J1L-AM-JZGB: Clinical Protocol AM0010 – 301 (Sequoia) Amendment 3.0

A Randomized Phase 3 Study of AM0010 in Combination with FOLFOX Compared with FOLFOX Alone as Second-line Therapy in Patients with Metastatic Pancreatic Cancer that has Progressed During or Following a First-Line Gemcitabine Containing Regimen

NCT02923921

Approval Date: 5-Oct-2018

CLINICAL PROTOCOL

STUDY TITLE	A Randomized Phase 3 Study of AM0010 in Combination with FOLFOX Compared with FOLFOX Alone as Second-Line Therapy in Patients with Metastatic Pancreatic Cancer that has Progressed during or following a First-Line Gemcitabine-Containing Regimen
INVESTIGATIONAL PRODUCT	AM0010 (Pegilodecakin; LY3500518) PEGylated Recombinant Human Interleukin 10 (PEG-rHuIL-10)
PROTOCOL NUMBER	AM0010-301 (Sequoia; J1L-AM-JZGB)
IND Number	131506
EudraCT	2016-003858-33
PROTOCOL AMENDMENT 3.0 DATE	See approval date stamp at the end of this page
PROTOCOL AMENDMENT 2.0 DATE	15 May 2018
PROTOCOL AMENDMENT 1.1 (ROW ONLY) DATE	19 July 2017
PROTOCOL AMENDMENT 1.0 DATE	19 June 2017
ORIGINAL PROTOCOL DATE	06 October 2016
SPONSOR	Eli Lilly and Company (Lilly) Indianapolis, Indiana, USA 46285

CONFIDENTIALITY STATEMENT

Approval Date: 05-Oct-2018 GMT

PROTOCOL APPROVAL PAGE

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

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 protocol, informed consent form (ICF), Institutional Review Board (IRB)/Independent Ethics Committee (IEC), procedures, instructions, Eli Lilly and Company (Lilly) representatives' guidelines, the Declaration of Helsinki, and 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 (ICH) guidance documents and with all applicable local regulations governing the conduct of clinical studies.

Principal Investigator

_____

Printed Name

_____ _____

Signature Date

_____

Institution Name

SYNOPSIS

Name of Sponsor	Eli Lilly and Company (Lilly)
Investigational Product	AM0010
Name of Active Ingredient	PEG-rHuIL-10
Other Study Drugs	FOLFOX (Oxaliplatin/5-FU/Leucovorin)
Phase of Development	3
Title of Study	A Randomized Phase 3 Study of AM0010 in Combination with FOLFOX Compared with FOLFOX Alone as Second-Line Therapy in Patients with Metastatic Pancreatic Cancer that has Progressed during or following a First-Line Gemcitabine-Containing Regimen
Indication	Advanced metastatic pancreatic cancer
Number of Centers and Regions	Approximately 150 study centers in North America, Europe, and Asia-Pacific
Number of Patients	Approximately 566
Study Duration	Approximately 36 months (screening, enrollment, and study completion)
STUDY OBJECTIVES	
Primary	To compare the efficacy of AM0010 in combination with FOLFOX versus FOLFOX alone in patients with metastatic pancreatic cancer as measured by OS.
Secondary	To compare the efficacy of AM0010 in combination with FOLFOX versus FOLFOX alone in patients with metastatic pancreatic cancer as measured by: • PFS • ORR, DCR, and DoR by RECIST v.1.1 • 1-year overall survival rate To compare the safety and tolerability of AM0010 in combination with FOLFOX versus FOLFOX alone.
Exploratory	To explore biomarkers that may correlate with tumor response, immune activation, and relationships to clinical efficacy outcomes. To explore associations between patient-reported symptoms, functioning, and global health status/Quality of Life (QoL) using the EORTC QLQ-C30 questionnaire as well as current health status and the EQ-5D Index used in the economic evaluation of health care using the EQ-5D-5L questionnaire.
METHODOLOGY	
Study Design	This is a randomized, open-label, global Phase 3 Study of AM0010 in combination with FOLFOX compared with FOLFOX alone as second-line therapy in patients with advanced metastatic pancreatic cancer that has progressed during or following a first-line gemcitabine-containing regimen. Approximately 566 patients will be randomized. Two interim analyses are planned. The first interim analysis will be performed when at least 60 randomized patients have had the

Study Design (continued)

opportunity to receive 4 months of therapy from the date of Randomization.

Based on the first interim analysis, the DMC will review the PK exposure-safety and PK exposure-efficacy on the composite aggregate data for a Go/No-Go decision to enroll the entire Phase 3 study.

The enrollment will continue during the analysis. The second interim analysis will occur when approximately 276 deaths (70% of total 393 deaths needed for the final analysis) have occurred. Based on the second interim analysis, the DMC will recommend modifying, continuing the trial as planned, or discontinuing the trial.

Patients will be randomized in a 1:1 ratio to AM0010 combined with FOLFOX or FOLFOX alone.

Patients will be stratified by 2 stratification factors:

- Prior single-agent gemcitabine therapy versus gemcitabine/nab-paclitaxel therapy
- North America versus Europe versus Asia-Pacific (APAC)

Treatment Arms:

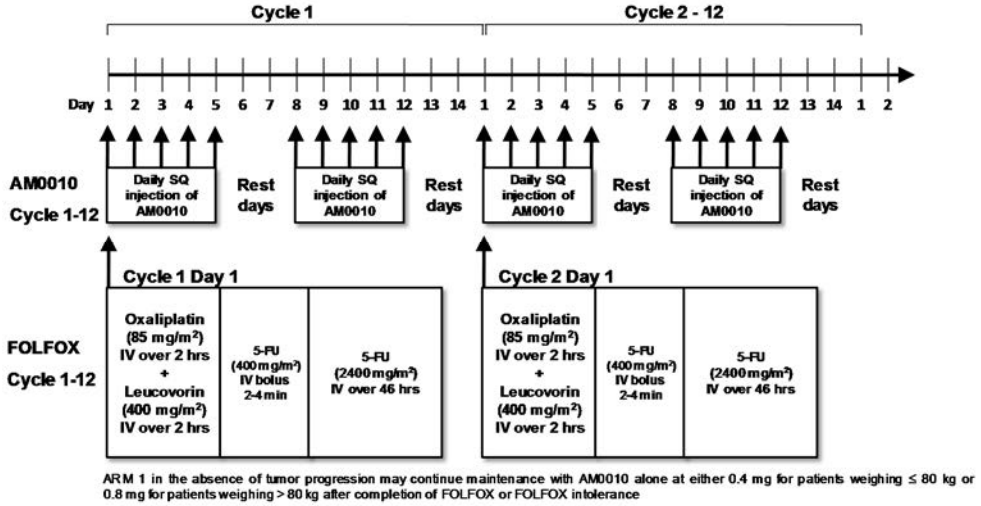
ARM 1: AM0010 (5 µg/kg) subcutaneous (SQ) dosed on Days 1–5 (with rest on Days 6 and 7) and Days 8–12 SQ (with rest on Days 13 and 14) plus a FOLFOX regimen (a 2-hour infusion of *dl*-LV 400 mg/m^2 and oxaliplatin 85 mg/m^2 followed by bolus 5-FU 400 mg/m^2 and a 46- to 48-hour infusion of 5-FU 2400 mg/m^2) initiated on Day 1 of a 14-day cycle for up to 12 cycles or until disease progression by RECIST v.1.1.

While receiving FOLFOX during Cycles 1–12, AM0010 at 5 µg/kg will be administered as 1 of 2 fixed doses, either 0.4 mg for patients weighing ≤80 kg or 0.8 mg for patients weighing >80 kg.

Patients in ARM 1 may continue on maintenance cycles with AM0010 (as shown below). After discontinuation of FOLFOX in the absence of tumor progression (ie, completion of the planned 12 cycles or unacceptable FOLFOX related toxicity), AM0010 at 10 µg/kg will be administered as 1 of 2 fixed doses, either 0.8 mg for patients weighing ≤80 kg or 1.6 mg for patients weighing >80 kg.

ARM 1: AM0010 plus FOLFOX, for up to 12 cycles or until disease progression by RECIST v.1.1.

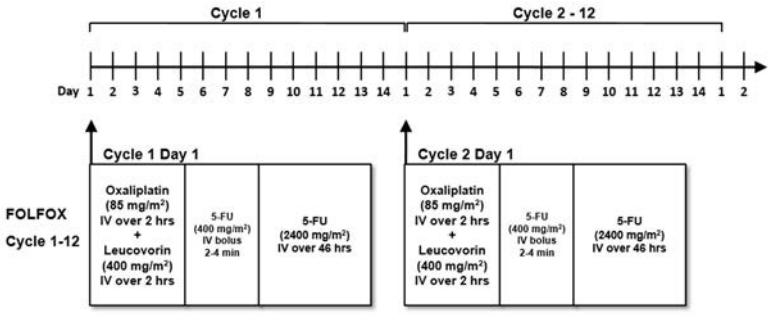
ARM 1: AM0010 plus FOLFOX



ARM 2: FOLFOX alone, initiated on Day 1 of a 14-day cycle, for up to 12 cycles or until disease progression by RECIST v.1.1.

Study Design (continued)

ARM 2: FOLFOX Alone

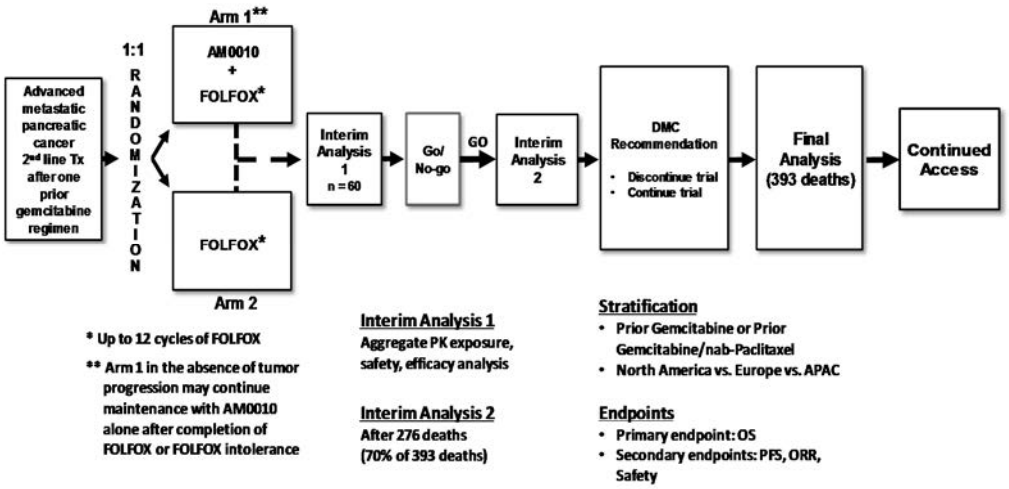


Crossover of patients from the FOLFOX-only treatment arm into the FOLFOX plus AM0010 treatment arm is not permitted.

Patients randomized to the investigational combination treatment (AM0010 plus FOLFOX) ARM 1, after completion of up to 12 cycles of combination chemotherapy or if experiencing chemotherapy intolerance (as defined as Grade 3 or 4 non-hematologic toxicity that does not resolve to baseline in 28 days with standard of care or hematologic Grade 4 toxicity that does not resolve to baseline in 28 days), may continue to receive maintenance AM0010 if the patient continues to receive clinical benefit (CR, PR, SD).

Patients may continue on treatment until they experience progressive disease, unacceptable toxicity, require palliative radiotherapy, withdraw consent, or their physician feels it is no longer in their best interest to continue on treatment. In case of toxicity due to 1 study drug patients can continue receiving the other study drugs based on the Investigator's assessment of risk-benefit.

Study Design Schema



Study Population/ Sample Size

Approximately 566 patients (283 per arm) will be randomized.

Randomization will be stratified by 2 stratification factors: prior single-agent gemcitabine therapy versus gemcitabine/nab-paclitaxel therapy and North America versus Europe versus APAC

Study Drug and

AM0010 is provided as a sterile, clear solution formulated at a concentration of 2 mg/mL and

Formulation	4 mg/mL. Patient should store the AM0010 at 2ºC to 8ºC.
Inclusion Criteria	1. The presence of metastatic pancreatic adenocarcinoma plus 1 of the following: a. Histological diagnosis of pancreatic adenocarcinoma confirmed pathologically, OR b. Pathologist-confirmed histological/cytological diagnosis of adenocarcinoma consistent with pancreas origin in conjunction with either: i. The presence of a mass in the pancreas, OR ii. A history of pancreatic adenocarcinoma. 2. Measurable disease per RECIST v.1.1. 3. Patient must have documented tumor progression during or following a gemcitabine-containing regimen for the treatment of metastatic disease. Diagnosis of progression (by computed tomography [CT] or magnetic resonance imaging [MRI] or clinical progression) must be within 28 days prior to Randomization. 4. Only 1 prior gemcitabine-containing therapy and no other prior therapies for metastatic disease. 5. Male or non-pregnant, non-lactating female, ≥18 years of age: a. If a female patient is of childbearing potential, as evidenced by menstrual periods, she must have a negative serum pregnancy test (β-hCG) documented prior to the first administration of study drugs. b. If sexually active, the patient must agree to use contraception considered adequate and appropriate by the Investigator (see Appendix H for full list of acceptable methods) during the period of administration of study drugs. In addition, male and female patients must utilize contraception after the end of the treatment as recommended in the individual drugs comprising FOLFOX product's Summary of Product Characteristics or Prescribing Information provided in the Pharmacy Manual and the Clinical Trial Facilitation Group, provided in Appendix H. 6. Provide signed written informed consent. 7. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0–1. 8. Patient must have completed prior chemotherapy and any investigational therapy at least 2 weeks (washout period) prior to Randomization and recovered from toxicity to Grade 1 or baseline. 9. Willingness and ability to comply with study requirements. 10. Patient has adequate organ function by the following laboratory assessments at baseline (obtained ≤21 days prior to Randomization): **Hematologic** o Platelets ≥100×10^9/L o Hemoglobin ≥9.0 g/dL o Absolute Neutrophil Count (ANC) ≥1.5×10^9/L o Patient has acceptable coagulation values obtained ≤21 days prior to Randomization as demonstrated by prothrombin time (PT) and partial thromboplastin time (PTT) ≤1.5.ULN (upper limit of normal) (if on Coumadin, patient must be changed to Low Molecular Weight Heparin (LMWH) or oral Factor II or Xa inhibitor with half-life less than 24 hours. **Hepatic** o AST/ALT ≤3×ULN (if liver metastases are present, ≤5×ULN) o Alkaline phosphatase ≤2.0×ULN (if liver metastases are present, ≤5×ULN) o Total bilirubin ≤1.5×ULN
Inclusion Criteria (continued)	

	○ Albumin ≥3.0 g/dL **Renal** ○ Serum creatinine <2.0 mg/dL or calculated creatinine clearance ≥60 mL/min for patients with serum creatinine levels above the institutional normal value. If using creatinine clearance, actual body weight should be used for calculating creatinine clearance (eg, using Modification of Diet in Renal Disease [MDRD] formula) (Levey, Coresh et al., 2006). For patients with a body mass index (BMI) >30 kg/m^2, lean body weight should be used instead. 11. Patient must have a life expectancy of ≥4 months in the opinion of the Investigator.
Exclusion Criteria	1. Diagnosis of pancreatic islet neoplasm, acinar cell carcinoma, non-adenocarcinoma (ie, lymphoma, sarcoma), adenocarcinoma originating from the biliary tree, or cystadenocarcinoma. 2. Patient has experienced a decrease in ECOG PS between Screening visit and within 72 hours prior to Randomization. 3. Patient on Coumadin and not willing to change to LMWH or oral Factor II or Xa inhibitor with half-life of less than 24 hours. 4. Patient has received prior treatment with AM0010 or a platinum-containing regimen. 5. Patients who were intolerant to gemcitabine-containing regimens (unable to receive at least 8 weeks of treatment). 6. History of prior malignancy, except for adequately treated in situ cancer, basal cell, squamous cell skin cancer, or other cancers (eg, breast, prostate) for which the patient has been disease-free for at least 3 years. Patients with prior cancer that is adequately controlled per the judgement of the Investigator will not be excluded from the study. 7. Any serious medical condition, laboratory abnormality, psychiatric illness, or comorbidity that, in the judgment of the Investigator, would make the patient inappropriate for the study. 8. Patients with abnormal electrocardiogram (ECG) at baseline (QT or QTc interval >450 ms for males; QT/QTc interval >470 ms for females) will be excluded from this study. 9. Serious systemic fungal, bacterial, viral, or other infection that is not controlled or requires intravenous (IV) antibiotics. 10. Known history of positivity (regardless of immune status) for human immunodeficiency virus (HIV). 11. Known history of, chronic active, or active viral hepatitis A, B, or C infection 12. Clinically significant bleeding within 2 weeks prior to Randomization (eg, gastrointestinal [GI] bleeding, intracranial hemorrhage). 13. Pregnant or lactating women. 14. Patients with a history of immune-mediated neurological disorders such as multiple sclerosis, Guillain-Barré, or inflammatory CNS/PNS disorders. 15. Myocardial infarction within the last 6 months prior to Randomization, symptomatic congestive heart failure (New York Heart Association Classification >Class II), unstable angina, or unstable cardiac arrhythmia requiring medication. 16. Clinically significant ascites defined as requiring ≥1 paracentesis every 2 weeks. 17. Major surgery, defined as any surgical procedure that involves general anesthesia and a significant incision (ie, larger than what is required for placement of central venous access, percutaneous feeding tube, or biopsy), within 28 days prior to Randomization or anticipated surgery during the study period. 18. Prior history of receiving immune checkpoint inhibitors (anti-CTLA4, anti-PD1, anti-PD-L1). 19. Peripheral neuropathy (>Grade 1).

20. Known history of dihydropyrimidine dehydrogenase deficiency (DPD).
21. Prior history of previous radiation therapy or surgery for the treatment of pancreatic cancer (eg, Whipple or pancreatectomy, etc.). Prior history of receiving gemcitabine or any other chemotherapy in the adjuvant setting.

Procedures

Screening:

Screening tests and evaluations will be performed only after a written Institutional Review Board (IRB)- and Independent Ethics Committee (IEC)-approved informed consent is signed by each patient. Procedures will be conducted within 21 days prior to Randomization unless otherwise noted.

- Clinical evaluation: complete medical and cancer history, baseline signs and symptoms, demographics, physical examination, ECOG Performance Status, height, weight, body surface area (BSA) calculation, vital signs, documentation of concomitant medications including prior anti-cancer therapy, and obtaining pathology reports of archival tissue. Physical examination performed as part of standard practice may be used if conducted within 21 days prior to Randomization and if it meets the guidelines outlined in Section 6.7.2.
- Laboratory studies: hematology (with differential and platelet counts); prothrombin time (PT) and partial thromboplastin time (PTT); and comprehensive chemistry panel (electrolytes, renal and liver function tests [LFT]), urinalysis (UA) (dipstick), and serum pregnancy test for females of childbearing potential. Laboratory tests performed as part of standard practice may be used if conducted within 21 days prior to Randomization.
- Baseline tumor assessment of all sites of disease: spiral CT with contrast or MRI (if allergic to contrast media) must be performed within 28 days prior to Randomization. The same radiographic procedures used to define measurable and non-measurable lesions must be used throughout the study for each patient. The RECIST v.1.1 guideline recommends spiral CT images for chest, abdomen, and pelvis should be performed. Scans will be collected following the Imaging Manual. Scans performed as part of standard practice may be used if conducted within 28 days prior to Randomization. Note that the initial scan showing progression must be used for eligibility and must be performed within 28 days prior to Randomization.
- Repeat ECOG assessment within 72 hours prior to Randomization.
- CA 19-9
- Patient-reported questionnaires (EORTC QLQ-C30 and EQ-5D-5L) data to be collected at baseline (Screening) and on Day 1 of every treatment cycle regardless of dosing (including patients receiving AM0010 maintenance therapy) until 30 days after EOT.
- Randomization:
    - Patient will be randomized within 21 days of their screening assessments
    - All patients must begin treatment within 3 days after Randomization.

Tumor Assessment of Response:

Spiral CT or MRI (if allergic to contrast media) scans will be performed at Week 8 (±3 days) and every 8 weeks (±3 days) to evaluate response to treatment by RECIST v.1.1. The RECIST v.1.1 guideline recommends spiral CT images for chest, abdomen, and pelvis should be performed. Patients will continue the assigned study treatments until tumor progression, withdrawal from the study, or in case of unacceptable toxicity to experimental treatment not manageable with dose modifications outlined in the protocol and/or supportive care. Patients who discontinue study treatment(s) with response of CR, PR, or SD will undergo spiral CT or MRI scan every 8 weeks (±3 days) evaluations per protocol until tumor progression. Patients who demonstrate clinical progression before their scans are due will have a scan conducted to document progression by RECIST v.1.1.

The first scheduled tumor response assessment will be performed at Week 8 (±3 days) after Randomization, and responders will have a confirmatory scan no less than 4 weeks (±3 days) after response has been established using the same technique as baseline scans.

In treatment ARM 1, to mitigate the chance of detecting false progression (ie, pseudoprogression) early in the course of treatment with AM0010 in combination with

Procedures (continued)	FOLFOX, patients whose scans show radiographic progression in the absence of clinical deterioration, including worsening ECOG PS, may remain on study treatments and an additional scan should be obtained 4 weeks (±3 days) later as outlined in Section 8.1.1. If this subsequent scan shows disease progression, the patient will be discontinued from study treatments and followed for survival. All on-study spiral CT/MRI scans for all patients enrolled on the study will be collected prospectively and submitted to a central imaging reader for archiving. These scans may be reviewed at a later time at the request of Lilly based on the criteria above. End of Treatment (EOT) and Follow-Up Visits (30 days after EOT Visit): All patients must have the EOT visit and Follow-Up visit 30 days after EOT visit with the procedures conducted as described in the protocol and schedule of events. In this event-driven study, it is critically important for patients to continue to be followed for survival every 8 weeks for 12 months and every 12 weeks thereafter via record review and/or telephone contact.
Assessments of Safety	Safety and tolerability will be monitored through continuous reporting of adverse events (AEs) and serious adverse events (SAEs). Safety will be assessed by physical examination, standard clinical and laboratory tests (hematology, blood chemistry, and coagulations), and incidence of patients experiencing dose modifications, dose interruptions, and/or premature discontinuation of study drugs with reasons for study drug discontinuation. All AEs will be assessed for the relationship to study treatments, and the toxicity grade will be defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.
Assessments of PK/ADA	PK blood samples will be collected from patients on ARM 1 and ADA samples on ARMs 1 and 2. Patients must give their permission to obtaining the PK/ADA blood samples as outlined in the ICF. Within each 14-day cycle (with the first day of dosing designated as Day 1). Blood samples will be obtained as follows: • Cycles 1 and 2, Days 1 and 13 • Cycle 3 Day 1 Only • Cycle 4 Day 13 Only • Cycle 5 Day 1 Only • EOT and follow-up visit 30 days after EOT (ADA only). In the event the clinical site business hours, weekends, or holiday schedule lead to missed PK/ADA time points, these time points will not need to be made up on a different day.
Assessments of Efficacy	Overall survival will be assessed from the date of Randomization. Tumors responses will be assessed by RECIST v.1.1 criteria (eg, spiral CT or MRI, if allergic to contrast media) at baseline, Week 8 (±3 days), and then every 8 weeks (±3 days) regardless of cycle number and regardless of any dose interruptions. Confirmatory scans will be conducted in patients who have PR or CR no less than 4 weeks (±3 days) after a response has been established using the same technique as baseline. If clinical progression of disease is observed, a spiral CT or MRI scan will be obtained to confirm disease progression. CA 19-9 and other exploratory biomarkers will be obtained to determine correlation with efficacy outcomes. Scans will be archived for possible evaluation by a blinded, centralized independent radiology review using the RECIST v.1.1 at a later time. The time of this review will be determined by Lilly based on achieving the primary survival endpoint.
Sample Size	Approximately 566 patients will be randomized to the 2 arms in a 1:1 ratio to observe at least 393 deaths. Assuming a median OS time for the FOLFOX arm of 5.9 months, 393 deaths are needed to detect a 35% increase in survival with 85% power using a log-rank test (2-sided) with an overall type 1 error (2-sided) of 0.05, which corresponds to a median survival of 8 months in the AM0010 in combination with FOLFOX arm (HR=0.7375).
Interim and	Two interim analyses are planned. The first interim analysis will be conducted once at least 60

Final Analyses	randomized patients have had the opportunity to receive 4 months of therapy. The purpose of the first interim analysis is to evaluate PK exposure-safety and to perform a PK exposure-efficacy analysis to derive a Go/No-Go decision. The criteria for Go/No-Go decision will be developed with the DMC and incorporated into the DMC charter. This interim analysis is not designed to stop the study early for outstanding efficacy. Based on review of the PK exposure-safety and PK exposure-efficacy on the aggregated data of composite efficacy endpoints, the DMC will recommend continuing the trial, amending the study protocol, or stopping the study. The study will continue to enroll while this analysis is being completed. A second interim analysis will occur after approximately 276 deaths (70% of the 393 required deaths for final analysis) have occurred. The purpose of this interim analysis is to evaluate the safety and efficacy with the possibility of claiming superiority. The final analysis will be conducted when at least 393 deaths occur.
Statistical Methods Efficacy Analyses	The primary efficacy analyses will be performed based on the Intent-to-Treat (ITT) population. Sensitivity analyses of all efficacy endpoints based on the Per-Protocol population will also be performed to confirm results obtained using the ITT population. The primary efficacy endpoint is overall survival in this Phase 3 study. Overall survival will be compared in the 2 randomized treatment arms at the interim and final analyses using a 2-sided log-rank test, stratified by 2 IVRS stratification factors: prior gemcitabine-containing regimen; gemcitabine versus gemcitabine/nab-paclitaxel and North America versus Europe versus APAC. Patient survival will be summarized by median survival time and 95% CI based on the Kaplan-Meier method. Progression-free survival will be summarized in the same manner as overall survival. Objective response rate will be summarized and compared using a Cochran-Mantel-Haenszel 2-sided test stratified by the Randomization stratification factors.
Statistical Methods Safety Analyses	The safety population includes all randomized patients who received at least 1 dose of study drug. Study treatment exposure and compliance will be summarized. AEs will be summarized in terms of treatment-emergent events defined to be any event that begins or worsens in grade after Randomization through 30 days after the last dose of study drug. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 by treatment arm. All treatment emergent AEs, drug-related AEs, SAEs, and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v4.03 criteria by system organ class and preferred term. On-study lab parameters including hematology and chemistry will be summarized using the worst grade per NCI CTCAE v4.04 criteria.
Data Monitoring Committee	An independent Data Monitoring Committee (DMC) will be established with the responsibility of safeguarding the interest of the study participants. The DMC will review safety data regularly during the conduct of the study as well as evaluate data from the first interim analysis to recommend continuing the Phase 3 study, amending the study protocol, or stopping the study. The Go/No-Go decision recommendation on the first interim analysis will be based on a review of the PK exposure-safety and PK exposure-efficacy on the aggregated data of composite efficacy endpoints from the first 60 randomized patients who have had the opportunity to receive 4 months of therapy from the date of Randomization. The DMC will also review the second interim analysis after approximately 276 deaths (70% of the 393 deaths required for the final analysis). Based on the second interim analysis, the DMC will recommend continuing the trial as planned, discontinuing the study, or amending the study protocol. In addition, safety reviews will be conducted by the DMC according to the frequency specified in the DMC charter (see the DMC Charter of Organization for details of DMC responsibilities).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

5-FU	5 fluorouracil
5-HT3	5-hydroxytryptamine-3
ACR	American College of Radiology
ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine transaminase
AM0010	PEGylated Recombinant Human IL-10
ANC	Absolute neutrophil count
APAC	Asia Pacific Countries
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the curve (pharmacological exposure)
β-hCG	Beta-human chorionic gonadotropin
BLA	Biologics license application
BMI	Body mass index
BOR	Best overall response
BSA	Body surface area
BUN	Blood urea nitrogen
CA 19-9	Cancer antigen 19-9
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum drug concentration
CMH	Cochran-Mantel Haenszel
C_{min}	Minimal drug concentration / serum trough concentration
CNS	Central nervous system
CR	Complete response (no measurable residual tumor)
CRA	Clinical research associate
CRC	Colorectal cancer
CRF	Case report form
CRO	Contract research organization
CRP	Clinical Research Physician
CT	Computer tomography
DCR	Disease control rate
DMC	Data Monitoring Committee
DoR	Duration of response
DPD	Dihydropyrimidine Dehydrogenase Deficiency
EC_{10}	10% effective concentration
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
ECG	Electrocardiogram
EMA	European Medicines Agency
End of trial	End of the 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, if applicable.
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Core 30-item
EOT	End of treatment

EQ-5D-5L	EuroQoL 5-dimension 5-level
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practices
HCT	Hematocrit
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
HRQOL	Health-related quality-of-life
HuIL-10	Human Interleukin 10
HUS	Hemolytic uremic syndrome
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFNγ	Interferon gamma
IL-10	Interleukin 10
IND	Investigational New Drug Application
INR	International normalized ratio
IRB	Institutional Review Board
irCR	Immune-related complete response
irPD	Immune-related progressive disease
irPR	Immune-related partial response
irSD	Immune-related stable disease
ITT	Intent-to-treat
IV	Intravenous(ly)
IVRS	Interactive voice-response system
LD	Longest diameter
LFT	Liver function test
LMWH	Lower molecular weight heparin
LPO	Last patient off
LV	Leucovorin
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mPFS	Median progression-free survival
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NA	Not available
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ND	Not done
NDA	New drug application
NHP	Non-human primate
NOAEL	No-observed-adverse-effect level
NSCLC	Non-small cell lung carcinoma
NYHA	New York Heart Association
OFF	Combination of 5-FU/leucovorin and oxaliplatin
OR	Objective response
ORR	Objective response rate
OS	Overall survival

PD	Progressive disease
PDAC	Pancreatic duct adenocarcinoma
PE	Physical examination
PEG-rHuIL-10	PEGylated recombinant human interleukin 10
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PNS	Peripheral nervous system
PR	Partial response
PRO	Patient-reported outcomes
PS	Performance status
PT/INR	Prothrombin time international normalized ratio
PTT	Partial thromboplastin time
qd	Latin: quaque die (once a day)
QoL	Quality of life
QRS	QRS interval
QT	QT interval
QTc	Corrected QT Interval
RBC	Red blood cell
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
rHuIL-10	Recombinant Human Interleukin 10
RI	Reconstruction interval
rMuIL-10	Recombinant Murine Interleukin 10
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SLD	Sum of the Longest Diameters
SOC	Standard of care
SOE	Schedule of Events
SOP	Standard Operating Procedure
SQ	Subcutaneous
Study completion	This study will be considered complete (that is, the scientific evaluation will be complete) once it has been determined by Lilly that the evaluation of primary and secondary objectives are sufficient and complete.
SUSAR	Suspected, unexpected, serious, adverse reaction
$t_{½}$	Half-life
TCR	T-cell receptor
TdP	Torsades de Pointes
TEAEs	treatment-emergent adverse events
TK	Toxicokinetics
TKI	Tyrosine kinase inhibitors
TrAE	Treatment-related adverse events
UA	Urinalysis
US	United States
UE	Unable to evaluate
ULN	Upper limit of normal
WBC	White blood cells
WHO	World Health Organization

1.0 INTRODUCTION AND RATIONALE

1.1 Introduction

1.1.1 Pancreatic Cancer

Pancreatic Cancer is the fourth leading cause of cancer-related death in Europe and the United States (Siegel, Miller et al., 2015), (Malvezzi, Bertuccio et al., 2013). It was estimated that 48,960 new cases would be diagnosed and that 40,560 patients would die in 2015. The 5-year survival rate for this disease is less than 5% (Rahib, Smith et al., 2014). The first-line standard-of-care (SOC) for patients with unresectable locally advanced or metastatic pancreatic cancer has been single-agent gemcitabine from 1993–2013. In patients with locally advanced or metastatic stage disease, modest improvements in survival have recently been attained with FOLFIRINOX (folinic acid, 5–fluorouracil [5-FU], irinotecan, and oxaliplatin), or albumin-bound paclitaxel (nab-paclitaxel) plus gemcitabine chemotherapy (Conroy, Desseigne et al., 2011), (Von Hoff, Ervin et al., 2013). A factor limiting the efficacy of treatment of pancreatic cancer is impaired drug delivery as a result of the unique desmoplastic response – the pervasive growth of dense fibrous tissue around the tumor that occurs in pancreatic duct adenocarcinoma (PDAC). Single-agent gemcitabine remains the SOC treatment for patients with Eastern Cooperative Oncology Group (ECOG) Grade 2 Performance Status (PS) (Sultana, Smith et al., 2007). Multiple randomized Phase 3 trials have failed to show any improvement in survival with chemotherapy doublets that included gemcitabine or with the addition of targeted therapies to gemcitabine chemotherapy (Philip, Benedetti et al., 2010), (Van Cutsem, van de Velde et al., 2004), (Kindler, Niedzwiecki et al., 2010), (Philip, Benedetti et al., 2010), (Van Cutsem, Vervenne et al., 2009), (Kindler, Ioka et al., 2011), (Goncalves, Gilabert et al., 2012), (Rougier, Riess et al., 2013). The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib in combination with gemcitabine gained regulatory approval following a 12-day improvement in median survival compared with gemcitabine alone in a large, randomized Phase 3 study, which is arguably not clinically meaningful for most patients and therefore erlotinib is not widely used in this disease (Moore, Goldstein et al., 2007).

Two positive randomized trials in first-line setting have been reported in patients with advanced-stage pancreatic cancer. First, the PRODIGE-III trial (Conroy, Desseigne et al., 2011) randomly assigned patients with metastatic disease to receive either FOLFIRINOX or gemcitabine. Enrollment was limited to patients <75 years of age with ECOG Grade 0–1 PS. The median survival in the FOLFIRINOX cohort was 11.2 months compared with 6.8 months in the gemcitabine control arm (HR 0.57; $p<0.001$). Although FOLFIRINOX was associated with a worse toxicity profile than

gemcitabine, patients who received FOLFIRINOX reported an improved quality of life, probably due to delayed disease progression (Gourgou-Bourgade, Bascoul-Mollevi et al., 2013). Of note, the median dose intensity of FOLFIRINOX in the investigational arm was 80% of the dose per protocol. Reports from institutions suggest that modified schedules of FOLFIRINOX are often favored, with no apparent detrimental effect on efficacy (Faris, Blaszkowsky et al., 2013), (Gunturu, Yao et al., 2013).

The second randomized study that reported an advance in the treatment of metastatic pancreatic cancer was the MPACT trial (Von Hoff, Ervin et al., 2013). In this study, an improvement in survival was achieved with nab-paclitaxel plus gemcitabine compared with single-agent gemcitabine (8.7 months versus 6.7 months, HR 0.72; p<0.0001). Unlike the PRODIGE-III trial, the MPACT trial included a small subset of patients (7%) of those enrolled with ECOG Grade 2 PS for whom no survival benefit of combined therapy was observed, consistent with previous evidence suggesting that gemcitabine doublets provide no benefit to patients with ECOG Grade 2 PS (Heinemann, Boeck et al., 2008).

Second-line therapy in pancreatic cancer was uncommon in the past. However, data showed that the combination of 5-FU/leucovorin (LV) and oxaliplatin (OFF) significantly prolongs overall survival (OS) by 2.52 months compared to best supportive care (p=0.0008) and compared to 5-FU (Pelzer, Schwaner et al., 2011, Oettle, Riess et al., 2014). Second-line therapy with gemcitabine can be beneficial for patients who were previously treated with FOLFIRINOX (Conroy, Desseigne et al., 2011). There are many small trials with various single agents and, in general, the data demonstrate a median progression-free survival (mPFS) of 3 months and a median OS of up to 6 months for second-line treatments. There is no standard of care for second-line treatment of these patients. FOLFOX second-line treatment is a reasonable option for patients with pancreatic cancer progressing after gemcitabine chemotherapy. Zaanan et al. published a paper summarizing the data for FOLFOX as second-line chemotherapy in patients with pretreated metastatic pancreatic cancer from the FIRGEM study (Zaanan, Trouilloud et al., 2014). Among 46 patients who received second-line chemotherapy, 27 patients were treated with FOLFOX after progression to first-line gemcitabine alone (n=20) or FOLFIRI alternating with gemcitabine (n=7). Grade 3 adverse events (AEs) were observed in 33% of the patients (no Grade 4 AEs). At the end of follow-up, all patients had progressed and 25 had died. There were no objective responses (ORs) observed, and the disease control rate (DCR) was 36%. Median PFS and OS were 1.7 and 4.3 months, respectively. For patients with ECOG PS of 0–1 versus 2–3, the median PFS was 3.0 versus 1.2 months (p=0.0002), and median OS was 5.9 months versus 2.6 months (p=0.001), respectively. This indicated that FOLFOX has an acceptable safety profile in metastatic pancreatic cancer patients with a good ECOG

PS. FOLFOX therapy after tumor progression on or after first-line therapy with gemcitabine or gemcitabine/nab-paclitaxel achieved a mOS of 4.5 or 6.4 months in the second line respectively (Chiorean, Von Hoff, Tabernero et al., 2016).

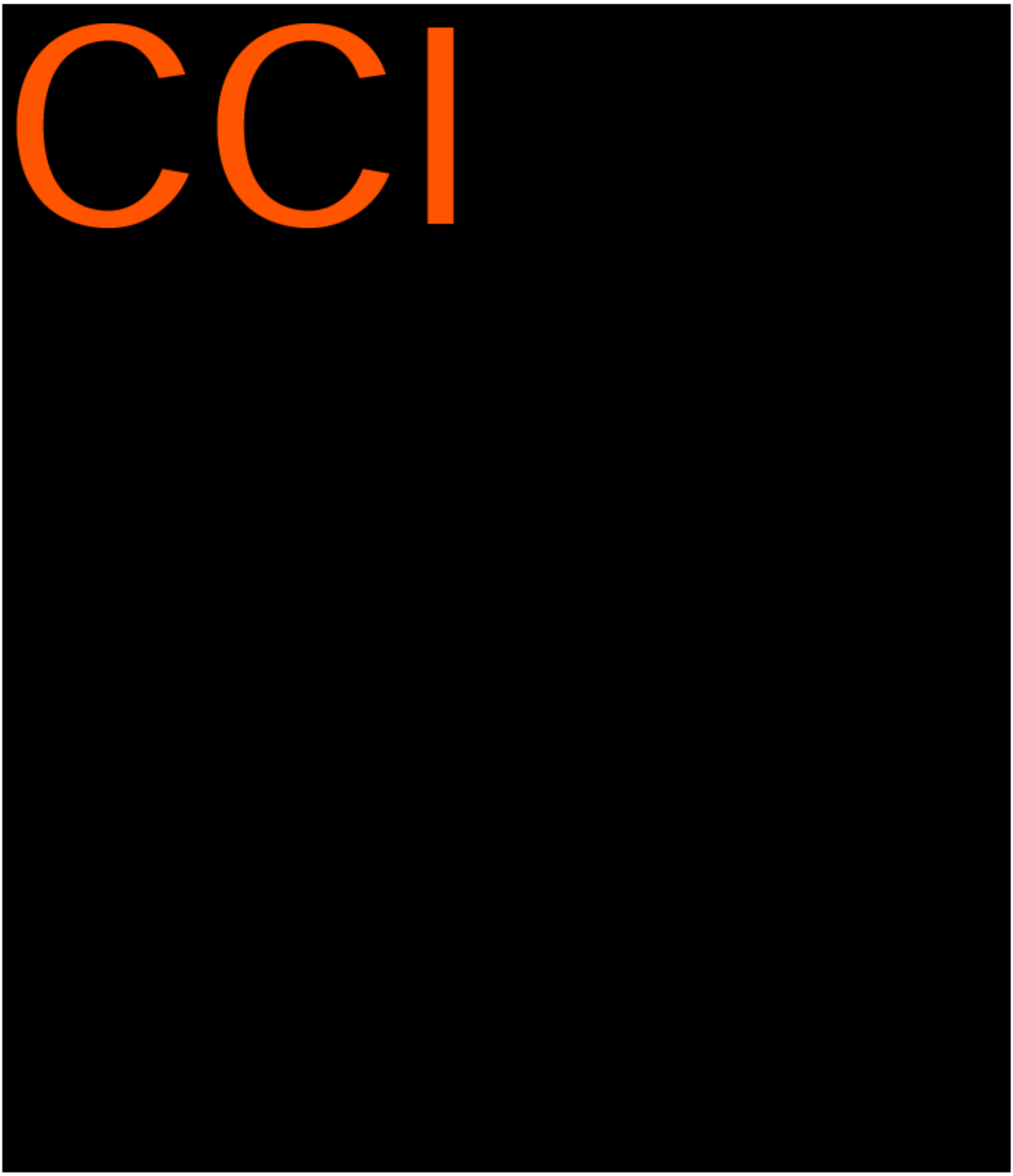
Most recently, 5-FU/LV versus FOLFOX for the second-line therapy of pancreatic cancer following gemcitabine-based regimen was investigated in the PANCREOX trial. The primary endpoint for the study was PFS. There was no difference in PFS observed between the 5-FU/LV and the FOLFOX arms. The study was terminated early, due to slow enrollment. In the PANCREOX study (n=108), the 5-FU/LV arm showed an unexpected survival of 9.9 months versus 6.1 months in the FOLFOX arm. Twenty-three percent of the 5-FU/LV patients received additional subsequent chemotherapy including FOLFOX or FOLFIRINOX after progression. This is compared with 8% of the FOLFOX patients, who only received monotherapy in the third line. The 5-FU/LV observed survival is unexpected compared to the data from several peer reviewed, published randomized trials, including the NAPOLI study (n=417). This unexpected outcome is possibly a result of the crossover of these patients to other treatments that confound any interpretation of the comparative survival data. In addition, there was a patient imbalance in disease characteristics and disease burden between the 2 arms. Since the majority of trials investigating 5-FU in pancreatic cancer consistently report an OS with 5-FU/LV of approximately 4 months both in first- and second line-treatment, the PANCREOX trial is considered an outlier by many experts in the pancreatic cancer field (Gill, Ko et al., 2016).

Recently, the Food and Drug Administration (FDA) approved nanoliposomal irinotecan in combination with 5-FU and folinic acid as second-line therapy after a previous gemcitabine-based therapy (NAPOLI-1) randomized Phase 3 study (Wang-Gillam, Li et al., 2016). This was a 3-arm trial, and patients received either nanoliposomal irinotecan monotherapy (120 mg/m^2) every 3 weeks or nanoliposomal irinotecan monotherapy (80 mg/m^2) in combination with fluorouracil and folinic acid every 2 weeks. The third arm was fluorouracil/ folinic acid alone. The median OS did not differ between patients assigned nanoliposomal irinotecan monotherapy and those allocated to fluorouracil and folinic acid at 4.9 months versus 2 months (p=0.94), respectively. The median OS for the combination of nanoliposomal irinotecan with folinic acid and 5-FU was 6.1 months with a hazard ratio (HR) of 0.67 (p=0.012) relative to folinic acid and 5-FU alone. Nanoliposomal irinotecan plus folinic acid and 5-FU increased survival and had a manageable safety profile as second-line therapy of metastatic pancreas cancer patients who previously received gemcitabine-based therapy.

The inclusion of an immune-oncology biological to an established chemotherapy regimen (eg, AM0010-001 plus FOLFOX) may result in additional/additive treatment-emergent adverse events

(TEAEs), compared with the chemotherapy regimen alone. Hence, although disease-related symptoms may subside with increased clinical efficacy, the corresponding treatment-associated symptoms may increase with the immune-oncology addition (eg, increased fatigue, appetite loss, or nausea and vomiting). These effects may also result in decrements to functioning and health-related Quality of Life (HRQOL).

In a population with few treatment options, a new regimen with AM0010 in combination with FOLFOX is a promising therapy to address an unmet medical need.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1.2.1 Pre-Clinical Pharmacology

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

treatment with PEGylated IL-10 remained tumor-free and developed a protective immune memory against the tumor. AM0010 stimulates the cytotoxic activity of murine or human peripheral $CD8^+$ T cells and the expression of cytotoxic enzymes and interferon gamma (IFNγ in memory $CD8^+$ T cells.

Further details on the pre-clinical pharmacology of AM0010 can be found in the Investigator's Brochure (IB).

1.2.2 Toxicology

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

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

In summary, the non-clinical toxicology program for AM0010 supports the continuation of clinical trials in humans.

Further details on the non-clinical toxicology of AM0010 can be found in the IB.

1.2.3 Non-Clinical Pharmacokinetics

The pharmacokinetics/toxicokinetics (PK/TK) of AM0010 were evaluated in CD1 mice and cynomolgus monkeys in non-GLP pharmacokinetic studies and further evaluated in GLP toxicokinetic studies in both species. PEG-rHuIL-10 showed a half-life ($t_{½}$) of approximately 10 hours in cynomolgus monkeys, compared with a $t_{½}$ of rHuIL-10 of approximately 2.5 hours.

The serum exposure of AM0010 in CD-1 mice ($AUC_{0-\infty}$ and C_{max}) increased proportionally with dose after SQ administration of 1 and 20 µg/kg. Mean serum $t_{½}$ of AM0010 was approximately 4.5 hours at 20 µg/kg. The trough serum AM0010 concentration of approximately 1–2 ng/mL was associated with a highly efficacious SQ dosing regimen of 0.1 mg/kg given daily in a murine syngeneic tumor model.

Further details on the pre-clinical PK of AM0010 are shown in the IB.

1.2.4 Human Pharmacokinetics

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

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

At the starting AM0010 dose (1 µg/kg), patients had a serum concentration of AM0010 between 0.68 and 1 ng/mL or equivalent to 10% effective concentration (EC_{10}). The average minimum AM0010 serum concentration at the 5 µg/kg was 3.5 ng/mL or the equivalent to the EC_{25}. The difference between C_{max} and C_{min} was approximately 33%, indicating a stable drug exposure with once-daily dosing (Table 1).

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

An interim PK analysis has been conducted on the data available from 193 patients in AM0010-001. These patients received extended treatment with AM0010, and samples were obtained intermittently throughout their treatment course.

1. AM0010 in the serum is cumulative, reaching steady-state conditions after approximately 1 week of daily dosing.
2. T_{max} following a single dose of AM0010 is approximately 12 hours.
3. The median absorption $t_{½}$ is 8.16 hours, the median elimination $t_{½}$ is 19.2 hours.
4. Apparent clearance (the sole determinant of area-under-the-curve) is proportional to weight, supporting a weight-normalized dosing regimen.
5. Apparent clearance (and, to a lesser extent, distribution volume) was smaller in patients assigned to higher-dose cohorts (values ranged from 1–40 µg/kg/dose).

None of the other covariates evaluated (age, gender, race, organ function, chemotherapy regimen) appear to influence the PK parameters.

The serum concentration of AM0010 was also evaluated after escalating doses of AM0010 in combination with FOLFOX chemotherapy. The analysis did not reveal a significant difference from AM0010 monotherapy.

1.2.5 Safety of AM0010

1.2.5.1 Clinical

A summary of safety events of special interest is provided below. For more information on the safety profile of AM0010, please refer to the most recent IB.

1.2.5.1.1 Hematologic Adverse Events

The safety and efficacy of rHuIL-10 was previously studied in normal patients 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 in platelet counts and anemia, resulting in lower hematocrit/hemoglobin (HCT/Hgb) levels. The transient thrombocytopenia did not lead to an increased frequency of bleeding.

In the Phase 1 study with AM0010, a reduction in RBCs as reflected in a reduction in HCT/Hgb and platelet counts was observed. CCI [redacted] Reactive increase in reticulocyte count was observed. Single-agent AM0010 was associated most commonly with Grade 1–2 anemia and thrombocytopenia. The reduction of platelets was not associated with bleeding in the Phase 1 study.


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Table 4: Treatment-Related Anemia – Pancreatic Cancer* – All Treatments

Severity (CTCAE Grade*)	Monotherapy			FOLFOX +			Gem/Nab-Paclitaxel	Capecitabine
	AM0010 5 µg/kg (N=1) n (%)	AM0010 20 µg/kg (N=22) n (%)	AM0010 40 µg/kg (N=1) n (%)	AM0010 2.5 µg/kg (N=2) n (%)	AM0010 5 µg/kg (N=25) n (%)	AM0010 10 µg/kg (N=2) n (%)	AM0010 5 µg/kg (N=6) n (%)	AM0010 10 µg/kg (N=5) n (%)
Overall	0 (0.0)	11 (50.0)	1 (100.0)	0 (0.0)	16 (64.0)	1 (50.0)	1 (16.7)	3 (60.0)
1	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	0 (0.0)	6 (27.3)	1 (100.0)	0 (0.0)	5 (20.0)	0 (0.0)	0 (0.0)	2 (40.0)
3	0 (0.0)	4 (18.2)	0 (0.0)	0 (0.0)	11 (44.0)	1 (50.0)	1 (16.7)	1 (20.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3 or 4	0 (0.0)	4 (18.2)	0 (0.0)	0 (0.0)	11 (44.0)	1 (50.0)	1 (16.7)	1 (20.0)

* NCI CTCAE v4.03.

Compensatory increases in reticulocyte counts were detectable throughout the dosing period. On Day 29 of dosing, reticulocytes were increased in 83 of 150 reporting patients (55%) compared to 63 of 310 patients (20%), with increased reticulocytes at the screening visit. The increased number of reticulocytes indicates increased RBC precursors and may limit a further reduction in HCT/Hgb with continued AM0010 dosing.

In non-human primates, hemosiderin-positive macrophages have been observed in several organs, indicating the phagocytosis of erythrocytes by macrophages. This mechanism was previously described during the development of rHuIL-10 (Tilg, Ulmer et al., 2002). CCI [redacted]

Many chemotherapy regimens are known to cause a reduction in hematocrit/hemoglobin, platelets, white blood cells, and absolute neutrophil counts. The safety of a combination of AM0010 with 5 different chemotherapy regimens was investigated in the Phase 1 study. The combined treatment of AM0010 with FOLFOX chemotherapy regimen did not lead to a greater frequency of reductions of hematocrit/hemoglobin and RBCs. The reductions in hemoglobin typically reverted to Grade 1 or baseline with dose interruptions or supportive treatment within 1 week. For further information, consult the IB for AM0010.


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Both 5-FU and oxaliplatin are associated with thrombocytopenia. In the Phase 1 study with AM0010, the combination of AM0010 with FOLFOX led to a reduction in platelet counts with a nadir at 7 days. Treatment-related Grade 3 and Grade 4 thrombocytopenia was observed in 55% of patients treated with uninterrupted daily dosing of AM0010 in combination with FOLFOX. In patients with Grade 3 or 4 thrombocytopenia, dosing was interrupted and platelet numbers recovered to Grade 1 or normal levels within 2-7 days following dose interruption of AM0010 dosing.

Sixty-four patients with pancreatic cancer have been treated with AM0010 in monotherapy or in combination with chemotherapy. One patient receiving AM0010 5 µg/kg with FOLFOX experienced Grade 2 gastric hemorrhage and 1 patient on AM0010 5 µg/kg with gemcitabine/paclitaxel experienced Grade 3 gastrointestinal hemorrhage.

Pancreatic cancer patients have a high incidence of thrombosis. Anticoagulants with a $t_{½}$ of less than 24 hours are frequently prescribed in this patient population and were allowed for patients with pancreatic cancer on the Phase 1 study. The use of anti-coagulant did not lead to bleeding events in AM0010-treated patients.

To avoid Grades 3–4 hematological toxicity and dose interruptions, intermittent dosing schedules were modeled to understand the decline and rapid recovery of platelets during AM0010 therapy. The AM0010 dosing schedule selected for the Phase 3 study, 5 days on, 2 days off, is predicted to avoid Grade 3 and 4 thrombocytopenia in advanced cancer patients receiving AM0010 in combination with FOLFOX without compromising the immune stimulatory mechanism of action of AM0010.

In the Phase 1 study with AM0010, 36 patients were on Low Molecular Weight Heparin (LMWH), 6 patients were on an oral factor Xa inhibitor, and 9 patients were on low-dose warfarin for IV port maintenance, with no major bleeding events reported.

In addition, the Phase 3 study will exclude patients on Coumadin. For patients who wish to participate, the prescription will be changed to a Factor II or Xa inhibitor with a $t_{½}$ of less than 24 hours or LMWH.

In summary, these data indicate that AM0010 alone and in combination with chemotherapy induces thrombocytopenia that is manageable in patients with advanced solid malignancies. CCI

[redacted]

CCI [redacted]

1.3 AM0010 Dose Rationale

1.3.1 Clinical Experience with AM0010

In a previous First-in-Human study, preliminary exposure and safety and efficacy data have been collected.

The previous dose escalation study defined the safety profile, maximum tolerated dose, recommended Phase 3 dose as monotherapy and in combination with chemotherapy, PK, and objective tumor responses (according to immune-related response criteria) in patients with advanced solid malignancies.

In the previous studies, 33 patients with advanced solid malignancies across several indications (melanoma, ovarian, pancreatic, prostate, renal cell, colorectal, and non-small cell lung carcinoma [NSCLC]) were 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 to be well tolerated.

Subsequently, clinical activity was further explored in 9 dose expansion cohorts with AM0010 monotherapy in specific disease indications such as cholangiocarcinoma, renal cell carcinoma (RCC), colorectal cancer (CRC), NSCLC, and PDAC. Efficacy of AM0010 in combination with chemotherapy, targeted therapy, or immune checkpoint inhibitors was explored in 9 additional combination regimens (Table 8).

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

1.3.2 AM0010 Dose Rationale for Pancreatic Cancer with FOLFOX

The safety, tolerability, and preliminary efficacy of AM0010 have been evaluated as monotherapy and in combination with chemotherapy, targeted agents, and immune checkpoint inhibitors at doses between 5 and 40 µg/kg SQ daily. Based on the clinical experience in 353 patients as of 29 October 2017, AM0010 has a manageable safety profile in patients with advanced solid malignancies including pancreatic cancer when combined with FOLFOX. The most commonly reported AE was reversible thrombocytopenia. In a Phase 1b study, Grade 3–4 thrombocytopenia was observed in 55% of patients receiving uninterrupted daily AM0010 dosing in combination with FOLFOX. In all patients with Grade 3–4 thrombocytopenia, dose interruption led to the recovery of platelet counts within 7 days. Modeling of the platelet counts indicates that 5 days AM0010 dosing followed by 2 days rest will prevent Grade 3–4 thrombocytopenia in patients treated with the AM0010 plus

FOLFOX regimen. CCI [redacted]

In a Phase 1b study 21 patients with PDAC who had progressed on prior gemcitabine-based therapy, and who did not receive any prior platinum-based regimen, were enrolled in a Phase 1b expansion cohort on 5 µg/kg AM0010 plus FOLFOX. The median age of those 21 patients was 64 years (range, 43–77 years). Median number of prior therapies is 2 (range 1–5).

In this cohort, 19 patients had a tumor response assessment; 2 had an irCR, 1 had an irPR-100% reduction in measurable lesions, 11 had an irSD, and 4 had a BOR of irPD. The median follow-up period is 20.3 months (range 15.8–25.9 months).

The time on prior treatments and on this study for PDAC patients receiving AM0010 plus FOLFOX is shown in Figure 1. Nine of 21 patients received more than 16 weeks of treatment. The best response for the reduction in the serum tumor marker CA 19-9 is shown in Figure 2. CA 19-9 is a serum tumor marker that is elevated in approximately 60% of pancreatic cancers. Any reduction in CA 19-9 and the best response in CA 19-9 are correlated with a prolonged OS of patients with pancreatic cancer treated with a gemcitabine-based regimen (Chiorean, Von Hoff et al. 2016). In this cohort, 9 of 12 patients (75.%) had a reduction of CA 19-9, with 7 of the 9 patients having a reduction of at least 20% (Figure 2).

In all 21 patients (ITT population), the median PFS was 2.6 months and the median OS was 10.2 months. The 1-year survival was 42.9% (Figure 3).

Based on early results, a 5-µg/kg dose combined with FOLFOX is proposed for this Phase 3 trial. At this dose level, thrombocytopenia associated with the combination treatment is manageable and is associated with early evidence of efficacy.

The proposed dosing schedule (5 days on, 2 days off) is predicted from hematologic and biomarker analysis and modeling to mitigate the risk of thrombocytopenia while maintaining the activation of the immune system and clinical benefit. These findings support the selection of a 5/2 regimen to replace the daily SQ regimen administered in a previous clinical trial. This 5/2 regimen is expected to decrease the incidence and magnitude of thrombocytopenia and permit recovery of platelet counts during the 2-day off rest period.

The rational for dosing at a flat rate with a cutoff at 80 kg is based on safety and on the PK/pharmacodynamic relationship. More specifically, immune activation with AM0010 requires a serum trough of at least 1 ng/mL. This minimal trough level is reached with actual doses of 2.5 µg/kg and higher. The maximum tolerated dose (MTD) of AM0010 monotherapy is 20 µg/kg.

In a Phase 1b study with AM0010 + FOLFOX, patients received individual weight-based doses of a median of 6.31 µg/kg AM0010 (range 4.19–9.11 µg/kg). Within this Phase 1b study, encouraging OS was observed in patients receiving more than 5 µg/kg, based on their individual weight. Safety and tolerability of AM0010 + FOLFOX was also explored in a dose escalation study, in which patients received up to 13.4 µg/kg. However, patients with doses above 10 µg/kg in combination with FOLFOX may have required dose reductions.

Table 9 provides the actual received dosage per kg for patients with weights between 40 and 160 kg. It shows that a safe and efficacious dose is obtained with the proposed flat rate dosing for patients above and below 80 kg.

AM0010 at 10 µg/kg was determined to be the optimal biologic dose for maintenance therapy. In 144 patients who received monotherapy in Phase 1 the MTD was determined to be 20 µg/kg as described in the IB. The pharmacodynamic analysis indicates immune activation at 10 µg/kg as monotherapy (Naing et al JCO, 2016). Therefore, AM0010 at 10 µg/kg was chosen for the maintenance dose.

1.3.3 Rationale for Evaluating CA 19-9

A biological marker widely used in clinical practice in the assessment and follow-up of patients with pancreatic cancer is CA 19-9. A strong correlation between marker decline during chemotherapy and patient outcomes has been observed, particularly in patients with metastatic pancreatic cancer. In the Phase 3 trial of ABI-007 in combination with gemcitabine for advanced adenocarcinoma of the pancreas, remarkable decreases of CA 19-9 were observed (Von Hoff, Ervin et al., 2013). A total of 61% in the nab-paclitaxel cohort had a decrease of at least 20% in CA 19-9. Patients with at least 90% decrease in CA 19-9 levels lived 13.5 months. In a recent publication by Chiorean et al, CA 19-9 decreases at 8 weeks are predictors of OS in a randomized Phase 3 study (MPACT) of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic pancreatic cancer (Chiorean, Von Hoff et al., 2016). Since CA 19-9 is being used only in an exploratory evaluation to determine whether there is a correlation with efficacy outcomes, increases in CA 19-9 levels in this study should not be used as evidence for progressive disease or for discontinuing patients from study treatment.

2.0 STUDY OBJECTIVES AND INVESTIGATIONAL PLAN

2.1 Study Objectives

2.1.1 Primary Objective

To compare the efficacy of AM0010 in combination with FOLFOX versus FOLFOX alone in patients with metastatic pancreatic cancer as measured by OS.

2.1.2 Secondary Objectives

The secondary objectives are:

- To compare the efficacy of AM0010 in combination with FOLFOX versus FOLFOX alone in patients with metastatic pancreatic cancer as measured by:
    - PFS
    - Objective response rate (ORR), DCR, and duration of response (DoR) by Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1
    - 1-year survival rate
- To compare the safety and tolerability of AM0010 in combination with FOLFOX versus FOLFOX alone

2.1.3 Exploratory Objectives

- To explore biomarkers that may correlate with tumor response, immune activation, and relationships to clinical efficacy outcomes.
- To explore associations between patient-reported symptoms, functioning, and global health status/QoL using the European Organisation for Research and Treatment of Cancer Quality of Life Core 30-item (EORTC QLQ-C30) questionnaire as well as current health status and the EuroQoL 5-dimension (EQ-5D) Index used in the economic evaluation of health care using the EuroQoL 5-dimension 5-level (EQ-5D-5L) questionnaire.

2.2 Study Design

This is a randomized, open label, global Phase 3 Study of AM0010 in combination with FOLFOX compared with FOLFOX alone as second-line therapy in patients with advanced metastatic pancreatic cancer that has progressed during or following a first-line gemcitabine-containing regimen.

Approximately 566 patients will be randomized. Two interim analyses are planned. The first interim analysis will be performed when at least 60 randomized patients have had the opportunity to receive 4 months of therapy from the date of Randomization. Based on the first interim analysis, the Data Monitoring Committee (DMC) will review the PK exposure-safety and PK exposure-efficacy on the composite aggregate data for a Go/No-Go decision to enroll the entire Phase 3 study. The enrollment will continue during the analysis. The second interim analysis will occur when approximately 276 deaths (70% of total 393 deaths needed for final analysis) have occurred. Based on the second interim analysis, the DMC will recommend modifying, continuing the trial as planned, or discontinuing the trial.

Patients will be randomized in a 1:1 ratio to AM0010 combined with FOLFOX or FOLFOX alone.

The randomization will be stratified by 2 stratification factors:

- Prior single-agent gemcitabine therapy versus gemcitabine/nab-paclitaxel therapy
- North America versus Europe versus APAC.

Treatment Arms:

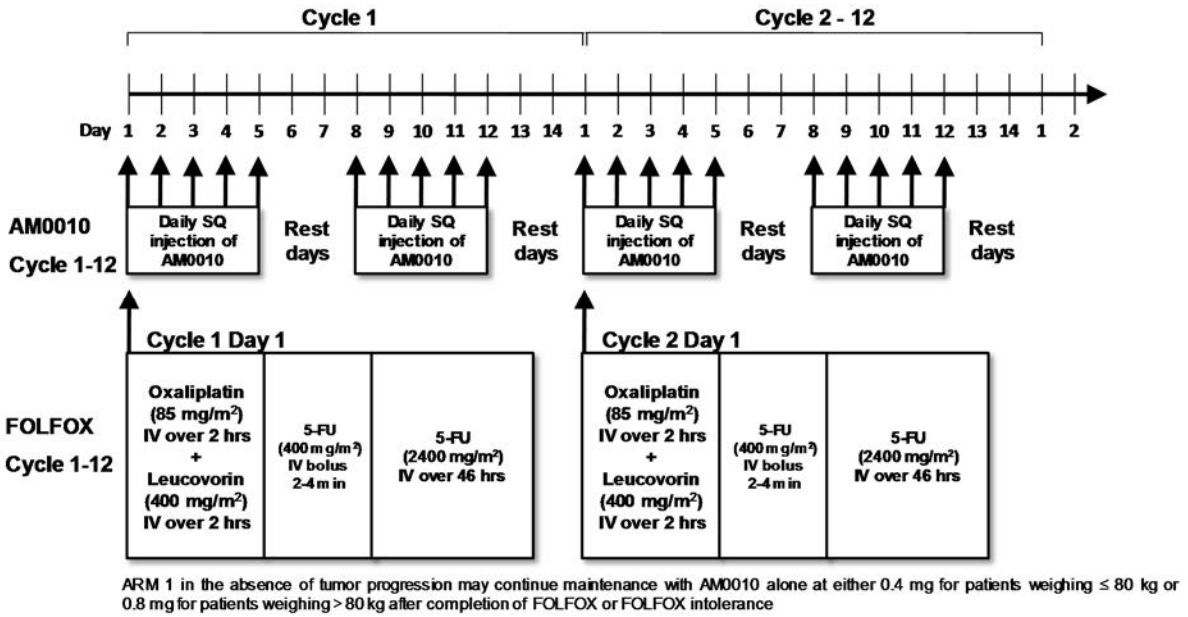
ARM 1: AM0010 (5 µg/kg) SQ dosed on Days 1–5 (with rest on Days 6 and 7) and Days 8-12 SQ (with rest on Days 13 and 14) plus FOLFOX (*dl*-LV 400 mg/m^2 and oxaliplatin 85 mg/m^2 followed by bolus 5-FU 400 mg/m^2 and a 46- to 48-hour infusion of 5-FU 2400 mg/m^2) initiated on Day 1 of a 14-day cycle, for up to 12 cycles or until disease progression by RECIST v.1.1.

While receiving FOLFOX during Cycles 1–12, AM0010 at 5 µg/kg will be administered as 1 of 2 fixed doses, either 0.4 mg for patients weighing ≤80 kg or 0.8 mg for patients weighing >80 kg.

Patients in ARM 1 may continue on maintenance cycles with AM0010 (as shown below). After discontinuation of FOLFOX in the absence of tumor progression (ie, completion of the planned 12 cycles or unacceptable FOLFOX related toxicity), AM0010 at 10 µg/kg will be administered as 1 of 2 fixed doses, either 0.8 mg patients weighing ≤80 kg or 1.6 mg for patients weighing >80 kg.

ARM 1: AM0010 plus FOLFOX, for up to 12 cycles or until disease progression by RECIST v.1.1.

Figure 4: ARM 1: AM0010 + FOLFOX



ARM 1 in the absence of tumor progression may continue maintenance with AM0010 alone at either 0.4 mg for patients weighing ≤ 80 kg or 0.8 mg for patients weighing > 80 kg after completion of FOLFOX or FOLFOX intolerance

ARM 2: FOLFOX alone, initiated on Day 1 of a 14-day cycle, for up to 12 cycles or until disease progression by RECIST v.1.1.

Figure 5: ARM 2: FOLFOX Alone

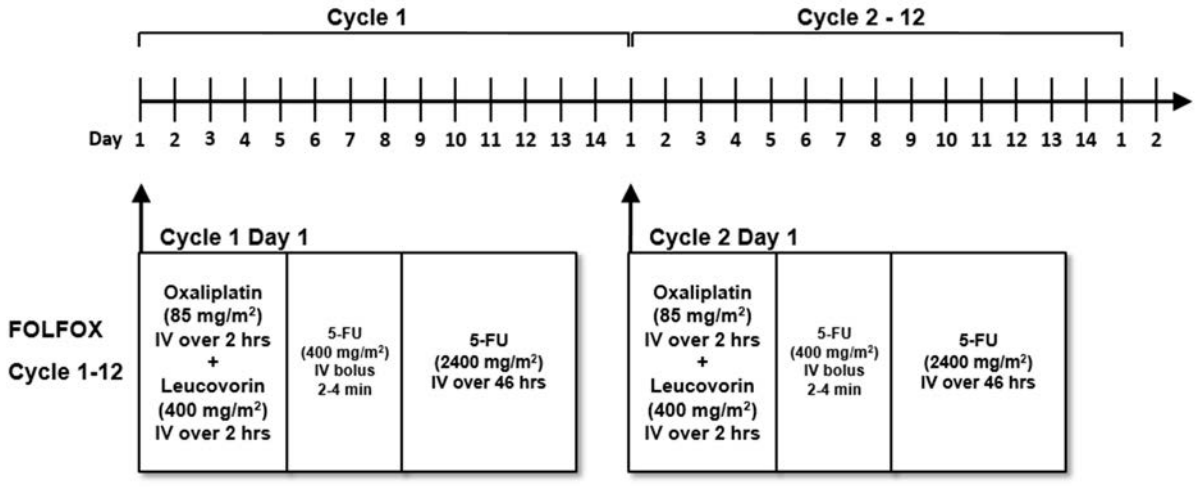
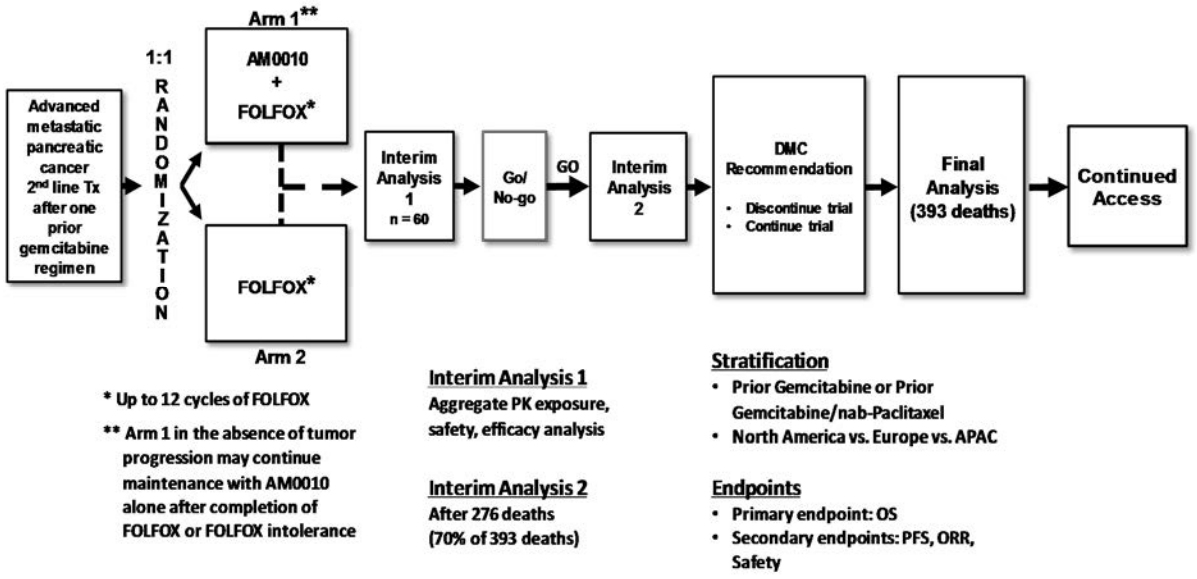


Figure 6: Study Design Schema



2.2.1 Treatment Duration

Each cycle is 14 days, with Days 6, 7, 13, and 14 being rest days for AM0010. FOLFOX will be administered on Day 1 of each cycle. Patients randomized to the investigational combination treatment (AM0010 plus FOLFOX) ARM 1, after completion of up to 12 cycles of combination chemotherapy or if experiencing chemotherapy intolerance (as defined as Grade 3 or 4 non-hematologic toxicity that has not resolved to baseline in 28 days or Grade 4 hematologic toxicity that has not resolved to baseline in 28 days) may continue to receive maintenance AM0010 if the patient continues to receive clinical benefit (CR, PR, or SD). Patients may receive FOLFOX on both study arms for up to 12 cycles or 24 weeks. Patients will be treated until tumor progression by RECIST v.1.1.

Patients may continue on treatment until they experience progressive disease, unacceptable toxicity, require palliative radiotherapy, withdraw consent, or their physician feels it is no longer in their best interest to continue on study treatments.

To mitigate the chance of detecting false-progression (ie, pseudoprogression) early in the course of treatment on ARM 1 with AM0010 in combination with FOLFOX, patients whose scans show radiographic progression in the absence of clinical deterioration including worsening ECOG PS as assessed by the Investigator may remain on study treatments and should have an additional scan 4

weeks (±3 days) later as outlined in Section 8.1.1. If this subsequent scan shows disease progression, the patient will be discontinued from study treatments.

2.2.2 Evaluation of Molecular Biomarkers

2.2.2.1 Carbohydrate CA 19-9

Serum levels of CA 19-9 will be evaluated over time to assess changes after treatment with AM0010 plus FOLFOX and FOLFOX alone. Since CA 19-9 is being used only in an exploratory evaluation to determine whether there is a correlation with efficacy outcomes, increases in CA 19-9 levels in this study should not be used as evidence for progressive disease or for removing patients from study treatments.

2.2.2.2 Other Exploratory Molecular Markers

The following additional optional biomarkers may be quantified and correlated with subsequent anti-tumor responses: i) Pre-treatment intratumoral CD8+ T cells and MHC I expression levels in archival tumor samples may be quantified to determine if a pre-treatment intratumoral immune signature effects AM0010 treatment outcomes; ii) Treatment-associated changes in the serum biomarkers IL-18, IFNγ, IL-4, and transforming growth factor-beta (TGFβ) may be quantified to assess both the duration of AM0010 mediated immune activation and whether there is an AM0010 serum immune signature that correlates with PR/CR anti-tumor responses; and iii) Peripheral blood T-cell receptor (TCR) β sequences and PBMC and mRNA may be obtained from on-treatment serial blood draws.

2.2.3 Number of Study Sites

This study will be conducted at approximately 150 sites in North America, Europe, and Asia-Pacific.

2.2.4 Number of Patients

The study will randomize approximately 566 patients.

2.2.5 Study Completion Definition

This study will be considered complete (ie, the scientific evaluation will be complete) once it has been determined by Lilly that the evaluation of primary and secondary objectives is sufficient and 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 drugs during the continued-access period.

2.2.6 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 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, the follow-up assessments should be completed prior to the initiation of the new therapy.

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

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

Serious adverse events (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.

2.2.7 End of Trial Definition

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

2.3 Study Endpoints

2.3.1 Primary Endpoint

The primary endpoint of this study is OS, defined as the time from date of Randomization to death due to any cause.

2.3.2 Secondary Endpoints

The secondary endpoints of the study include:

- PFS is defined as the time from date of Randomization to the earlier of first documentation of definitive disease progression (the initial PD that was confirmed by the consecutive scan) or death due to any cause.
- ORR is defined as the proportion of patients who achieve a CR or PR as assessed by RECIST v.1.1.
- DoR is defined as the time from the date of the first documentation of objective tumor response (CR or PR) to the date of the first documentation of objective tumor progression or death due to any cause, whichever occurs first.
- 1-year OS rate is defined as the survival rate as estimated using the Kaplan-Meier method at the end of the first year.

2.3.3 Exploratory Endpoints

Baseline and change from baseline in immune and molecular biomarkers and their relationship to clinical efficacy endpoints will be explored.

In addition to baseline and change from baseline in the EORTC QLQ-C30 and EQ-5D-5L, time to deterioration in patient-reported symptoms and functioning will be explored using symptom items that correspond with the TEAE profile (eg, fatigue, anorexia, and nausea/vomiting) as well as the subscales for functioning and HRQoL.

2.3.4 Trial Duration

Approximately 36 months (screening, enrollment, and study completion). Twenty-five months for patient enrollment, opportunity to have at least 6 months of treatment or until PD by RECIST v.1.1, 2-months follow-up, and 2 months of data auditing and analysis.

3.0 STUDY POPULATION

3.1 Patient Selection Criteria

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

3.1.1 Inclusion Criteria

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

1. The presence of metastatic pancreatic adenocarcinoma plus 1 of the following:
    a. Histological diagnosis of pancreatic adenocarcinoma confirmed pathologically, OR
    b. Pathologist-confirmed histological/cytological diagnosis of adenocarcinoma consistent with pancreas origin in conjunction with either:
        i. The presence of a mass in the pancreas, OR
        ii. A history of pancreatic adenocarcinoma.
2. Measurable disease per RECIST v.1.1.
3. Patient must have documented tumor progression during or following a gemcitabine-containing regimen for the treatment of metastatic disease. Diagnosis of progression (by computed tomography [CT] or magnetic resonance imaging [MRI] scan or clinical progression) must be within 28 days prior to Randomization.
4. Only 1 prior gemcitabine-containing therapy and no other prior therapies for metastatic disease.
5. Male or non-pregnant, non-lactating female, ≥18 years or age.
    a. If a female patient is of child-bearing potential, as evidenced by menstrual periods, she must have a negative serum pregnancy test (beta-human chorionic gonadotropin [β-hCG]) documented prior to the first administration of study drugs.
    b. If sexually active, the patient must agree to use contraception considered adequate and appropriate by the Investigator (see Appendix H for full list of acceptable methods) during the period of administration of study drugs. In addition, male and female patients must utilize contraception after the end of the treatment as recommended in the individual drugs comprising FOLFOX product's Summary of Product Characteristics or Prescribing Information provided in the Pharmacy Manual and the Clinical Trial Facilitation Group, provided in Appendix H.

6. Provide signed written informed consent.
7. ECOG PS of 0–1.
8. Patient must have completed prior chemotherapy and any investigational therapy at least 2 weeks (washout period) prior to Randomization and recovered from toxicity to Grade 1 or baseline.
9. Willingness and ability to comply with study requirements.
10. Patient has adequate organ function by the following laboratory assessments at baseline (obtained ≤21 days prior to Randomization):

    Hematologic

    - Platelets $\geq 100 \times 10^9$/L
    - Hemoglobin ≥9.0 g/dL
    - Absolute Neutrophil Count (ANC) $\geq 1.5 \times 10^9$/L
    - Patient has acceptable coagulation values obtained ≤21 days prior to Randomization as demonstrated by prothrombin time (PT) and partial thromboplastin time (PTT) ≤1.5× upper limit of normal (ULN) (if on Coumadin, patient must be changed to LMWH or on Factor II or Xa anticoagulant with a $t_{½}$ of less than 24 hours.

    Hepatic

    - Aspartate transaminase (AST)/alanine transaminase (ALT) ≤3×ULN (if liver metastases are present, ≤5×ULN)
    - Alkaline phosphatase ≤2.0×ULN (if liver metastases are present, ≤5×ULN)
    - Total bilirubin ≤1.5×ULN
    - Albumin ≥3.0 g/dL

Renal

- Serum creatinine <2.0 mg/dL or calculated creatinine clearance ≥60 mL/min for patients with serum creatinine levels above the institutional normal value. If using creatinine clearance, actual body weight should be used for calculating creatinine clearance (eg, using the Modification of Diet in Renal Disease [MDRD] formula, (Levey, Coresh et al., 2006)). For patients with a body mass index (BMI) >30 kg/m^2, lean body weight should be used instead.

11. Patient must have a life expectancy of ≥4 months in the opinion of the Investigator.

3.1.2 Exclusion Criteria

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

1. Diagnosis of pancreatic islet neoplasm, acinar cell carcinoma, non-adenocarcinoma (ie, lymphoma, sarcoma), adenocarcinoma originating from the biliary tree, or cystadenocarcinoma.
2. Patient has experienced a decrease in ECOG PS (Appendix E) between Screening visit and within 72 hours prior to Randomization.
3. Patient on Coumadin and not willing to change to LMWH or oral Factor II or Xa inhibitor with $t_{½}$ of less than 24 hours.
4. Patient has received prior treatment with AM0010 or a platinum-containing regimen.
5. Patients who were intolerant to gemcitabine-containing regimens (unable to receive at least 8 weeks of treatment).
6. History of prior malignancy, except for adequately treated in situ cancer, basal cell, squamous cell skin cancer, or other cancers (eg, breast and prostate) for which the patient has been disease-free for at least 3 years. Patients with prior cancer that is adequately controlled per the judgement of the Investigator will not be excluded from the study.
7. Any serious medical condition, laboratory abnormality, psychiatric illness, or comorbidity that, in the judgment of the Investigator, would make the patient inappropriate for the study
8. Patients with abnormal electrocardiogram (ECG) at baseline (QT or QTc interval >450 ms for males; QT or QTc interval >470 ms for females) will be excluded from this study.
9. Serious systemic fungal, bacterial, viral, or other infection that is not controlled or requires intravenous antibiotics.

10. Known history of positivity (regardless of immune status) for human immunodeficiency virus (HIV).
11. Known history of chronic active or active viral hepatitis A, B, or C infection.
12. Clinically significant bleeding within 2 weeks prior to Randomization (eg, gastrointestinal [GI] bleeding or intracranial hemorrhage).
13. Pregnant or lactating women.
14. Patients with a history of immune-mediated neurological disorders such as multiple sclerosis, Guillain-Barré, or inflammatory central nervous system (CNS)/peripheral nervous system (PNS) disorders.
15. Myocardial infarction within the last 6 months prior to Randomization, symptomatic congestive heart failure (New York Heart Association Classification >Class II, [Appendix F]), unstable angina, or unstable cardiac arrhythmia requiring medication.
16. Clinically significant ascites defined as requiring ≥1 paracentesis every 2 weeks.
17. Major surgery, defined as any surgical procedure that involves general anesthesia and a significant incision (ie, larger than what is required for placement of central venous access, percutaneous feeding tube, or biopsy) within 28 days prior to Randomization or anticipated surgery during the study period.
18. Prior history of receiving immune checkpoint inhibitors (anti-CTLA4, anti-PD1, anti-PD-L1).
19. Peripheral neuropathy (>Grade 1).
20. Known history of dihydropyrimidine dehydrogenase deficiency (DPD).
21. Prior history of previous radiation therapy or surgery for the treatment of pancreatic cancer (eg Whipple or pancreatectomy, etc.). Prior history of receiving gemcitabine or any other chemotherapy in the adjuvant setting.

3.2 Randomization

All patients must personally sign, 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 examination, or blood tests) performed within the specified screening period may be used for Screening if conducted within 21 days prior to Randomization. Patient eligibility will be established at the conclusion of the screening evaluations.

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.

3.3 Rescreening Criteria

Re-screening may be allowed. Patients who are re-screened after 30 days must be re-consented with a new screening number and repeat the screening assessments. For patients re-screened within 30 days, assessments with results that would exclude the patient will need to be repeated.

4.0 STUDY TREATMENT DISCONTINUATION AND STUDY DISCONTINUATION

4.1 Study Treatments Discontinuation

AM0010 or any of the components of FOLFOX can be discontinued for any of the following reasons.

- Adverse events
- Pregnancy
- Investigator decision to discontinue the patient from the components of the study treatments, in consultation with Lilly Medical Monitor
- Clinical disease progression
- Radiographic disease progression by RECIST v.1.1
- Intercurrent illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree
- Initiation of new anti-neoplastic therapy in the absence of tumor progression
- Patient request to discontinue study treatments
- Withdrawal of consent
- Death
- Discontinuation of the study at the request of Lilly, a regulatory agency, or an Institutional Review Board or Independent Ethics Committee (IRB/IEC)
- Poor or non-compliance with study procedures
- Major protocol violation
- Loss to follow-up

Should this occur, the corresponding study drugs completion CRF should be entered to document the reason for discontinuation. In addition, the patient should continue with the rest of the treatment regimen and the study-related procedures per the protocol.

4.2 Study Discontinuation

Patient study participation may be ended due to any of the following reasons:

- Withdrawal of consent
- Death
- Discontinuation of the study at the request of Lilly, a regulatory agency, or an IRB/IEC
- Loss to follow-up

5.0 AM0010 AND FOLFOX TREATMENT

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 and inventory. Please see the Pharmacy Manual for complete details.

5.1 Treatment Administration

5.1.1 AM0010

AM0010 is provided as a sterile, clear solution formulated at a concentration of 2 mg/mL and 4 mg/mL.

The AM0010 drug product is stored at the pharmacy at 2ºC to 8ºC. Patients will store their AM0010 in their refrigerator (2ºC to 8ºC).

While receiving FOLFOX during Cycles 1–12, AM0010 5 µg/kg will be administered as 1 of 2 fixed doses, either 0.4 mg for patients weighing ≤80 kg or 0.8 mg for patients weighing >80 kg.

AM0010 will be administered as a fixed dose, bracketed in 2 weight groups. Ongoing PK analysis has shown that the apparent clearance is proportional to weight supporting a weight-based dosing.

The rationale for dosing at a flat rate with a cutoff at 80 kg is based on safety and on the PK/Pharmacodynamic relationship. More specifically, immune activation with AM0010 requires a serum trough of at least 1 ng/mL. This trough level is reached with actual doses of 2.5 µg/kg and higher. The MTD of AM0010 is 20 µg/kg. Following the bracketed fixed dosing regimen, all patients will receive between 5 and 10 µg/kg AM0010. This dose range correlated with a survival benefit in a Phase 1b study with AM0010 + FOLFOX in PDAC patients.

The effects of overdose with AM0010 and an antidote to overdose with AM0010 are unknown. Non-human primates have been exposed to 5-10 times the expected serum concentration in humans without acute adverse reactions.

For any subject experiencing AM0010 overdose, observation for any symptomatic side effects should be instituted and vital signs and biochemical and hematologic parameters should be followed closely

(consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated.

After discontinuation of FOLFOX (ie, completion of the planned 12 cycles or unacceptable FOLFOX-related toxicity), the AM0010 dose at the 10-µg/kg dose level will be administered as 1 of 2 fixed doses (ie, either 0.8 mg in 0.2 mL for body weight ≤80 kg or 1.6 mg in 0.4 mL for body weight >80 kg), based on the patient's weight during the course of the study.

In 144 patients who received AM0010 monotherapy, the MTD was determined at 20 µg/kg (Naing et al., 2016). Pharmacodynamic analysis indicates immune activation at 10 µg/kg in a monotherapy setting.

Patients will be trained to self-administer AM0010 and will self-administer the dose throughout the study, starting with the first dose. The Investigator or a qualified designee must be present during administration of the first dose. A Dosing Diary must be kept by the patient with date and time of administration for dosing compliance monitoring. The diary will be a part of the source documentation and should be reviewed with the patient at every visit. Note that if the patient is unable or unwilling to self-administer the SQ injection of AM0010, the dose may be given by a caregiver.

5.1.2 FOLFOX Administration

FOLFOX treatment will be continued for up to 12 cycles or until disease progression or unacceptable chemotherapy-related toxicity. The FOLFOX dosing regimen will consist of *dl*-LV 400 mg/m^2 and oxaliplatin 85 mg/m^2 followed by bolus 5-FU 400 mg/m^2 and a 46- to 48-hour infusion of 5-FU 2400 mg/m^2. Note: if the institution is using l-LV (non-racemic), the dose is 200 mg/m^2.

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.

A 5-hydroxytryptamine-3 (5-HT3) antagonist (eg, 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.

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 patient's hematology and chemistry panels, liver function tests, and the incidence of hematologic and non-hematologic toxicities prior to and during chemotherapy regimens.

5.1.3 Dosing Schedule

Patients will be treated on an outpatient basis with AM0010 plus FOLFOX or FOLFOX alone. Each cycle is 14 days.

ARM 1: AM0010 plus FOLFOX

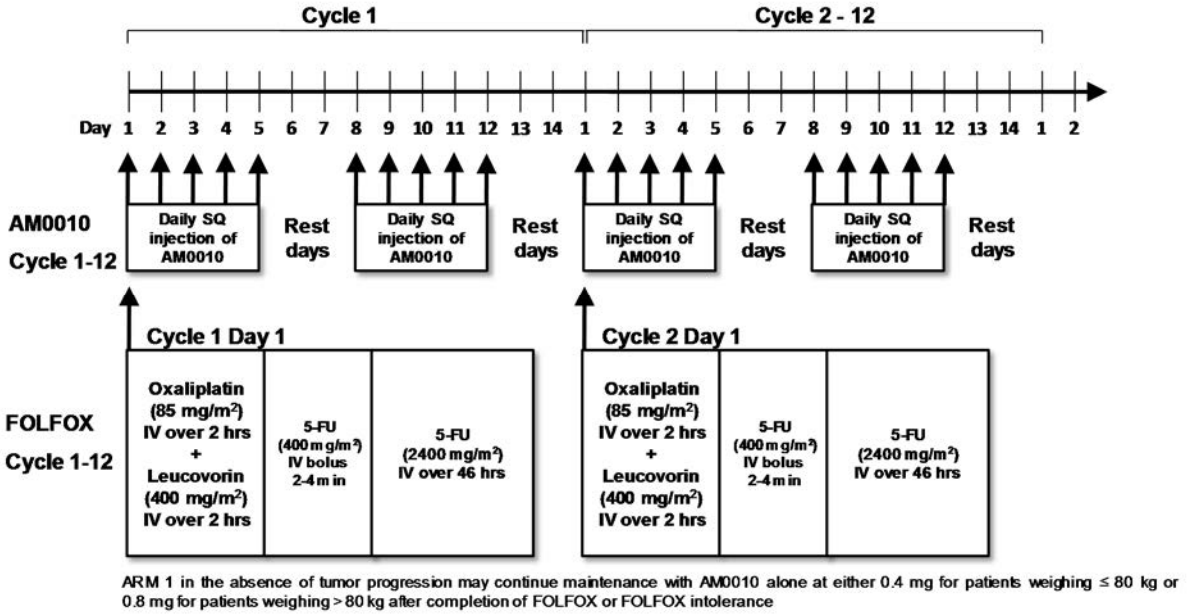
AM0010 dose should be administered on Days 1–5 and Days 8–12 in the morning, ideally with 24 hours (±2 hours) between doses. Days 6, 7, 13, and 14 will be rest days. FOLFOX dosing should be initiated on Day 1 of each cycle, after AM0010 administration on investigational ARM 1 (Figure 7). ARM 2 consists of FOLFOX administration alone as shown below, initiated on Day 1 of a 14-day cycle (Figure 8).

For patients in the combination therapy (AM0010 + FOLFOX) arm, after the last scheduled chemotherapy cycle in the absence of tumor progression, up to 12 cycles, or chemotherapy intolerance, maintenance dosing of AM0010 may continue 5 days on and 2 days off at 10 µg/kg SQ qd (see Section 5.1.1).

Crossover of patients from the FOLFOX-only treatment arm into the FOLFOX plus AM0010 treatment arm is not permitted. Supportive care per the institution's normal standard of care, including concomitant medications, can be provided at the Investigator's discretion.

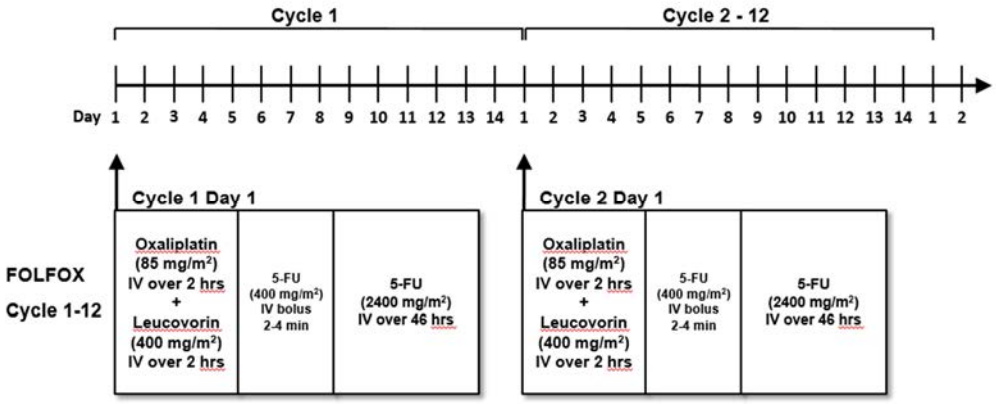
The documentation of the investigational product administration will be noted on the CRF page and in the source documentation. The date, dose volume, and time of administration for each dose will be recorded in the patient diary and on the respective CRF page. Details of preparing and administering AM0010 will be provided to the patient and are included in the Pharmacy Manual.

Figure 7: ARM 1: AM0010 + FOLFOX



ARM 1 in the absence of tumor progression may continue maintenance with AM0010 alone at either 0.4 mg for patients weighing ≤ 80 kg or 0.8 mg for patients weighing > 80 kg after completion of FOLFOX or FOLFOX intolerance

Figure 8: ARM 2: FOLFOX Alone



5.2 Dose Interruption, Reduction, and Dose Schedule Modifications

If a non-hematologic AE is attributed to only 1 drug (ie, AM0010, oxaliplatin, or 5-FU), the Investigator should determine if the drug will be continued based on the Investigator's assessment of risk-benefit per the guidelines outlined below. For example, neuropathy, is clearly related to oxaliplatin; therefore, 5-FU/LV as well as AM0010 would not be responsible for this AE.

Hematologic Toxicity Dose Schedule Adjustment Requirements (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03, Appendix G; see also Table 10):

- Thrombocytopenia Grades 3-4 with platelet count <50,000/mm^3: delay treatment with AM0010 and FOLFOX until platelet count returns to ≥100,000/mm^3. Re-introduction of AM0010 should be administered at 80% and FOLFOX at dose level −1. If on a subsequent cycle these toxicities recur, AM0010 is reintroduced at 60% (−2 dose level) and FOLFOX at dose level −2 after the first recurrence. This will be accomplished by altering the dose schedule from 5 days on and 2 days off to 4 days on and 3 days off (80%), and 3 days on 4 days off (60%), respectively.
- Anemia Grades 3–4 with Hgb<8 g/dL: delay treatment with AM0010 and FOLFOX until Hgb returns to ≥10 g/dL. Re-introduction of AM0010 should occur at 80% and FOLFOX at dose level −1. If on a subsequent cycle these toxicities recur, AM0010 is reintroduced at 60% and FOLFOX at dose level −2 after the first recurrence.

Table 10: Hematologic Toxicity Dose Schedule Adjustment (Thrombocytopenia and Anemia Only)

Occurrence of Hematologic TrAE*	FOLFOX Reintroduction	AM0010 Re-Introduction Dosing	Day 1 (FOLFOX Start)	Day 2 (FOLFOX End)	Day 3	Day 4	Day 5	Day 6	Day 7
–	Full dose	100%	X	X	X	X	X	Rest	Rest
1st	−1	80%	X	X	X	X	Rest	Rest	Rest
2nd	−2	60%	X	X	X	Rest	Rest	Rest	Rest

TrAE = Treatment-related Adverse Event; X = dosing

- Neutropenia and neutropenic fever Grades 3–4 with ANC <1,000/mm^3: delay treatment with FOLFOX until ANC returns to >1,000/mm^3. Re-introduction of FOLFOX should occur at dose level −1. If on a subsequent cycle these toxicities recur, FOLFOX is reduced to dose level −2 after the first recurrence. AM0010 dosing will continue without interruption.

Non-Hematologic Toxicity Dose Schedule Adjustment Requirements (graded according to the NCI CTCAE v4.03, Appendix G):

- ≥Grade 3 fatigue, elevations in AST, ALT, alkaline phosphatase, or bilirubin require dose interruption and delay in subsequent therapy until recovered to ≤Grade 1 or pre-therapy baseline. Re-introduction of all agents at the previous dose level.
- ≥Grade 3 GI AEs such as diarrhea, nausea, vomiting, diarrhea, abdominal pain, and bloating require a delay in subsequent therapy until recovered to ≤Grade 1 or pre-therapy baseline. Re-introduction: Reduce offending agent by 1 dose level. Keep other agents unchanged.
- Other non-hematologic toxicities with an impact on organ function of ≥Grade 3 require dose reduction. Hold treatment for the offending agent (or all agents, see Table 11), delay in subsequent therapy until recovered to ≤Grade 1 or pre-therapy baseline. Re-introduction: Reduce offending agent by 1 dose level. Keep other agents unchanged.
  If AM0010 is suspected to be one of the offending agents, reintroduction will be at the original dose after the first occurrence. If on a subsequent cycle these toxicities recur, the AM0010 treatment schedule will be decreased to 80%. Upon second recurrence of Grade 3 or 4 AE, the AM0010 dose will be decreased to 60%. This will be accomplished by altering the dose schedule from 5 days on and 2 days off to 4 days on and 3 days off (80%), and 3 days on 4 days off (60%), respectively. See below.
- It is common for oxaliplatin to cause Grade 3 or 4 neuropathy by 4 months of therapy. On both treatment arms following the dose modification in Table 11 for neuropathy, if oxaliplatin needs to be discontinued, continue therapy with 5-FU/LV.

Table 11: Dose Interruption, Reduction, and Dose Schedule Modifications

Adverse Event	Occurrence	Oxaliplatin	5-Fluorouracil	AM0010
Hematological AEs				
Grades 3-4 Anemia or Grades 3-4 Thrombocytopenia	1st	Hold until G1 or baseline Reintroduce at dose level −1	Hold until G1 or baseline Reintroduce at dose level −1	Hold until G1 or baseline Reintroduce to Dose Level −1
	2nd	Hold until G1 or baseline Reintroduce at dose level −2	Hold until G1 or baseline Reintroduce at dose level −2	Hold until G1 or baseline reintroduce to Dose Level −2
	3rd	Hold until G1 or baseline No change in dose	Hold until G1 or baseline No change in dose	Hold until G1 or baseline No change in dose
Grades 3–4 neutropenia or Grades 3–4 leukopenia or Grades 3–4 neutropenic fever	1st	Hold until G1 or baseline Reintroduce at dose level −1	Hold until G1 or baseline Reintroduce at dose level −1	Continue dosing; no change in dose schedule
	2nd	Hold until G1 or baseline Reintroduce at dose level −2	Hold until G1 or baseline Reintroduce at dose level −2	
Hemolytic uremic syndrome (HUS)[2]	1st	Discontinue	Hold until G1 or baseline No change in dose	Hold until G1 or baseline No change in dose
Non-hematological AEs				
Grade 3 Diarrhea		Hold until G1 or baseline No change in dose level	Hold until G1 or baseline Reintroduce at dose level −1	Continue dosing; no change in dose schedule
Grade 4 Diarrhea		Hold until G1 or baseline Reintroduce at dose level −1	Hold until G1 or baseline Reintroduce at dose level −1	
Cough ≥Grade 3 Dyspnea ≥Grade 3 Hypoxia ≥Grade 3 Pneumonitis ≥Grade 3		Hold oxaliplatin until interstitial lung disease is ruled out. If interstitial lung disease, discontinue oxaliplatin.	Hold until G1 or baseline No change in dose	Hold until G1 or baseline No change in dose schedule
Grade 3 Fatigue		Hold until G1 or baseline No change in dose level	Hold until G1 or baseline No change in dose level	Hold until G1 or baseline No change in dose schedule

Table 11: Dose Interruption, Reduction, and Dose Schedule Modifications

Adverse Event	Occurrence	Oxaliplatin	5-Fluorouracil	AM0010
Non-hematological AEs				
Other G3/G4 non-hematological AEs[3,4]		Hold until G1 or baseline Reduce offending agent by 1 dose level[1]		No change in dose schedule
Hypomagnesemia		Hold until G1 or baseline No change in dose level		
Neurological AEs				
Persistent[5] Grade 2 Paresthesias/ Dysesthesias[6]		Reduce dose to level −1	No change in dose	Continue dosing; no change in dose schedule
Grade 3 Paresthesias/ dysesthesias[6]Dysesthesias[6]		Hold until G1 or baseline Discontinue, if persistent[5]		
Grade 4 Paresthesias/ dysesthesias[6]Dysesthesias[6]		Discontinue		
Grade 2 = moderate (also recommended is administration of benzodiazepine and patient education. Management of patient if ≥ Grade 2 laryngeal dysesthesias occurs while treatment is being administered.) Grade 3 = severe		Stop oxaliplatin infusion. Administer benzodiazepine and give patient reassurance. At the discretion of the Investigator, the infusion can be restarted at 1/3 the original rate of infusion. Continue 5-FU		Continue dosing; no change in dose schedule

[1] If an AE is believed likely to be due to only 1 of the drugs, it is permissible to decrease dose of that drug only.
[2] Recommended evaluation of suspected HUS: Evaluation should include complete blood count (CBC) differential, platelets, PT, PTT, fibrinogen, FDP, Anti thrombin III, Von Willebrand factor, anti-nuclear antibody, rheumatoid factor, Compliment Cascade C3, C4, and CH50, anti-platelet antibodies, platelet-associated IgG, and circulating immune complexes. Renal evaluation should include creatinine, BUN, and urinalysis. Other laboratory and hematologic evaluations as appropriate should also be obtained, including peripheral blood smear and free hemoglobin.
[3] Exceptions: fatigue, anorexia, nausea/vomiting if can be controlled by antiemetics, and viral infections.
[4] Dose modifications for other non-hematologic adverse events at the start of subsequent courses of therapy, and at time of retreatment are also based on NCI CTCAE v4.03 criteria.
[5] Not resolved by the beginning of the next cycle.
[6] May be cold-induced.

5.2.1 FOLFOX

Recommended dose reduction for the components of FOLFOX is described in Table 12 and is based on the AE table described in Table 11 and Appendix D. Leucovorin doses may be adjusted per institutional guidelines in the event of a supply shortage.

Table 12: Dose Reduction Levels[a] for FOLFOX

Drug	Dose Level		
	Starting Dose	−1	−2[b]
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2
5-FU bolus	400 mg/m^2	Omit	Omit
5-FU continuous infusion over 46–48 hours	2400 mg/m^2	1900 mg/m^2	1500 mg/m^2
dl-Leucovorin/l-Leucovorin[c]	400 mg/m^2	100%	100%

[a]If an AE is believed likely to be due to 1 drug, it is permissible to decrease dose of that drug only.
[b]Further dose levels (−3, −4, etc.) will be 20% dose reductions from the previous level for oxaliplatin and 5-FU continuous infusion. In addition, the bolus dose of 5-FU will continue to be omitted and the leucovorin dose will remain unadjusted (100%).
[c]Dosing of leucovorin will remain fixed at 100% of the recommended dose. Non-racemic L-leucovorin dose is 200 mg/m^2.

5.2.2 AM0010 and FOLFOX Dose Modifications

If a patient experiences any of the following treatment-related toxicities, dosing will be postponed until the toxicity has resolved to Grades 0–1 (as defined by NCI CTCAE v4.03) or returns to the patient's baseline value. Re-initiation of therapy may occur during a cycle of therapy or at the beginning of the next cycle of dosing. Dose reductions for AM0010 plus FOLFOX are shown Table 13.

Table 13: Dose Reduction Levels for AM0010 plus[a] FOLFOX

FOLFOX	Dose Level			
	Starting Dose	**−1**	**−2[b]**	
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2	50 mg/m^2
5-FU bolus	400 mg/m^2	Omit	Omit	Omit
5-FU continuous infusion over 46–48 hours	2400 mg/m^2	1900 mg/m^2	1500 mg/m^2	1500 mg/m^2
dl-Leucovorin/l-Leucovorin [c]	400 mg/m^2	100%	100%	100%
AM0010	Dose Level			
	Starting Dose	−1	−2	
	100% (5 days on and 2 days off)	80% (4 days on and 3 days off)	60% (3 days on and 4 days off)	

[a]If an AE is believed likely to be due to 1 drug, it is permissible to decrease dose of that drug only.
[b]Further dose levels (−3, −4, etc.) will be 20% dose reductions from the previous level for oxaliplatin and 5-FU continuous infusion. In addition, the bolus dose of 5-FU will continue to be omitted, and the leucovorin dose will remain unadjusted (100%).
[c]Dosing of leucovorin will remain fixed at 100% of the recommended dose. Non-racemic L-leucovorin dose is 200 mg/m^2.

5.3 Study Treatment Dose Delays

Patients who do not meet the minimum re-treatment criteria on Day 14 (±3 days) of the cycle and do not meet the criteria for discontinuation will delay treatment and be followed for resolution of toxicity to levels specified in the package insert for resuming FOLFOX. Cycles may also be delayed for logistic or personal reasons, but patients who have not received therapy for 28 days from the scheduled start of cycle should be discontinued from AM0010 and/or FOLFOX treatment unless:

1. The patient is clinically benefiting from therapy, defined as radiographic or symptomatic improvement in the opinion of the Investigator, and
2. Approval is obtained from Lilly or Lilly's designee Medical Monitor in collaboration with the Investigator. Study treatment should be discontinued for any dose delay greater than eight weeks (>56 days).

5.4 Supportive Care and Excluded Therapies

During the course of the clinical trial, patients are anticipated to continue the use of prescribed medications identified during the screening procedures, consistent with study inclusion and exclusion criteria.

The following therapies are not permitted at any point during the trial beginning with Cycle 1 Day 1 (if administered, the patient may be removed from the trial):

- Anti-cancer therapy, experimental or approved, other than FOLFOX and AM0010 administered in this study
- Immunomodulatory agents including, but not limited to, anti-CTLA4, anti-PD1, anti-PD-L1, sipuleucel-T, cyclosporine, and tacrolimus
- Coumadin
    - Patients on Coumadin should be changed to SQ administered LMWH or oral Factor II or Xa inhibitors with a $t_{½}$ of less than 24 hours
- Factor II or Xa inhibitor with a t½ of greater than 24 hours
- High dose steroids (eg, dexamethasone $\geq$10 mg/day for more than 5 sequential days)
- Radiation therapy
- 5-FU must not be used or given in combination with brivudine, sorivudine, and analogues. An interval of at least 4 weeks between administration of fluorouracil and brivudine, sorivudine, or analogues should be kept.
- Cimetidine, metronidazole, and interferons during 5-FU treatment.
- Oxaliplatin has a known risk of Torsades de Pointes (TdP). Please refer to www.crediblemeds.org for a combined list of drugs that prolong QT and/or cause TdP.

6.0 STUDY PROCEDURES

All procedures and tests will be performed as summarized in the Schedule of Events (SOE) (Appendix A).

Unless otherwise stated in the following subsections, all samples collected for specified laboratory tests will be destroyed within 60 days after receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

6.1 Screening

Within 21 days prior to Randomization (unless otherwise noted) and after IRB/IEC-approved informed consent has been obtained, patients who have been identified by Investigators will undergo Screening to establish eligibility. The following Screening evaluations will be performed for all patients:

- Written informed consent
- Clinical evaluations:
  - Complete medical and cancer history, including prior anti-cancer therapy (including dates of therapy and best response to therapy and demographics); a copy of the pathology report will be collected
  - Evidence for disease progression (eg, CT or MRI by RECIST v.1.1, documentation of new tumor or clinical deterioration)
  - Physical examination (performed as part of standard practice may be used if conducted within 21 days prior to Randomization and if it meets the guidelines outlined in Section 6.7.2)
  - Demographics
  - Baseline signs and symptoms
  - ECOG PS should be performed at Screening and within 3 days prior to Randomization and ECOG cannot be deteriorating from Screening to 3 days before Randomization
  - Weight and height
  - Body surface area (BSA) calculation
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- Baseline Quality of Life (QoL) Questionnaires (EORTC QLQ-C30 and EQ-5D-5L)

- 12-Lead ECG
  - Patients with abnormal ECG at baseline (QT or QTc interval >450 ms for males; QT/QTc interval >470 ms for females) will be excluded from this study.
- Concomitant medications
- Safety laboratory assessments (laboratory tests performed as part of standard practice may be used if conducted within 21 days prior to Randomization):
  - Hematology (with differential and platelet counts, PT, and PTT)
  - Serum chemistry (electrolytes, renal, and liver function tests)
  - Urinalysis (dipstick)
  - Serum pregnancy test (all females of childbearing potential) should be performed at Screening
- CA 19-9
- Baseline tumor assessment of all sites of disease: spiral CT with contrast or MRI (if allergic to contrast media) must be performed within 28 days prior to Randomization. The same radiographic procedures used to define measurable and non-measurable lesions must be used throughout the study for each patient. The RECIST v.1.1 guideline recommends spiral CT images for chest, abdomen, and pelvis should be performed. Scans will be collected following the Imaging Manual. Scans performed as part of standard practice may be used if conducted within 28 days prior to Randomization. Note that the initial scan showing progression must be used for eligibility and must be performed within 28 days prior to Randomization.

The collection of archived tumor tissues is not mandatory or required for eligibility. However, attempts should be made to acquire these tissues starting after enrollment. Pathology reports should be obtained if available. These samples should be sent to the Central Laboratory. Fresh tumor biopsies are not required, but should replace archival tissue if it is not available.

6.2 Study Drug Treatments

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

Patients will be randomized within 21 days of obtaining their screening assessments. All patients must begin study treatments within 3 days after the date of Randomization. Please see the Pharmacy Manual for details.

6.2.1 ARM 1: AM0010 plus FOLFOX

6.2.1.1 AM0010 plus FOLFOX: Cycles 1–12, Day 1

Patients are assigned to ARM 1 dose 5 μg/kg AM0010 SQ on Days 1–5 followed by 2 days off treatment (Day 6 and 7) and 5 μg/kg AM0010 on Day 8–12, followed by 2 days off treatment (Day 13 and 14).

The following procedures and assessments will be performed:

6.2.1.1.1 AM0010 plus FOLFOX: Cycles 1–12, Day 1 (or up to 3 Days Prior) – Pre-Dose

- Clinical evaluations:
  - Physical exam (modified physical examination at odd-numbered cycles capturing changes from prior examinations)
  - ECOG status
  - Weight
  - BSA calculation
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- 12-lead ECG (Cycles 1, 2, 3, and 5) pre-dose
- Concomitant medications
- Adverse events
- PK/ADA
  - Cycles 1 and 2, Day 1
  - Cycle 3 Day 1 Only
  - Cycle 5 Day 1 Only
- Patient-reported questionnaires (EORTC QLQ-C30 and EQ-5D-5L) :–data to be collected on Day 1 of every treatment cycle regardless of dosing (including patients receiving AM0010 maintenance therapy) until 30 days after end of treatment (EOT)
- Exploratory Biomarker Cycle 1 Day 1
- 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
  - Urine pregnancy test (all females of childbearing potential – only on odd-numbered cycles)
- CA 19-9 on Day 1 of every odd-numbered cycle.

Note: In the event the clinical site business hours, weekends, or holiday schedule lead to missed PK/ADA time points, these time points will not need to be made up on a different day.

6.2.1.1.2 AM0010 plus FOLFOX: Cycles 1–12, Day 1 – Dosing

- Self-administer SQ Injection of AM0010; Dispense AM0010, and AM0010 Dosing Diary
- Administer FOLFOX every 14 days ±3 days (Section 5.1.2) for up to 12 cycles.

  - Patients will be treated with AM0010 administered SQ 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 daily throughout the study, starting with the first dose on Cycle 1, Day 1.

  Note that if the patient is unable or unwilling to self-administer SQ injection of AM0010, the dose may be given by a caregiver.

6.2.1.1.3 AM0010 plus FOLFOX: Cycles 1, 2, and 4, Day 13

The following procedures and assessments will be conducted on Day 13 (±3 days):

- Laboratory assessments (Day 13): CBC and differential with platelet count
- PK/ADA

  - Cycles 1 and 2, Day 13
  - Cycle 4 Day 13 Only

- Exploratory Biomarker Sample Cycle 1 Day 13, Cycle 2 Day 13, and Cycle 4 Day 13
- 12-lead ECG (Cycles 1, 2, and 4)

Note: In the event the clinical site business hours, weekends, or holiday schedule lead to missed PK/ADA time points, these time points will not need to be made up on a different day.

6.2.2 ARM 2: FOLFOX

6.2.2.1 FOLFOX Cycles 1–12: Day 1 (or up to 3 Days Prior) – Pre-Dose

- Clinical evaluations:

  - Physical examination (modified physical examination at odd-numbered cycles capturing changes from prior examinations)
  - ECOG status
  - Weight
  - BSA calculation

- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- Concomitant medications
- Adverse events
- Patient-reported questionnaire (EORTC QLQ-C30 and EQ-5D-5L) – data to be collected on Day 1 of every treatment cycle regardless of dosing until 30 days after EOT
- ADA
    - Cycles 1 and 2, Day 1
    - Cycle 3 Day 1 Only
    - Cycle 5 Day 1 Only
- Exploratory Biomarker Cycle 1 Day 1
- 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
    - Urine pregnancy test (all females of childbearing potential – only on odd-numbered cycles)
- CA 19-9 on Day 1 of every odd cycle

Note: In the event the clinical site business hours, weekends, or holiday schedule lead to missed ADA time points, these time points will not need to be made up on a different day.

6.2.2.2 FOLFOX Cycles 1–12: Day 1 – Dosing

- Administer FOLFOX every 14 days ±3 days for up to 12 cycles.

6.2.2.2.1 FOLFOX: Cycles 1, 2, and 4, Day 13

The following procedures and assessments will be conducted on Day 13 (±3 days):

- ADA
    - Cycles 1 and 2, Day 13
    - Cycle 4, Day 13 Only
- Exploratory Biomarker Sample Cycle 1 Day 13, Cycle 2 Day 13, and Cycle 4 Day 13

Note: In the event the clinical site business hours, weekends, or holiday schedule lead to missed ADA time points, these time points will not need to be made up on a different day.

6.3 ARM 1 Subsequent Cycles AFTER Discontinuation of FOLFOX

6.3.1 ARM 1 (Investigational) Maintenance Cycles after Termination of FOLFOX (Every 28 Days)

In the absence of tumor progression, after completion of up to 12 planned cycles of FOLFOX or discontinuation of FOLFOX due to toxicity, patients assigned to ARM 1 may continue on AM0010 monotherapy at 10 µg/kg (either 0.8 mg for patients weighing ≤80 kg or 1.6 mg for patients weighing >80 kg, administered 5 days on and 2 days off).

Dose reductions in maintenance are the same as in combination at 80% and 60% by altering dose schedule. The 80% dose is administered 4 days on and 3 days off and the 60% dose is administered 3 days on and 4 days off.

The numbering of cycles during maintenance treatment in ARM 1 will follow the convention of "Maintenance Cycles" with Maintenance C1D1 beginning after discontinuation of FOLFOX and start of monotherapy AM0010 as described above. Each Maintenance Cycle will be 28 days/4 weeks in duration.

6.3.1.1 ARM 1 Only – AM0010 Maintenance Cycles

The following procedures and assessments will be performed on Day 1 (±3 days) of every 4-week Maintenance cycle:

- Collection, review, and Dispensation of study drug/diary: AM0010

  Self-administer SQ Injection of 1 dose of AM0010; Injection #1 for the monotherapy AM0010 cycle for patients in ARM 1. Note that if the patient is unable or unwilling to self-administer SQ injection of AM0010, the dose may be given by a caregiver.

- QoL Questionnaire (EORTC QLQ-C30 and EQ-5D-5L) – data to be collected on Day 1 of every maintenance cycle regardless of dosing
- Clinical evaluations:

  - Physical examination (modified physical examination at odd-numbered cycles capturing changes from prior examinations)
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- Concomitant medications
- Adverse events
- Safety laboratory assessments (up to 3 days prior):
  - Hematology
  - Serum chemistry
  - Urine or serum pregnancy test (if applicable)
- CA 19-9

6.4 Tumor Assessment of Response – Every 8 Weeks (±3 Days)

Tumor assessment of all sites of disease following RECIST v.1.1 (Appendix C): Spiral CT or MRI, if allergic to contrast. The same radiographic procedure used to define measurable lesions must be used throughout the study for each patient. The RECIST v.1.1 guideline recommends spiral CT images for chest, abdomen, and pelvis should be performed. Assessment should be obtained 8 weeks (±3 days) after Randomization and every 8 weeks (±3 days) regardless of cycle number and regardless of any dose interruptions until tumor progression. Patients with clinical progression must obtain an unscheduled scan to document progression. Patients on the investigational arm (ARM 1) with suspected "pseudoprogression" on scans in the absence of clinical deterioration, including worsening ECOG PS, should remain on study treatments and should have an additional scan 4 weeks (±3 days) later. If progression is confirmed on the subsequent scan, then discontinue study treatments and follow study procedures for EOT and survival follow-up.

6.5 End of Treatment

The EOT visit will occur on the day of the last visit or within 7 days of the last dose/EOT. The end of study treatment may be due to disease progression (clinical or radiographic), study drug(s) intolerance, withdrawal of consent, or upon termination decision by Lilly. Patients in ARM 2 who complete 12 cycles of FOLFOX and start a new treatment regimen will also complete their EOT visit.

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

- Clinical evaluations:
  - Physical examination (modified physical examination capturing changes from prior examinations)
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- 12-lead ECG
- Concomitant medications
- Adverse events
- ADA
- QoL Questionnaires (EORTC QLQ-C30 and EQ-5D-5L)
- Safety laboratory assessments:
  - Hematology
  - Serum chemistry
  - Urine pregnancy test (all females of childbearing potential – only on odd-numbered cycles)
- Exploratory biomarker sample
- CA 19-9
- Tumor assessment (if not done within 4 weeks prior)

Note: In the event the clinical site business hours, weekends, or holiday schedule lead to missed ADA time points, these time points will not need to be made up on a different day.

6.6 Follow-Up Visit

After discontinuation of study treatments, a patient follow-up visit should occur at 30 days (±5 days) after EOT. If the patient starts new anti-cancer therapy within 30 days of the last dose of study medication, the Follow-up visit should be performed prior to the start of new anti-cancer therapy, within the 30-day window. 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 examination
  - ECOG status
  - Weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- Adverse events
- Safety laboratory assessments:
  - Hematology
  - Serum chemistry
  - Urine pregnancy test (all females of childbearing potential) (if applicable)
- QoL Questionnaires (EORTC QLQ-C30 and EQ-5D-5L)
- ADA

Note: In the event the clinical site business hours, weekends, or holiday schedule lead to missed ADA time points, these time points will not need to be made up on a different day.

6.6.1 Patient Follow-Up – for Tumor Assessment of Response

Patients who are discontinued from study treatments in the absence of disease progression (eg, patients removed for unacceptable toxicity) will undergo repeat imaging and tumor response assessments every 8 weeks (±3 days), regardless of cycle number or dose interruptions, until disease progression is documented. It is recommended that subsequent therapy not be instituted until disease progression is documented. If any of the components or the combination are continued, this should be considered as continuation of the study treatment regimen and imaging should continue. If a patient starts a new anti-cancer therapy prior to disease progression, then repeat imaging and tumor response assessments should be discontinued.

6.6.2 Patient Long-Term Follow-Up – for Survival

Post study, patients will be contacted via phone call to determine long-term survival status and record of any other anti-cancer therapy and cancer-related surgery every 8 weeks for 12 months, then every 12 weeks thereafter until death, the study closes, or 3 years have elapsed since patient discontinuation

from study treatments. This evaluation may be conducted by record review and/or telephone contact with the patient's treating physician.

Patients who are not deceased by the time Lilly has made the determination the study will be ended will receive a final follow-up phone call to assess survival status and communicate the Sponsor's decision.

The Investigator will make every effort to contact the patient or a close relative or caretaker by phone to collect survival information. The Investigator should show due diligence by documenting in the source documents steps taken to contact the patient (ie, dates of phone calls, registered letters, etc.).

6.7 Study Assessments

6.7.1 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 (eg, prior hospitalizations or surgeries), any concurrent medical illness, and concomitant medications including prescription, non-prescription medications, vitamins, herbal medications, and minerals taken up to 21 days prior to Randomization. The medical history findings and concomitant medications will be recorded on the CRF page.

Patients must not have received >1 prior gemcitabine-containing therapy. Patients having received gemcitabine or other chemotherapy in the adjuvant setting are not eligible for this study. Patients must have completed gemcitabine or any other prior chemotherapy or investigational therapy at least 2 weeks (washout period) prior to Randomization.

Patients may not have a past history of receiving immune checkpoint inhibitors (anti-CTLA4, anti-PD1, anti-PD-L1). Patients may not receive immune checkpoint inhibitors while on study.

Patient may not have received prior treatment with AM0010 or a platinum-containing regimen.

6.7.2 Physical Examination

A physical examination will be performed at Screening. This will include assessment of clinical signs and symptoms. The exam will be performed by a physician, a physician's assistant, or nurse practitioner qualified to perform assessments. Breast, genital, and rectal examinations are not

required unless warranted in the opinion of the Investigator. Physical examination performed as part of standard practice may be used if conducted within 21 days prior to Randomization.

A modified physical examination capturing changes from prior examinations will be performed on Day 1 of each odd-numbered cycle (ie, Cycles 1, 3, 5, etc.) and at the EOT. Height will be collected at Screening only. The BSA to determine the dose for FOLFOX will be calculated using height in centimeters and weight in kilograms. If a patient experiences at least 10% increase or decrease of body weight, the BSA should be recalculated to determine FOLFOX dose.

6.7.3 Vital Signs

Vital signs, including blood pressure, heart rate, respiratory rate, and temperature, will be measured by the Investigator or qualified designee at the time points listed in the SOE (Appendix A). Patients must be seated or in a semi-recumbent position to vital sign measurement. All measurements will be recorded on the appropriate CRF page with appropriate source documentation. Any abnormal measurements may be repeated and reported as AEs by the Investigator if it represents a change from baseline grade.

6.7.4 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 minutes). Patients should be seated, semi-recumbent, or supine for at least 5 minutes before each ECG is obtained. The 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 data reported on the CRF.

6.7.5 Adverse Events

Adverse events will be followed as outlined in Section 9.0.

6.7.6 Safety Laboratory Tests

The Central Laboratory will be responsible for chemistry, hematology, coagulation, and serum pregnancy testing (per Table 14), as well as processing and/or storage of other study samples, including the archival tumor samples. Specific instructions for processing, labeling, and shipping

samples will be provided in a Central Laboratory Manual. The date and time of sample collection will be reported to the Central Laboratory.

Local laboratories will be used for dosing decisions. Local laboratory assessments resulting in a dose change or as part of an AE assessment, which is not supported by Central Laboratory results, will be reported on the electronic case report form (eCRF).

Urine pregnancy test will be performed at the site.

Table 14: Blood, Hematology, and Chemistry Evaluations

Chemistry	Hematology	Other
Albumin Alkaline phosphatase ALT AST Bicarbonate BUN Calcium Chloride Creatinine[a] Glucose Lipase Magnesium Phosphorus Potassium Sodium Total bilirubin Direct bilirubin Total protein CA 19-9	WBC Hemoglobin Hematocrit Platelet ANC <u>Differential</u> Eosinophils Lymphocytes Monocytes Neutrophils Coagulation PT/INR aPTT	Serum β-hCG or urine pregnancy test[b]

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; INR = international normalized ratio; PT = prothrombin time; WBC = white blood cells.
[a]Estimated creatinine clearance (CL_{cr})/glomerular filtration rate will be calculated based on the MDRD formula.
[b]Females of child-bearing potential only. Serum pregnancy will be conducted at Screening. Urine pregnancy will be conducted pre-dose on Day 1 of every odd-numbered cycle.

Blood samples will be obtained at the time points indicated in the SOE (Appendix A).

At any time during the study, abnormal laboratory parameters that are clinically relevant (eg, lead to clinical symptoms or signs or require therapeutic intervention) and constitute an AE must be recorded in the eCRF.

If a study patient experiences elevated ALT≥5×ULN and elevated total bilirubin ≥2×ULN, or ALT≥8×ULN, liver tests (Appendix I), including ALT, AST, total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests (Appendix I) and in consultation with the Lilly Clinical Research Physician (CRP). Monitoring of ALT, AST, and total bilirubin should continue until levels normalize or return to approximate baseline levels.

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

6.7.6.1 Pregnancy Test

All females of childbearing potential will have a serum pregnancy test at Screening. Urine pregnancy tests will be performed on Day 1 of each odd-numbered cycle, every 28 days in patients who continue AM0010 monotherapy after FOLFOX discontinuation, at EOT, and 30 days after EOT. The results must be confirmed as negative prior to administration of investigational product.

6.7.6.2 Health Outcomes

The assessment of patient-reported outcomes (PROs), including symptoms, functioning, and health status, will be assessed using the EORTC QLQ-C30 questionnaire (Version 3) and EQ-5D-5L. Both instruments should be administered together at the beginning of the study visit prior to any extensive contact or consultation with study site personnel, which may bias patient responses. The EORTC QLQ-C30 will be presented first, followed by EQ-5D-5L. Patients will only complete either instrument if a validated translation is made available in a language in which the patient is fluent.

The EORTC QLQ-C30 is a self-administered questionnaire that assesses multiple dimensions of HRQoL of cancer patients participating in international clinical trials. The EORTC QLQ-C30 includes 5 functional domains (physical, role, emotional, cognitive, and social), 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and global health status/QoL.

The EQ-5D-5L (Rabin et al., 2011) is a PRO measure designed to assess current health status for clinical and economic appraisal. Patients are asked to rate 5 dimensions of HRQOL - Mobility, Self-care, Usual activities, Pain/discomfort, and Anxiety/depression - using 5 ordered response categories:

no problems (1), slight problems (2), moderate problems (3), severe problems (4), and extreme problems (5).

The questionnaires will be completed by all patients as detailed in the SOE (Appendix A).

6.8 Sample Collection

6.8.1 Collection of Archival Tumor Tissue

Collection of archival tumor material is neither mandatory nor required for eligibility. However, attempts should be to acquire these archival tissue samples, if available, starting after the patient is enrolled. Patients will be asked to consent to the access of pre-existing samples (slides or blocks) (frozen and/or paraffin-embedded tumor samples) for biomarker development. Pathology reports should be obtained if available. 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 the Laboratory Manual for additional information. These materials will not be used for any other purpose at the end of the study. Fresh tumor biopsies are not required, but should replace archival tissue if it is not available.
No fresh tumor biopsies are required for participation in the study.

6.8.2 Pharmacokinetic Sample Collection

Lilly will attempt to collect PK samples in patients randomized to ARM 1 and ADA samples from ARM 1 and 2 patients at clinical sites. Patients must give their permission to obtain the additional blood samples as outlined in the ICF. Within each 14-day cycle (with the first day of dosing designated as Day 1).

Blood samples will be obtained as shown in Table 15:

- Cycles 1 and 2, Days 1 and 13
- Cycle 3 Day 1 Only
- Cycle 4 Day 13 Only
- Cycle 5 Day 1 Only
- EOT and follow-up visit 30 days after EOT (ADA only).

In the event of clinical site business hours, weekends, or holiday schedule leading to missed PK/ADA time points, these time points will not need to be made up on a different day. Patients will be instructed to administer AM0010 in the usual manner at home on days of PK sampling. The time at

which AM0010 is administered on that day will be queried by site personnel and entered in the CRF. Dose times for other days will be obtained from the Dosing Diary.

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

Table 15: Pharmacokinetic Sparse Sampling Regimens

Cycle	Day
1 and 2	1 and 13 of each cycle
3	1 Only
4	13 Only
5	1 Only

6.8.3 Carbohydrate CA 19-9

Serum levels of CA 19-9 will be evaluated over time to assess changes after treatment with AM0010 plus FOLFOX and FOLFOX alone. Since CA 19-9 is being used only in an exploratory evaluation to determine whether there is a correlation with efficacy outcomes, increases in CA 19-9 levels in this study should not be used as evidence for progressive disease or for discontinuing patients from study treatments.

6.8.4 Exploratory Biomarkers

Potential relationships between biomarker data and efficacy outcomes may be evaluated.

These exploratory predictive biomarker analyses will beconducted on biomarkers measured in blood and in tumor samples. Pre-treatment biomarkers may focus on immunological proteins expressed in archival tumor samples associated with AM0010 mechanism of action, and CD8+ T-cell secretion of IFNγ in response to AM0010 treatment. These data will be used to determine whether there are predictive biomarker signatures that correlate with subsequent objective tumor responses.

Treatment associated serum biomarkers may also be measured. The treatment-associated magnitude of changes in serum IL-18, IFNγ, IL-4, TGFβ and CA 19-9 may be quantified. In addition, the mRNA/DNA from whole blood samples may be analyzed for TCRβsequences and the expression of immune regulatory molecules. These data may be used to determine the peripheral blood immune activation signature of AM0010 treatment that correlates with PR/CR/SD responses and rate of CA 19-9 decline.

7.0 STATISTICAL CONSIDERATIONS

7.1 Study Objectives

This is an open-label, multi-center, randomized, Phase 3 study designed to compare the efficacy and safety of AM0010 in combination with FOLFOX versus FOLFOX alone in patients with metastatic adenocarcinoma of the pancreas who have progressed on 1 prior gemcitabine-containing regimen.

7.2 Determination of Sample Size

The sample size is calculated in order to compare the OS between patients randomized to receive AM0010 in combination with FOLFOX versus FOLFOX alone.

Approximately 566 patients will be randomized to the 2 arms in a 1:1 ratio to observe at least 393 death events. Assuming a median OS time for the FOLFOX arm of 5.9 months, 393 events are needed to detect a 35% increase with 85% power using a log-rank test (2-sided) with an overall type 1 error of 0.05, which corresponds to a median survival of 8 months in the AM0010 in combination with FOLFOX arm (HR=0.7375).

Table 16: Schedule of Analyses

		Interim Analysis 1	**Interim Analysis 2**	**Final Analysis**
Conditions		60 randomized patients who have had the opportunity to receive 4 months of therapy	Approximately 276 OS events	393 OS events
Alpha level		0.0001*	0.015	0.045
HR Boundaries	Upper	2.145	1.342	1.224
	Lower	0.466	0.745	0.817

* A very small alpha is planned to be spent at the first interim analysis. Hazard Ratio boundaries are calculated based on the alpha spent. The O'Brien-Fleming (OBF) spending function is used to allocate the alpha at analysis 2 and final analysis with total alpha level of 0.049. The actual alpha at each interim analysis will be recalculated based on the number of events observed at each analysis. The HR boundaries are for reference only and they are not for decision making.

7.3 Analysis Populations

- Intent-to-treat population: All patients who are randomized, with study drug regimen assignment designated to initial Randomization, regardless of whether patients receive any study drug(s) or receive a different drug(s) from that to which they were randomized. This is the primary dataset for analyses of efficacy and baseline disease characteristics.
- Safety Population: All patients who receive any amount of study drug(s) with study drug assignment designated according to actual study drug(s) received. This is the primary dataset for treatment administration/compliance and safety.
- Per-Protocol Population: All patients who are in the Safety population and have no major protocol deviations.

7.4 Study Endpoints

The primary objective of Phase 3 is to evaluate OS comparing 2 treatment arms. The primary endpoint is OS. The key secondary endpoints are PFS, ORR, DoR, DCR, 1 year-OS rate, and safety.

7.4.1 Efficacy Endpoints

7.4.1.1 Primary Endpoint

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

7.4.1.2 Secondary Endpoints

7.4.1.2.1 Progression-Free Survival

Progression-free survival is defined as the time from Randomization to the date of the initial documented objective tumor progression that is confirmed by subsequent radiotherapy as determined by the Investigator (per RECIST v.1.1 criteria) or death due to any cause, whichever occurs first. If no subsequent scan is available, the initial progression will be used as the objective PD date. If the subsequent scan does not confirm the initial progression, the patient will continue to be followed up for future scans. Patients who experience clinical disease progression should undergo scanning to document radiographic disease progression per RECIST v.1.1. Patients who die without a reported

prior progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last tumor assessment. Patients who did not have any post-baseline tumor assessment and did not die will be censored on the date they were randomized with a duration of 1 day. Patients who received any subsequent anti-cancer therapy without a prior documented disease progression event will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy. Patients who have documented disease progression or death after missing ≥2 consecutive postbaseline tumor assessments will be censored to the last adequate tumor assessment before the missed assessments or date of randomization, whichever is later.

7.4.1.2.2 Objective Response Rate

Objective response rate is defined as the proportion of patients with a confirmed CR or confirmed PR relative to the total analysis population. Best overall response is defined as the best response as determined by the Investigator, recorded between the date of Randomization and the date of objectively documented progression per RECIST v.1.1 or the date of subsequent therapy, whichever occurs first. For patients without documented progression or subsequent anti-cancer therapy, all available response assessments will contribute to the BOR determination. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (approximately 4 weeks later). For patients who continue AM0010 in combination with FOLFOX treatment beyond progression due to suspected "pseudoprogression," the BOR should be determined based on response assessment recorded at the next scheduled CT scan, which is done approximately 4 weeks after pseudoprogression to assess BOR. If the patient subsequently responds or returns to baseline, that assessment of objective tumor response is achieved after pseudoprogression as the response Designation of best response of SD requires the criteria to be met at least 8 weeks (±3 days) after Randomization.

7.4.1.2.3 Disease Control Rate

The DCR is defined as the proportion of patients who achieve confirmed CRs, PRs, and SD.

7.4.1.2.4 Duration of Response

Duration of response is defined as the time from the date of the first documentation of objective tumor response (CR or PR), as determined by the Investigator using RECIST v.1.1, that is

subsequently confirmed to the date of the first documentation of objective tumor progression or to death due to any cause, whichever occurs first.

7.4.1.2.5 1-Year Overall Survival Rate

The 1-year OS rate is estimated using the Kaplan-Meier method.

7.4.2 Safety

Safety will be evaluated by the incidence of TEAEs and SAEs, physical examination, ECOG PS, vital signs, ECG, and laboratory abnormalities during study drug(s) dosing. Toxicities will be graded using the NCI CTCAE v4.03.

7.5 Statistical Analysis

7.5.1 Patient Disposition

Patient disposition including the number in each analysis population and reason for discontinuation of study treatment will be summarized by treatment arm. Consort diagram will be provided.

7.5.2 Demographics and Baseline Disease Characteristics

Demographic and baseline disease characteristics will be summarized by randomized treatment arm using descriptive statistics.

7.5.3 Prior Cancer Therapy and Concomitant Medications

All concomitant medications and prior medications administered will be coded to therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug Classification. The incidence of prior and concomitant medication usage will be summarized by therapeutic drug class and generic drug names.

7.5.4 Efficacy Analyses

The primary efficacy endpoint for the study is OS. The secondary efficacy endpoints include PFS and ORR. The primary analysis will be based on the OS at a cumulative 2-sided alpha at 0.05. If OS is statistically significant, statistical analysis will be conducted on the secondary efficacy endpoints. The PFS and ORR will be tested and sequentially gated and the details will be provided in the statistical analysis plan (SAP).

7.5.4.1 Primary Endpoint – Overall Survival

Overall survival will be compared in 2 randomized treatment arms using a 2-sided log-rank test, stratified by Interactive voice response system (IVRS) prior gemcitabine-containing regimen (gemcitabine or gemcitabine/nab-paclitaxel) and North America versus Europe versus APAC.

The first interim analysis will be performed when approximately 60 randomized patients have had the opportunity to complete 4 months of therapy from the date of Randomization. The nominal significance will be calculated based on O'Brien and Fleming (Lan-Demets) alpha spending function in EAST v6.4. The second interim analysis is planned after approximately 276 deaths (70% of the 393 events) have been observed. The stopping boundaries will be derived based on the actual observed deaths at the second interim analyses. If the second interim analysis is performed approximately at 276 deaths, the study could be stopped by the DMC for efficacy if the p-value is ≤0.015. The nominal significance level for the final look of OS after 393 events would then be 0.045.

The null (H_o) and alternative (H_a) hypotheses for testing OS are:

H_o: $HR_{\text{AM0010 plus FOLFOX/FOLFOX alone}} = 1$

H_a: $HR_{\text{AM0010 plus FOLFOX/FOLFOX alone}} \neq 1$

The Kaplan-Meier curve for survival will be presented for each treatment arm and the difference in the curves will be tested using the stratified log-rank test. Patient median survival time (including 95% confidence interval [CI]) for each treatment arm will be estimated using the Kaplan-Meier method. In addition, the Kaplan-Meier method will be used to estimate OS rates at fixed time points for each treatment group. These rates will be compared based on a normal approximation for the difference between the rates.

A stratified Cox proportional hazard model (Cox 1972) with treatment as a factor will be used to estimate the HR and corresponding 95% CI. An additional unstratified Cox regression model will be employed to explore the effects of prognostic variables, such as of the stratification variables and intrinsic/extrinsic factors, on treatment response.

7.5.4.2 Progression-Free Survival

The PFS will only be tested inferentially for significance only if the test of OS is significant. The Kaplan-Meier curve for PFS will be presented for each treatment arm and the difference in the curves

will be tested using the stratified log-rank test. Patient median PFS time (including 95% CI) for each treatment arm will be estimated using the Kaplan-Meier method.

A stratified Cox proportional hazard model with treatment as a factor will be used to estimate the HR and corresponding 95% CI. An additional unstratified Cox regression model will be employed to explore the effects of prognostic variables, such as of the stratification variables and intrinsic/extrinsic factors, on treatment response.

7.5.4.3 Objective Response Rate

The ORR, defined as the proportion of patients who achieve confirmed CRs+PRs, will be summarized by treatment arm and compared using a Cochran-Mantel Haenszel (CMH) 2-sided test stratified by the interactive voice-response system (IVRS) stratification factors. The odds ratio and 95% CI will also be provided.

7.5.4.4 Disease Control Rate

The DCR, defined as the proportion of patients who achieve confirmed CRs + confirmed PRs and SDs will be analyzed in the same manner as objective tumor response.

7.5.4.5 Duration of Response and Time to Response

Duration of response is defined as the time from the date of the first documentation of objective tumor response (CR or PR), as determined by the Investigator using RECIST v.1.1, that is subsequently confirmed to the date of the first documentation of objective tumor progression or to death due to any cause, whichever occurs first. Duration of response will be censored on the date of the last tumor assessment on study for patients who do not have objective tumor progression and who do not die due to any cause while on study. For patients who have an ongoing objective response, but discontinued to have tumor scans assessments before disease progression, the DOR will be censored at the date of the last tumor assessment.

Duration of response will be estimated for each treatment arm using the Kaplan-Meier method for patients who have CR or PR.

Time to response is defined as the time from date of Randomization to the date of the first documentation of objective tumor response that is subsequently confirmed. Duration of response and

time to response will only be evaluated in patients with objective response of CR or PR and will be summarized by treatment arm.

7.5.5 Health Outcomes

The global health status/QoL and disease/treatment related scales will be scored according to the EORTC QLQ-C30 and EQ-5D-5L scoring manuals. Health-related QoL subscales and single-item sum scores may be summarized by the mean and median for each treatment arm and may be plotted by time. The change from baseline for all scales may be examined by treatment arm. Further analysis details will be described in the SAP.

7.6 Safety Analyses

Safety analyses will be based on Safety Population. Safety parameters include AEs, physical examination, and laboratory assessments including hematology, chemistry, and coagulation, vital signs, and ECG.

7.6.1 Treatment Exposure and Compliance

Study treatment exposure and compliance will be summarized. Number and percentage of patients experiencing dose modifications, interruptions, and/or discontinuation for each treatment arm, and reasons for the deviations from planned therapy will also be provided. Percentage of planned dose administered before a patient discontinues dosing will also be analyzed.

7.6.2 Adverse Events

Adverse events will be analyzed in terms of TEAEs defined to be any AEs that begin or worsen in intensity after study drug initiation through 30 days after EOT or any treatment-related SAE that occurred any time during the study. All AEs will be coded based on the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.

All TEAEs due to any cause, drug-related TEAEs, TE-SAEs, drug-related TE-SAEs, and TEAEs leading to discontinuation from the study treatments will be tabulated using the worst grade per NCI CTCAE v4.03 criteria by system organ class and preferred term. Additional summaries include AEs by intensity (Grade 1–4).

7.6.3 Clinical Laboratory Data

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

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

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

7.6.4 ECOG Performance Status

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

7.6.5 Vital Signs

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

7.6.6 12-Lead ECG

The ECG parameters including QTc and change from baseline will be summarized by treatment arm.

Number and percent of patients for each QTc parameter for the following categories will be summarized:

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

7.6.7 CA 19-9 and Immunologic Biomarkers

CA 19-9 levels and change from baseline will be summarized by treatment arm using descriptive statistics. The proportion of patients who experience ≥20% and ≥50% reduction in CA 19-9 relative to baseline will be summarized by treatment arm. Descriptive statistics of percent decline relative to baseline at 8 weeks after Randomization will be evaluated.

The correlation between CA 19-9 with OS, objective response, and PFS may be explored.

Associations between biomarkers and efficacy outcomes may be analyzed on all patients with available biomarker data. Models to predict clinical activity based on combinations of biomarkers may also beinvestigated.

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

7.7 Subgroup Analysis

The subgroup analysis of OS and PFS will be performed for a set of potential prognostic subgroup variables. The further details of the subgroup variables and analyses will be provided in the SAP.

7.8 Sensitivity Analysis

Sensitivity analyses will be undertaken for calculation of the primary endpoint in order to evaluate the robustness of the analysis. Of specific note, OS sensitivity analyses will be performed in the following subgroups of the ITT population:

- Per protocol population

Other sensitivity analyses include:

- Defining survival time as the time from the date of study enrollment to the date of death due to disease
- Censoring patients that started additional anticancer therapy.

Further details can be found in the SAP.

7.9 Interim Analysis

7.9.1 Interim Analysis 1

A planned first interim analysis will occur once at least 60 randomized patients who have had the opportunity to receive 4 months of therapy from the date of Randomization (Table 16). The purpose of this interim analysis is to evaluate overall clinical benefit with the possibility of stopping the study early due to lack of efficacy. The interim analysis is not designed to stop the study early for

outstanding efficacy. Based on review of the PK exposure-safety and PK exposure-efficacy on the aggregated data of efficacy endpoints, the DMC will recommend continuing the Phase 3 trial, amending the study protocol, or stopping the study. The criteria for Go/No-Go decision will be developed with the DMC and Sponsor's steering committee to be incorporated into the DMC charter. The study will continue to enroll while this analysis is being completed.

7.9.2 Interim Analysis 2

A second interim analysis is planned when approximately 276 deaths (70%) of 393 deaths are reached in this event-driven trial (Table 16).

Details of the interim analysis results will be reviewed by the DMC. The DMC will provide the Sponsor with a recommendation to continue the trial as planned, modify, or discontinue the trial.

7.10 Data Monitoring Committee

An independent DMC will be established with responsibility of safeguarding the interest of study participants. The DMC will review safety data regularly during the conduct of the study as well as evaluate data from the first interim analysis to recommend continuing the Phase 3 study, amending the study protocol, or stopping the study. The Go/No-Go decision recommendation for the first interim analysis will be based on review of the PK exposure-safety and PK exposure-efficacy on the aggregated data of composite efficacy endpoints from the first 60 randomized patients who have had the opportunity to receive 4 months of therapy from the date of Randomization. The criteria for the Go/No-Go decision will be developed with the DMC and Sponsor's steering committee to be incorporated into the DMC charter. The DMC will also review the second interim analysis after approximately 276 death events (70% of the 393 death events in the final analysis) occur. Based on the second interim analysis, the DMC will recommend continuing the trial as planned, modifying, or discontinuing the trial.

The DMC will have access to unblinded patient treatment assignment information. The DMC will meet regularly to ensure that patient safety is carefully monitored. The DMC will convene additional ad hoc meetings, if necessary. Following each meeting, the DMC will recommend continuation, modification, or discontinuation of the study. The DMC will also review the interim analysis results and make recommendations. Further details of DMC responsibilities, membership, organization, and possible recommendations to the Sponsor will be outlined in the DMC Charter of Organization.

8.0 EFFICACY

8.1 Clinical Response Assessments

Patients will be evaluated by CT scan with contrast or MRI (if allergic to contrast) at Screening within 28 days of Randomization, at Week 8 (±3 days), and every 8 weeks (±3 days) thereafter, regardless of cycle number and regardless of any dose interruptions. The same radiographic procedure used to define measurable lesions and non-measurable lesions must be used throughout the study for each patient. Response will be evaluated using RECIST v.1.1.

Patients who have not had progression of their cancer should undergo repeat imaging and tumor response assessments until radiographic disease progression is documented. In addition, patients randomized to either treatment arm who are discontinued from study treatment (AM0010, 1 or all components of FOLFOX) in the absence of disease progression (eg, patients with AE or intolerance) should undergo repeat imaging and tumor response assessments until radiographic disease progression is documented. Any patient with symptoms suggestive of clinical disease progression should be evaluated by radiographic scan at the time the symptoms occur.

Objective responses (CR or PR) will be confirmed no less than 4 weeks after the criteria for the response are first met following RECIST v.1.1 (Appendix C).

If a patient starts a new anti-cancer therapy prior to disease progression, then repeat imaging and tumor response assessments should be discontinued. The PFS will be censored at the last tumor assessment prior to initiation of antitumor treatment.

8.1.1 Pseudoprogression and Confirmation of Disease Progression

Accumulating evidence indicates a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Patients treated with FOLFOX alone will not be permitted to continue their treatment beyond initial RECIST v1.1 defined PD.

Patients treated with AM0010 during the maintenance cycles in Arm 1 will be permitted to continue treatment beyond initial RECIST v1.1 defined PD if they meet the following criteria:

1. Investigator-assessed clinical benefit, and do not have rapid disease progression
2. Continue to meet all other study protocol eligibility criteria
3. Tolerance of study drug
4. Stable ECOG PS
5. Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)

A radiographic assessment/scan should be performed 4 weeks (±3 days) after original PD to determine whether there has been a decrease in tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the patients is clinically deteriorating and unlikely to receive any benefit from continued treatment with AM0010. A confirmatory scan will be required in the case of clinical deterioration suspected to be disease progression.

If the Investigator feels that the patient is deriving clinical benefit with continued treatment, the patients should remain on the trial and be monitored according to the SOE (Appendix A). The decision to continue treatment should be discussed with the Lilly Medical Monitor and documented in the study records.

For patients who continue AM0010 beyond initial progression, further progression is defined as an additional 10% increase in tumor burden volume from the time of initial PD. This includes an increase in the sum of all target lesions and/or the development of new measurable lesions. When assessing disease progression, the Investigator should use a new baseline tumor burden that includes new lesions that developed at the time of initial progression. Patients will discontinue study treatment upon confirmed PD (4 weeks after initial PD).

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Global deterioration of health status requiring discontinuation of study treatments without objective evidence of disease progression at that time should be reported as “clinical progression.” Every effort

should be made to document objective progression (ie, radiographic confirmation) even after discontinuation from study treatments.

8.2 Central Imaging Independent Review

All on-study spiral CT/MRI scans for all patients enrolled in the study will be collected prospectively and submitted to a central imaging reader for archiving and storage and may be reviewed at the end of study at the request of Lilly. A central imaging reviewer blinded to treatment assignment will provide an independent review of tumor response and tumor progression for patients enrolled in the Phase 3. Film or electronic copies should be collected by the investigative sites and sent to the central image reader. Complete details regarding image handling and submission can be found in the Radiology Technical Manuals.

9.0 ADVERSE EVENTS

9.1 Definition of Adverse Events

9.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An 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..

Investigators are responsible for:

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

Adverse event terms should be recorded concisely, using acceptable medical terms. When possible, a diagnosis (ie, disease or syndrome) rather than the component signs and symptoms should be recorded on the AE CRF (eg, congestive heart failure rather than dyspnea, rales, and cyanosis). However, signs and symptoms considered unrelated to syndromes or diseases are to be recorded as individual AEs on the CRF (eg, if congestive heart failure and severe headache are observed at the same time, each event is to be recorded as an individual AE). Only abnormal laboratory values that result in clinical sequelae or require medication for treatment should be recorded as an AE. The AE should not be recorded as a procedure or clinical measurement (ie, a laboratory or vital sign). The underlying reason for the procedure or the abnormal clinical measurements, and, whenever possible, a diagnosis, should be recorded. The diagnosis should be recorded; not the individual laboratory test name.

A pre-existing condition is one that is present at the start of the study and is reported as part of the patient's medical history. It should be reported as an AE if the frequency, intensity, or character of the condition worsens during study treatment.

"Death" as an outcome of an AE may occur and should not be reported as an AE, but the cause of death should be reported on the AE eCRF.

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

If there is any uncertainty about an AE being due to the progression of cancer, it should be reported as an (S)AE.

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

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

9.1.2 Serious Adverse Events

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

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

For the purposes of this trial, the following will NOT be considered SAEs:

- Hospitalizations <24 hours, or for planned surgeries or procedures.
- Progression of underlying malignancy as a stand-alone event term; clinical events associated with disease progression should be reported as AEs or SAEs as applicable.

Serious AEs, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment.

9.1.3 Unexpected Adverse Events

Unexpected AEs are defined as any AE, the nature, specificity, or severity of which is inconsistent with the Referenced Safety Information within the Guidance to Investigator section of the Clinical IB for AM0010 and the package inserts for the individual drugs that comprise FOLFOX.

9.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR) Definition

A suspected, unexpected, serious, adverse reaction (SUSAR) is any AE for which there is evidence to suggest a causal relationship between the study drug(s) and the AE and which is assessed as both unexpected and serious. An unexpected adverse reaction, ie, any untoward and unintended response to the study drug(s), is one for which the nature and severity is inconsistent with the applicable reference safety information (eg, IB or package insert of the approved drugs in the combination). Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

9.2 Grading of Adverse Events

If the NCI CTCAE v4.03 cannot be applied, the AE severity should be graded on the following scale:

1 = Mild: Usually transient; requires no special treatment and does not interfere with the patient's daily activities

2 = Moderate: Produces a low level of inconvenience to the patient and may interfere with daily activities. These events are usually ameliorated by simple therapeutic measures

3 = Severe: Interrupts daily activity and requires systemic drug therapy or other medical treatment.

4 = Life-Threatening: Places the patient, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, ie, it does not include a reaction that, had it occurred in a more severe form, might have caused death.

5 = Death: Refers to **death related to an AE**. The AE resulted in the patient's death.

9.3 Relationship to AM0010 and/or FOLFOX

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the disease, concomitant treatments, or pathologies. A "reasonable possibility" means that there is a cause-and-effect relationship between the study treatment and/or study procedure and the AE. The Investigator or qualified Sub-Investigator is responsible for assessing the relationship to AM0010 and FOLFOX using clinical judgment and the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study drug(s). For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes:** There is reasonable possibility that the event may have been caused by the investigational medicinal product.

9.4 Reporting of Adverse Events

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

At each visit assessment, all AEs either observed by the Investigator or one of the Investigator's professional collaborators, or reported by the patient spontaneously, or in response to a direct question will be recorded on the AEs eCRF, whether believed by the Investigator to be related or unrelated to the study medication. If any AE occurs after dosing with study medication, the patient should be followed with the appropriate treatment and close medical supervision. The AEs that started after signing the ICF and up to 30 days after the last dose of study drug(s) will be collected. The Investigator will record the AE on the CRF and will provide the date of onset, severity,

relationship to study medication, date of resolution (or the fact that it is still continuing), action taken, and outcome of the AE. A causality assessment will be made to determine whether or not the AE is thought to be drug related. Removal of a patient from the study because of AEs or changes in laboratory test values, whether by the Investigator or by the patient's own volition, should be reported to Lilly or designee promptly. Study site personnel must report any treatment discontinuations that result from AEs to Lilly or its designee via eCRF, clarifying, if possible, the circumstances leading to the discontinuation of treatment.

9.4.1 Reporting of Serious Adverse Events

After signing the ICF, all AEs are recorded by the site in the eCRF. The SAE reporting to Lilly or designee begins after the patient has signed the ICF and has received study treatment. However, if an SAE occurs after signing the ICF, but prior to receiving study treatment, it needs to be reported ONLY if it is considered reasonably possibly related to the 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 EOT 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.

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 been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly or 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.

9.4.2 Pregnancy

9.4.2.1 Females of Childbearing Potential

Pregnancy during maternal or paternal exposure to study treatment does not meet the definition of an AE, but should be reported. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus. Pregnancies (including a positive pregnancy test regardless of age or disease state) of a female patient occurring while the patient is on the study, or within 90 days of the patient's last dose of study treatments, are considered immediately reportable events. The study treatments should be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Lilly or the Designee Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form or approved equivalent form.

The Investigator will follow the female patient until completion of the pregnancy and must notify Lilly or the Designee Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Lilly or the Designee Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the study treatments should be reported to Lilly or the Designee Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form or approved equivalent form.

9.4.2.2 Male Patients

If a female partner of a male patient taking study treatments becomes pregnant, the male patient taking the study treatments should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately and followed up for complications.

10.0 STUDY DRUGS

10.1 Study Drug Accountability

The Investigator or designee (eg, pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational medicinal product during the study. This includes acknowledgement of receipt of each shipment of study drug (quantity and condition) and tracking of doses assigned/utilized for patient dosing.

AM0010 accountability records will be provided to each study site to:

- Record the date received and quantity of study drug doses
- Record the date, patient number, patient initials, doses, and number dispensed
- Record the date, quantity of used and unused doses returned to the site from the patient, along with the initials of the person who recorded the information
- Record the date, quantity of used and unused doses returned, along with the initials of the person recording the information
- Dispensing records will include the initials of the person dispensing the study drug or supplies

10.2 Study Drug Handling and Disposal

Used and unused study drug supplies and FOLFOX should be stored on site until Lilly or its designee approves of destroying the drug supply on site by their standard operating procedure (SOP). The site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

The study monitor will evaluate each study center's AM0010 disposal procedures and provide appropriate instruction for destruction of unused study drug supplies on site. The Investigator must maintain accurate records for all AM0010 destroyed at the site. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of AM0010. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Lilly or designees.

If destruction of AM0010 on site is not possible, the study drug is to be returned to the shipping facility for eventual destruction. The monitor will provide further instructions for the return.

The study monitor will review study drug supplies and associated records at study monitoring visits.

10.3 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.

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

11.0 INVESTIGATOR REQUIREMENTS

11.1 Good Clinical Practice

The procedures set out in this protocol are designed to ensure that Lilly, Lilly's designees, and the Investigator abide by the principles of the GCP guidelines of the International Conference on Harmonisation (ICH), the Declaration of Helsinki, and local ethical and regulatory requirements. Each Investigator confirms this by signing this study protocol.

11.2 Protocol Adherence and Conditions for Modification

Each Investigator must conduct the study according to the procedures, specifications, and standards detailed in this protocol. Each Investigator must ensure that only those patients who have met protocol eligibility criteria are enrolled in the study. Any changes to protocol-specific procedures and requirements that could potentially adversely affect the safety of study participants, or that could affect the scientific quality of the study or significant elements of the experimental design (such as study drug dosage, dosing schedule, or assessment variables) may be made only through consultation with and approval by an authorized representative of Lilly. None of the revised procedures may be implemented prior to IRB/IEC review and approval, unless implementation of the changes is needed due to patient safety reasons. Lilly will submit protocol amendments to the FDA as required.

11.3 Source Document Maintenance

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.

11.4 Study Monitoring Requirements

Site visits will be conducted by an authorized Lilly' representative to inspect study data, patients' medical records, and CRFs in accordance with ICH guidelines, GCPs, and the respective local and national government regulations and guidelines. The Investigator will permit authorized representatives of Lilly and the respective national or local health authorities to inspect facilities and records relevant to this study.

11.5 Site Study File Management

It will be the responsibility of the Investigator to ensure that their site files (including the Site Study File, Pharmacy Binder, and Laboratory Binder) are maintained. The site study files will contain, but will not be limited to:

- Current IB and all previous versions from the date of study initiation of the participating site
- Final study protocol (signed)
- Protocol amendments (if applicable)
- Master ICF (the ICF signed by the patient and Investigator must be held in the patient's file)
- Revised ICFs and/or all addenda (the ICF signed by the patient and Investigator must be held in the patient's file)
- Copy of signed form(s) FDA 1572
- Curricula Vitae and current license of Investigator and Sub-Investigators
- Financial Disclosure Form
- Documentation of IRB compliance with local regulatory requirements and FDA regulations
- Documentation of IRB approval of protocol, consent form, any protocol amendments, and any consent form revisions
- Annual IRB updates and approvals
- All correspondence between the Investigator, IRB, Lilly's designees and Lilly
- Copies of all information included in the expedited Investigational New Drug (IND) safety reports submitted to the FDA, and correspondence documenting their submission to the IRB

- Name and address of all clinical laboratories used in the study with laboratory certifications and normal laboratory value ranges
- Screening log
- Clinical Research Associate (CRA) monitoring log
- Drug accountability records and invoices for receipt and/or return of study drug
- Master patient list.

11.6 Study Completion

Lilly requires the following data and materials before a study site can be considered closed:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period
- CRFs (including Data Correction Forms) properly completed by appropriate study personnel and signed and dated by the Investigator
- Complete drug accountability records (drug inventory logs and an inventory of returned or destroyed clinical material)
- Copies of the protocol, protocol amendments, and IRB approval/notification
- A summary of the study prepared by the Investigator (an IRB summary letter is acceptable).

11.7 Retention of Records

United States (US) IND exemption regulations (21 Code of Federal Regulations 312.62 [c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drugs, including CRFs, consent forms, laboratory test results, and medication inventory records, must be kept on file by the Investigator for a minimum of 2 years after notification by the Sponsor of either new drug application (NDA)/Biologics License Application (BLA) approval or discontinuation of the IND. If no application is filed, these records must be kept for 2 years after the investigation has been discontinued and the FDA and applicable foreign authorities have been notified. Lilly or its designee will notify the Investigator of these events. No study records shall be destroyed without prior authorization from Lilly. For trials conducted outside the US under a US IND, the Investigator must comply with US FDA IND regulations and with those of the relevant national and local health authorities.

11.8 Monitoring by Lilly or its Designees

Monitoring visits by a professional representative of the Sponsor will be scheduled to take place after entry of the first patient, during the study at appropriate intervals, and after the last patient has completed the study. These visits are for the purpose of confirming that Lilly-sponsored trials are being conducted in compliance with the relevant GCP regulations and guidelines, verifying adherence to the protocol, and the completeness and exactness of data entered on the CRFs and drug inventory forms. The monitor will verify CRF entries by comparing them with the hospital/clinic/office records which will be made available for this purpose. Adequate time and space for these visits must be made available by the Investigator.

12.0 ETHICAL CONSIDERATIONS

This study will be conducted in accordance with current ICH and GCP guidelines, the Declaration of Helsinki, and local ethical and regulatory requirements.

12.1 Good Clinical Practice

This study will be conducted in accordance with GCP, as defined by the ICH and in accordance with the ethical principle underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21 CFR 50).

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the patient informed consent will receive IRB/IEC approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to Lilly immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol which is likely to affect, to a significant degree, the safety or physical or mental integrity of the patients of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

12.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the Investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, patient recruitment materials/process (eg, advertisements), and other written information to be provided to patients. The Investigator or Sponsor should also provide the IRB/IEC with a copy of the IB or product labeling, information to be provided to patients, and any updates.

The Investigator or Sponsor should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

12.3 Informed Consent

Investigators must ensure that patients are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical trials in which they volunteer to participate.

Lilly or its designee will provide the Investigator with an appropriate (ie, global or local) sample ICF, which will include all elements required by ICH, GCP, and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1. Provide a copy of the consent form and written information about the study in the language in which the patient is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2. Allow time necessary for patient to inquire about the details of the study.
3. Obtain a signed and dated informed consent from the patient and the person who conducted the informed consent discussion.
4. Obtain the IRB/IEC's written approval/favorable opinion of the written ICF and any other information to be provided to the patients prior to the beginning of the study and after any revisions are completed for new information.
5. Revise the informed consent whenever important new information becomes available that is relevant to the patient's consent. The Investigator, or a person designated by the Investigator, should fully inform the patient of all pertinent aspects of the study and of any new information relevant to the patient's willingness to continue participation in the study. The communication should be documented.

The confidentiality of records that could identify the patient must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the patient's signed ICF and, in the US, the patient's signed Health Insurance Portability and Accountability Act (HIPAA) Authorization.

The consent form must also include a statement that Lilly and its designees and regulatory authorities have direct access to patient records.

The patient must also be informed about the nature of the study to the extent compatible with the patient's understanding, and should they become capable, personally sign and date the consent form as soon as possible. The explicit wish of a patient unable to give his or her written consent who is

capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the Investigator.

The rights, safety, and well-being of the study patients are the most important consideration and should prevail over interests of science and society.

13.0 SPONSOR RESPONSIBILITIES

Lilly is the Sponsor for this study. PPD, Inc. will have regional Medical Monitors for this study, and safety reporting for this trial.

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15.0 APPENDICES

Appendix A: Schedule of Events

Activities	Screening	Randomization (p)	Treatment Repeat Every 14 days		Maintenance Repeat Every 28 days (±3 Days)	End of Treatment	Follow-Up		
								Long-Term (p)	
	-21 to -1 Days		Cycles 1-12	Cycles 1, 2, & 4	ARM 1 only AM0010 after discontinuation of FOLFOX	Within 7 days of last dose	30 days after EOT (u)	Every 8 wks for 12 months	Every 12 wks after 12 months
			Day 1 (±3 Days)	Day 13 (±3 Days)			±5 Days	±3 Days	±7 Days
GENERAL and SAFETY AWARENESS									
Informed Consent	X								
Inclusion/Exclusion	X								
Demographic/Medical and Cancer History	X								
Prior Cancer Therapy	X								
Physical Examination (a)	X		X		X	X	X		
Height	X								
Weight	X		X		X	X	X		
BSA Calculations	X		X						
ECOG Performance Status	X Within 3 days prior to Randomization		X(b)		X	X	X		
Baseline Signs and Symptoms	X								
Health Outcomes Assessments	X		X(c)		X(c)	X(c)			
Vital Signs (d)	X		X		X	X	X		

Activities	Screening	Randomization (p)	Treatment Repeat Every 14 days		Maintenance Repeat Every 28 days (±3 Days)	End of Treatment	Follow-Up		
							30 days after EOT (u)	Long-Term (p)	
	-21 to -1 Days		Cycles 1-12	Cycles 1, 2, & 4	ARM 1 only AM0010 after discontinuation of FOLFOX	Within 7 days of last dose		Every 8 wks for 12 months	Every 12 wks after 12 months
			Day 1 (±3 Days)	Day 13 (±3 Days)			±5 Days	±3 Days	±7 Days
GENERAL and SAFETY AWARENESS									
12-lead ECG (e)	X		ARM 1 (e)	ARM 1(e)		X			
Concomitant Medication	X		X		X	X			
Adverse Events			X		X	X	X		
Survival Status (f)								X	X
AM0010 / FOLFOX ARM 1									
Treatment: AM0010 (g)			X(r)		X				
Collect/Dispense AM0010 Dosing Diary (ARM 1 only) (h)			X		X				
Dispense AM0010 (h)			X		X				
Treatment: FOLFOX (i)			X						
AM0010 PK (j)			◄	►					
FOLFOX ALONE ARM 2									
Treatment: FOLFOX(i)			X						

Activities	Screening	Randomization (p)	Treatment Repeat Every 14 days		Maintenance Repeat Every 28 days (±3 Days)	End of Treatment	Follow-Up		
								Long-Term (q)	
	-21 to -1 Days		Cycles 1-12	Cycles 1, 2, & 4	ARM 1 only AM0010 after discontinuation of FOLFOX	Within 7 days of last dose	30 days after EOT (u)	Every 8 wks for 12 months	Every 12 wks after 12 months
			Day 1 (±3 Days)	Day 13 (±3 Days)			±5 Days	±3 Days	±7 Days
LABORATORY ASSESSMENTS									
Hematology (k)	X		X	X (t)	X	X	X		
Chemistry (k)	X		X		X	X	X		
Urinalysis (Dipstick) (k)	X								
Pregnancy Test (l)	X		X		X	X	X		
CA 19-9 (m)	X		X		X	X			
Exploratory Biomarker Sample (j)			X	X		X			
ADA Sample Collection (j)			X	X		X	X		
Archival Tumor Tissue (n)	X								
IMAGING ASSESSMENT									
Tumor assessment (o)	Within 28 days of Randomization		Every 8 weeks (s)			X (o)			

[a] Clinical Evaluation will include: full physical examination at Screening and modified physical examination at Day 1 of odd cycles (capturing changes from prior exams) and EOT, ECOG status (Appendix E), weight, and BSA calculation (for FOLFOX treatment visits only). Weight measurement in kg without shoes. Medical and anti-cancer history (dates and BOR) and height at Screening only, baseline signs and symptoms. BSA should be recalculated if >10% weight loss or gain. Physical examination performed as part of standard practice may be used for Screening if conducted within 21 days prior to Randomization. Day 1 Treatment Clinical Evaluations may be performed 3 days prior.

[b] Patient may not experience a decrease in ECOG PS between Screening visit and within 72 hours prior to Randomization.

[c] Patients will complete 2 instruments, the EORTC QLQ-C30 and EQ-5D-5L. Both instruments will be administered at baseline (Screening), Day 1 of every treatment cycle regardless of dosing (both during the FOLFOX regimen and during the maintenance cycles), at EOT, and at the follow-up visit 30 days after EOT. Both instruments should be administered together at the beginning of the study visit prior to any extensive contact or consultation with study site personnel, which may bias patient responses. The EORTC QLQ-C30 will be presented first, followed by the EQ-5D-5L.

[d] Vital signs (pulse, blood pressure, respiratory rate, and temperature) will be collected after being seated or in a semi-recumbent position. Day 1 Treatment vital signs may be performed 1 day prior.

[e] ECG will be performed in patients seated, semi-recumbent, or supine for at least 5 minutes. A 12-lead ECG should be performed at Screening and EOT (ARM 1 and 2), ARM 1 only at pre-dose Cycles 1, 2, 3, and 5; and on Day 13 on Cycles 1,2, and 4. Day 1 Treatment ECG may be performed 3 days prior.

[f] Survival Status, every 8 weeks for the first 12 months then every 12 weeks thereafter.

[g] In patients assigned to AM0010 and FOLFOX (ARM 1), 1 dose of 5 µg/kg AM0010 will be administered daily by SQ injection on Days 1–5 and Days 8–12 of each 2-week cycle. Rest days when AM0010 will not be administered are Days 6–7 and Days 13–14.

[h] AM0010 study drug and Dosing Diary will be dispensed to patients for self/caregiver administration. The diary will be a part of source documentation and should be reviewed with the patient at every visit. See Pharmacy Manual.

[i] FOLFOX; Day 1 of each 14-day cycle for 12 cycles: *dl*-LV 400 mg/m^2 and oxaliplatin 85 mg/m^2 followed by bolus 5-FU 400 mg/m^2 and a 46- to 48-hour infusion of 5-FU 2400 mg/m^2.

[j] PK samples obtained in patients on ARM 1 and ADA samples obtained in patients on ARMs 1 and 2. Samples will be collected during Cycles 1 and 2, Days 1 and 13, Cycle 3 Day 1 only, Cycle 4 Day 13 only, Cycle 5 Day 1 only. ADA will also be collected at EOT and at follow-up visit 30 days after EOT. Blood samples for biomarkers (PD samples) are collected pre-dose on C1D1, C1D13, C2D13, C4D13, and EOT for patients on both arms. See Lab Manual for further details.

[k] Safety lab tests are listed. If Screening labs are done within 3 days prior, then Screening labs can be used as Day 1 labs. Laboratory tests performed as part of standard practice may be used for Screening if conducted within 21 days prior to Randomization.

[l] Serum pregnancy test performed at Screening; urine pregnancy test performed locally at all other time points by dipstick as appropriate for women of child-bearing age. A urine sample for pregnancy testing for female patients will also be obtained at Day 1 of every odd-numbered cycle, every 28 days in patients who continue AM0010 monotherapy after FOLFOX discontinuation, EOT, and 30 days after EOT.

[m] CA 19-9 (±3 days) will be evaluated at Screening, on Day 1 of every odd cycle, every 28 days after discontinuation of FOLFOX, and at EOT.

[n] The collection of archived tumor tissues is not mandatory or required for eligibility. Attempts should be made to acquire these tissues starting once the patient is enrolled in the study. Pathology reports should be obtained.

[o] Tumor response will be assessed by the study site and by an independent radiology reviewer. The process for collection of CT images for purpose of central independent review is described in the Imagining Manual. Patients whose scans show radiographic progression in the absence of clinical deterioration including worsening ECOG PS as assessed by the Investigator may remain on AM0010 plus FOLFOX study treatments and have an unscheduled scan, 4 weeks later as outlined in Section 8.1.1. If this subsequent scan shows disease progression, the patient will be discontinued from the study. Patients on subsequent scan and response (CR, PR, and SD) will remain on study treatments. Patients with CR or PR need to have a confirmatory scan (≥4 weeks). EOT scan done if not done within 4 weeks prior.

[p] Randomization should occur within 21 days of starting baseline. Patients must begin treatment within 3 days after the date of Randomization.

[q] Patients will be contacted via phone call to determine long-term survival status and record of any other anti-cancer therapy and cancer related surgery. The evaluation may be conducted by record review and/or telephone contact with the patient's treating physician.

[r] Staff administered dose and training for AM0010 self-injection on Cycle 1, Day 1. FOLFOX; Day 1 of each 14-day cycle for 12 cycles: *l-dl*-LV 400 mg/m^2 and oxaliplatin 85 mg/m^2 followed by bolus 5-FU 400 mg/m^2 and a 46- to 48-hour infusion of 5-FU 2400 mg/m^2.

[s] Tumor evaluation by CT or MRI will be performed during Screening (within 4 weeks prior to Randomization), at Week 8 (±3 days) and every 8 weeks (±3 days) regardless of cycle number and regardless of any dose interruptions until PD by RECIST v.1.1. The same radiographic procedure used to define measurable or non-measurable lesions must be used throughout the study for each patient. The RECIST v.1.1 guideline recommends spiral CT images for chest, abdomen, and pelvis should be performed. Scans performed as part of standard practice may be used if conducted within 28 days prior to Randomization.

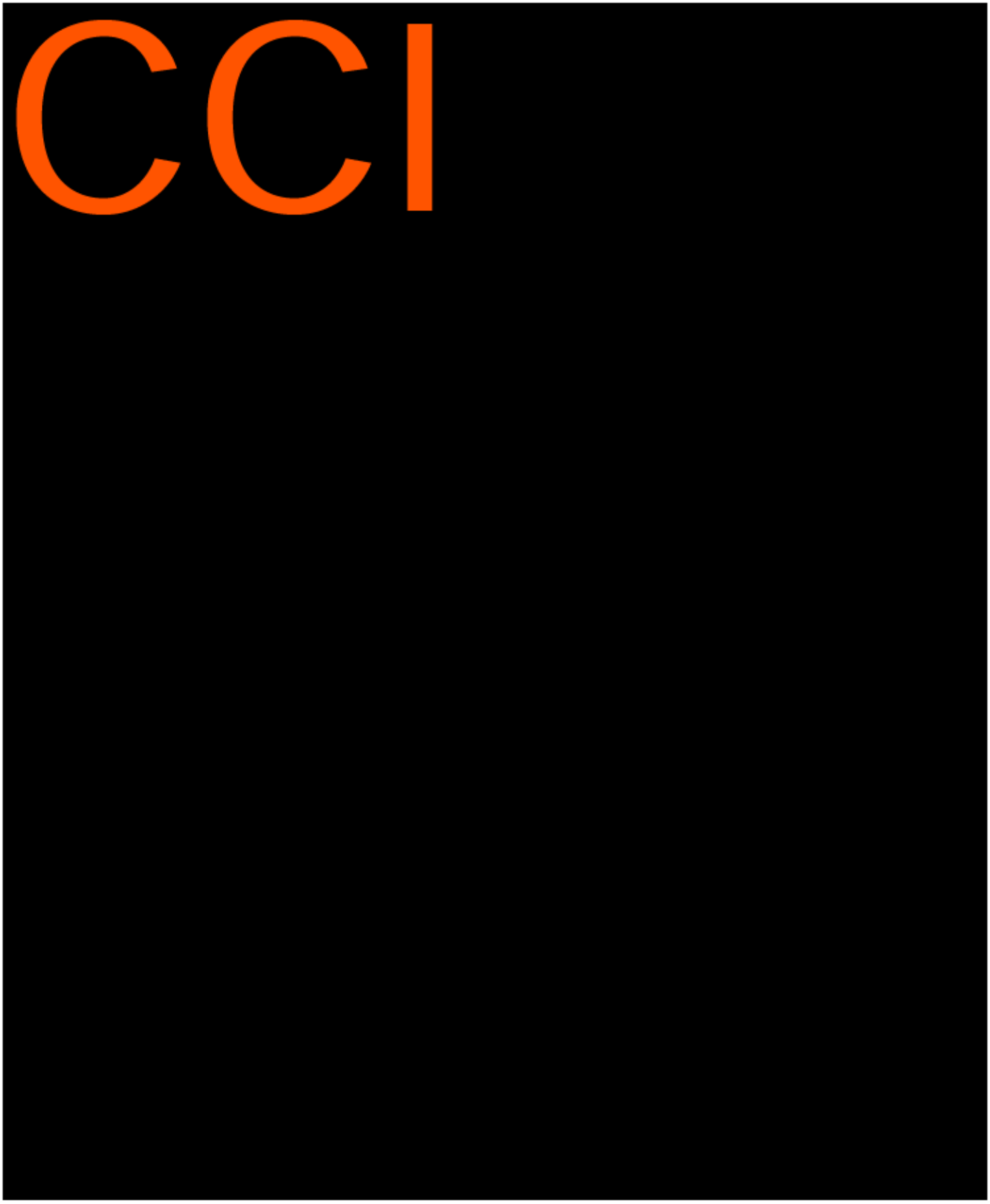
[t] ARM 1: CBC and platelets only at Cycles 1, 2, and 4 Day 13.

[u] If patient starts a new anti-cancer therapy within 30 days of the last dose of study medication, the Follow-Up visit should be performed prior to the start of the new anti-cancer therapy, within the 30-day window.

Appendix B: Continued-Access Period Assessments

	Continued-Access Treatment Visits ±3 Days	Continued-Access Follow-Up Visits 30 days (±7 days) after the last dose of study treatment
Treatment: AM0010	X	
Adverse event	X	X
Survival assessment [a]	X	X

a Every 12 weeks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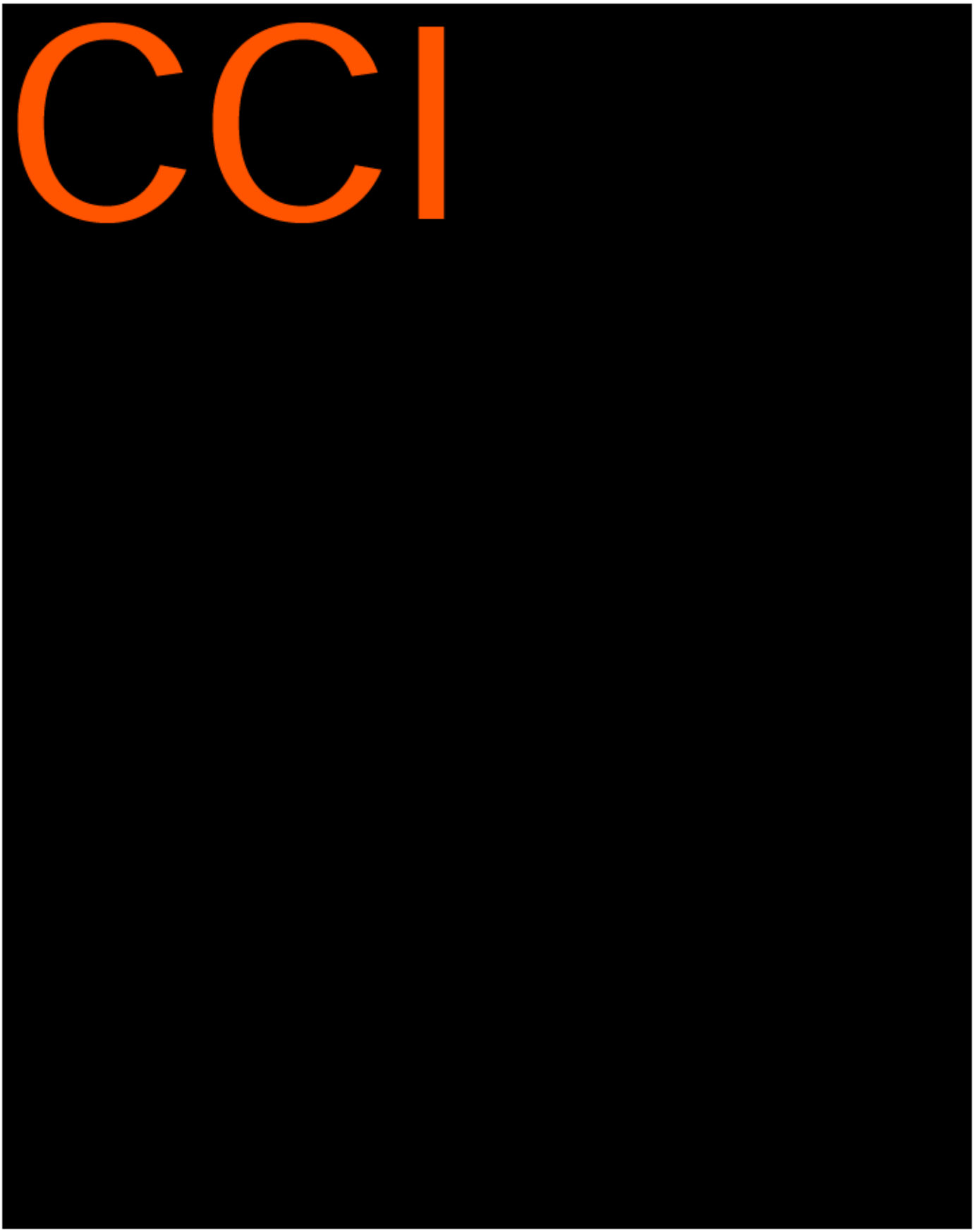
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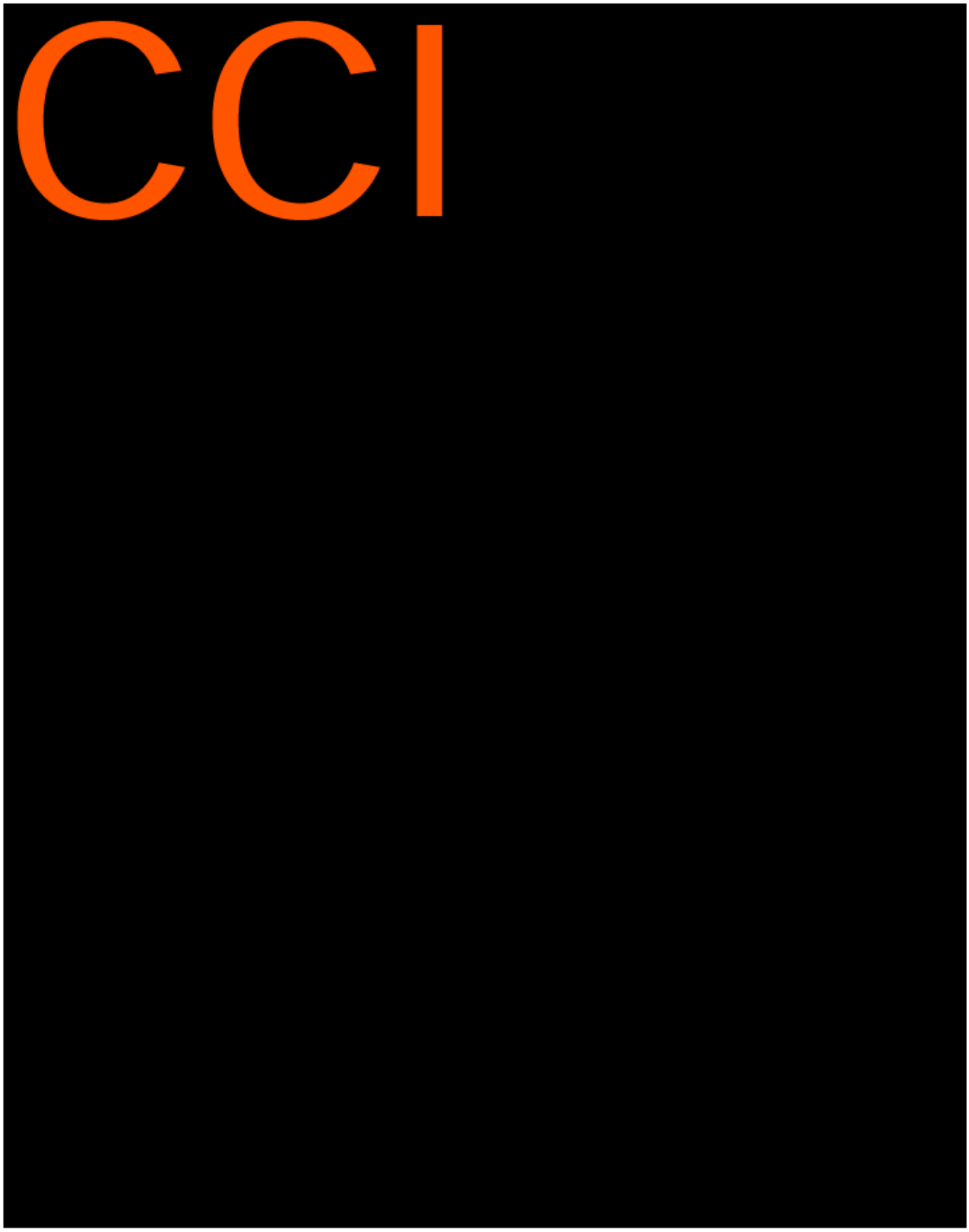
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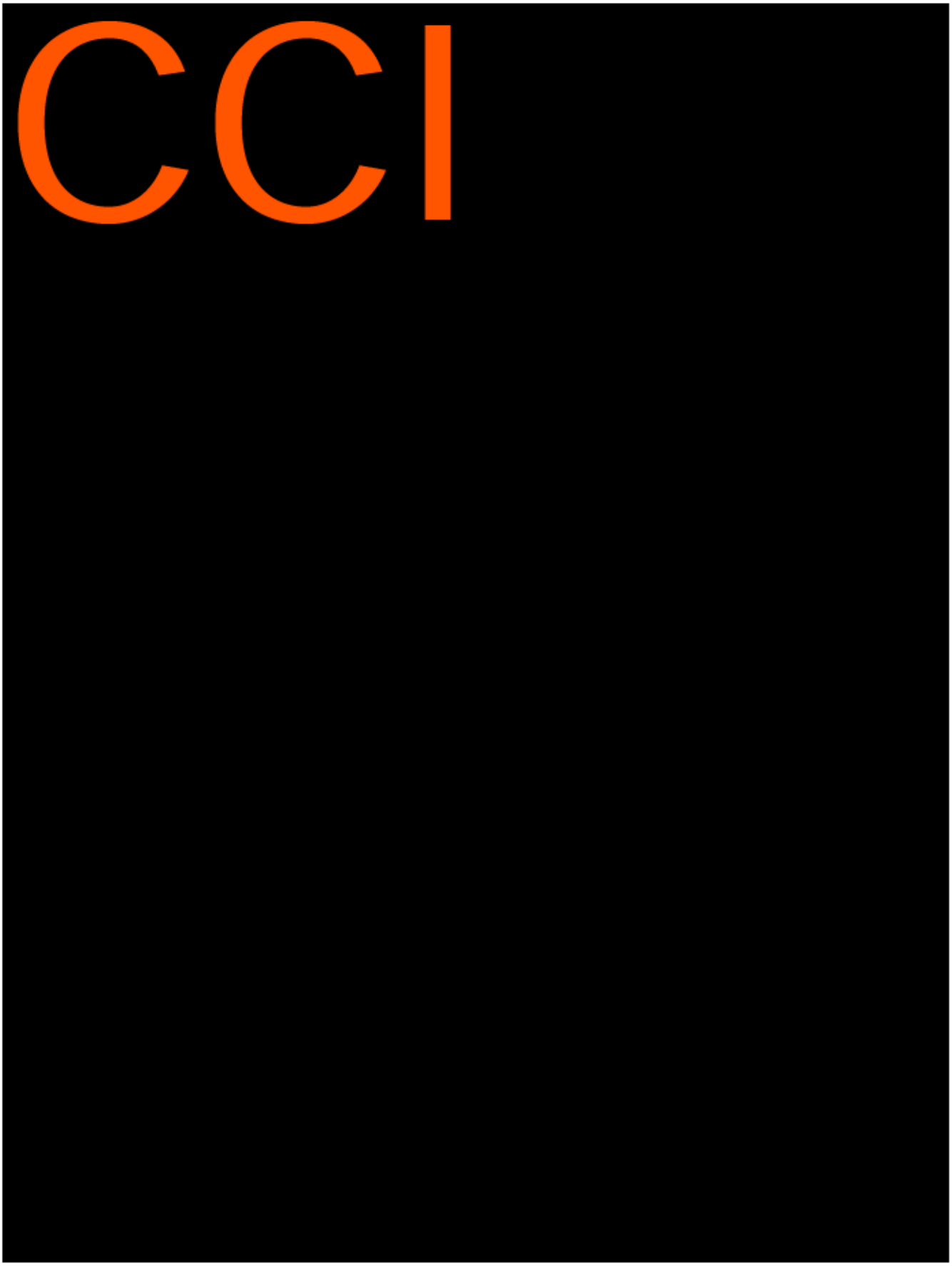
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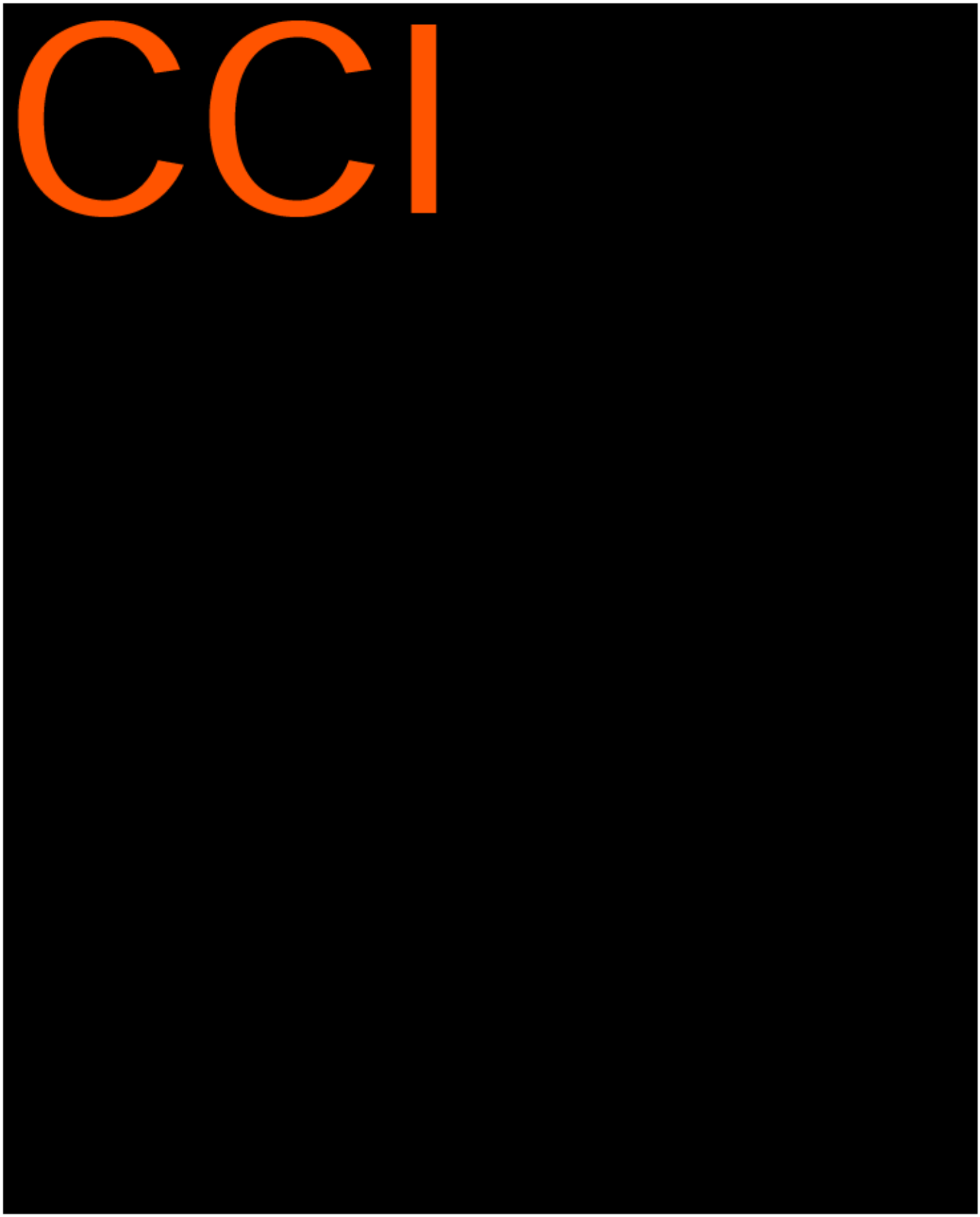
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Appendix D: Dose Modification Tables for FOLFOX – FOLFOX/AM0010

Adverse Event	Occ.	Oxaliplatin	5-Fluorouracil	AM0010
Hematological AEs				
Grades 3-4 anemia or Grades 3-4 thrombocytopenia	1st	Hold until G1 or baseline Reintroduce at dose level −1	Hold until G1 or baseline Reintroduce at dose level −1	Hold until G1 or baseline Reintroduce to Dose Level −1
	2nd	Hold until G1 or baseline Reintroduce at dose level −2	Hold until G1 or baseline Reintroduce at dose level −2	Hold until G1 or baseline Reintroduce to Dose Level −2
	3rd	Hold until G1 or baseline No change in dose	Hold until G1 or baseline No change in dose	Hold until G1 or baseline No change in dose
Grades 3-4 neutropenia or Grades 3-4 leukopenia or Grades 3-4 neutropenic fever	1st	Hold until G1 or baseline Reintroduce at dose level −1	Hold until G1 or baseline Reintroduce at dose level −1	Continue dosing; no change in dose schedule
	2nd	Hold until G1 or baseline Reintroduce at dose level −2	Hold until G1 or baseline Reintroduce at dose level −2	
Hemolytic uremic syndrome (HUS)[2]	1st	Discontinue	Hold until G1 or baseline No change in dose	Hold until G1 or baseline No change in dose
Non-hematological AEs				
Grade 3 Diarrhea		Hold until G1 or baseline No change in dose level	Hold until G1 or baseline Reintroduce at dose level −1	Continue dosing; no change in dose schedule
Grade 4 Diarrhea		Hold until G1 or baseline Reintroduce at dose level −1	Hold until G1 or baseline Reintroduce at dose level −1	
Cough ≥Grade 3 Dyspnea ≥Grade 3 Hypoxia ≥Grade 3 Pneumonitis ≥Grade 3		Hold oxaliplatin until interstitial lung disease is ruled out. If interstitial lung disease, discontinue oxaliplatin	Hold until G1 or baseline No change in dose	Hold until G1 or baseline No change in dose schedule
Grade 3 Fatigue		Hold until G1 or baseline No change in dose level	Hold until G1 or baseline No change in dose level	Hold until G1 or baseline No change in dose schedule
Other non- hematological AEs[3,4]		Hold until G1 or baseline		No change in dose schedule

		Reduce offending agent by 1 dose level[1]	

Appendix D Dose Modification Tables for FOLFOX – FOLFOX / AM0010 (Cont'd)

Adverse Event	Occ.	Oxaliplatin	5-Fluorouracil	AM0010
Non-hematological AEs				
Hypomagnesemia		Hold until G1 or baseline No change in dose level		
Neurological AEs				
Persistent[5] Grade 2 paresthesias/ dysesthesias[6]		Reduce dose to level −1	No change in dose	Continue dosing; no change in dose schedule
Grade 3 paresthesias/ dysesthesias[6]		Hold until G1 or baseline Discontinue, if persistent[5]		
Grade 4 paresthesias/ dysesthesias[6]		Discontinue		
Grade 2 = moderate (also recommended is administration of benzodiazepine and patient education. Management of patient if ≥Grade 2 laryngeal dysesthesias occurs while treatment is being administered.) Grade 3 = severe		Stop oxaliplatin infusion. Administer benzodiazepine and give patient reassurance. At the discretion of the Investigator, the infusion can be restarted at 1/3 the original rate of infusion. Continue 5-FU		Continue dosing; no change in dose schedule

[1] If an AE is believed likely to be due to only 1 of the drugs, it is permissible to decrease dose of that drug only.
[2] Recommended evaluation of suspected HUS: Evaluation should include CBC differential, platelets, PT, PTT, fibrinogen, FDP, Anti thrombin III, Von Willebrand factor, anti-nuclear antibody, rheumatoid factor, Compliment Cascade C3, C4, and CH50, anti-platelet antibodies, platelet-associated IgG, and circulating immune complexes. Renal evaluation should include creatinine, BUN, and urinalysis with microscopic examination. Other laboratory and hematologic evaluations as appropriate should also be obtained, including peripheral blood smear and free hemoglobin.
[3] Exceptions: fatigue, anorexia, nausea/vomiting if can be controlled by antiemetic, and viral infections.
[4] Dose modifications for other non-hematologic AEs at the start of subsequent courses of therapy, and at time of retreatment are also based on NCI CTCAE v4.03 criteria.
[5] Not resolved by the beginning of the next cycle.
[6] May be cold-induced.

Leucovorin doses may be adjusted per institutional guidelines in the event of a supply shortage.

Dose Reduction Levels[a] for FOLFOX

Drug	Dose Level		
	Starting Dose	**−1**	**−2[b]**
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2
5-FU bolus	400 mg/m^2	Omit	Omit
5-FU continuous infusion over 46–48 hours	2400 mg/m^2	1900 mg/m^2	1500 mg/m^2
dl-Leucovorin/l-Leucovorin[c]	400 mg/m^2	100%	100%

[a] If an AE is believed likely to be due to 1 drug, it is permissible to decrease dose of that drug only.

[b] Further dose levels (−3, −4, etc.) will be 20% dose reductions from the previous level for oxaliplatin and 5-FU continuous infusion. In addition, the bolus dose of 5-FU will continue to be omitted, and the leucovorin dose will remain unadjusted (100%).

[c] Dosing of leucovorin will remain fixed at 100% of recommended dose. Non-racemic L-leucovorin dose at 200 mg/m^2.

Appendix E: ECOG Performance Status*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

*As published in (Oken, Creech et al., 1982).


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Appendix G: NCI CTCAE v4.03

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_4.03.xlsx

Appendix H: Birth Control Methods That May Be Considered Highly Effective

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

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation 1:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation 1:
  - oral
  - injectable
  - implantable
  - intrauterine device (IUD)
  - intrauterine hormone-releasing system (IUS)
  - bilateral tubal occlusion
  - vasectomized partner
  - sexual abstinence

Guidance on the acceptable contraception methods can be found here:

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

Appendix I: Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

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

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

a Assayed by Lilly-designated laboratory.

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

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

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