NCT03023722

Unique Protocol ID: 1608018265

Brief Title: Phase II Anetumab Ravtansine in Pre-treated Mesothelin-expressing Pancreatic Cancer

19-September-2018

1. Title page

An open-label, Phase II study of intravenous anetumab ravtansine (BAY 94-9343), an anti-mesothelin antibody drug conjugate, in pretreated mesothelin-expressing advanced pancreatic cancer

Phase II anetumab ravtansine in pre-treated mesothelin-expressing pancreatic cancer

Test drug:	BAY 94-9343 / anetumab ravtansine
Study purpose:	Assess the efficacy and safety of anetumab ravtansine as 2nd or 3rd line treatment in advanced pancreatic cancer
Clinical study phase:	II
Date:	19-September-2018
Sponsor's study no.:	Yale HIC# 1608018265
Sponsor:	**Yale Cancer Center, Yale University**
Principal Investigator:	Stacey Stein, MD
Statistician:	Daniel Zelterman, PhD (Yale School of Public Health)

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Signature of principal investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Affiliation:

Date: _____ Signature: _____

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

2. Synopsis

Title	An, open-label, Phase II study of intravenous anetumab ravtansine (BAY 94-9343), an anti-mesothelin antibody drug conjugate, in pretreated mesothelin-expressing advanced pancreatic cancer
Short title	Phase II anetumab ravtansine as 2nd or 3rd line treatment for pancreatic cancer
Clinical study phase	II
Study objective(s)	The primary objective of this study is to: • Test the activity/response rate per RECIST 1.1 criteria of anetumab ravtansine in patients with advanced pancreatic cancer who stain for mesothelin expression The secondary objectives of this study are to: • Time to Progression (TTP) defined as time from study treatment to RECIST progression, or death (others going off study will be censored) • Toxicity in pancreatic cancer patients (at 6.5 mg/kg dose)
Test drug(s)	Anetumab ravtansine
Name of active ingredient	Anetumab ravtansine / BAY 94-9343
Dose(s)	6.5 mg/kg every 3 weeks (Q3W)
Route of administration	Intravenous (IV) infusion over 1 h
Duration of treatment	Patients will continue on treatment until one of the following occurs: • Progressive disease (PD) as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by Investigator. However, all scans will also be read independently by radiologists in Precision Metrics (previously known as Tumor Imaging Metrics Core [TIMC]) or an equivalent system and archived therein. • Clinical progression as assessed by investigator. • Death • Any other criterion for withdrawal from study treatment.
Reference drug(s)	Not applicable
Indication	Pre-treated advanced pancreatic cancer, Mesothelin positive by IHC
Diagnosis and main criteria for inclusion /exclusion	Patients with advanced metastatic pancreatic cancer who have measurable disease; must have at least one and not more than two prior chemotherapy regimens for advanced disease (neoadjuvant or adjuvant chemotherapy would not be counted as a line of therapy). If prior radiation, measurable lesion outside radiation portal. ECOG PS 0-1; Mesothelin positive (defined as 30% of cells with staining 2+ or 3+ on IHC for mesothelin). Must have normal organ function with LFTs <2.5 x ULN, no history of keratitis or corneal disease. Excluded from study if have uncontrolled medical illness or infections, peripheral neuropathy interfering with function, history of corneal disease or keratitis
Study design	A nonrandomized, open-label, single arm, 2-3 center, Phase II study.

	Patients will be treated and undergo imaging scan every 6 weeks. RECIST 1.1 criteria to be used for response Descriptive statistics of RR (response rate) + 95% CI Time to Progression calculated by K-M method All patients treated with at least one dose of Anetumab to be included A maximum of 30 patients will be enrolled in a minimax, Simon 2-stage design with a single early stopping rule for lack of efficacy. The target population is those patients with pancreatic cancer who have failed an earlier treatment. All patients will be treated with an anti-mesothelin immuno-conjugate, in this single arm, non-randomized trial. The endpoint is any response using the RECIST 1.1 criteria. The minimax, Simon 2-stage design testing 5% null hypothesis versus a 21% alternative requires a maximum of 30 patients. If there are no patients exhibiting any response among the first 20, which indicates a response rate less than 5%, then the trial will terminate early. If there is at least one response among the first 20 (indicating response rate of at least 5%), then the trial will accrue an additional 10 patients for a maximum of 30. Four or more responses out of 30 will reject the null hypothesis in favor of the 21% response alternative. These criteria have significance level (alpha) 0.1 and power 90%. The probability of stopping early is 36% if the response rate is 5% or lower. The expected sample size is 26.4.
Methodology	Primary efficacy will be assessed based on radiological tumor evaluation by contrast-enhanced computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI) of chest/abdomen/pelvis. During treatment as well as active follow-up, tumor imaging will be performed with the same modality to the extent possible, every 6 weeks during the first 6 months after the start of study treatment, every 9 weeks until the end of year 2, and every 12 weeks thereafter until RECIST confirmed radiological disease progression or end of study. Safety evaluations will be done at full screening, at each clinic visit during the treatment period, and at the safety follow-up visit. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 will be used to grade severity of adverse events (AEs).
Type of control	Not applicable
Data Monitoring Committee	Yes
Number of patients	A maximum of 30 patients will be enrolled
Primary variable	Response rate as measured per RECIST 1.1 criteria
Plan for statistical analysis	The minimax, Simon 2-stage design testing 5% null hypothesis versus a 21% alternative requires a maximum of 30 patients. If there are no patients exhibiting any response among the first 20, which indicates a response rate less than 5%, then the trial will terminate early. If there is at least one response among the first 20 (indicating response rate of at least 5%), then the trial will accrue an additional 10 patients for a maximum of

	30. Four or more responses out of 30 will reject the null hypothesis in favor of the 21% response alternative. These criteria have significance level (alpha) 0.1 and power 90%. The probability of stopping early is 36% if the response rate is 5% or lower. The expected sample size is 26.4.

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List of abbreviations

5-HT3	5-hydroxytryptamine (serotonin)
ADC	Antibody-drug conjugate
AE	Adverse event
AG	Joint stock company, *Aktiengesellschaft*
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BCVA	Best corrected visual acuity
β-HCG	β subunit of human chorionic gonadotropin
BIO	Biomarker set
BM	Biomarker
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
°C	Celcius degree(s)
C	Cycle
CBC	Complete blood count
C_{max}	Maximum drug concentration
CNS	Central nervous system
COA	Clinical Outcomes Assessment
CR	Complete response
CRF	Case report form
CSF	Colony stimulating factor
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP2D6	Cytochrome P450, family 2, subfamily D, polypeptide 6
CYP3A4	Cytochrome P450, family 3, subfamily A, polypeptide 4
D	Day
dL	Deciliter
DM4	Derivatives of maytansine 4
DM4-Me	Methyl-DM4
DSMC	Data and Safety Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
EchoCG	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ENR	Enrolled set

ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
°F	Fahrenheit degree(s)
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
g	Gram(s)
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
GPV	Global Pharmacovigilance
h	Hour(s)
H0	Null hypothesis
HA	Alternative hypothesis
Hb	Hemoglobin
HIC	Human Investigation Committee
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IDS	Investigational Drug Service
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G subclass 1
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IM	Immunogenicity
IMP	Investigational medicinal product
INR	International normalized ratio
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent-to-treat (set)
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
kg	Kilogram(s)
LDH	Lactic dehydrogenase
LLN	Lower limit of normal
LPLV	Last patient last visit
LVEF	Left ventricular ejection fraction
m^2	Square meter(s)
MCU	Multi-Center Unit
MD	Doctor of Medicine

MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
Min	Minute(s)
miRNA	Micro ribonucleic acid
mL	Milliliter(s)
mm^3	Cubic millimeter(s)
mmHg	Millimeter of mercury
MoA	Mechanism of action
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition
N	Number of patients
n	Number of non-missing values
N HCl	Normal hydrochloric acid
NC	No change
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NE	Not evaluated
NGS	Next generation sequencing
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PFT	Pulmonary function test
P-gp	Permeability glycoprotein
PhD	Doctor of Philosophy
PI	Principal Investigator
PK(s)	Pharmacokinetic(s)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
Q3W	Every 3 weeks
QA	Quality assurance
QW	Once weekly
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RPIID	Recommended Phase II dose
RR	Respiratory rate
RT	Radiotherapy
SAE	Serious adverse event

SAF	Safety set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Stable disease
SoC	Standard of care
SPDB	N-succinimidyl 4-(2-pyridyldithio)butyrate (reducible disulfide linker)
SPK	Superficial punctate keratitis
SQR RT	Square root (√)
SUSAR	Suspected, unexpected, serious adverse reaction
T1	Tumor invades lamina propria
Ta	Non-invasive tumor
TEAE	Treatment-emergent adverse event
Temp	Body temperature
Tis	Carcinoma *in situ*
TMF	Trial master file
TTP	Time to progression
ULN	Upper limit of normal
US(A)	United States of America
USP	United States Pharmacopeia
WBC	White blood cell count
WOCBP	Women of childbearing potential
YCC	Yale Cancer Center
YCCI	Yale Center for Clinical Investigation

3. Introduction

3.1 Background

Mesothelin is a membrane associated differentiation antigen present on normal mesothelial cells and overexpressed in a vast majority of ductal pancreatic adenocarcinomas, mesotheliomas, and adenocarcinomas of the ovary. The biological function of mesothelin remains unknown and mesothelin-deficient mice have no obvious phenotype of defect. Mesothelin is an internalizing antigen and shows a restricted expression profile in normal tissue making it an excellent target for antibody directed cytotoxic drug delivery.

BAY 94-9343, anetumab ravtansine, is an antibody-drug conjugate consisting of a fully human IgG1 antibody (MF-T, BAY 86-1903) directed at the mesothelin antigen and conjugated to a synthetic cytotoxic anticancer agent, maytansine derivative (DM4, BAY 1006640) as toxophore through a reducible disulfide linker (SPDB). Preclinical efforts have shown specific effects on mesothelin positive cell lines and in xenograft models including activity in pancreatic BxPC3 xenograft model. Toxicology studies showed a number of important signals but specifically skin toxicity.

Human phase 1 and PK studies were performed showing terminal phase half-life values of the ADC and Total Antibody were approximately 5.5 to 6 days. Plasma DM4 and DM4-Me concentrations declined with a half-life of approximately 3 days and 5.5 days at the MTD. DM4-Me pharmacokinetics exhibited moderate to high variability and exposure increased in a substantially more than dose proportional manner in the dose range studied.

The safety results from the dose escalation part of the first-in-human study 15051 in 45 patients with advanced cancer (BAY 94-9343 dose range, 0.15-7.5 mg/kg q3w) were as follows: 1) The non-tolerable dose of BAY 94-9343 was 7.5 mg/kg q3w; the non-tolerable toxicities at 7.5 mg/kg q3w were corneal toxicity (blurry vision and keratitis due to corneal epitheliopathy), peripheral neuropathy and increase in serum amylase and lipase; 2) The maximum tolerated dose was 6.5 mg/kg q3w; the only dose-limiting toxicity observed at this dose level was the asymptomatic Grade 3 increase in serum AST/ALT; 3) The most common treatment-emergent adverse events at least possibly related to BAY 94-9343 were fatigue, nausea, vomiting, anorexia, peripheral neuropathy, myalgia, weakness and diarrhea. The most common treatment-emergent lab abnormalities were lymphopenia, hypoalbuminemia, hyponatremia, hyperglycemia and hypokalemia; 4) at doses below the non-tolerated dose, the TEAEs were mostly mild and not clinically significant except for cardiac chest pain, hypertension, grade 3 increase in ALT and AST, and decrease in platelets and sodium.

The safety results from the MTD Expansion 6.5 mg/kg q3w cohort, which evaluated the MTD for BAY 94-9343 determined in the dose escalation cohorts were as follows: 1) BAY 94-9343 at 6.5 mg/kg given IV once every 3 weeks was considered tolerable in the two cohorts of subjects with ovarian cancer (n=20) and pleural or peritoneal mesothelioma (n=12); 2) Overall, 16 of 32 (50%) subjects treated at 6.5 mg/kg q3w have required dose reduction to 5.5 mg/kg q3w and 4 (25%) of these subjects required another dose reduction to 4.5 mg/kg; 3) the safety finding of particular relevance was the high incidence of corneal toxicity (blurred vision and keratitis with vision impairment due to corneal epithelial microcysts or deposits in 12 of 32 subjects) causally attributed to BAY 94-9343; 4) although being fully reversible in the vast majority of cases, the corneal toxicity invariably necessitated lengthy treatment interruption and dose reduction; 5) otherwise the safety profile of BAY 94-9343 in the MTD

Expansion 6.5 mg/kg q3w cohort was very similar to that observed in dose escalation cohorts up to and including the Cohort 9 (6.5 mg/kg q3w), with mostly mild TEAEs and remarkably low incidence of drug-related SAEs. One patient in a Japanese cohort with pancreatic cancer developed drug-induced liver injury.

We will therefore pursue the 6.5 mg/kg dose, as having an acceptable incidence of corneal toxicity and keratitis and as the phase II dose in use for current studies.

3.2 Rationale of the study

The need for new treatments for pancreatic cancer is great. At the MTD of 6.5 mg/kg Q3W, anetumab ravtansine has demonstrated a tolerable safety profile and efficacy in pancreatic cancer. If this study shows promise, with at least 21% of treated patients showing RECIST response, or prolonged delay in progression compared with historical controls, this would suggest the potential to impart large clinical benefit and warrant larger controlled trials.

4. Study objectives

The primary objective of this study is to:

- Test the activity/response rate per RECIST 1.1 criteria of anetumab ravtansine in patients with advanced pancreatic cancer who stain for mesothelin expression

The secondary objectives of this study are to:

- Time to Progression (TTP) defined as time from study treatment to RECIST 1.1 progression, or death (others going off study will be censored)
- Toxicity in pancreatic cancer patients (at 6.5 mg/kg dose)

5. Study design

5.1 Design overview

This is a non-randomized, open-label, multicenter, Phase II study to evaluate the efficacy and safety of intravenous anetumab ravtansine (BAY 94-9343), an anti-mesothelin antibody drug conjugate, in pretreated mesothelin-expressing advanced pancreatic cancer.

At the time of the start of study treatment, the patients will have pretreated advanced pancreatic cancer that also overexpresses mesothelin as determined by immunohistochemistry (IHC). Mesothelin testing will be performed centrally.

A maximum of 30 patients will be enrolled in a minimax, Simon 2-stage design with a single early stopping rule for lack of efficacy. The target population is those patients with pancreatic cancer who have failed an earlier treatment. All patients will be treated with an anti-mesothelin immuno-conjugate, in this single arm, non-randomized trial and all patients treated with at least one dose of Anetumab will be included. The endpoint is any response using the RECIST 1.1 criteria.

The minimax, Simon 2-stage design testing 5% null hypothesis versus a 21% alternative requires a maximum of 30 patients. If there are no patients exhibiting any response among the first 20, which indicates a response rate less than 5%, then the trial will terminate early. If there is at least one response among the first 20 (indicating response rate of at least 5%) then the trial will accrue an additional 10 patients for a maximum of 30. Four or more responses out of 30 will reject the null hypothesis in favor of the 21% response alternative. These

criteria have significance level (alpha) 0.1 and power 90%. The probability of stopping early is 36% if the response rate is 5% or lower. The expected sample size is 26.4.

The start of the treatment period is defined by first administration of study drug (anetumab ravtansine). Patients will receive anetumab ravtansine IV infusion at a dose of 6.5 mg/kg (recommended Phase II dose [RPIID]) on Day 1 of a 21-day cycle. Treatment will be continued until death or occurrence of PD as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and assessed by blinded radiology review, or clinical progression, or until another criterion for withdrawal from the study is met.

Patients who discontinue study treatment for any reason other than confirmed radiological PD will be followed for progression during active follow-up (which includes the safety follow-up period) until confirmed PD for this patient is observed.

All patients who end study treatment for any reason will be followed for OS and the start of any new anti-cancer treatment every 3 months during the long-term follow-up period until data maturation for the OS final analysis is reached, or until death, consent withdrawal or end of study, whichever occurs first.

Primary efficacy will be assessed based on radiological tumor evaluation by contrast-enhanced computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI) of chest/abdomen/pelvis. During treatment as well as active follow-up, tumor imaging will be performed with the same modality to the extent possible, every 6 weeks during the first 6 months after the start of study treatment, every 9 weeks until the end of year 2, and every 12 weeks thereafter until RECIST confirmed radiological disease progression or end of study.

Safety evaluations will be done at full screening, at each clinic visit during the treatment period, and at the safety follow-up visit. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 will be used to grade severity of adverse events (AEs).

Patients will be contacted to assess survival status every 3 months during long-term follow-up. In addition, extra survival sweep contacts will be conducted at the time of PFS final analysis and prior to OS final analysis to ensure that long-term follow-up data is current.

5.2 Primary variable

The primary variable of this study is response rate as measured per RECIST 1.1 criteria.

6. Study population

6.1 Inclusion criteria

Patients eligible for inclusion into the study must meet the following inclusion criteria.

6.1.1 Eligibility criteria for prescreening

Prescreening can be performed without evidence of disease progression after the initial treatment at the investigator's discretion.

1. Written informed consent for prescreening.

2. Unresectable locally advanced or metastatic pancreatic cancer, confirmed by histology.
3. At least one but not more than two prior chemotherapy regimens with progression or documented intolerance (neoadjuvant or adjuvant chemotherapy would not be counted as a line of therapy. If prior radiation, measurable lesion outside radiation portal).
4. Availability of archival or fresh tissue for testing of mesothelin expression level.

   Note: Archival tissue is preferred and fresh biopsy should only be obtained if no archival tissue is available and if in the investigator's judgement, there is no additional risk for the patient's safety. Patients with a sarcomatoid histology are not expected to have mesothelin overexpression and should not enter prescreening.
5. Age ≥ 18 years.
6. Life expectancy of at least 3 months.
7. No prior treatment with anetumab ravtansine (or any other mesothelin-based therapy)

Besides these basic criteria, any criterion as outlined below under inclusion eligibility criteria for the full study and exclusion criteria already known to prohibiting the patient's participation in the study should be considered. No study-related procedures should be performed which are not covered by the prescreening ICF.

6.1.2 Eligibility criteria for full study

The following inclusion criteria must be met at the time of screening, prior to the start of study drug, unless otherwise specified.

1. Written informed consent for full study.
2. Histological documentation of overexpressing mesothelin at the moderate (2+) or stronger (3+) level in at least 30% of tumor cells as determined by IHC.
3. Unresectable locally advanced or metastatic pancreatic cancer
4. At least one but not more than two prior chemotherapy regimens with progression or documented intolerance (neoadjuvant or adjuvant chemotherapy would not be counted as a line of therapy. If prior radiation, measurable lesion outside radiation portal).
5. Patients must have at least 1 measurable lesion according to RECIST v 1.1 (specified in Section 9.4.1).
6. ECOG PS of 0 or 1 (specified in Appendix 16.1).
7. Life expectancy of at least 3 months.
8. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days before starting study treatment:

   - Total bilirubin ≤ 1.5 x the upper limit of normal (ULN). Documented Gilbert syndrome is allowed if total bilirubin is mildly elevated (< 6 mg/dL).
   - ALT and AST ≤ 2.5 x ULN (≤ 5 x ULN for patients with liver involvement of their cancer).
   - ALP limit ≤ 2.5 x ULN (≤ 5 x ULN for patients with liver involvement of their cancer).

- Extent of baseline tumor burden will not interfere with causal assessment of treatment-emergent hepatotoxicity, at the investigator's discretion.
- Amylase and lipase ≤ 1.5 x ULN.
- Glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease (MDRD) abbreviated formula (see Appendix 16.6).
- Adequate coagulation, as assessed by the following laboratory test results:
  - International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN (CTCAE Grade ≤ 1).
  - Partial thromboplastin time (PTT) or activated PTT (aPTT) ≤ 1.5 x ULN (CTCAE Grade ≤ 1).

    Note: Patients on stable dose of anti-coagulation therapy will be allowed to participate if they have no sign of bleeding or clotting and INR / PT and PTT / aPTT test results are compatible with the acceptable benefit-risk ratio at the investigator's discretion (see Section 8.1).
- Platelet count ≥ 75,000/mm^3 , without platelet transfusion within 3 weeks before the start of study treatment (see Section 8.1).
- Hemoglobin (Hb) ≥ 8 g/dL,

  Note: Patients receiving chronic low-dose erythropoietin for chronic renal failure are allowed provided no dose adjustment is undertaken within 6 weeks before signing consent for full study and until safety follow-up visit and provided that they fulfill conditions of eligibility criteria (see also exclusion criterion number 18).
- Absolute neutrophil count (ANC) ≥ 1000/mm^3

9. Left ventricular ejection fraction (LVEF) ≥ 50% or the lower limit of normal (LLN) according to local institution ranges of normality.

6.2 Exclusion criteria

Patients who meet the following criteria at the time of full screening and on C1D1 will be excluded:

1. Previous assignment to treatment during this study. Patients permanently withdrawn from study participation will not be allowed to re-enter the study.
2. Previous (within 5 drug half-lives – if drug half-life in subjects is known – or 28 days, whichever is shorter, before the start of study treatment) or concomitant participation in another clinical study with investigational medicinal product(s) (IMP[s]).
3. Patients with corneal epitheliopathy or any eye disorder that may predispose the patients to this condition at the discretion of the investigator.
4. Previous or concurrent cancer that is distinct in primary site or histology within 5 years. Exceptions: curatively treated
   - Cervical cancer *in situ*.

- Non-melanoma skin cancer.
- Superficial bladder tumors (Non-invasive tumor [Ta], Carcinoma *in situ* [Tis] and Tumor invades lamina propria [T1]).

5. Major surgery, open biopsy or significant traumatic injury within 28 days before the start of study treatment.
6. Pregnant or breast-feeding patients. WOCBP must have a serum pregnancy test performed a maximum of 7 days before the start of study treatment, and a negative result must be documented before the start of study treatment.
7. Pre-existing cardiac conditions as outlined below:
   - Congestive heart failure ≥ New York Heart Association (NYHA) class 2 (specified in Appendix 16.2).
   - Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months). Myocardial infarction less than 6 months before the start of study treatment.
   - Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted).
8. Clinically significant uncontrolled hypertension (systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management).
9. Arterial thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), or venous pulmonary embolism within 6 months before the start of study treatment; venous thrombotic events such as deep vein thrombosis within 3 months before the start of study treatment.
10. Ongoing or active infection (bacterial, fungal, or viral) of NCI-CTCAE version 4.03 Grade > 2.
11. Known history of human immunodeficiency virus (HIV) infection.
12. Known history of chronic hepatitis B or C.
13. Patients with seizure disorder requiring medication.
14. Symptomatic brain metastases or meningeal tumors or other uncontrolled metastases in the central nervous system (CNS) unless the patient
    - Is > 6 months from definitive therapy,
    - Has a negative imaging study within 4 weeks before study entry (ICF signature for full study) and
    - Is clinically stable with respect to the tumor at the time of study entry.
15. History of organ allograft, stem cells or bone marrow transplant.
16. Patients with evidence or history of bleeding diathesis. Any hemorrhage or bleeding event ≥ CTCAE Grade 3 within 4 weeks before the start of study treatment.
17. Non-healing wound, ulcer, or bone fracture.
18. Renal failure requiring peritoneal dialysis or hemodialysis.

19. Known hypersensitivity to anetumab ravtansine, study drug classes or excipients in the formulation.
20. Any illness or medical conditions that are unstable or could jeopardize the safety of the patient and his/her compliance in the study.
21. Unresolved toxicity higher than NCI-CTCAE version 4.03 Grade 1 attributed to any prior therapy/procedure excluding anemia or neuropathy Grade 2 (see Section 6.1.2, inclusion criterion 8) and alopecia of any Grade.
22. Any prohibited prior or concomitant therapy (see **Table 2-8** in Section 8.1).

6.3 Withdrawal of patients from study

6.3.1 Screening failure

6.3.1.1 Prescreening failure

A patient whose tumor tissue is tested by IHC for mesothelin overexpression and whose result is not moderate (2+) and stronger (3+) mesothelin overexpression in at least 30% of the tumor cells, or who fails to meet any of the other eligibility criteria for prescreening, is regarded as a "prescreening failure". These patients should not undergo any further screening procedures.

6.3.1.2 Full screening failure

A patient who passes the prescreening, including the mesothelin overexpression testing, but for any other reason (e.g., failure to satisfy the remaining selection criteria) terminates the study before enrollment is regarded as a "full screening failure". See Section 11.1 for data to be collected for screening failures.

Re-starting the defined set of screening procedures to enable the "screening failure" patient's participation at a later time point is not allowed – with the following exceptions:

- The patient had successfully passed the screening procedures, but could not start subsequent treatment on schedule.
- Initial screening occurred too early to complete the required washout period after prior therapy.
- The in- / exclusion criteria preventing the patient's initial attempt to participate have been changed (via protocol amendment).
- Equivocal screening results require further testing for clarification even if, for logistical reasons, the further testing cannot be performed within the allocated time window (e.g. equivocal laboratory creatinine clearance requiring formal creatinine clearance measurement).
- Resolution of toxicity, now meeting all criteria

In any case, the investigator has to ensure that the repeated screening procedures do not expose the patient to an unjustifiable health risk. Also, for re-screening, the patient has to resign the main consent document (for the full study), even if it was not changed after the patient's previous screening.

6.3.2 Withdrawal criteria

All patients who enter the study should complete all phases of the study unless they are screen failures or meet the criteria for withdrawal. Phases of the study include:

1. Prescreening
2. Full screening
3. Registration
4. Treatment
5. Safety follow-up
6. Active follow-up
7. Long-term follow-up

Study treatment discontinuation (i.e., discontinuation during the treatment period) does not constitute withdrawal from the study.

Every effort should be made to retain patients who discontinue the treatment period for any reason. These patients are to be encouraged to remain on the study for follow-up of primary, secondary and other objectives (i.e., continue in the safety follow-up, active follow-up and/or long-term follow-up periods).

Patients are expected to participate in the follow-up unless they explicitly object. Withdrawal of consent to treatment should be documented in the patient's medical record. If the patient does not wish to be followed up further, this additional consent withdrawal for follow up would have to be documented, too.

Withdrawal from study treatment, active follow-up and long-term follow-up

Patients withdrawn from **the study treatment** phase of the study should be followed for primary, secondary and other objectives (i.e. continue in the safety follow-up, active followup and/or long-term follow-up periods) (see Figure 2-1 for withdrawal criteria).

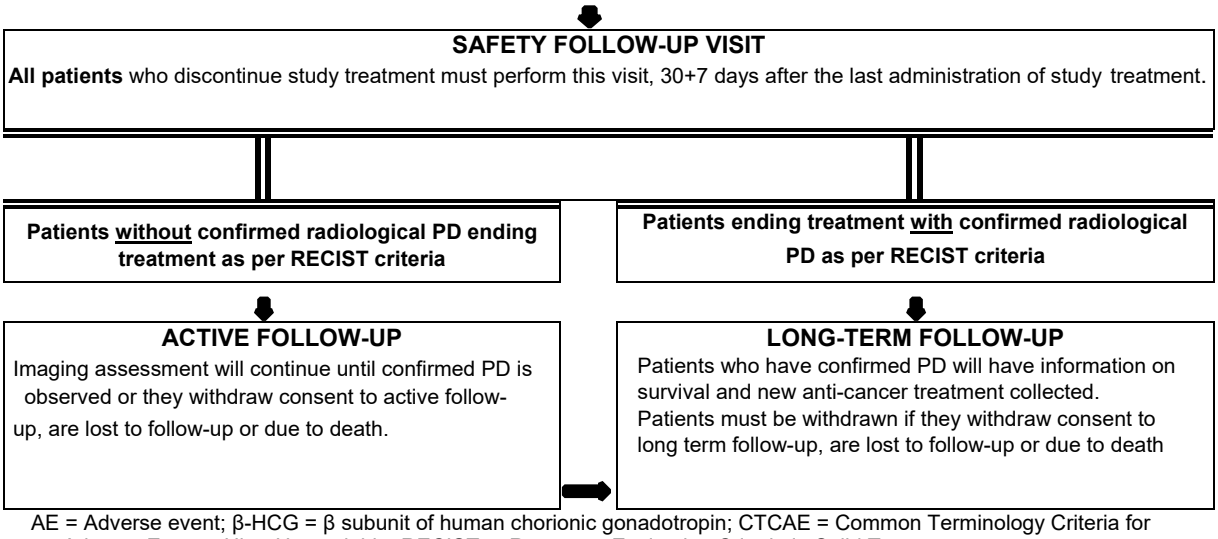
Figure 2-1 Withdrawal criteria

PATIENTS MUST BE WITHDRAWN FROM THE STUDY TREATMENT IF ANY OF THE FOLLOWING OCCURS:

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a patient may decline to participate further. The patient will not suffer any disadvantage as a result.
- If, in the investigator's opinion, continuation of the study treatment would be harmful to the patient's well-being.
- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).
- Confirmed radiological PD as per RECIST criteria.
- Clinical progression as assessed by investigator. Occurrence of unacceptable toxicity to anetumab ravtansine (see also Section 7.3.2).
- CTCAE Grade 4 hypersensitivity and acute infusion reaction.
- An adverse reaction deemed sufficiently serious to warrant discontinuation of treatment by the investigator or his designated associate(s).
- Development of a secondary malignancy.
- Patient starts treatment with any other anti-cancer therapy or any other prohibited medication as per Section 8.1.
- Positive serum β-HCG test consistent with pregnancy. Pregnancy should be reported along the same timelines as an SAE.
- Use of illicit drugs or other substances that may, in the opinion of the investigator or his designated associate(s), have a reasonable chance of contributing to toxicity or otherwise confound the results.
- Development of any intercurrent illness or situation which may, in the judgment of the investigator, affect assessments of clinical status and study endpoints to a relevant degree.
- Lost to follow-up.
- Death.

Patients must be withdrawn from **treatment with anetumab ravtansine** if any of the following occurs:

- CTCAE Grade 4 non-hematological AE and Bayer Grade 4 corneal toxicity (see Table 2-6) (except at the investigator's discretion in case of certain Grade 4 abnormality of laboratory assessments, such as abnormal laboratory assessments without corresponding clinical symptoms, or abnormal laboratory assessments that can be easily clinically managed).
- If any type of TEAE requiring dose modification does not resolve to Grade ≤ 1 (or Hb ≥ 8 g/dL in case of anemia) within 6 weeks after the last dose of anetumab ravtansine.
- Delay in anetumab ravtansine administration of 3 weeks (max. 6 weeks between 2 infusions of study drug).
- TEAE requiring dose reduction when already at the 4.5 mg/kg Q3W dose level (minimum dose).
- More than 2 dose reductions required due to a TEAE.



AE = Adverse event; β-HCG = β subunit of human chorionic gonadotropin; CTCAE = Common Terminology Criteria for Adverse Events; Hb = Hemoglobin; RECIST = Response Evaluation Criteria in Solid Tumors; PD = Progressive disease; Q3W = Every 3 weeks; SAE = Serious adverse event; TEAE = Treatment-emergent adverse event

6.3.3. Lost to follow-up patients

When a patient is lost to follow-up at any stage of the study, the site should try to contact the patient, the patient's relatives, or another doctor treating the patient, unless prohibited by local regulations. All attempts to contact the patient or relatives should be documented.

6.3.4 General withdrawal procedures

In all cases, the reason for withdrawal must be recorded in the CRF and in the patient's medical records.

The patient may object to the generation and processing of post-withdrawal data as specified below.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12.

6.3.5 Replacement

No replacement of patients will be allowed during this study.

6.4 Patient identification

After a patient has signed the prescreening consent form, the coordinating center will provide a patient identification number to be entered into OnCore (Clinical Trials Management System).

7. Treatment(s)

7.1 Treatments to be administered

All patients who meet the entry criteria will receive the test drug anetumab ravtansine, considered to be an IMP: anetumab ravtansine 6.5 mg/kg IV Q3W

7.2 Identity of study treatment

All study drugs will be labeled according to the requirements of local law and legislation.

Anetumab ravtansine will receive study-specific labeling and will be provided by the sponsor.

For all study drugs, a system of numbering in accordance with all requirements of GMP will be used, ensuring that each dose of study drug can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by Bayer's clinical supplies quality assurance (QA) group.

A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor's study file.

7.2.1 Test drug - anetumab ravtansine

Anetumab ravtansine is an ADC consisting of a fully human IgG1 antibody (MF T, BAY 861903) directed at the mesothelin antigen and conjugated to a synthetic maytansine derivative as toxophore (DM4, BAY 100-6640) through a reducible disulfide linker (SPDB linker).

The details of the investigational drug are given in **Table 2-1**.

Table 2-1 Identity of anetumab ravtansine

Chemical name	Mesothelin antibody-drug conjugate: Immunoglobulin G1, anti-(human mesothelin) human monoclonal MF-T-IgG1 heavy chain, disulfide with human monoclonal MF-T-IgG1 □-chain, dimer, triamide with N2′-[4-[(3-carboxypropyl) dithio]-4-methyl-1oxopentyl]-N2′-deacetylmaytasine
Substance code number(s)	BAY 94-9343
Appearance	
Freeze-dried drug product	White to off-white lyophilized cake or powder
Reconstituted solution	Clear or slightly opalescent solution
Formulation	Freeze-dried product in a 30 mL injection vial, containing 5 mg/mL of active ingredient after reconstitution
Composition	Anetumab ravtansine / BAY 94-9343 / L-histidine / glycine / sucrose / polysorbate 80 / 1 N HCl
Type of packaging and content	30 mL injection vial

IgG1 = Immunoglobulin G subclass 1; N HCl = Normal hydrochloric acid

The drug product is available as a lyophilizate. Each vial contains 62.5 mg of anetumab ravtansine; the amount available for administration, based on retractable volume of reconstituted solution, is 60 mg of anetumab ravtansine. It should be reconstituted in water for injection and diluted in 0.9% sodium chloride solution (normal saline) prior to administration as IV infusion.

The drug product is to be stored at 2°C to 8°C (36°F to 46°F).

7.2.1.1 Reconstitution

The drug product should be reconstituted and processed under aseptic conditions (i.e. qualified laminar flow unit and trained personnel) to preclude microbial contamination.

Using a sterile syringe, gently add 11.9 mL of water for injection through the middle of the stopper to the freeze-dried product into the 30 mL injection vial to obtain a solution (approximate reconstituted volume is 12.5 mL). During reconstitution, make sure that the needle does not come into contact with the cake or resulting solution; avoid shaking. The lyophilizate should dissolve completely.

The reconstituted lyophilizate may be diluted only after the solution is clear.

Dilution of the reconstituted solution

Dilution of the reconstituted solution with 0.9% sodium chloride solution (normal saline) should be done under aseptic conditions (i.e. qualified laminar flow unit and trained personnel) to preclude microbial contamination. A slight turbidity may occur during the dilution which does not affect the quality of the drug product. Pharmacy will consider the use of inline filters for subsequent administrations.

Stability of the reconstituted solution

Exposure to bright light should be avoided; standard room illumination does not necessitate any precautions.

The reconstituted solution is physically and chemically stable for 24 h at room temperature and between 2°C and 8°C. However, unless administered immediately, for microbiologic consideration, the reconstituted solution should be stored between 2°C and 8°C and used within 6 h according to USP 797 "Pharmaceutical Compounding – Sterile preparations". If not reconstituted under aseptic conditions, the solution should be used immediately or stored at 2°C to 8°C and used within 1 h, according to USP 797.

If frozen or stored above 25°C (77°F), the solution should be discarded.

Stability of the diluted solution

Exposure to bright light should be avoided; standard room illumination does not necessitate any precautions.

Stability investigations have shown that if diluted under aseptic conditions, concentrations between 0.1 and 3.0 mg/mL are stable for the period of use (24 h) at room temperature and between 2°C and 8°C. However, unless administered immediately, for microbiologic consideration, diluted solution should be stored between 2°C and 8°C and used within 6 h according to USP 797 "Pharmaceutical Compounding – Sterile preparations".

If not diluted under aseptic conditions, the solution should be used immediately or stored at 2°C to 8°C and used within 1 h, according to USP 797.

If frozen or stored above 25°C, the solution should be discarded.

Refer to IB for anetumab ravtansine for details regarding drug properties and formulation.

7.3 Dosage and administration

7.3.1 Administration of anetumab ravtansine

After reconstitution and dilution (as described in Section 7.2.1), anetumab ravtansine will be administered as a 1-hour IV infusion every 3 weeks on Day 1 of each 21-day cycle until confirmed radiological PD by RECIST 1.1, clinical progression as assessed by investigator, or any other criteria for withdrawal of treatment.

The individual dose will be 6.5 mg/kg per infusion from Cycle 1 onwards. In obese patients, anetumab ravtansine dose should be calculated considering a maximum weight of 100 kg.

Strict IV administration has to be ensured to avoid local intolerance reactions. After completion of the 1-hour anetumab ravtansine infusion, the infusion line will be rinsed with ≥ 100 mL of 0.9% saline solution to be administered as a short infusion.

See Section 9.1 for details on scheduled administrations.

7.3.2 Dose modification

The NCI-CTCAE v4.03 will be used to assess toxicities; in addition, a Bayer grading system (see **Table 2-6** and **Table 2-7**) will be used to assess corneal toxicity.

TEAE requiring dose modification (temporary treatment interruption, dose reduction, or permanent discontinuation of treatment) will be defined as any of the events described below that is possibly, probably, or definitely related to anetumab ravtansine and occurs anytime during the study (not only in Cycle 1).

The dose reduction levels of anetumab ravtansine will follow pre-defined dose levels shown in **Table 2-2**.

Table 2-2 Dose levels of anetumab ravtansine

Dose level 1 (starting dose):	6.5 mg/kg Q3W
Dose level -1:	5.5 mg/kg Q3W
Dose level -2:	4.5 mg/kg Q3W

Q3W = Every 3 weeks

7.3.2.1 Hematological toxicities

Dose modifications for hematological toxicity

- If treatment modification is required due to a hematological TEAE, and the continuation of treatment is appropriate, the anetumab ravtansine dose will be adjusted as described in **Table 2-3** and **Table 2-4** below.
- G-CSF and other hematopoietic growth factors may be used during the study in the management of acute toxicity such as febrile neutropenia when clinically indicated per ASCO Recommendations for Therapeutic Use of CSF (26) or at the discretion of the investigator; however, they may not be substituted for a required dose reduction.
- Blood transfusions and therapy with IV or subcutaneous erythropoietin-stimulating agents (epoetin alpha, darbepoetin alpha) are allowed per institution guidelines but may not be used as substitute for a required dose reduction (see also **Table 2-8**).
- Platelet transfusion may be used during the study in the management of acute toxicity such as hemorrhage or bleeding events, however they may not be used as substitute for a required dose reduction.

Table 2-3: Dose adjustments in response to neutrophil and platelet nadir [a] counts of the previous cycle

Absolute neutrophil nadir count of the previous cycle (/mm^3)		**Platelet nadir count of the previous cycle (/mm^3)**	**Anetumab ravtansine dose adjustment [b]**
≥ 500 or < 500 for < 7 days	and	≥ 25,000	No change
< 500 for ≥ 7 days	and/	< 25,000 regardless of the presence of active bleeding (or ≥ 25,000 with clinically significant bleeding, i.e. bleeding requiring platelet transfusion)	Decrease 1 dose level [b]
Febrile neutropenia [c]	and/	< 25,000 regardless of the presence of active bleeding (or ≥ 25,000 with clinically significant bleeding, i.e. bleeding requiring platelet transfusion)	Decrease 1 dose level [b]

ANC = Absolute neutrophil count; C = Cycle; CBC = Complete blood count; D = Day; Q3W = Every 3 weeks

a Site visits and blood test for CBC (and biochemistry) on D8 and D15 will be performed on C1, C2 and C3 only. From Cycle 4 onwards, visits and procedures on D8 and D15 are no longer required.

b Dose reduction by 1 dose level translates to a change from 6.5 mg/kg Q3W to 5.5 mg/kg Q3W, or from 5.5 mg/kg Q3W to 4.5 mg/kg Q3W. Not more than 2 dose reductions from the starting dose level are permitted.

c Febrile neutropenia is defined as ANC < 1000/mm^3 and fever (a single body temperature reading of > 38.3°C [101°F] or a sustained body temperature of ≥ 38°C [100.4°F] for more than 1 hour).

Table 2-4: Dose adjustments in response to pre-infusion values

Absolute neutrophil count (/mm^3)	**Platelets (/mm^3)**	**Hemoglobin (g/dL)**	**Treat**	**Anetumab ravtansine dose adjustment**
≥ 1,000	and	≥ 75,000	Treat on time	Adjust dose by nadir [a] counts in previous cycle per investigator's discretion
< 1,000	and	< 75,000	Delay until ANC ≥ 1.0 and platelets ≥ 75,000[b]	Decrease by 1 dose level [c]
		< 8	Delay until Hb ≥ 8 [b]	Re-start at the same dose or decrease by 1 dose level [c] (at investigator's discretion)

ANC = Absolute neutrophil count; C = Cycle; CBC = Complete blood count; D = Day; Hb = Hemoglobin; Q3W = Every 3 weeks; TEAE = Treatment-emergent adverse event

a Site visits and blood test for CBC (and biochemistry) on D8 and D15 will be performed on C1, C2 and C3 only. From Cycle 4 onwards, visits and procedures on D8 and D15 are no longer required.

b Treatment will be discontinued if the TEAE fails to resolve to Grade ≤ 1 (or Hb ≥ 9 g/dL in case of anemia) within 6 weeks after the last dose of anetumab ravtansine.

c Dose reduction by 1 dose level translates to a change from 6.5 mg/kg Q3W to 5.5 mg/kg Q3W, or from 5.5 mg/kg Q3W to 4.5 mg/kg Q3W. Not more than 2 dose reductions from the starting dose level are permitted.

7.3.2.2 Non-hematological toxicities

Non-hematological toxicities requiring dose or infusion modification

- CTCAE Grade 2 or Grade 3 anetumab ravtansine infusion reaction or other CTCAE Grade 2 or Grade 3 hypersensitivity events (see Section 7.3.2.1.3)
- AST and/or ALT increase > 5.0 x ULN (CTCAE Grade ≥ 3)
- AST and/or ALT increase > 3.0 x ULN (CTCAE Grade ≥ 2) with concomitant increase in total bilirubin > 1.5 x ULN (CTCAE Grade ≥ 2)
- Total bilirubin > 3.0 x ULN (CTCAE Grade ≥ 3)
- Bayer Grade ≥ 3 corneal toxicity (see below and **Table 2-6**)
- Any other Grade ≥ 3 non-hematological toxicity that, in the investigator's opinion, warrants treatment modification (see **Table 2-5**), **excluding** the following:
    - Nausea, vomiting, or diarrhea if manageable with anti-emetics or antidiarrheals within 7 days
    - Hair loss
    - Fatigue lasting ≤ 72 h
    - Certain asymptomatic laboratory assessments without a clear clinical correlate, if the investigator determines that this TEAE would not require treatment modification
- Any other toxicity irrespective of the type or severity that represents a clinically significant risk to patient in the investigator's opinion.

Dose modifications for non-hematological toxicity

If treatment modification is required due to a **non-hematological TEAE** as listed above, other than corneal toxicity and infusion reaction/hypersensitivity events, and the continuation of treatment is appropriate, the anetumab ravtansine dose will be either reduced or maintained as is at investigator's discretion (see **Table 2-5**).

Table 2-5: Dose adjustments in response to non-hematologic toxicities

CTCAE v4.03 grade	Anetumab ravtansine dose delay / interruption	Anetumab ravtansine dose modification
Grade 1 – 2 [a]	Treat on time	No change required (at investigator's discretion)
Grade 3	1st appearance: Delay/Interruption until Grade ⩽ 2 [b] 2nd appearance: Delay/Interruption until Grade ⩽ 2 [b] 3rd appearance: Permanently discontinue	Re-start at the same dose or decrease by 1 dose level [c] (at investigator's discretion) Decrease by 1 more dose level [c]
Grade 4	Permanently discontinue	

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; Q3W = Every 3 weeks; TEAE = Treatment-emergent adverse event

a AST and/or ALT increase of CTCAE Grade 2 with concomitant increase in total bilirubin of CTCAE Grade 2 will be treated as a CTCAE Grade 3 event.

b Treatment will be discontinued if the TEAE fails to resolve to Grade ⩽ 1 within 6 weeks after the last dose of anetumab ravtansine.

c Dose reduction by 1 dose level translates to a change from 6.5 mg/kg Q3W to 5.5 mg/kg Q3W, or from 5.5 mg/kg Q3W to 4.5 mg/kg Q3W. Not more than 2 dose reductions from the starting dose level are permitted.

The anetumab ravtansine dose reduction due to non-hematological TEAE will be done as described below:

- If the patient experienced a TEAE requiring dose reduction at the 6.5 mg/kg Q3W dose level, the subsequent anetumab ravtansine dose should be reduced to 5.5 mg/kg Q3W.
- If the patient experienced a TEAE requiring dose reduction at the 5.5 mg/kg Q3W dose level, the subsequent anetumab ravtansine dose should be reduced to 4.5 mg/kg Q3W.

After dose reduction, there could be no intra-patient dose escalation irrespective of the type of TEAE that has led to dose reduction in this patient.

7.3.2.3 Miscellaneous toxicities

IV infusion reaction and other hypersensitivity events

If a patient experiences a CTCAE Grade 2 or Grade 3 anetumab ravtansine infusion reaction or other CTCAE Grade 2 or Grade 3 hypersensitivity event deemed at least possibly related to anetumab ravtansine, the infusion of anetumab ravtansine will be interrupted.

If treatment interruption is caused by a CTCAE Grade 2 or Grade 3 anetumab ravtansine infusion reaction or other CTCAE Grade 2 or Grade 3 hypersensitivity event deemed at least possibly related to anetumab ravtansine, treatment may be re-started at the time determined at the investigator's discretion. Re-treatment should be at the infusion rate reduced by 50%, along with anti-allergic prophylaxis (e.g. anti-histamines, acetaminophen, and/or corticosteroids) chosen at the investigator's discretion or according to the institutional guidelines.

Miscellaneous toxicities requiring dose modification

For any toxicity ≤ Grade 2 assessed as related to anetumab ravtansine by the investigator, dose modification should be considered. Such toxicities might be ≤ Grade 2 toxicities which interfere with the activities of daily life, such as long lasting fatigue, or anorexia, or corneal toxicity with vision impairment etc. A dose change might be necessary in order to ensure the patient's compliance. These toxicities may be declared "TEAE requiring treatment modification" after consultation between the investigator and the sponsor.

Dose modifications for corneal toxicity

For the TEAE of corneal morphology changes and the best corrected visual acuity (BCVA) changes (blurred vision), the Bayer severity grading system (see **Table 2-6** and **Table 2-7**) will be used to assess the severity of TEAEs requiring modification of anetumab ravtansine treatment.

TEAE of corneal morphology changes deemed to be at least possibly related to anetumab ravtansine would require modification of anetumab ravtansine treatment (dose reduction or permanent discontinuation of treatment) according to the following principles (see **Table 2-6**).

Table 2-6: Bayer classification and management of corneal epitheliopathies

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Corneal Morphology	No pathologic changes	Any stage of superficial punctate keratitis [a]	Epithelial opacities Micro-Cysts Micro-deposits Corneal erosion Corneal erosion Stromal opacity: non-central	Corneal ulcer without risk of acute rupture Stromal opacity: central	Corneal ulcer more severe than Grade 3

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Eye Treatment [b]	Ocular lubricants at the discretion of investiga-tor, in consult with ophthalmo-logist	Ocular lubricants; add topical steroids if superficial punctate keratitis shows treatment-emergent progression by $\geqslant$ 2 SPK Grades	Intensive Treatment with ocular lubricants enhanced with ointments; topical steroids; therapeutic contact lens may be considered at the discretion of investigator in consult with ophthalmo-logist	Intensive therapy with ointments; topical steroids; therapeutic contact lens or occlusion recomme-nded at the discretion of investigator in consult with ophthalmo-logist	Intensive therapy with lubricants, ointments, topical steroids and antibiotics as needed; occlusion or therapeutic contact lens recommended; amniotic membrane transplant and other locally approved therapies to be considered at the discretion of investigator in consult with ophthalmo-logist

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Anetumab ravtansine[c]	No change	No change	Keep treatment dose level and schedule if the ophthalmol-ogical exam can be performed as needed; otherwise consider dose reduction by -1 dose level without dose schedule change at the discretion of investigator in consult with ophthalmologist	1) Decrease dose to -1 dose level (or -2 dose level if event does not resolve to Grade $\leqslant$ 2 at the -1 dose level within 3 weeks) 2) Re-start at the original dose level if the first Grade 3 event resolves to Grade $\leqslant$ 2 within 3 weeks and does not recur 3) If not resolved within 3 weeks continue at reduced -2 dose level (or -3 dose level)	Discontinue treatment

SPK = Superficial punctate keratitis a Oxford Schema must be used for grading SPK from stage 0 to VI.

b Other remedial therapies for corneal epitheliopathy may be added or substituted at investigator's discretion or according to the institutional standards.

c Treatment decisions are based on corneal morphology changes only, not on visual acuity changes.

Table 2-7: Bayer classification of visual acuity changes

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Visual acuity	No findings, no reporting from the patient	Symptomatic visual acuity loss < 3 lines (ETDRS Equivalent [a])	Visual acuity loss ⩾ 3 lines, but < 6 lines (ETDRS equivalent [a])	Visual acuity loss ⩾ 6 lines (ETDRS equivalent [a]	Visual acuity loss ⩾ 6 lines (ETDRS equivalent [a]) leading to blindness

ETDRS = Early Treatment Diabetic Retinopathy Study

a In the ETDRS chart, each loss of 3 lines corresponds to halving the visual acuity. In other charts, an equivalent amount of visual acuity loss must be reached in order to meet this threshold.

Recommended measures in case of eye dryness and ocular hypertension

Changes in tear production as evaluated by the Schirmer test and in intraocular pressure (IOP) are not expected to occur as a direct consequence of anetumab ravtansine therapy. However, IOP may increase in some patients as a consequence of the therapy with topical steroid eyedrops. Since these drugs may be required to manage the corneal epitheliopathy syndrome, IOP will be monitored during this study for patients receiving topical steroid eyedrops.

Changes in IOP should be managed by the investigator following exam by an ophthalmologist. The remedial therapy should be chosen at investigator's discretion or according to the institutional standards; therapeutic measures can include modification of the type or posology of topical steroid eye drop, initiation of topical IOP lowering drugs and any other therapeutic options according to the local SoC. Ophthalmological monitoring should be maintained until the IOP has returned to normal values.

Reductions in tear production evaluated by the Schirmer test, while not being a part of the corneal epitheliopathy syndrome, are a risk factor for developing ocular surface disease including corneal epithelial defects. Therefore, the tear production will be evaluated in this study to determine if changes in this parameter may be helpful to identify patients at higher risk of developing the corneal epitheliopathy syndrome. Abnormal values in the Schirmer test should be evaluated and managed by the investigator following exam by an ophthalmologist to provide adequate protection to the corneal epithelium. The remedial therapy for the treatment-emergent changes in the Schirmer's test (dry eye) should be chosen at investigator's discretion or according to the institutional standards. These measures may include topical lubricants such as eye drops and ointments, punctual occlusion, use of therapeutic contact lenses and any other treatment approaches according to the local SoC.

7.3.2.4 Continuation of treatment with anetumab ravtansine

Treatment with anetumab ravtansine could be re-started at the appropriate dose if the TEAE requiring dose modification has resolved to Grade < 2 within 6 weeks after the last dose of anetumab ravtansine.

7.3.2.5 Permanent discontinuation of anetumab ravtansine due to TEAEs

See Section 6.3.1.2 for withdrawal criteria.

7.4 Drug logistics and accountability

All study drugs will be stored at the investigational site in accordance with GCP and GMP requirements and the instructions given by the clinical supplies department of the sponsor, and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor's study file; the site-relevant elements of this information will be available in the investigator site file. The personnel will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

The Yale Cancer Center (YCC) will be the coordinating center for the distribution of drugs or supplies to the participating institution(s). The Investigational Drug Service (IDS) at Yale-New Haven Hospital will be employed to serve as the central pharmacy. Distribution of drugs and supplies will be conducted in adherence with the established policies of Yale-New Haven Hospital and Medical Center

The study drug will be provided by Bayer and shipped to the IDS at Yale-New Haven Hospital which will then distribute to the collaborating sites. Drug vials will be provided by Bayer with a generic non-study specific label on the cartons containing the vials. Any study specific labeling to the vials to meet local requirements will need to be done by the IDS. The vials will be distributed to collaborating sites as required by IDS.

The number of vials used will be recorded on the appropriate treatment dispensing form. Reasons for dose delay and reduction will be recorded in the source documents and on the CRF.

Treatment accountability on patient level must be verified at every cycle, starting on C1D1. The monitor will review overall drug accountability and destruction per the site documentation only.

Written instructions on medication destruction will be made available to affected parties as applicable.

7.5 Treatment compliance

The administration of anetumab ravtansine will be performed in the clinic on Day 1 of each 21-day cycle for anetumab ravtansine. Each administration must be recorded on the CRF and Drug Dispensing / Accountability Form.

Reasons for dose delay, reduction, or omission will also be recorded in the source documents and on the CRF.

An adequate record of receipt, distribution, and return of all study drugs must be kept in the form of a Drug Accountability Form.

The preparation and administration of anetumab ravtansine will be performed by members of the investigator team during hospitalization and site visits. These persons will ascertain and document that the patient receives all treatments as planned.

Patient compliance with the treatment and protocol includes willingness to comply with all aspects of the protocol, and to have blood collected for all safety evaluations. At the discretion of the principal investigator or sponsor, a patient may be discontinued from the study treatment for non-compliance with visits or study drug.

8. Non-study therapy

8.1 Prior and concomitant therapy

Any medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study treatment, may be given at the discretion of the investigator. In general, patients should be closely monitored for side effects of all concomitant medications regardless of elimination path, especially those with narrow therapeutic indices, such as warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporine, and digoxin. From signing of consent for full study to safety follow-up visit, all concomitant medications (including start/stop dates, dose, frequency, route of administration and indication) must be recorded in the patient's source documentation, as well as on the appropriate pages of the CRF. At prescreening and during active follow-up period, only concomitant medications that are administered to treat AEs related to study-specific procedures are mandatory to be reported. Administration of contrast media for protocol-specified radiological procedures (CT scan or MRI) does not need to be reported on the concomitant medication CRF page, unless there is an AE related to the contrast medium injection (e.g. allergic reaction).

Prohibited prior and concomitant therapies and permitted concomitant therapies are listed in **Table 2-8** and **Table 2-9**, respectively.

Table 2-8 Prohibited prior and concomitant therapies

Prohibited prior and concomitant therapy (see also Section 6.2)	Time period when	Comments prohibited
Prohibited for all patients		
Anetumab ravtansine (or any other mesothelin-based therapy)	Prior to study treatment	
Other systemic anticancer treatment (except study treatment) (cytotoxic therapy, targeted therapies, immunotherapy, hormonal therapy, or any other experimental or approved therapy)	Prior to study treatment until safety follow-up visit	
Use of biologic response modifiers, such as G-CSF	Within 6 weeks before the start of study treatment	G-CSF and other hematopoietic growth factors may be used during the study in the management of acute toxicity such as febrile neutropenia when clinically indicated per ASCO Recommendations for Therapeutic Use of CSF (26) or at the discretion of the investigator or according to local label guidance (if medically necessary, growth factors may be administered at recommended doses no earlier than 24 h after and not in the 24 h before anetumab ravtansine administration; see also (27); however they may not be substituted for a required dose reduction).
Blood transfusions and chronic therapy with IV or subcutaneous erythropoietin-stimulating agents (epoetin alpha, darbepoetin alpha)	Within 6 weeks before the start of study treatment. Thereafter, they are allowed per institution guidelines but may not be used as substitute for a required dose reduction.	Patients receiving chronic low-dose erythropoietin for chronic renal failure are allowed provided no dose adjustment is undertaken within 6 weeks before signing consent for full study and until safety follow-up visit and provided that they fulfill conditions of inclusion criterion number 7 and exclusion criterion number 18.
Platelet transfusions	Within 3 weeks before the start of study treatment. Thereafter, they may not be used as substitute for a required dose reduction.	
Anti-arrhythmic therapy other than beta blockers or digoxin		
Acute steroid therapy or taper		Chronic steroid therapy is acceptable, provided that the dose is stable for 1 month before the start of study treatment and thereafter.
Radiotherapy	Within 4 weeks before the start of screening for full study	Except for pain control, see below in Table 2-9. Patients must have recovered from all therapy-related toxicities. The site of previous radiotherapy should have evidence of PD if this is the only site of disease: measurable pleural disease should be assessed on a contrast enhanced CT/MRI done at

Prohibited prior and concomitant therapy (see also Section 6.2)	Time period when	Comments prohibited
		the minimum 4 weeks after the end of RT and compared with previous imaging; unequivocal progression should be judged by the investigator as per mRECIST per MPM.
Drugs with known bone marrow toxicity		
Strong inhibitors and strong inducers of CYP3A4 (listed in Appendix 16.5), including: - Herbal preparations containing CYP3A4 inducers (e.g. St John's Wort) - Grapefruit and grapefruit juice (CYP3A4 inhibitor)	Within 2 weeks before the start of study treatment until the safety follow-up visit	DM4 is a substrate of CYP3A4. During study treatment, moderate and weak CYP3A4 inducers should be used with caution as decrease in plasma concentrations of DM4 cannot be ruled out.

ASCO = American Society of Clinical Oncology; CSF = Colony stimulating factor; CT = Computed tomography; CYP3A4 = Cytochrome P450, family 3, subfamily A, polypeptide 4; DM4 = Derivatives of maytansine 4; GCSF = Granulocyte-colony stimulating factor; IV = Intravenous; MPM = Malignant pleural mesothelioma; mRECIST = Modified Response Evaluation Criteria in Solid Tumors; MRI = Magnetic resonance imaging; PD = Progressive disease; RT = Radiotherapy

Table 2-9 Permitted concomitant therapies

Permitted concomitant therapies	Comments
Permitted for all patients	
Oral and parenteral anti-coagulant agents, e.g. heparin, enoxaparin, warfarin, rivaroxaban, dabigatran, apixaban or aspirin at a dose ≤ 100 mg	Allowed if continued maintenance therapy is necessary at the investigator's discretion and provided that they fulfill conditions of inclusion criterion number 8 (Section 6.1.2).
Institutional standards for the management of infusion reactions	May be utilized at the discretion of the investigator. Pre-treatment with anti-nausea medication is allowed at the investigators discretion. See anti-emetic note below.
Palliative radiotherapy for pain control	Allowed provided that: - In the opinion of the investigator, the patient does not have PD, - No more than 10% of the patient's bone marrow is irradiated, - The radiation field does not encompass a non-pleural target lesion or a pleural measurable lesion, - The radiation field does not encompass a lung field (to reduce the risk for interstitial lung disease [ILD] caused by irradiation pneumonitis), and - Anetumab ravtansine administration is interrupted during radiotherapy. Study treatment can be restarted after end of radiotherapy, provided all requirements outlined in Section 7.3 of this protocol are taken into account. The maximum interruption period for both drugs should not be exceeded.

Permitted concomitant therapies	Comments
Standard therapies for concurrent medical conditions	
Prophylactic standard anti-emetics	May be administered according to standard practice: dexamethasone plus 5-HT3 blockers, such as granisetron, ondansetron, or an equivalent agent, are allowed on "as needed" basis.
Treatment with non-conventional therapies (for example herbs, except St John's Wort, or endpoints, in the opinion of the	investigator. acupuncture), and vitamin/mineral supplements Acceptable provided that they do not interfere with the study
Bisphosphonates or denosumab, with supplement of calcium and vitamin D	
Palliative (e.g. analgesics) and supportive care (e.g. nutritional therapy) for other disease-related symptoms and for toxicity associated with treatment	
Strong P-gp inhibitors (e.g. amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil)	DM4-Me (metabolite of DM4) is a P-gp substrate. Caution should be exercised with concomitant administration of strong P-gp inhibitors. If anetumab ravtansine must be co-administered with a strong P-gp inhibitor, then the patient should be carefully monitored or the strong P-gp inhibitor replaced at investigator's discretion.
Narrow therapeutic index medications	Patients taking narrow therapeutic index medications should be monitored proactively, if these medications cannot be avoided.
Beta blockers or digoxin	Permitted for patients with cardiac arrhythmias requiring therapy

5-HT3 = 5-hydroxytryptamine (serotonin); DM4 = Derivatives of maytansine 4; DM4-Me = Methyl-DM4; ILD = Interstitial lung disease; PD = Progressive disease; P-gp = Permeability glycoprotein

All prior anti-cancer therapies, and all concomitant therapies including ophthalmological therapies as of full screening will be recorded on the CRF. At prescreening and during active follow-up period, only concomitant medications that are administered to treat AEs related to study-specific procedures are mandatory to be reported.

8.2 Post-study therapy

At the end of study treatment, further therapy is at the discretion of the investigator.

No results are available from human interaction studies between anetumab ravtansine and other chemotherapies. No data are available to evaluate the potential interaction between anetumab ravtansine and radiation treatment. Therefore, when administering these agents after study treatment is withdrawn, it should be taken into consideration that anetumab ravtansine, DM4 or DM4-Me levels may be detectable for several weeks and could interact with chemotherapy and radiotherapy including palliative radiotherapy as outlined in **Table 2-9** following discontinuation of anetumab ravtansine.

Once the expected final number of events is reached and results are available, the remaining patients on anetumab ravtansine treatment, who are considered by the investigator to benefit from continued anetumab ravtansine treatment, can be continued in the trial until disease progression.

9. Procedures and variables

9.1 Tabular schedule of evaluations

Schedule of procedures is presented in Table 2-10 below

Table 2-10: EVALUATION SCHEDULE

Day / **Cycle**	**Pre-Screening**	**Screening[c]**	**1** / **1**	**8** / **1**	**15**	**1** / **2+**	**8** / **2 and 3 only**	**15** / **2 and 3 only**	**EOT[d]**	**Active FU[o]**	**LTFU (every 3 months)**
Anetumab ravtansine IV[d]			x			x					
Informed Consent	x	x									
Confirm Eligibility Criteria	x	x	x[n]								
Demographics	x										
Medical History[f]		x									
Concomitant Medications[j]	x	x	x	x	x	x	x	x	x	x	
Complete physical exam		x									
Brief physical exam			x	x	x	x	x	x	x		
ECOG Performance Status		x	x			x			x		
Vital signs[e]		x	x	x	x	x	x	x	x		
Height		x[e]	x[e]								
12-lead ECG[l]		x	x			x			x		
Complete Blood Count[a]		x	x	x	x	x	x	x	x		

Day / **Cycle**	**Pre-Screening**	**Screening[c]**	**1** / **1**	**8** / **1**	**15**	**1** / **2+**	**8** / **2 and 3 only**	**15** / **2 and 3 only**	**EOT[d]**	**Active FU[o]**	**LTFU (every 3 months)**
Electrolyte and Chemistry Panel[a]		x	x	x	x	x	x	x	x		
Coagulation Panel[a]		x				x					
Serum pregnancy test (WOCBP only)		x	Every 6 weeks until EOT						x		
Dipstick Urinalysis		x	x			x					
Serum CEA, CA19-9[g]			x			x					
AE Evaluation	x[m]	x	x	x	x	x	x	x	x	x	
Radiologic Evaluation[b]		x	x[b]							x[b]	
Echocardiogram/ MUGA[h]		x				x[h]					
Ophthalmologic Exam[i]		x	x			x			x		
Archival or Fresh Tumor Tissue for mesothelin expression testing[k]	x										
Research specimens for mesothelin and exploratory analysis (biomarkers)			x			x[p]			x		
Survival Follow-Up											x

ALL VISITS AND PROCEDURES WILL BE PERFORMED WITHIN 48 HOURS (+/- 1 day) WINDOW UNLESS OTHERWISE SPECIFIED.

[a] Complete blood count with differential. Electrolyte and Chemistry panel includes amylase, albumin, alkaline phosphatase (ALP), bicarbonate, total bilirubin, direct bilirubin, urea or BUN, calcium, chloride, creatinine, eGFR, gamma-glutamyl transferase (GGT), glucose, lactic dehydrogenase (LDH), lipase, phosphorus, potassium, total protein, AST, ALT, sodium, and uric acid. Specific assessments to be run per visit are detailed below. Coagulation tests including PTT and INR or PT.
[b] Contrast-enhanced CT or MRI of chest/abdomen/pelvis or PET/CT will be done every 6 weeks for the first 6 months after the start of treatment, or more frequently if clinically indicated, every 9 weeks until the end of year 2 and every 12 weeks thereafter until disease progression or end of study, whichever comes first. To be done in +/- 7 days.
[c] Screening procedures are to be completed within 7 days of treatment initiation unless otherwise specified below. CT or MRI c/a/p scans will be done within 28 days of treatment. An ophthalmologic examination will be done within 3 weeks before the start of study treatment.
[d] Treatment will be continued until disease progression, intolerable toxicities or withdrawal. End of treatment (EOT) visit will occur 30 days (+/- 7 days) after treatment discontinuation.
[e] Vital signs will include measurement of weight, blood pressure, heart rate, temperature, and respiratory rate. Height to be done at baseline only or at Cycle 1 Day 1 prior to the first dose of study drug.
[f] Includes medical, surgical and prior cancer treatment history.
[g] CEA and CA 19-9 will be checked every 3 weeks during the treatment period including on day 1 of cycle 1 and in follow up until progression
[h] Echocardiogram or MUGA to be done at baseline, C2D1, C4D1 (+/- 7 days) and as clinically indicated thereafter.
[i] Ophthalmology exam as below every cycle.
[j] All prior anti-cancer therapies and all concomitant therapies including ophthalmological therapies. At prescreening and during active follow-up period, only concomitant medications that are administered to treat adverse events related to study-specific procedures are mandatory to be reported.
[k] Archival tissue is preferred and fresh biopsy should only be obtained if no archival tissue is available and if in the investigator's judgement, there is no additional risk for the patient's safety.
[l] 12-lead ECG to be done at screening, C1D1, C2D1, C3D1, C4D1, C5D1, C6D1, and EOT.
[m] At prescreening, only adverse events that are related to study-specific procedures are mandatory to be reported.
[n] Prior to first dose of study drug.
[o] Patients who discontinue study treatment due to any other reason than confirmed radiological PD will continue clinic visits during active follow-up for efficacy assessments including tumor response. These assessments will continue until disease progression, consent withdrawal, lost to follow-up or end of study.
[P] Biomarker plasma for exploratory analysis will be done at C6D1 (+/- 1 cycle).

9.2 Visit description

Unless stated otherwise, the measurements listed in the following sections will be performed by or under the supervision of an investigator or a delegate.

9.2.1 Prescreening

A prescreening step, including mesothelin expression level testing, can be performed without evidence of disease progression after the initial treatment at the investigator's discretion. Written patient informed consent for prescreening must be obtained before any prescreening

or study-specific procedures. Enrollment in the study is defined as the signing of the consent form.

Written informed consent for prescreening.

Enroll patient in OnCore.

Demographics (see Section 9.3.1).

Study disease characteristics and prior therapies for the study indication (see Section 9.3.3).

Check eligibility criteria for prescreening (see Section 6.1.1).

Toxicity/AE assessment (see Section 9.5.1). At prescreening, only AEs and SAEs that are related to study-specific procedures are mandatory to be reported.

Concomitant medication review (see Section 8.1). At prescreening, only concomitant medications that are administered to treat AEs related to study-specific procedures are mandatory to be reported.

Mandatory biomarker archival or fresh biopsy tissue (see Section 9.6.1).

All patients enrolled into the study will be listed on a patient enrollment log maintained in OnCore.

9.2.2 Full screening period

Written patient informed consent for full study must be obtained before any study-specific procedures. The maximum interval allowed between signature of informed consent and the start of study treatment is 30 days. Certain results from diagnostic testing prior to the informed consent date may be used to fulfill screening criteria.

Within 28 days before the start of study treatment:

Written informed consent for full study.

Updates of study disease characteristics and prior therapies for the study indication (see Section 9.3.3).

Medical history (see Section 9.3.2) and non-study-indication-related medications (see Section 9.3.3).

Check eligibility criteria for full study, and exclusion criteria (see Section 6.1.2 and 6.2, respectively).

Radiological tumor evaluation with contrast-enhanced CT/MRI of chest/abdomen/pelvis (see Section 9.4.1). Pre-study CT/MRI may be acceptable as a baseline scan if done within 28 days, if evaluable for RECIST 1.1.

Concomitant medication review (see Section 8.1).

Complete physical examination (see Section 9.5.3.2.1).

Weight and height.

12-lead electrocardiogram (ECG) (see Section 9.5.3.5).

ECOG PS assessment (see Section 9.5.3.3).

Echocardiogram (EchoCG) or multiple gated acquisition (MUGA) scan (see Section 9.5.3.6).

A detailed ophthalmologic examination (visual acuity, IOP, Schirmer test and slit lamp) (see Section 9.5.3.7) will be done within 3 weeks before the start of study treatment.

Within 7 days before the start of study treatment:

- Toxicity/AE assessment (see Section 9.5.1).
- Vital signs (see Section 9.5.3.4).
- Laboratory (see Section 9.5.3.1).
    - Complete blood count with differential.
    - Electrolyte and chemistry panel.
    - Measurement of estimated GFR (eGFR) (see Appendix 16.6). o Coagulation panel.
    - Urine dipstick. During the study, complete urinalysis should be done when dipstick results are indicative or clinically indicated.
    - Serum pregnancy test. Test should be repeated at least every 6 weeks until end of treatment visit; only for WOCBP.

9.2.3 Treatment period

After all screening assessments have been completed and the patient's eligibility has been confirmed and documented (confirmation of mesothelin overexpression moderate [2+] and stronger [3+] in at least 30% of tumor cells will be obtained from central lab and confirmation of at least 1 measurable lesion present will be obtained from radiological review), the patient may begin treatment.

9.2.3.1 Treatment – Cycle 1

Cycle 1 Day 1

The following procedures should be performed on C1D1 **before receiving study treatment** unless otherwise specified in the protocol:

Check eligibility criteria for full study, and exclusion criteria (see Section 6.1.2 and 6.2, respectively).

Enroll patient on treatment in OnCore.

Toxicity/AE assessment (see Section 9.5.1).

Concomitant medication review (see Section 8.1).

Brief physical examination (see Section 9.5.3.2.2).

Vital signs (see Section 9.5.3.4).

Weight.

Height will be measured if it was not measured during the screening period.

ECOG PS assessment (see Section 9.5.3.3).

Laboratory (see Section 9.5.3.1):

- Complete blood count with differential.
- Electrolyte and chemistry panel (CMP).
- Urine dipstick.
- Serum CEA and CA19-9.

Biomarker plasma collection for soluble mesothelin (see Section 9.6.1).

Biomarker plasma collection for exploratory analysis (see Section 9.6.1).

Study treatment administration (IV infusion [see Section 7.3]).

12-lead ECG (see Section 9.5.3.5).

Ophthalmologic examination (Schirmer test only) (see Section 9.5.3.7). If the screening period Schirmer test is conducted within 7 days of starting study treatment, the test does not need to be repeated at C1D1.

Cycle 1 Day 8

For assessments of this visit, time windows of -1 day and +1 day are acceptable unless otherwise specified in the protocol.

The following procedures should be performed on C1D8 **before receiving study treatment** unless otherwise specified in the protocol:

Toxicity/AE assessment (see Section 9.5.1).

Concomitant medication review (see Section 8.1).

Brief physical examination (see Section 9.5.3.2.2).

Vital signs (see Section 9.5.3.4).

Weight.

Laboratory (see Section 9.5.3.1):

- Complete blood count with differential.
- Electrolyte and chemistry panel (CMP).

Cycle 1 Day 15

For assessments of this visit, time windows of -1 day and +1 day are acceptable unless otherwise specified in the protocol.

The following procedures should be performed on C1D15 **before receiving study treatment** unless otherwise specified in the protocol:

Toxicity/AE assessment (see Section 9.5.1).

Concomitant medication review (see Section 8.1).

Brief physical examination (see Section 9.5.3.2.2).

Vital signs (see Section 9.5.3.4).

Weight.

Laboratory (see Section 9.5.3.1):

- Complete blood count with differential.
- Electrolyte and chemistry panel (CMP).

9.2.3.2 Treatment – Cycle 2 and higher

Cycle 2 and higher Day 1

For assessments of this visit, time windows of -2 day and +2 day are acceptable unless otherwise specified in the protocol.

The following procedures should be performed on Cycle 2 and higher, Day 1 **before receiving study treatment** unless otherwise specified in the protocol.

Toxicity/AE assessment (see Section 9.5.1).

Concomitant medication review (see Section 8.1).

Brief physical examination (see Section 9.5.3.2.2).

Vital signs (see Section 9.5.3.4).

Weight.

12-lead ECG (see Section 9.5.3.5) on C2D1, C3D1, C4D1, C5D1 and C6D1.

ECOG PS assessment (see Section 9.5.3.3).

EchoCG or MUGA scan (see Section 9.5.3.6) on C2D1, C4D1, and afterwards at the investigator's discretion based on clinical need.

Ophthalmologic examinations (visual acuity and slit lamp mandatory; Schirmer test mandatory at Cycle 4 Day 1 and Cycle 7 Day 1 only; IOP and additional Schirmer tests optional) (see Section 9.5.3.7) every cycle from C2D1 onwards, or more frequently at investigator's discretion (**important to refer to Table 2-6 and Table 2-7)**. To be performed within 7 days before anetumab ravtansine infusion.

Laboratory (see Section 9.5.3.1).

- Complete blood count.

- Electrolyte and chemistry panel.
- Measurement of eGFR (see Appendix 16.6).
- Coagulation panel.
- Urine dipstick.

Serum Pregnancy testing; only for WOCBP (every odd cycle, every 6 weeks) Biomarker plasma for exploratory analysis (see Section 9.6.1) will be collected on C6D1. Study treatment administration (IV infusion).

Cycle 2 and higher Day 8

Site visits and below-described procedures on D8 will be performed on C1, C2 and C3 only. From Cycle 4 onwards, visits on D8 are no longer required.

For assessments of this visit, time windows of -1 day and +1 day are acceptable unless otherwise specified in the protocol.

The following procedures should be performed on Cycle 2 and higher, Day 8 **before receiving study treatment** unless otherwise specified in the protocol:

Toxicity/AE assessment (see Section 9.5.1).

Concomitant medication review (see Section 8.1).

Brief physical examination (optional as per local practice and/or at investigator's discretion, see Section 9.5.3.2.2).

Vital signs (see Section 9.5.3.4).

Weight.

Laboratory (see Section 9.5.3.1):

- Complete blood count with differential.
- Electrolyte and chemistry panel (CMP).

Cycle 2 and higher Day 15

Site visits and below-described procedures on D15 will be performed on C1, C2 and C3 only. From Cycle 4 onwards, visits on D15 are no longer required.

For assessments of this visit, time windows of -1 day and +1 day are acceptable unless otherwise specified in the protocol.

The following procedures should be performed on Cycle 2 and higher, Day 15 **before receiving study treatment** unless otherwise specified in the protocol:

Toxicity/AE assessment (see Section 9.5.1).

Concomitant medication review (see Section 8.1).

Brief physical examination (optional as per local practice and/or at investigator's discretion, see Section 9.5.3.2.2).

Vital signs (see Section 9.5.3.4).

Weight.

Laboratory (see Section 9.5.3.1):

- Complete blood count with differential.
- Electrolyte and chemistry panel (CMP).

9.2.4 Efficacy assessments

9.2.4.1 Radiological tumor evaluations and forced vital capacity measurements

Radiological tumor evaluation with contrast-enhanced CT or MRI of chest/abdomen/pelvis will be performed at the following intervals (for further details, see Sections 9.4.1).

Full screening (baseline):

Within 28 days before the start of study treatment.

Treatment and active follow-up:

Every 6 weeks during the first 6 months after the start of study treatment.

Every 9 weeks until the end of year 2.

Every 12 weeks thereafter until confirmed radiological disease progression or end of study per Investigator's assessment.

Visit window of +/- 7 days is allowed.

9.2.5 Follow-up periods

9.2.5.1 Safety follow-up (End of Treatment visit)

When a patient discontinues the study treatment for any reason (except death, consent withdrawal or lost to follow-up) a safety follow-up visit will be performed 30 ($\pm$7) days after the last administration of study treatment.

The following assessments should be performed at **the safety follow-up (End of Treatment) visit**:

Toxicity/AE assessment (see Section 9.5.1).

Concomitant medication review (see Section 8.1).

Brief physical examination (see Section 9.5.3.2.2).

Vital signs (see Section 9.5.3.4).

Weight.

12-lead ECG (see Section 9.5.3.5).

ECOG PS assessment (see Section 9.5.3.3).

Ophthalmologic examinations (visual acuity and slit lamp mandatory; IOP and Schirmer test optional) (see Section 9.5.3.7)

Laboratory (see Section 9.5.3.1).

- Complete blood count.
- Electrolyte and chemistry panel.
- Measurement of eGFR (see Appendix 16.6).
- Serum pregnancy test; only for WOCBP.

Biomarker plasma collection for soluble mesothelin (see Section 9.6.1).

Biomarker plasma collection for exploratory analysis (see Section 9.6.1).

9.2.5.2 Active follow-up

Patients who discontinue study treatment due to any other reason than confirmed radiological PD will continue clinic visits during active follow-up for efficacy assessments including tumor response. These assessments will continue until disease progression, consent withdrawal, lost to follow-up or end of study.

Radiological tumor evaluation with contrast-enhanced CT/MRI of chest/abdomen/pelvis. During active follow-up, tumor scans will be performed with the same modality every 6 weeks during the first 6 months after the start of study treatment, every 9 weeks until the end of year 2, and every 12 weeks thereafter until confirmed radiological disease progression or end of study (see Section 9.4.1). Visit window of +/- 7 days is allowed.

Toxicity/AE assessment (see Section 9.5.1), in parallel with CT/MRI. During active follow-up period, only AEs and SAEs that are related to study-specific procedures are mandatory to be reported. However, at the investigator's discretion, SAEs may be reported if considered potentially relevant. In such cases, the SAEs will be processed by the sponsor according to all applicable regulations.

Concomitant medication review (see Section 8.1), in parallel with CT/MRI. During active follow-up period, only concomitant medications that are administered to treat AEs related to study-specific procedures are mandatory to be reported.

New anti-cancer treatment, in parallel with CT/MRI.

9.2.5.3 Long-term follow-up

Patients enter the long-term follow-up period following confirmed radiological progression, or withdrawal of consent to active follow-up. Patients with confirmed PD during the treatment period enter long-term follow-up immediately after the safety follow-up visit.

All patients in the long-term follow-up period will be contacted every 3 months (±14 days) until data maturation for the OS final analysis is reached, death, withdrawal of consent, lost to follow-up or end of study, whichever occurs first. Patients or their health care providers will be contacted either in person or by telephone. In addition, extra survival sweep contacts will be conducted at the time of PFS final analysis and prior to OS final analysis to ensure that long-term follow-up data is current.

The information to be recorded at these contacts:

Survival status.

Date of death.

Date of locally confirmed progression.

New anti-cancer treatment.

9.3 Population characteristics

Population characteristics including patient demographics, medical history, and other baseline characteristics listed in this section must be documented on the CRF by the investigator before the start of study treatment.

9.3.1 Demographic

Baseline patient data pertaining to demographic information will be collected at prescreening, including:

- Date of birth and age.
- Sex.
- Race (where legally allowed).
- Ethnicity (where legally allowed).
- Region.

9.3.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected after consent for full study is signed as available to the investigator:

- Start before signing of the informed consent for full study.
- Considered relevant for the patient's study eligibility.

Detailed instructions on the differentiation between (i) medical history and (ii) AEs can be found in Section 9.5.1.1.

9.3.3 Other baseline characteristics

The following **study disease characteristics** will be collected as of prescreening and will be updated if applicable during screening for full study:

Date of diagnosis.

Stage of at diagnosis.

Treatment of pancreatic cancer before enrollment (e.g. surgery, radiation and systemic therapy).

All **non-study-indication-related** medications and significant non-drug therapies taken within 30 days before ICF signature for full study will be documented, including:

- Trade name of medication.
- Reason for medication (indication).
- Dose of medication.
- Start date and end date or if continuing at patient's last visit.

9.4 Efficacy

The primary efficacy variable is progression-free survival (PFS) based on assessment of the investigator's review. For definition and analysis of the primary variable and for description of secondary and other variables, please refer to Section 10.2.

9.4.1 Radiological tumor assessments

The first radiological (contrast-enhanced CT/MRI of chest/abdomen/pelvis) tumor evaluation will be conducted during full screening within 28 days before the start of study treatment (see flow chart in Section 9.1). Pre-study CT/MRI may be acceptable as a baseline scan if done within 28 days, if evaluable for RECIST measurement in TIMC. Baseline CT/MRI should be obtained prior to start of treatment. A sole positron emission tomography (PET) scan without a diagnostic CT/MRI is not acceptable for radiological evaluation of target lesions; findings must be confirmed by CT or MRI. Although PET scan findings may be used as supportive evidence of tumor assessment, the CT or MRI results will be the definitive and documented data for the study. All subsequent scans should be done with the identical method and technique (e.g. slice thickness, field of view) to those obtained at baseline. These screening images will be reviewed to confirm there are measurable lesions in TIMC. If focal neurological symptoms are present at screening, a CT scan or MRI of the brain is required to rule out brain metastasis by the investigator. All additional suspected sites of disease should be imaged (e.g. cervical lymph nodes, bone etc.).

During treatment as well as active follow-up, tumor imaging and local assessments will be performed for the following time points: every 6 weeks for the first 6 months after the start of study treatment, every 9 weeks until the end of year 2, and every 12 weeks thereafter until confirmed radiological disease progression or end of study. Visit window of +/- 7 days is allowed. MRI shall be performed instead of CT when local regulations do not permit the use of CT as requested per protocol schedule.

All images need to be sent to the Yale Diagnostic Radiology (YDR) Precision Metrics service immediately after they are obtained.

Investigators will determine treatment response locally at each investigational site according to RECIST 1.1 criteria. Preferably all scans should be interpreted by the same radiologist/investigator during the study.

In the event of locally suspected progression, the imaging will be reviewed by radiology and investigator. Radiological confirmation by independent blinded evaluation is required before a final decision to stop the treatment is made. The site should also wait for the review results before administering the next dose of treatment. In case of uncertain radiological disease progression, the patient may stay on treatment at the investigator's discretion until progression is definitely confirmed by review on the subsequent tumor assessment.

When the review assessment confirms progression, study treatment should be stopped permanently and patient will enter safety follow-up (safety follow-up visit to be scheduled 30 (+/-7) days after the last administration of study treatment) and long-term follow-up period.

In the event the review assessment does not find progression, the severity and clinical significance of local PD finding should be assessed. If patient has not significantly clinically deteriorated and has no toxicity requiring withdrawal, the patient should continue on treatment and further imaging should be conducted as per protocol required timelines. If patient has clinically deteriorated or has toxicity such that keeping patient on treatment would be against patient's interest, the study treatment should be stopped permanently. The patient will enter the safety follow-up (safety follow-up visit to be scheduled 30 (+/-7) days after the last administration of study treatment) and active follow-up period.

The PD events for the primary endpoint of this study, and the time point and best response values for the secondary response endpoints, will be determined by independent blinded reviewers according to RECIST criteria.

The final evaluation of treatment response will be done by Yale Diagnostic Radiology Precision Metrics review retrospectively. The reviewer will determine the response per RECIST 1.1 criteria of each patient as of each time point. Responses of CR and PR will be confirmed by repeated observation per mRECIST criteria. Confirmed responses of CR and PR will be dated per mRECIST criteria.

In case a patient discontinues study for reasons other than confirmed disease progression and does not want to enter or stay in the active-follow-up, information on locally confirmed date of progression should be collected during long-term follow-up. Progression results not documented by collected imaging will be classified as clinical progression and used in sensitivity analysis.

9.4.2 Survival

Patients will be contacted for survival every 3 months (±14 days) during long-term follow-up until data maturation for the OS final analysis is reached, death, withdrawal of consent, lost to follow-up or the end of study, whichever occurs first (see flow chart in Section 9.1). In addition, extra survival sweep contacts will be conducted at the time of PFS final analysis and prior to OS final analysis to ensure that long-term follow-up data is current.

9.5 Safety

9.5.1 Adverse events

9.5.1.1. Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the patient should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

New lesions or disease progression per se should not be regarded as AEs. Instead, the associated signs and symptoms should be recorded as AEs.

In the following differentiation between medical history and AEs, the term “condition” may include abnormal e.g. physical examination findings, symptoms, diseases, laboratory, ECG.

- Conditions that started before signing of informed consent for full study and for which no symptoms or treatment are present until signing of informed consent for full study are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent for full study and for which symptoms or treatment are present after signing of informed consent for full study, at unchanged intensity, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent for full study will be documented as AEs. This includes intercurrent illnesses.

9.5.1.2 Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death.

b. Is life-threatening. The term ‘life-threatening’ in the definition refers to an event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization.

   A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

   –The admission results in a hospital stay of less than 12 hours.

   –The admission is pre-planned.

(e.g. elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2).

–The admission is not associated with an AE
(e.g. social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity. Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect.

f. Is another serious or important medical event as judged by the investigator.

9.5.1.3 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.5.1.1.

Intensity

The intensity of an AE should be documented using the NCI-CTCAE v4.03. For events not listed in the NCI-CTCAE, the following scale will be used:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Life-threatening Grade 5: Fatal

Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the CRF.

The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question.

Possible answers are "yes" or "no"

An assessment of "no" would include:

1. The existence of a highly likely alternative explanation, e.g. mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g. the patient is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of "yes" indicates that that the AE is reasonably associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Patient's response after de-challenge or re-challenge should be considered in view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication or treatment:
  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might have caused the event in question.
- Known response pattern for this class of drug: Clinical/preclinical.
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual patient's pharmacodynamics should be considered.
- The assessment is not possible.

Causal relationship to protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no".

Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Not applicable
- Unknown

Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

9.5.1.4 Assessments and documentation of adverse events

AEs observed, mentioned upon open questioning by a member of the investigator team or spontaneously reported by the patient will be documented in the patient's records and on the appropriate CRF. AEs will be documented in an event-based manner, using NCI-CTCAE version 4.03 guidelines. In addition, since the NCI-CTCAE may not adequately capture the severity of new corneal epitheliopathy, an alternative severity grading system for ocular adverse drug reactions will be used (see **Table 2-6** and **Table 2-7**).

9.5.1.5 Reporting of serious adverse events

The definition of SAEs is given in Section 9.5.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

It is not mandatory to report new SAEs occurring after the protocol-defined observation period, however, at the investigator's discretion these may be reported if considered potentially relevant. In such cases, the SAEs will be processed by the sponsor according to all applicable regulations.

Investigator's notification of the sponsor

The Investigator/ Sponsor shall report to Bayer within 24 hours of the investigator's awareness of other events such as:

An adverse event related to study specific procedures.

Any new and important event related to treatment with the study drug(s).

Any pregnancy during which a female patient was exposed to the study drug(s).

Any pregnancy in the partner of a male patient, where the male patient was exposed to study drug at the time of conception or conception occurred within two weeks of the last dose of study drug(s).

Any other relevant safety information including but not limited to reports on drug interaction, overdose, drug abuse or misuse, drug dependency, withdrawal syndrome, medication error, occupational exposure and lack of drug effect (LODE) occurring at any time during the treatment phase;

Any communication concerning safety related information to regulatory authorities or ethics committees including but not limited to:

- Development Safety Update Reports (DSUR) / relevant parts of IND reports for the STUDY;
- Any other safety related reports, issues and queries that are either raised by or communicated to regulatory authorities or ethics committees;

The Investigator/Sponsor may report SAEs using: A

MedWatch form available at http://www.fda.gov/medwatch/

All reports shall be sent electronically to:

Electronic Mailbox: DrugSafety.GPV.US@bayer.com

Facsimile: (973) 709-2185

Address: Global Pharmacovigilance - USA
Mail only Bayer HealthCare
P.O. Box 915
Whippany, NJ 07981-0915

Address: 100 Bayer Blvd., Whippany, NJ 07981

FDX or UPS only 67 Whippany Road, Whippany NJ 07981 for UPS

Reports for all Bayer products can also be phoned in via our Medical Communications Department

Phone: 1-888-842-2937

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The investigator must report immediately (within 24 hours of the investigator's awareness) all SAEs occurring during the observation period defined in Section 9.5.1.3 to the Yale Center for Clinical Investigation (YCCI) Project Manager as detailed in the instructions for SAE reporting included in the Investigator File. For this, an AE page in the CRF as well as the complementary pages provided in the Investigator File must be completed for each SAE.

SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

If disease progression leads to signs and symptoms that meet the criteria for seriousness (see Section 9.5.1.1), the associated signs and symptoms should be reported as SAE, not the underlying cause (i.e. "progressive disease" should not be recorded as SAE**). In this case, disease progression should be mentioned on the SAE form as "alternative explanation".** If a new primary malignancy is noted at any time before end of active follow-up, it must be reported as an SAE, whether or not it is assessed as related to study treatment.

For documentation of laboratory findings as SAE, please refer to Section 9.5.3.1.

Notification of the IECs / IRBs

Notification of the IECs / IRBs and Bayer Health Care about all relevant events (e.g. SAEs, suspected, unexpected, serious adverse reactions [SUSARs]) will be performed by the sponsor and/or by the investigator according to all applicable regulations and local policies.

All SAEs, whether originating at Yale or at collaborating sites, meeting the criteria for prompt reporting will be reported to the Yale University Human Investigation Committee (HIC) as per IRB Policy 710.

The Yale University HIC prompt reporting criteria are: Unexpected (in terms of nature, specificity, severity, or frequency) AND related or possibly related to participation in the research AND the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized. Collaborating sites should report adverse events to their local IRB per institutional policy.

Notification of the authorities

The processing and reporting of all relevant events (e.g. SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification of the investigational site

The sponsor will inform all investigational sites about reported relevant events (e.g. SUSARs) according to all applicable regulations.

9.5.1.5 Expected adverse events

For this study, the applicable reference document for anetumab ravtansine is the most current version of the IB.

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

9.5.1.6 Adverse events of special safety interest

Anetumab ravtansine is an investigational drug and current knowledge of the AEs associated with this compound is limited.

As with any new chemical entity, there is always potential for unexpected AEs, including hypersensitivity reactions.

Corneal disorders are considered as AEs of special interest. Specific dose modification schemes are defined in Section 7.3.2.1. An alternative severity grading system for ocular adverse drug reactions will be used in addition to NCI-CTCAE version 4.03 criteria, since the NCI-CTCAE may not adequately capture the severity of these novel adverse reactions (see **Table 2-6** and **Table 2-7**).

There is no need to report corneal toxicities as SAEs unless they meet the criteria for an SAE as defined in Section 9.5.1.1; however these events will need to be closely monitored and reviewed, and documented timely and accurately both in source data and on the CRF. Details of ophthalmologic examination will be documented on the "ophthalmologic examination" CRF page and in case AEs occur, also on "AE" CRF page, ensuring the reporting terminology used on those pages matches and reflects the source.

9.5.2 Pregnancies

The investigator must report to the sponsor any pregnancy occurring in a female study patient during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

The child's health should be followed up until 4 weeks after birth.

For a pregnancy in the partner of a male study patient, all efforts will be made to obtain similar information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE.

9.5.3 Further safety

9.5.3.1 Laboratory evaluations

Safety laboratory analyses will be performed locally according to the schedule summarized in the flow chart of Section 9.1.

Complete blood count: Hemoglobin, hematocrit, platelet count, white blood cell count (WBC). WBC must include differential including neutrophil, lymphocyte, monocyte, basophil, and eosinophil counts.

Electrolyte and chemistry panel: sodium, potassium, chloride, bicarbonate, calcium, phosphorus, glucose (fasting or random/unspecified), AST, ALT, gamma-glutamyl transferase (GGT), bilirubin (total and direct), ALP, uric acid, total protein, albumin, lipase, amylase, lactic dehydrogenase (LDH), blood urea nitrogen (BUN) or urea, and creatinine.

Coagulation panel: PTT, and PT or PT-INR.

Urinalysis: Only dipstick test will be done, and complete urinalysis (e.g. microscopic analysis of the urine sediment) will only be done if the dipstick results are indicative or clinically indicated.

Serum pregnancy test in WOCBP. Test should be repeated at least every 6 weeks until safety follow-up visit. Postmenopausal women who have not had periods for more than 1 year without an alternative medical cause or surgically sterilized women will not be required to undergo a serum pregnancy test (this information should be recorded under medical history on the CRF).

eGFR according to the MDRD abbreviated formula (see Appendix 16.6).

An isolated laboratory abnormality that meets the criteria for a CTCAE Grade 4 classification is not reportable as an SAE, unless the investigator assesses that the event meets standard International Conference on Harmonization (ICH) criteria for an SAE (see SAE definition in Section 9.5.1.1). All laboratory abnormalities, including CTCAE Grade 4 abnormalities, will be documented on the laboratory CRF.

9.5.3.2 Physical examination

Physical examinations will be performed according to the schedule summarized in the flow chart of Section 9.1. Clinically significant abnormal physical examination findings are recorded either as medical history or as AEs (see Section 9.5.1.1).

Complete physical examination

Complete physical examination of all organ systems per usual standards.

Brief physical examination

Brief physical examination includes, but is not limited to, review of organ systems and physical areas of symptomatic concern or investigator's degree of suspicion for any abnormality. After Cycle 1, brief physical examinations are only mandatory on Day 1 of each cycle and are optional as per local practice at Day 8 and Day 15 visits.

9.5.3.3 ECOG Performance Status

Change of ECOG PS will be measured for safety reason; grading definitions are given in Appendix 16.1. ECOG PS will be assessed at prescreening, full screening, on Day 1 of each cycle and at safety follow-up visit (see flow chart in Section 9.1).

9.5.3.4 Vital signs

Body weight, height, heart rate, blood pressure, body temperature, and respiratory rate will be assessed according to the schedule summarized in the flow chart of Section 9.1. Any clinically relevant measurements or changes are to be reported as AEs (e.g. weight gain or loss, hypertension, tachycardia, bradycardia, etc.).

9.5.3.5 12-lead ECG

12-lead ECGs will be performed according to the schedule summarized in the flow chart of Section 9.1. The overall interpretation of the ECG (normal/abnormal, clinical relevance) and the ECG diagnosis will be documented in the source documents and on the CRF. This review should be completed by a qualified physician and signed and dated at the time of review.

9.5.3.6 Cardiac function

Cardiac function test is mandatory. It will be measured by EchoCG or MUGA scan at full screening and on C2D1, C4D1, and afterwards at the investigator's discretion based on clinical need (see flow chart in Section 9.1). EchoCG shall be performed instead of MUGA when local regulations do not permit the use of MUGA as requested per protocol schedule.

9.5.3.7 Ophthalmologic examinations

Corneal toxicity has been identified as a TEAE of special interest for which a causal relationship with anetumab ravtansine has been deemed probable by the investigators in Phase I trial. A detailed ophthalmologic examination (visual acuity [BCVA according to ETDRS, or Snellen, or Landolt C or other charts], IOP, dry eye test [Schirmer test] and slit lamp) will be done for all patients during full screening within 3 weeks before the start of study treatment (see flow chart in Section 9.1). Visual acuity test and slit lamp examination will be repeated before infusion in every cycle except C1D1, and at safety follow-up visit, or more frequently at investigator's discretion (**important to refer to Table 2-6 and Table 2-7**).

IOP measurement is to be repeated during anetumab ravtansine therapy if the patient receives steroid eye drops as treatment for eye toxicity. IOP measurements should be repeated at two weeks and six weeks after starting topical corticosteroids for any subjects who are treated with topical corticosteroids for more than ten days. If neither the two week nor the six week IOP evaluation reveal elevated IOP (i.e., IOP increase by ≥ 7 mmHg), the frequency of IOP

evaluations can be reduced to every 4 months. If IOP evaluation reveals an elevated IOP, appropriate medical management should be initiated with follow-up appropriate for the elevation in IOP. Changes in IOP should be managed by the investigator. The remedial therapy should be chosen at investigator's discretion or according to the institutional standards; therapeutic measures can include modification of the type or posology of topical steroid eye drop, initiation of topical IOP lowering drugs and any other therapeutic options according to the local SoC. Ophthalmological monitoring should be maintained until the IOP has returned to normal values.

Dry eye (Schirmer) tests will be repeated at C1D1 (if screening period Schirmer test is conducted within 7 days of starting study treatment, the test does not need to be repeated at C1D1), and on treatment prior to C4D1 and C7D1. Schirmer tests may be repeated more frequently during treatment at investigator's discretion (e.g. in case of eye dryness during anetumab ravtansine therapy).

During treatment, ophthalmologic examination can be done up to 7 days before anetumab ravtansine infusion.

9.6 Other procedures and variables

9.6.1 Biomarkers

Preclinical and Phase I evidence suggests that mesothelin expression (or expression level above a certain threshold) in human tumors may be required for binding, internalization, and anti-tumor activity of anetumab ravtansine. All patients will have formalin-fixed, paraffin-embedded (FFPE) tumor samples available for IHC determination of mesothelin expression at prescreening as a potential predictive biomarker (see also flow chart in Section 9.1). In the absence of archival tissue, fresh biopsies may be used if deemed safe by the investigator and there is no additional risk for the patient in the investigator's judgement. Only patients whose tumors express mesothelin at staining intensity of moderate (2+) or stronger (3+) in at least 30% of tumor cells will participate further in this study. Mesothelin levels will be determined using an IHC assay (clone SP74).

In addition to obligatory measurement of mesothelin expression levels, biomarker plasma (from whole blood) will be collected on C1D1 pre-dose, C6D1 (+/- 1 cycle), and at end of treatment if possible, to be banked for future correlative research.

Exploratory biomarker analysis may also be performed using additional tumor tissue for future studies of scientific interest; these might include alterations in tumor-associated genes and to perform gene expression analysis.

The exploratory biomarkers may include, but are not limited to, DNA sequencing of tumor-associated genes and gene expression profiling. Next generation sequencing (NGS), and RNA, protein or miRNA expression analysis may be performed.

In addition to the biomarkers listed above, other biomarkers deemed relevant to gain further knowledge about the pathomechanism of the disease or about the drug (i.e. mode of action-

related effect or safety of the drug) and/or the pathomechanism of the disease may be measured, based on newly emerging data from other ongoing studies and/or literature data.

Details on the collection, processing, storage and shipment of biomarker samples will be provided in separate documents (e.g. sample handling sheets or lab manual).

9.7 Appropriateness of procedures / measurements

The efficacy assessments used in the study include those considered SoC to evaluate antitumor activity in patients with advanced or metastatic pancreatic cancer.

The safety assessments are appropriate and standard to monitor safety and assess toxicity.

Appropriateness of RECIST criteria. RECIST 1.1 criteria, designed to assess response of solid tumors is highly appropriate for determination of the primary endpoint of RR.

10. Statistical methods and determination of sample size

10.1 General considerations

Statistical analysis will be performed using SAS version 9.2 or later; the version used will be specified in the SAP.

In general, continuous variables will be summarized using number of non-missing values (n), number of missing values, means, standard deviations, medians, maximum, minimum, and interquartile range.

Ordinal variables will be summarized using n, number of missing values, medians, maximum, minimum, and interquartile range.

Categorical variables will be summarized using n, number of missing values, and percentages.

Time-to-event variables will be summarized using Kaplan-Meier estimates.

Further details on the statistical analyses will be provided in the SAP.

10.2 Variables and planned statistical analyses

10.2.1 Population characteristics

Population characteristics (see Section 9.3) will be reported by summary statistics and listings. Further details will be described in the SAP.

10.2.2 Primary efficacy variable

Response rate is defined as time from start of treatment until disease progression (according to RECIST, per blinded radiology review) or death. Patients not experiencing death or progression will be censored at the last tumor assessment.

Additional details, including additional censoring rules, will be described in the SAP.

10.2.2.1 Primary efficacy analysis

The primary efficacy analysis tests the following hypotheses:

H0: In patients with advanced or metastatic pancreatic cancer overexpressing mesothelin and pretreated with prior chemotherapy, a response per RECIST under treatment with anetumab ravtansine at 6.5 mg/kg Q3W would not be seen.

versus

HA: In patients with advanced or metastatic pancreatic cancer overexpressing mesothelin and pretreated with prior chemotherapy, a response per RECIST under treatment with anetumab ravtansine at 6.5 mg/kg Q3W would be seen.

The minimax, Simon 2-stage design testing 5% null hypothesis versus a 21% alternative requires a maximum of 30 patients. If there are no patients exhibiting any response among the first 20 then the trial will terminate early. If there is at least one response among the first 20 then the trial will accrue an additional 10 patients for a maximum of 30. Four or more responses out of 30 will reject the null hypothesis in favor of the 21% response alternative. These criteria have significance level (alpha) 0.1 and power 90%. The probability of stopping early is 36% if the response rate is 5% or lower. The expected sample size is 26.4.

Sensitivity analyses will be performed, including analyses to assess the impact of missing data and the possibility of survivorship and selection biases. Further details will be described in the SAP.

10.2.2.2 Safety variables

Safety variables will include AEs, laboratory changes (hematology, clinical chemistry and clinical urinalysis), abnormal findings in physical examination, changes in ECOG PS, changes in vital signs (weight, blood pressure, heart rate, respiratory rate, and body temperature), changes in ECG, changes in cardiac function test (EchoCG or MUGA scan) and changes in ophthalmologic examinations (visual acuity and slit lamp examination, IOP and Schirmer test if repeated). All AEs whether considered drug-related or not, will be reported on the CRF with a diagnosis, start/stop dates, action taken, whether treatment was discontinued, any corrective measures taken, outcome and other possible causes. For all events, the relationship to treatment and the intensity of the event according to CTCAE v4.03 will be determined by the investigator, using the terms and definitions given in Section 9.5.1.2.

Definition of treatment-emergent safety events

The treatment period for safety purposes is defined as the start of study treatment until 30 days after the last day of study treatment.

Treatment-emergent safety events (e.g. TEAEs) are safety events which arise or worsen during the treatment period.

Additional details will be described in the SAP.

Safety analysis

The final safety analysis will be performed at the time of the final primary endpoint analysis..

All enrolled patients who receive at least 1 dose of treatment will be valid for safety analysis.

All observations pertinent to the safety of treatment will be recorded on the CRF and included in the Clinical Study Report (CSR).

Descriptive summary tables will be presented for all safety parameters. All TEAEs, treatment-emergent and hematological/biochemical toxicities based on laboratory measurements, as well as drug-related AEs and SAEs, will be graded by CTCAE v4.03 and categorized by MedDRA.

Results of physical examination, vital signs, ECG, and other safety variables as described in the SAP will be summarized. The number (%) of patients who discontinue study drug due to AE or for whom a dose reduction or interruption is needed due to AE will also be summarized.

10.2.3 Other variables

10.2.3.1 Biomarker variables

An analysis of mesothelin expression levels in all patients evaluated for mesothelin expression will be performed. Biomarker parameters that may predict response, e.g. mesothelin expression levels in tumors and in plasma, may be analyzed by patient, and associated with tumor response using descriptive statistics, if appropriate. The association between biomarker and selected safety, efficacy, or PK parameters may be graphically displayed. Further exploratory statistical analyses may be performed. Biomarker variables and analyses will be further described in the SAP.

10.3 Planned interim analyses

An interim analysis for RR at the time 20 patients are evaluable will be performed.

11. Data handling and quality assurance

11.1 Data recording

The data collection tool for this study will be via the Yale OnCore system. Data forms will be available within the trial webpage and all data will be entered remotely via web access. Non-Yale sites will have access to OnCore for this purpose.

11.1.1 Source documentation

The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.

It is the expectation of the sponsor that all data entered into the CRF has source documentation available at the site.

11.1.2 Data recorded from prescreening and full screening failures

At minimum, the following data should be recorded in the CRF:

- Demographic information (patient number; year of birth / age; sex; if applicable race / ethnicity)
- Date of all informed consent(s)that were signed
- Relevant inclusion/exclusion criteria for prescreening and for full study (if available)
- Reason for premature discontinuation
- Result of mesothelin overexpression level testing (if available)
- Date of last visit.

These data will be transferred to the respective database.

For prescreening failures who experienced an SAE related to prescreening procedures, and for full screening failures who had signed consent for full study and who experienced an SAE, the following data should be collected in the CRF in addition to the data specified above:

- All information related to the SAE such as:
    - The SAE itself
    - Concomitant medication
    - Medical history
    - Other information needed for SAE complementary page.

11.2 Monitoring

The study principal investigator and YCCI are responsible for monitoring the performance of all of the participating sites. This will be performed by conducting a study site initiation visit, as well as regularly scheduled monitoring visits and/or remote monitoring throughout the life of the protocol. At the end of the trial, the monitor will then perform a study site close-out visit at all participating sites.

YCCI will utilize their institution’s initiation, monitoring and close-out visit reports. Following each site visit, a visit report will be generated containing information on site activities, and a summary of pertinent points and action items together with a copy of the follow-up letter will be sent to each investigative site.

During these monitoring visits, some of the items that will be reviewed are the following:

- Training of the sites
- Site personnel qualifications to participate in the trial

- That study related documents are current
- That regulatory compliance is accomplished
- That each subject has signed the informed consent
- That the current and approved protocol is complied with (including reporting and logging of all protocol deviations)
- That all SAEs and AEs have been reported to the local regulatory and Ethics/IRB Committees, YCCI, and Bayer as appropriate
- That source documentation matches CRFs
- That required procedures for study drug accountability, distribution, and storage are followed.

YCCI will document the required study monitoring activities in a Study Monitoring Plan.

11.3 Audit and inspection

To ensure compliance with GCP and regulatory requirements, the YCCI Office of Quality Assurance and Training will audit the trial at least annually or as determined by the Yale Cancer Center DSMC. The overall principal investigator, study coordinator and/or data manager may request access to all source documents and other study documentation for onsite or remote monitoring, audit or inspection.

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator or Yale. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, and any applicable regulatory requirements.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The Sponsor-Investigator/institution and participating site investigators/institutions agree to allow the auditor or inspector direct access to all relevant documents and allocate their time and the time of their staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11.4 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files including tumor images will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The reading institution will archive the data for at least 15 years.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study center.

12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; dropout rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.
- In the event of a partial study closure, ongoing patients, including those in post-study follow-up, must be taken care of in an ethical manner.

Details for individual patient's withdrawal can be found in Section 6.3.1.

13. Ethical and legal aspects

13.1 Investigator(s) and other study personnel

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an

abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g. health authority, ethics committee, sponsor) before patient recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor's study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

13.2 External data evaluation bodies Data Safety Monitoring Committee (DSMC)

The Yale Cancer Center DSMC will serve at the DSMC of record. The Yale DSMC will review and monitor compliance, toxicity and deviations from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator.

The DSMC will review this protocol at a minimum of once every six months. Information to be provided to the committee includes: a study narrative by the PI, a summary DSMC report produced by OnCore (which includes participant accrual, response, trial status history, SAEs, Adverse Events, Deviations and survival); audit results, and monitoring reports as applicable. Other information (e.g. scans, laboratory values) will be provided upon request.

13.3 Funding and financial disclosure

13.3.1 Funding

This study will be funded by Bayer Health Care via grant to the sponsor.

13.3.2 Financial disclosure

Each investigator (including principal and/or any sub investigators) who is directly involved in the treatment or evaluation of research patients has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the TMF.

13.4 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the sponsor. The responsible unit (e.g. IEC/IRB, head of the study center/medical institution) must supply to the sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial patients without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

13.5 Patient information and consent

13.5.1 Patient information and informed consent form for prescreening

An ICF for prescreening with brief information on the study will be provided to patients with unresectable locally advanced or metastatic pancreatic cancer who would like to participate in this study.

The ICF for prescreening includes the general aspects of the study conduct, details on the tissue samples required to perform the mesothelin overexpression test, and information on risks in case a fresh biopsy is needed.

The patient has the right to ask the investigator to explain the study in detail and the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

13.5.2 Patient information and informed consent form for full study

An ICF for screening of study treatment eligibility (ICF for full study) will be provided no longer than 28 days prior to start of study treatment to the patient who passes the

prescreening, including mesothelin overexpression level test, and who still has interest to participate in this study. The ICF for full study should be provided prior to activities related to the screening for full study.

All relevant information on the study will be summarized in the ICF for full study provided by the sponsor or the study center.

The investigator or designee will explain all relevant aspects of the study to each patient / legal representative or proxy consenter (if the patient is under legal protection), prior to his/her entry into the full study (i.e. before any examinations and procedures associated with the selection for the full study are performed excluding the prescreening procedures or further study-specific data is recorded on study-specific forms).

The patient has the right to ask the investigator to explain the study in detail and the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

The investigator and research team will follow all YCC CTO SOPs at Yale and local SOPs on consent elsewhere.

13.6 Publication policy and use of data

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

13.7 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Patient names will not be supplied to the sponsor. Only the patient number will be recorded in the CRF, and if the patient name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the patients will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the patient’s identity will remain confidential.

The investigator will maintain a list to enable patients to be identified.

14. Reference list

1. Golfier, S., et al., *Anetumab ravtansine: a novel mesothelin-targeting antibody-drug conjugate cures tumors with heterogeneous target expression favored by bystander effect.* Mol Cancer Ther, 2014. **13**(6): p. 1537-48.
2. Bera, T.K. and I. Pastan, *Mesothelin is not required for normal mouse development or reproduction.* Mol Cell Biol, 2000. **20**(8): p. 2902-6.
3. Argani, P., et al., *Mesothelin is overexpressed in the vast majority of ductal adenocarcinomas of the pancreas: identification of a new pancreatic cancer marker by serial analysis of gene expression (SAGE).* Clin Cancer Res, 2001. **7**(12): p. 38628.
4. Hassan, R., T. Bera, and I. Pastan, *Mesothelin: a new target for immunotherapy.* Clin Cancer Res, 2004. **10**(12 Pt 1): p. 3937-42.
5. Hassan, R. and M. Ho, *Mesothelin targeted cancer immunotherapy.* Eur J Cancer, 2008. **44**(1): p. 46-53.
6. Bharadwaj, U., et al., *Mesothelin confers pancreatic cancer cell resistance to TNFalpha-induced apoptosis through Akt/PI3K/NF-kappaB activation and IL-6/Mcl-1 overexpression.* Mol Cancer, 2011. **10**: p. 106.
7. Bharadwaj, U., et al., *Mesothelin overexpression promotes autocrine IL-6/sIL-6R trans-signaling to stimulate pancreatic cancer cell proliferation.* Carcinogenesis, 2011. **32**(7): p. 1013-24.

15. Protocol amendments

Protocol Version 4.0, 19-September-2018

Page #	Section	Change & Rationale
-	Header	Version date changed to 19-September-2018
-	Version number	Updated from 3.0 to 4.0
Page 1	Title Page	Updated version date
Page 3	2. Synopsis—Duration of Treatment	Language was updated to clarify that scans will be read by precision metrics or an equivalent system
Page 3	2. Synopsis—Diagnosis and main criteria for inclusion /exclusion	The eligibility criterion was updated to be consistent with language in eligibility criteria in body of the protocol. Neoadjuvant *or adjuvant* chemotherapy would not be counted as a line of therapy.
Page 6	Table of Contents	Updated
Page 15	5.1 Design Overview	Language "by the Bayer designated vendor with the companion diagnostic" was removed.
Page 21	6.3.1.2 Full screening failure	"Re-testing for mesothelin expression after obtaining an initial negative result is not allowed" was removed from the protocol as retesting has been allowed.
Page 23	Figure 2-1	Minor grammatical and formatting updates
Page 29	7.3.2.2 Non-hematological toxicities	• Minor formatting updates were made • The following sentence was clarified; "If treatment modification is required due to Grade ≥3 non-hematological TEAE" to "If treatment modification is required due to a non-hematological TEAE as listed above" • Table 2-5 was updated to clarify that dose adjustments for Grade 1–2 toxicities can be made at investigator's discretion
Page 35	7.4	Sentence "On the day of receipt, the responsible site personnel will confirm receipt of study drug via OnCore." was removed. This procedure is occurring via fax confirmation.
Page 38	Table 2-9 Permitted	Information on infusion reaction management was clarified to state that "Pre-treatment with anti-nausea medication is allowed at the investigators discretion. See anti-emetic note below. "

Page #	Section	Change & Rationale
	Concomitant therapies	
Page 45	9.2.3.1 Treatment—Cycle 1 Day 1	The following language was added to clarify C1D1 Schirmer testing: "If the screening period Schirmer test is conducted within 7 days of starting study treatment, the test does not need to be repeated at C1D1."
Page 45	9.2.3.1 Treatment—Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 and higher Day 8, & Cycle 2 and higher Day 15	Laboratory testing was clarified: • "Complete Blood Count" was updated to "Complete blood count with differential" • "Electrolyte and chemistry panel (only AST, ALT, and bilirubin)" was updated to "Electrolyte and chemistry panel (CMP)
Page 62	9.5.3.7 Ophthalmologic examinations	The following language was added to clarify C1D1 Schirmer testing: "If the screening period Schirmer test is conducted within 7 days of starting study treatment, the test does not need to be repeated at C1D1."
Page 73	15. Protocol amendments	Updated protocol amendment summary

16. Appendices

16.1 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-diseases performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work). (Karnofsky 70-80)
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. (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)

4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)

16.2 New York Heart Association (NYHA) functional classification

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while **at rest**. Mostly bedbound patients.

Source (43)

16.3 Response assessment

Tumor response will be evaluated in this study using the RECIST 1.1 criteria.

Response Criteria

Complete response (CR): Disappearance of all target lesions. Disappearance of all nontarget lesions and normalization of tumor marker level, if applicable. Any pathological lymph nodes (whether target or non-target) must have decreased in size to have a short axis of < 10 mm.

Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters. No appearance of new lesions. Non-target lesions must be stable or can be not evaluable.

Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study = nadir (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. For non-target lesions, unequivocal progression of existing lesions represents PD.
Note: the appearance of one or more new lesions is also considered progression.

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Table below provides an overview how the overall response is assessed.

Overall Response Assessment

Target lesions	Non-target lesions	New lesions	Overall response

CR	CR	No	CR
CR	NE	Non-CR/Non-PD	No PR
PR	Non-PD or not all evaluated		
SD	Non-PD or not all evaluated	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or No	
Any	PD	Yes or No	
Any	Any	Yes	

PD

CR = Complete response; NE = Not evaluated; PD = Progressive disease; PR = Partial response; SD = Stable disease
Adapted from (44)

16.4 National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03

This study will utilize the NCI-CTCAE v4.03 for toxicity and SAE reporting by sites. A copy of the CTCAE v4.03 can be downloaded from the website (45).

16.5 CYP3A4 inhibitors and inducers

Table below provides an overview of strong CYP3A4 inhibitors and inducers.

Strong CYP3A4 inhibitors	Strong CYP3A4 inducers
Boceprevir	Avasimibe
Clarithromycin	Carbamazepine
Conivaptan	Phenytoin Rifampin
Grapefruit juice	St. John's wort
Indinavir	
Itraconazole	
Ketoconazole	
Lopinavir / Ritonavir	
Mibefradil (withdrawn in US)	
Nefazodone	
Nelfinavir	
Posaconazole	
Ritonavir	
Saquinavir	
Telaprevir	
Telithromycin	
Voriconazole	

CYP3A4 = Cytochrome P450, family 3, subfamily A, polypeptide 4 Source
(46)

16.6 Calculation of glomerular filtration rate by the Modification of Diet in Renal Disease formula

In accordance with established nephrology practice and guidelines, renal function at baseline and throughout the study will be assessed by means of the estimated GFR, calculated using the abbreviated MDRD study formula.

This equation of 4 variables (serum creatinine level, age, sex, and ethnicity) is recommended by the National Kidney Foundation for use in individuals 18 years or older. The formula can be found at the following website (47).

Patients with a baseline GFR < 30 mL/min/1.73 m^2 calculated by this method will not be allowed to participate in the study.

16.7 Mosteller Equation for calculation of body surface area (BSA)

BSA (m^2) = SQR RT ([Height(cm) x Weight(kg)]/ 3600)

Where SQR RT is square root (√).