Mayo Clinic Cancer Center

Phase I/II Study of the Human Anti-Mesothelin Antibody Drug Conjugate Anetumab Ravtansine (AR), Combined with the PD-L1 Inhibitor Atezolizumab in Non-Small Cell Lung Cancer

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Statistician: [redacted]

* Investigator having NCI responsibility for this protocol
√ Study contributor(s) not responsible for patient care

Drug Availability
Commercial Agents: Atezolizumab
Drug Company Supplied: Anetumab ravtansine (BAY 94-9343)

Document History	Effective Date
Activation/Amendment 1	23Oct2018
Amendment 2	09Apr2019
Amendment 3	24Jul2019

Protocol Resources

Questions:	Contact Name:
Patient eligibility*; test schedule; treatment delays, interruption or adjustments; dose modifications; adverse events; forms completion and submission	[redacted] Quality Assurance Specialist/Data Manager Telephone: [redacted]
Drug administration, infusion pumps, nursing guidelines	[redacted] Telephone: [redacted] [redacted] Telephone: [redacted] [redacted] Telephone: [redacted]
Forms completion and submission	[redacted] Clinical Research Coordinator Telephone: [redacted]
Protocol document, consent form, regulatory issues	[redacted] Research Protocol Specialist Telephone: [redacted]
Serious Adverse Events	[redacted] Telephone: [redacted]

*No waivers of eligibility

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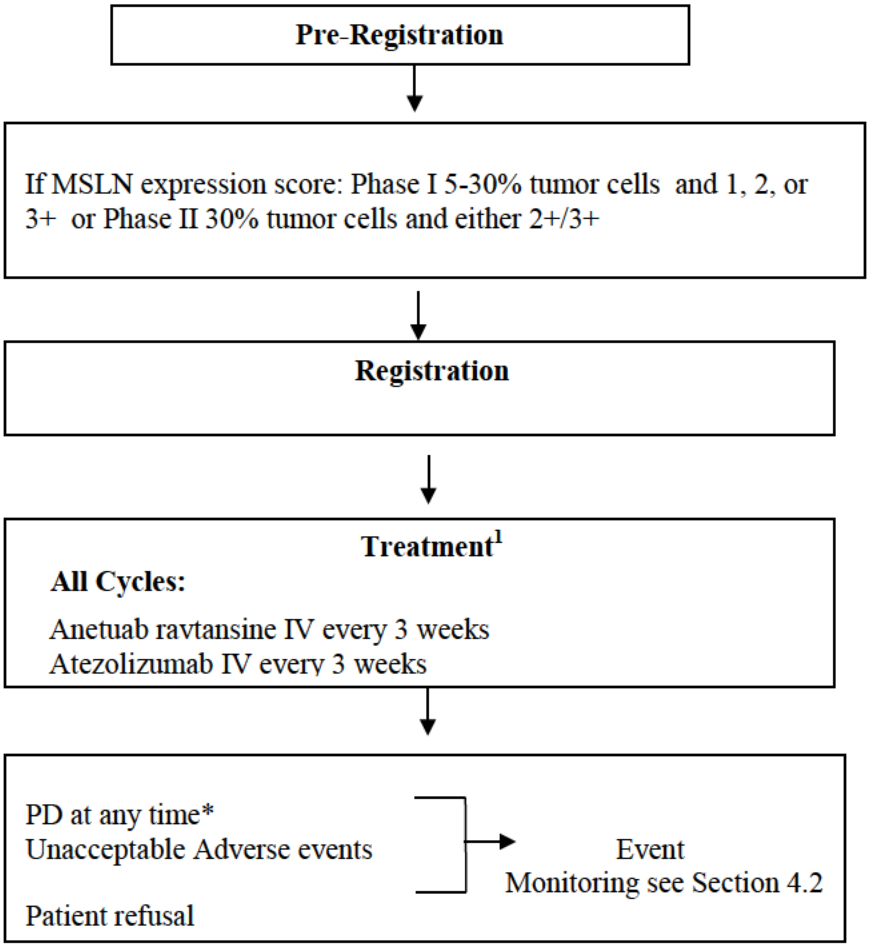
Schema

Study Participants: Limited to Mayo Clinic

Phase I only: Prior to discussing protocol entry with the patient, call the MCCC Registration Office at [redacted] for dose level and to ensure that a place on the protocol is open to the patient.



Anetumab ravtansine, 3+3 dose-escalation from 4.5-6.5 mg/kg IV every 3 weeks-cycle
Atezolizumab, 1200 mg IV every 3 weeks-cycle

*unless otherwise specified

[1] Cycle length = 21 days

If a patient is deemed ineligible or a cancel, please refer to Section 13.0 for follow-up information.

Generic name: Atezolizumab Brand name(s): Tecentriq® Mayo Abbreviation: ATEZOLIZUMAB Availability: Commercial supply	Generic name: Anetumab ravtansine Brand name(s): Mayo Abbreviation: ANETUMAB RAVTANSINE Availability: Supplied by sponsor Bayer

Protocol Synopsis

Title / Phase	A Phase I/II Study of the human anti-mesothelin antibody drug conjugate anetumab ravtansine (AR), combined with the PD-L1 inhibitor Atezolizumab in non-small cell lung cancer
Mayo Clinic Study Number	MC1711
Mayo Clinic Cancer Center Investigator	Alex A Adjei MD, PhD
Study Drug(s)	Anetumab ravtansine (AR, BAY 94-9343), Atezolizumab
Objectives	**Primary Goals(s)** **Phase I** To identify the recommended phase II dose of anetumab ravtansine combined with atezolizumab in advanced MSLN+ NSCLC. **Phase II** To determine the confirmed response rate for the combination of anetumab ravtansine and atezolizumab in MSLN+ 2nd line NSCLC **Secondary Goals** **Phase I** 1. To describe adverse events and toxicities of the combination treatment of anetumab ravtansine and Atezolizumab; 2. To identify preliminary evidence of clinical activity (i.e. response, timed endpoints, etc.) **Phase II** 1. To determine the progression-free survival (PFS) and the 1-year PFS rate for the combination of anetumab ravtansine and atezolizumab in 2nd-line NSCLC 2. To determine the overall survival of anetumab ravtansine combined with atezolizumab in second-line therapy of NSCLC 3. Adverse events will also be summarized as well. **Correlative** 1. To determine using flow cytometry the levels of Bcl-2 interacting mediator of cell death (BIM) in circulating CD8+ CD11a+ PD-1+ T-cells, in peripheral blood samples collected from patients prior to initiation of therapy (baseline) and correlating these with confirmed response rate during and following treatment with the combination regimen. 2. To determine tissue MSLN and PD-L1 expression and correlate with response to combination therapy with atezolizumab and anetumab ravtansine 3. To correlate baseline serum soluble PDL-1 (sPDL-1) with response to therapy.

Study Design

This is a non-randomized dose escalation Phase I study designed to determine the maximum tolerated dose (MTD) and dose-limiting toxicities of anetumab ravtansine (which will be dose-escalated) in combination with atezolizumab (administered at the standard fixed dose) in the treatment of advanced, treatment-refractory mesothelin expressing NSCLCs. This phase of the study uses a standard cohort 3+3 dose-escalation design. The patients will be treated with standard dose atezolizumab along with starting dose level 1 of anetumab ravtansine. Subsequent patient cohort(s) will be enrolled depending on the safety and tolerability of the initial cohort. If <33% patients treated at Dose Level 1 experience dose-limiting toxicity (DLT) by the end of first treatment cycle (21 days), then next cohort of 3 patients will be enrolled and treated at Dose Level 2. The MTD is defined as the maximum dose level at which ≤1/6 patients have DLTs. If DLT meets the stopping boundaries set by the above dose escalation algorithm at dose level 1 (for example, more than 1 out of 3 patients or more than 1 out of 6 patients), the next cohort of three patients will be entered at a dose level of -1. Further dose re-escalation will depend on the toxicity profile observed at dose level -1, and re-evaluation of the regimen by the study team may be done. A subsequent phase II study will be implemented once the recommended Phase 2 dose (RP2D) is ascertained. Anetumab ravtansine will be given IV once every 3 weeks and is subject to dose-escalation and atezolizumab is administered as a one-hour infusion every 3 weeks.

Number of Patients	**Cohort Level**	Anetumab ravtansine **(mg/kg) Q3W**	**Atezolizumab (mg) Q3W**
3-6	-1	4.5	1200 mg
3-6	1*	5.5	1200 mg
3-6	2	6.5	1200 mg

*Starting dose

3+3 design; 3-6 pts/dose level. Total 6-12 patients in phase I.

Dose level I is starting dose level

Target Accrual and Study Duration	**Duration:** **Phase I**: 3 months (maximum 6 months). In the phase I portion, there will be 3-6 patients per dose level for a total of 6-12 patients. **Phase II** stage 1: 6 months; stage II: 6 months. Total duration: 15-18 months In this part of the trial, 17 patients will be accrued (this will include the patients treated at the MTD from the phase I component). If 3 responses or less are observed in the first 17 patients, then the trial will be terminated and the treatment deemed not worthy of further study. If at least 4 responses are observed among these 17 patients, then an additional 20 patients will be accrued to the second stage. If 11 or more responses are observed at the end of the trial the treatment will be considered promising. This design yields at least 90% probability of a positive result if the true response rate is at least 40%. A maximum of 12 patients will be accrued to the phase I portion leading to a maximum of 49 patients for this study.

Study Procedures	**Disease Evaluation:** Tumors will be measured using the Full Analysis Set via imaging (CT scan) at baseline and after every 2 doses of anetumab ravtansine and atezolizumab (i.e. q 6 weeks). ORR will be defined as the total number of patients with confirmed responses of either CR or PR divided by the total number of patients who are evaluable for response prior to or on Cycle 3 Day 1 and prior to or on Day 1 of every other cycle thereafter. **Adverse Events:** Drug safety will be monitored and evaluated continuously throughout the study by obtaining, reviewing and analyzing data on adverse events (AEs), changes in laboratory values, vital signs, electrocardiograms (ECGs), and physical examination findings. Using the Common Terminology Criteria for Adverse Events (CTCAE) V.4.0, the frequency of AEs will be tabulated by grade across all dose levels and cycles. **Eye examination** (slit lamp) every 3 weeks (since anetumab ravtansine and atezolizumab have eye AE) **Hematology:** Baseline, Cycle 1 Day 1, and on Day 1 of each subsequent cycle and end of treatment. **Chemistry:** Baseline, Cycle 1 Day 1, and on Day 1 of each subsequent cycle and end of treatment. **Urinalysis:** Baseline, Day 1 of each cycle, and end of treatment. **Performance Status:** Baseline, Cycle 1 Day 1, and on Day 1 of each subsequent cycle and end of treatment. **Physical Examination** (including neurological examination, vital signs, and body weight): Baseline, Cycle 1 Day 1, and on Day 1 of each subsequent cycle and end of treatment. **12-Lead Electrocardiogram:** Baseline, and as clinically indicated during the study. **Biomarker Assessment/Correlative Studies:** Tissue PD-L1 expression, Treg accumulation and IFN-gamma expression in response to atezolizumab plus anetumab ravtansine will be determined. The correlation in expression of Bim levels in CD8+ CD11a+ PD-1+ T-cells to response rate and also the percentage change of Bim levels at baseline, during and after treatment will be assessed. Hence, Bim expression at baseline, followed by every 6 weeks of atezolizumab therapy and upon completion of therapy will be assessed.

Statistical Analysis	Sample Size Assumptions / Target Number of Valid Cases A Simon two-stage design will be used in which a 20% response rate is considered not promising, a 40% response rate is considered promising, and the probabilities of a type I error (falsely accepting a nonpromising therapy) and type II error (falsely rejecting a promising therapy) are set at 0.10 and 0.10, respectively. In this scenario, the maximum trial size would be 37 patients. In the first stage of this design, 17 patients will be accrued (this will include the patients treated at the MTD from the phase I component). If 3 responses or less are observed in the first 17 patients, then the trial will be terminated and the treatment deemed not worthy of further study. If at least 4 responses are observed among these 17 patients, then an additional 20 patients will be accrued to the second stage. If 11 or more responses are observed at the end of the trial the treatment will be considered promising. This design yields at least 90% probability of a positive result if the true response rate is at least 40%. A maximum of 12 patients will be accrued to the phase I portion leading to a maximum of 49 patients for this study. Interim Analyses After 17 patients accrued on the phase II portion including patients treated at RP2D

1.0 Background

1.1 Non- small cell lung cancers (NSCLC)

Lung cancer is the leading cause of cancer-related mortality worldwide, accounting for more than one million deaths every year. NSCLC comprises of 85% of lung cancers, and approximately 40% of patients with newly diagnosed NSCLC have advanced stage disease.(1) The outcomes of advanced NSCLC remain dismal, with overall survival of about 1 year. Platinum-based chemotherapy, which is considered the standard of care and better than best supportive care, can be associated with significant morbidity.(2) More recently, advances in identifying actionable molecular targets like EGFR mutations and ALK translocations have demonstrated significantly improved survival in the patients who harbor these alterations. However, the proportion of NSCLC patients with any targetable alterations is less than 25%.(3) There is a need for effective and safe therapies for optimizing outcomes in patients with advanced NSCLC.

1.2 Anetumab ravtansine (BAY 94-9343)

Anetumab ravtansine (BAY 94-9343) is an antibody-drug conjugate (ADC) targeting mesothelin, a protein normally present on mesothelial cells and overexpressed in the majority of mesotheliomas. Mesothelin expression is seen in approximately 40-60% patients with NSCLC (4, 5) The expression profile as well as the fact that mesothelin is an internalizing antigen highlights mesothelin as an adequate target for antibody-mediated delivery of cytotoxics. The biological function of mesothelin is unknown; mesothelin-deficient mice do not display a specific phenotype (6).

Anetumab ravtansine is a fully human IgG1 antibody (MF-T, BAY 86-1903) directed at the mesothelin antigen and conjugated to a synthetic maytansine derivative as toxophore (DM4, BAY 100-6640) by a disulfide linker moiety to its lysine residues. DM4 is a

spindle poison, and its mechanism of action (MoA) is inhibition of microtubule assembly (similar to that of vinca alkaloids).

1.21 Non clinical experience

In vivo, AR showed potent inhibition of the growth of the tumor xenograft models (7). Anetumab ravtansine eradicated tumors in 5 out of 6 animals in the MIA PaCa-2/meso pancreatic cancer model at a dose of 0.05 mg/kg, while it demonstrated tumor regression in 25% of the animals in the HT-29/meso colon cancer model ($P<0.001$). In the OVCAR-3 ovarian cancer model treated with anetumab ravtansine at a dose of 0.05 mg/kg (Q3Dx3), 100% of mice responded to the treatment, and 4 out of 6 mice had complete tumor eradication lasting for at least 12 weeks after last dose. In the mesothelioma model (NCI-H226), 2 cycles of triple IV inoculations of 0.2 mg/kg AR (related to the concentration of DM4) significantly reduced tumor growth compared with the vehicle control (94%, $P < 0.001$) and achieved a 63% response rate (partial response [PR] in 5 out of 8 mice). In contrast, treatment with free active methyl-DM4 (DM4-Me) did not affect tumor growth significantly. In the same study, cisplatin alone and in combination with pemetrexed resulted in 70% reduction of tumor growth ($P < 0.01$), with anetumab ravtansine therapy demonstrating 14-fold lower tumor weight as compared with the combination of cisplatin and pemetrexed ($P < 0.05$).

The efficacy of anetumab ravtansine monotherapy was also demonstrated in preclinical patient-derived xenograft (PDX) MPM tumor models.(7) Anetumab ravtansine administered at a dose of 0.2 mg/kg resulted in transient regression in 6 out of 8 tumors in the pancreatic tumor model PAXF736 ($P < 0.001$), and a complete eradication of all tumors in the ovarian tumor model OVCAR6719 ($P < 0.001$). It also demonstrated at least a partial tumor regression in all the mice in the mesothelioma model Meso7212 ($P < 0.001$). This was compared to the standard of care therapies and revealed that therapy was anetumab ravtansine was more efficacious than gemcitabine in the pancreatic model ($P < 0.01$), cisplatin in the ovarian model ($P < 0.01$), and cisplatin ($P < 0.05$) and pemetrexed ($P < 0.001$) in the mesothelioma model. The difference between the effects of a microtubule-targeting drug vinorelbine and anetumab ravtansine was not significant.

Further details can be found in the latest available version of the investigator's brochure (IB), which contains comprehensive information on the study drug.

1.22 Clinical experience

As of 13 July 2015, a total of 148 patients with advanced refractory solid tumors expressing mesothelin have been treated with anetumab ravtansine given as a single agent by 1-hour IV infusion in the Phase I First in Human (FiH) 15051 study. The dose-escalation part of the FiH study 15051 was completed in FEB 2013 with 45 patients evaluated in 10 cohorts spanning the dose range from 0.15 mg/kg to 7.5 mg/kg given by 1-hour IV infusion Q3W. The maximum tolerated dose (MTD) was defined as 6.5 mg/kg Q3W. Subsequently 2 expansion cohorts (n=32) were treated at 6.5 mg/kg Q3W. Two further randomized expansion cohorts of anetumab ravtansine (n=71) given QW in mesothelioma and ovarian cancer were initiated on 16 Jan 2014. Of these 71 patients, 19 with ovarian

cancer received 1.8 mg/kg QW and 21 received 2.2 mg/kg QW; 16 with mesothelioma received 1.8 mg/kg QW and 15 received 2.2 mg/kg QW. Data from one of the subjects in 1.8 mg/kg QW was not available in the listings.

Using the data cut on 13 JUL 2015, mesothelin protein expression levels at the membrane of tumor cells have been determined using the SP74 MSLN IHC assay under development by Ventana Roche. Although mesothelin expression has determined retrospectively in the Q3W dosing schedule, only patients with tumors exhibiting ≥ 30% positive tumor cells with moderate or stronger membrane staining have been enrolled in the QW expansion cohort.

A total of 53 males and 94 females were treated, with a mean age of 60.5 years. Within the escalation cohorts (total 45 patients) the most common cancers were mesothelioma (n=21), pancreatic (n=9), breast (n=5), and ovarian cancer (n=4) while in the three expansion cohorts (n=32 receiving 6.5 mg/kg Q3W and n=70 receiving either 1.8 mg/kg QW or 2.2 mg/kg QW) subjects had ovarian cancer (n=59) or mesothelioma (n=43).

Information on secondary pharmacologic effects of the ADC was available on 38 patients among both the dose escalation and expansion cohort combined. The formation of anti- anetumab ravtansine antibodies with titer of ≥32 occurred in 6 out of 38 subjects (16%) treated at the MTD of 6.5 mg/kg Q3W. The formation of anti- anetumab ravtansine antibodies seemed to have no discernible correlation to the incidence of adverse effects.

Clinical pharmacokinetic information on anetumab ravtansine has been characterized in the dose-escalation study 15051. Following IV administration, maximum ADC concentrations were typically observed within 1 hour of the end of infusion, and declined with a mean terminal phase half-life values of approximately 5 to 6 days. The maximum concentration of drug (C_{max}) and area under the curve (AUC) increased in a dose-proportional manner in the 0.15 mg/kg to 7.5 mg/kg Q3W dose range studied. C_{max} of DM4 and DM4 Me were observed within a median duration of 5 hours and 8-24 hours, respectively, after anetumab ravtansine infusion. At MTD, the average terminal half-lives of DM4 and DM4-Me were approximately 3 days and 5.5 days, respectively. This is generally consistent with the range of half-life values reported for biologics and with no accumulation expected after Q3W dosing.

In the dose-escalation part of the study 15051, the MRD for anetumab ravtansine was 6.5 mg/kg and lower, with 7.5mg/kg being the non-tolerated dose. 58 of 147 subjects (39.5%) had at least one treatment-emergent adverse event (TEAE), of which 11 (7.5%) were deemed possibly related to anetumab ravtansine itself. In the Q3W dose escalation cohorts, 2 subjects (4.4%) experienced TEAEs likely related to anetumab ravtansine (hyponatremia and cardiac chest pain). In the Expansion 6.5 mg/kg Q3W cohort in subjects with ovarian cancer and mesothelioma, 5 subjects (15.6%) experienced TEAEs deemed secondary to AR (sinus tachycardia and hypotension in first subject, infusion related reaction, dyspnea, hypoxia, flushing and noncardiac chest pain in the second subject, fatigue in the third subject, hyponatremia and decreased appetite in the fourth subject, and esophagitis in the fifth subject). In the Exp 1.8 mg/kg QW cohort, 3 subjects (8.8%) experienced TEAEs considered at least possibly related to the

study drug (pericardial effusion and noncardiac chest pain in the first subject, amylase increased in the second subject, and maculopapular rash in the third subject). In the Exp 2.2 mg/kg QW cohort, 1 subject experienced TEAEs from the drug (pericarditis, pleural effusion, and hypoxia). All of these adverse events have resolved completely, except a subject with amylase rise in Exp 1.8 mg/kg QW cohort and another subject with pleural effusion in Exp 2.2 mg/kg cohort).

In the dose escalation cohorts, 1 subject in 6.5 mg/kg dose cohort had a dose reduction due to grade 3 rise in AST (aspartate aminotransferase) on day 8 after first dose of anetumab ravtansine, and another subject in 7.5 mg/kg dose cohort had a dose reduction due to Grade 3 peripheral neuropathy after second dose of anetumab ravtansine. In the Exp 6.5 mg/kg cohort, 15 of 32 (46.9%) subjects had dose reduction to 5.5 mg/kg Q3W (10 subjects with corneal epitheliopathy and 6 subjects with peripheral neuropathy). Four of the 15 patients above had further dose reductions to 4.5 mg/kg Q3W (3 due to corneal epitheliopathy and 1 due to peripheral neuropathy). In the Exp 1.8 mg/kg QW cohort, 1 out of 34 subjects had annular keratopathy leading to dose reduction to 1.5 mg/kg QW. In the Exp 2.2 mg/kg QW cohort, 4 of 36 patients had TEAEs (one each of neutropenia, blurred vision, ocular hyperemia, corneal deposits, or neuropathy peripheral) leading to dose reduction to 1.8 mg/kg QW.

In the Q3W dose escalation cohort, 6 subjects (13.3%) had TEAEs leading to drug discontinuation (Grade 2 diarrhea in a subject in Cohort 3, Grade 5 dyspnea leading to death in a subject in Cohort 5, Grade 2 flushing in a second subject in Cohort 5, Grade 2 pericardial effusion in a subject in Cohort 7, Grade 5 neutropenic sepsis leading to death in a subject in Cohort 10, and Grade 3 corneal disorder in a second subject in Cohort 10). Two out of these adverse events were deemed likely secondary to the study drug itself (Grade 2 flushing in Cohort 5 and Grade 3 corneal disorder in Cohort 10). In the Exp 6.5 mg/kg Q3W cohort, 3 subjects had drug discontinuation due to TEAEs (1 subject with Grade 5 sepsis leading to death; 1 subject with Grade 2 performance status decreased; and 1 subject with Grade 2 neuropathy peripheral, Grade 1 atrial tachycardia, and Grade 2 decrease in ejection fraction). One of these TEAEs was felt not to be causally related to the study drug (Grade 2 peripheral neuropathy). In the Exp 1.8 mg/kg QW cohort, 1 of 34 subjects had drug discontinuation due to Grade 4 amylase increase which was deemed likely secondary to anetumab ravtansine itself. In the Exp 2.2 mg/kg QW cohort, 3 of 36 subjects had drug discontinuation due to TEAEs (Grade 2 pleural effusion, Grade 2 pneumothorax and Grade 2 failure to thrive), of which the pleural effusion was likely secondary to the drug.

A significantly higher incidence of dose modifications due to drug-related TEAEs at the MTD of 6.5 mg/kg Q3W could be at least in part explained by the much longer drug exposure (duration of time on treatment) in patients who start treatment at this dose. The ORR, as determined by the incidence of PR, was notably better in patients who started at 6.5 mg/kg Q3W. Among the 38 patients treated with AR at 6.5 mg/kg Q3W in the study 15051, 5 of 16 (31.3%) subjects with advanced, recurrent predominantly epithelial mesothelioma and 1 of 21 (5%) subjects with advanced, recurrent predominantly epithelial ovarian cancer had a confirmed PR. 7 of 16 (44%) subjects with mesothelioma and 12 of 21 (57%) subjects with ovarian cancer in this cohort had stable disease; 1 subject with mesothelioma and 3 with ovarian cancer had durable stable disease (≥6

months). Nine of 16 (56.2%) mesothelioma subjects in the Exp 6.5 mg/kg Q3W cohort have received only one regimen of systemic cytotoxic chemotherapy before entering the study 15051, with 5 of the 9 subjects (55.6%) showing a PR that lasted 174 days in 1 subject and ≥600 days in the other 4 subjects. AR showed less activity in mesothelioma subjects treated on QW schedule (1 subject each in Exp 1.8 mg/kg QW cohort nd Exp 2.2 mg/kg QW cohort).

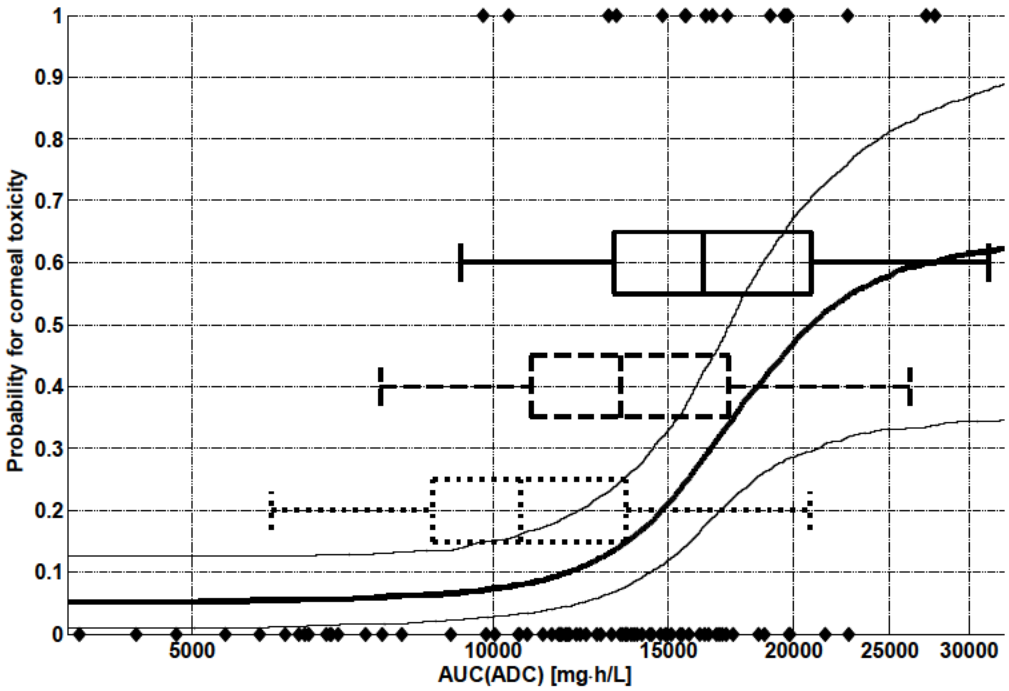
Objective tumor responses persisted in 6 of 7 patients with PR in whom the starting dose of 6.5 mg/kg Q3W had to be reduced to 5.5 mg/kg Q3W due to a drug-related TEAE, and even in 2 of 4 patients who required a second dose reduction to 4.5 mg/kg Q3W due to another related TEAE. In contrast, none of the 35 patients who started at doses < 6.5 mg/kg Q3W had a PR, and only 1 of 9 patients who started at 5.5 mg/kg Q3W had an unconfirmed PR. If patients were to start treatment at doses < 6.5 mg/kg Q3W, the potential for clinical benefit could be reduced despite the lower risk of dose modification due to a drug-related TEAE.

Objective responses or prolonged SD occurred only in patients with strong mesothelin expression (e.g. MPM of epithelioid and mixed histology).
The safety finding of particular interest at the 6.5 mg/kg Q3W dose has been the corneal epitheliopathy and keratitis with and without blurred vision probably related to anetumab ravtansine: 11 of 38 patients (29%) developed corneal adverse events (AEs). None of these events affected the deep corneal stroma or were considered serious or led to drug discontinuation and all events were reversible.

Furthermore, population, physiologically-based pharmacokinetic (PopPBPK) modeling of preliminary data from the FiH study 15051, combined with a probabilistic regression analysis provided evidence that the area under the ADC plasma concentration-time curve at steady state, AUC (ADC), is a descriptor for the occurrence of corneal epitheliopathy, as shown in

Figure **1**. Based on the on average linear PK of AR (see above in this section), it can be assumed that dose reduction will lead to a reduced total drug exposure, i.e. AUC (ADC), and thus, also to a reduced probability of corneal epitheliopathy (see Figure 1 below)

Figure 1: Probability of corneal epitheliopathy versus model-predicted drug exposure –



ADC = Antibody-drug conjugate; AUC = Area under the curve; N = Number of patients; PopPBPK = Population, physiologically-based pharmacokinetic; Q3W = Every 3 weeks
Drug exposure versus the probability of corneal toxicity relationship with AUC(ADC) equals the PopPBPK model-predicted area under the AR plasma concentration-time curve at steady state.

The solid line indicates the median estimate and the thin lines represent the 90% confidence interval; data used for logistic regression model development are shown as diamonds.

The box plots represent simulated AUC (ADC) distributions in a virtual population of N=1000 subjects receiving either 4.5 mg/kg (dotted box), 5.5 mg/kg (dashed box) or 6.5 mg/kg (solid box) AR given Q3W.

Further details can be found in the latest available version of the investigator's brochure (IB), which contains comprehensive information on the study drug.
In summary, anetumab ravtansine has demonstrated durable ORR when given at the MTD of 6.5 mg/kg Q3W in refractory metastatic mesothelioma. This preliminary potential for clinical benefit in an unmet medical need indication and overall safety profile lead to the selection of 6.5 mg/kg Q3W as the starting dose for anetumab ravtansine in the 2nd line treatment of patients with unresectable or metastatic pleural mesothelioma in this study.

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.

1.3 Atezolizumab

Atezolizumab is a human monoclonal antibody directed against programmed death-ligand 1 (PD-L1) with potential immune checkpoint inhibitory and antineoplastic activities.

Atezolizumab targets immune cells or tumor cells and prevents interaction with either programmed death-1 (PD-1) receptor or B7.1 (CD80), both of which function as inhibitory receptors expressed on T cells. Interference of the PD-L1: PD-1 and PDL1: B7.1 interactions may enhance the magnitude and quality of the tumor-specific T-cell response through increased T-cell priming, expansion, and/or effector function (8, 9) . In May 2016, atezolizumab (Tecentriq™) was approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease had worsened during or following platinum-containing chemotherapy, or within 12 months of receiving platinum-containing chemotherapy.

Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and, consequently, eliminates detectable Fc-effector function. By eliminating Fc-effector function and antibody dependent cell-mediated cytotoxicity (ADCC), antibody-mediated clearance of activated effector T cells is also eliminated.

PD-L1 expression is prevalent in many human tumors (e.g., lung, bladder, ovarian, melanoma, colon carcinoma), and its overexpression has been associated with poor prognosis in patients with several cancers (9-12). PD-L1 binds to two known receptors, PD-1 and B7.1 (CD80). PD-l is expressed on activated T cells, and receptor expression is sustained in states of chronic stimulation such as chronic infection or cancer (13, 14) .

Ligation of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or inhibition of T cells. Similarly, while the receptor B7.1 has been best defined as a costimulatory molecule expressed by B lymphocytes and other antigen-presenting cells (APCs), B7.1 expressed on the surface of T cells may provide an additional signaling mechanism through which PD-L1 can negatively regulate T cell responses (8). As a result, aberrant expression of PD-L1 on tumor cells and tumor-infiltrating immune cells, such as macrophages and dendritic cells, has been reported to impede anti-tumor immunity and contribute to immune evasion (15, 16)
Given the inhibitory effects of PD-L1 signaling on T cell proliferation and activity, targeted interruption of the PD-L1/PD-1 and PD-L1/B7.1 pathways represent an attractive strategy to reinvigorate tumor-specific T-cell immunity. The other known ligand of PD-1, programmed death-ligand 2 (PD-L2), is primarily expressed in normal tissues such as the lung. As a result, targeting tumor-overexpressed PD-L1 is a more promising strategy than targeting PD-1, as it preserves the immune homeostatic PD-L2:PD-1 interaction in normal tissues while dually inhibiting the PD-L1:PD-1 and PD-L1:B7.1 pathways to enhance anti-tumor T cell immunity.

Blockade of PD-L1 or PD-1 with monoclonal antibodies has been reported to result in strong and often rapid antitumor effects in several mouse tumor models (17, 18). These data suggest that tumor-specific T cells may be present in the tumor microenvironment in an inactive or inhibited state, and blockade of the PD-L1/PD-1 pathway can reinvigorate

tumor-specific T-cell responses.
Collectively, these data establish the PD-L1/PD-1 pathway as a promising new therapeutic target in patients with advanced tumors. Immune-related adverse events reported from the two recent studies were consistent with the role of the PD-L1/PD-1 pathway in regulating peripheral tolerance.

1.31 Non clinical experience

The safety, pharmacokinetics (PK), and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, PK, and toxicokinetics of atezolizumab.

Overall, the nonclinical PK and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed phase 1 starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of down-modulating the PD-L1/PD-1 pathway and supported entry into clinical trials in patients. Please refer to the Investigator's Brochure for details on the nonclinical studies.

1.32 Clinical Experience

Current clinical studies of atezolizumab include one ongoing phase 1a monotherapy study, three ongoing combination studies, five phase 2 studies, and one phase 3 study. Details of all ongoing studies can be found in the Atezolizumab Investigator's Brochure.

1.4 Rationale for combination of anetumab ravtansine and atezolizumab in mesothelin-expressing NSCLC

Although the results with immunotherapy are encouraging as compared to the standard chemotherapy, a proportion of patients that have been treated with immunotherapy eventually experience disease relapse. This phenomenon has sometimes been attributed to tumor escape mechanisms or T-cell exhaustion. The patients who do not respond to these agents are noted to have an inability to mount an immune attack due to poor antigenicity. The use of AR could theoretically overcome this barrier to response. Mechanistically, AR binds to human mesothelin and internalizes the antigen, DM4 binding then results in disruption of microtubule dynamics and cell death which could result in the release of neoantigens. This increased antigenic burden could synergize with the restored T-cell function due to PD-L1 blockade and result in increased cell death. Preliminary data in ovarian cancer mice models have confirmed a synergistic effect between ADCs and PD1 inhibitors. In addition, trastuzumab emtansine (T-DM1) renders HER2+ breast cancer highly susceptible to CTLA-4/PD-1 blockade (19).

1.5 Rationale for Correlative Studies

The Mayo Clinic group led by Dr Haidong Dong was the first to describe soluble PDL-1 (sPDL-1) as a potential predictive biomarker of efficacy of PD1/PDL1 inhibitors. His data indicate that high levels of circulating sPDL-1 are associated with poor clinical

outcomes in melanoma patients. His group went on to demonstrate in a cohort of 80 melanoma patients that none of those patients with detectable sPDL-1in their blood responded to treatment with pembrolizumab. (Dronca R, Harrington SM, Enninga EAL, et al.). Thus, sPD-L1 may represent a blood-based biomarker of resistance to PD-1/PDL-1 inhibition. In addition, this group has demonstrated that Bim is overexpressed in a tumor-reactive T cell subset (T_{TR}) that engages with PD-L1 expressing tumors. Not only was upregulation of Bim in circulating T_{TR} a negative prognostic factor in a historic group of patients with metastatic melanoma who did not receive immunotherapy, but upregulation of Bim in circulating T_{TR} was also predictive of responses to the PD-1 inhibitor pembrolizumab in a more recent cohort of patients. Moreover, Bim levels in circulating T_{TR} decreased in both responders and those with pseudo-progression. Based on these data, we will evaluate levels of sPD-L1 and upregulation of Bim in T_{TR} as blood-based biomarkers in this trial.

2.0 Goals

2.1 Primary Goals

Phase I

To identify the recommended phase II dose of anetumab ravtansine combined with atezolizumab in advanced MSLN+ NSCLC.

Phase II

To determine the confirmed response rate for the combination of anetumab ravtansine and atezolizumab in MSLN+ 2nd line NSCLC

2.2 Secondary Goals

Phase I

2.21 To describe adverse events and toxicities of the combination treatment of anetumab ravtansine and atezolizumab

2.22 To identify preliminary evidence of clinical activity (i.e. response, timed endpoints, etc.)

Phase II

2.23 To determine the progression-free survival (PFS) and the 1-year PFS rate for the combination of anetumab ravtansine and atezolizumab in 2nd-line NSCLC

2.24 To determine the overall survival of anetumab ravtansine combined with atezolizumab in second-line therapy of NSCLC

2.25 Adverse events will also be summarized as well.

2.3 Correlative Goals

2.31 To determine using flow cytometry the levels of Bcl-2 interacting mediator of cell death (BIM) in circulating CD8+ CD11a+ PD-1+ T-cells, in peripheral blood samples collected from patients prior to initiation of therapy (baseline) and correlating these with confirmed response rate during and following treatment with the combination regimen.

2.32 To determine tissue MSLN and PD-L1 expression and correlate with response to combination therapy with atezolizumab and anetumab ravtansine

2.33 To correlate baseline serum soluble PDL-1 (sPDL-1) with response to therapy.

3.0 Patient Eligibility

Phase I only: Prior to discussing protocol entry with the patient, call the MCCC Registration Office at [redacted] for dose level and to ensure that a place on the protocol is open to the patient.

3.1 Pre Registration - Inclusion Criteria

3.11 Ability to understand and the willingness to sign a written informed consent document.

3.12 Age ≥18 years.

3.13 Patient has disease amenable to biopsy if the archival tissue sample is unavailable. Note: Archive sample must not be older than 36 months.

3.2 Registration - Inclusion Criteria

3.21 **Phase I only:** Diagnosis of advanced/metastatic NSCLC for which no standard treatment option. **Phase II only:** Advanced NSCLC patients who have received at least 1 platinum-based systemic chemotherapy regimen

3.22 Patients with tumors having actionable genomic alterations should have received prior therapy with FDA approved agents targeting these aberations (ie EGFR, ALK, ROS1,BRAF V600E)

3.23 ECOG performance status 0 or 1. (See Appendix A)

3.24 **Phase II only:** Must have at least one measurable lesion as defined by RECIST criteria (see Section 11).

3.25 Ability to understand and the willingness to sign a written informed consent document.

3.26 Histological or cytologically confirmed NSCLC that shows moderate or stronger mesothelin expression in 30% of tumor cells by a companion assay. MSLN expression score using Ventana IHC SP74 assay. Phase I only: In addition 5-30% tumor cells and 1, 2, or 3+ MSLN score. Phase II only: 30% tumor cells and either 2+/3+.

3.27 Life expectancy of ≥12 weeks.

3.27 Adequate bone marrow and organ function as defined by the following laboratory values ≤14 days prior to registration:

- Absolute neutrophil count ≥1.5 × 10^9/L
- Platelets ≥100 × 10^9/L
- Hemoglobin ≥9 g/dL
- Chemistries as follows:
  - Potassium ≥lower limit of normal (LLN) range for the institution
  - Calcium ≥LLN (corrected for serum albumin, if albumin abnormal)
  - Magnesium ≥LLN
  - Sodium ≥LLN
  - Phosphorus ≥LLN.
    NOTE: Supplementation may be given before the first dose of study medication.
- INR ≤1.5

- Serum creatinine ≤1.5mg/dL or creatinine clearance ≥50 mL/min (calculated by Cockcroft Gault equation)

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{(140 - \text{age})(\text{weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$

Creatinine clearance for females = $\frac{(140 - \text{age})(\text{weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$

- ALT and AST ≤2.5 x ULN or ≤5 x ULN if liver metastases are present.
- Total bilirubin ≤ 1. 5 x ULN

3.28 Standard 12-lead ECG with the following parameters at screening (defined as the mean of the triplicate ECGs):
  - QTcF interval at screening < 450msec (using Fridericia' s correction)

3.29a Negative pregnancy test performed ≤7 days prior to registration (women of childbearing potential only).

3.29b Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study)

3.29c Willing to provide blood samples for correlative research purposes

3.3 Registration - Exclusion Criteria

3.31 Prior treatment with anti-PD-1, or anti-PD-L1antibody which resulted in a patient having serious (grade 3-4) immune related adverse events.

Note:

- Patients who have received prior treatment with anti-CTLA-4 may be enrolled, provided the following requirements are met:
  - Minimum of 12 weeks from the first dose of anti-CTLA-4 and >6 weeks from the last dose
  - No history of severe immune-related adverse effects from anti-CTLA-4 (NCI CTCAE Grade 3 and 4)

3.32 More than one prior taxane regimen at any stage of the disease under study ("taxane" refers to paclitaxel, docetaxel, Abraxane® and cabazitaxel). Adjuvant and/or neoadjuvant treatments are considered together as one prior regimen.

3.33 Treatment with any other investigational agent or investigational device within 4 weeks prior to registration (or within five half-lives of the investigational product, whichever is longer). Patients must be ≥ 2 weeks since any investigational agent administered as part of a Phase 0 study (also referred to as an "early Phase I study" or "pre-Phase I study" where a sub- therapeutic dose of drug is administered) at the Coordinating Center PI's discretion, and should have recovered to eligibility levels from any toxicities.

3.34 Treatment with systemic immunostimulatory agents (including, but not limited to, interferon-α or interleukin-2) within 6 weeks or five half-lives of the drug (whichever is shorter) prior to registration.

3.35 Received radiotherapy ≤4 weeks or limited field radiation for palliation ≤2 weeks prior to registration, and who has not recovered to Grade 1 or better from related side effects of such therapy (exceptions include alopecia) and/or in whom ≥25% of the bone marrow was irradiated.

3.36 Patients who have a previous or concurrent cancer that is distinct in primary site or histology from the cancer being evaluated in this study, except

- Cervical carcinoma in situ, non-melanoma skin cancer, superficial non-invasive bladder tumors, DCIS or any previous cancer curatively treated >3 years before the start of anetumab ravtansine.

3.37 Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) ≤ 2 weeks prior to registration.
Note:

- Patients who have received acute, low dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled.
- The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

3.38 Patients with known primary central nervous system (CNS) malignancy or symptomatic CNS metastases are excluded, with the following exceptions:

- Patients with asymptomatic untreated CNS disease may be enrolled, provided all of the following criteria are met:
  - Evaluable or measurable disease outside the CNS
  - No metastases to brain stem, midbrain, pons, medulla, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm)
  - No history of intracranial hemorrhage or spinal cord hemorrhage
  - No ongoing requirement for dexamethasone for CNS disease; patients on a stable dose of anticonvulsants are permitted.
  - No neurosurgical resection or brain biopsy ≤28 days prior to registration
- Patients with asymptomatic treated CNS metastases may be enrolled, provided all the criteria listed above are met as well as the following:
  - Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
  - No stereotactic radiation or whole-brain radiation ≤28 days prior to registration
  - Screening CNS radiographic study ≥4 weeks from completion of radiotherapy and ≥ 2 weeks from discontinuation of corticosteroids

3.39a History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins

3.39b Patients who have a history or current evidence of bleeding disorder, i.e., any hemorrhage/bleeding event of CTCAE Grade ≥2, ≤28 days prior to registration.

3.39c History or current evidence of uncontrolled cardiovascular disease including, but not limited to, the following conditions:

- Congestive heart failure of New York Heart Association (NYHA, refer to appendix C) Class III or IV.
- Unstable angina (symptoms of angina at rest) or new-onset angina ≤6 months before the start of anetumab ravtansine.

3.39d Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.39e Pregnant women are excluded from this study because atezolizumab is an investigational agent with the unknown potential for teratogenic or abortifacient effects. Note: Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with atezolizumab, breastfeeding should be discontinued if the mother is treated with atezolizumab.

3.39f Patients on supraphysiologic doses of steroids or use of such ≤6weeks prior to registration.

3.39g Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver; and inherited liver disease.

Note:

- Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible.
- Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA

3.39h History or risk of autoimmune disease, including, but not limited to, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis.

Note:

- Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone are eligible.
- Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen are eligible.
- Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
  - Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations
  - Rash must cover less than 10% of body surface area (BSA)
  - Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate

0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)

- No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)

3.39i History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan. Note: History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

3.39j Severe infections ≤4 weeks prior to registration, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia.

3.39k Signs or symptoms of infection ≤2 weeks prior to registration.

3.39l Major surgical procedure ≤28 days prior to registration or anticipation of need for a major surgical procedure during the course of the study.

3.39m Patients with corneal epitheliopathy or any eye disorder that may predispose the patients to this condition as judged by an ophthalmologist.

- Note: Low grades of superficial punctate keratitis, within the range seen in the normal population, should not lead to the exclusion of the patient.

3.39n Non-healing serious wound, ulcer, or bone fracture unrelated to the primary tumor.

3.39o Previous assignment to treatment during this study. Patients permanently withdrawn from study participation will not be allowed to re-enter the study.

3.39p Substance abuse, psychological, or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.

4.0 Test Schedule

4.1 Study Calendar

Tests and procedures	Pre-registration	Screening ≤14 days prior to registration	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1 and subsequent cycles	End of Treatment[1]
Window				(±5days)	(±5days)	(±5days)	
History and exam, Weight, PS		X	X	X	X	X	X
Height		X					
Hematology: CBC with differential		X	X[2]	X	X	X	X
Serum chemistry[3]		X	X[2]	X	X	X	X
Urinalysis		X	X[2]	X	X		
Serum pregnancy test (if applicable)		X[4]					
Coagulation panel[5]		X	X				
12-lead EKG[6]		X					
Echocardiogram		X					
Ophthalmologic examination [7]		X		X	X	X	X

[1] End of treatment visit should be at least 21 days from last dose of study drug.
[2] Need not be repeated if performed within 14 days of Cycle 1 Day 1
[3] Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium. TSH (at baseline only)
[4] Pregnancy test must be performed ≤7 days prior to registration
[5] Coagulation panel: INR or PT and PTT or aPTT.
[6] Baseline and as clinically indicated
[7] A detailed ophthalmologic examination (visual acuity, IOP, Schirmer test and slit lamp) will be done for all patients during screening ≤ 28 days before the start of study treatment, as indicated during the study. During treatment, ophthalmologic examination (visual acuity and slit lamp only) can be performed ≤7 days before planned anetumab ravtansine infusion and at the safety follow-up exam. The IOP measurement is to be repeated during anetumab ravtansine therapy if the patient receives steroid eye drops for ≥10 days as treatment for corneal epitheliopathy. This measurement is performed at 2 weeks and 6 weeks after the initiation of steroid treatment. If IOP increases by <7 mmHg, the frequency of IOP

Tests and procedures	Pre-registration	Screening ≤14 days prior to registration	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1 and subsequent cycles	End of Treatment[1]
Window				(±5days)	(±5days)	(±5days)	
Adverse event evaluation		X	X[2]	X	X	X	X
Tumor measurements[8]		X			X		X
Mandatory tissue (archival or fresh biopsy) for MSLN determination[9]	X						
Mandatory Blood for Biomarker study[10]		X			X		X[11]
Anetumab Ravtansine administration followed by Atezolizumab Administration			X	X	X	X	

evaluation can be reduced to every 4 months. If IOP increases by ≥7 mmHg, a medical management plan with follow-up IOP evaluations will be initiated after consultation with an ophthalmologist and investigator. The Schirmer test is performed at C3D1 and C5D1. All these tests may be repeated during treatment at the investigator's discretion.

[8] Contrast-enhanced CT/MRI is acceptable as a baseline scan if done within 28 days before C1D1. Visit window of ≤7 days is allowed. Tumor measurements are repeated every odd cycle starting with Cycle 3. Documentation (radiologic) must be provided for patients removed from study for progressive disease.

[9] Mandatory biopsy will be collected before treatment if archival tissue (≤12 months of registration) not available. See Section 17.

[10] Mandatory blood will be collected before treatment, every odd cycle starting with cycle C3D1 (in conjunction with imaging, for efficacy) and EOT. See section 14.

[11] Optional blood sample collection at Disease Progression. See section 14 for further details.

4.2 Event Monitoring/Survival Follow-up

	Event Monitoring Phase*				
	Every 3 months until PD	At PD	After PD every 6 months	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

*If a patient is still alive 2 years after registration, no further follow-up is required.

5.0 Grouping Factor

Phase: Phase I vs. Phase II

6.0 Pre-registration/Registration Procedures

6.1 Pre-Registration (Step 1)

6.11 Phase I: Prior to discussing protocol entry with the patient, call the MCCC Registration Office at [redacted] for dose level and to ensure that a place on the protocol is open to the patient.

6.12 Phase II: To pre- register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/ randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 5:00 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted]. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.13 Prior to accepting the pre-registration, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient pre-registration eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information.

6.14 A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.29c and 17.1).

6.2 Registration Requirements (Step 2):

6.21 Phase I: To register a patient, fax [redacted] a completed eligibility checklist to the Mayo Clinic Cancer Center (MCCC) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.22 Phase II: To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The

registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted]. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.23 Phase I and II

6.231 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [redacted] If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.232 At the time of registration, Registration/Randomization Application will verify the following:

- IRB approval
- Patient eligibility
- Existence of a signed consent form

6.233 At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research at Mayo.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.

6.234 Corrlative Research

A mandatory correlative research component is part of this study, the patient will automatically be registered onto this component (see Section 14).

An optional correlative research component is part of this study, there will be an option to select if the patient is to be registered onto this component (see Section 17.0).

- Patient has/has not given permission to give his/her recurrence tissue sample for research testing

6.235 Consent and treatment on this protocol must commence at Mayo Clinic Rochester, Mayo Clinic Florida, or Mayo Clinic Arizona under the supervision of a medical oncologist.

6.236 Treatment cannot begin prior to registration and must begin ≤ 28 days after registration.

6.237 Screening tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.238 All required baseline symptoms (see Section 10.6) must be documented and graded**.**

6.239 Study drug is available on site

7.0 Protocol Treatment

7.1 Phase I Treatment Schedule

Use actual weight or estimated dry weight if fluid retention

7.11 Treatment table

Number of Patients	Cohort Level	Anetumab ravtansine (mg/kg) Q3W IV	Atezolizumab (mg) Q3W IV
3-6	-1	4.5	1200 mg
3-6	1*	5.5	1200 mg
3-6	2	6.5	1200 mg

*Starting dose

7.2 Determination of Maximum Tolerated Dose (MTD)

In Phase I, dose escalation of anetumab ravtansine in combination with Atezolizumab will be performed according to the standard 3+3 design of dose cohorts. Dose escalation decisions will be based on the incidence of Treatment Emergent Adverse Events (TEAEs) observed after Cycle 1 (C1) that fulfills the criteria for a DLT. If a clinically significant TEAE related to anetumab ravtansine is observed more frequently after C1, then this event may be declared a DLT at the investigators' discretion in consultation with the sponsor. If a clinically significant TEAE related to atezolizumab is observed more frequently, or with greater severity than what has been reported in the prescribing information or in the literature, this event also may be declared a DLT at the discretion of investigators in consultation with the sponsor.

At least 3 subjects in each cohort need to provide sufficient safety data after the first treatment cycle (21 days) before a decision can be made whether it is safe to proceed to the next dose level of anetumab ravtansine. To be evaluable for a dose escalation decision, subjects must complete one treatment cycle in their assigned dose cohort; receive one complete infusion of each treatment (anetumab ravtansine and atezolizumab). If a DLT occurs in 2 out of 3 subjects at a given dose level (or in 2 of 4 subjects, if the 4th subject has been enrolled), or in 2 out of up to 6 subjects in the Phase II portion at a given dose level, then dose escalation will stop and the current dose will be declared the non-tolerable dose.

7.3 Patient Must Return to Treating Institution During Study Treatment

For this protocol, the patient must return to the treating institution for all visits during study treatment.

7.4 Clinically Indicated Treatment or Supportive Care by a Local Medical Doctor

Clinically indicated treatment or supportive care by a local medical doctor (LMD) is not allowed throughout the study.

7.5 Reporting of DLTs

Investigators are to contact the Study Chair as soon as any dose-limiting toxicity (DLT) occurs.

7.6 Definition of DLT

Dose-limiting toxicity (DLT) will be defined as an AE occurring in Cycle 1 of the study, attributed (definitely, probably, or possibly) to treatment and meeting the following criteria:

- Grade 4 ANC ≥7 days or ≥Grade 3 ANC of any duration with fever > 38.3ºC.
- Grade 4 platelet count or Grade 3 platelet count associated with bleeding.
- AST/ALT/ alkaline phosphatase ≥ Grade 3 if total bilirubin < 1.5 x UNL.
- AST/ALT/alkaline phosphatase ≥ 2.5xUNL together with ≥ Grade 2 total bilirubin (> 1.5 x UNL).
- Other ≥ Grade 3 non-hematologic toxicities (except transient asymptomatic electrolyte abnormality and nausea, vomiting or diarrhea untreated with anti-emetic support or anti-diarrheal agents, respectively).

Grade 3 laboratory abnormalities without clinically significant sequel (e.g., amylase elevation, etc) will NOT be considered DLT.

7.7 Dose Escalation Rule

Please refer to Section 16 for specifics of dose-finding algorithm.

7.8 Phase II Treatment Schedule

Agent	**Dose**	**Schedule**
Anetumab ravtansine	MTD from Phase I	IV D1 every 3 weeks
Atezolizumab	1200 mg	IV D1 every 3 weeks

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table until individual treatment tolerance can be ascertained. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Dose modifications apply to the treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

In the event that individual patients experience Grade 3 or Grade 4 treatment related toxicity or intolerable Grade 2 toxicity despite optimal supportive care, treatment might be delayed and/or dose reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Subjects are to be instructed to notify Investigators at the first occurrence of any adverse symptom. Decisions on dose reduction and resumption of treatment determined according to the judgment of the investigator.

The start of a new cycle may be delayed by up to 12 weeks due to study treatment-related toxicities. In the event that a cycle has to be delayed by more than 2 weeks due to toxicity, the patient will be taken off study treatment unless otherwise specified below. Note: Patients can coninue with Atezolizumab if removed from anetumab ravtansine and remain on study.

8.1 Dose Adjustment and Management Recommendation of anetumab ravtansine

For all TEAEs except for the corneal epitheliopathy and BCVA changes, CTCAE v.4.03 will be used to assess severity.

For TEAEs representing corneal epitheliopathy and BCVA changes, the Bayer Severity

Grading system will be used to assess severity of TEAEs.
TEAEs requiring anetumab ravtansine treatment modification (temporary treatment interruption, dose reduction, or permanent discontinuation of treatment) will be defined as any of the events described below that are possibly, probably, or definitely related to anetumab ravtansine.

8.11 Hematological TEAEs requiring treatment modification

- ANC <500/mm^3 (CTCAE Grade 4) for ≥7 days
- Febrile neutropenia (ANC <1000/mm^3 and a single body temperature reading of >38.3°C (≥101°F) or a sustained body temperature of ≥38.0°C (≥100.4°F) for more than 1 hour
- Platelet count <25,000/mm^3 (CTCAE Grade 4) for ≥7 days regardless of the presence of active bleeding or platelet count > 50,000/mm3 (CTCAE Grade ≥3) with clinically significant bleeding (i.e., bleeding requiring platelet transfusion)

8.12 Nonhematological TEAEs requiring treatment modification of any or all agents of study treatment

- CTCAE Grade 4 non-hematologic toxicity
- CTCAE Grade 3 non-hematologic toxicity that, in the investigator's opinion, warrants treatment modification excluding the following:
  - CTCAE Grade 3 nausea, vomiting, or diarrhea if manageable with antiemetic or antidiarrheal agents within 7 days would not require treatment modification
  - CTCAE Grade 3 fatigue lasting ≤72 hours would not require treatment modification
  - Certain asymptomatic CTCAE Grade 3 laboratory abnormalities without a clear clinical correlate, if the investigator determines that this TEAE would not require treatment modification.
  - Grade 3 corneal epitheliopathy according to the Bayer Severity Grading that, in the investigator's opinion, warrant treatment modification.
- Grade 2 corneal epitheliopathy according to the Bayer Severity Grading that, in the investigator's opinion, warrants treatment modification.
  CTCAE Grade ≥ 2 neurotoxicity
- 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). For patients with liver metastases, AST/ALT increase > 5.0 x ULN with concomitant increase in total bilirubin > 2.0 x ULN

8.13 IV infusion-related reaction and other hypersensitivity events

If a subject experiences CTCAE Grade ≥2 anetumab ravtansine infusion reaction or other CTCAE Grade ≥2 hypersensitivity event deemed at least possibly related to anetumab ravtansine, the infusion of anetumab ravtansine will be held. In case of a CTCAE Grade 2 or 3 event, anetumab ravtansine treatment may be restarted at the time determined at the investigator's discretion. In case of a CTCAE Grade 4 event, anetumab ravtansine treatment should be permanently discontinued

8.14 Miscellaneous

Any drug-related CTCAE Grade ≤ 2 TEAE thought to be at least possibly related to anetumab ravtansine that, in the investigator's opinion, is thought to require treatment modification. Such TEAEs might be CTCAE Grade ≤ 2 toxicities, which interfere with daily life activities, such as long lasting fatigue, anorexia, or corneal toxicity.

8.15 Anetumab ravtansine treatment modification due to corneal epitheliopathy

The Bayer Severity Grading system will be used to assess the severity of TEAEs of corneal epitheliopathy and BCVA changes (attached table). The worst Bayer severity grade in the worst eye will be considered as the overall grade of corneal epitheliopathy for the purpose of treatment modification decisions.

TEAEs of corneal epitheliopathy (confirmed by slit lamp biomicroscopy examination that are deemed to be at least possibly related to anetumab ravtansine should be managed according to the principles for the modification of anetumab ravtansine treatment due to this type of TEAE (i.e., no change, temporary treatment interruption, dose reduction, or permanent discontinuation of treatment) outlined in the attached table below. Treatment modification decisions should be based only on the severity of corneal epitheliopathy and not the severity of BCVA changes (attached table).

Bayer classification and management of corneal epitheliopathy

Toxicity (worst grade, worst eye)	**Corneal morphology changes**	**Anetumab ravtansine interruption and dose reduction**	**Remedial eye treatment [a]**
Grade 0	No pathologic changes	No change/continue treatment	Treatment with ophthalmic lubricants [b]
Grade 1	Treatment-emergent superficial punctate keratitis (SPK) (new or worsening by ≥2 grades)	no change/continue treatment	Treatment with ophthalmic lubricants should be used. Topical steroids may be added. [b]
Grade 2	Epithelial opacities Corneal microcysts or microdeposits	Treat on time at the same dose if ophthalmological exam can be performed as frequently as prescribed	Intensive treatment with ophthalmic lubricants (may be enhanced with ointments [b]). Topical steroids should be

	Corneal erosion Stromal opacity (non-central)	by the investigator. If ophthalmological exam cannot be performed as frequently as prescribed by the investigator, treatment may be held until the event has resolved to the acceptable severity level. [b] The event must resolve to acceptable level within 6 weeks after the last dose. [c, d] Treatment may be restarted at the same dose or at the dose reduced by 1 level. [b,e]	added. Therapeutic contact lenses may be used. [b]
Grade 3	Corneal ulcer without risk of acute rupture Stromal opacity (central)	Treatment should be held until the event has resolved to the acceptable severity level. [b] The event must resolve to acceptable level within 6 weeks after the last dose. [c, d] Treatment should be restarted at the dose reduced by 1 level. [e] If Grade 3 corneal morphology change occurs again after dose reduction, the current dose should be reduced by 1 level or permanently discontinued. [b]	Intensive treatment with ophthalmic lubricants, enhanced with ointments. Topical steroids should be added. Therapeutic contact lenses or eye occlusion are recommended. [b]
Grade 4	Corneal ulcer more severe than Grade 3	Permanently discontinue treatment.	Intensive treatment with ophthalmic lubricants, enhanced with ointments, should be used. Topical steroids should be added. Topical antibiotics may be added. [b] Therapeutic contact lenses or eye occlusion are recommended. [b] Amniotic membrane transplant and other locally approved treatments may be used. [b]
a Other remedial therapies for corneal epitheliopathy may be added or substituted at investigator's discretion or according to the institutional guidelines. b At the investigator's (and / or the ophthalmologist's) discretion. c Worsening or resolution of corneal epitheliopathy must be confirmed by slit lamp biomicroscopy. d Treatment may be restarted at the investigator's discretion even if the epitheliopathy change has resolved to the acceptable severity level >6 weeks after the last dose, if the investigator in consultation with the			

sponsor deems that continued treatment is appropriate based on the investigator's assessment of the benefit-risk ratio.
e Anetumab ravtansine dose reduction by 1 dose level translates to a change from 6.5 mg/kg Q21D to 5.5 mg/kg Q21D or from 5.5 mg/kg Q21D to 4.5 mg/kg Q21D. Dose reductions of anetumab ravtansine are permitted for as long as the continuation of treatment is appropriate based on the investigator's assessment of the benefit-risk ratio.

Recommendations for changes in tear production and intraocular pressure (IOP)

Reduced tear production is a risk factor for developing ocular surface disease, including corneal epitheliopathy. Therefore, tear production will be evaluated by Schirmer's test in this study to determine if changes in this parameter may be helpful to identify subjects at higher risk of developing corneal epitheliopathy.

Treatment-emergent abnormal values in the Schirmer test (dry eye) should be evaluated and managed by an ophthalmologist to provide adequate protection to the corneal epithelium.

Remedial therapy for treatment-emergent changes in Schirmer test (dry eye) should be chosen at the investigator's discretion or according to institutional standards. These measures may include topical lubricants such as eye drops and ointments, punctual occlusion, use of therapeutic contact lenses, and / or any other locally approved treatment chosen at the discretion of the investigator and the ophthalmologist. Ophthalmological monitoring should be maintained until changes in the Schirmer test (dry eye) have resolved.

Increases in the intraocular pressure (IOP) may occur in some subjects with corneal epitheliopathy as a consequence of remedial therapy with topical steroid eye drops. Because this treatment may be required for adequate remedial treatment of corneal epitheliopathy, IOP will be monitored during this study.

Treatment-emergent changes in IOP should be evaluated and managed by an ophthalmologist.

Remedial therapy for IOP changes should be chosen at the investigator's discretion or according to institutional standards. These measures can include modification of the type or posology of topical steroid eye drop, initiation of topical IOP lowering drugs, or any other locally approved treatment chosen at the discretion of the investigator and the ophthalmologist. Ophthalmological monitoring should be maintained until IOP changes have resolved.

8.16 Continuation of anetumab ravtansine after treatment modification

Anetumab ravtansine treatment may be restarted at the appropriate dose if the TEAE requiring treatment modification has resolved to CTCAE Grade 1. Treatment modification epitheliopathy) within 42 days after the last dose of anetumab ravtansine (i.e., the next scheduled dose would be delayed by ≤21 days).

If treatment modification of anetumab ravtansine is caused by a hematological TEAE, and the continuation of treatment is appropriate at investigator's discretion, the anetumab ravtansine dose will be adjusted as described in table below.

8.17 Anetumab ravtansine dose adjustments in response to neutrophil and platelet nadir counts of the previous cycle:

CTCAE System/Organ/Class (SOC)	GRADE	ADVERSE EVENT	AGENT	ACTION**
INVESTIGATIONS	Grade 2	Neutrophil count decrease >500 or <500 for <7 days AND Platelet count decreased ≥25,000	Anetumab ravtansine	No change
INVESTIGATIONS	Grade	Neutrophil count decrease <500 for ≥7 days **AND** Platelet count decreased <25,000 for ≥7 days with or without active bleeding, **OR** <50,000 for ≥7 days with clinically significant bleeding [b]	Anetumab ravtansine	Decrease 1 dose level
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Grade 3	Febrile neutropenia **AND** Platelet count <25,000 for ≥7 days with or without active bleeding, **OR** <50,000 for ≥7 days with clinically significant bleeding [b]		Decrease 1 dose level

a Anetumab ravtansine dose reduction by 1 dose level translates to a change from 6.5 mg/kg (BW) Q21D to 5.5 mg/kg Q21D, or from 5.5 mg/kg Q21D to 4.5 mg/kg Q21D.
b Clinically significant bleeding is that which requires platelet transfusion.
c Febrile neutropenia is defined as ANC < 500 with fever of >38.3°C [101°F] or a sustained body temperature of ≥38.0°C [100.4°F] for more than one hour).

If anetumab ravtansine treatment modification is required due to a nonhematological TEAE, and the continuation of anetumab ravtansine treatment is appropriate at the investigator's discretion, then the anetumab ravtansine dose will be reduced after CTCAE Grade 4 nonhematologic TEAE and Bayer Grade 3 corneal epitheliopathy, or either reduced or maintained at the investigator's discretion after CTCAE Grade 3 non-hematologic TEAE or Bayer Grade 2 corneal epitheliopathy change (attached table).

The anetumab ravtansine dose reduction due to nonhematological TEAEs will be performed by 1 mg/kg Q21D as appropriate, i.e., from 6.5 mg/kg Q21D to 5.5 mg/kg Q21D, or from 5.5 mg/kg Q21D to 4.5 mg/kg Q21D.

If treatment interruption is caused by a CTCAE Grade 2 or 3 anetumab ravtansine infusion related reaction or other CTCAE Grade 2 or 3 hypersensitivity events deemed at least possibly related to anetumab ravtansine, treatment may be restarted at the time determined at the investigator's discretion. Retreatment should be started at the infusion rate reduced by 50%, along with anti-allergic prophylaxis (e.g., antihistamines, acetaminophen, and / or corticosteroids) chosen at the investigator's discretion (but not to exceed 42 days since last dose) or according to institutional guidelines.

Treatment with anetumab ravtansine should be withdrawn if a TEAE resolved to CTCAE Grade ≤ 1 (or Bayer severity Grade ≤ 2 for corneal epitheliopathy) in >42 days after the last dose of anetumab ravtansine.

Dose re-escalation

Dose re-escalation for anetumab ravtansine after dose reduction is not allowed, except reescalation after dose reduction for corneal epitheliopathy if the first Grade 3 event resolves to Grade ≤ 2 within 21 days and does not recur.

8.2 Treatment Delay and Dose Reduction of Atezolizumab

8.21 General AE Management and Dose Modification Guidelines

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment for up to 84 days (12 weeks) beyond the scheduled date of delayed infusion if study drug-related toxicity requiring dose suspension is experienced. If atezolizumab is held because of AEs for ≥84 days beyond the scheduled date of infusion, the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in this protocol.

If a patient must be tapered off steroids used to treat AEs, atezolizumab may be held for additional time beyond 84 days (12 weeks) from the scheduled dose until steroids are discontinued or reduced to a prednisone dose (or dose equivalent) of 10 mg/day. The acceptable length of interruption will be at the discretion of the investigator.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed.

Any toxicity associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology. Although most immune- related adverse events (irAEs) observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (20) (Appendix C). Discontinuation of atezolizumab may not have an immediate therapeutic effect, and there is no available antidote for atezolizumab. In severe cases, immune-related toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents. The investigator should consider the benefit-risk balance prior to further administration of atezolizumab. In patients who have met

the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving clinical benefit and has fully recovered from the immune-related event.

Patients can be re-challenged with atezolizumab ONLY after careful consideration of benefit- risk balance and medical judgment by the trial Principal Investigator. Atezolizumab may NOT be resumed if the patient experiences any of the following events, regardless of benefit:

- Grade 3 or 4 pneumonitis
- AST or ALT >5×ULN or total bilirubin >3×ULN
- Grade 4 diarrhea or colitis
- Grade 4 hypophysitis
- Any grade myasthenic syndrome/myasthenia gravis, Guillain-Barré, or meningoencephalitis
- Grade 3 or 4 ocular inflammatory toxicity
- Grade 4 or any grade of recurrent pancreatitis
- Grade 3 or 4 infusion-related reactions
- Grade 4 rash

Treatment may, under limited and compelling circumstances, be resumed in patients who have recovered from the following events after consultation with the trial Principal Investigator:

- Grade 2 pneumonitis
- Grade 2 ocular inflammatory toxicity
- Grade 2 infusion-related reactions

For detailed information regarding management of adverse events associated with atezolizumab, please refer to the most current version of the Atezolizumab Package Insert and the FDA product label.

The primary approach to grade 1 to 2 irAEs is supportive and symptomatic care with continued treatment with atezolizumab; for higher-grade irAEs, atezolizumab should be withheld and oral and/or parenteral steroids administered. Recurrent grade 2 irAEs may also mandate withholding atezolizumab or the use of steroids. Assessment of the benefit-risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in patients with life-threatening irAEs.

Patients should be assessed clinically (including review of laboratory values) for toxicity prior to, during, and after each infusion. If unmanageable toxicity due to atezolizumab occurs at any time during the study, treatment with atezolizumab should be discontinued.

8.22 Management of Specific AEs

Management of certain AEs of concern are presented in the table below as they have been observed with this agent and are potentially immune related.

8.221 Pleural and pericardial effusion: Patients experiencing dyspnea, chest pain, or unexplained tachycardia should be evaluated for the presence of

a pericardial effusion. Patients with pre- existing pericardial effusion should be followed closely for pericardial fluid volume measurements and impact on cardiac function. When intervention is required for pericardial or pleural effusions, atezolizumab should be held, and appropriate workup includes cytology, lactate dehydrogenase (LDH), glucose, cholesterol, protein concentrations (with pleural effusions), and cell count.

8.222 Pulmonary events: Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have CT scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in the table below.

8.223 Endocrine disorders: Patients experiencing one or more unexplained AEs possibly indicative of endocrine dysfunction (including fatigue, myalgias, impotence, mental status changes, and constipation) should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free T3 and T4 levels should be obtained to determine whether thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency. The table below describes dose management guidelines for hyperthyroidism, hypothyroidism, symptomatic adrenal insufficiency, and hyperglycemia.

8.224 Meningoencephalitis: Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines.

8.225 Neurologic disorders: Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies.

8.226 The table below presents management and dose modification guidelines for specific AEs. For recommendations to hold atezolizumab and begin corticosteroid treatment, use the following guidance for tapering the corticosteroid and resuming atezolizumab therapy after resolution of the event:

- Corticosteroids must be tapered over ≥1 month to <10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- Atezolizumab may be held for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≥10 mg/day oral prednisone or equivalent.
- If the recommended course of action in the table below is to "permanently discontinue atezolizumab," resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event under limited and compelling circumstances after consultation with the trial Principal Investigator.

CTCAE SOC	Adverse Event	Grade	Dose Adjustment and Management Recommendations
Endocrine disorders	Adrenal insufficiency	Grade 2+ (symptomatic)	Hold atezolizumab. Refer patient to endocrinologist. Perform appropriate imaging. Initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. Resume atezolizumab if event resolves to grade 1 or better and patient is stable on replacement therapy (if required) within 12 weeks. Permanently discontinue atezolizumab and contact Medical Monitor if event does not resolve to grade 1 or better or patient is not stable on replacement therapy within 12 weeks.
	Hyperthyroidism	Grade 1 (asymptomatic)	TSH ≥0.1 mU/L and <0.5 mU/L: Continue atezolizumab. Monitor TSH every 4 weeks. TSH <0.1 mU/L: Follow guidelines for symptomatic

CTCAE SOC	Adverse Event	Grade	Dose Adjustment and Management Recommendations
			hyperthyroidism.
		Grade 2+ (symptomatic)	Hold atezolizumab. Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. Consider patient referral to endocrinologist. Resume atezolizumab when symptoms are controlled and thyroid function is improving. Permanently discontinue atezolizumab and contact CTEP Medical Monitor for life-threatening immune-related hyperthyroidism.
	Hypothyroidism	Grade 1 (asymptomatic)	Continue atezolizumab. Start thyroid-replacement hormone. Monitor TSH weekly.
		Grades 2+ (symptomatic)	Hold atezolizumab. Start thyroid-replacement hormone. Consider referral to an endocrinologist. Monitor TSH weekly. Restart atezolizumab when symptoms arecontrolled and thyroid function is improving.
Eye disorders	Uveitis or retinopathy	Grade 1	Continue atezolizumab. Patient referral to ophthalmologist is strongly recommended. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. If symptoms persist, treat as a grade 2 event.
		Grade 2	Hold atezolizumab. Patient referral to ophthalmologist is strongly recommended. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. Resume atezolizumab if event resolves to grade 1 or better within 12 weeks. Permanently discontinue atezolizumab and contact Medical Monitor if event does not resolve to grade 1 or better within 12 weeks.
		Grade 3 or 4	Permanently discontinue atezolizumab and contact Medical Monitor. For grade 3, patient may only resume treatment after consultation with the trial PI; for grade 4, patient cannot resume treatment, regardless of benefit. Refer patient to ophthalmologist. Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent.

CTCAE SOC	Adverse Event	Grade	Dose Adjustment and Management Recommendations
			If event resolves to grade 1 or better, taper corticosteroids over ≥1 month
Gastrointestinal disorders	Diarrhea or entercolitis	Any grade	Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased CRP, f count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.
		Grade 1	Continue atezolizumab. Initiate symptomatic treatment. Endoscopy is recommended if symptoms persist for ≥7 days. Monitor closely.
		Grade 2	Hold atezolizumab. Initiate symptomatic treatment. Patient referral to GI specialist is recommended. For recurrent events or events that persist >5 days, initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. Resume atezolizumab if event resolves to grade 1 or better within 12 weeks. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab and contact Medical Monitor if event does not resolve to grade 1 or better within 12 weeks. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event.
		Grade 3	Hold atezolizumab. Refer patient to GI specialist for evaluation and confirmatory biopsy. Initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon

CTCAE SOC	Adverse Event	Grade	Dose Adjustment and Management Recommendations
			improvement. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event.
		Grade 4	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Refer patient to GI specialist for evaluation and confirmation biopsy. Initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to grade 1 or better, taper corticosteroids over ≥1 month. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event.
	Pancreatitis (immune related)	Grade 2 or 3	Hold atezolizumab. Refer patient to GI specialist. Initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. Resume atezolizumab if event resolves to grade 1 or better within 12 weeks. Permanently discontinue atezolizumab and contact Medical Monitor if event does not resolve to grade 1 or better within 12 weeks. For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. Patient may not resume treatment, regardless of benefit.
		Grade 4	Permanently discontinue atezolizumab and contact Medical Monitor. Patient may not resume treatment, regardless of

CTCAE SOC	Adverse Event	Grade	Dose Adjustment and Management Recommendations
			benefit Refer patient to GI specialist. Initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to grade 1 or better, taper corticosteroids over 1 month.
Infections and infestations	Meningitis or encephalitis	All grades	Permanently discontinue atezolizumab and contact Medical Monitor. Patient may not resume treatment, regardless of benefit. Refer patient to neurologist. Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. If event resolves to grade 1 or better, taper corticosteroids over ≥1 month. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.
Investigations	Lipase increase or serum amylase increase	Grade 1 >ULN - 1.5 x ULN	Continue atezolizumab. Monitor amylase and lipase prior to dosing.
		Grade 2 (>1.5 - 2.0 x ULN)	Continue atezolizumab. Monitor amylase and lipase weekly.

CTCAE SOC	Adverse Event	Grade	Dose Adjustment and Management Recommendations
		Grade 3 (>2.0 - 5.0 x ULN) or 4 (>5.0 x ULN)	Hold atezolizumab. Refer patient to gastrointestinal (GI) specialist. Monitor amylase and lipase every other day. If no improvement, consider treatment with 1-2 mg/kg/day oral prednisone or equivalent. Resume atezolizumab if event resolves to grade 1 or better within 12 weeks. Permanently discontinue atezolizumab and contact Medical Monitor if event does not resolve to grade 1 or better within 12 weeks. For recurrent events associated with pancreatitis symptoms, permanently discontinue atezolizumab and contact Medical Monitor. Treatment for recurrent events not associated with pancreatitis symptoms may be resumed after consultation with the trial Principal Investigator.
Metabolism and nutrition disorders	Hyperglycemia	Grade 1 or 2	Continue atezolizumab. Initiate treatment with insulin if needed. Monitor for glucose control.
		Grade 3 or 4	Hold atezolizumab. Initiate treatment with insulin. Monitor for glucose control. Resume atezolizumab when symptoms resolve and glucose levels are stable.
Nervous system disorders	Peripheral motor neuropathy or Peripheral sensory neuropathy	Grade 1	Continue atezolizumab. Evaluate for alternative etiologies.
		Grade 2	Hold atezolizumab. Evaluate for alternative etiologies. Initiate treatment as per institutional guidelines. Resume atezolizumab if event resolves to grade 1 or better within 12 weeks. Permanently discontinue atezolizumab and contact Medical Monitor if event does not resolve to grade 1 or better within 12 weeks.
		Grade 3 or 4	Permanently discontinue atezolizumab and contact Medical Monitor. Initiate treatment as per institutional guidelines.
Respiratory, thoracic and	All pulmonary events	All grades	Evaluate thoroughly for other commonly reported etiologies such as

CTCAE SOC	Adverse Event	Grade	Dose Adjustment and Management Recommendations
mediastinal disorders			pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease (COPD), or pulmonary hypertension.
		Grade 1	Continue atezolizumab and monitor closely. Re-evaluate on serial imaging. Consider patient referral to a pulmonary specialist. For recurrent pneumonitis, treat as a grade 3 or 4 event.
		Grade 2	Hold atezolizumab. Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or bronchoscopic alveolar lavage (BAL). Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. Resume atezolizumab if event resolves to grade 1 or better within 12 weeks (consult tapering guideline above). Permanently discontinue atezolizumab and contact Medical Monitor if event does not resolve to grade 1 or better within 12 weeks. For recurrent events, treat as a Grade 3 or 4 event.
		Grade 3 or 4	Permanently discontinue atezolizumab and contact Medical Monitor. For grade 3, patient may only resume treatment after consultation with the trial PI For grade 4, patient may not resume treatment, regardless of benefit. Bronchoscopy or BAL is recommended. Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.
Skin and subcutaneous tissue disorders	Rash maculo-papular or purpura	Grade 1	Continue atezolizumab. Consider topical steroids and/or other symptomatic therapy (e.g., antihistamines).
		Grade 2	Continue atezolizumab. Consider dermatologist referral. Administer topical corticosteroids. Consider higher potency topical corticosteroids if event does not improve.

CTCAE SOC	Adverse Event	Grade	Dose Adjustment and Management Recommendations
		Grade 3	Hold atezolizumab. Refer patient to dermatologist. Administer oral prednisone 10 mg or equivalent. If the event does not improve within 48-72 hours, increase dose to1–2 mg/kg/day or equivalent. Restart atezolizumab if event resolves to grade 1 or better within 12 weeks. Permanently discontinue atezolizumab and consult CTEP Medical Monitor if event does not resolve to grade 1 or better within 12 weeks.
		Grade 4	Permanently discontinue atezolizumab and contact CTEP Medical Monitor. Patient may not resume treatment, regardless of benefit.
		Persistent and/or severe rash or pruritus, any grade	A dermatologist should evaluate the event. A biopsy should be performed unless contraindicated.
Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with administration of other immunomodulatory agents. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for obstruction, as well as serum amylase and lipase tests. See the guidelines for "Amylase and/or lipase increase" and "Immune- related pancreatitis" elsewhere in this table, as needed. Right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should be evaluated for potential hepatotoxicity (see the "Hepatotoxicity" guideline elsewhere in this table).			
Myasthenia gravis and Guillain-Barré syndrome All grades Permanently discontinue atezolizumab and contact Medical Monitor. Patient may not resume treatment, regardless of benefit. Refer patient to neurologist. Initiate treatment as per institutional guidelines. Consider initiation of 1-2 mg/kg/day oral or IV prednisone or equivalent.			

8.3 Duration of Treatment

In the absence of treatment delays due to adverse event(s), treatment may continue for until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

9.0 Ancillary Treatment/Supportive Care

9.1 Full Supportive Care

Patients should receive full supportive care while on this study, per physician discretion. This includes blood product support, antibiotic treatment and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, anti-emetics received from the first administration of study drugs until 30 days after the final dose are to be recorded in the medical record.

9.2 Anti-emetics

Participants may be pretreated for nausea and vomiting with appropriate anti-emetics.

9.3 Diarrhea

Diarrhea could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.4 Prohibited prior treatments and concomitant medications/conditions

9.41 Patients who have received systemic antitumor therapy (except topical or intracavitary treatments with negligible absorption in systemic circulation) within 28 days before the start of anetumab ravtansine, or within 5 half-lives of the chemotherapeutic agent before the start of anetumab ravtansine, whichever is longer. Mitomycin C or nitrosoureas must be excluded within 42 days before the start of anetumab ravtansine.

- Systemic antitumor therapy is defined as any agent or combination of agents with clinically proven antineoplastic activity that achieves non-negligible systemic bioavailability after being administered by any route for affecting the malignancy, either directly or indirectly, including palliative and therapeutic endpoints. This includes, but is not limited to, cytotoxic therapy, targeted agents, anti-cancer immunotherapy, hormonal therapy, experimental therapy or device.

9.42 Patients who have received granulocyte colony-stimulating factors (G-CSFs) or granulocyte macrophage-stimulating factors (GM-CSFs) within 21 days before the start of screening.

9.43 Patients who have received erythropoietin-stimulating agents (epoetin alpha, darbepoetin alpha) within 21 days before the start of screening. Patients on chronic therapy with erythropoietin-stimulating agents may be eligible at the investigator's discretion, provided no dose adjustment is undertaken from 21 days before the start of screening until the end of therapy.

9.44 Blood transfusions within 21 days before C1D1

9.45 Platelet transfusions within 21 days before C1D1

9.46 Anti-arrhythmic therapy other than beta blockers or digoxin during study treatment until safety follow-up visit.

9.47 Acute steroid therapy or taper. Exceptions include chemotherapy pre- and post-medication and allergic reaction (e.g. infusion related reaction, contrast media reaction, etc.) management. Chronic steroid therapy is allowed provided that the dose is stable for 30 days before the start of study treatment and thereafter for the duration of study treatment.

9.48 Concomitant live attenuated virus vaccines (e.g. yellow fever) within 14 days before C1D1 until safety follow-up visit.

9.49a Use of therapeutic oral or parenteral anticoagulation therapy started within 14 days before the start of anetumab ravtansine until the end of therapy. Aspirin at a dose ≤100 mg per day is permitted.

9.49b No prior treatment with anetumab ravtansine (or any other mesothelin-based therapy) or any vinca-containing compound or spindle poison.

9.49c No prior use of experimental therapy (defined as not approved for this indication) or device for systemic anti-cancer treatment.

9.49d Patients who have a recent history (within 28 days before the start of anetumab ravtansine) of abusing alcohol, prescription or illicit drugs, or of medical, psychological, or social conditions that may interfere with the patient's compliance in this study.

10.0 Adverse Event (AE) Monitoring and Reporting

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting [redacted]	Mayo Sites – attach to MCCC Electronic SAE Reporting Form
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form [redacted] AND attach MedWatch 3500A: [redacted]	Will automatically be sent to [redacted]

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest

Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

Unanticipated Adverse Device Event (UADE)
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:
[redacted]

a. Identify the grade and severity of the event using the CTCAE version 4.0.

b. Determine whether the event is expected or unexpected (see Section 10.2).

c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

e. Determine if other reporting is required (see Section 10.5).

f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

   NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to Agent(s) or Procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.31 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME (Combination) Arm

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting.**

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for **investigational** agents/interventions.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report, unless hospitalization is required. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

- An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.
- Commercial agent expedited reports must be submitted to the FDA via MedWatch 3500A for Health Professionals (complete all three pages of the form).

  http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

  or

  http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/ListFormsAlphabetically/default.htm

  Instructions for completing the MedWatch 3500A:

http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM387002.pdf

10.32 EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*

*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.
*Report an expected event that is greater in severity or specificity than expected as an expedited event.

System Organ Class (SOC)	**Adverse Event/ Symptoms**	CTCAE Grade at which the event **will not** be expeditedly reported[1].
General disorders and administration site conditions	Fatigue	Grade 2
	Chills	
	Fever	
	Flu-like symptoms	
Blood and lymphatic systems disorder	Anemia	Grade 2
Metabolism and nutrition disorders	Anorexia	Grade 2
	Hyperglycemia	Grade 1
Investigations	Alanine aminotransferase increased	Grade 1
	Aspartate aminotransferase increased	
	Lymphocyte count decreased	
	Platelet count decreased	
	White blood cell count decreased	
Gastrointestinal disorders	Nausea	Grade 2
	Vomiting	
	Diarrhea	
	Dyspepsia	
Skin and subcutaneous tissue disorders	Rash maculo-papular	Grade 2
	Pruritus	Grade 2
Musculoskeletal and	Arthralgia	Grade 2

System Organ Class (SOC)	Adverse Event/ Symptoms	CTCAE Grade at which the event **will not** be expeditedly reported[1].
connective tissue disorders	Myalgia	

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization or other serious outcomes for signs and symptoms of progression of the cancer.

10.4 Expedited Reporting Requirements for IND/IDE Agents

10.41 Phase I and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

NOTE: Refer to Section 10.32 for exceptions to Expedited Reporting

10.42 General reporting instructions

The Mayo IND Coordinator will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report form [redacted] for investigational agents or commercial/investigational agents on the same arm.

Mayo Clinic Cancer Center (MCCC) Institutions:

Submit using Mayo Expedited Event Report form [redacted] AND attach MedWatch 3500A: [redacted] which will be copied to the following email address: [redacted]. This email will be managed by the SAE, IND and Safety Reporting Coordinators.

10.43 Reporting of Reoccurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:
If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, use Mayo Expedited Event Report form [redacted] and provide appropriate documentation to [redacted] The Mayo Regulatory Affairs Office will review and process the submission to the Mayo Clinic IRB.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE will be reported. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

10.55 Pregnancy, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form:

[redacted]

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other**

(pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.554 Corneal epitheliopathy is considered as AE of special interest. Specific dose modification schemes are defined in the Protocol. An alternative severity grading system for corneal epitheliopathy will be used in addition to the CTCAE criteria, since the CTCAE may not adequately capture the severity of these novel adverse reactions (see Table 7–9 and Table 7– 10). The relationship to treatment and the intensity of corneal epitheliopathy will be determined by the investigator, in consultation with the ophthalmologist, using the terms and definitions given in Section 9.6.1.2. There is no need for expedited reporting to report corneal epitheliopathy, unless it meets the criteria for an SAE; however these events will need to be closely monitored.

10.6 Required Routine Reporting

10.61 Baseline and Adverse Events Evaluations

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation. Grading is per CTCAE v4.0 **unless** alternate grading is indicated in the table below:

CTCAE System Organ Class (SOC)	Adverse Event/ Symptoms	Baseline	Each Evaluation
General disorders and site administration conditions	Fatigue	x	x
	Fever	x	x
	Flu-like symptoms	x	x
Skin and subcutaneous tissue disorders	Rash maculo-papular	x	x
	Pruritus	x	x
Gastrointestinal disorders	#stools each day	x	
	diarrhea		x
	nausea	x	x
	vomiting	x	x

CTCAE System Organ Class (SOC)	Adverse Event/ Symptoms	Baseline	Each Evaluation
Respiratory, thoracic and mediastinal disorders	dyspnea	x	x

10.62 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.621 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

- Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.
- Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

Report to Bayer: All SAE reports regardless of suspected causality on the date of receipt or within 24 hours after learning of the event by Investigator/Sponsor:

Electronic Mailbox: [redacted]

Facsimile: [redacted]

Address: Global Pharmacovigilance - USA
Mail only: [redacted]

Address: [redacted]
FDX or UPS only: [redacted]

Phone: [redacted]

11.0 Treatment Evaluation Using RECIST Guideline

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measureable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1)[22]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations:

For the purposes of this study, patients should be reevaluated every 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: Tumor lesions in a previously irradiated area are not considered measurable disease.

11.22 Non-Measurable Disease

11.221 All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

NOTE: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- Chest X-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scans are preferable.
- Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.33 Measurement at Follow-up Evaluation:

- A subsequent scan must be obtained at least 4 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).
- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see Section 11.44).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between

response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.21), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

Complete Response (CR): All of the following must be true:

a. Disappearance of all target lesions.

b. Each target lymph node must have reduction in short axis to <1.0 cm.

Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).

Progression (PD): At least one of the following must be true:

a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis

of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

Complete Response (CR): All of the following must be true:

a. Disappearance of all non-target lesions.

b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

Progression (PD): At least one of the following must be true:

a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following table:

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the NCCTG protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

11.45 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

12.0 Descriptive Factors

12.1 Number of prior regimens ≤2 versus > 2

12.2 Dose Level

To be assigned by Registration Office: -1 vs. 1 vs. 2

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Continuation of treatment

Patients who are CR, PR, or SD will continue treatment per protocol.

13.2 Progressive disease (PD)

Patients who develop PD while receiving therapy will go to the event-monitoring phase.

13.3 Off protocol treatment

Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase per Section 4.0.

13.4 CNS PD

Patients who develop PD in the CNS only should receive local therapy and continue treatment on study after completion of local therapy for up to a total of 6 cycles.

13.5 Non-CNS PD

Patients who develop non-CNS PD at any time should go to event monitoring. These patients should be treated with alternative chemotherapy if their clinical status is good enough to allow further therapy.

13.6 Inevaluable patients

If a patient fails to complete the first cycle (21 days) of treatment for reasons other than toxicity, the patient will be regarded as inevaluable and will be replaced during the phase I portion of the trial.

13.7 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 4.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per Section 4.0 of the protocol.

13.8 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 4.0 of the protocol.

13.9 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood Specimens to be Collected for this Protocol

Correlative Study	Mandatory or Optional	Blood to Collect	Type Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Days to be Collected	Storage /Shipping
Biomarker study	Mandatory	Whole blood	EDTA (purple top)	6 mL (3)	Screen, C3D1, C5D1, C7D1	Ambient
Biomarker study	Optional	Whole blood	EDTA (purple top)	6 mL (3)	At disease progression	Ambient

14.2 Collection and Processing

14.21 Whole blood samples will be collected via venipuncture for immune analysis (peripheral t-cell and other leukocyte phenotypes). Samples will be collected using 3 anticoagulant, spray-coated K2EDTA (plastic) purple-top tubes at the following timepoints:

- Screen
- Cycle 3 Day 1, Cycle 5 Day 1 and Cycle 7 Day 1 (prior to treatment)
- Optional at disease progression

14.22 Samples will be kept at ambient temperature prior to processing.

14.23 Samples will be processed and analyzed in Dr. Haidong Dong's laboratory. Dr. Dong's lab will pick up samples as soon as they are drawn for Rochester. For MCF and MCA ship ambient overnight so that samples arrive within 24 hours of being drawn.

14.3 Shipping and Handling

14.31 Kits *will not* be used for this study.

14.32 Samples collected in Rochester will picked up by [redacted] lab.

14.33 Fresh (not frozen) samples collected at Florida or Arizona will be shipped overnight via Fed Express Monday through Thursday only (do not ship on a Friday or the day before a holiday) at ambient temperature to:

[redacted]
Mayo Clinic
[redacted]
Telephone: [redacted]

15.0 Drug Information

15.1 Anetumab Ravtansine (BAY 94-9343)

15.11 **Background:** Anetumab ravtansine is an antibody drug conjugate consisting of the monoclonal antibody BAY 86-1903 directed against the mesothelin antigen, a SPDB- (N-succinimidyl-4-(2-pyridyldithio) butanoate) linker and the tubulin polymerization inhibitor N-methyl-N- [4-mercapto-4-methyl-1-oxopentyl-L-alanine ester of maytansinol (DM4; BAY 1006640).

15.12 **Formulation**: Anetumab ravtansine is supplied as a freeze-dried product containing 60 mg anetumab ravtansine in a 30 mL injection vial. The following excipients are used to manufacture the medicinal drug product: histidine, hydrochloric acid, glycine, sucrose, polysorbate 80, and water for injection.

15.13 **Preparation and storage**: Vials containing the freeze dried product should be stored at 2-8°C. The lyophilisate is reconstituted with 11.9 mL sterile water for injection to produce a 5 mg/mL solution of active substance. The solution is further diluted in 0.9% sodium chloride or dextrose 5% solution (in a PVC or non-PVC infusion bag) to a concentration range of 0.1-3 mg/mL. A slight turbidity may occur during the dilution which does not affect the quality of the drug product. The reconstituted and diluted solutions are physically and chemically stable for 24 hours at room temperature and between 2-8°C. However, unless administered immediately, for microbiologic consideration, the reconstituted and diluted solutions should be stored between 2°C and 8°C and used within 6 hours. Exposure to bright light should be avoided.

15.14 **Administration**: Infuse over 60 minutes using an in-line 0.2 micron infusion filter.

15.15 **Pharmacokinetic information**: (Based on limited information from a small sample size). Maximum plasma concentrations of the anetumab ravtansine and total antibody were typically observed within 1 hour of end of infusion and, at the MTD of 6.5 mg/kg every three weeks, concentrations declined with geometric mean terminal phase t1/2 values of approximately 5 to 6 days.

15.16 **Potential Drug Interactions**: No data available.

15.17 **Known potential toxicities:** Corneal epithelial microcysts (15.8%), keratitis (28.9%), vision blurred (26.3%). diarrhea (52.6%), nausea (57.9%), vomiting (39.5%), infusion-related reaction (10.5%), asthenia (15.8%), fatigue (63.2%), ALT increased (18.4%), AST increased (28.9%), platelet count decreased (21.1%), decreased appetite (50.0%), peripheral neuropathy (21.1%)

15.18 **Drug procurement**: Bayer will provide drug to Biologics, Inc. Each participating site will order/monitor drug supply. Fax the Drug Order Request Form (found in the forms packet) to:

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.19 **Nursing Guidelines:**

15.191 Infusion is over 60 minutes and requires an in line 0.2 micron infusion filter.

15.192 Given the early nature of this agent, not all side effects can be known at this time. Monitor patients closely and report any side effects to the study team.

15.193 Monitor LFT's , instruct patients to report abdominal pain and/or jaundice to study team.

15.194 Gastrointestinal side effects are common. Treat symptomatically and monitor for effectiveness.

15.195 Infusion related reaction can occur. Be sure to have emergency equipment available during infusion and monitor patient per protocol during infusion.

15.196 Eye related toxicity can occur and includes corneal epithelial microcysts, keratitis, and blurred vision. Instruct patients to report any visual changes, pain, tearing, etc to the study team immediately.

15.197 Fatigue is very common. Instruct patient in energy conserving lifestyle and monitor level of fatigue throughout treatment.

15.198 Peripheral neuropathy can be seen. Instruct patients to report any pain, numbness or tingling of the hand or feet to the study team immediately.

15.2 **Atezolizumab** for IV Administration

15.21 **Background**: Atezolizumab is a human immunoglobulin (IgG1) monoclonal antibody that is produced in Chinese hamster ovary (CHO) cells. Atezolizumab targets programmed death-ligand 1 (PD-L1) on immune cells or tumor cells and prevents interaction with either programmed death−1 (PD-1) receptor or B7.1 (CD80), both of which function as inhibitory receptors expressed on T cells. Interference of the PD-L1:PD-1 and PD-L1:B7.1 interactions may enhance the magnitude and quality of the tumor-specific T-cell response through increased T-cell priming, expansion, and/or effector function. Atezolizumab shows anti-tumor activity in various nonclinical models and is being investigated as a potential therapy for cancer patients with locally advanced or metastatic malignancies.

15.22 **Formulation**: Atezolizumab is supplied in a single use vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

15.23 **Preparation and storage**: Atezolizumab must be refrigerated at 2°C−8°C (36°F−46°F) upon receipt until use. No preservative is used in atezolizumab drug product; therefore, the vial is intended for single use only. Discard any unused portion of drug left in a vial. Vial contents should not be frozen or shaken and should be protected from direct sunlight. Atezolizumab is administered using 0.9% sodium chloride 250 mL IV bags and infusion lines equipped with

0.2 micron in-line filters (filter membrane of polyethersulfone [PES]). Bags may be constructed of polyvinyl chloride (PVC) or polyolefin (PO).

15.24 **Administration:** The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse effects, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes.

15.25 **Pharmacokinetic information**:
Distibution: V_{dss}: 6.9 L
Half-life elimination: 27 days
Hepatic Impairment: No clinically relevant effect with mild hepatic impairment. The effect of moderate or severe hepatic impairment on the pharmacokinetics of atezolizumab is unknown.
Renal Impairment: No clinically relevant effect with renal impairment.

15.26 **Potential Drug Interactions**: No formal PK drug-drug interaction studies have been conducted with atezolizumab. The drug interaction potential of atezolizumab is unknown.

15.27 **Known potential toxicities**: Consult the package insert and investigator's brochure for the most current and complete information.
Common known potential toxicities, > 10%:
Cardiovascular: Peripheral edema
Central nervous system: Fatigue
Dermatologic: Skin rash, pruritus
Endocrine & metabolic: Hyponatremia
Gastrointestinal: Decreased appetite, nausea, constipation, colitis, diarrhea, abdominal pain, vomiting
Genitourinary: Urinary tract infection, hematuria
Hematologic & oncologic: Lymphocytopenia
Infection: Infection
Neuromuscular & skeletal: Back pain, neck pain, arthralgia
Respiratory: Dyspnea, cough
Miscellaneous: Fever
Less common known potential toxicities, 1% - 10%:
Cardiovascular: Venous thromboembolism
Central nervous system: Guillain-Barre syndrome, meningoencephalitis, myasthenia, myasthenia gravis, confusion
Endocrine & metabolic: Hyperglycemia, hypothyroidism, hypoalbuminemia, hyperthyroidism
Gastrointestinal: Increased serum amylase, increased serum lipase, pancreatitis, intestinal obstruction
Genitourinary: Urinary tract obstruction
Hematologic & oncologic: Anemia
Hepatic: Increased serum ALT/AST, hepatitis, increased serum alkaline phosphatase, serum bilirubin
Infection: Sepsis
Ophthalmic: Intraocular inflammation
Renal: Increased serum creatinine, acute renal failure

Respiratory: Pneumonitis, pneumonia
Miscellaneous: Infusion related reaction
Rare known potential toxicities, <1% (Limited to important or life-threatening):
Adrenocortical insufficiency, diabetes mellitus (with ketoacidosis), hypophysitis

15.28 **Drug procurement:** Atezolizumab will be from commercial sources.

15.29 **Nursing Guidelines:**

15.291 Anti PD-L1 side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids

15.292 Diarrhea can be common and can be very severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.

15.293 Rash/pruirits/dermatitis is seen. Patients should report any rash to the study team. Treat per section 8.0 and monitor for effectiveness.

15.294 Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.

15.295 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.

15.296 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysistis, and adrenal insufficiency) are a concern given the mechanism of action of this agent. Patients may present only with the vague sense of fatigue and "not feeling well" . Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.

15.297 Pancreatitis is possible with anti PD-L1 therapy based on mechanism of action. Instruct patients to report abdominal pain, nausea and vomiting to the study team.

15.298 Patients who are started on steroid therapy for any side effects of anti PD-L1 toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report

any increase or change in side effects with any dosage decrease as patients may need a slower taper.

16.0 Statistical Considerations and Methodology

16.1 Overview

This is a non-randomized Phase I/II study designed to identify the recommended dose of anetumab ravtansine combined with atezolizumab and confirmed response rate in second line therapy of advanced NSCLC.

16.11 Primary Endpoint

The primary endpoint of the phase I portion of this trial is to assess the maximum tolerated dose (MTD) of anetumab ravtansine combined with atezolizumab.

The primary endpoint of the phase 2 portion is the rate of confirmed response. A confirmed response is defined as a patient who has achieved a PR or CR on two consecutive evaluations at least 4 weeks apart. All patients meeting the eligibility criteria, who have signed a consent form and have begun treatment will be evaluable for response, unless they are determined to be a major violation. The first 6 months of treatment (i.e. 8 cycles) will be used to evaluate the primary endpoint of confirmed response.

16.12 Sample Size

In the phase I portion, the study may involve as few as 6 patients (2 DLTs in Dose Level 1 and Dose Level -1) or as many as 12 patients (6 for each Dose Level). In addition, up to 37 patients will be treated at the recommended Phase II dose during the study (6 from phase I, 31 from phase II). Therefore, the maximum number of evaluable patients is 43 because the recommended Phase II dose will include 6 patients from the phase I portion. An additional 6 patients may be accrued to account for patients that need to be replaced bringing the maximum overall accrual to 49.

16.13 Accrual Rate and Study Duration

Given previous data from Mayo, it is estimated that this study will accrue 2-3 patients per month. Each cohort of 3 will require approximately 2.5 months (1.5 months for accrual and treatment, and an additional month data maturity and evaluation) to assess. Therefore, the overall study duration (including enrolling, treatment and evaluation) will range approximately from minimum of 5 months (when only 2 cohorts are required) to a maximum of 10 months (when 4 cohorts of 3 are required) for the dose escalation (Phase I) portion of the trial. The additional patients at the MTD will require approximately 16 months to accrue and an additional 4 months to assess. This means the study will take somewhere between 25 months and 30 months.

16.2 **Phase I** Study Design

The primary endpoint of the phase I portion of this trial is to estimate the MTD of anetumab ravtansine combined with atezolizumab. A standard 3+3 phase I design will be utilized. Three patients will be treated at each dose level and observed for a minimum of three weeks (i.e. one full cycle) before new patients are treated. Doses will not be escalated in any individual patient.

16.21 MTD Definition

MTD is defined as the dose level below the lowest dose that induces dose-limiting toxicity (DLT) in at least one-third of patients (at least 2 of a maximum of 6 new patients). A total of 6 patients treated at the MTD will be sufficient to

identify common toxicities at the MTD. For instance, those toxicities with an incidence of at least 25% will be observed with a probability of at least 82% (1-(1-0.25)^6). Refer to Section 7.6 for definition of dose-limiting toxicity (DLT).

16.22 MTD Determination:
Dose Escalation: The phase I portion of this study will utilize a standard cohort of three design. The first cohort of three patients will be treated at dose level 1. Decisions on when and how to dose escalate are described below.

16.23 The first cohort of three patients will be treated at the starting dose level 1.

16.24 Three patients will be treated at a given dose level combination and observed for at least 21 days from start of treatment to assess toxicity.

16.25 If DLT is not seen in any of the 3 patients, 3 new patients will be accrued and treated at the next higher dose level. If DLT is seen in 2 or 3 of 3 patients treated at a given dose level, then the next 3 patients will be treated at the next lower dose level, if only 3 patients were enrolled and treated at this lower level.

16.26 If DLT is seen in 1 of 3 patients treated at a given dose level, up to 3 additional will be enrolled and treated at the same dose level. If DLT is seen in at least one of these additional three patients (≥2 of 6), the MTD will have been exceeded, and further accrual will cease to this cohort (see 16.113 for further details). If dose-limiting toxicity (DLT) is not seen in any of the three additional patients, 3 new patients will be accrued and treated at the next higher dose level.

16.27 After enrolling 6 patients on a specific dose level, if DLT is observed in at least 2 of 6 patients, then the MTD will have been exceeded and defined as the previous dose unless only 3 patients were treated at the lower dose level. In that case, 3 additional patients will be treated at this lower dose level such that a total of 6 patients are treated at the MTD to more fully assess the toxicities associated with the MTD.

16.28 Dose de-escalation: If DLT meets the stopping boundaries set by the above dose escalation algorithm at dose level 1 (for example, more than 1 out of 3 patients or more than 1 out of 6 patients), the next cohort of three patients will be entered at a dose level of -1. Further dose re-escalation will depend on the toxicity profile observed at dose level -1, and re-evaluation of the regimen by the study team may be done.

16.29a If a patient fails to complete the initial course of therapy (defined as drug administration and 21 days) for reasons other than DLT defined adverse events, the patient will be regarded as uninformative in regard to the primary study goal and an additional patient will be treated at the current dose level; however, all toxicity information will be utilized in the analysis.

16.29b Operating Characteristics for Phase I portion of trial

The following table gives the probability of dose escalation at a single dose level as a function of the true probability of DLT at that level using the Cohort 3+3 design described in section 16.2.

True Rate of DLT (%)	Probability of Dose Escalation
10	0.91
20	0.71

30	0.49
40	0.31
50	0.17

16.3 Analysis Plans for Phase I portion:

All the relevant results pertaining to toxicity, MTD, response, and timed endpoints will be examined in an exploratory and hypothesis-generating fashion. The small sample size and the heterogeneous patient population associated with phase I studies restricts the generalizability of the results. Any notable statistical result should only be viewed as preliminary evidence for further study in Phase II trials rather than a definitive finding in and of itself. All results will be shown overall and by dose level.

16.31 Adverse Events Profile

The number and severity of all adverse events (overall and by dose-level) will be tabulated and summarized in this patient population. The Grade 3+ adverse events will also be described and summarized in a similar fashion. This will provide an indication of the level of tolerance for this treatment combination in this patient group.

16.32 Toxicity Profile

The term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. Non-hematologic toxicities will be evaluated via the ordinal CTC standard toxicity grading. Hematologic toxicity measures of thrombocytopenia, neutropenia, and leukopenia will be assessed using continuous variables as the outcome measures (primarily nadir) as well as categorization via CTC standard toxicity grading. Overall toxicity incidence as well as toxicity profiles by dose level, patient and tumor site will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of these analyses.

16.33 To identify preliminary evidence of clinical activity (i.e. confirmed response, timed endpoints, etc.). A confirmed response is defined to be a CR or PR noted as the objective status on two consecutive evaluations at least 4 weeks apart. Confirmed response will be evaluated using the first 6 months of treatment. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response. Responses will be summarized by simple descriptive summary statistics delineating complete and partial responses as well as stable and progressive disease in this patient population.

The data on time-related variables will be summarized descriptively. These include time until any treatment related toxicity, time until treatment related grade 3+ toxicity, time until hematologic nadirs (ANC, platelets, hemoglobin), time to progression and time to treatment failure, where time to treatment failure is defined as the time from registration to documentation of progression, unacceptable toxicity, or refusal to continue participation by the patient.

Other clinical activity endpoints will also be explored, including overall survival, progression-free survival, etc. overall and by dose level. These endpoints will be more fully explored during the Phase II portion of the

study.

16.4 **Phase II** Statistical Design

16.41 Interim Analysis: In the expanded cohort part of the trial, 17 patients will be accrued (this will include the patients treated at the MTD from the phase I component). If 3 confirmed responses or less are observed in the first 17 eligible patients, then the trial will be terminated and the treatment deemed not worthy of further study. If at least 4 confirmed responses are observed among these 17 patients, then an additional 20 patients will be accrued to the second stage.

16.42 Final Analysis: If 11 or more confirmed responses are observed at the end of the trial in the first 37 eligible patients, the treatment will be considered promising. This design yields at least 90% probability of a positive result if the true response rate is at least 40%.

16.43 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the final decision rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.54.

16.44 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study

16.5 Analysis Plan for Phase II portion of trial

The analysis for this trial will commence at planned time points (see 16.3) and at the time the patients have become evaluable for the primary endpoint. The Statistician and Study Chair will make the decision, in accord with CCS Standard Operating Procedures, availability of data for secondary endpoints (e.g., laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is when last patient has been followed for at least 6 months.

16.51 Primary Outcome Analyses:

16.511 Definition: The primary endpoint of this trial is the proportion of patients who achieve a confirmed response. A confirmed response is defined as PR or CR noted as the objective status on two consecutive evaluations at least 4 weeks apart. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, unless they are determined to be a major violation.

16.512 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true success proportion will be calculated.

16.52 Secondary Outcome Analyses

16.522 Overall survival is defined as the time from registration to death due to any cause. The distribution of overall survival will be estimated using the method of Kaplan-Meier (Kaplan and Meier, 1958).

16.523 Progression-free survival is defined as the time from registration to the earliest date of documentation of disease progression or death due to any cause. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier. We will also report the 1-year progression free survival (PFS) rate for the combination of anetumab ravtansine and atezolizumab in 2nd-line NSCLC.

16.524 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.53 Correlative Analyses: Due to the small overall sample size, the results of these analyses will be considered exploratory and hypothesis-generating in nature.

To determine using flow cytometry the levels of Bcl-2 interacting mediator of cell death (BIM) in circulating CD8+ CD11a+ PD-1+ T-cells, in peripheral blood samples collected from patients prior to initiation of therapy (baseline) and correlating these with ORR during and following treatment with the combination regimen. We'll also determine tissue MSLN and PD-L1 expression and correlate with response to combination therapy with atezolizumab and anetumab ravtansine . Finally, we'll correlate baseline serum soluble PDL-1 (sPDL-1) with response to therapy. These data will be explored in a descriptive manner using basic data summaries and graphics.

16.54 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the final decision rule or used in any decision making processes; however, they will be included in final endpoint estimates and confidence intervals.

16.6 Data & Safety Monitoring:

16.61 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.62 Adverse Event Stopping Rules: The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

16.621 <u>Phase I (includes all phase I patients):</u>
By the nature of the "cohorts of three" phase I study design, stopping rules are in place for each dose level. Specifically, if 2 or more dose-limiting toxicities (DLTs) are observed during cycle 1 at any given dose level, accrual to that dose level will be stopped, and patients will

be accrued to the next lower dose level until a maximum of 6 patients are treated at the lower level. Note that a DLT that affects dose escalation is only that which is observed in the first cycle of treatment.

16.622 Phase II (includes all phase II patients, including phase I patients treated at the MTD):

Accrual will be temporarily suspended to this study if at any time we observe events with an attribution of possibly, probably, or definitely related to study treatment that satisfy one of the following:

- If 5 or more patients in the first 15 treated patients experience a grade 4 or higher non-hematologic adverse event
- If after the first 15 patients have been treated, 33% of all patients experience a grade 4 or higher non-hematologic adverse event.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.7 Results Reporting on ClinicalTrials.gov:

At study activation, this study will have been registered within the "ClincialTrials.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on www.ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 3 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has been followed for at least 6 months.

16.8 Inclusion of Women and Minorities

This study will be available to all eligible patients regardless of race, gender, or ethnic group. There is no information currently available regarding differential agent effects of either regimen in subsets defined by gender, race, or ethnicity, and there is no reason to expect such differences exist. Therefore, although the planned analyses will, as always, look for differences in treatment effect based on gender and racial groupings, the samples sizes are not increased in order to provide additional power for such subset analyses.

To predict the characteristics of patients likely to enroll in this trial we have reviewed the Mayo registration classified by race and gender. This revealed that roughly 3% of patients registered into cancer trials during the past three years could be classified as minorities and about 60% of patients were women. This would suggest that only 2 patients in the study sample are expected to be classified as minorities. This precludes the possibility of a separate subset analysis beyond simple inspection of results for the minority patients. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	1	1	**2**
Not Hispanic or Latino	28	19	**47**
Ethnic Category: Total of all subjects	**29**	**20**	**49**

Racial Category			
American Indian or Alaskan Native	0	0	**0**
Asian	0	1	**1**
Black or African American	1	0	**1**
Native Hawaiian or other Pacific Islander	0	0	**0**
White	28	19	**47**
Racial Category: Total of all subjects	**29**	**20**	**49**

Ethnic Categories:	**Hispanic or Latino** – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino." **Not Hispanic or Latino**
Racial Categories:	**American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment. **Asian –** a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.) **Black or African American –** a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American." **Native Hawaiian or other Pacific Islander –** a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. **White –** a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Tissue Biospecimens/Pathology Considerations

17.1 Summary Table of Research Tissue Specimens to be collected

Correlative Study (Section for more information)	Mandatory or Optional	Type of Tissue to Collect	Blocks/Slides /Cores	Collection	Process at site	Storage /Shipping
Archived	Mandatory	Paraffin embedded	1 H&E slide and 2 unstained 4 micron plus slides	Pre-registration	Yes	Ambient
Fresh tissue biopsy	Mandatory only if archival not available	Fresh	1-2 cores	Pre-registration	Yes	Ambient

17.2 Tissue collection and processing

Mandatory tissue collection at baseline for IHC mesothelin testing. If archival tissue is not available, a fresh biopsy must be completed Criteria for the submission of tissue are:

- Archival tissue must have been collected within 36 months prior to registration, not previously irradiated, and after diagnosis of metastatic disease.

17.21 Biopsy Procedure

If archival tissue not available a tumor biopsy will be obtained at baseline. If a site is deemed appropriate for biopsy with minimal risk to the participant by agreement between the investigators an attempt for biopsy will be made. Because approximately 20% of tumor biopsies collected on research trials are not usable due to the presence of stroma or normal and/or necrotic tissue and paired biopsies are necessary for analysis, up to 5 core biopsies 18-gauge in diameter and ≥1 cm in length will be obtained during each procedure to try and ensure adequate tumor content and quality. Cores from different areas of the tumor are preferred when feasible. An H&E stain for each core to identify whether the core actually contains tumor or not. Unstained slides for staining will need to be prepared from the cores. Acceptable biopsy procedures are:

- Percutaneous biopsy with local anesthetic.
- Excisional cutaneous biopsy with local anesthetic
- Other biopsy with local anesthetic and/or sedation that has been shown to have a risk of severe complications < 2%

17.22 Tissue kits will not be provided for this protocol.

17.23 Tissue submission

17.231 Submit 1 H&E slide and 2 unstained 4 micron plus slides for archival tissue and 1-2 tissue cores at baseline and if applicable, at disease progression.

17.232 The samples should be sent directly to the IHC Lab. If lab is not local, send by FedEx standard next day delivery service. Ship only Monday to Thursday to avoid delivery on a weekend. Ship samples to:

[redacted]

Mayo Clinic
[redacted]
Telephone: [redacted]

17.3 Mesothelin tissue analysis

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. Mesothelin expression will be prospectively evaluated for patient selection. All patients will provide formalin-fixed, paraffin-embedded (FFPE) tumor samples or fresh tissue to analyze mesothelin expression as a potential predictive biomarker. If archival material is not available a fresh biopsy can be taken, if the investigator deems the procedure to be safe for the patient. Patients will be stratified to the appropriate cohort based on the following criteria: High mesothelin expression of ≥30% of viable tumor cells with 2+ or 3+ membrane staining intensity will be in the "mesothelin high" group. Low-mid mesothelin expression of at least 5% viable tumor cells positive for MSLN expression (all intensities) but <30% 2+ or 3+ membrane staining will be in the "mesothelin low" group. The IHC test used to detect mesothelin expression (Ventana MSLN [SP74] IHC assay) is currently investigational and not approved by FDA or other regulatory authorities. Both groups will be enrolled in the phase I dose escalation portion but only the "mesothelin high' group will be enrolled in the phase II expansion portion of the study.

18.0 Records and Data Collection Procedures

Baseline data will be entered ≤10 working days of patient registration. This will include patient ID, age, gender, tumor type, dose level, and baseline symptoms.

Cycle 1 toxicity data will be entered ≤24 hours after evaluation of the patient and ≤10 working days after evaluation on all other cycles.

Response status will be entered ≤10 working days of evaluation for response as defined by protocol.

Phase I only: Three months after the patient goes off treatment, follow-up information will be collected and entered. This includes off treatment, off study, survival, and death data. After 3 months have elapsed from off treatment date, no further follow-up is required (i.e., patient goes off study).

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Event monitoring (Phase II only)

See Section 4.0 and data submission table for the event monitoring schedule.

18.3 CRF completion

This study will use Medidata Rave for remote data capture (rdc) of all study data.

18.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for evidence of response to study therapy and progression after study therapy.

18.6 Labelling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Incomplete materials

Any data entered into a form will result in that form being marked as "received." However, missing data will be flagged by edit checks in the database.

18.8 Overdue lists

A list of overdue materials is automatically available to each site at any time. A list of overdue materials and forms for study patients will be generated monthly. The listings will be sorted by location and will include the patient study registration number. The appropriate co-sponsor/participant will be responsible to submit the overdue material.

18.9 Corrections forms

If a correction is necessary the QAS will query the site. The query will be sent to the appropriate site to make the correction in the database and respond back to the QAS.

19.0 Budget

19.1 Costs charged to patient: Routine clinical care

19.2 Tests to be research funded: Research blood, ECG, Echocardiogram, Anetumab ravtansine and the administration, biopsy costs, if necessary

20.0 References

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APPENDIX A: ECOG PERFORMANCE STATUS SCORES

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

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html

APPENDIX B: 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.