients of a cohort with less than or equal to 33% of patients experiencing dose limiting toxicities (DLT) for at least 28 days.

Dose Escalation will stop at the appearance of AM0010 related DLTs in more than 33% of six patients in one cohort or upon unequivocal induction of efficacy or at dose levels saturating AM0010 induced mechanisms. The highest dose with DLTs in less than or equal to 33% of the patients defines the MTD. The safety and efficacy of doses at or below the MTD will be further explored in the Expansion Cohorts.

Upon dosing of at least three patients in the highest planned dose and in the absence of DLTs in less than or equal to 33% of the patients, further dose escalation cohorts are planned, continuing the schedule of two fold dose increases.

Tolerability will be re-evaluated with successive dosing to allow dose reduction in the event of potentially occurring cumulative toxicity.

If a DLT occurs in a cohort with 3 patients after 28 days, 3 additional patients will be enrolled in that cohort. The MTD determination for a treatment duration (e.g., X consecutive treatment days) will follow the procedure outlined in Section 8.4.2. If DLTs occur in more than 33% of a cohort of six patients for a treatment duration, the MTD for this number of treatment days will be the highest dose tolerated safely for this treatment duration.

Tumor assessment will occur every 8 weeks, and the tumor burden will be analyzed according to the irRC (Wolchok, Hoos et al. 2009) (Section 9.14.1) or other response criteria as detailed in Section 9.14. Patients with unconfirmed progressive disease (irPD) without rapid clinical deterioration will continue on study treatment until a second scan confirming disease progression has been obtained.

Patients with confirmed irPD may continue to receive study treatment in the absence of clinical deterioration and if the investigator considers that the patient continues to receive benefit from the treatment.

Patients who completed the chemotherapy or immunotherapy course or who dose reduce or interrupt one chemotherapy or immunotherapy component due to therapy related toxicity may continue to receive AM0010 until confirmed irPD or after confirmed irPD in the absence of clinical deterioration and if the investigator considers the patient continues to receive benefit from the AM0010 treatment. If a patient stops chemotherapy or immunotherapy prematurely but the investigator recommends continuation of AM0010 treatment, the patient will be re-consented.

Should the dosing of a patient be stopped following irCR, the patient may be allowed to re-enter subsequent dosing cycles should tumor burden be detected in one of the follow-up evaluations.

5.4.2 Expansion Cohorts

The first Expansion Cohort of 15 patients, not including patients of the escalation cohorts, will be dosed at dose levels up to the MTD defined as the highest dose level with an observed incidence of DLT in ≤ 33% of patients in the Dose Escalation. DLTs will be monitored in the expansion cohort(s) and dose reconsidered if DLT rate exceeds 33%. Further Expansion Cohorts may be enrolled based upon emerging safety, efficacy, PK, or pharmacodynamic data from the Dose Escalation Phase and first Expansion Cohort.

The clinical activity of AM0010 will be evaluated in expansion cohorts in selected patient populations

5.4.2.1 Part H in PD-1 Refractory Melanoma Patients

Melanoma patients with tumor progression after four to six doses of anti-PD-1 antagonistic antibodies (anti-PD1 early refractory melanoma patients) have very limited probability for a delayed tumor response (early pseudoprogression = 3.8%) (Hodi, Ribas et al. 2014). Early anti-PD-1 refractory melanoma patients may have an increased ORR when treated with the combination of anti PD-1 and AM0010 after progression on anti PD-1 monotherapy. To test this hypothesis, an expansion cohort of 20 early anti-PD-1 refractory patients will be enrolled for the treatment with AM0010 and pembrolizumab.

5.4.2.2 Part C in Pancreatic Carcinoma Progressed on Prior Gemcitabine

More than 50% of patients with locally advanced or metastatic pancreatic carcinoma receive a gemcitabine based therapy (Gemcitabine or Gemcitabine based regimen) as a first line of treatment (LOT). The majority of those patients progress and are in need to receive additional efficacious treatment. Therapeutic options include 5-FU and oxaliplatin based regimens including FOLFOX (NCCN 2014). Less than 5% of patients have a response to FOLFOX (ORR) and the mOS is 5.9 months (Oettle, Riess et al. 2014, Wang-Gillam, Li et al. 2015). The FDA recently approved a combination of liposomal irinotecan (Onivyde) plus fluorouracil/leucovorin for the treatment of this disease population. Preliminary evidence obtained in this study with a combination of AM0010 and FOLFOX indicates that this combination treatment is beneficial for patients with progressed pancreatic cancer. AM0010 FOLFOX combination may therefor also provide benefits to patients with locally advanced or metastatic pancreatic carcinoma progressed on a 1st LOT gemcitabine based therapy. To test this hypothesis, a cohort of 30 pancreatic cancer patients which progressed on or after prior gemcitabine based therapy will be enrolled in Part C.

5.4.2.3 Part I Expansion Cohort 1 – NSCLC Patients

Nineteen percent of patients with advanced NSCLC (n=292) respond to nivolumab monotherapy (Borghaei, Paz-Ares et al. 2015). Preliminary evidence suggests that patients treated with a combination of AM0010 and a PD-1 inhibitor may have a significantly improved response rate. To test this hypothesis, a cohort of 30 anti PD-1 naïve NSCLC patients will be enrolled in Part I expansion Cohort 1 (AM0010 + nivolumab). Using exact binomial testing with a one-sided 5% alpha, a cohort of 30 patients would have 84% power

to detect an observed response rate in the experimental patients of 43% or 13 patients (as statistically higher than 19%).

5.4.2.4 Part I Expansion Cohort 2 – RCC Patients

Twenty-five percent of patients with advanced renal-cell carcinoma (n=410) had a response to nivolumab (Motzer, Escudier et al. 2015). Preliminary evidence suggests that RCC patients treated with a combination of AM0010 and a PD-1 inhibitor may have a significantly improved response rate than on nivolumab monotherapy. To test this hypothesis, a cohort of 30 anti PD-1 naïve RCC patients will be enrolled in Part I expansion Cohort 2 (AM0010 + nivolumab). Using exact binomial testing with a one-sided 5% alpha, a cohort of 30 patients would have 84% power to detect an observed response rate in the experimental patients of 43% or 13 patients (as statistically higher than 25%).

5.4.2.5 Part J – TNBC Patients

One of the preferred 1st or 2nd line of treatments for patients with TNBC is a combination therapy with carboplatin and gemcitabine (NCCN 2014). The ORR for this treatment is only 32%. Preliminary evidence obtained in this study indicates that a combination of carboplatin and paclitaxel with AM0010 provides significant benefit to patients with TNBC at very progressed stages of the disease. The combination of AM0010 with carboplatin and gemcitabine may therefor also provide benefits to patients at 1st or 2nd LOT. To test this hypothesis, a cohort of 20 TNBC patients with a maximum of 1 prior therapy for metastatic disease will be enrolled in Part J.

5.4.3 Number of Centers

This study will be conducted at approximately 8 – 25 research centers in the United States.

5.4.4 Number of Patients

The study will initially enroll approximately 45 patients in each of the 3 initial Parts A–C for a total of approximately 135 patients. Six to 30 patients will be enrolled in the Dose Escalation Phases and 15 to 30 for each Expansion Phase (3 x 45 = 135).

Additional 2 expansion cohorts for further exploration and confirmation of safety and anti-tumor activity will enroll 20 to 30 patients to allow statistical relevant evaluation of toxicity and response rates compared to historical controls (2 x 30 = 60).

Enrollment of additional 5 parts (D – H) is anticipated to include a total of 105 patients. Up to 12 patients in dose escalation cohorts (5 parts x 12 = 60) followed by dose specific expansion cohorts of up to 15 patients in up to 3 parts (3 x 15 = 45). It is not anticipated that all parts of D–H will contain expansion cohorts (45 + 60 = 105).

Part I will enroll approximately 6 patients in the dose escalation portion and additional 30 patients in each of the 2 dose expansion phase (6 + 2 x 30 = 66).

Part J will enroll approximately 6 patients in the dose escalation portion and additional 20 to 30 patients in one dose expansion phase (6 + 20 = 26).

The total number of patients included in the study is therefore 392 (135 + 60 + 105 + 66 + 26 = 392).

Dose Escalation will continue until DLTs are observed in more than 33% of the patients in a cohort; the exact number of patients entering this trial can therefore not be accurately predicted. In the Dose Escalation Phase, at least 3 patients are enrolled per dose level; upon the observation of DLTs in one patient, an additional 3 patients will be enrolled at the same dose level. In the Dose Expansion Phase, 10 to 30 patients will be enrolled at or below the MTD at the Sponsor's discretion to expand on the safety, efficacy, and pharmacodynamics of AM0010.

The sample size is based on practical and statistical considerations and is consistent for this type of study. To detect an event which is expected to occur in more than 20% of a patient population, we intend to enroll a dose expansion cohort (DEC) of 10 patients.

To detect an event which is expected to occur in 10% of a patient population, we intend to enroll a DEC of 20 patients.

5.4.5 Estimated Study Duration

5.4.5.1 Study Duration for Participants

The patient participation time is planned to be maximally 24 months consisting of a screening period of up to 28 days, up to 22 months of treatment, and a 30-day follow-up period. Patients may continue to receive treatment longer than 22 months at the sponsor and investigator's discretion or until progressive disease, toxicity, or patient or physician decision. All patients will be followed for survival after the 30-day follow-up period until study completion.

5.4.6 Study Completion Definition

This study will be considered complete when the final analysis of the primary and secondary objectives is complete. 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 treatment during the continued access period.

5.4.7 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 study treatment who continue to experience clinical benefit may continue to receive study treatment until, at the physician's discretion, disease progression, death, unacceptable toxicity, or end of trial. Patients who are in the 30-day follow-up but have not yet completed the visit will complete the necessary follow-up visit when the continued access period begins, and then discontinue the study. 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, 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).

During the continued access period, if a patient experiences a suspected systemic hypersensitivity reaction involving the skin or mucous membranes, respiratory, cardiovascular, gastrointestinal, urinary, or other systems, after administration of study drug(s), the following guidance should be followed:

- Study drug should be temporarily withheld immediately and appropriate supportive care provided according to local standard practice (for example, administration of epinephrine, anti-histamine, systemic steroids, and/or bronchodilators).
- After patient's stabilization, blood samples for immunogenicity and PK analysis will be taken at the following time points: as soon as possible after the onset, at the resolution of suspected hypersensitivity event, at 30 days ±3 days, and 12-16 weeks after the hypersensitivity event.
- The patient should be monitored until resolution or stabilization of the symptoms, as clinically appropriate.
- If study drug induced hypersensitivity reaction is deemed serious in nature or is of ≥grade 3 in severity, and is confirmed or considered highly probably by the investigator, the study drug(s) should be permanently discontinued. The patient should undergo post-treatment follow-up procedures after study drug discontinuation.
- The medical monitor should be notified as soon as feasible.

Serious adverse events (SAEs) 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.

5.4.8 End of Trial Definition

End of Trial is defined as the date of the last visit or last scheduled procedure for the last patient, including the continued access follow-up visit.

6 PATIENT ELIGIBILITY

Investigators will maintain a screening log of all potential study candidates that includes limited information about the potential candidate (e.g., initials, age, and gender), date, and outcome of the screening process (e.g., enrolled into study, reason for ineligibility, or refused to participate).

6.1 Inclusion Criteria

To be eligible for this study, potential patients must fulfill all of the following inclusion criteria:

1. Provide signed written informed consent
2. Part A Escalation Cohorts:

Histologically or cytologically confirmed advanced malignant solid tumor, limited to melanoma, castration resistant prostate cancer, ovarian cancer, renal cell carcinoma, colorectal carcinoma (CRC), pancreatic carcinoma, or non-small cell lung carcinoma (NSCLC) that is refractory to, intolerant of, for which no standard of therapy is available or where the patient refuses existing therapies.

Part A Expansion Cohorts, Part B and J Escalation, and Expansion Cohorts:

- Tumors with all histological diagnosis or tissue origin may be enrolled.
- Patients must have failed prior standard curative chemotherapy for their disease, refuse existing therapies, OR the proposed chemotherapy regimen to which AM0010 is added represents an acceptable standard treatment for their disease.

3. Measurable or evaluable disease according to irRC or bone metastatic disease evaluable by PCWG2 for patients with metastatic CRPC or according to tumor evaluation criteria best suitable and accepted for the tumor type evaluated.

4. Metastatic prostate cancer must also meet any of the following criteria for progressive metastatic disease according to PCWG2 criteria:

- a rise in PSA (minimal value 2 ng/mL; ≥ three consecutive rising values)
- transaxial imaging showing new measurable disease, or

- radionuclide bone scan (≥ 2 new metastases)

AND

- GnRH analog or antagonist treatment for the duration of the study (or orchiectomy) and
- serum testosterone < 50 ng/mL
- metastatic CRPC patients who are receiving an anti-androgen as part of their first-line hormonal therapy must have shown progression of disease off the anti-androgen prior to enrollment.

5. At least 18 years of age

6. ECOG Performance Status of 0 or 1

7. Life expectancy of > 16 weeks, in the opinion of the Investigator

8. Women of childbearing age must have a negative pregnancy test at study entry and bi-weekly / monthly thereafter. All patients of reproductive potential must practice an acceptable form of contraception (e.g., condom, diaphragm plus spermicide, or oral contraceptive) and have their partners agree to an additional barrier method of contraception for the duration of the study

9. Willingness and ability to comply with study requirements

10. Adequate organ function defined as follows:

Hematologic

- Platelets ≥ 100×10^9/L
  - Patients with Platelets < 100×10^9/L on Day 1 should confirm platelets > 50×10^9/L on Day 4 or 5
- Hemoglobin ≥ 9.0 g/dL (Part A, H, I), HGB ≥ 10 g/dL (Parts B – G, J)
- Absolute Neutrophil Count (ANC) ≥ 1.5 × 109/L

- PT/INR and PTT ≤ 1.5 × clinical laboratory upper limit of normal (clULN) and ≤ 2.5 × clULN if patient receives anti-coagulants

Hepatic

- AST/ALT ≤ 2.5 × clULN (if liver metastases are present, ≤ 5 × clULN)
- Alkaline phosphatase ≤ 2.0 × clULN (if liver or bone metastases are present, ≤ 5 × clULN)
- Total bilirubin ≤ 1.5 × clULN

Renal

- Serum creatinine < 2.0 mg/dL

11. Patients in expansion Cohort C must consent to providing:

    - Archival tumor tissue specimen and/or a fresh tumor biopsy to be collected prior to first dose (up to 10 days prior)

    AND

    - Fresh tumor biopsy at 8 weeks after the first study treatment (± 10 days of Cycle 4, Day 1)

6.2 Exclusion Criteria

Patients meeting any of the following criteria are not eligible for study participation:

1. History or evidence of clinically significant disorder, condition, or disease that, in the opinion of the Investigator and Lilly study team, would pose a risk to patient safety or interfere with the study evaluations, procedures, or completion

2. Hematologic malignancies (Part A Escalation cohorts only)

3. Pregnant or lactating

4. Present or history of immune mediated neurological disorders such as Multiple Sclerosis and Guillain-Barré or inflammatory CNS/PNS disorders

5. Myocardial infarction within the last 6 months prior to study Day 1, symptomatic congestive heart failure (New York Heart Association Classification > Class II), unstable angina, or unstable cardiac arrhythmia requiring medication
6. History of surgery within 28 days prior to study Day 1 or anticipated surgery during the study period
7. Systemic fungal, bacterial, viral, or other infection that is not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement) despite appropriate antibiotics or other treatment
8. Anti-tumor therapy (antibodies, chemotherapy, molecular targeted therapy, retinoid therapy, hormonal therapy) within 14 days prior to study Day 1 (six weeks for nitrosoureas, mitomycin C, and four weeks for molecular agents with $t_{½}$ > 10 days); (concurrent use of GnRH analog or antagonist for prostate cancer is permitted and required); Patients on anti-PD-1, continuing anti-PD-1 treatment in combination with AM0010 (Part H) can start receiving AM0010 anti-PD-1 combination without washout of the prior anti-PD-1 antibody.
9. Treatment with non-study immune modulators including, but not limited to, anti-CTLA4, anti-PD1, anti-PDL1, sipuleucel-T, cyclosporine and tacrolimus within 14 days prior to study Day 1 (four weeks for molecular agents with $t_{½}$ >10 days); Patients on anti-PD-1, continuing anti-PD-1 treatment in combination with AM0010 (Part H, I) can start receiving AM0010 anti-PD-1 combination without washout of the prior anti-PD-1 antibody.
10. Concurrent or prior (5 days or 5 half-lives of the anticoagulant prior AM0010 treatment) anticoagulation therapy; (low-dose warfarin [< 2 mg/day] or equivalent for prophylaxis against central venous catheter thrombosis is allowed). Patients with pancreatic or advanced biliary cancer are allowed to use short lived injectable or oral anticoagulants (half-life < 24 hours) for the prevention or treatment of thrombosis.
11. History of bleeding diathesis within the last 6 months prior to study Day 1
12. Patient with tumor that is infiltrating or invading a major blood vessel

13. Patients known to be positive for human immunodeficiency virus (HIV), hepatitis C, or hepatitis B virus; patients with hepatocellular cancer may be positive for HBV or HCV

14. Participation in an investigational drug or device trial within 30 days prior to study Day 1 or within 5 times the half-life of the investigational drug in the other clinical study, whichever is shorter, if known. Patients on anti-PD-1, continuing anti-PD-1 treatment in combination with AM0010 (Part H, I) can start receiving AM0010 anti-PD-1 combination without washout of the prior anti-PD-1 antibody.

15. Unavailable for follow-up assessment or concerns for patient's compliance with the protocol procedures

16. Any other condition that might reduce the chance of obtaining data required by the protocol or renders the patient at high risk for treatment complications.

7 PATIENT ENROLLMENT

All patients or legally acceptable representatives must personally sign and date and receive a copy of the informed consent form (ICF) before any study specific screening procedures are performed. Standard medical practice procedures (CT, MRI, physical exam, blood tests) performed within the specified screening period may be used for screening.

All patients who sign an informed consent will be identified by a unique patient number. This number will be used to identify the patient throughout the clinical study and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the entire clinical study.

A patient is considered enrolled when study medication is administered on Day 1.

7.1 Treatment Assignment

In the Dose Escalation Phase of Study Part A, B, and C, patients will be assigned sequentially into cohorts of up to six patients per cohort. In the first cohort of the Dose Escalation Phase for Part A only, a single patient will initially be enrolled to evaluate any unexpected adverse effects. Provided that there are no significant safety signals up to 24 hours post-dose, additional patients can be dosed. Remaining cohorts will not contain this sentinel provision. Three to six patients are planned for each cohort. However, a total of six patients will be enrolled in each cohort in the event that a DLT is observed in one of the first three patients during the DLT assessment period (28 days).

In the Expansion Phase of Study Part A, B, and C, patients will be assigned sequentially into cohorts of 15 patients per cohort. The first Expansion Cohort will be dosed up to the MTD defined in the Dose Escalation Phase as the highest dose level with an observed incidence of dose limiting toxicity (DLT) in less than or equal to 33% of patients of a cohort. Additional Expansion Cohorts may be enrolled based upon emerging safety, PK, pharmacodynamic data, and/or preliminary evidence of anti-tumor efficacy from the Dose Escalation Phase and the first Expansion Cohort.

Patient eligibility will be established at the conclusion of the screening evaluations. Once eligibility is confirmed, a site representative will complete and send a “Patient Enrollment

Request Form" to the sponsor. A sponsor representative will assign the patient to a cohort and assign the AM0010 dose level for that individual patient.

8 TREATMENT PROCEDURES

8.1 Investigational Product Dosage, Administration, and Schedule

AM0010 is provided by Lilly. AM0010 is a sterile, clear solution CCI [redacted].

The AM0010 dose will be assigned according to the table below based on the patient's weight at Screening. Doses denoted as 1, 2.5, 5, 10, 20, and 40 µg/kg in will be administered as flat doses from one of 2 dosing bands per level. These are either 0.1 or 0.125 mg (patients<80 kg or ≥80 kg) for the first dose level, denoted as 1 µg/kg; corresponding flat doses dependent on body weight for subsequent dose levels are 0.2 or 0.25 mg, 0.4 or 0.5 mg, 0.8 or 1 mg, 1.6 or 2 mg, and 3.2 or 4 mg.

CCI [redacted]

CCI [redacted]

The following SC doses of AM0010 are planned: 1, 2.5, 5, 10, 20, and 40 μg/kg for Part A and 2.5, 5, 10, 20, and 40 μg/kg in Part B through J. In the absence of DLTs and continued benefit, the dose may be further escalated, following a two-fold increase.

Patients will be treated with AM0010 administered SC at the research clinic by a qualified staff member in the morning on study Day 1. The Investigator or a qualified designee must be present during administration.

Patients will be trained to self-administer AM0010 and will self-administer the dose throughout the study.

The AM0010 dose should be administered every day in the morning with 24 hours (± 2 h) between doses, ideally with 24 hours (± 1 h) between doses.

Dosing and schedules of the chemotherapy regimens in Part B through H are described in Section 8.3.

The Documentation of the investigational product administration will be noted on the case report form (CRF) page and in the source documentation. The date, dose volume, and time of administration for each dose will be recorded in the patient diary and 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 Lilly.

8.2 Compliance in Investigational Product Administration

All study investigational product administration will occur under medical supervision or by the patient after proper instruction by medical personnel and must comply with protocol-specified criteria. Complete drug accountability records must be maintained. All records and undispensed supplies of the investigational product must be available for inspection during every monitoring visit for the conduct of AM0010 investigational product accountability.

8.3 Regimens for Combination Therapy

Immune- and chemotherapy agents 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. Immune- and chemotherapy regimens should be applied following the guidelines in the protocol or established institutional practices. Investigators or designees will review the subject's hematology and chemistry panels, liver function tests, and the incidence of hematologic and non-hematologic toxicities prior and during chemotherapy regimens.

8.3.1 Platinum / Taxane

Platinum / Taxane treatment will be continued for 6 cycles or until disease progression or unacceptable chemotherapy related toxicity following NCCN or ASCO guidelines. Patients will receive either Paclitaxel or Docetaxel in combination with either Carboplatin or Cisplatin. The selection of Paclitaxel vs. Docetaxel and Carboplatin vs. Cisplatin treatment will be made by the investigator following NCCN guidelines for the treatment of cancer by site (NCCN 2014) or ASCO guidelines (ASCO 2014). Prior to and during the initiation of treatment with either Carboplatin or Cisplatin and Paclitaxel or Docetaxel at the beginning of each treatment cycle, premedication may be given per the institution's standard for the prophylaxis of nausea, vomiting, and diarrhea or following the guidelines below.

For courses where Paclitaxel is administered, this regimen may include a standard oral dose of dexamethasone, an anti-histamine H1 (diphenhydramine 25 – 50 mg IVP or orally, or an equivalent dose of an alternate H1 blocker such as loratadine or fexofenadine) and a standard dose of antihistamine H2 IVP (such as cimetidine, ranitidine, or famotidine).

For all courses where Docetaxel is administered, this regimen may include a standard dose of dexamethasone for three days starting the night before each treatment (total dose, 24 mg/wk), and an anti-histamine H1 (diphenhydramine 25 – 50 mg IVP or orally, or an equivalent dose of an alternate H1 blocker such as loratadine or fexofenadine) one hour prior to Docetaxel.

AM0010 will be injected daily; on days with chemotherapy treatment, AM0010 will be applied prior to the chemotherapy schedule.

Platinum / Taxane combination repeats every 21 days (21 days = 1 cycle), Day 1.

- Paclitaxel 200 / 175 mg/m^2 IV,

or

- Docetaxel 75/65 mg/m^2 IV

And

- Carboplatin AUC6/5/4 (max. 6 x 150 mg) IV,

or

- Cisplatin 75 mg/m^2 IV.

After the last scheduled chemotherapy dose, dosing of AM0010 will continue. The dose level should be escalated stepwise to the RP2D for AM0010 monotherapy (20 μg/kg).

Table 11: Platinum / Taxane and AM0010

Agent	Dose	Volume	Route	Day	Schedule*
AM0010 (2 mg/mL)	Assigned Cohort Dose:	Patient weight 80 / ≥80 kg	SC	Daily	Continuous
	2.5 μg/kg	100 125 μL			
	5 μg/kg	200 250 μL			
	10 μg/kg	400 500 μL			
	20 μg/kg or	800 1000 μL			
	40 μg/kg (optional)	1600 2000 μL			
Followed by					
Paclitaxel	200 or 175 mg/m^2	500 mL 0.9% Sodium Chloride	IV over 3 hours	1	Q21 days
or Docetaxel	75 or 65 mg/m^2	250 mL 0.9% Sodium Chloride	IV over 1 hour	1	
Followed by					
Carboplatin	AUC 6 / 5 /4	500 mL 5% Glucose	IV, over 30 min	1	
or Cisplatin**	75 mg/m^2	2000 mL 5% Dextrose in 1/2 or 1/3 normal saline containing 37.5 g of mannitol	IV over 6 – 8 hours	1	

* If necessary to accommodate holidays, subject schedule, or other justifiable circumstance, the every 3-week schedule may be modified ± 2 days
** Chemotherapy dilution, pretreatment and post-treatment hydration should follow the manufacturer's prescribing information or established institutional practices.

If a patient's glomerular filtration rate (GFR) is estimated based on serum creatinine measurements by the IDMS method, FDA recommends that physicians consider capping the dose of Carboplatin for desired exposure (AUC) to avoid potential toxicity due to

overdosing. Based on the Calvert formula described in the Carboplatin label, the maximum doses can be calculated as:

Total Carboplatin Dose (mg) = (target AUC) x (GFR + 25) [Calvert formula]

Maximum Carboplatin Dose (mg) = target AUC (mg·min/mL) x (150 mL/min)

The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC = 6, the maximum dose is 6 x 150 = 900 mg
For a target AUC = 5, the maximum dose is 5 x 150 = 750 mg
For a target AUC = 4, the maximum dose is 4 x 150 = 600 mg

Investigators should adjust the Carboplatin dosing according to the above information to maximize the therapeutic benefit derived by the patient.

8.3.2 FOLFOX

FOLFOX treatment will be continued for 12 cycles or until disease progression or unacceptable chemotherapy related toxicity following NCCN or ASCO guidelines.

Detailed instruction for the FOLFOX4 or FOLFOX6 regimen are included below. FOLFOX6 can replace the FOLFOX4 regimen following the instructions in Table 12 or established institutional protocols.

Prior to and during the treatment with either Oxaliplatin or 5-FU at the beginning of each treatment cycle, premedication may be given per institution standard for the prophylaxis of nausea, vomiting, and diarrhea or following the guidelines below.

5-hydroxytryptamine-3 (5-HT3) antagonist (e.g. ondansetron or granisetron) and dexamethasone may be administered for the prophylaxis of nausea and vomiting. Dexamethasone (10 to 20 mg) may be administered as an IV bolus administered over 30 to 60 seconds.

AM0010 will be injected daily; on days with chemotherapy treatment, prior to the FOLFOX schedule.

FOLFOX4 (5-fluorouracil [5-FU], leucovorin [LV], and Oxaliplatin) every 2 weeks (14 days = 1 cycle) Day 1

- Oxaliplatin 85 mg/m^2 IV over 2 hours
- Leucovorin 200 mg/m^2 as a 2-hour IV,

followed by

- 5-FU 400 mg/m^2 IV bolus
- 5-FU 600 mg/m^2/day IV over 22 hours
- Leucovorin 200 mg/m^2 as a 2-hour IV on Day 2,

followed by

- 5-FU 400 mg/m^2 IV bolus and
- 5-FU 600 mg/m^2/day IV over 22 hours

Or

FOLFOX6 (5-fluorouracil [5-FU], leucovorin [LV], and Oxaliplatin) every 2 weeks (14 days = 1 cycle) Day 1

- Oxaliplatin 85 mg/m^2 IV over 2 hours
- Leucovorin 400 mg/m^2 as a 2-hour IV

followed by

- 5-FU 400 mg/m^2 IV bolus
- 5-FU 2400 mg/m^2/day IV over 46 hours

All medications should be applied following the manufacturers prescribing information, institutional guidelines, or the guidelines indicated below.

After the last scheduled chemotherapy dose, dosing of AM0010 will continue. The dose level should be stepwise escalated to the RP2D for AM0010 monotherapy (20 μg/kg).

Table 12: Oxaliplatin + 5-Fluorouracil/Leucovorin (FOLFOX4 Regimen) + AM0010

	Agent	Dose	Volume	Route	Day	Schedule
	AM0010 (2 mg/mL)	Assigned Cohort Dose:	Patient weight < 80 / ≥ 80 kg	SC	Daily	Continuous

	Agent	Dose	Volume	Route	Day	Schedule
		2.5 µg/kg 5 µg/kg 10 µg/kg 20 µg/kg or 40 µg/kg (optional)	100 125 µL 200 250 µL 400 500 µL 800 1000 µL 1600 2000 µL			
Followed by (on Day 1) FOLFOX4						Q14 days
FOLFOX4	Oxaliplatin, and	85 mg/m^2	250–500 mL 5% Dextrose	IV over 2 hours	1	
	Leucovorin	200 mg/m^2	5% Dextrose	IV over 2 hours	1	
	5-fluorouracil	400 mg/m^2		IV bolus over 2 to 4 min	1 (after leucovorin)	
	5-fluorouracil	600 mg/m^2	500 mL 5% Dextrose	IV, via an ambulatory infusion pump of choice over 22 hours	1 (after 5-fluorouracil bolus)	
	Followed by (on Day 2)					
	Leucovorin	200 mg/m^2	5% Dextrose	IV over 2 hours	2	
	5-fluorouracil	400 mg/m^2		IV bolus over 2 to 4 min	2 (after leucovorin)	
	5-fluorouracil	600 mg/m^2	500 mL 5% Dextrose	IV, via an ambulatory infusion pump of choice over 22 hours	2 (after 5-fluorouracil bolus)	

	Agent	Dose	Volume	Route	Day	Schedule
Or FOLFOX6 (on Day 1 / replacing FOLFOX4 day 1 and 2)						Q14 days
FOLFOX6	Oxaliplatin, and	85 mg/m^2	250 – 500 mL 5% Dextrose	IV over 2 hours	1	
	Leucovorin	400 mg/m^2	5% Dextrose	IV over 2 hours	1	
	5-fluorouracil	400 mg/m^2		IV bolus over 2 to 4 min	1 (after leucovorin)	
	5-fluorouracil	2400 mg/m^2	500 mL 5% Dextrose	IV, via an ambulatory infusion pump of choice over 46 hours	1 (after 5-fluorouracil bolus)	

8.3.3 Gemcitabine and nab-Paclitaxel

AM0010 will be injected daily; on days with chemotherapy treatment, prior to the chemotherapy infusion. Gemcitabine and nab-paclitaxel will be applied weekly for three weeks followed by one week dosing holiday every 28 days cycle (Von Hoff, Ervin et al. 2013).

Patients do not require premedication prior to nab-paclitaxel. Premedication prior to gemcitabine should follow recommended premedication strategies in the prescribing information or institutional practices.

Chemotherapy will be applied following manufacturers recommendations or established institutional procedures.

Table 13: Gemcitabine and nab-Paclitaxel + AM0010

Agent	Dose	Volume	Route	Day	Schedule*
AM0010 (2 mg/mL)	Assigned Cohort Dose: 5 µg/kg 10 µg/kg or 20 µg/kg	Patient weight <80 / >80 kg 200 250 µL 400 500 µL 800 1000 µL	SC	Daily	Continuous
Followed by					
Nab-paclitaxel	125 mg/m^2		IV over 30 – 40 minutes	1	Weekly x 3 followed by 1 week rest (=28 day cycle)
Followed by					
Gemcita-bine***	1000 mg/m^2		IV, over 30 min	1	

* If necessary to accommodate holidays, subject schedule, or other justifiable circumstance, the every 4-week schedule may be modified ± 2 days
** Pretreatment should follow the manufacturer's prescribing information or established institutional practices.

Patients may continue chemotherapy until they experience progressive disease or unacceptable toxicity, withdraw consent, or their physician feels it is no longer in their best interest to continue the treatment.

After discontinuation of the chemotherapy regimen, patients may continue with AM0010 monotherapy until confirmed irPD. Patients may continue to receive AM0010 after confirmed irPD in the absence of clinical deterioration and if the investigator considers that the patient continues to receive benefit from the treatment.

8.3.4 Capecitabine

AM0010 will be injected daily; on days with chemotherapy treatment, prior to the chemotherapy. Capecitabine will be dosed twice daily for two weeks, followed by one week rest for every 21 days cycle (Cartwright, Cohn et al. 2002).

Chemotherapy will be applied following manufacturer's recommendations or established institutional procedures.

Table 14: Capecitabine + AM0010

Agent	Dose	Volume	Route	Day	Schedule*
AM0010 (2 mg/mL)	Assigned Cohort Dose: 10 μg/kg or 20 μg/kg	Patient weight < 80 / ≥ 80 kg 400 500 μL 800 1000 μL	SC	Daily	Continuous
Followed by					
Capecitabine*	1000 mg/m^2	NA	po	q2d	2 weeks followed by 1 week rest (= 21 day cycle)

* If necessary to accommodate holidays, subject schedule, or other justifiable circumstance, the every 3-week schedule may be modified ± 2 days

Patients may continue chemotherapy until they experience progressive disease or unacceptable toxicity, withdraw consent, or their physician feels it is no longer in their best interest to continue the treatment.

After discontinuation of the chemotherapy regimen, patients may continue with AM0010 monotherapy until confirmed irPD. Patients may continue to receive AM0010 after confirmed irPD in the absence of clinical deterioration and if the investigator considers that the patient continues to receive benefit from the treatment.

8.3.5 Paclitaxel

AM0010 will be injected daily; on days with chemotherapy treatment, prior to the chemotherapy infusion. Paclitaxel will be applied weekly for three weeks followed by one week dosing holiday every 28 days cycle (Wilke, Muro et al. 2014).

Chemotherapy will be applied following manufacturer's recommendations or established institutional procedures.

Table 15: Weekly Paclitaxel + AM0010

Agent	Dose	Volume	Route	Day	Schedule*
AM0010 (2 mg/mL)	Assigned Cohort Dose: 10 μg/kg or 20 μg/kg	Patient weight < 80 / ≥ 80 kg 400 500 μL 800 1000 μL	SC	Daily	Continuous
Followed by					
Paclitaxel	80 mg/m^2	500 mL 0.9% Sodium Chloride	IV over 3 hours	1	Weekly x 3 followed by 1 week rest (= 28 day cycle)

* If necessary to accommodate holidays, subject schedule, or other justifiable circumstance, the every 4-week schedule may be modified ± 2 days

Patients may continue chemotherapy until they experience progressive disease or unacceptable toxicity, withdraw consent, or their physician feels it is no longer in their best interest to continue the treatment.

After discontinuation of the chemotherapy regimen, patients may continue with AM0010 monotherapy until confirmed irPD. Patients may continue to receive AM0010 after confirmed irPD in the absence of clinical deterioration and if the investigator considers that the patient continues to receive benefit from the treatment.

8.3.6 Pazopanib

AM0010 will be injected daily; on days with pazopanib treatment, prior to the pazopanib application. Pazopanib will be taken daily throughout the study (Hainsworth, Rubin et al. 2013).

Pazopanib will be applied following manufacturers recommendations or established institutional procedures.

Table 16: Pazopanib + AM0010

Agent	Dose	Volume	Route	Day	Schedule*
AM0010 (2 mg/mL)	Assigned Cohort Dose: 10 μg/kg or 20 μg/kg	Patient weight < 80 / ≥ 80 kg 400 500 μL 800 1000 μL	SC	Daily	Continuous
Followed by					
Pazopanib	800 mg	NA	PO	Daily	QD 1h prior or 2h post breakfast; continuous

* If necessary to accommodate holidays, subject schedule, or other justifiable circumstance, the every 4-week schedule may be modified ± 2 days

Patients may continue pazopanib until they experience progressive disease or unacceptable toxicity, withdraw consent, or their physician feels it is no longer in their best interest to continue the treatment.

After discontinuation of pazopanib, patients may continue with AM0010 monotherapy until confirmed irPD. Patients may continue to receive AM0010 after confirmed irPD in the absence of clinical deterioration and if the investigator considers that the patient continues to receive benefit from the treatment.

8.3.7 PD1 Immune Checkpoint Antagonist – Pembrolizumab

AM0010 will be injected daily; on days with PD1 antagonist treatment, AM0010 will be injected prior to the PD1 antagonist infusion.

Pembrolizumab will be injected every three weeks (Hamid, Robert et al. 2013).

The PD1 antagonist will be applied following manufacturer's recommendations or can follow established institutional procedures.

Application of PD1 blocking antibody (pembrolizumab): 2 mg/kg bolus IV infusion over 30 minutes following the prescribing information; repeat every three weeks until disease progression. Patients may continue with PD1 antagonist if the patient continues to derive benefit from the treatment.

Table 17: Pembrolizumab + AM0010

Agent	Dose	Volume	Route	Day	Schedule*
AM0010 (2 mg/mL)	Assigned Cohort Dose: 10 μg/kg or 20 μg/kg	Patient weight <80 / ≥80 kg 400 500 μL 800 1000 μL	SC	Daily	Continuous
Followed by					
Keytruda	2 mg/kg	in 0.9% NaCl	IV	Day 1	Q21D

* If necessary to accommodate holidays, subject schedule, or other justifiable circumstance, the every 3-week schedule may be modified ± 2 days

After discontinuation of the PD1 antagonist, patients may continue with AM0010 monotherapy until confirmed irPD. Patients may continue to receive AM0010 after confirmed irPD in the absence of clinical deterioration and if the investigator considers that the patient continues to receive benefit from the treatment.

8.3.8 PD1 Immune Checkpoint Antagonist – Nivolumab

AM0010 will be injected daily; on days with PD1 antagonist treatment, AM0010 will be injected prior to the PD1 antagonist infusion.

Nivolumab will be injected every two weeks following manufacturer's recommendations or following established institutional procedures.

Application of PD1 blocking antibody (nivolumab): 3 mg/kg bolus IV infusion over 60 minutes following the prescribing information; repeat every two weeks until disease progression. Patients may continue with nivolumab if the patient continues to derive benefit from the treatment.

Table 18: Nivolumab + AM0010

Agent	Dose	Volume	Route	Day	Schedule*
AM0010 (2 mg/mL)	Assigned Cohort Dose: 20 μg/kg	Patient weight <80 / ≥80 kg 800 1000 μL	SC	Daily	Continuous
Followed by					
Opdivo	3 mg/kg	in 0.9% NaCl	IV	Day 1	Q15D

* If necessary to accommodate holidays, subject schedule, or other justifiable circumstance, the every 2-week schedule may be modified ± 2 days

After discontinuation of Nivolumab, patients may continue with AM0010 monotherapy until confirmed irPD. Patients may continue to receive AM0010 after confirmed irPD in the absence of clinical deterioration and if the investigator considers that the patient continues to receive benefit from the treatment.

8.3.9 Gemcitabine and Carboplatin

AM0010 will be injected daily; on days with chemotherapy treatment, prior to the chemotherapy infusion. Gemcitabine and Carboplatin will be applied on Days 1 and 8 for every 21 days cycle (O'Shaughnessy, Osborne et al. 2011).

Premedication prior to gemcitabine or carboplatin should follow recommended premedication strategies in the prescribing information or institutional practices.

Chemotherapy will be applied following manufacturers recommendations or established institutional procedures.

Table 19: Gemcitabine and Carboplatin + AM0010

Agent	Dose	Volume	Route	Day	Schedule*
AM0010 (2 mg/mL)	Assigned Cohort Dose: 10 µg/kg or	Patient weight <80 / >80 kg 400 500 µL	SC	Daily	Continuous
	20 µg/kg	800 1000 µL			
Followed by					
Gemcita-bine**	500 mg/m^2		IV, over 30 min	1, 8	Day 1 and 8 of each 21 day cycle
Followed by					
Carboplatin**	AUC2		IV over 60 min.	1, 8	

* If necessary to accommodate holidays, subject schedule, or other justifiable circumstance, the every 3-week schedule may be modified ± 2 days
** Pretreatment should follow the manufacturer's prescribing information or established institutional practices.

Patients may continue chemotherapy until they experience progressive disease or unacceptable toxicity, withdraw consent, or their physician feels it is no longer in their best interest to continue the treatment.

After discontinuation of the chemotherapy regimen, patients may continue with AM0010 monotherapy until confirmed irPD. The dose level should be escalated stepwise to the RP2D for AM0010 monotherapy (20 µg/kg). Patients may continue to receive AM0010 after confirmed irPD in the absence of clinical deterioration and if the investigator considers that the patient continues to receive benefit from the treatment.

8.4 Dose Escalation, MTD Determination, and Stopping Rules

In the Dose Escalation Phase of the study of Study Part A – J, patients will be assigned sequentially into cohorts of up to six patients in each cohort. Three to six patients will initially be enrolled in each cohort for DLT observation. A total of six patients will be enrolled in a cohort in the event that a DLT is observed in one of the first three patients and/or additional safety, PK, or pharmacodynamic data are needed.

8.4.1 Determination of the MTD

The DLT assessment window is 28 days. In the absence of DLTs, patients continue consecutive treatment.

To understand and safeguard against potential cumulative toxicities, the study team will continue to monitor the occurrence of study drug related SAEs and AEs throughout the treatment period and during potential treatment extensions to allow for dose correction in the event of cumulative immune mediated toxicities.

8.4.2 Dose Escalation and Stopping Rules

The decision to proceed to the next dose level will be made after the first three patients in a cohort have completed 28 days of dosing. Upon reviewing the safety data, the decision to proceed to the next dose level will be made by Lilly in conjunction with the Investigators after careful consideration and review of all available safety and laboratory findings.

Dose escalation decisions will be made in accordance with a standard 3 + 3 design using the rules below:

1. If the first 3 patients of a cohort do not experience an AM0010-related DLT for 28 days, then dose escalation to the next higher dose cohort will occur.

2. If one of the initial 3 patients of a cohort experience an AM0010-related DLT during the DLT assessment window (28 days), then a total of six patients will be enrolled in the cohort. If $\leq$ 33% of those six patients experience DLTs in 28 days, then dose escalation to the next higher dose level cohort will occur.

3. If more than 33% of the patients experience AM0010-related DLTs in one cohort during the DLT assessment window (28 days), the dose escalation to the next higher dose level will NOT occur.

Dose escalation will occur at the planned dose levels until the MTD is determined. The MTD is defined as the highest dose level with an observed incidence of DLT in ≤ 33% of patients enrolled in a dose escalation cohort (see Section 8.4.1). The recommended Phase 2 dose (RP2D) will be based on safety and preliminary efficacy data from the dose escalation and dose expansion cohorts.

If a DLT occurs in a cohort with 3 patients after Day 28, 3 additional patients will be enrolled in that cohort. The MTD determination for a treatment duration (e.g., X consecutive treatment cycles) will follow the procedure outlined in Section 8.4.2 for one cycle. If DLTs occur in more than 33% of a cohort for a treatment duration, the MTD for this number of treatment cycles will be the highest dose tolerated safely for this treatment duration.

8.4.3 Immune Related Adverse Events and Dose Limiting Toxicity – Definitions (DLT)

AM0010 may induce immune-related adverse events (irAE). Together with supportive medical treatment, dose reductions and dose interruptions will be used to temporarily reduce the exposure to AM0010 in the event of irAEs. To maximize safety monitoring of the study drugs, and minimize premature termination of dosing due to potential toxicities of AM0010, all adverse events (whether these are suspected to be adverse events or irAEs) will be reported in the eCRFs and reviewed by the Medical Monitor or Clinical Operations.

AM0010 related transient Grade 3 and 4 immune mediated toxicities, Grade 3 and 4 anemia, or Grade 3 and 4 thrombocytopenia will not be adjudicated as DLT if they resolve to ≤ Grade 1 or study baseline within three weeks with supportive treatment, dose reductions, or the interruption of dosing. Patients experiencing Grade 3 and 4 anemia or Grade 3 and 4 thrombocytopenia related to the AM0010 will not receive additional doses of AM0010 until the AE is alleviated to ≤ Grade 1 or study baseline. Patients may receive supportive treatment for the anemia or thrombocytopenia.

Patients in Part A, H, and I requiring more than three transfusions of blood or blood products in a month due to AM0010 related toxicity will not be allowed to receive additional treatment with AM0010. However, if the medical monitor and investigator/treating physician feel a patient in Parts A, H, or I is receiving benefit from the treatment, then they may be allowed to continue on the study after requiring more than 3 transfusions within a month.

The occurrence of hematological toxicity in Part B, C, D, E, G, and J of the protocol should be managed by the investigator as appropriate for best clinical practice (growth factor, transfusions), if possible without interruption in study drug or change in dose. However, growth factors must be discontinued once the AE has recovered to Grade 1 or better. They may be resumed if the leukopenia/anemia develop again and discontinued once it recovers.

Packaged red blood cells to treat the metastatic disease or toxicities related to therapy are allowed.

A DLT is defined as any not transient Grade 3 or higher hematological toxicity and any not transient Grade 3 or higher non-hematologic toxicity considered related to AM0010. For determination of the relatedness of a toxicity to the study drug, consult Section 11.2.

Grade 3 adverse event of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor will not be adjudicated as DLT.

The assessment of DLT will follow the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.02. These criteria are available online at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae_4_with_lay_terms.pdf

If an AE is not specified in the CTCAE, the severity grading of the AE should be recorded and graded as follows:

- **Mild (Grade 1):** Awareness of signs or symptoms, but easily tolerated
- **Moderate (Grade 2):** Discomfort sufficient to cause interference with usual activities
- **Severe (Grade 3 or 4):** Incapacitation with inability to work or perform usual activities.

Grade 5 (death) is an outcome and will not be recorded as a severity.

Guidelines for Treatment of Injection Site Reactions

Injection site reactions will be judged using the following grading system (adapted to cancer patient care from the FDA Guidance document “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, 2007” and the CTCAE 4.03)

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours and interferes with	Any use of narcotic pain reliever and limiting self-care	Requires operative intervention or hospitalization

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
		instrumental ADL***	ADL****	
Tenderness	Mild discomfort to touch	Discomfort with movement and interferes with instrumental ADL	Significant discomfort at rest and limiting self-care ADL	Requires operative intervention or hospitalization
Erythema/ Redness *	> 2.5 cm	> 5 cm and interferes with instrumental ADL	> 10 cm and limiting self-care ADL	Necrosis or exfoliative dermatitis
Induration/ Swelling **	> 2.5 cm and does not interfere with daily activity	> 5 cm or interferes with instrumental ADL	> 10 cm and limiting self-care ADL	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded, if the size of the lesion increases with continuous injections.
** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.
Activities of Daily Living (ADL) following CTCAE 4.03
*** Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.4.4 Intra-Patient Dose Escalation

Intra-patient dose escalation is permitted for patients who have completed 91 days at their assigned dose level. Patients may be escalated one dose level every 28 days, up to the highest AM0010 dose level which has been proven tolerable (Section 8.4.2).

If AM0010 is not tolerated at the increased dose level, the dose will be de-escalated one dose level and the patient may continue on study at that dose level.

If a patient after initial dose reduction continues to tolerate the reduced dose level well, the investigator may re-escalate AM0010 to the previous or original dose level.

8.5 Dosage Adjustments

If one or several drugs in a regimen are temporarily halted, dosing of the remaining drugs in the regimen may continue. In the absence of AM0010 related AEs, AM0010 dosing may continue, even if the chemotherapy regimen is halted. If drug treatment is on hold, the

current cycle will be elongated. The start of a new treatment cycle is marked by the re-introduction of all drugs which are not permanently discontinued.

8.5.1 Dose Reductions and Dose Interruptions – AM0010 Monotherapy

Table 20: Dose Modification Guidelines for AM0010 Monotherapy

Event	AM0010 Modifications in Monotherapy Cohorts
Anemia G3/4 (HGB< 8 g/dL) and/or thrombocytopenia G3/4 (< 50 k/mm^3) (1st occurrence)	Hold until return to baseline or Grade 1 Restart at original dose (100%)
Anemia G3/4 (HGB < 8 g/dL) and/or thrombocytopenia G3/4 (< 50 k/mm^3) (2nd occurrence)	Hold until return to baseline or Grade 1 Restart one dose level lower (50%) If thrombocytes > 100 k/mm^3 for ≥ 7 days, increase to 100%
Anemia G3/4 (HGB < 8 g/dL) and/or thrombocytopenia G3/4 (< 50 k/mm^3) (3rd occurrence)	Hold until return to baseline or Grade 1 Restart two dose level lower (at 25 %) If thrombocytes ≥ 100 k/mm^3 for ≥ 7 days, increase to 50%, subsequently to 100%
Low G2 anemia (HGB < 9 g/dL) or G2 thrombocytopenia (< 75 k/mm^3) for > 8 days	Reduce one dose level If thrombocytes ≥ 100 k/mm^3 or HGB > 10 g/dL for ≥ 7 days, increase to 100%

A patient experiencing a DLT related to AM0010 will not receive additional AM0010 treatment and will be followed until resolution of toxicity. The decision regarding individual subject management with respect to study therapy will be based on ongoing assessment of benefit/risk and in consultation with the Investigators and the Sponsor. Patients withdrawn or withheld from AM0010 treatment will be treated as deemed appropriate by the Investigator and the Sponsor after reviewing all available safety data.

Patients experiencing ≥ Grade 3 anemia or ≥ Grade 3 thrombocytopenia related to the AM0010 will not receive additional doses of AM0010 until the AE is alleviated to ≤ Grade 1 or to study baseline, whichever is lower. Patients may receive supportive treatment for the anemia or thrombocytopenia; however, patients in Part A which require within one month more than three transfusions of blood or blood products due to AM0010 related toxicity will not be allowed to receive additional treatment with AM0010. Packaged red blood cells to treat the metastatic disease or toxicities related to prior therapy are allowed.

After resolution of an AM0010 related hematologic toxicity ≥ Grade 3, the patient will first be re-started at the original dose of AM0010. Upon re-occurrence of the adverse event, the

patient will be re-started at one dose escalation step lower and after the third re-occurrence at two dose escalation steps lower. Upon the fourth re-occurrence of the toxicity in a patient dosed at 25% of the original dose, the patient should no longer receive AM0010. However, if the medical monitor and investigator/treating physician feel a patient in Parts A, H, or I is receiving benefit from the treatment, then they may be allowed to continue on the study. If a patient after initial dose reduction continues to tolerate the reduced dose level well, the investigator may, after consulting with the medical monitor, re-escalate AM0010 to the previous or original dose level.

A patient experiencing an AM0010 related AE requiring dose interruptions for more than 4 weeks and without established clinical benefit will not be allowed to receive additional treatment with AM0010.

If a patient experiences Grade 3 or higher toxicities or SAEs that are not considered related to AM0010, AM0010 treatment can be postponed until the toxicity is resolved to Grade 1 (as defined by the CTCAE, v 4.02), mild (as defined in Section 8.4), or returns to the patient's baseline value. Patients requiring > 4 weeks to recover from unrelated Grade 3 or higher toxicities will be discussed by Lilly and the Investigator on a case-by-case basis to determine continued eligibility. If the patient is withdrawn, EOT procedures should be performed and the appropriate CRFs should be completed.

An unscheduled or scheduled interruption of AM0010 dosing should be recorded in the eCRF. If a scheduled dosing is delayed > 1 day, it will be considered a missed dose, and the patient will proceed to the next scheduled dosing. A missed dose will not be made up.

AM0010 dosing should be interrupted for scheduled surgery 3 days prior and 1 week post-surgery.

No intra-patient dose adjustments will be allowed other than described in Section 8.5.1.

8.5.2 Dose Adjustment AM0010 in Combination Regimens

The dosing for patients experiencing G3/4 AEs in cohorts with AM0010 – chemotherapy combination (B, C, E – G, and J) should be modified, following the schedule below:

Table 21: Dose Adjustments and Modifications for Part B, C, E -- G, J

Event	Chemotherapy Modification in Next Cycle	AM0010 Modification
G3/4 AE, including anemia (HGB < 8 g/dL) and/or platelet counts (< 50 k/mm^3) (1st occurrence)	Reduce one dose level (to 80%)	Hold until return to baseline or Grade 1 Restart at original dose
G3/4 AE, including anemia (HGB < 8 g/dL) and/or platelet counts (< 50 k/mm^3) (2nd occurrence)	Reduce 2 dose levels (to 50%)	Hold until return to baseline or Grade 1 Restart at original dose
G3/4 AE, including anemia (HGB < 8 g/dL) and/or platelet counts (< 50 k/mm^3) (3rd occurrence)	Keep at 50%	Hold until return to baseline or Grade 1 Restart at one dose level reduced
Low G2 AE, anemia (HGB < 9 g/dL) or platelet counts (< 75 k/mm^3) for > 8 days	No reduction	Reduce one dose level Restart at original dose level when AE returns to G1 or baseline

8.5.2.1 Dose Adjustments and Modifications for AM0010 – Part D

Table 22: Dose Level Reductions for Abraxane, Gemcitabine and AM0010 – Part D

Dose Level	Abraxane (mg/m^2)	Gemcitabine (mg/m^2)	AM0010
Full dose	125	1000	
1st dose reduction	100	800	50% of original
2nd dose reduction	75	600	25% of original
3rd dose reduction	60	500	No further reduction
If additional dose reduction required	Discontinue	Discontinue	

Table 23: Dose Adjustments and Modifications for Neutropenia and/or Thrombocytopenia – Part D – at the Start of a Cycle or within a Cycle

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	Abraxane / Gemcitabine	AM0010 (Dose Reduce AM0010 Only for Platelet Counts)
Cycle 1					
Day 1	< 1500	OR	< 100,000	Delay doses until recovery (≤22 days)	Delay doses until recovery (≤ 22 days)
Day 8	500 to < 1000	OR	50000 to < 75,000	Reduce 1 dose level	No change

	<500	OR	< 50,000	Withhold doses	Withhold doses
Day 15	If Day 8 doses were reduced or given without modification:				
	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8	No change
	< 500	OR	< 50,000	Withhold doses	Withhold dose
Day 15	If Day 8 doses were withheld:				
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1	No change
	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1	Reduce one dose level
	< 500	OR	< 50,000	Withhold doses	Withhold doses
Subsequent Cycles – Restart at last used dose level					
Day 1	< 1500	OR	< 100,000	Delay doses until recovery (≤ 22 days)	Delay doses until recovery (≤ 22 days)
Day 8	500 to < 1000	OR	50000 to < 75,000	Reduce 1 dose level	No change
	<500	OR	< 50,000	Withhold doses	Withhold doses
Day 15:	If Day 8 doses were reduced or given without modification:				
	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8*	No change
	< 500	OR	< 50,000	Withhold doses	Withhold doses
Day 15:	If Day 8 doses were withheld:				
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1*	No change
	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1*	Reduce one dose level
	< 500	OR	< 50,000	Withhold doses	Withhold doses

* If at the lowest dose level, patient can continue therapy at the same dose if in the best interest of the patient

In general, growth factors (GCSF, Erythropoietin) are not recommended in favor of dose reduction. However, in specific cases after discussion with the sponsor, growth factors can be used following ASCO guidelines

Table 24: Dose Adjustments and Modifications for Other Adverse Drug Reactions (Aside from Neutropenia and Thrombocytopenia) – Part D

Adverse Drug Reaction	Abraxane	Gemcitabine	AM0010
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC > 1500 Resume at next lower dose level		Withhold until AE improves to ≥ Grade 1; Resume at original dose
Peripheral Neuropathy: Grade 3 or 4	Withhold until improves to Grade 1; resume at next lower dose level	No dose reduction	

Cutaneous Toxicity: Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity : Grade 3 mucositis or diarrhea	Withhold until improves to Grade 1; Resume at next lower dose level	

If a patient, after initial dose reduction of AM0010, continues to tolerate the reduced dose level well, the investigator may, after consulting with the medical monitor, re-escalate AM0010 to the previous or the original dose level.

8.5.3 Dose Adjustment Part B

Patients should be closely monitored for Carboplatin/Cisplatin and/or Paclitaxel/Docetaxel induced toxicities. The dose regimens may be adjusted depending on the patient's tolerance following standard practice and the prescribing information.

In the case of chemotherapy induced toxicities, subsequent chemotherapy cycles should be delayed until the ANC is >1.5 x 10^9/L, thrombocytes > 100 x 10^9/L, skin toxicity or diarrhea ≤ 1. Treatment with AM0010 should continue as a monotherapy.

In the case of the occurrence of febrile neutropenia or Grade 4 neutropenia lasting longer than 7 days, the following dose reductions will be initiated:

- Reduction of Carboplatin by one AUC
- Reduction of Docetaxel, Paclitaxel, or Cisplatin by one dose level

Uncomplicated and shorter neutropenia will not lead to dose reductions in the chemotherapy.

In the case of chemotherapy induced neurotoxicity > 2 or other major organ toxicity > 2, chemotherapy should be halted.

In case of the interruption or discontinuation of one of the chemotherapy arms due to toxicity, treatment with the other chemotherapy may continue. In case of the interruption or discontinuation of chemotherapy arms treatment with AM0010 should continue.

8.5.3.1 Paclitaxel / Docetaxel Hypersensitivity Reaction

In case of moderate hypersensitivity symptoms (moderate rash, dyspnea, mild chest discomfort or mild hypotension), Paclitaxel/Docetaxel infusion will be stopped and IV antihistamines and IV dexamethasone (10 mg) will be given. Paclitaxel/Docetaxel infusion may be continued at lower speed after symptoms reside.

In case of severe hypersensitivity symptoms (respiratory distress or hypotension requiring treatment, generalized urticarial or angioedema), Paclitaxel/Docetaxel infusion will be stopped and IV antihistamines and dexamethasone will be given as above. Epinephrine or bronchodilators may be given, if indicated.

Treatment with AM0010 should continue as a monotherapy.

8.5.3.2 Cardiac Toxicity

In case of asymptomatic bradycardia, isolated and asymptomatic ventricular extrasystoles, or a first degree AV block, chemotherapy will continue under continuous cardiac monitoring.

In case of symptomatic arrhythmia or AV block (except 1^{st} degree) or other heart block, paclitaxel/docetaxel will be discontinued; manage arrhythmia according to standard practice.

Treatment with AM0010 should continue as a monotherapy.

8.5.4 Dose Adjustments Part C

Subjects should be closely monitored for FOLFOX4 toxicity, and the doses of Oxaliplatin and 5-FU may be adjusted depending on the patient's tolerance following standard practice and the prescribing information.

FOLFOX4 cycles are repeated every two weeks. However, the introduction of a new cycle will be delayed for up to 4 weeks in the presence of the following toxicities: ANC < 1.5 x 10^9/L, thrombocytes below 75 x 10^9/L, fatigue > 2, stomatitis, skin toxicity, or diarrhea > 1.

In the event of a toxicity caused delay in the FOLFOX4 cycle, all component of FOLFOX4 are delayed. Treatment with AM0010 should continue as a monotherapy.

For patients experiencing persistent Grade 2 neurosensory events (following CTCAE) Oxaliplatin may be reduced to 75 mg/m^2. For patients experiencing persistent Grade 3 neurosensory events, Oxaliplatin therapy should be discontinued. When neurosensory events are reduced in severity to less than Grade 2, patients may be restarted on Oxaliplatin at a later cycle following NCCN guidelines Version 3.2014 – Colon Cancer.

In the event of Oxaliplatin interruption due to Oxaliplatin related toxicity, 5-FU/Leucovorin and AM0010 therapy should continue.

8.5.5 Dose Adjustments Part D

Doses of Gemcitabine and nab-paclitaxel will be reduced for hematological and other toxicities following Section 8.5.2.1. Two levels of dose reductions to 80% and 50% of the full dose are permitted. Dosing delays of the chemotherapy for up to 21 days are permitted.

8.5.6 Dose Adjustments Part E

Doses of capecitabine will be reduced to 80% of the capecitabine dose with the second occurrence of a Grade 2 or the first occurrence of Grade 3 toxicity in a patient. Capecitabine dose will be reduced to 50% with the re-occurrence of Grade 3 toxicity.

8.5.7 Dose Adjustments Part F

Doses of paclitaxel will be reduced to 80% in the following cycle when Grade 4 hematopoietic or Grade 3 non-hematopoietic toxicities occur (Wilke, Muro et al. 2014). Doses of paclitaxel will be reduced to 50% on re-occurrence of a $\geq$ G3 toxicity.

8.5.8 Dose Adjustments Part G

Dosing of pazopanib will be interrupted when Grade 3 or 4 toxicities are observed. Dosing will restart at 400 mg when the toxicity improves to Grade 1 or baseline, whichever is lower (Hainsworth, Rubin et al. 2013).

8.5.9 Dose Adjustments Part H

Dose interruptions for pembrolizumab will follow the prescribing information and Table 25.

Table 25: Dose Modification for immune related AEs – Part H

Keytruda			
Immune Mediated Adverse Event	**Grade 2**	**Grade 3**	**Grade 4**
Immune mediated Pneumonitis	Withhold	Discontinue	Discontinue
Immune mediated Colitis	Withhold	Withhold	Discontinue
Immune mediated Hepatitis	Withhold	Discontinue	Discontinue
Immune mediated Hypophysitis	Withhold	Withhold/discontinue	Discontinue
Immune mediated Nephritis	Withhold	Discontinue	Discontinue
Immune mediated Hyperthyroidism / Hypothyroidism		Withhold	Discontinue
Other immune mediated clinically significant AE (exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures, myasthenic syndrome, optic neuritis, and rhabdomyolysis)	Withhold	Withhold / discontinue	Discontinue
AM0010			
Immune Mediated Adverse Event	**Grade 2**	**Grade 3**	**Grade 4**
All clinically significant immune related AEs		Withhold AM0010 until AE $\leq$ Grade 1 or baseline; Restart at original dose at first occurrence, dose reduce to 50% after the second occurrence, dose reduce to 25% after the third occurrence	
Corticosteroid Use – Restart with Keytruda / AM0010			
Suspected clinically significant immune-mediated adverse event (except thrombocytopenia and anemia)	Treat with high dose corticosteroids $\geq$ 40 mg prednisone per day. When AE $\leq$ Grade 1, initiate taper over at least two weeks. • Restart Keytruda and AM0010 if AE returns $\leq$ Grade 1. • If AE recurs: permanently discontinue Keytruda, withhold AM0010 • Repeat corticosteroid treatment • if AE returns $\leq$ Grade 1, restart AM0010 at original dose • if AE recurs: discontinue AM0010		

8.5.10 Dose Adjustments Part I

Dose interruption or discontinuation of nivolumab follows the prescribing information:

Withhold nivolumab for any of the following:

- Grade 2 pneumonitis
- Grade 2 or 3 colitis
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times clULN or total bilirubin greater than 1.5 and up to 3 times clULN
- Creatinine greater than 1.5 and up to 6 times clULN or greater than 1.5 times baseline
- Any other severe or Grade 3 treatment-related adverse reactions
- Resume nivolumab in patients whose adverse reactions recover to Grade 0 – 1.

Permanently discontinue nivolumab for any of the following:

- Any life-threatening or Grade 4 adverse reaction
- Grade 3 or 4 pneumonitis
- Grade 4 colitis
- AST or ALT greater than 5 times clULN or total bilirubin greater than 3 times clULN
- Creatinine greater than 6 times clULN
- Any severe or Grade 3 treatment-related adverse reaction that recurs
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks

Withhold AM0010 for all clinically significant immune related AEs ≥ Grade 3 until the AE is ≤ Grade 1 or baseline. Restart AM0010 at original dose at first occurrence, dose reduce to 50% after the second occurrence, dose reduce to 25% after the third occurrence.

8.5.11 Dose Adjustments Part J

Patients should be closely monitored for Carboplatin/Gemcitabine related toxicities. The dose regimens may be adjusted depending on the patient's tolerance following standard practice, Table 21, and the prescribing information.

In the case of chemotherapy induced toxicities, subsequent chemotherapy cycles should be delayed until the ANC is > 1.5 x 10^9/L, thrombocytes > 100 x 10^9/L, skin toxicity or diarrhea ≤ 1. Treatment with AM0010 should continue as a monotherapy.

In the case of the occurrence of febrile neutropenia or Grade 4 neutropenia lasting longer than 7 days, the following dose reductions will be initiated:

- Reduction of Carboplatin by one AUC
- Reduction of Gemcitabine by 20%

Uncomplicated and shorter neutropenia will not lead to dose reductions in the chemotherapy.

In the case of carboplatin related neurotoxicity > 2 or other major organ toxicity > 2, carboplatin chemotherapy should be halted.

In case of the interruption or discontinuation of one of the chemotherapy arms due to toxicity, treatment with the other chemotherapy may continue. In case of the interruption or discontinuation of chemotherapy arms, treatment with AM0010 should continue.

8.5.12 General Guidelines for Hematotoxicity

For subjects with serious neutropenic complications, such as febrile neutropenia, sepsis syndrome, or fungal infections, granulocyte-colony-stimulating factor (G-CSF) should be used according to the prescribing information or treatment guidelines.

AM0010 mediated reduction of HGB may be caused by a reduction of available serum iron. Iron supplements may therefore be effective to mitigate the HGB reduction.

Chemotherapy induced anemia > Grade 2 may be treated with erythropoietin or transfusion of blood or blood products according to the prescribing information or treatment guidelines.

Recurrent non-transient (> 1 week) Grade 4 thrombocytopenia may be treated with thrombopoietic medications.

8.6 Concomitant Therapy

8.6.1 Prostate Cancer Patients

Prostate cancer patients should continue androgen deprivation therapy (GnRH analogs or antagonists) during the study. Throughout the study, the Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate medical care, including steroid replacement doses. Any use of concomitant therapy or treatments will be recorded in the applicable CRF.

8.7 Excluded Therapy

During the course of the clinical trial, study patients are anticipated to continue the use of prescribed medications, identified during the screening procedures, consistent with study inclusion and exclusion criteria. Other concomitant medication use is not planned within this study except for medication to treat adverse effects.

The following therapies are not permitted during the trial (if administered, the patient may be removed from the trial):

- Any non-study anti-cancer therapy (other than androgen deprivation therapy in metastatic CRPC)
- Non-study immunotherapy (except approved systemic corticosteroids for the treatment of irAE, AE or SAE or for steroid replacement therapy (up to 20 mg/m^2/day hydrocortisone equivalent) or steroid treatment as part of the chemotherapy protocol)
- Use of another investigational product
- Radiation, palliative radiation of pre-existing lesions may be performed.

If concomitant medication is taken during the study, the details will be recorded in the CRF. The generic name, dosage, duration, and reason for the concomitant medication should be included.

9 STUDY PROCEDURES

All procedures and tests will be performed as summarized in the Schedule of Events (SOE) (Table 29 through Table 38).

9.1 Screening

Within 28 days prior to first dose (Day 1) and after informed consent has been obtained, patients who have been identified by Investigators based on clinical history will be screened to establish eligibility.

The following evaluations and procedures will be performed within 28 days prior to Day 1:

- Written informed consent
- Clinical evaluations:
  - Medical and cancer history, including demographics
  - Physical Exam
  - ECOG status (must be 0 or 1 for eligibility)
  - Weight and height
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- 12-Lead ECG – single
- Baseline tumor assessment of all sites of disease: CT, MRI, CT with contrast. Patients with CRPC must also undergo bone scintigraphy. The same radiographic procedures used to define measurable and non-measurable lesions must be used throughout the study for each patient. Scans will be collected following the study manual.
- Safety laboratory assessments (non-fasting):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Serum pregnancy test (all females of childbearing age)
- Castrate levels of testosterone (< 50 ng/dL) in CRPC patients only
- Concomitant medications.

9.2 Treatment

The following procedures will be conducted after patient eligibility has been established.

9.2.1 Part A, B, C Escalation

9.2.1.1 Part A, B, C Escalation, Day 1

The following procedures and assessments will be performed:

Pre-dose: Day 1

- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG: three separate 12-lead ECGs (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior; If screening labs are done within 3 days prior then screening labs can be used as Day 1 labs):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (all females of childbearing potential)
- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior)
- Serum tumor markers as appropriate (Day 1 [up to 3 days prior] and collect tumor marker assessments up to six months prior)
- Collect archival tumor tissue specimen and/or fresh biopsy (optional / up to 10 days prior)
- Part A, B, C: Administer SC Injection of AM0010; Injection #1 (staff administered and training for AM0010 self-injection up to 3 days prior)

Post-dose Day 1

Part B, C – Chemotherapy regimen (Section 8.3)

Post-dose: Day 1, 2 hours after the injection (± 15 minutes)

- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- Adverse events
- Post-dose 2 hours (± 15 minutes) PK sample – Day 1

Post-dose: Day 1, 6 hours after the injection (± 30 minutes)

- Post-dose 6 hours (± 30 minutes) PK sample – Day 1
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- 12-Lead ECG – single
- Adverse events
- Safety laboratory assessments
  - Hematology
  - Serum chemistry

Post-dose: Day 1, 8, 12 hours after the injection

- Post-dose 8 hours (± 30 minutes) PK sample – Day 1
- Post-dose 12 hours (± 60 minutes) PK sample – Day 1

9.2.1.2 Part A, B, C Escalation, Day 2

The following procedures and assessments will be performed on Day 2:

- Post-dose 24 hours (± 1 hour) PK sample / Pre dose – Day 2
- Dispense AM0010 kit
- Patient training for self-administration (up to 3 days prior)
- Self-administer SC Injection of AM0010; Injection # 2
- Clinical evaluations:
  - Physical Exam
  - ECOG status
  - Weight

- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- 12-Lead ECG – single
- Concomitant medications
- Adverse events
- Safety laboratory assessments:
  - Hematology
  - Serum chemistry
  - Urinalysis

9.2.1.3 Part A, B, C Escalation, Days 3 – 7

- Self-administer SC Injection of AM0010; Injection #3 – 7

9.2.1.4 Part A, B, C Escalation, Day 8

The following procedures and assessments will be performed on Day 8 (or 1 day prior):

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 8
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #8
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis

9.2.1.5 Part A, B, C Escalation, Days 9 – 14

- Self-administer SC Injection of AM0010; Injection #9 – 14

9.2.1.6 Part A, B, C Escalation, Day 15

The following procedures and assessments will be performed on Day 15 (or 1 day prior):

- Pre-dose PK sample – Day 15
- Dispense AM0010 kit
- Self-administer SC injection of AM0010: Injection #15
- Part C – Chemotherapy (Section 8.3.2)
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (if applicable)

9.2.1.7 Part A, B, C Escalation, Days 16 – 21

- Self-administer SC Injection of AM0010; Injection #16 – 21

9.2.1.8 Part A, B, C Escalation, Day 22

The following procedures and assessments will be performed on Day 22 (or 1 day prior):

- Pre-dose PK sample – Day 22
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #22

- Part B – Chemotherapy (Section 8.3.1)
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events (or 1 day prior)
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis

9.2.1.9 Part A, B, C Escalation, Days 23 – 28

- Self-administer SC Injection of AM0010; Injection #23 – 28

9.2.1.10 Part A, B, C Escalation, Day 29

For all patients in the Dose Escalation, this is the end of the DLT assessment window. The following procedures and assessments will be performed on Day 29 (or 1 day prior):

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 29
- Exploratory biomarker sample (optional) – Day 29 (up to 3 days prior)
- Serum tumor markers as appropriate (up to 3 days prior):
- Dispense AM0010 kit
- Part C – Chemotherapy (Section 8.3.2)
- Self-administer SC Injection of AM0010; Injection #29
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)

- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 day prior):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (if applicable)

Post-dose: Day 29

- Post-dose 2h PK sample (± 30 minutes) – Day 29
- Post-dose 6h PK sample (± 30 minutes) – Day 29
- Post-dose 8h PK sample (± 30 minutes) – Day 29
- Post-dose 12h PK sample (± 60 minutes) – Day 29
- Post-dose 24h PK sample (± 60 minutes) – Day 29

9.2.1.11 Part A, B, C Escalation, Days 30 – 35

- Self-administer SC Injection of AM0010; Injection #30 – 35

9.2.1.12 Part A, B, C Escalation, Day 36

The following procedures and assessments will be performed on Day 36 (± 1 day):

- Pre-dose PK sample – Day 36
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #36
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior)

- Hematology
- Serum chemistry
- Urinalysis

9.2.1.13 Part A, B, C Escalation, Days 37 – 42

- Self-administer SC Injection of AM0010; Injection #37 – 42

9.2.1.14 Part A, B, C Escalation, Day 43

The following procedures and assessments will be performed on Day 43 (± 1 day):

- Pre-dose PK sample – Day 43
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #43
- Part B – Chemotherapy (Section 8.3.1)
- Part C – Chemotherapy (Section 8.3.2)
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (if applicable)

9.2.1.15 Part A, B, C Escalation, Days 44 – 49

- Self-administer SC Injection of AM0010; Injection #44 – 49

9.2.1.16 Part A, B, C Escalation, Day 50

The following procedures and assessments will be performed on Day 50 (± 1 day):

- Pre-dose PK sample – Day 50
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #50
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events (or 1 day prior)
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis

9.2.1.17 Part A, B, C Escalation, Days 51 – 56

- Self-administer SC Injection of AM0010; Injection #51 – 56

9.2.1.18 Part A, B, C Escalation, Day 57

The following procedures and assessments will be performed on Day 57 (± 1 day):

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 57
- Dispense AM0010 kits
- Self-administer SC Injection of AM0010; Injection #57
- Part C – Chemotherapy (Section 8.3.2)
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight

- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (if applicable)
- Serum tumor markers as appropriate (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 57 (up to 3 days prior)
- Collect fresh biopsy (optional): treatment response biopsy (± 7 days)

9.2.1.19 Part A, B, C Escalation, Continuing Treatment Visits

The following procedures and assessments will be performed every two weeks (± 2 day):

- Pre-dose PK sample
- Dispense AM0010 kits
- Self-administer SC Injection of AM0010
- Part B – chemotherapy every 21 days (for a total of 5 cycles, until Day 106)
- Part C – chemotherapy every 14 days
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology

- Serum chemistry
- Urine or serum pregnancy test (if applicable)
- Exploratory biomarker sample (optional) – (up to 3 days prior) every 8 weeks starting on C1D1
- Serum tumor markers as appropriate – (up to 3 days prior) every 4 weeks
- Collect fresh biopsy (optional): treatment response biopsy – every 8 weeks (± 7 days)

9.2.2 Treatments – Part A Expansion Cohorts

9.2.2.1 Part A Expansion Cycle 1

9.2.2.1.1 Part A Exp. Cycle 1 Day 1

The following procedures and assessments will be performed:

Pre-dose: Day 1

- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG: three separate 12-lead ECGs (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior; if screening labs are done within 3 days prior, then screening labs can be used as Day 1 labs):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (all females of childbearing potential)
- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior)

- Serum tumor markers as appropriate (Day 1 [up to 3 days prior] and collect tumor marker assessments up to six months prior)
- Collect archival tumor tissue specimen and/or fresh biopsy (optional / up to 10 days prior)
- Patient training for self-administration (up to 3 days prior)
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection # 1

Post-dose: Day 1, 6 hours after the injection (± 30 minutes)

- Post-dose 6 hours (± 30 minutes) PK sample – Day 1
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- Adverse events

9.2.2.1.2 Part A Exp. Cycle 1 Days 2 – 7

- Self-administer SC Injection of AM0010; Injection #2 – 7

9.2.2.1.3 Part A Exp. Cycle 1 Day 8

The following procedures and assessments will be performed on Day 8 (or 1 day prior):

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 8
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #8
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology

- Serum chemistry
- Urinalysis

9.2.2.1.4 Part A Exp. Cycle 1 Days 9 – 14

- Self-administer SC Injection of AM0010; Injection #9 – 14

9.2.2.1.5 Part A Exp. Cycle 1 Day 15

The following procedures and assessments will be performed on Day 15 (or 1 day prior):

- Pre-dose PK sample – Day 15
- Dispense AM0010 kits
- Self-administer SC injection of AM0010: Injection #15
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (if applicable)

9.2.2.1.6 Part A Exp. Cycle 1 Days 16 – 28

- Self-administer SC Injection of AM0010; Injection #16 – 28

9.2.2.1.7 Part A Exp. Cycle 1 Day 29

The following procedures and assessments will be performed on Day 29 (or 1 day prior):

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 29

- Exploratory biomarker sample (optional) – Day 29 (up to 3 days prior)
- Serum tumor markers as appropriate (up to 3 days prior)
- Dispense AM0010 kits
- Self-administer SC Injection of AM0010; Injection #29
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 day prior):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (if applicable)

9.2.2.1.8 Part A Exp. Cycle 1 Days 30 – 42

- Self-administer SC Injection of AM0010; Injection #30 – 42

9.2.2.1.9 Part A Exp. Cycle 1 Day 43

The following procedures and assessments will be performed on Day 43 (± 1 day):

- Pre-dose PK sample – Day 43
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #43
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)

- Concomitant medications (or 1 day prior)
- Adverse events (or 1 day prior)
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (if applicable)

9.2.2.1.10 Part A Exp. Cycle 1 Days 44 – 56

- Self-administer SC Injection of AM0010; Injection #44 – 56

9.2.2.1.11 Part A Exp. Continuing Visits – Every 28 Days

The following procedures and assessments will be performed on Day 1 (± 1 day):

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1
- Dispense 4 AM0010 kits
- Self-administer SC Injection of AM0010; Injection #1
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urine or serum pregnancy test (if applicable)
- Serum tumor markers as appropriate (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior) - repeated every 8 weeks

- Collect fresh biopsy (optional): treatment response biopsy (± 7 days) – repeated every 8 weeks

9.2.3 Treatments – Part B Expansion Cohorts

9.2.3.1 Part B Exp. Cycle 1

9.2.3.1.1 Part B Exp. Cycle 1 Day 1

The following procedures and assessments will be performed:

Pre-dose: Day 1

- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG: three separate 12-lead ECGs (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior; If screening labs are done within 3 days prior then screening labs can be used as Day 1 labs):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (all females of childbearing potential)
- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior)
- Serum tumor markers as appropriate (Day 1 [up to 3 days prior] and collect tumor marker assessments up to six months prior)
- Collect archival tumor tissue specimen and/or fresh biopsy (optional / up to 10 days prior)
- Patient training for self-administration (up to 3 days prior)

- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection # 1
- Chemotherapy Platinum – Taxane (Section 8.3.1)

Post-dose: Day 1, 6 hours after the injection (± 30 minutes)

- Post-dose 6 hours (± 30 minutes) PK sample – Day 1
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- Adverse events

9.2.3.1.2 Part B Exp. Cycle 1 Days 2 – 7

- Self-administer SC Injection of AM0010; Injection #2 – 7

9.2.3.1.3 Part B Exp. Cycle 1 Day 8

The following procedures and assessments will be performed on Day 8 (or 1 day prior):

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 8
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #8
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis

9.2.3.1.4 Part B Exp. Cycle 1 Days 9 – 14

- Self-administer SC Injection of AM0010; Injection #9 – 14

9.2.3.1.5 Part B Exp. Cycle 1 Day 15

The following procedures and assessments will be performed on Day 15 (or 1 day prior):

- Pre-dose PK sample – Day 15
- Dispense AM0010 kit
- Self-administer SC injection of AM0010: Injection #15
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (if applicable)

9.2.3.1.6 Part B Exp. Cycle 1 Days 16 – 21

- Self-administer SC Injection of AM0010; Injection #16 – 21

9.2.3.2 Part B Exp. Cycle 2 – 6 (Starting Day 22)

Repeat every 21 days ± 2 days.

9.2.3.2.1 Part B Exp. Cycle 2 – 6 Day 1

The following procedures and assessments will be performed:

Pre-dose: Day 1

- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (all females of childbearing potential)
- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior / every 8 weeks)
- Serum tumor markers as appropriate (up to 3 days prior)
- Collect fresh biopsy (optional): treatment response biopsy (± 7 days) – repeated every 8 weeks
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection # 1
- Chemotherapy Platinum – Taxane (Section 8.3.1)

9.2.3.2.2 Part B Exp. Cycle 2 – 6 Days 2 – 7

- Self-administer SC Injection of AM0010; Injection #2 – 7

9.2.3.2.3 Part B Exp. Cycle 2 – 6 Day 8

The following procedures and assessments will be performed on Day 8 (or 1 day prior):

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 8
- Dispense AM0010 kits
- Self-administer SC Injection of AM0010; Injection #8
- Clinical evaluations (or 1 day prior):

- Physical Exam
- ECOG status
- Weight

- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis

9.2.3.2.4 Part B Exp. Cycle 2 – 6 Days 9 – 14

- Self-administer SC Injection of AM0010; Injection #9 – 14

9.2.3.2.5 Part B Exp. Cycle 2 – 6 Day 15

The following procedures and assessments will be performed on Day 15:

- Self-administer SC injection of AM0010: Injection #15
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry

9.2.3.2.6 Part B Exp. Cycle 2 – 6 Days 16 – 21

- Self-administer SC Injection of AM0010; Injection #16 – 21
- Continue to Part B Exp. Cycle 2 – 6 Day 1 (Section 9.2.3.2.1) or Continued Treatment (Section 9.3.1).

9.2.4 Treatments – Part C Expansion Cohorts

9.2.4.1 Part C Exp. Cycle 1

9.2.4.1.1 Part C Exp. Cycle 1 Day 1

The following procedures and assessments will be performed:

Pre-dose: Day 1

- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG: three separate 12-lead ECGs (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior; if screening labs are done within 3 days prior then screening labs can be used as Day 1 labs):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (all females of childbearing potential)
- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior)
- Serum tumor markers as appropriate (Day 1 [up to 3 days prior] and collect tumor marker assessments up to six months prior)
- Consent to providing pre-treatment archival tumor tissue specimen and/or collect fresh biopsy (mandatory / up to 10 days prior)
- Patient training for self-administration (up to 3 days prior)
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection # 1
- Chemotherapy FOLFOX (Section 8.3.1)

Post-dose: Day 1, 6 hours after the injection (± 30 minutes)

- Post-dose 6 hours (± 30 minutes) PK sample – Day 1
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- Adverse events
- Safety laboratory assessments
  - Hematology
  - Serum chemistry

9.2.4.1.2 Part C Exp. Cycle 1 Days 2 – 7

- Self-administer SC Injection of AM0010; Injection #2 – 7

9.2.4.1.3 Part C Exp. Cycle 1 Day 8

The following procedures and assessments will be performed on Day 8 (or 1 day prior):

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 8
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #8
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis

9.2.4.1.4 Part C Exp. Cycle 1 Days 9 – 14

- Self-administer SC Injection of AM0010; Injection #9 – 14

9.2.4.1.5 Part C Exp. Cycle 1 Day 15

The following procedures and assessments will be performed on Day 15 (or 1 day prior):

- Pre-dose PK sample – Day 15
- Dispense AM0010 kit
- Self-administer SC injection of AM0010: Injection #15
- Chemotherapy FOLFOX (Section 8.3.1)
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (if applicable)

9.2.4.1.6 Part C Exp. Cycle 1 Days 16 – 21

- Self-administer SC Injection of AM0010; Injection #16 – 21

9.2.4.1.7 Part C Exp. Cycle 1 Day 22

The following procedures and assessments will be performed on Day 22 (or 1 day prior):

- Dispense AM0010 kit
- Self-administer SC injection of AM0010: Injection #22
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events

- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry

9.2.4.2 Part C Exp. Cycle 2 – 12 (Starting Day 29)

Repeat every 15 days ± 2 days.

9.2.4.2.1 Part C Exp. Cycle 2 – 12 Day 1

The following procedures and assessments will be performed:

Pre-dose: Day 1

- Clinical evaluations:
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urine or serum pregnancy test (all females of childbearing potential)
- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior / every 28 days)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior / every 8 weeks)
- Serum tumor markers as appropriate (up to 3 days prior) (every 28 days)
- Cycle 4, Day 1: Collect fresh treatment response biopsy (± 10 days)
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection # 1
- Chemotherapy FOLFOX (Section 8.3.1)

9.2.4.2.2 Part C Exp. Cycle 2 – 12 Days 2 – 7

- Self-administer SC Injection of AM0010; Injection #2 – 7

9.2.4.2.3 Part C Exp. Cycle 2 – 12 Day 8

The following procedures and assessments will be performed on Day 8 (or 1 day prior):

- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #8
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
- Continue to Part C Exp. Cycle 3-12 Day 1 (Section 9.2.4.2) or Continued Treatment (Section 9.3.1).

9.2.5 Treatments – Part D Escalation and Expansion Cohorts

9.2.5.1 Part D Cycle 1

9.2.5.1.1 Part D Cycle 1 Day 1

The following procedures and assessments will be performed:

Pre-dose: Day 1

- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG: three separate 12-lead ECGs (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events

- Safety laboratory assessments (up to 3 days prior; If screening labs are done within 3 days prior then screening labs can be used as Day 1 labs):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (all females of childbearing potential)

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior)
- Serum tumor markers as appropriate (Day 1 [up to 3 days prior] and collect tumor marker assessments up to six months prior)
- Collect archival tumor tissue specimen and/or fresh biopsy (optional / up to 10 days prior)
- Patient training for self-administration (up to 3 days prior)
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection # 1
- Chemotherapy Gemcitabine and nab-Paclitaxel (Section 8.3.3)

Post-dose: Day 1, 6 hours after the injection (± 30 minutes)

- Post-dose 6 hours (± 30 minutes) PK sample – Day 1
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- Adverse events
- Safety laboratory assessments
  - Hematology
  - Serum chemistry

9.2.5.1.2 Part D Cycle 1 Days 2 – 7

- Self-administer SC Injection of AM0010; Injection #2 – 7

9.2.5.1.3 Part D Cycle 1 Day 8

The following procedures and assessments will be performed on Day 8 (or 1 day prior):

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 8

- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #8
- Chemotherapy Gemcitabine and nab-Paclitaxel (Section 8.3.3)
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry

9.2.5.1.4 Part D Cycle 1 Days 9 – 14

- Self-administer SC Injection of AM0010; Injection #9 – 14

9.2.5.1.5 Part D Cycle 1 Day 15

The following procedures and assessments will be performed on Day 15 (or 1 day prior):

- Pre-dose PK sample – Day 15
- Dispense AM0010 kit
- Self-administer SC injection of AM0010: Injection #15
- Chemotherapy Gemcitabine and nab-Paclitaxel (Section 8.3.3)
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urine or serum pregnancy test (if applicable)

9.2.5.1.6 Part D Cycle 1 Days 16 – 21

- Self-administer SC Injection of AM0010; Injection #16 – 21

9.2.5.1.7 Part D Cycle 1 Day 22

The following procedures and assessments will be performed on Day 22 (or 1 day prior):

- Dispense AM0010 kit
- Self-administer SC injection of AM0010: Injection #22
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry

9.2.5.2 Part D Subsequent Cycles (Starting Day 29)

Repeat every 28 days ± 2 days

9.2.5.2.1 Part D Subsequent Cycles Day 1

The following procedures and assessments will be performed:

Pre-dose: Day 1

- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology

- Serum chemistry
- Urine or serum pregnancy test (all females of childbearing potential)

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior / every 8 weeks)
- Serum tumor markers as appropriate (up to 3 days prior) (every 28 days)
- Collect fresh biopsy (optional): treatment response biopsy (± 7 days) – repeated every 8 weeks
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection # 1
- Chemotherapy Gemcitabine and nab-Paclitaxel (Section 8.3.3)

9.2.5.2.2 Part D Subsequent Cycles Days 2 – 7

- Self-administer SC Injection of AM0010; Injection #2 – 7

9.2.5.2.3 Part D Subsequent Cycles Days 8

The following procedures and assessments will be performed on Day 8 (or 1 day prior):

- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #8
- Chemotherapy Gemcitabine and nab-Paclitaxel (Section 8.3.3)
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry

9.2.5.2.4 Part D Subsequent Cycles Days 9 – 14

- Self-administer SC Injection of AM0010; Injection #9 – 14

9.2.5.2.5 Part D Subsequent Cycles Days 15

The following procedures and assessments will be performed on Day 15 (or 1 day prior):

- Dispense AM0010 kit
- Self-administer SC injection of AM0010: Injection #15
- Chemotherapy Gemcitabine and nab-Paclitaxel (Section 8.3.3)
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
    - Hematology
    - Serum chemistry
    - Urine or serum pregnancy test (all females of childbearing potential)

9.2.5.2.6 Part D Subsequent Cycles Days 16 – 21

- Self-administer SC Injection of AM0010; Injection #16 – 21

9.2.5.2.7 Part D Subsequent Cycles Days 22

The following procedures and assessments will be performed on Day 22 (or 1 day prior):

- Dispense AM0010 kit
- Self-administer SC injection of AM0010: Injection #22
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
    - Hematology
    - Serum chemistry

- Continue to Part D Subsequent Cycles Day 1 (Section 9.2.5.2.1) or Continued Treatment (Section 9.3.1).

9.2.6 Treatments – Part E Escalation and Expansion Cohorts

9.2.6.1 Part E Cycle 1

9.2.6.1.1 Part E Cycle 1 Day 1

The following procedures and assessments will be performed:

Pre-dose: Day 1

- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG: three separate 12-lead ECGs (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior; If screening labs are done within 3 days prior then screening labs can be used as Day 1 labs):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (all females of childbearing potential)
- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior)
- Serum tumor markers as appropriate (Day 1 [up to 3 days prior] and collect tumor marker assessments up to six months prior)
- Collect archival tumor tissue specimen and/or fresh biopsy (optional / up to 10 days prior)
- Patient training for self-administration (up to 3 days prior)
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection # 1
- Chemotherapy Capecitabine (Section 8.3.4)

Post-dose: Day 1, 6 hours after the injection (± 30 minutes)

- Post-dose 6 hours (± 30 minutes) PK sample – Day 1
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- Adverse events

9.2.6.1.2 Part E Cycle 1 Days 2 – 7

- Self-administer SC Injection of AM0010; Injection #2 – 7
- Chemotherapy Capecitabine (Section 8.3.4)

9.2.6.1.3 Part E Cycle 1 Day 8

The following procedures and assessments will be performed on Day 8 (or 1 day prior):

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 8
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #8
- Chemotherapy Capecitabine (Section 8.3.4)
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis

9.2.6.1.4 Part E Cycle 1 Days 9 – 14

- Self-administer SC Injection of AM0010; Injection #9 – 14
- Chemotherapy Capecitabine (Section 8.3.4)

9.2.6.1.5 Part E Cycle 1 Day 15

The following procedures and assessments will be performed on Day 15 (or 1 day prior):

- Pre-dose PK sample – Day 15
- Dispense AM0010 kit
- Self-administer SC injection of AM0010: Injection #15
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry

9.2.6.1.6 Part E Cycle 1 Days 16 – 21

- Self-administer SC Injection of AM0010; Injection #16 – 21

9.2.6.2 Part E Subsequent Cycles (Starting Day 22)

Repeat every 21 days ± 2 days

9.2.6.2.1 Part E Subsequent Cycles Day 1

The following procedures and assessments will be performed:

<u>Pre-dose: Day 1</u>

- Clinical evaluations:
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events

- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (all females of childbearing potential)
- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior / every 6 weeks)
- Serum tumor markers as appropriate (up to 3 days prior)
- Collect fresh biopsy (optional): treatment response biopsy (± 7 days) – repeated every 8 weeks
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #1
- Chemotherapy Capecitabine (Section 8.3.4)

9.2.6.2.2 Part E Subsequent Cycles Days 2 – 7

- Self-administer SC Injection of AM0010; Injection #2 – 7
- Chemotherapy Capecitabine (Section 8.3.4)

9.2.6.2.3 Part E Subsequent Cycles Day 8

The following procedures and assessments will be performed on Day 8 (or 1 day prior):

- Dispense AM0010 kits
- Self-administer SC Injection of AM0010; Injection #8
- Chemotherapy Capecitabine (Section 8.3.4)
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events (or 1 day prior)
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis

9.2.6.2.4 Part E Subsequent Cycles Days 9 – 14

- Self-administer SC Injection of AM0010; Injection #9 – 14
- Chemotherapy Capecitabine (Section 8.3.4)

9.2.6.2.5 Part E Subsequent Cycles Day 15

The following procedures and assessments will be performed on Day 15 (or 1 day prior):

- Dispense AM0010 kit
- Self-administer SC injection of AM0010: Injection #15
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry

9.2.6.2.6 Part E Subsequent Cycles Days 16 – 21

- Self-administer SC Injection of AM0010; Injection #16 – 21
- Continue to Part E Subsequent Cycles Day 1 (Section 9.2.6.2.1) or Continued Treatment (Section 9.3.1).

9.2.7 Treatments – Part F Escalation and Expansion Cohorts

9.2.7.1 Part F Cycle 1

9.2.7.1.1 Part F Cycle 1 Day 1

The following procedures and assessments will be performed:

<u>Pre-dose: Day 1</u>

- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight

- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG: three separate 12-lead ECGs (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior; If screening labs are done within 3 days prior then screening labs can be used as Day 1 labs):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (all females of childbearing potential)
- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior)
- Serum tumor markers as appropriate (Day 1 [up to 3 days prior] and collect tumor marker assessments up to six months prior)
- Collect archival tumor tissue specimen and/or fresh biopsy (optional / up to 10 days prior)
- Patient training for self-administration (up to 3 days prior)
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #1
- Chemotherapy Paclitaxel (Section 8.3.5)

Post-dose: Day 1, 6 hours after the injection (± 30 minutes)

- Post-dose 6 hours (± 30 minutes) PK sample – Day 1
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- Adverse events
- Safety laboratory assessments
  - Hematology
  - Serum chemistry

9.2.7.1.2 Part F Cycle 1 Days 2 – 7

- Self-administer SC Injection of AM0010; Injection #2 – 7

9.2.7.1.3 Part F Cycle 1 Day 8

The following procedures and assessments will be performed on Day 8 (or 1 day prior):

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 8
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #8
- Chemotherapy Paclitaxel (Section 8.3.5)
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry

9.2.7.1.4 Part F Cycle 1 Days 9 – 14

- Self-administer SC Injection of AM0010; Injection #9 – 14

9.2.7.1.5 Part F Cycle 1 Day 15

The following procedures and assessments will be performed on Day 15 (or 1 day prior):

- Pre-dose PK sample – Day 15
- Dispense AM0010 kit
- Self-administer SC injection of AM0010: Injection #15
- Chemotherapy Paclitaxel (Section 8.3.5)
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events

- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urine or serum pregnancy test (if applicable)

9.2.7.1.6 Part F Cycle 1 Days 16 – 21

- Self-administer SC Injection of AM0010; Injection #16 – 21

9.2.7.1.7 Part F Cycle 1 Day 22

The following procedures and assessments will be performed on Day 22 (or 1 day prior):

- Dispense AM0010 kit
- Self-administer SC injection of AM0010: Injection #22
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry

9.2.7.2 Part F Subsequent Cycles (Starting Day 29)

Repeat every 28 days ± 2 days.

9.2.7.2.1 Part F Subsequent Cycles Day 1

The following procedures and assessments will be performed:

Pre-dose: Day 1

- Clinical evaluations:
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)

- 12-Lead ECG – single ECG (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urine or serum pregnancy test (all females of childbearing potential)

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior / every 8 weeks)
- Serum tumor markers as appropriate (up to 3 days prior) (every 28 days)
- Collect fresh biopsy (optional): treatment response biopsy (± 7 days) – repeated every 8 weeks
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection # 1
- Chemotherapy Paclitaxel (Section 8.3.5)

9.2.7.2.2 Part F Subsequent Cycles Days 2 – 7

- Self-administer SC Injection of AM0010; Injection #2 – 7

9.2.7.2.3 Part F Subsequent Cycles Day 8

The following procedures and assessments will be performed on Day 8 (or 1 day prior):

- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #8
- Chemotherapy Paclitaxel (Section 8.3.5)
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry

9.2.7.2.4 Part F Subsequent Cycles Days 9 – 14

- Self-administer SC Injection of AM0010; Injection #9 – 14

9.2.7.2.5 Part F Subsequent Cycles Day 15

The following procedures and assessments will be performed on Day 15 (or 1 day prior):

- Dispense AM0010 kit
- Self-administer SC injection of AM0010: Injection #15
- Chemotherapy Paclitaxel (Section 8.3.5)
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urine or serum pregnancy test (all females of childbearing potential)

9.2.7.2.6 Part F Subsequent Cycles Days 16 – 21

- Self-administer SC Injection of AM0010; Injection #16 – 21

9.2.7.2.7 Part F Subsequent Cycles Day 22

The following procedures and assessments will be performed on Day 22 (or 1 day prior):

- Self-administer SC injection of AM0010: Injection #22
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry

- Continue to Part F Subsequent Cycles Day 1 (Section 9.2.7.2.1) or Continued Treatment (Section 9.3.1).

9.2.8 Treatments – Part G Escalation and Expansion Cohorts

9.2.8.1 Part G Cycle 1

9.2.8.1.1 Part G Cycle 1 Day 1

The following procedures and assessments will be performed:

Pre-dose: Day 1

- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG: three separate 12-lead ECGs (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior; If screening labs are done within 3 days prior then screening labs can be used as Day 1 labs):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (all females of childbearing potential)
- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior)
- Serum tumor markers as appropriate (Day 1 [up to 3 days prior] and collect tumor marker assessments up to six months prior)
- Collect archival tumor tissue specimen and/or fresh biopsy (optional / up to 10 days prior)
- Patient training for self-administration (up to 3 days prior)
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection # 1
- Administer Pazopanib (Section 8.3.6)

Post-dose: Day 1, 6 hours after the injection (± 30 minutes)

- Post-dose 6 hours (± 30 minutes) PK sample – Day 1
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- Adverse events
- Safety laboratory assessments
  - Hematology
  - Serum chemistry

9.2.8.1.2 Part G Cycle 1 Days 2 – 7

- Self-administer SC Injection of AM0010; Injection #2 – 7
- Administer Pazopanib (Section 8.3.6)

9.2.8.1.3 Part G Cycle 1 Day 8

The following procedures and assessments will be performed on Day 8 (or 1 day prior):

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 8
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #8
- Administer Pazopanib (Section 8.3.6)
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis

9.2.8.1.4 Part G Cycle 1 Days 9 – 14

- Self-administer SC Injection of AM0010; Injection #9 – 14
- Administer Pazopanib (Section 8.3.6)

9.2.8.1.5 Part G Cycle 1 Day 15

The following procedures and assessments will be performed on Day 15 (or 1 day prior):

- Pre-dose PK sample – Day 15
- Dispense AM0010 kit
- Self-administer SC injection of AM0010: Injection #15
- Administer Pazopanib (Section 8.3.6)
- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (if applicable)

9.2.8.1.6 Part G Cycle 1 Days 16 – 21

- Self-administer SC Injection of AM0010; Injection #16 – 21
- Administer Pazopanib (Section 8.3.6)

9.2.8.1.7 Part G Cycle 1 Day 22

The following procedures and assessments will be performed on Day 22 (or 1 day prior):

- Dispense AM0010 kit

- Self-administer SC injection of AM0010: Injection #22
- Administer Pazopanib (Section 8.3.6)
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry

9.2.8.1.8 Part G Cycle 1 Days 23 – 28

- Self-administer SC Injection of AM0010; Injection #23 – 28
- Administer Pazopanib (Section 8.3.6)

9.2.8.2 Part G Subsequent Cycles (Starting Day 29)

Repeat every 28 days ± 2 days.

9.2.8.2.1 Part G Subsequent Cycles Day 1

The following procedures and assessments will be performed:

Pre-dose: Day 1

- Clinical evaluations:
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry

- Urine or serum pregnancy test (all females of childbearing potential)

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior / every 8 weeks)
- Serum tumor markers as appropriate (up to 3 days prior)
- Collect fresh biopsy (optional): treatment response biopsy (± 7 days) – repeated every 8 weeks
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection # 1
- Administer Pazopanib (Section 8.3.6)
- Continue to Part G Subsequent Cycles Day 1 (Section 9.2.8.2) or Continued Treatment (Section 9.3.1).

9.2.9 Treatments – Part H Escalation and Expansion Cohorts

9.2.9.1 Part H Cycle 1

9.2.9.1.1 Part H Cycle 1 Day 1

The following procedures and assessments will be performed:

Pre-dose: Day 1

- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG: three separate 12-lead ECGs (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior; If screening labs are done within 3 days prior then screening labs can be used as Day 1 labs):
  - Hematology
  - Serum chemistry

- Urinalysis
- Urine or serum pregnancy test (all females of childbearing potential)

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior)
- Serum tumor markers as appropriate (Day 1 [up to 3 days prior] and collect tumor marker assessments up to six months prior)
- Collect archival tumor tissue specimen and/or fresh biopsy (optional / up to 10 days prior)
- Patient training for self-administration (up to 3 days prior)
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection # 1
- Administer Pembrolizumab (Section 8.3.7)

Post-dose: Day 1, 6 hours after the injection (± 30 minutes)

- Post-dose 6 hours (± 30 minutes) PK sample – Day 1
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- Adverse events
- Safety laboratory assessments
  - Hematology
  - Serum chemistry

9.2.9.1.2 Part H Cycle 1 Days 2 – 7

- Self-administer SC Injection of AM0010; Injection #2 – 7

9.2.9.1.3 Part H Cycle 1 Day 8

The following procedures and assessments will be performed on Day 8 (or 1 day prior):

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 8
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #8
- Clinical evaluations (or 1 day prior):
  - Physical Exam

- ECOG status
- Weight

- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry

9.2.9.1.4 Part H Cycle 1 Days 9 – 14

- Self-administer SC Injection of AM0010; Injection #9 – 14

9.2.9.1.5 Part H Cycle 1 Day 15

The following procedures and assessments will be performed on Day 15 (or 1 day prior):

- Pre-dose PK sample – Day 15
- Dispense AM0010 kit
- Self-administer SC injection of AM0010: Injection #15
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry

9.2.9.1.6 Part H Cycle 1 Days 16 – 21

- Self-administer SC Injection of AM0010; Injection #16 – 21

9.2.9.2 Part H Subsequent Cycles (Starting Day 22)

Repeat every 21 days ± 2 days.

9.2.9.2.1 Part H Subsequent Cycles Day 1

The following procedures and assessments will be performed:

Pre-dose: Day 1

- Clinical evaluations:
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urine or serum pregnancy test (all females of childbearing potential)
- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior / every 6 weeks)
- Serum tumor markers as appropriate (up to 3 days prior)
- Collect fresh biopsy (optional): treatment response biopsy (± 7 days) – repeated every 8 weeks
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection # 1
- Administer Pembrolizumab (Section 8.3.7)

9.2.9.2.2 Part H Subsequent Cycle Days 2-7

- Self-administer SC Injection of AM0010; Injection #2-7

9.2.9.2.3 Part H Subsequent Cycles Day 8

The following procedures and assessments will be performed on Day 8 (or 1 day prior):

- Dispense AM0010 kits
- Self-administer SC injection of AM0010: Injection # 8
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry

9.2.9.2.4 Part H Subsequent Cycle Days 9 – 21

- Self-administer SC Injection of AM0010; Injection #16 – 21
- Continue to Part H Subsequent Cycles Day 1 (Section 9.2.9.2.1) or Continued Treatment (Section 9.3.1).

9.2.10 Treatments – Part I Escalation and Expansion Cohorts

9.2.10.1 Part I Cycle 1

9.2.10.1.1 Part I Cycle 1 Day 1

The following procedures and assessments will be performed:

Pre-dose: Day 1

- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG: three separate 12-lead ECGs (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior; if screening labs are done within 3 days prior, then screening labs can be used as Day 1 labs):
  - Hematology

- Serum chemistry
- Urinalysis
- Urine or serum pregnancy test (all females of childbearing potential)

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior)
- Serum tumor markers as appropriate (Day 1 [up to 3 days prior] and collect tumor marker assessments up to six months prior)
- Collect archival tumor tissue specimen and/or fresh biopsy (optional / up to 10 days prior)
- Patient training for self-administration (up to 3 days prior)
- Self-administer SC Injection of AM0010; Injection # 1
- Administer Nivolumab (Section 8.3.8)
- Dispense AM0010 kits

9.2.10.1.2 Part I Cycle 1 Days 2 – 14

- Self-administer SC Injection of AM0010; Injection #2 – 14

9.2.10.2 Part I Subsequent Cycles (Starting Day 15)

Repeat every 14 days ± 2 days.

9.2.10.2.1 Part I Subsequent Cycles Day 1

The following procedures and assessments will be performed:

Pre-dose: Day 1

- Clinical evaluations (or 1 day prior) (every 4 weeks):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior) (every 4 weeks)
- Concomitant medications (or 1 day prior)

- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urine or serum pregnancy test (all females of childbearing potential)
- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior / every 8 weeks)
- Serum tumor markers as appropriate (up to 3 days prior) (every 4 weeks)
- Collect fresh biopsy (optional): treatment response biopsy (± 7 days) – repeated every 8 weeks
- Self-administer SC Injection of AM0010; Injection # 1
- Administer Nivolumab (Section 8.3.8)
- Dispense AM0010 kits

9.2.10.2.2 Part I Subsequent Cycle Days 2 – 14

- Self-administer SC Injection of AM0010; Injection #2 – 14
- Continue to Part I Subsequent Cycles Day 1 (Section 9.2.10.2.1) or Continued Treatment (Section 9.3.1).

9.2.11 Treatments – Part J Escalation and Expansion Cohorts

9.2.11.1 Part J Cycle 1

9.2.11.1.1 Part J Cycle 1 Day 1

The following procedures and assessments will be performed:

Pre-dose: Day 1

- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)

- 12-Lead ECG: three separate 12-lead ECGs (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior; if screening labs are done within 3 days prior then screening labs can be used as Day 1 labs):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (all females of childbearing potential)
- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior)
- Serum tumor markers as appropriate (Day 1 [up to 3 days prior] and collect tumor marker assessments up to six months prior)
- Collect archival tumor tissue specimen and/or fresh biopsy (optional / up to 10 days prior)
- Patient training for self-administration (up to 3 days prior)
- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection # 1
- Chemotherapy Gemcitabine and Carboplatin (Section 8.3.9)

Post-dose: Day 1, 6 hours after the injection (± 30 minutes)

- Post-dose 6 hours (± 30 minutes) PK sample – Day 1
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- Adverse events
- Safety laboratory assessments
  - Hematology
  - Serum chemistry

9.2.11.1.2 Part J Cycle 1 Days 2 – 7

- Self-administer SC Injection of AM0010; Injection #2 – 7

9.2.11.1.3 Part J Cycle 1 Day 8

The following procedures and assessments will be performed on Day 8 (or 1 day prior):

- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #8
- Chemotherapy Gemcitabine and nab-Paclitaxel (Section 8.3.3)
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry

9.2.11.1.4 Part J Cycle 1 Days 9 – 14

- Self-administer SC Injection of AM0010; Injection #9 – 14

9.2.11.1.5 Part J Cycle 1 Day 15

The following procedures and assessments will be performed on Day 15 (or 1 day prior):

- Dispense AM0010 kit
- Self-administer SC injection of AM0010: Injection #15
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (samples up to 3 days prior):
  - Hematology
  - Serum chemistry

9.2.11.1.6 Part J Cycle 1 Days 16 – 21

- Self-administer SC Injection of AM0010; Injection #16 – 21

9.2.11.2 Part J Subsequent Cycles (Starting Day 22)

Repeat every 21 days ± 2 days

9.2.11.2.1 Part J Subsequent Cycles Day 1

The following procedures and assessments will be performed:

Pre-dose: Day 1

- Clinical evaluations (or 1 day prior):
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- 12-Lead ECG – single (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urine or serum pregnancy test (all females of childbearing potential)
- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1 (up to 3 days prior)
- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior / every 6 weeks)
- Serum tumor markers as appropriate (up to 3 days prior)
- Collect fresh biopsy (optional): treatment response biopsy (± 7 days) – repeated every 8 weeks
- -Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection # 1
- Chemotherapy Gemcitabine and Carboplatin (Section 8.3.9)

9.2.11.2.2 Part J Subsequent Cycles Days 2 – 7

- Self-administer SC Injection of AM0010; Injection #2 – 7

9.2.11.2.3 Part J Subsequent Cycles Days 8

The following procedures and assessments will be performed on Day 8 (or 1 day prior):

- Dispense AM0010 kit
- Self-administer SC Injection of AM0010; Injection #8
- Chemotherapy Gemcitabine and Carboplatin (Section 8.3.9)
- Vital signs (pulse, blood pressure, respiratory rate, and temperature) (or 1 day prior)
- Concomitant medications (or 1 day prior)
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry

9.2.11.2.4 Part J Subsequent Cycles Days 9 – 21

- Self-administer SC Injection of AM0010; Injection #9 – 21
- Continue to Part J Subsequent Cycles Day 1 (Section 9.2.11.2.1) or Continued Treatment (Section 9.3.1).

9.2.12 Tumor Assessment – Every 8 Weeks

- Tumor assessment of all sites of disease: CT or MRI, CT with contrast, PET-CT. The same radiographic procedure used to define measurable lesions must be used throughout the study for each patient. Assessment should be obtained at Week 8 (± 1 week). Patients with metastatic CRPC must also be assessed by bone scintigraphy for evaluation of bone metastases at these same intervals.

9.3 Continued Treatment, End of Study Treatment, and Follow-up Visit

9.3.1 Continued Treatment with AM0010 Monotherapy (All Parts)

- Patients who do not show evidence of disease progression by clinical assessment, by CT or MRI according to irRC, or by bone scintigraphy (for patients with metastatic CRPC or according to the best accepted response criteria for the indication may continue on study treatment until disease progression (clinical or radiographic), study drug

intolerance, or withdrawal of consent or upon termination decision by Study Investigator or Lilly.

- In addition, patients may continue to receive study treatment beyond confirmed PD in the absence of clinical deterioration and if the investigator considers that the patient continues to receive benefit from treatment.
- Tumor assessment will be monitored according to irRC or the most suitable response criteria every 8 weeks (± 1 week), using CT, MRI, or CT with contrast. Tumor assessment for metastatic CRPC involving bone will also be monitored by PCWG2 criteria every 8 weeks (± 1 week). The same radiographic procedure used to define measurable or non-measurable lesions must be used throughout the study for each patient.

9.3.1.1 Continued Visits after Termination of Combination Therapy (Every 28 Days)

The following procedures and assessments will be performed on Day 1(± 2 day):

- Pre-dose PK sample / Anti-AM0010 antibody collection – Day 1
- Dispense 4 AM0010 kits
- Self-administer SC Injection of AM0010; Injection #1
- Clinical evaluations:
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- 12-Lead ECG – single
- Concomitant medications
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urine or serum pregnancy test (if applicable)
- Serum tumor markers as appropriate (up to 3 days prior)

- Exploratory biomarker sample (optional) – Day 1 (up to 3 days prior) – every 8 weeks
- Collect fresh biopsy (optional): treatment response biopsy (± 7 days) – every 8 weeks

9.3.2 EOT

The EOT visit will occur on the day of the last visit or within 7 days of the end of treatment. The end of study treatment may be due to disease progression (clinical or radiographic), study drug intolerance, withdrawal of consent, or upon termination decision by Lilly.

The following procedures and assessments will be performed at the EOT Visit for all patients, including early termination:

- Pre-dose PK sample/Anti-AM0010 antibody collection
- Clinical evaluations:
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- 12-Lead ECG – single
- Concomitant medications
- Adverse events
- Safety laboratory assessments (up to three day prior):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (if applicable)
- Exploratory biomarker sample (optional) – (up to 7 days prior)
- Serum tumor markers as appropriate (up to 3 days prior)
- Collect fresh biopsy (optional): treatment response biopsy (up to 7 days prior)
- Tumor assessment (if not done within 4 prior weeks)

9.3.3 Follow-Up Visit

After cessation of dosing, a patient follow up visit should occur at 30 days (- 3 / + 15 days) after EOT. The following procedures and assessments will be performed on the day of the Follow-up Visit for all patients, including early termination:

- Clinical evaluations:
  - Physical Exam
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- 12-Lead ECG – single
- Concomitant medications
- Adverse events
- Follow-up PK sample / Anti-AM0010 antibody collection
- Safety laboratory assessments (up to three day prior):
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine or serum pregnancy test (if applicable)

9.3.4 Patient Follow-up – for Tumor Assessment

In the absence of tumor progression and if patients do not receive additional anti-neoplastic medication, tumor progression will be monitored according to irRC or most suitable response criteria every 8 weeks (± 1 week), using CT, MRI, or CT with contrast and bone scintigraphy (per PCWG2 criteria) every 8 weeks (± 1 week) for patients with metastatic CRPC. The same radiographic procedure used to define measurable or non-measurable lesions must be used throughout the study for each patient. Serum for tumor marker analysis will be collected if applicable.

9.3.5 Patient Follow-Up – for Survival

After PD or bone progression per PCWG2 or other cessation of treatment, a telephone call to follow up the patient's survival should occur every 3 month (± 1 week) for up to one year

after the last dosing day of the last study patient recording the patient's additional cancer therapies and survival status.

9.3.6 Continued Access

Please refer to Section 5.4.7 for details on the Continued Access period and Appendix B for a list of procedures included in the Continued Access period.

9.4 Medical and Concomitant Medication History

A complete medical and concomitant medication history will be obtained by the Investigator or designee. Medical history will include information on the patient's significant past medical events (e.g., prior hospitalizations or surgeries), any concurrent medical illness, and concomitant medications including prescription, non-prescription medications, vitamins and minerals taken up to 28 days prior to study Day 1. The medical history findings and concomitant medications will be recorded on the CRF page.

9.5 Physical Examination

The Investigator or qualified designee will perform a physical examination at Screening and time points outlined in the SOE (Table 29 through Table 38). Pre-dose abnormal findings will be reported on the medical history page of the CRF. Any changes from the study Day 1 pre-dose (baseline) physical examination which represent a clinically significant deterioration will be documented on the adverse events page of the CRF.

Height measurement (in centimeters and without shoes) will be obtained at Screening. Weight measurement (in kg and without shoes) will be obtained at Screening, weekly or bi-weekly during the treatment period, and at the end of the study.

9.6 Vital Signs

Vital signs, including blood pressure, heart rate, respiratory rate, and oral temperature, will be measured by the Investigator or qualified designee at the time points listed in the SOE (Table 29 through Table 38). Patients must be seated or in a semi-recumbent position to vital signs measurement. All measurements will be recorded on the appropriate CRF page with appropriate source documentation. Any abnormal measurements may be repeated and reported as adverse events if appropriate.

9.7 Electrocardiogram

12-lead ECGs reporting ventricular rate, PR, QRS, QT, and QTc intervals will be obtained by the Investigator or designee at the time points indicated in the SOE (± 30 min) (Table 29 through Table 38). Patients should be seated, semi-recumbent, or supine before each ECG is obtained. At pre-dose on Day 1, three separate ECGs will be performed. ECGs collected at pre-dose on Day 1 will be considered baseline ECGs (for continuous measures, e.g., QT and PR interval, the mean of the 3 values will be used as the baseline value). When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn.

The Investigator or qualified designee will review all ECGs. The original ECG tracings will be maintained in the source documentation of each patient and the appropriate data reported on the CRF.

9.8 Adverse Events and Concomitant Medications

Patients will be assessed for adverse events (Section 11.1.1) and concomitant medication(s) during each outpatient visit as outlined in the SOE (Table 29 through Table 38). Any AEs or concomitant medication use reported throughout the study will be recorded in the CRF with appropriate source documentation.

9.9 Safety Laboratory Tests

Blood and urine samples for local laboratory safety tests (clinical chemistry, hematology, and urinalysis) will be collected according to the SOE (Table 29 through Table 38). The date and time of blood and urine collection will be recorded in the patient's source documentation. The tests will be analyzed using standard procedures. White blood cell differentials will be reported as absolute counts. All laboratory tests must be reviewed by the Investigator or qualified designee.

Safety laboratory test related to the safety of the chemotherapy arms B and C will be performed following institutional protocols. Additional safety laboratory assessments may be performed if clinically indicated.

The following analytes will be tested (see Table 26 and Table 27):

Table 26: Blood Samples Collected During the Course of the Study

Serum Chemistry	Hematology	Other
Sodium	Red Blood Cell (RBC) Count	β-hCG
Potassium	White Blood Cell (WBC) Count	
Chloride	Hemoglobin	
Iron (if appropriate)	Hematocrit	
Bicarbonate	Platelet Count	
Glucose	Differential	
Cholesterol	ANC	
HDL-C	Neutrophils	
LDL-C	Lymphocytes	
BUN/Urea	Monocytes	
Creatinine	Eosinophils	
LDH	Basophils	
ALT	PT/INR	
AST	aPTT	
GGT	Reticulocytes	
Alkaline phosphatase		
Total bilirubin		
Total protein		
Albumin		
Calcium		
Magnesium		
Phosphate		
Creatine Phosphokinase		
Pancreatic lipase		
Pancreatic amylase		

Table 27: Urinalysis

Urinalysis	
Specific gravity	pH
Blood	Protein
Glucose	Ketones
Bilirubin	Urobilinogen
WBC	RBC
Epithelial Cells	Bacteria
Casts (optional)	Crystals (optional)

9.10 AM0010 PK Collection

Serum samples for central laboratory PK analysis will be collected according to the SOE (Table 31 through Table 38). The serum will be stored at the site and shipped to a central laboratory according to the Study Manual. A portion of the serum collected for PK analysis will be analyzed for anti-AM0010 analysis.

For sample collection during the continued access period, refer to Section 5.4.7.

9.11 Anti-AM0010 Antibody Collection

Serum samples for central laboratory Anti-AM0010 analysis will be collected together with the PK sample according to the SOE (Table 31 through Table 38). The serum will be stored at the site and shipped to a central laboratory according to the Study Manual. Serum will be allotted to PK and anti-AM0010 antibody analysis, respectively. Anti-AM0010 analysis is planned for pre-dose, day 8, 29, 57, EOT, and 30 day follow up samples.

For sample collection during the continued access period, refer to Section 5.4.7.

9.12 Other Screening Laboratory Tests

All female patients of childbearing age will have a serum pregnancy test at Screening and urine or serum pregnancy tests bi-weekly and at EOT. The results must be confirmed as negative prior to administration of investigational product.

9.13 CT or MRI and Bone Scintigraphy

CT scan (with/without contrast) or MRI at the discretion of the investigator will be performed at Screening (within 28 days prior to Day 1) and Week 8 and 16 (± 1 week). CT or MRI will also be performed every 8 weeks afterwards in patients who continue on study. The same radiographic procedure used to define measurable lesions must be used throughout the study for each patient. Responding disease (CR or PR) will be confirmed at least 4 weeks after the criteria for the response are first met. Any patient with symptoms suggestive of disease progression should be evaluated for tumor response at the time the symptoms occur. Tumor response assessment for measurable disease will be carried out according to the Section 9.14.

18F-Fludeoxyglucose (FDG) positron emission tomography (PET) can be used in combination with a CT scan (PET/CT) at the discretion of the investigator to evaluate the metabolic response of lesions. Metabolic tumor responses will be classified following EORTC or PERCIST criteria.

Metastatic CRPC patients will also be monitored by bone scintigraphy at the same interval frequency as other imaging studies, including at screening (within 28 days prior to Week 1), Week 8, Week 16 (± 1 week) and every 8 weeks thereafter for all patients who continue on study. CRPC tumor progression in bone will be assessed per PCWG2 criteria (Section 9.14.2). Tumor responses will be assessed by the study site. Lilly or an independent reviewer may re-assess tumor responses. The process for collection of CT images for the purpose of Lilly review or independent review is described in the study manual.

9.14 Response Evaluation

9.14.1 Immune Related Response Criteria

Tumor measurement will follow irRC guidelines (Wolchok, Hoos et al. 2009, refer also to Appendix C). For irRC, the antitumor response is based on total measurable tumor burden. Only index and measurable new lesions are taken into account (in contrast to conventional WHO criteria, which do not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden). At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥ 5 × 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden:

$$\text{Tumor Burden} = SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$$

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out irPD). Decreases in tumor burden must be

assessed relative to baseline measurements (i.e., the SPD of all index lesions at screening). The irRC were derived from WHO criteria and, therefore, the thresholds of response remain the same.

The overall response according to the irRC (derived from time-point response assessments based on Tumor Burden) is as follows:

- irCR, complete disappearance of all lesions (whether measurable or not, and no new lesions), confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented
- irPR, decrease in tumor burden ≥ 50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation
- irSD, not meeting criteria for irCR or irPR, in absence of irPD
- irPD, increase in tumor burden ≥ 25% relative to nadir (minimum recorded tumor burden); in the absence of rapid clinical deterioration, confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented. Patients will continue with study drug until confirmation scan is obtained.

9.14.2 Prostate Cancer Working Group 2 Criteria in Bone

Bone is the most common site of metastatic disease in prostate cancer and frequently the only site of disease. As bone is considered not measurable by RECIST or irRC criteria and PSA is not an accurate biomarker in this disease, metastatic prostate cancer will be evaluated by Prostate Cancer Working Group 2 (PCWG2) criteria for progression in bone (Scher, Halabi et al. 2008, Ryan, Smith et al. 2013). PCWG2 criteria distinguishes between progression versus non-progression in bone. A patient is considered to have progressed by bone scan in this trial if:

- The first bone scan with ≥ 2 new lesions compared to baseline is observed ≤ 13 weeks from Cycle 1 Day 1 and is confirmed by a second bone scan taken ≥ 6 weeks later showing ≥ 2 additional new lesions (a total of ≥ 4 new lesions compared to baseline). This confirmatory bone scan is required given the prevalence of pseudoprogression often referred to as “bone scan flare”. Hence for this trial the presence of two new

lesions on the Week 7 scan must be confirmed and demonstrate an additional two new lesions on the Week 13 scan (i.e., 4 new lesions from baseline) to be considered for progression at these early timepoints.

- For interval assessment bone scans performed after 13 weeks from Cycle 1 Day 1, at least 2 new lesions from baseline must be seen visualized, and a confirmatory bone scan should be performed and demonstrate confirmation of these two (or more) new lesions (a total of $\geq$ 2 new lesions from baseline)
- The date of progression is considered the date of the first scan that demonstrates $\geq$ 2 new lesions.
- Changes in intensity of bone lesions or the extent of existing bone lesions on bone scintigraphy are not considered in the assessment of bone disease progression per PCWG2 criteria.
- Ambiguous results on bone scintigraphy may be clarified with other imaging modalities (CT/MRI) per investigator discretion.

9.14.3 Additional Tumor Response Criteria

In clinical scenarios where the tumor burden is more appropriately measured by other response criteria, such as in lymphoma patients, tumor burden should be evaluated using the most appropriate and accepted response criteria for the indication.
Tumor evaluation following RECIST 1.1 may be performed by central review in addition to irRC. Radiographic evaluation by central review may be used at the discretion of the sponsor.

9.15 Serum Tumor Markers

Serum tumor markers will be collected according to the SOE (Table 29 through Table 38). Tumor markers include CA-125 (ovarian cancer), CEA (colorectal cancer), CA 19-9 (pancreatic adenocarcinoma), and PSA (prostate cancer) and will be analyzed at the local lab.

9.16 Exploratory Biomarker Analysis (optional)

As a part of the study, exploratory biomarker analyses may be conducted with the biomarker samples. The collection of blood, body fluids, and tissue samples for biomarker analysis is optional and patients will be asked to provide written consent. Samples will be collected

according to the SOE (Table 29 through Table 38). Exploratory analyses include but are not limited to whole blood DNA samples for patient stratification (only pre-dose), serum for anti-tumor humeral immune response, Heparin blood for anti-tumor T cell responses (CPT tubes), tumor tissue for immune responses, RNA transcription profiling, proteomic methods, or pharmacogenetic analysis. Body fluids such as peritoneal or pleural exudates collected in the course of the treatment of the underlying disease can be analyzed for biomarker responses such as anti-tumor immune responses or inflammatory cytokines, pending patients consent. These analyses will be used to identify patient characteristics that may characterize or predict responsiveness to AM0010 treatment. Approximately 30 mL of blood will be collected for each biomarker sample draw.

9.17 Collection of Tumor Tissue (optional)

Collection of archived tumor material and fresh biopsies is optional and patients will be asked to consent to the access of pre-existing and/or samples collected during treatment frozen and/or paraffin-embedded tumor samples for biomarker development (according to SOE, Table 31 through Table 38). Immunohistochemical staining of these tumor samples may be conducted to assess the degree of immune cell infiltration and expression of immune cell surface molecules and cytokines within the tumor. Refer to Laboratory Manual for additional information.

9.18 Blood Volume

It is anticipated that subjects enrolled in this study will agree to provide whole blood for safety, PK, and PD assessment during their participation in this study as listed in Table 28. Blood draws for exploratory biomarkers are optional.

Table 28: Approximate Total Blood Volume between Screening and Day 113

Procedure	Volume per Collection, mL	Number of Collections	Total Volume, mL
Laboratory safety (chemistry + hematology)	15	17	255
PK / Anti-AM0010 antibody sample collection	5	24	120
Serum pregnancy test (women only)	5	10	50
Serum tumor marker	5	4	20
Exploratory Biomarkers (optional)			130

EDTA blood	4	4	
PaxGene RNA	2.5	4	
• Serum	10	4	
• CPT tubes (PBMC)	2 x 8	4	
TOTAL			575

10 REMOVAL AND REPLACEMENT OF PATIENTS

10.1 Removal of Patients

Patients have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution. The Investigator and Lilly also have the right to withdraw a patient from the study at any time for any reason.

Withdrawal of full consent for a study means that the patient does not wish to receive further investigational treatment and does not wish to or is unable to continue further study participation. Any patient may withdraw full consent to participate in the study at any time during the study. The Investigator will discuss with the patient the most appropriate way to withdraw to ensure the patient's health.

Withdrawal of partial consent means that the patient does not wish to take investigational product any longer but is still willing to collaborate in providing further data by continuing on study (e.g., participate in all subsequent study visits or procedures). Patients may decline to continue receiving investigational product at any time during the study. These patients, as well as those who have stopped receiving investigational product for other reasons (e.g., Investigator or Sponsor concern), should continue the schedule of study events.

The reason for withdrawal will be recorded on the study completion CRF page. If the patient is withdrawn due to an adverse event, the Investigator will arrange for the patient to have follow-up visits until the adverse event has resolved or stabilized.

Reasons for removal from investigational product or observation may include:

- Withdrawal of consent
- Disease progression as defined by irRC (after confirmation scan is obtained) or the tumor evaluation criteria most appropriately used or rapid clinical deterioration
- Study is terminated by the sponsor
- Significant protocol deviation
- Patient noncompliance in the opinion of the investigator or the medical monitor
- Repeated dose interruptions

- Adverse event (report on adverse event CRF page)
- Other as specified by the Investigator
- DLT related to AM0010

Should a patient (or a legally acceptable representative) request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal.

10.2 Replacement of Patients

In Dose Escalation, if a study patient is withdrawn from the study for any reason other than DLT prior to completion of the 28 day DLT observation period, a replacement patient may be enrolled at the same dose level as the replaced patient. In Expansion Cohorts, if study patients are withdrawn from the study prior to the imaging assessment by CT or MRI in Week 8 for any reason other than a DLT, an additional patient may be enrolled. Up to a maximum of 10 patients per dose escalation cohort may be added.

11 SAFETY DATA COLLECTION, RECORDING, AND REPORTING

11.1 Definitions

11.1.1 Adverse Events (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation patient after administration of a pharmaceutical (investigational) product and which does not necessarily have a causal relationship with study drug. An AE 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 (ICH E2A II/A/1, 21 CFR 312.32).

11.1.1.1 Progressive Disease

Natural progression or deterioration of the solid tumor under study should be recorded as an AE or SAE only if judged by the Investigator to have unexpectedly worsened in severity and/or frequency or changed in nature during the study. When recording an unanticipated worsening of the solid tumor under study (including new sites of metastasis and death due to progression of primary solid tumor) on an AE CRF page, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “Accelerated progression of carcinoma” or “Metastases to bone”).

11.1.1.2 Pregnancy

Any pregnancy that occurs in a patient during the study should be recorded on a Pregnancy Reporting Form and expeditiously reported to the Sponsor to facilitate outcome follow-up. Abortion, whether it is accidental, therapeutic, or spontaneous, should be reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the investigational treatment should be reported as an SAE.

A female patient should immediately inform the Investigator if she becomes pregnant during the study and will no longer receive AM0010. Pregnancies beginning within 90 days after the completion of the last dose of study drug must also be reported to the Investigator. The Investigator should counsel the patient, discussing the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue

until conclusion of the pregnancy. Male patients should not father a child while participating in this study. Pregnancy occurring in the partner of a male patient participating in the study should be reported to the Investigator and Sponsor.

11.1.2 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes:

- Death
- Life threatening event (results in an immediate risk of death from the reaction as it occurred)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and/or may require intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (ICH E2A/II/B, 21 CFR 312.32).

11.2 Reporting Procedures for All Adverse Events

The Investigator is responsible for ensuring that all adverse events (as defined in Section 11.1.1 and as further specified below) observed by the Investigator or reported by patients are collected and recorded in the patients' medical records, in the CRF, and, for serious adverse events (SAEs), on the serious adverse event report (SAER) form. The principal method of collection of adverse events will be through interview with study patients. These adverse events will include the following:

- All serious adverse events as defined in Section 11.1.2
- All non-serious adverse events as defined in Section 11.1.1

Serious and non-serious adverse events need to be reported if they occur after the first receipt of the investigational product and

- before the 30 day follow up visit
- within 30 days after stopping treatment, if patient is lost to follow up

The following adverse event attributes must be assigned by the Investigator: adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known); event description (with detail appropriate to the event); 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, discharge summaries, and extracts from medical records or CRF pages.

Investigators are required to assess whether there is a reasonable possibility that the investigational product caused or contributed to an AE.

Many terms and scales are used to describe the degree of causality between an investigational product and an event. There is currently no standard international nomenclature. The expression “reasonable causal relationship” is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship (ICH E2A, III/A/1).

Determination of whether there is a reasonable possibility that an investigational product caused or contributed to an AE includes assessing temporal relationships, biologic plausibility, dechallenge/rechallenge information (if available), association (or lack of association) with underlying disease, and presence (or absence) of a more likely cause.

The relationship to study drug therapy should be assessed using the following definitions:

Not Related: Evidence exists that the adverse event has an etiology other than the study drug (such as a preexisting condition, underlying disease, intercurrent illness, or concomitant medication).

Related: A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the patient’s clinical state or concomitant therapies and appears with some degree of certainty to be related based on the known

therapeutic and pharmacologic actions of the drug. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

Attribution to the investigational product should be considered a causal relationship when an adverse event is at least a reasonable possibility (i.e., a noxious and unintended response to any dose of a drug product for which there is a reasonable possibility that the product caused the response). In this definition, the phrase "a reasonable possibility" means that the relationship cannot be ruled out. Classifying a case as "probably related," "possibly related," "remotely related," or "unlikely related" to the drug or biological product would signify that a causal relationship between the product and an adverse event could not be ruled out and, thus, the adverse event would be considered a serious adverse drug reaction.

Medically significant adverse events considered related to the investigational product by the Investigator or the Sponsor will be followed until resolved or considered stable. All serious adverse events will be followed until resolution or until the Investigator and Sponsor both judge the event to be chronic or stable.

The Investigator will classify the intensity of an adverse event on the case report forms. Specific criteria for the intensity of adverse events are described in the Common Terminology Criteria for Adverse Events v 4.02 (CTCAE: National Cancer Institute) grades (Grades 1 to 5).

It will be left to the Investigator’s clinical judgment to determine whether an adverse event is related and of sufficient severity to require the patient’s removal from treatment or from the study. A patient may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the patient should be strongly encouraged to undergo an EOT assessment and be under medical supervision until symptoms cease or the condition becomes stable.

11.3 Serious Adverse Event Reporting Procedures

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

- Death

- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect

All AEs occurring after signing the ICF are recorded in the CRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the participant has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 8.3.1) if it is considered reasonably possibly related to study procedure.

If an ongoing SAE that is considered related to study drug remains unresolved at the conclusion of the study treatment, additional follow-up must continue until resolution or stabilization of the SAE.

If an SAE is present at the End of Treatment visit, the SAE (and associated AEs and concomitant medications) should be followed to resolution or until the Investigator assesses the subject as stable, or the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the event.

If study drug is discontinued because of an SAE, this information must be included in the SAE report.

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. Participants with a serious hepatic adverse event should have additional data collected using the CRF.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. 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.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (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 ended participation with 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 the designee.

The Investigator has responsibility for notifying the relevant IRB of all SAEs or new safety information in accordance with international and local laws and regulations. It is the responsibility of Lilly or the designees to notify regulatory agencies of all SUSARS within the timeframes required by applicable local laws or regulations.

11.4 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, monitor quality, and to facilitate process and product improvements.

Participants 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.

12 STATISTICAL CONSIDERATIONS

12.1 Sample Size Considerations

The exact number of patients required for this trial is dependent on the MTD and cannot be accurately predicted. This trial with AM0010 is expected to enroll at least 3 patients per cohort in Dose Escalation, depending upon the observation of DLTs. 15 additional patients will be enrolled at or below the MTD in every Dose Expansion Cohort, at the Sponsor's discretion, to evaluate further the safety, PK, and pharmacodynamics of AM0010. The cohort size of 15 excludes a 33% DLT rate if 2 or less patients experience a DLT in one of the indication specific expansion cohorts or expansion cohorts. An administrative decision to stop the trial may be made by the Sponsor at any time.

12.1.1 Part H in PD-1 Refractory Melanoma Patients

Melanoma patients with tumor progression after four to six doses of anti-PD-1 antagonistic antibodies (anti-PD1 early refractory melanoma patients) have very limited probability for a delayed tumor response (early pseudoprogression = 3.8%) (Hodi, Ribas et al. 2014). Early anti-PD-1 refractory melanoma patients may have an increased ORR when treated with the combination of anti PD-1 and AM0010 after progression on anti PD-1 monotherapy. To test this hypothesis, an expansion cohort of 20 early anti-PD-1 refractory patients will be enrolled for the treatment with AM0010 and pembrolizumab. If 4 responses occur in this cohort of 20 patients, the true response rate is at least 10% with a probability of at least 80%.

12.1.2 Part C in Pancreatic Carcinoma Progressed on Prior Gemcitabine

More than 50% of patients with locally advanced or metastatic pancreatic carcinoma receive a gemcitabine based therapy (Gemcitabine or Gemcitabine based regimen) as a first LOT. The majority of those patients progress and are in need to receive additional efficacious treatment. Therapeutic options include 5-FU and oxaliplatin based regimens including FOLFOX (NCCN 2014). Less than 5% of patients had an objective response to FOLFOX in this patient population, but the mOS was 5.9 months (Oettle, Riess et al. 2014). In a dose escalation study of AM0010 and FOLFOX, all patients with very advanced pancreatic cancer treated with this combination had at least stable disease (disease control rate 100%). One of 5 patients had a partial response. A combination of AM0010 and FOLFOX may therefore

provide benefit to patients with locally advanced or metastatic pancreatic carcinoma progressed on a 1st LOT gemcitabine based therapy. To test this hypothesis, a cohort of 20 pancreatic cancer patients, which progressed on or after prior gemcitabine based therapy, will be enrolled in Part C expansion Cohort 1. Using exact binomial testing with a one-sided 5% alpha, a cohort of 20 patients would have 81% power to detect an observed response rate in the experimental patients of 30% or 6 patients as statistically higher than 5%.

12.1.3 Part I Expansion Cohort 1 – NSCLC Patients

Nineteen percent of patients with advanced NSCLC (n=292) respond to nivolumab monotherapy (Borghaei, Paz-Ares et al. 2015). Preliminary evidence suggests that patients treated with a combination of AM0010 and a PD-1 inhibitor may have a significantly improved response rate. To test this hypothesis, a cohort of 30 anti PD-1 naïve NSCLC patients will be enrolled in Part I expansion Cohort 1 (AM0010 + nivolumab). Using exact binomial testing with a one-sided 5% alpha, a cohort of 30 patients would have 84% power to detect an observed response rate.

12.1.4 Part I Expansion Cohort 2 – RCC Patients

Twenty-five percent of patients with advanced renal-cell carcinoma (n=410) had a response to nivolumab (Motzer, Escudier et al. 2015). Preliminary evidence suggests that RCC patients treated with a combination of AM0010 and a PD-1 inhibitor may have a significantly improved response rate than on nivolumab monotherapy. To test this hypothesis, a cohort of 30 anti PD-1 naïve RCC patients will be enrolled in Part I expansion Cohort 2 (AM0010 + nivolumab). Using exact binomial testing with a one-sided 5% alpha, a cohort of 30 patients would have 84% power to detect an observed response rate in the experimental patients of 43% or 13 patients (as statistically higher than 25%).

12.1.5 Part J – TNBC Patients

One of the preferred 1st or 2nd line of treatments for patients with TNBC is a combination therapy with carboplatin and gemcitabine (NCCN 2014). The ORR for this treatment is only 32%. Preliminary evidence obtained in this study indicates that a combination of carboplatin and paclitaxel with AM0010 provides significant benefit to patients with TNBC at very progressed stages of the disease. The combination of AM0010 with carboplatin and

gemcitabine may therefor also provide benefits to patients at 1st or 2nd LOT. To test this hypothesis, a cohort of 20 TNBC patients with a maximum of 1 prior therapy for metastatic disease will be enrolled in Part J. Using exact binomial testing with a one-sided 5% alpha, a cohort of 20 patients would have 80% power to detect an observed response rate in the experimental patients of 62% (as statistically higher than 32%).

12.2 Access to Individual Patient Treatment Assignments

This is an open label study and all patients in this study will receive AM0010.

12.3 General Methods of Data Analysis

Data from this study will be summarized descriptively by dose and time as appropriate. Descriptive statistics including means, medians, standard deviations, and ranges will be calculated for continuous variables, and categorical data will be summarized using frequency counts and percentages.

12.4 Analysis Populations

The Safety Population comprises all patients who received any amount of study medication.

The DLT Population comprises all patients who complete the DLT assessment period. The Response Population will be comprised of all patients who have a baseline and a post baseline measurement of tumor burden.

12.5 Demographic and Safety Data

Demographic variables include: age, sex, ethnicity, and race. Other baseline characteristics include height, weight, body mass index, and medical history. Demographic and baseline characteristics will be summarized by treatment group.

12.6 Clinical Safety Data

Safety variables to be summarized include vital signs, adverse events, and clinical laboratory results (hematology, chemistry, and urinalysis).

Vital signs (including heart rate, diastolic blood pressure, systolic blood pressure, and temperature) will be summarized in terms of observed values and changes from baseline.

Adverse events will be coded to the preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries will present by preferred term the frequency and percentage of patients reporting each observed event with onset on or after initiation of study medication.

Laboratory data will be summarized in terms of observed values, changes from baseline, values relative to normal ranges, and changes from baseline relative to normal ranges. Listings will flag laboratory values that are outside of normal range.

12.6.1 Pharmacokinetics Data Analysis

Summary statistics (mean, standard deviation, minimum, maximum, n, and coefficient of variation) will be calculated for serum concentrations of AM0010 at each time point. Individual and mean AM0010 serum concentration vs. time curves will also be generated.

Pharmacokinetic parameter values will be estimated using WinNonlin pharmacokinetic software (v5.2 or a more recent version). A non-compartmental model will be used to generate parameter estimates, provided there are sufficient data to permit calculations. Pharmacokinetic parameters to be calculated include C_{max}, $C_{min,}$ AUC, Cl, and $t_{½}$.

Summary statistics (i.e., mean, standard deviation, median, minimum, maximum, n, and coefficient of variation) will be presented for all pharmacokinetic parameters.

13 ETHICS

13.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

This study will be conducted in accordance with the US Code of Federal Regulations governing the protection of human patients (21 CFR 50), Institutional Review Board (IRB) or Independent Ethics Committees (IEC) (21 CFR 56), the obligations of clinical Investigators (21 CFR 312) and the ICH document “Guidance for Industry—E6 Good Clinical Practice: Consolidated Guidance,” dated April 1996.

The Protocol and Informed Consent used must be approved by the Investigator's IRB/IEC before the study is initiated. Documentation of this approval signature and the date of the IRB/IEC approval must be provided to the study Sponsor (Lilly).

The Sponsor expects the Investigator to comply with local IRB/IEC requirements. The Investigator will also comply with current standards of Good Clinical Practice (GCP), particularly in reference to the safety and rights of the patients. Investigators are encouraged to discuss any ethical issues that arise prior to or during the conduct of the study with the Sponsor.

13.2 Ethical Conduct of the Study

This study will be conducted in compliance with GCP according to the US Code of Federal Regulations (21 CFR), International Conference on Harmonization (ICH) guidelines, and local ethical and legal requirements that are consistent with the most current version of the Declaration of Helsinki.

13.3 Informed Consent

The Informed Consent must comply with all applicable US Code of Federal Regulations (21 CFR 50), the Health Insurance Portability and Accountability Act (HIPAA) if required, and the ICH document “Guidance for Industry—E6 Good Clinical Practice: Consolidated Guidance,” dated April 1996. It should also include any additional information required by local laws relating to institutional review.

A statement that patient medical records must be available for investigations into serious adverse events must be included in the Informed Consent Form. It should also include any additional information required by local laws relating to institutional review.

The acquisition of informed consent should be documented in the patient's medical records, and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed informed consent form should be retained in the patient's source record, and a copy of the signed consent form should be provided to the patient or legally acceptable representative.

If a potential patient is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the informed consent form to the patient and must allow for questions. Thereafter, both the patient and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

Written informed consent and HIPAA authorization (if required) will be obtained from all study patients prior to any tests or evaluations as required by the institution and applicable regulations. A copy of the signed informed consent will be provided to each patient and will also be maintained in the patient's medical record.

14 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for complying with all local, state, and federal regulations relating to performing clinical research with an investigational product. The Investigator is responsible for ensuring that the investigation is conducted according to the signed Investigator Agreement (FDA Form 1572), the approved protocol, and applicable regulations for protecting the rights, safety, and welfare of study patient under the Investigator's care. The Investigator is additionally responsible for the control of investigational product and for providing accurate and verifiable data to the Sponsor.

The Investigator must obtain the Informed Consent and HIPAA authorization of each patient before participation in the study. The Investigator must assure initial and continuing review of the study by an IRB/IEC that complies with applicable national and local regulations.

The Investigator will maintain minutes of meetings with study staff and document training of research study personnel for conduct of the study, including qualifications, experience, and study role.

Other Investigator responsibilities relative to the IRB/IEC include the following:

- Submit to the IRB/IEC for review any advertisements that will be used to recruit patients
- Submit all protocol amendments, revisions of the Investigator’s Brochure, or revisions of the Informed Consent to the IRB/IEC for review
- If Lilly notifies the Investigator about serious adverse events reported in other studies associated with this investigational product, report that information to the IRB/IEC
- Provide the IRB/IEC with any other information it requests before or during the conduct of the study
- Report to the IRB/IEC all adverse drug reactions that are serious, unexpected, and possibly or probably related to investigational product
- Maintain a file of study-related information
- Update the IRB/IEC on a minimum of a yearly basis.

14.1 Investigator's Brochure and Standard Operating Procedures

The Investigator will be given a copy of the most current version of the Investigator's Brochure and appropriate SOPs for all laboratory procedures. The Investigator is obligated to become familiar with all sections of these documents prior to initiation of the study.

14.2 Informed Consent

The Investigator is responsible for the content of the Informed Consent and HIPAA authorization, with approval by the Sponsor.

The Investigator (or properly qualified designee) is responsible for obtaining Informed Consent and HIPAA authorization from each study patient participating in the study. All pertinent aspects of the study must be explained to the study patient before he/she signs the Informed Consent and HIPAA authorization. Informed Consent and HIPAA authorization must be obtained from the patient before any activity or treatment is undertaken which is not part of routine care. This includes but is not limited to the performance of diagnostic or therapeutic procedures and the administration of the investigational product. The patient must be informed that their medical records must be made available for investigation of adverse events and serious adverse events.

14.3 Study Initiation

Before the investigational product can be shipped to the study site and before the study can begin, the following documents must be submitted and received by the Sponsor:

- Original US FDA Form 1572, signed by the Principal Investigator
- Documentation of the IRB/IEC approval of the protocol and Informed Consent
- A copy of the IRB/IEC-approved Informed Consent and HIPAA authorization that will be used
- Copy of current curriculum vitae and medical licenses of the Principal Investigator
- A membership list of the IRB/IEC or statement of compliance
- Investigator's financial disclosure form.

The Sponsor will notify the site when the study can begin.

14.4 Data Handling and Record Keeping

The Investigator must maintain a file for each patient that includes the signed Informed Consent and Investigator copies of all CRFs completed for that patient.

14.5 Study Documentation and Archive

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 ECG result reports, pharmacy records, microfiches, radiographs, and correspondence.

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

In addition, all original source documents supporting entries on the case report forms must be maintained and be readily available.

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

14.6 Audits and Inspections

The Investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the Quality Assurance Unit or its designees or to health authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents.

14.7 Monitoring the Study

It is understood that the responsible monitor (or designee) will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various records of the study (CRFs and other pertinent data), provided that patient confidentiality is maintained in accordance with local requirements.

The monitor is responsible for inspection of the CRFs at regular intervals throughout the study, verification of the adherence to the protocol, and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to laboratory test reports and other patient records needed to verify the entries on the CRF. The Investigator (and his/her deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

14.8 Confidentiality of Trial Documents and Patients Records

The Investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the Sponsor, patients should not be identified by their names but by an identification code. The Investigator should keep a patient enrollment log relating codes to the names of patients. The Investigator should maintain documents not for submission to Lilly, e.g., patients' written consent forms, in strict confidence.

14.9 Retention of Data

Data related to this study must be stored according to the regulations pertaining to studies performed under an IND (21 CFR §312.62[c]).

An Investigator shall retain records required to be maintained under this part (case histories and data collected as part of this trial for all study patients) for a period of 2 years following the date a marketing application is approved for the drug for the indications for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the FDA is notified.

15 SPONSOR RESPONSIBILITIES

Lilly is the Sponsor for this study.

16 REFERENCES

Asadullah, K., W. Sterry and H. D. Volk (2003). "Interleukin-10 therapy--review of a new approach." Pharmacol Rev **55**(2): 241-269.

ASCO. (2014). "ASCO guidelines for the treatment of cancer." from http://www.asco.org/quality-guidelines/guidelines.

Borghaei, H., L. Paz-Ares, L. Horn, D. R. Spigel, M. Steins, N. E. Ready, L. Q. Chow, E. E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhaufl, O. Arrieta, M. A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D. E. Gerber, S. N. Gettinger, C. M. Rudin, N. Rizvi, L. Crino, G. R. Blumenschein, Jr., S. J. Antonia, C. Dorange, C. T. Harbison, F. Graf Finckenstein and J. R. Brahmer (2015). "Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer." N Engl J Med **373**(17): 1627-1639.

Burger, R. A., M. F. Brady, M. A. Bookman, G. F. Fleming, B. J. Monk, H. Huang, R. S. Mannel, H. D. Homesley, J. Fowler, B. E. Greer, M. Boente, M. J. Birrer, S. X. Liang and G. Gynecologic Oncology (2011). "Incorporation of bevacizumab in the primary treatment of ovarian cancer." N Engl J Med **365**(26): 2473-2483.

Cartwright, T. H., A. Cohn, J. A. Varkey, Y. M. Chen, T. P. Szatrowski, J. V. Cox and J. J. Schulz (2002). "Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer." J Clin Oncol **20**(1): 160-164.

Douillard, J. Y., K. S. Oliner, S. Siena, J. Tabernero, R. Burkes, M. Barugel, Y. Humblet, G. Bodoky, D. Cunningham, J. Jassem, F. Rivera, I. Kocakova, P. Ruff, M. Blasinska-Morawiec, M. Smakal, J. L. Canon, M. Rother, R. Williams, A. Rong, J. Wiezorek, R. Sidhu and S. D. Patterson (2013). "Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer." N Engl J Med **369**(11): 1023-1034.

Fedorak, R. N., A. Gangl, C. O. Elson, P. Rutgeerts, S. Schreiber, G. Wild, S. B. Hanauer, A. Kilian, M. Cohard, A. LeBeaut and B. Feagan (2000). "Recombinant human interleukin 10 in the treatment of patients with mild to moderately active Crohn's disease. The Interleukin 10 Inflammatory Bowel Disease Cooperative Study Group." Gastroenterology **119**(6): 1473-1482.

Fridman, W. H., F. Pages, C. Sautes-Fridman and J. Galon (2012). "The immune contexture in human tumours: impact on clinical outcome." Nat Rev Cancer **12**(4): 298-306.

Hainsworth, J. D., M. S. Rubin, E. R. Arrowsmith, J. Khatcheressian, E. J. Crane and L. A. Franco (2013). "Pazopanib as second-line treatment after sunitinib or bevacizumab in patients with advanced renal cell carcinoma: a Sarah Cannon Oncology Research Consortium Phase II Trial." Clin Genitourin Cancer **11**(3): 270-275.

Hamid, O., C. Robert, A. Daud, F. S. Hodi, W. J. Hwu, R. Kefford, J. D. Wolchok, P. Hersey, R. W. Joseph, J. S. Weber, R. Dronca, T. C. Gangadhar, A. Patnaik, H. Zarour, A. M. Joshua, K. Gergich, J. Elassaiss-Schaap, A. Algazi, C. Mateus, P. Boasberg, P. C. Tumeh, B. Chmielowski, S. W. Ebbinghaus, X. N. Li, S. P. Kang and A. Ribas (2013). "Safety and

tumor responses with lambrolizumab (anti-PD-1) in melanoma." N Engl J Med **369**(2): 134-144.

Hodi, F. S., S. J. O'Day, D. F. McDermott, R. W. Weber, J. A. Sosman, J. B. Haanen, R. Gonzalez, C. Robert, D. Schadendorf, J. C. Hassel, W. Akerley, A. J. van den Eertwegh, J. Lutzky, P. Lorigan, J. M. Vaubel, G. P. Linette, D. Hogg, C. H. Ottensmeier, C. Lebbe, C. Peschel, I. Quirt, J. I. Clark, J. D. Wolchok, J. S. Weber, J. Tian, M. J. Yellin, G. M. Nichol, A. Hoos and W. J. Urba (2010). "Improved survival with ipilimumab in patients with metastatic melanoma." N Engl J Med **363**(8): 711-723.

Hodi, F. S., A. Ribas, A. Daud, O. Hamid, C. Robert, R. Kefford, W.-J. Hwu, T. C. Gangadhar, A. M. Joshua, P. Hersey, P. Weber, R. W. Joseph, H. Zarour, R. Dronca, L. Gammage, D. Hille, D. Xue, S. P. Kang, P. Chun, S. W. Ebbinghaus, A. Perrone and J. D. Wolchok (2014). "Patterns of response in patients with advanced melanoma treated with Pembrolizumab (MK-3475) and evaluation of immune-related response criteria (irRC)." Journal for ImmunoTherapy of Cancer **2 (suppl 3)**: 103.

Motzer, R. J., B. Escudier, D. F. McDermott, S. George, H. J. Hammers, S. Srinivas, S. S. Tykodi, J. A. Sosman, G. Procopio, E. R. Plimack, D. Castellano, T. K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T. C. Gauler, T. Ueda, Y. Tomita, F. A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J. S. Simon, L. A. Xu, I. M. Waxman, P. Sharma and I. CheckMate (2015). "Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma." N Engl J Med **373**(19): 1803-1813.

Mumm, J. B., J. Emmerich, X. Zhang, I. Chan, L. Wu, S. Mauze, S. Blaisdell, B. Basham, J. Dai, J. Grein, C. Sheppard, K. Hong, C. Cutler, S. Turner, D. LaFace, M. Kleinschek, M. Judo, G. Ayanoglu, J. Langowski, D. Gu, B. Paporello, E. Murphy, V. Sriram, S. Naravula, B. Desai, S. Medicherla, W. Seghezzi, T. McClanahan, S. Cannon-Carlson, A. M. Beebe and M. Oft (2011). "IL-10 elicits IFNgamma-dependent tumor immune surveillance." Cancer Cell **20**(6): 781-796.

NCCN. (2014). "NCCN guidelines for the treatment of cancer by site." from http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site.

O'Shaughnessy, J., C. Osborne, J. E. Pippen, M. Yoffe, D. Patt, C. Rocha, I. C. Koo, B. M. Sherman and C. Bradley (2011). "Iniparib plus chemotherapy in metastatic triple-negative breast cancer." N Engl J Med **364**(3): 205-214.

Oettle, H., H. Riess, J. M. Stieler, G. Heil, I. Schwaner, J. Seraphin, M. Gorner, M. Molle, T. F. Greten, V. Lakner, S. Bischoff, M. Sinn, B. Dorken and U. Pelzer (2014). "Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial." J Clin Oncol **32**(23): 2423-2429.

Ryan, C. J., M. R. Smith, J. S. de Bono, A. Molina, C. J. Logothetis, P. de Souza, K. Fizazi, P. Mainwaring, J. M. Piulats, S. Ng, J. Carles, P. F. Mulders, E. Basch, E. J. Small, F. Saad, D. Schrijvers, H. Van Poppel, S. D. Mukherjee, H. Suttmann, W. R. Gerritsen, T. W. Flaig, D. J. George, E. Y. Yu, E. Efstathiou, A. Pantuck, E. Winquist, C. S. Higano, M. E. Taplin, Y. Park, T. Kheoh, T. Griffin, H. I. Scher, D. E. Rathkopf and C.-A.-. Investigators (2013).

"Abiraterone in metastatic prostate cancer without previous chemotherapy." N Engl J Med **368**(2): 138-148.

Scher, H. I., S. Halabi, I. Tannock, M. Morris, C. N. Sternberg, M. A. Carducci, M. A. Eisenberger, C. Higano, G. J. Bubley, R. Dreicer, D. Petrylak, P. Kantoff, E. Basch, W. K. Kelly, W. D. Figg, E. J. Small, T. M. Beer, G. Wilding, A. Martin, M. Hussain and G. Prostate Cancer Clinical Trials Working (2008). "Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group." J Clin Oncol **26**(7): 1148-1159.

Von Hoff, D. D., T. Ervin, F. P. Arena, E. G. Chiorean, J. Infante, M. Moore, T. Seay, S. A. Tjulandin, W. W. Ma, M. N. Saleh, M. Harris, M. Reni, S. Dowden, D. Laheru, N. Bahary, R. K. Ramanathan, J. Tabernero, M. Hidalgo, D. Goldstein, E. Van Cutsem, X. Wei, J. Iglesias and M. F. Renschler (2013). "Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine." N Engl J Med **369**(18): 1691-1703.

Wang-Gillam, A., C. P. Li, G. Bodoky, A. Dean, Y. S. Shan, G. Jameson, T. Macarulla, K. H. Lee, D. Cunningham, J. F. Blanc, R. A. Hubner, C. F. Chiu, G. Schwartsmann, J. T. Siveke, F. Braiteh, V. Moyo, B. Belanger, N. Dhindsa, E. Bayever, D. D. Von Hoff, L. T. Chen and N.-S. Group (2015). "Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial." Lancet.

Weiss, G. and L. T. Goodnough (2005). "Anemia of chronic disease." N Engl J Med **352**(10): 1011-1023.

Wilke, H., K. Muro, E. Van Cutsem, S. C. Oh, G. Bodoky, Y. Shimada, S. Hironaka, N. Sugimoto, O. Lipatov, T. Y. Kim, D. Cunningham, P. Rougier, Y. Komatsu, J. Ajani, M. Emig, R. Carlesi, D. Ferry, K. Chandrawansa, J. D. Schwartz, A. Ohtsu and R. S. Group (2014). "Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial." Lancet Oncol **15**(11): 1224-1235.

Wolchok, J. D., A. Hoos, S. O'Day, J. S. Weber, O. Hamid, C. Lebbe, M. Maio, M. Binder, O. Bohnsack, G. Nichol, R. Humphrey and F. S. Hodi (2009). "Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria." Clin Cancer Res **15**(23): 7412-7420.

Wolchok, J. D., H. Kluger, M. K. Callahan, M. A. Postow, N. A. Rizvi, A. M. Lesokhin, N. H. Segal, C. E. Ariyan, R. A. Gordon, K. Reed, M. M. Burke, A. Caldwell, S. A. Kronenberg, B. U. Agunwamba, X. Zhang, I. Lowy, H. D. Inzunza, W. Feely, C. E. Horak, Q. Hong, A. J. Korman, J. M. Wigginton, A. Gupta and M. Sznol (2013). "Nivolumab plus ipilimumab in advanced melanoma." N Engl J Med **369**(2): 122-133.

17 APPENDICES

Appendix A – Schedule of Events

Patients enrolled into the Continued Access period, as defined in Section 5.4.7, will follow the procedures in the table provided in Appendix B.

Table 29: Appendix A1 – Schedule of Events for PART A, B, C Escalation Cohorts

Examination	Screening	Treatment																				Follow up		
Weeks		1					2	3	4	5						6	7	8	9	Continued Visits Bi- Weekly	EOT	30 days	Every 8 weeks	Every 3 months
Days	-28 to -1	1					2	8	15	22	29					36	43	50	57			- 3 / +15 days	± 7 days	± 7 days
Hours (relative to dosing)		0	2	6	8	12	0	0			0	2	6	8	12	24								
GENERAL AND SAFETY AWARENESS																								
Informed Consent	X																							
Clinical Evaluation (a)	X	X					X	X	X	X	X						X	X	X	X	X	X	X		
Vital signs (b)	X	X	X	X			X	X	X	X	X						X	X	X	X	X	X	X		
12-lead ECG (c)	X1	X3		X1			X1	X1	X1		X1							X1		X1	X1	X1	X1		
Prior/Concomitant Medication Review	X	X					X	X	X	X	X						X	X	X	X	X	X	X		X (n)
Adverse Events Review		X	X	X			X	X	X	X	X						X	X	X	X	X	X	X		
Survival Status																									X
STUDY DRUG ADMINISTRATION																								
Administer AM0010 daily dose		X (p)					X	X	X	X	X						X	X	X	X	X				
PART B-CHEMOTHERAPY (j)		X								X							X			64,85,106				
PART C-CHEMOTHERAPY (k)		X							X		X							X		X	X				
LABORATORY ASSESSMENTS																								
Safety Lab Tests (d)	X	X		X			X	X	X	X	X						X	X	X	X	X	X	X		
Pregnancy Test (e)	X	X							X		X							X		X	X	X	X		
Dispense AM0010 kit							X	X	X	X	X						X	X	X	X2	X2				
AM0010 PK / Anti AM0010 Antibody Collection (o)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Exploratory Biomarker Sample (g)		X									X								X	X (m)	X			
Serum Tumor Markers (h)		X									X								X	X (l)	X		X	
Tumor Tissue (i)		X	Every 8 weeks																		X			
IMAGING ASSESSMENTS																								
Tumor assessment CT or MRI; and bone scintigraphy for CRPC patients (f)	X	(Every 8 weeks)																		X (m)	X		X	

(a) Clinical evaluation will be obtained at screening weekly up to Week 57, then bi-weekly, and at the EOT. Clinical Evaluation will include: physical exam, ECOG status and weight. Weight measurement in kg and without shoes. Medical history and height at screening only.
(b) Vital signs (pulse, blood pressure, respiratory rate and temperature) will be collected after being seated or in a semi-recumbent position.
(c) ECG will be performed in patients seated, semi-recumbent, or supine for at least 5 minutes. X1 = single ECG; X3 = three independent single ECG.
(d) Safety lab tests are listed in Table 26 and Table 27. If screening labs are done within 3 days prior, then screening labs can be used as Day 1 labs.
(e) Serum pregnancy test performed at Screening; urine or serum pregnancy test at all other time points.
(f) Tumor evaluation by CT or MRI and bone scintigraphy (CRPC patients only) will be performed during screening (within 4 weeks prior to Day 1); at Week 8 and 16 (± 1 week), and every 8 weeks until irPD. The same radiographic procedure used to define measurable or non-measurable lesions must be used throughout the study for each patient). Tumor Response will be assessed by the study site and may also be reviewed by Lilly or by an independent reviewer. The process for collection of CT images for purpose of Lilly or central response review is described in the study manual.
(g) Collection of blood samples for biomarkers is optional and patients will be asked to provide written consent (up to 3 days prior).
(h) Serum tumor markers include CA-125, CEA, CA 19-9, and PSA as appropriate based on the patient's tumor type (up to 3 days prior).
(i) The collection of archived tumor tissues and fresh biopsies is optional and patients will be asked to provide written consent. Although scheduled for every 8 weeks from Day 1, collection timepoints are up to the Investigator's discretion, as long as they pose minimal risk to the patient (up to 10 days prior to Day 1 and ± 7 days during other visits).
(j) Part B- Daily SC injection with AM0010;
Day 1 of each 21-day cycle: Paclitaxel or Docetaxel and Carboplatin or Cisplatin
After a maximum of 5 or 6 cycles of chemotherapy, patients may continue with AM0010 monotherapy
(k) Daily SC injection with AM0010 with
– Part C: FOLFOX; Day 1/2 of each 14-day cycle: Oxaliplatin, Leucovorin followed by 5FU. After discontinuation of Oxaliplatin, patients may continue to receive AM0010, Leucovorin and 5-FU.
(l) Every 4 weeks, up to 3 days prior
(m) Every 8 weeks (starting on C1D1)
(n) Cancer treatment only
(o) PK/Anti-AM0010 antibody collection windows
Day 1: pre-dose (3 days prior), post-dose 2h (± 15 min), 6h (± 30 min), 8h (± 30 min), 12h (± 60 min)
Day 2: 24 hours after Day 1 dose (± 1 hour)
Days 8, 15, 22, 29: pre-dose (up to 1 day prior)

Days 36, 43, 57: pre-dose (± 1 day)
Continued visits: pre-dose (± 2 days)

(p) Staff administered and training for AM0010 self-injection

Table 30: Appendix A2 – Schedule of Events for Parts A Expansion Cohorts

Examination	Screening	Treatment								Follow up		
Cycles		Cycle 1						Continued AM0010 (starting Day 57)	EOT	30 days after EOT	Every 8 weeks	Every 3 months
Days	-28 to -1	1		8	15	29	43	Repeat every 28 days		- 3 / +15 days	± 7 days	± 7 days
Hours (relative to dosing)		0	6									
GENERAL AND SAFETY AWARENESS												
Informed Consent	X											
Clinical Evaluation (a)	X	X		X	X	X	X	X	X	X		
Vital signs (b)	X	X	X	X	X	X	X	X	X	X		
12-lead ECG (c)	X1	X3		X1	X1	X1		X1	X1	X1		
Prior/Concomitant Medication Review	X	X		X	X	X	X	X	X	X		X (n)
Adverse Events Review		X	X	X	X	X	X	X	X	X		
Survival Status												X
STUDY DRUG ADMINISTRATION												
Administer AM0010 daily dose		X (p)		X	X	X	X	X				
LABORATORY ASSESSMENTS												
Safety Lab Tests (d)	X	X		X	X	X	X	X	X	X		
Pregnancy Test (e)	X	X			X	X		X	X	X		
Dispense AM0010 kit		X		X	X	X2	X2	X4				
AM0010 PK / Anti AM0010 Antibody Collection (o)		X	X	X	X	X	X	X	X	X		
Exploratory Biomarker Sample (g)		X				X		X (m)	X			
Serum Tumor Markers (h)		X				X		X (l)	X		X	
Tumor Tissue (i)		X	every 8 weeks						X			
IMAGING ASSESSMENTS												
Tumor assessment (f)	X	every 8 weeks							X		X	

(a) Clinical Evaluation will include: physical exam, ECOG status and weight. Weight measurement in kg and without shoes. Medical history and height at screening only.
(b) Vital signs (pulse, blood pressure, respiratory rate and temperature) will be collected after being seated or in a semi-recumbent position.
(c) ECG will be performed in patients seated, semi-recumbent, or supine for at least 5 minutes. X1 = single ECG; X3 = three independent single ECG.
(d) Safety lab tests are listed in Table 26 and Table 27. If screening labs are done within 3 days prior then screening labs can be used as Day 1 labs.
(e) Serum pregnancy test performed at Screening; urine or serum pregnancy test at all other time points.
(f) Tumor evaluation by CT or MRI and bone scintigraphy (CRPC patients only) will be performed during screening (within 4 weeks prior to Day 1); at Week 8 and 16 (± 1 week), and every 8 weeks until irPD. The same radiographic procedure used to define measurable or non-measurable lesions must be used throughout the study for each patient). Tumor Response will be assessed by the study site and may also be reviewed by Lilly or by an independent reviewer. The process for collection of CT images for purpose of Lilly or central response review is described in the study manual.
(g) Collection of blood samples for biomarkers is optional and patients will be asked to provide written consent (up to 3 days prior).
(h) Serum tumor markers include CA-125, CEA, CA 19-9, and PSA as appropriate based on the patient's tumor type (up to 3 days prior).
(i) The collection of archived tumor tissues and fresh biopsies is optional and patients will be asked to provide written consent. Although scheduled for every 8 weeks from Day 1, collection timepoints are up to the Investigator's discretion, as long as they pose minimal risk to the patient (up to 10 days prior to Day 1 and ± 7 days during other visits).
(j) NA
(k) NA
(l) Every 4 weeks
(m) Every 8 weeks (starting on C1D1)
(n) Cancer treatment only
(o) PK/Anti-AM0010 antibody collection windows
Day 1: pre-dose (3 days prior), post-dose 6h (± 30 min)
Days 8, 15, 29: pre-dose (up to 1 day prior)
Days 43, continued visits: pre-dose (± 1 day)
Continued visits: pre-dose (± 2 days)
(p) Staff administered and training for AM0010 self-injection

Table 31: Appendix A3 – Schedule of Events for Parts B Expansion Cohorts

Examination	Screening	Treatment									Follow up		
Cycles		Cycle 1				Cycle 2 – 6 (repeat every 21 days) (starting at Day 22)			Continued visits with AM0010 monotherapy	EOT	30 days after EOT	Every 8 weeks	Every 3 months
Days	-28 to -1	Day 1		Day 8	Day 15	1	8	15	Repeat every 28 days		- 3 / +15 days	± 7 days	± 7 days
Hours (relative to dosing)		0	6										
GENERAL AND SAFETY AWARENESS													
Informed Consent	X												
Clinical Evaluation (a)	X	X		X	X	X	X		X	X	X		
Vital signs (b)	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG (c)	X1	X3		X1	X1	X1	X1		X1	X1	X1		
Prior/Concomitant Medication Review	X	X		X	X	X	X	X	X	X	X		X (n)
Adverse Events Review		X	X	X	X	X	X	X	X	X	X		
Survival Status													X
STUDY DRUG ADMINISTRATION													
Administer AM0010 daily dose		X (p)		X	X	X	X	X	X				
PART B-Platinum Taxane (j)		X				X							
LABORATORY ASSESSMENTS													
Safety Lab Tests (d)	X	X		X	X	X	X	X	X	X	X		
Pregnancy Test (e)	X	X			X	X			X	X	X		
Dispense AM0010 kit		X		X	X	X	X2		X4				
AM0010 PK / Anti AM0010 Antibody Collection (o)		X	X	X	X	X			X	X	X		
Exploratory Biomarker Sample (g)		X				X (m)			every 8 weeks	X			
Serum Tumor Markers (h)		X				X			X	X		X	
Tumor Tissue (i)		X	every 8 weeks (m)							X			
IMAGING ASSESSMENTS													
Tumor assessment (f)	X	every 8 weeks								X		X	

(a) Clinical Evaluation will include: physical exam, ECOG status and weight. Weight measurement in kg and without shoes. Medical history and height at screening only.
(b) Vital signs (pulse, blood pressure, respiratory rate and temperature) will be collected after being seated or in a semi-recumbent position.
(c) ECG will be performed in patients seated, semi-recumbent, or supine for at least 5 minutes. X1 = single ECG; X3 = three independent single ECG.
(d) Safety lab tests are listed in Table 26 and Table 27. If screening labs are done within 3 days prior then screening labs can be used as Day 1 labs.
(e) Serum pregnancy test performed at Screening; urine or serum pregnancy test at all other time points.
(f) Tumor evaluation by CT or MRI and bone scintigraphy (CRPC patients only) will be performed during screening (within 4 weeks prior to Day 1); at Week 8 and 16 (± 1 week), and every 8 weeks until irPD. The same radiographic procedure used to define measurable or non-measurable lesions must be used throughout the study for each patient). Tumor Response will be assessed by the study site and may also be reviewed by Lilly or by an independent reviewer. The process for collection of CT images for purpose of Lilly or central response review is described in the study manual.
(g) Collection of blood samples for biomarkers is optional and patients will be asked to provide written consent (up to 3 days prior).
(h) Serum tumor markers include CA-125, CEA, CA 19-9, and PSA as appropriate based on the patient's tumor type (up to 3 days prior).
(i) The collection of archived tumor tissues and fresh biopsies is optional and patients will be asked to provide written consent. Although scheduled for every 8 weeks from Day 1, collection timepoints are up to the Investigator's discretion, as long as they pose minimal risk to the patient (up to 10 days prior to Day 1 and ± 7 days during other visits).
(j) Part B- Daily SC injection with AM0010;
Day 1 of each 21-day cycle: Paclitaxel or Docetaxel and Carboplatin or Cisplatin
After a maximum of 5 or 6 cycles of chemotherapy, patients may continue with AM0010 monotherapy
(k) NA
(l) NA
(m) Every 8 weeks (starting C1D1)
(n) Cancer treatment only
(o) PK/Anti-AM0010 antibody collection windows
Day 1: pre-dose (3 days prior), post-dose 6h (± 30 min)
Days 8, 15: pre-dose (up to 1 day prior)
Cycle 2-6, Day 1: pre-dose (up to 3 day prior)
Cycle 2-6, Day 8: pre-dose (up to 1 day prior)
Continued visits: pre-dose (± 2 days)
(p) Staff administered and training for AM0010 self-injection

Table 32: Appendix A4 – Schedule of Events for Parts C Expansion Cohorts

Examination	Screening	Treatment									Follow up		
Weeks		Cycle 1					Subsequent cycles (Repeat every 14 days) (starting at Day 29)		Continued visits with AM0010 monotherapy	EOT	30 days after EOT	Every 8 weeks	Every 3 months
Days	-28 to -1	Day 1		Day 8	Day 15	Day 22	1	8	Repeat every 28 days		- 3 / +15 days	± 7 days	± 7 days
Hours (relative to dosing)		0	6	0									
GENERAL AND SAFETY AWARENESS													
Informed Consent	X												
Clinical Evaluation (a)	X	X		X	X		X		X	X	X		
Vital signs (b)	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG (c)	X1	X3		X1	X1		X1		X1	X1	X1		
Prior/Concomitant Medication Review	X	X		X	X	X	X	X	X	X	X		X (n)
Adverse Events Review		X	X	X	X	X	X	X	X	X	X		
Survival Status													X
STUDY DRUG ADMINISTRATION													
Administer AM0010 daily dose		X (p)		X	X	X	X	X	X				
PART C-FOLFOX (k)		X			X		X						
LABORATORY ASSESSMENTS													
Safety Lab Tests (d)	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Test (e)	X	X			X		X		X	X	X		
Dispense AM0010 kit		X		X	X	X	X	X	X4				
AM0010 PK / Anti AM0010 Antibody Collection (o)		X	X	X	X		X (l)		X	X	X		
Exploratory Biomarker Sample (g)		X					X (m)		X (m)	X			
Serum Tumor Markers (h)		X					X (l)		X (l)	X		X	
Tumor Tissue (i)		X					C3D1			X			
IMAGING ASSESSMENTS													
Tumor assessment (f)	X	every 8 weeks								X		X	

(a) Clinical Evaluation will include: physical exam, ECOG status and weight. Weight measurement in kg and without shoes. Medical history and height at screening only.
(b) Vital signs (pulse, blood pressure, respiratory rate and temperature) will be collected after being seated or in a semi-recumbent position.
(c) ECG will be performed in patients seated, semi-recumbent, or supine for at least 5 minutes. X1 = single ECG; X3 = three independent single ECG.
(d) Safety lab tests are listed in Table 26 and Table 27. If screening labs are done within 3 days prior then screening labs can be used as Day 1 labs.
(e) Serum pregnancy test performed at Screening; urine or serum pregnancy test at all other time points.
(f) Tumor evaluation by CT or MRI and bone scintigraphy (CRPC patients only) will be performed during screening (within 4 weeks prior to Day 1); at Week 8 and 16 (± 1 week), and every 8 weeks until irPD. The same radiographic procedure used to define measurable or non-measurable lesions must be used throughout the study for each patient). Tumor Response will be assessed by the study site and may also be reviewed by Lilly or by an independent reviewer. The process for collection of CT images for purpose of Lilly or central response review is described in the study manual.
(g) Collection of blood samples for biomarkers is optional and patients will be asked to provide written consent (up to 3 days prior).
(h) Serum tumor markers include CA-125, CEA, CA 19-9, and PSA as appropriate based on the patient's tumor type (up to 3 days prior).
(i) Patients in expansion Cohort C must consent to providing:
    a. Archival tumor tissue specimen and/or a fresh tumor biopsy to be collected prior to first dose (up to 10 days prior)
    AND
    b. Fresh tumor biopsy at 8 weeks after the first study treatment (± 10 days of Cycle 4, Day 1)
(j) NA
(k) Daily SC injection with AM0010 with
– Part C: FOLFOX; Day 1/2 of each 14-day cycle: Oxaliplatin, Leucovorin followed by 5FU. After discontinuation of Oxaliplatin, patients may continue to receive AM0010, Leucovorin and 5-FU.
(l) Every 4 weeks, up to 3 days prior
(m) Every 8 weeks (starting C1D1)
(n) Cancer treatment only
(o) PK/Anti-AM0010 antibody collection windows
Day 1: pre-dose (3 days prior), 6h (± 30 min)
Days 8, 15: pre-dose (up to 1 day prior)
Cycle 2–12, Day 1: pre-dose (up to 3 day prior)
Continued visits: pre-dose (± 2 days)
(p) Staff administered and training for AM0010 self-injection

Table 33: Appendix A5 – Schedule of Events for Parts D, F Escalation and Expansion Cohorts

Examination	Screening	Treatment											Follow up		
Cycles		Cycle 1					Subsequent Cycles (Repeat every 28 days) (Starting day 29)				Continued visits with AM0010 monotherapy	EOT	30 days after EOT	Every 8 weeks	Every 3 months
Days	-28 to -1	1		8	15	22	1	8	15	22	Repeat every 28 days		- 3 / +15 days	± 7 days	± 7 days
Hours (relative to dosing)		0	6												
GENERAL AND SAFETY AWARENESS															
Informed Consent	X														
Clinical Evaluation (a)	X	X		X			X				X	X	X		
Vital signs (b)	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG (c)	X1	X3		X1			X1				X1	X1	X1		
Prior/Concomitant Medication Review	X	X		X	X	X	X	X	X	X	X	X	X		X (n)
Adverse Events Review		X	X	X	X	X	X	X	X	X	X	X	X		
Survival Status															X
STUDY DRUG ADMINISTRATION															
Administer AM0010 daily dose		X (p)		X	X	X	X	X	X	X	X				
PART D-Gemcitabine nab-pacl. (k)		X		X	X		X	X	X						
PART F-Paclitaxel (k)		X		X	X		X	X	X						
LABORATORY ASSESSMENTS															
Safety Lab Tests (d)	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Test (e)	X	X			X		X		X		X	X	X		
Dispense AM0010 kit				X	X	X	X	X	X	X	X4				
AM0010 PK / Anti AM0010 Antibody Collection (o)		X	X	X	X		X				X	X	X		
Exploratory Biomarker Sample (g)		X					X (m)				X (m)	X			
Serum Tumor Markers (h)		X					X				X	X		X	
Tumor Tissue (i)		X	every 8 weeks												
IMAGING ASSESSMENTS															
Tumor assessment (f)	X	every 8 weeks										X		X	

(a) Clinical Evaluation will include: physical exam, ECOG status and weight. Weight measurement in kg and without shoes. Medical history and height at screening only.
(b) Vital signs (pulse, blood pressure, respiratory rate and temperature) will be collected after being seated or in a semi-recumbent position.
(c) ECG will be performed in patients seated, semi-recumbent, or supine for at least 5 minutes. X1 = single ECG; X3 = three independent single ECG.
(d) Safety lab tests are listed in Table 26 and Table 27. If screening labs are done within 3 days prior then screening labs can be used as Day 1 labs.
(e) Serum pregnancy test performed at Screening; urine or serum pregnancy test at all other time points.
(f) Tumor evaluation by CT or MRI and bone scintigraphy (CRPC patients only) will be performed during screening (within 4 weeks prior to Day 1); at Week 8 and 16 (± 1 week), and every 8 weeks until irPD. The same radiographic procedure used to define measurable or non-measurable lesions must be used throughout the study for each patient). Tumor Response will be assessed by the study site and may also be reviewed by Lilly or by an independent reviewer. The process for collection of CT images for purpose of Lilly or central response review is described in the study manual.
(g) Collection of blood samples for biomarkers is optional and patients will be asked to provide written consent (up to 3 days prior).
(h) Serum tumor markers include CA-125, CEA, CA 19-9, and PSA as appropriate based on the patient's tumor type (up to 3 days prior).
(i) The collection of archived tumor tissues and fresh biopsies is optional and patients will be asked to provide written consent. Although scheduled for every 8 weeks from Day 1, collection timepoints are up to the Investigator's discretion, as long as they pose minimal risk to the patient (up to 10 days prior to Day 1 and ± 7 days during other visits).
(j) NA
(k) Daily SC injection with AM0010 with
– Part D Gemcitabine nab-paclitaxel on Day 1, 8, 15 of every 28 day cycle
– Part F Paclitaxel on Day 1, 8, 15 of every 28 day cycle
(l) NA
(m) Every 8 weeks (starting C1D1)
(n) Cancer treatment only
(o) PK/Anti-AM0010 antibody collection windows
Day 1: pre-dose (3 days prior), 6h (± 30 min)
Days 8, 15: pre-dose (up to 1 day prior)
Subsequent cycles, Day 1: pre-dose (up to 3 day prior)
Continued visits: pre-dose (± 2 days)
(p) Staff administered and training for AM0010 self-injection

Table 34: Appendix A6 – Schedule of Events for Parts E Escalation and Expansion Cohorts

Examination	Screening	Treatment									Follow up		
		Cycle 1				Subsequent Cycles (Repeat every 21 days) (Starting day 22)			Continued visits with AM0010 monotherapy (Repeat every 28 days)	EOT	30 days after EOT	Every 8 weeks	Every 3 months
Days	-28 to -1	1		8	15	1	8	15	Day 1		- 3 / +15 days	± 7 days	± 7 days
Hours (relative to dosing)		0	6										
GENERAL AND SAFETY AWARENESS													
Informed Consent	X												
Clinical Evaluation (a)	X	X		X		X			X	X	X		
Vital signs (b)	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG (c)	X1	X3		X1	X1	X1			X1	X1	X1		
Prior/Concomitant Medication Review	X	X		X	X	X	X	X	X	X	X		X (n)
Adverse Events Review		X	X	X	X	X	X	X	X	X	X		
Survival Status													X
STUDY DRUG ADMINISTRATION													
Administer AM0010 daily dose (k)		X (p)		X	X	X	X	X	X				
PART E- Capecitabine daily		X		X		X	X						
LABORATORY ASSESSMENTS													
Safety Lab Tests (d)	X	X		X	X	X	X	X	X	X	X		
Pregnancy Test (e)	X	X				X			X	X	X		
Dispense AM0010 kit		X		X	X	X	X	X	X4				
AM0010 PK / Anti AM0010 Antibody Collection (o)		X	X	X	X	X			X	X	X		
Exploratory Biomarker Sample (g)		X				X (q)			every 8 weeks	X			
Serum Tumor Markers (h)		X				X (l)			X (l)	X		X	
Tumor Tissue (i)		X	every 8 weeks										
IMAGING ASSESSMENTS													
Tumor assessment (f)	X	every 8 weeks								X		X	

(a) Clinical Evaluation will include: physical exam, ECOG status and weight. Weight measurement in kg and without shoes. Medical history and height at screening only.
(b) Vital signs (pulse, blood pressure, respiratory rate and temperature) will be collected after being seated or in a semi-recumbent position.
(c) ECG will be performed in patients seated, semi-recumbent, or supine for at least 5 minutes. X1 = single ECG; X3 = three independent single ECG.
(d) Safety lab tests are listed in Table 26 and Table 27. If screening labs are done within 3 days prior then screening labs can be used as Day 1 labs.
(e) Serum pregnancy test performed at Screening; urine or serum pregnancy test at all other time points.
(f) Tumor evaluation by CT or MRI and bone scintigraphy (CRPC patients only) will be performed during screening (within 4 weeks prior to Day 1); at Week 8 and 16 (± 1 week), and every 8 weeks until irPD. The same radiographic procedure used to define measurable or non-measurable lesions must be used throughout the study for each patient). Tumor Response will be assessed by the study site and may also be reviewed by Lilly or by an independent reviewer. The process for collection of CT images for purpose of Lilly or central response review is described in the study manual.
(g) Collection of blood samples for biomarkers is optional and patients will be asked to provide written consent (up to 3 days prior).
(h) Serum tumor markers include CA-125, CEA, CA 19-9, and PSA as appropriate based on the patient's tumor type (up to 3 days prior).
(i) The mandatory tissues collected are either archived tumor tissues (C1D1) and/or 2 fresh biopsies taken (on Day 1 up to 10 days prior and on C4D1 ± 10 days). Biopsy must not be considered to be more than minimal risk to the patient.
(j) NA
(k) Daily SC injection with AM0010 with
– Part E Capecitabine on Day 1 – 14 of every 21 day cycle
(l) Every 4 weeks
(m) Every 8 weeks (starting C2D1)
(n) Cancer treatment only
(o) PK/Anti-AM0010 antibody collection windows
Day 1: pre-dose (3 days prior), 6h (± 30 min)
Days 8, 15: pre-dose (up to 1 day prior)
Subsequent cycles, Day 1: pre-dose (up to 3 day prior)
Continued visits: pre-dose (± 2 days)
(p) Staff administered and training for AM0010 self-injection
(q) Every 6 weeks (starting C2D1)

Table 35: Appendix A7 – Schedule of Events for Parts G Escalation and Expansion Cohorts

Examination	Screening	Treatment								Follow up		
Cycle		Cycle 1					Subsequent Cycles (Repeat every 28 days) (Starting day 29)	Continued visits with AM0010 monotherapy (Repeat every 28 days)	EOT	30 days after EOT	Every 8 weeks	every 3 months
Days	-28 to -1	Day 1		Day 8	Day 15	Day 22	Day 1	Day 1		- 3 / +15 days	± 7 days	± 7 days
Hours (relative to dosing)		0	6									
GENERAL AND SAFETY AWARENESS												
Informed Consent	X											
Clinical Evaluation (a)	X	X		X	X		X	X	X	X		
Vital signs (b)	X	X	X	X	X	X	X	X	X	X		
12-lead ECG (c)	X1	X3		X1	X1		X1	X1	X1	X1		
Prior/Concomitant Medication Review	X	X		X	X	X	X	X	X	X		X (n)
Adverse Events Review		X	X	X	X	X	X	X	X	X		
Survival Status												X
STUDY DRUG ADMINISTRATION												
Administer AM0010 daily dose		X (p)		X	X	X	X	X				
PART E- Pazopanib daily (k)		X		X	X	X	X					
LABORATORY ASSESSMENTS												
Safety Lab Tests (d)	X	X	X	X	X	X	X	X	X	X		
Pregnancy Test (e)	X	X			X		X	X	X	X		
Dispense AM0010 kit		X		X	X	X	X4	X4				
AM0010 PK / Anti AM0010 Antibody Collection (o)		X	X	X	X		X	X	X	X		
Exploratory Biomarker Sample (g)		X					X (m)	every 8 weeks	X			
Serum Tumor Markers(h)		X					X	X	X		X	
Tumor Tissue (i)		X	every 8 weeks									
IMAGING ASSESSMENTS												
Tumor assessment (f)	X	every 8 weeks							X		X	

(a) Clinical Evaluation will include: physical exam, ECOG status and weight. Weight measurement in kg and without shoes. Medical history and height at screening only.
(b) Vital signs (pulse, blood pressure, respiratory rate and temperature) will be collected after being seated or in a semi-recumbent position.
(c) ECG will be performed in patients seated, semi-recumbent, or supine for at least 5 minutes. X1 = single ECG; X3 = three independent single ECG.
(d) Safety lab tests are listed in Table 26 and Table 27. If screening labs are done within 3 days prior then screening labs can be used as Day 1 labs.
(e) Serum pregnancy test performed at Screening; urine or serum pregnancy test at all other time points.
(f) Tumor evaluation by CT or MRI and bone scintigraphy (CRPC patients only) will be performed during screening (within 4 weeks prior to Day 1); at Week 8 and 16 (± 1 week), and every 8 weeks until irPD. The same radiographic procedure used to define measurable or non-measurable lesions must be used throughout the study for each patient). Tumor Response will be assessed by the study site and may also be reviewed by Lilly or by an independent reviewer. The process for collection of CT images for purpose of Lilly or central response review is described in the study manual.
(g) Collection of blood samples for biomarkers is optional and patients will be asked to provide written consent (up to 3 days prior).
(h) Serum tumor markers include CA-125, CEA, CA 19-9, and PSA as appropriate based on the patient's tumor type (up to 3 days prior).
(i) The collection of archived tumor tissues and fresh biopsies is optional and patients will be asked to provide written consent. Although scheduled for every 8 weeks from Day 1, collection timepoints are up to the Investigator's discretion, as long as they pose minimal risk to the patient (up to 10 days prior to Day 1 and ± 7 days during other visits).
(j) NA
(k) Daily SC injection with AM0010 with
– Part G Pazopanib daily
(l) NA
(m) Every 8 weeks (starting C1D1)
(n) Cancer treatment only
(o) PK/Anti-AM0010 antibody collection windows
Day 1: pre-dose (3 days prior), 6h (± 30 min)
Days 8, 15: pre-dose (up to 1 day prior)
Subsequent cycles, Day 1: pre-dose (up to 3 day prior)
Continued visits: pre-dose (± 2 days)
(p) Staff administered and training for AM0010 self-injection

Table 36: Appendix A8 – Schedule of Events for Parts H Escalation and Expansion Cohorts

Examination	Screening	Treatment								Follow up		
Cycle		Cycle 1				Subsequent Cycles (Repeat every 21 days) (Starting Day 22)		Continued visits with AM0010 monotherapy (Repeat every 28 days)	EOT	30 days after EOT	Every 8 weeks	Every 3 months
Days	-28 to -1	Day 1		Day 8	Day 15	Day 1	8	Day 1 (Repeat every 28 days)				
Windows				- 1 day	- 1 day	± 2 day				- 3 / +15 days	± 7 days	± 7 days
Hours (relative to dosing)		0	6									
GENERAL AND SAFETY AWARENESS												
Informed Consent	X											
Clinical Evaluation (a)	X	X		X		X		X	X	X		
Vital signs (b)	X	X	X	X	X	X	X	X	X	X		
12-lead ECG (c)	X1	X3		X1		X1		X1	X1	X1		
Prior/Concomitant Medication Review	X	X		X	X	X	X	X	X	X		X (n)
Adverse Events Review		X	X	X	X	X	X	X	X	X		
Survival Status												X
STUDY DRUG ADMINISTRATION												
Administer AM0010 daily dose		X (p)		X	X	X	X	X				
PART H- Pembrolizumab (k)		X				X						
LABORATORY ASSESSMENTS												
Safety Lab Tests (d)	X	X	X	X	X	X	X	X	X	X		
Pregnancy Test (e)	X	X				X		X	X	X		
Dispense AM0010 kit		X		X	X	X	X2	X4				
AM0010 PK / Anti AM0010 Antibody Collection (o)		X	X	X	X	X		X	X	X		
Exploratory Biomarker Sample (g)		X				X (q)		X (m)	X			
Serum Tumor Markers (h)		X				X (l)		X (l)	X		X	
Tumor Tissue (i)		X	every 8 weeks									
IMAGING ASSESSMENTS												
Tumor assessment (f)	X	every 8 weeks							X		X	

(a) Clinical Evaluation will include: physical exam, ECOG status and weight. Weight measurement in kg and without shoes. Medical history and height at screening only.
(b) Vital signs (pulse, blood pressure, respiratory rate and temperature) will be collected after being seated or in a semi-recumbent position.
(c) ECG will be performed in patients seated, semi-recumbent, or supine for at least 5 minutes. X1 = single ECG; X3 = three independent single ECG.
(d) Safety lab tests are listed in Table 26 and Table 27. If screening labs are done within 3 days prior then screening labs can be used as Day 1 labs.
(e) Serum pregnancy test performed at Screening; urine or serum pregnancy test at all other time points.
(f) Tumor evaluation by CT or MRI and bone scintigraphy (CRPC patients only) will be performed during screening (within 4 weeks prior to Day 1); at Week 8 and 16 (± 1 week), and every 8 weeks until irPD. The same radiographic procedure used to define measurable or non-measurable lesions must be used throughout the study for each patient). Tumor Response will be assessed by the study site and may also be reviewed by Lilly or by an independent reviewer. The process for collection of CT images for purpose of Lilly or central response review is described in the study manual.
(g) Collection of blood samples for biomarkers is optional and patients will be asked to provide written consent (up to 3 days prior).
(h) Serum tumor markers include CA-125, CEA, CA 19-9, and PSA as appropriate based on the patient's tumor type (up to 3 days prior).
(i) The collection of archived tumor tissues and fresh biopsies is optional and patients will be asked to provide written consent. Although scheduled for every 8 weeks from Day 1, collection timepoints are up to the Investigator's discretion, as long as they pose minimal risk to the patient (up to 10 days prior to Day 1 and ± 7 days during other visits).
(j) NA
(k) Daily SC injection with AM0010 with
– Part H Pembrolizumab on Day 1 of every 21 day cycle
(l) Every 4 weeks, up to 3 days prior
(m) Every 8 weeks
(n) Cancer treatment only
(o) PK/Anti-AM0010 antibody collection windows
Day 1: pre-dose (3 days prior), 6h (± 30 min)
Days 8, 15: pre-dose (up to 1 day prior)
Subsequent cycles, Day 1: pre-dose (up to 3 day prior)
Continued visits: pre-dose (± 2 days)
(p) Staff administered and training for AM0010 self-injection
(q) Every 6 weeks (starting C1D1)

Table 37: Appendix A9 – Schedule of Events for Parts I Escalation and Expansion Cohorts

Examination	Screening	Treatment				Follow up		
Cycle		Cycle 1	Subsequent Cycles (Repeat every 14 days) (Starting Day 15)	Continued visits with AM0010 monotherapy (Repeat every 28 days)	EOT	30 days after EOT	Every 8 weeks	Every 3 months
Days	-28 to -1	Day 1	Day 1	Day 1 (Repeat every 28 days)				
Windows		- 1 day	± 2 day			- 3 / +15 days	± 7 days	± 7 days
Hours (relative to dosing)		0						
GENERAL AND SAFETY AWARENESS								
Informed Consent	X							
Clinical Evaluation (a)	X	X	X (l)	X	X	X		
Vital signs (b)	X	X	X	X	X	X		
12-lead ECG (c)	X1	X	X1 (l)	X1	X1	X1		
Prior/Concomitant Medication Review	X	X	X	X	X	X		X (n)
Adverse Events Review		X	X	X	X	X		
Survival Status								X
STUDY DRUG ADMINISTRATION								
Administer AM0010 daily dose		X (p)	X	X				
PART I - Nivolumab (IV q2w) (k)		X	X					
LABORATORY ASSESSMENTS								
Safety Lab Tests (d)	X	X	X	X	X	X		
Pregnancy Test (e)	X	X	X	X	X	X		
Dispense AM0010 kit		X2	X2	X4				
AM0010 PK / Anti AM0010 Antibody Collection (o)		X	X	X	X	X		
Exploratory Biomarker Sample (g)		X	X (m)	X (m)	X			
Serum Tumor Markers (h)		X	X (l)	X (l)	X		X	
Tumor Tissue (i)		X	every 8 weeks					
IMAGING ASSESSMENTS								
Tumor assessment (f)	X	every 8 weeks			X		X	

(a) Clinical Evaluation will include: physical exam, ECOG status and weight. Weight measurement in kg and without shoes. Medical history and height at screening only.
(b) Vital signs (pulse, blood pressure, respiratory rate and temperature) will be collected after being seated or in a semi-recumbent position.
(c) ECG will be performed in patients seated, semi-recumbent, or supine for at least 5 minutes. X1 = single ECG; X3 = three independent single ECG.
(d) Safety lab tests are listed in Table 26 and Table 27. If screening labs are done within 3 days prior then screening labs can be used as Day 1 labs.
(e) Serum pregnancy test performed at Screening; urine or serum pregnancy test at all other time points.
(f) Tumor evaluation by CT or MRI and bone scintigraphy (CRPC patients only) will be performed during screening (within 4 weeks prior to Day 1); at Week 8 and 16 (± 1 week), and every 8 weeks until irPD. The same radiographic procedure used to define measurable or non-measurable lesions must be used throughout the study for each patient). Tumor Response will be assessed by the study site and may also be reviewed by Lilly or by an independent reviewer. The process for collection of CT images for purpose of Lilly or central response review is described in the study manual.
(g) Collection of blood samples for biomarkers is optional and patients will be asked to provide written consent (up to 3 days prior).
(h) Serum tumor markers include CA-125, CEA, CA 19-9, and PSA as appropriate based on the patient's tumor type (up to 3 days prior).
(i) The collection of archived tumor tissues and fresh biopsies is optional and patients will be asked to provide written consent. Although scheduled for every 8 weeks from Day 1, collection timepoints are up to the Investigator's discretion, as long as they pose minimal risk to the patient (up to 10 days prior to Day 1 and ± 7 days during other visits).
(j) NA
(k) Daily SC injection with AM0010 with
– Part I Nivolumab on Day 1 of every 14 day cycle
(l) Every 4 weeks, up to 3 days prior
(m) Every 8 weeks (starting C1D1)
(n) Cancer treatment only
(o) PK/Anti-AM0010 antibody Collection windows
Day 1: pre-dose (3 days prior)
Subsequent cycles, Day 1: pre-dose (up to 3 day prior)
Continued visits: pre-dose (± 2 days)
(p) Staff administered and training for AM0010 self-injection

Table 38: Appendix A10 – Schedule of Events for Parts J Expansion Cohorts

Examination	Screening	Treatment								Follow up		
Weeks		Cycle 1				Subsequent cycles (Repeat every 21 days) (starting at Day 22)		Continued visits with AM0010 monotherapy	EOT	30 days after EOT	Every 8 weeks	Every 3 months
Days	-28 to -1	Day 1		Day 8	Day 15	1	8	Repeat every 28 days		- 3 / +15 days	± 7 days	± 7 days
Hours (relative to dosing)		0	6									
GENERAL AND SAFETY AWARENESS												
Informed Consent	X											
Clinical Evaluation (a)	X	X				X		X	X	X		
Vital signs (b)	X	X	X	X	X	X	X	X	X	X		
12-lead ECG (c)	X1	X3		X1		X1		X1	X1	X1		
Prior/Concomitant Medication Review	X	X		X	X	X	X	X	X	X		X (n)
Adverse Events Review		X	X	X	X	X	X	X	X	X		
Survival Status												X
STUDY DRUG ADMINISTRATION												
Administer AM0010 daily dose		X (p)		X	X	X	X	X				
PART J-Gemcitabine and Carboplatin (k)		X		X		X	X					
LABORATORY ASSESSMENTS												
Safety Lab Tests (d)	X	X	X	X	X	X	X	X	X	X		
Pregnancy Test (e)	X	X				X		X	X	X		
Dispense AM0010 kit		X		X	X	X	X2	X4				
AM0010 PK / Anti AM0010 Antibody Collection (o)		X	X			X(l)		X	X	X		
Exploratory Biomarker Sample (g)		X				X (q)		every 8 weeks	X			
Serum Tumor Markers (h)		X				X (l)		X (l)	X		X	
Tumor Tissue (i)		X	every 8 weeks						X			
IMAGING ASSESSMENTS												
Tumor assessment (f)	X	every 8 weeks							X		X	

(a) Clinical Evaluation will include: physical exam, ECOG status and weight. Weight measurement in kg and without shoes. Medical history and height at screening only.
(b) Vital signs (pulse, blood pressure, respiratory rate and temperature) will be collected after being seated or in a semi-recumbent position.
(c) ECG will be performed in patients seated, semi-recumbent, or supine for at least 5 minutes. X1 = single ECG; X3 = three independent single ECG.
(d) Safety lab tests are listed in Table 26 and Table 27. If screening labs are done within 3 days prior then screening labs can be used as Day 1 labs.
(e) Serum pregnancy test performed at Screening; urine or serum pregnancy test at all other time points.
(f) Tumor evaluation by CT or MRI and bone scintigraphy (CRPC patients only) will be performed during screening (within 4 weeks prior to Day 1); at Week 8 and 16 (± 1 week), and every 8 weeks until irPD. The same radiographic procedure used to define measurable or non-measurable lesions must be used throughout the study for each patient). Tumor Response will be assessed by the study site and may also be reviewed by Lilly or by an independent reviewer. The process for collection of CT images for purpose of Lilly or central response review is described in the study manual.
(g) Collection of blood samples for biomarkers is optional and patients will be asked to provide written consent (up to 3 days prior).
(h) Serum tumor markers include CA-125, CEA, CA 19-9, and PSA as appropriate based on the patient's tumor type (up to 3 days prior).
(i) The collection of archived tumor tissues and fresh biopsies is optional and patients will be asked to provide written consent. Although scheduled for every 8 weeks from Day 1, collection timepoints are up to the Investigator's discretion, as long as they pose minimal risk to the patient (up to 10 days prior to Day 1 and ± 7 days during other visits).
(j) NA
(k) Daily SC injection with AM0010 with
– Part J Gemcitabine / carboplatin on Day 1 and 8 of every 21 day cycle
(l) Every 3 weeks
(m) Every 8 weeks
(n) Cancer treatment only
(o) PK/Anti-AM0010 antibody Collection windows
Day 1: pre-dose (3 days prior), 6h (± 30 min)
Subsequent cycles, Day 1: pre-dose (up to 3 day prior)
Continued visits: pre-dose (± 2 days)
(p) Staff administered and training for AM0010 self-injection
(q) Every 6 weeks (starting C1D1)

Appendix B – Continued Access Period Schedule of Assessments

Procedure	Protocol Section	Continued Access Treatment Visits ±3 Days	Continued Access Follow-Up Visits 30 days (±7 days) after the last dose of study treatment	Comments
Adverse Events Collection / CTCAE Grading	11.0	X	X	All AEs / SAEs will be followed for up to 30 days after the patient and investigator agree that the patient will no longer continue study treatment.
Study Treatment (AM0010)	8.0	X		Self-administration, QD
AM0010 PK / Anti-AM0010 Antibody Collection	5.4.7	X[a]	X[a]	

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; PK = pharmacokinetic; QD = once daily; SAE = serious adverse event.

(a) Only if a patient experiences a suspected systemic hypersensitivity reaction involving the skin or mucous membranes, respiratory, cardiovascular, gastrointestinal, urinary, or other systems, after an administration of study drug(s). After patient's stabilization, blood samples for anti AM0010 antibody and PK analysis will be taken at the following time points: as soon as possible after the onset, at the resolution of the suspected hypersensitivity event, at 30 days (±3 days) after the event, and 12 to 16 weeks after the event.

Appendix C – irRC according to Wolchok, Kluger et al. 2013

17.1.1.1 Definitions of Measurable/Non-Measurable Lesions

All measurable and non-measurable lesions should be assessed at Screening and at the defined tumor assessment time points. Additional assessments may be performed, as clinically indicated for suspicion of progression. The Investigator will base response to treatment using the irRC.

17.1.1.1.1 Measurable Lesions

Measurable lesions are lesions that can be accurately measured in 2 perpendicular diameters, with at least 1 diameter ≥ 20 mm and the other dimension ≥ 10 mm (10 mm x 10 mm for spiral CT with cuts of 5 mm). The area will be defined as the product of the largest diameter with its perpendicular.

Lymph nodes may also be considered measurable. To be considered pathologically enlarged and measurable, a lymph node must be at least 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

17.1.1.1.2 Non-Measurable Lesions

Non-measurable (evaluable) lesions are all other lesions, including unidimensional measurable disease and small lesions (lesions without at least 1 diameter ≥ 20 mm, or pathological lymph nodes with short axis ≤ 15 mm), and any of the following: lesions occurring in a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques and cystic lesions. Lymph nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

17.1.1.2 Definitions of Index/Non-Index Lesions

17.1.1.2.1 Index Lesions

Measurable lesions, up to a maximum of 5 lesions per organ and ten lesions in total, must be identified as index lesions to be measured at Screening. The index lesions should be

representative of all involved organs. In addition, index lesions must be selected based on their size (e.g., lesions with the longest diameters), their suitability for accurate repeat assessment by imaging techniques, and how representative they are of the subject's tumor burden. At Screening, a Sum of the Product Diameters (SPD) for all index lesions will be calculated and considered the baseline SPD. The baseline sum will be used as the reference point to determine the objective tumor response of the index lesions at tumor assessment.

17.1.1.2.2 Non-Index Lesions

Measurable lesions, other than index lesions, and all sites of non-measurable disease will be identified as non-index lesions. Non-index lesions will be evaluated at the same assessment time points as the index lesions. In subsequent assessments, changes in non-index lesions will contribute only in the assessment of complete response.

17.1.1.3 Calculation of Sum of Product of Diameters (SPD)

Sum of Product of Diameters is an estimate of tumor burden. The 2 greatest perpendicular diameters are used to estimate the size of each tumor lesion. The SPD is calculated as the sum of the product of the diameters for index tumor lesions. Several variations of the SPD are identified for the purpose of classification of tumor responses.

SPD at Baseline: The sum of the product of the diameters for all index lesions identified at baseline prior to treatment on Day 1.

SPD at tumor assessment: For every on-study tumor assessment collected per protocol or as clinically indicated, the SPD at tumor assessment will be calculated using tumor imaging scans. All index lesions and all new measurable lesions that have emerged after baseline will contribute to the SPD at tumor assessment (irSPD).

SPD at NADIR: For tumors that are assessed more than 1 time after baseline, the lowest value of the SPD (SPD Baseline or SPD at tumor assessment) is used to classify subsequent tumor assessments for each subject. The SPD at tumor assessment using the irRC for progressive disease incorporates the contribution of new measurable lesions.

Each net percentage change in tumor burden per assessment using irRC accounts for the size and growth kinetics of both old and new lesions as they appear. In this study the

irRC as defined by the Investigator will serve as the basis of key endpoints for efficacy analyses and guide clinical care.

17.1.1.4 Definition of Index Lesion Response

Immune-related Complete Response (irCR), which is defined as complete disappearance of all index lesions. Lymph nodes that shrink to < 10 mm short axis are considered normal.

Immune-related Partial Response (irPR), which is defined as a decrease, relative to baseline, of 50% or greater in the sum of the products of the 2 largest perpendicular diameters of all index and all new measurable lesions (i.e., Percentage Change in Tumor Burden) in the absence of irCR.

Note: the appearance of new measurable lesions is factored into the overall tumor burden but does not automatically qualify as progressive disease until the SPD increases by ≥ 25% when compared to SPD at nadir.

Immune-related Stable Disease (irSD), which is defined as not meeting the criteria for irCR or irPR, in the absence of immune-related progressive disease (irPD).

Immune-related Progressive Disease (irPD), which is defined as at least a 25% increase in Tumor Burden (i.e., taking sum of the products of all index lesions and any new measurable lesions) when compared to SPD at nadir.

17.1.1.5 Definition of Non-Index Lesion Response

Immune-related Complete Response (irCR), which is defined as complete disappearance of all non-index lesions. Lymph nodes that shrink to < 10 mm short axis are considered normal.

Immune-related Partial Response (irPR), non-index lesion(s) are not considered in the definition of PR; this term does not apply.

Immune-related Stable Disease (irSD), non-index lesion(s) are not considered in the definition of SD; this term does not apply.

Immune-related Progressive Disease (irPD), increases in number or size of non-index lesion(s) does not constitute progressive disease unless/until Tumor Burden increases by

25% (i.e., the SPD at nadir of index lesions and any new measurable lesions increases by the required amount).

17.1.1.6 Impact of New Lesions on irRC

New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is included in the SPD which in turn feeds into the irRC for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

17.1.1.7 Definition of Overall Response Using irRC Will Be Based on the Following Criteria:

Immune-related Complete Response (irCR): Complete disappearance of all tumor lesions (index and non-index), together with no new measurable or unmeasurable lesions, for at least 4 weeks from the date of documentation of irCR. All lymph nodes short axes must be < 10 mm.

Immune-related Partial Response (irPR): The sum of the products of the 2 largest perpendicular diameters of all index lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the sum of the products of the 2 largest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of the Product of the Diameters (irSPD). A decrease, relative to baseline of the irSPD of 50% or greater is considered an irPR, in the absence of irCR. Must be confirmed no less than 4 weeks from the first irPR.

Immune-related Stable Disease (irSD): irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.

Immune-related Progressive Disease (irPD): It is recommended in difficult cases (e.g., increase in SPD or irSPD accompanied with significant individual lesion regression, “mixed response,” or in presence of stable or improving performance status/clinical condition) to confirm PD at the following tumor assessment. Any of the following will constitute progressive disease:

At least 25% increase in the SPD of all index lesions over nadir SPD calculated for these lesions.

At least a 25% increase in the SPD of all index lesions and new measurable lesions (irSPD) over the nadir SPD calculated for the index lesions.

Table 39: irRC Definitions

Index Lesion Definition	Non Index Lesion Definition	New Measureable Lesions	New Unmeasureable Lesions	% Change in irSPD Tumor Burdon (including measurable new lesions when present)	Overall irRC Response
Complete Response	Complete Response	No	No	-100%	irCR
				≤ -50%	irPR
Partial Response	Any	Any	Any	> -50% to < + 25%	irSD
				≥ +25%	irPD
Stable Disease	Any	Any	Any	> -50% to < + 25%	irSD
				≥ +25%	irPD
Progressive Disease	Any	Any	Any	≤ +25%	irPD

17.1.1.8 Best Overall Response and Date of Progression Using irRC (irBOR)

The Investigator will be asked to provide all responses on study and date(s) of progression, if applicable, and the best overall response will be calculated by the sponsor or designee based on the time point responses and tumor measurements provided by the Investigators.

Appendix D – Investigator Signature Page

I have read the foregoing protocol and agree to conduct the study as outlined. In addition, I agree to conduct the study 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 Conference on Harmonisation guidance documents and with all applicable regulations and guidelines as stated in the protocol and other information supplied to me.

Investigator

Printed Name

Signature Date

Institution

Leo Document ID = ec82e275-3df0-45a3-85c0-011f4f45574e

Approver: PPD
Approval Date & Time: 20-Feb-2019 16:46:27 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 25-Feb-2019 14:39:26 GMT
Signature meaning: Approved