Abbreviated Title: Anetumab ravtansine in lung CA

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Title: Phase II Trial with Safety Run-in of the Anti-Mesothelin Antibody Drug Conjugate Anetumab Ravtansine for Mesothelin Expressing Lung Adenocarcinoma

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Investigational Agents:

Drug or Device Name:	Anetumab ravtansine	Mesothelin Expression Testing
IND Number:	130915	NSR device
Sponsor:	Center for Cancer Research	Center for Cancer Research
Manufacturer:	Bayer HealthCare Pharmaceuticals, Inc.	NCI Laboratory of Pathology

PRÉCIS

Background:

- Lung cancer is the leading cause of cancer-related death worldwide, accounting for more than one million deaths every year.
- Non-small-cell lung cancer (NSCLC) constitutes approximately 85% of lung cancers and about 40% of patients with newly diagnosed NSCLC have advanced disease. The median year overall survival for advanced NSCLC is ~1 year.
- In recent years, identification of oncogenic alterations such as mutations in EGFR and ALK translocations and therapies targeting tumor immune escape mechanisms have led to a substantial improvement in the prognosis of patients with advanced lung cancer; however, such alterations have been detected in less than half of all advanced NSCLC patients in only a small subset of patients respond to immunotherapeutic interventions available today.
- Anetumab ravtansine (BAY 94-9343) is an antibody-drug conjugate targeting mesothelin, a protein normally present on mesothelial cells. A Phase I trial showed the overall acceptable and manageable safety profile. It is being developed for patients with mesothelin expressing cancers; clinical development is furthest along in mesothelioma, where it is in a registration phase II clinical trial.
- NCI researchers have demonstrated that mesothelin mRNA and protein are present in a substantial number of lung adenocarcinoma cell lines; mesothelin expression has been observed in over 50% of advanced lung adenocarcinomas by immunohistochemical assessment

Objectives:

Safety Run-in

- To evaluate safety and tolerability of anetumab ravtansine in patients with previously treated unresectable mesothelin expressing advanced lung adenocarcinoma (stage IIIB or IV).

Phase 2

- To determine the efficacy (objective response rate) of anetumab ravtansine in patients with advanced (Stage IIIb) or metastatic (Stage IV) mesothelin expressing lung adenocarcinoma.

Eligibility:

- Age >18 years.
- Histologically or cytologically confirmed previously treated unresectable mesothelin expressing advanced lung adenocarcinoma (stage IIIB or IV)
- Positive mesothelin expression in the archival tumor tissue, defined as the mesothelin membrane intensity score of 2+ or 3+ (on the 0-3 scale) expressed on the membrane of ≥10% of tumor cells.

- Should have received at least one prior platinum based chemotherapy and an immune checkpoint targeted agent. In addition, subjects with epidermal growth factor receptor [EGFR]-mutated and anaplastic lymphoma kinase [ALK]-translocated NSCLC should have received FDA-approved targeted therapies as appropriate.
- Normal organ function

Design:

- This is an open label, single center, phase I/II study of anetumab ravtansine in subjects with mesothelin positive lung adenocarcinoma.
- During the safety run-in portion of the study, de-escalating doses will be assessed to determine a recommended phase 2 dose (RP2D).
- During the phase 2 portion of the study, the (RP2D) will be assessed for objective response rate.
- During both portions of the study, anetumab ravtansine will be administered intravenously every 3 weeks until disease progression in the absence of clinical benefit, patient withdrawal or the occurrence of intolerable toxicities.
- Response assessments (imaging) will occur every 6 weeks for the first 6 months, then every 9 weeks until the end of year 2, then every 12 weeks thereafter.
- Up to 12 evaluable patients will be enrolled in the safety run-in portion of the study. Approximately twenty patients, including 6 from the safety run-in portion of the study, will be evaluated in the phase 2 portion of the study. The accrual ceiling will be set at 55 to accommodate screen failures (a 50% failure rate with regard to mesothelin expression) and inevaluable subjects.

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1.1 STUDY OBJECTIVES

1.1.1 Primary Objectives

Safety Run-in

- To evaluate safety and tolerability of anetumab ravtansine in patients with previously treated unresectable mesothelin expressing advanced lung adenocarcinoma (stage IIIB or IV).

Phase 2

- To determine the efficacy (objective response rate) of anetumab ravtansine in patients with previously treated, unresectable, advanced (Stage IIIb) or metastatic (Stage IV) mesothelin expressing lung adenocarcinoma.

1.1.2 Secondary Objectives

All phases

- To determine the duration of response, progression free survival, overall survival in the study population.
- To correlate mesothelin expression with clinical activity defined as partial response and complete response

1.1.3 Exploratory Objectives

All phases

- To determine if treatment with anetumab ravtansine induces a humoral response to mesothelin and to correlate a response (if any) with tumor characteristics
- To characterize the molecular changes that occur within the tumors following treatment with anetumab ravtansine
- To assess myeloid derived suppressor cells in subjects with lung adenocarcinoma

1.2 BACKGROUND AND RATIONALE

1.2.1 Lung cancer

Lung cancer is the leading cause of cancer-related death worldwide, accounting for more than one million deaths every year[1]. Non-small-cell lung cancer (NSCLC) constitutes approximately 85% of lung cancers and about 40% of patients with newly diagnosed NSCLC have advanced disease. Until the late 1990s, treatment of advanced lung cancer followed the straightforward algorithm of platinum-based combination therapy, irrespective of histological subtype, without any option for further lines of treatment[2]. With the introduction of so-called third-generation cytotoxic drugs such as gemcitabine, vinorelbine, docetaxel, and paclitaxel, treatment of non-small-cell lung cancer changed, and overall survival improved to about 8 months in clinical trial settings[3]. However, the median overall survival was less than a year; only 3.5% of patients are alive five years after diagnosis[3]. Chemotherapy was also associated with high morbidity.

However, since then, overall survival has improved to a median survival of 12 months and longer in clinical studies. This progress was enabled by the introduction of new drugs, and patient selection based on the recognition that different histological subtypes and driver mutations determine the biology of these malignancies, and predict drug efficacy. The most widely recognized genomic alterations include epidermal growth factor receptor (*EGFR*) mutations, which have been recorded more frequently in Asian than in non-Asian patients[4], and echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (*EML4-ALK*) rearrangements[5]. Targeting of the proteins affected by such genetic changes improved the prognosis of these patients dramatically. These genetic modifications are significantly more common in patients who have never smoked, which makes non-small-cell lung cancer in this population a different disease entity to lung cancers caused by cigarette smoke and other toxicants.

The predictive power of an EGFR mutation was confirmed in the Iressa Pan Asian Study (IPASS), a randomized phase 3 study that compared first-line gefitinib with standard chemotherapy in 1217 Asian non-smokers or light smokers with pulmonary adenocarcinoma[4]. A subgroup analysis of 417 patients with known EGFR mutation status confirmed improvement in progression-free survival in patients with EGFR mutations (HR 0·48, 95% CI 0·36–0·64) and a detrimental effect in patients with wild-type tumor (2·87, 2·05–3·98) ($p<0·001$). Multiple additional studies of first generation and second generation EGFR tyrosine kinase inhibitors, including gefitinib, erlotinib, and afatinib, have confirmed similar improvements in tumor response rate and progression-free survival. However, no overall survival benefit was reported in any of these studies because most patients in the chemotherapy group also received EGFR tyrosine kinase inhibitors as second-line or third-line therapy. In view of the significant clinical benefit and low toxicity, EGFR tyrosine kinase inhibitors are the first-line therapy of choice for patients with an activating EGFR mutation. Rociletinib is active and is approved for patients with EGFR-mutated NSCLC associated with the T790M resistance mutation[6].

ELM4-ALK is a rearrangement on chromosome 2. The 5′ fusion is a potent oncogenic rearrangement that activates the downstream *ALK* function. Crizotinib is a small molecule tyrosine kinase inhibitor that is highly specific for inhibition of cMET, ALK, and ROS-1. Treatment outcomes were reported in a randomized phase 3 study (PROFILE 1007) in which investigators compared crizotinib with standard single-agent second-line chemotherapy of either pemetrexed or docetaxel[2,5]. Shaw and colleagues reported higher tumor response rate and prolongation of progression-free survival (7·7 vs 3·0 months, HR 0·49, 95% CI 0·37–0·64). Ceritinib and alectinib are now approved for patients with resistance to or are intolerant to crizotinib[7,8].

However, “druggable” alterations have been detected in less than half of all advanced NSCLC patients in only a small subset of patients respond to immunotherapeutic interventions available today. Clearly there is an urgent need for novel therapies for this deadly disease.

1.2.2 Mesothelin

Mesothelin is a 40-kDa cell surface glycoprotein that is present on normal mesothelial cells lining the pleura, peritoneum and pericardium [9]. Mesothelin expression in normal human tissues is observed only in a single layer of mesothelial cells lining the pleura, peritoneum and pericardium[10]. However, mesothelin is highly expressed in several cancers, including epithelioid mesotheliomas, pancreatic, biliary adenocarcinomas, gastric and ovarian cancers. The high expression of mesothelin in cancers have led to its successful therapeutic targeting using a variety of strategies

including immunotoxins, monoclonal antibodies, antibody drug conjugates, vaccines and adoptive T cell therapy[11].

1.2.2.1 Targeting mesothelin in lung cancer

Several lines of evidence suggest that mesothelin is an attractive target in lung adenocarcinoma. We and others have described high expression of mesothelin in lung adenocarcinoma. Mesothelin expression was observed in over 50% of advanced lung adenocarcinomas by immunohistochemical assessment in a series of 93 patients (Figure 1)[12]. High mesothelin expression, defined as mesothelin positivity in more than 25% of cells, was observed in nearly 25% of cases. Patients with high mesothelin-expressing tumors had significantly shorter overall survival compared with patients with low or no mesothelin expression (median 18.2 months vs. 32.9 months; $P = 0.014$). High mesothelin expression was strongly associated with mutant KRAS ($P < 0.0001$) and wild-type EGFR ($P = 0.002$) (Figure 2). Similar results have been observed by other investigators in early stage lung cancer[13]. NCI researchers have demonstrated that mesothelin mRNA and protein are present in a substantial number of lung adenocarcinoma cell lines[14].

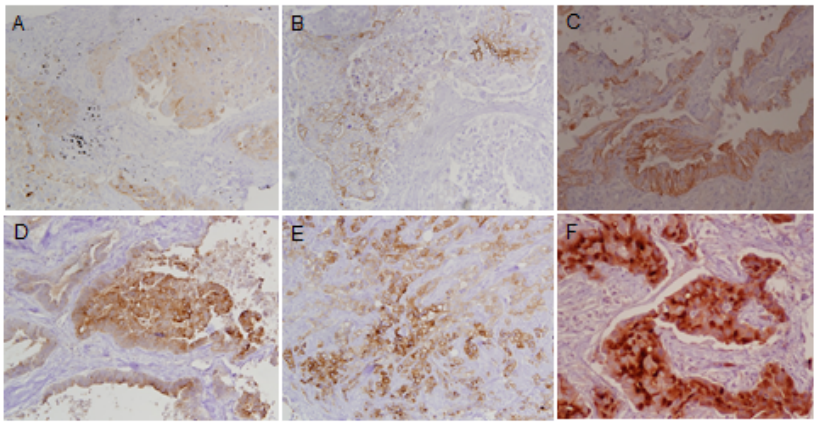


Figure 1: Tumor expression of mesothelin in lung adenocarcinoma was evaluated using immunohistochemistry. Representative images are depicted (original magnification x400). Focal cytoplasmic immunostaining of 2+ intensity in 15% cells (A), membranous and cytoplasmic immunostaining of 2+ intensity in 1% cells (B), membranous immunostaining in of 3+ intensity in 30% cells (C), membranous and cytoplasmic immunostaining of 3+ intensity in 60% cells (D), membranous and cytoplasmic immunostaining of 3+ intensity in 80% cells (E), membranous and cytoplasmic immunostaining of 3+ intensity in 100% cells (F).

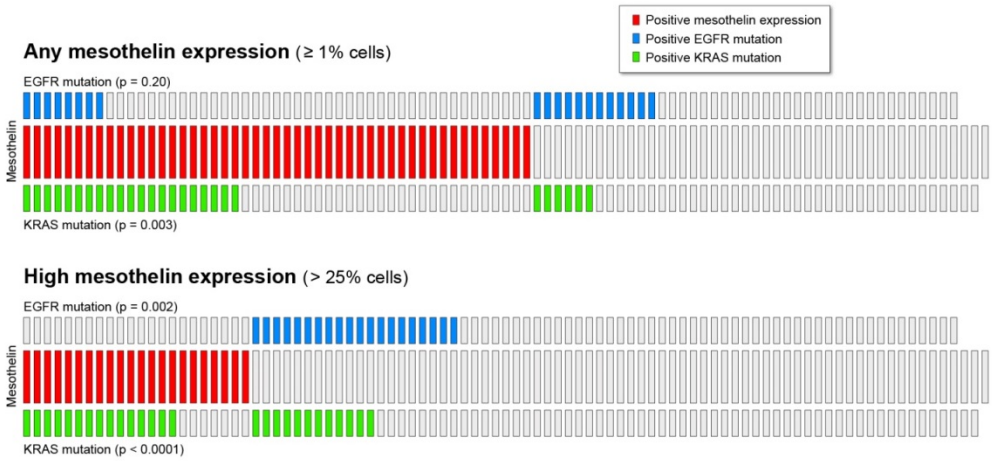


Figure 2: Association of mesothelin expression with KRAS and EGFR mutations. Individual boxes are present a tumor.

1.2.2.2 Risk designation for the use of mesothelin expression levels as an eligibility criterion

In order to be eligible for this study, subjects are required to have positive mesothelin expression in the archival tumor tissue, defined as the mesothelin membrane intensity score of 2+ or 3+ (on the 0-3 scale) expressed on the membrane of ≥10% of tumor cells. Mesothelin expression testing is not FDA approved for this purpose; however, it is being used as a companion diagnostic device. It has been assessed by the sponsor as non-significant risk. There is no significant risk incurred by the subjects in obtaining the archival specimens; therefore, it is the opinion of the Sponsor that the use of this diagnostic device does not pose a serious risk to the health, safety, or welfare of the subject and therefore is considered Non-Significant Risk under 21 CFR 812.3(m).

A similar assay performed by Bayer on other studies of anetumab ravtansine has received the non-significant risk designation from the FDA. (See Appendix A)

1.2.3 Anetumab ravtansine

Anetumab ravtansine (BAY 94-9343) is an antibody drug conjugate (ADC) targeting mesothelin. The differential overexpression in NSCLC as well as the fact that mesothelin is an internalizing antigen suggests mesothelin as an excellent target for antibody-mediated delivery of cytotoxics.

Anetumab ravtansine is composed of the human anti-mesothelin-monoclonal antibody BAY 86-1903 and the maytansinoid DM4 (BAY 100-6640), conjugated by a disulfide linker moiety to lysine residues of the antibody (Figure 3). DM4 is a spindle poison, and its mechanism of action is inhibition of microtubule assembly (similar to that of vinca alkaloids). *In vivo*, anetumab ravtansine showed potent inhibition of the growth of mesothelin expressing cells (Figure 4)[15]. In tumors from NCI- H322 cells which have 2+ mesothelin expression, 72% tumor growth inhibition was observed at 15 mg/kg and 56% tumor growth inhibition at 5 mg/kg. Anetumab ravtansine has also demonstrated monotherapy anti-tumor efficacy in vivo in mesothelin-positive tumor models[15]; only 3 administrations of anetumab ravtansine at 0.2 mg/kg resulted in at least partial tumor regression in all mice using a Meso7212 PDX mesothelioma model ($P < 0.001$). The anti-tumor efficacy of anetumab ravtansine was more pronounced than cisplatin ($P < 0.05$) and pemetrexed ($P < 0.001$).

Figure 3

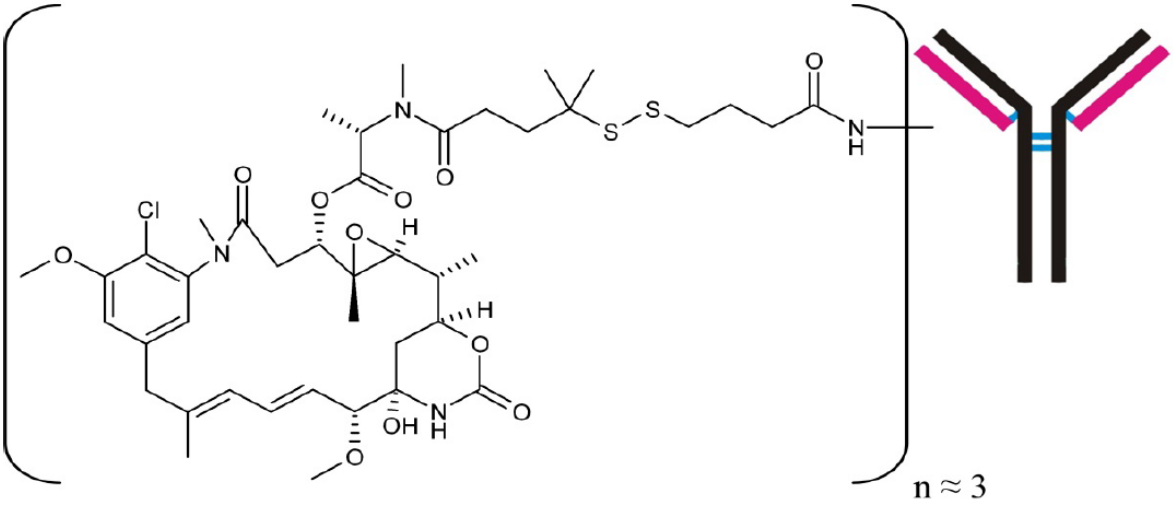
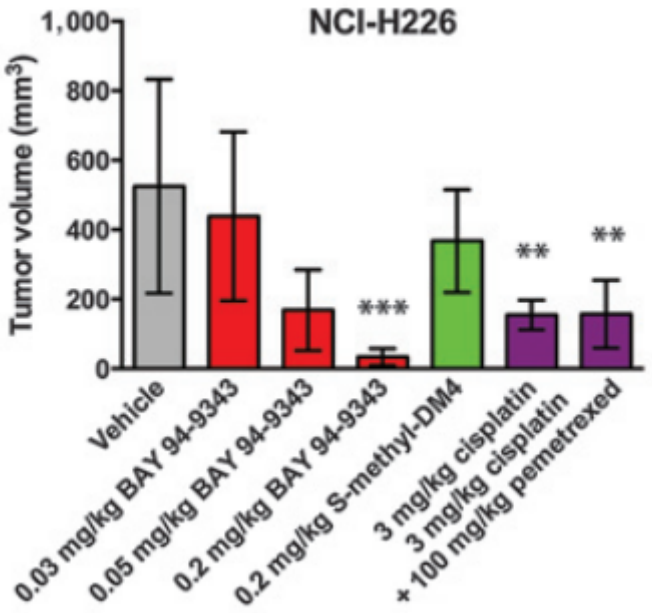


Figure 4



1.2.3.1 Anetumab ravtansine clinical experience

Seventy seven patients with advanced solid tumors expressing mesothelin were treated with anetumab ravtansine in the Phase I study[16] with a Q3W schedule (Table 1).

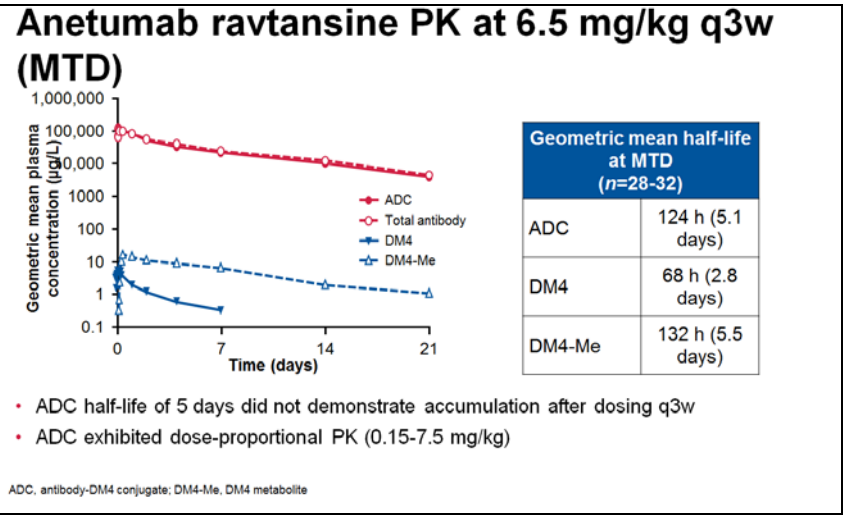
Table 1. Patient disposition		
Patients treated (FPFV 7-Sep-11)	Total (n)	Active (n)
Overall Q3W	77	--
Dose escalation (0.15– 7.5 mg/kg Q3W)	45	--
MTD Expansion (6.5 mg/kg Q3W)	32	3
Mesothelioma	12	3
Ovarian	20	--

The dose-escalation part of the trial enrolled 45 patients who were 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. The non-tolerated dose was determined to be 7.5 mg/kg Q3W. Subsequently 2 expansion cohorts (n=32) were treated at 6.5mg/kg Q3W.

A total of 32 males and 45 females were treated, with a mean age of 61.4 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) whilst in the 6.5 mg/kg Q3W expansion cohorts (total 32 patients) patients had ovarian cancer (n=20) or mesothelioma (n=12).

Following IV administration, maximum ADC concentrations were typically observed around the end of infusion or within 1 h after the end of infusion. The maximum drug concentration (C_{max}) and area under the curve (AUC) of the ADC, generally increased in a dose proportional manner in the 0.15 mg/kg to 7.5 mg/kg dose range studied. At the MTD, average half-life values of the ADC, total antibody and DM4-Me were approximately 5 to 6 days, and approximately 3 days for DM4, generally consistent with the range of half-life values reported for biologics and with no accumulation expected after Q3W dosing (Figure 5). A total of 38 patients were treated at the MTD level of 6.5 mg/kg Q3W during the escalation (cohort 9, n=6) and subsequent expansion cohort (n=32). Of these, 16 patients had mesothelioma, 21 patients had ovarian cancer and 1 patient had triple-negative breast cancer (TNBC).

Figure 5



Response rate in the overall patient population treated at the MTD was 18.4%. Of the 16 mesothelioma patients who were treated at the MTD (data presented at WCLC, Denver 2015. Hassan et al. Table 2), 5 (31%) achieved PRs according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) (4 with pleural and 1 with peritoneal epithelial mesothelioma). 10 of these 16 patients with mesothelioma had received only 1 previous line of systemic cytotoxic chemotherapy before enrolling in the study. 5 of 10 patients in this group (50%) had a confirmed PR (4 PRs in pleural mesothelioma patients and 1 PR in peritoneal mesothelioma patients). Responses were durable.

Table 2

Objective tumor response at the MTD (6.5 mg/kg q3w)

n (%)	All patients treated at MTD (*n*=38)	Mesothelioma patients treated at MTD	
		All patients (*n*=16)	1 prior line of systemic cytotoxic treatment (*n*=10)
Best overall response, RECIST[a]			
Complete response (CR)	0	0	0
Partial response (PR)	7 (18.4)	**5 (31.3)**	**5 (50.0)**
Stable disease (SD)	18 (47.4)	7 (43.8)	4 (40.0)
Progressive disease (PD)	10 (26.3)	4 (25.0)	1 (10.0)
Overall response (CR or PR)	7 (18.4)	5 (31.3)	5 (50.0)
Disease control rate (CR, PR, or SD)	25 (65.8)	**12 (75.0)**	**9 (90.0)**

RECIST, Response Evaluation Criteria in Solid Tumors

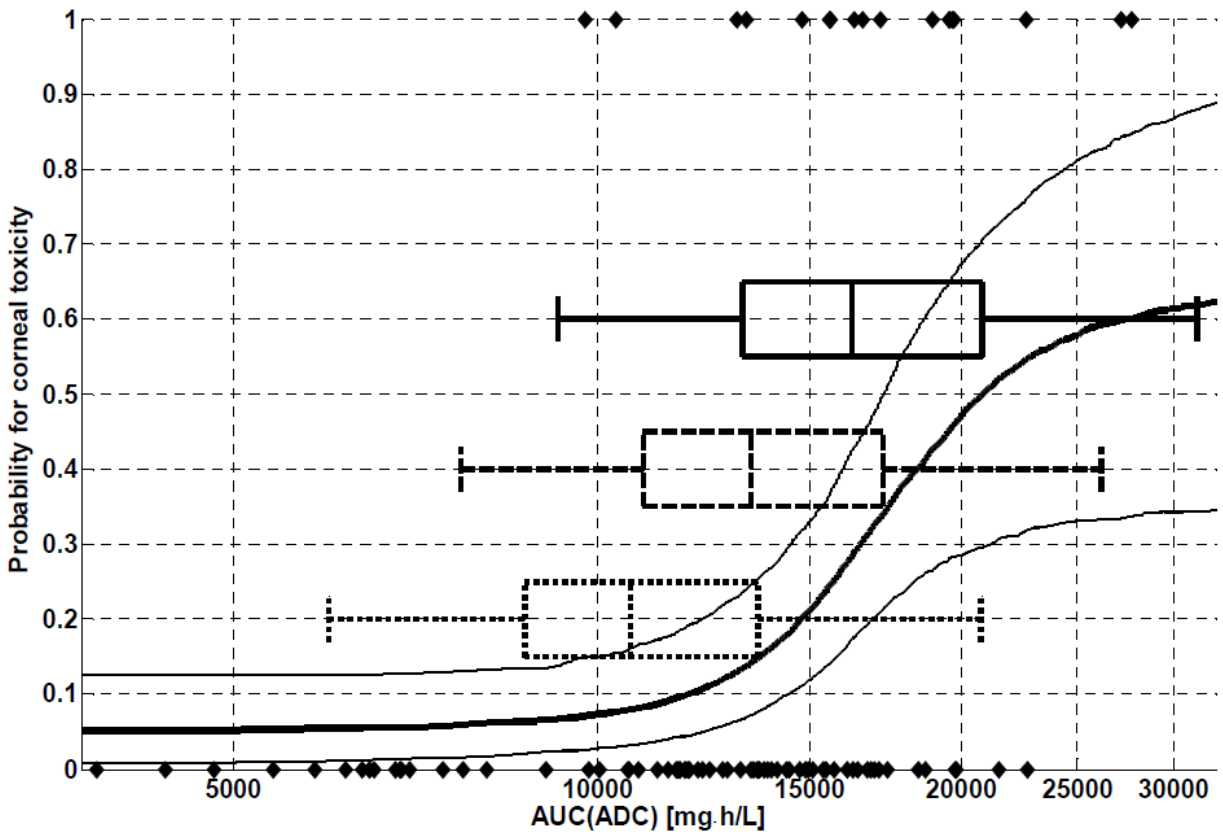
Data from the phase I trial also indicate an overall acceptable and manageable safety profile. At the MTD of 6.5 mg/kg Q3W, the most common treatment-emergent adverse events (TEAEs) that

were assessed to be at least possibly related to anetumab ravtansine were corneal epitheliopathy, peripheral neuropathy, myalgia, weakness, fatigue, anorexia, nausea, vomiting and diarrhea. The incidence of treatment-emergent serious adverse events (SAEs) that were considered to be at least possibly related to anetumab ravtansine was low in all patients treated at 6.5 mg/kg Q3W (5 of 38 patients). There were no drug-related deaths throughout the study.

The safety finding of particular interest at the 6.5 mg/kg Q3W dose has been the corneal epitheliopathy probably related to anetumab ravtansine (blurred vision and keratitis with possible vision impairment due to corneal epitheliopathy): 11 of 38 patients (29%) developed corneal adverse events. None of these events 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 first in human study 15051 "An open label Phase 1 dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and MTD of the anti-mesothelin ADC anetumab ravtansine in subjects with advanced solid tumors" (NCT01439152), 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 6. Based on the on average linear PK of anetumab ravtansine (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.

Figure 6: 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 anetumab ravtansine 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 4.5 mg/kg (dotted box), 5.5 mg/kg (dashed box) or 6.5 mg/kg (solid box) anetumab ravtansine given Q3W.

The other identified risks so far include peripheral neuropathy, liver function test increases and hypersensitivity reaction. In the Q3W MTD dose level, 16 of 38 patients (42%) experienced peripheral neuropathy and associated disorders (muscle spasms and cramps, gait disorder etc.) as expected for the treatment with a taxanes-like anti-cancer agent; all but 1 case were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2, 1 patient developed a Grade 3 event. It commonly led to dose interruption and reduction but it did not frequently cause treatment discontinuation. A notable incidence of the liver function test increases was observed in patients treated at the MTD of 6.5 mg/kg Q3W: aspartate aminotransferase (AST) increase in 7 patients (1 Grade 3), alanine aminotransferase (ALT) increase in 5 patients (no Grade 3), alkaline phosphatase (ALP) increase in 4 patients (1 Grade 3), and total bilirubin increase in 1 patient (no Grade 3). 2 patients treated at 6.5 mg/kg had a dose-limiting toxicity (DLT) or TEAE requiring dose reduction due to drug-related Grade 3 AST increase.

In the dose-escalation part of the Study 15404 in Japanese subjects with advanced solid tumors, anetumab ravtansine given IV as single agent was generally well tolerated at the dose of 4.5 mg/kg Q3W. The most common TEAEs at least possibly related to anetumab ravtansine in the dose escalation part of Study 15404 were hematological toxicities (Grade 2-4 thrombocytopenia and Grade 2-4 neutropenia). One of the 2 subjects treated at the dose of 6.5 mg/kg Q3W died due to hepatic failure that the investigator has considered to be related to anetumab ravtansine.

In summary, the high tumor response rate and long-lasting responses in Study 15051 would indicate a potential for anetumab ravtansine to impart clinical benefit in an unmet medical need when given as single agent at the MTD of 6.5 mg/kg Q3W in the treatment of advanced predominantly epithelial mesothelioma and ovarian cancer. However, anetumab ravtansine may have a narrow therapeutic index, based on the severe and dose-limiting drug-related AEs observed at 7.5 mg/kg Q3W in the Study 15051, and on the fact that approximately half of the Western subjects with advanced cancer treated at the MTD of 6.5 mg/kg (BW) Q3W required dose reduction and/or treatment interruption (most commonly due to drug-related corneal toxicity, peripheral neuropathy, fatigue, asthenia/weight loss, anorexia and diarrhea). On the other hand, these events in Western subjects were non-life threatening and fully reversible (or showed a clear trend to complete resolution at the time of last follow up), and manageable by treatment modification. The Japanese subjects with advanced cancer should be carefully monitored for bone marrow toxicity and hepatotoxicity during treatment with anetumab ravtansine. The Study 15404 is ongoing and the maximum tolerated dose of anetumab ravtansine in Japanese subjects has not been determined yet. Given the clinical benefit in mesothelioma and ovarian cancer as the high unmet medical need, anetumab ravtansine is expected to have an acceptable benefit-risk ratio when given as single agent at doses up to 6.5 mg/kg Q3W in patients with advanced cancer in clinical trials.

1.2.4 Rationale for the study

There is clearly an unmet need to identify improved therapies for patients with NSCLC. Anetumab ravtansine is an ADC targeting mesothelin. It was well tolerated in phase I clinical studies with the predictable toxicity profile and evidence of clinical activity. Clinical and pre-clinical data indicate that anetumab ravtansine is active in mesothelin-expressing cancers. We have described mesothelin expressing lung adenocarcinoma as a specific subgroup of NSCLC with distinct mutational characteristics. The primary objectives of this trial are to assess the safety and tolerability of anetumab ravtansine in patients with previously treated unresectable locally advanced or metastatic lung adenocarcinoma (stage IIIB or IV), and to determine a preliminary estimate of the response rate of the treatment.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Subjects must have histologically or cytologically confirmed previously treated unresectable mesothelin expressing advanced lung adenocarcinoma (stage IIIB or IV) as confirmed by the Laboratory of Pathology, NCI

2.1.1.2 Subjects must have positive mesothelin expression in the archival tumor tissue, defined as the mesothelin membrane intensity score of 2+ or 3+ (on the 0-3 scale) expressed on the membrane of ≥10% of tumor cells.

2.1.1.3 Subjects must provide sample of archival tumor tissue (tissue block preferred, at least 5 formalin-fixated, paraffin-embedded [FFPE] slides acceptable) collected any time before the general screening. A fresh biopsy will be collected if archival sample is unavailable or insufficient.

2.1.1.4 Subjects must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan. See Section 6.3 for the evaluation of measurable disease.

2.1.1.5 Subjects with resected primary tumors who have documented metastases are eligible.

2.1.1.6 Subjects should have received at least one prior platinum based chemotherapy and an immune checkpoint targeted agent. Subjects with epidermal growth factor receptor [EGFR]-mutated and anaplastic lymphoma kinase [ALK]-translocated NSCLC should have received FDA-approved targeted therapies as appropriate.

2.1.1.7 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of anetumab ravtansine in subjects <18 years of age, children are excluded from this study.

2.1.1.8 ECOG performance status ≤2 (see Appendix B).

2.1.1.9 Subjects must have adequate bone marrow function as assessed by the following laboratory test results:

- Hemoglobin ≥9.0 g/dL or ≥5.6 mmol/L
- Absolute neutrophil count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L
- Platelet count ≥100,000/mm^3 or ≥100 x 10^9/L

2.1.1.10 Subjects must have adequate kidney function, with serum creatinine <1.5 x ULN or calculated glomerular filtration rate (GFR) of > 45/mL/min/1.73 m2

2.1.1.11 Subjects must have adequate liver function as assessed by the following laboratory test results:

- Total bilirubin ≤1.5 times the upper limit of normal (ULN)
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 times ULN in subjects without liver metastases or ≤5.0 times ULN in subjects with liver metastases

2.1.1.12 Subjects must have adequate coagulation, as assessed by the following laboratory test results:

- INR or PT ≤ 1.5 x ULN
- PTT ≤ 1.5 x ULN

2.1.1.13 Due to the lack of adequate reproductive toxicity data on anetumab ravtansine, subjects must use 2 forms of highly effective contraception concomitantly from the initiation of study therapy until 6 months after the last dose of study therapy. Additionally, the use of condoms is required. It should also be noted that, where 2 forms of effective

contraception are required, a subject may choose to use a double-barrier method consisting of condom and cervical occlusive cap / diaphragm with spermicide

2.1.1.14 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.1.15 Subjects must provide a signed informed consent before any screening procedures.

2.1.2 Exclusion Criteria

2.1.2.1 Subjects who have a previous or concurrent cancer that is distinct in primary site or histology from lung adenocarcinoma, except cervical carcinoma in situ, treated basal cell carcinoma, superficial noninvasive bladder tumors or any previous cancer curatively treated <2 years before the start of study treatment.

2.1.2.2 Subjects who have a history or current evidence of bleeding disorder, i.e. any hemorrhage/bleeding event of CTCAE Grade ≥2 within 4 weeks before the start of study treatment.

2.1.2.3 History of symptomatic metastatic brain or meningeal tumors unless the subject is > 3 months from definitive therapy and has no evidence of tumor growth on an imaging study within 2 weeks prior to study entry. Subjects with brain metastases must not be undergoing acute corticosteroid therapy or steroid taper. Chronic steroid therapy is acceptable provided that the dose is stable for one month prior to screening.

2.1.2.4 Subjects who have a history or current evidence of uncontrolled cardiovascular disease including but not limited to the following conditions:

2.1.2.4.1 Congestive heart failure of New York Heart Association (NYHA) Class III or IV

2.1.2.4.2 Unstable angina (symptoms of angina at rest) or new-onset angina within <3 months before the start of study treatment.

2.1.2.4.3 Arterial thrombosis, deep vein thrombosis, or pulmonary embolism within <3 months before the start of study treatment.

2.1.2.4.4 Myocardial infarction or stroke within <3 months before the start of study treatment.

2.1.2.4.5 Pericarditis (any CTCAE grade), pericardial effusion (CTCAE Grade ≥2) or pleural effusion (CTCAE Grade ≥2)

2.1.2.4.6 Cardiac arrhythmia requiring anti-arrhythmic therapy. Subjects receiving digoxin, calcium channel blockers except verapamil, or beta-adrenergic blockers except propranolol are eligible at the investigator's discretion if the dose has been stable for at least 2 weeks before the start of study treatment. Subjects with sinus arrhythmia and infrequent premature ventricular contractions are eligible at the investigator's discretion.

2.1.2.5 Subjects who have a left ventricular ejection fraction (LVEF) <50%, as assessed by echocardiogram performed at screening.

2.1.2.6 Subjects who have a corrected QT (QTcF) interval >480 ms (CTCAE Grade >1) determined by the electrocardiogram (ECG) recorder's algorithm on the screening ECG.

2.1.2.7 Subjects who have a history or current evidence of uncontrolled hypertension defined as systolic blood pressure >150 mmHg or diastolic blood pressure >95 mmHg at screening despite optimal medical management. Subjects with a history of mild to moderate hypertension are eligible at the investigator's discretion if the hypertension is adequately controlled by antihypertensive treatment used at a stable dose for at least 2 weeks before the start of study treatment.

2.1.2.8 Subjects who have a heart rate ≥100 beats per minute (bpm) or ≤45 bpm determined by the ECG recorder's algorithm on the screening ECG.

2.1.2.9 Women who are pregnant or breast-feeding. Women of reproductive potential must have a negative serum beta human chorionic gonadotropin (β-HCG) pregnancy test obtained within 7 days before the start of study treatment.

2.1.2.10 Subjects who have had a major surgery or significant trauma within 4 weeks before the start of study treatment.

2.1.2.11 Subjects who have had solid organ or bone marrow transplantation.

2.1.2.12 Subjects who have a history of hypersensitivity to any of the study drugs or their excipients, or a history of severe hypersensitivity to any other antigen.

2.1.2.13 Subjects who have a history of human immunodeficiency virus (HIV) infection or subjects who have an active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection requiring treatment due to a theoretical concern that the degree of immune suppression associated with the treatment may result in progression of HIV infection. Subjects with chronic HBV or HCV infection are eligible at the investigator's discretion if the subject is considered non-infectious based on serological markers.

2.1.2.14 Subjects who have an active clinically serious infection of CTCAE Grade ≥2.

2.1.2.15 Subjects with a non-healing serious wound, ulcer, or bone fracture unrelated to the primary tumor.

2.1.2.16 Subjects with corneal epitheliopathy or any eye disorder that may predispose the subjects to drug-induced corneal epitheliopathy, or may interfere with diagnosis of treatment-emergent corneal epitheliopathy at the discretion of the investigator in consultation with the ophthalmologist/optometrist. Low grades of superficial punctate keratitis, within the range seen in the normal population, should not lead to the exclusion of the patient

2.1.2.17 Subjects experiencing unresolved toxicity of previous antitumor therapy which is CTCAE Grade >1 before the start of study treatment, except for alopecia or hemoglobin ≥9.0 g/dL or ≥5.6 mmol/L.

2.1.2.18 Subjects with any clinical condition that is considered unstable or might jeopardize the safety of the subject and/or influence the subject's compliance in the study.

2.1.2.19 Subjects who have received systemic anticancer therapy within 3 weeks before the start of study treatment. Mitomycin C or nitrosoureas must be excluded within 6 weeks before the start of study treatment.

2.1.2.20 Subjects who have received radiotherapy to tumor lesions that would be chosen as target lesions (measurable disease) within 4 weeks before the start of treatment, except if there is objective evidence of progression of the lesion by RECIST 1.1 between the prior radiotherapy and the screening CT or MRI scan. Palliative radiotherapy to non-target lesions is allowed at the investigator's discretion..

2.1.2.21 Use of drugs that inhibit renal tubular secretion (e.g. probenecid and cimetidine) within 2 weeks before the start of study treatment.

2.1.2.22 Use of strong cytochrome P450 3A4 (CYP3A4) inhibitors or strong CYP3A4 inducers within 2 weeks before the start of study treatment.

2.1.2.23 Subjects who have previously received anetumab ravtansine.

2.1.2.24 Subjects who are concurrently receiving any other investigational agents.

2.2 SCREENING EVALUATION

Step 1: The following assessments may be performed as soon as the initial 1st line treatment cycles with platinum/pemetrexed are administered.

- NCI LP confirmation of diagnosis
- NCI LP determination of mesothelin expression
- Medical History and Physical Examination

Step 2: Once mesothelin expression and diagnosis are confirmed, then proceed with the following tests described below.

The following screening assessments will occur within 28 days prior to initiation of study therapy:

- Medical history and physical examination including vital signs
- ECOG Performance Status
- CT scan of chest, abdomen and/or pelvis and areas of known or suspected disease involvement; MRI may also be performed when appropriate
- FDG-PET scan
- Echocardiogram
- Electrocardiogram
- Viral markers – HBsAg, anti-HCV, anti-HIV

The following screening assessments will occur within 21 days prior to initiation of study therapy:

- Ophthalmologic exam (within 3 weeks before start of study therapy)
  - Visual acuity (BCVA according to ETDRS, or Snellen, or Landolt C or other charts)
  - Measurement of ophthalmic pressure (IOP)
  - Dry eye test [Schirmer test]
  - Slit lamp

The following screening assessments will occur within 7 days prior to initiation of study therapy:

- CBC with differential; Acute Care Panel (sodium, potassium, chloride, bicarbonate, creatinine, glucose, urea nitrogen, eGFR); Hepatic Panel (alkaline phosphatase, ALT, AST, Total Bilirubin, Direct Bilirubin)
- PT, PTT
- Urinalysis
- β-HCG in women of childbearing potential

2.3 REGISTRATION PROCEDURES

Registration will be a two part process as patients are screened on this protocol. Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. To initially register a subject after the participant has signed the consent, complete the top portion the registration Eligibility Checklist from the website (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) indicating that the patient is being registered for screening and send via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. Once eligibility is confirmed after completion of Step 2 screening studies, complete the remainder of the form which is the eligibility checklist, indicating that the patient is being registered for treatment and email the completed registration checklist to the CRO at NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

Subjects that do not meet screening criteria should be removed from the study following the procedure in section 3.5.3.

2.4 TREATMENT ASSIGNMENT AND RANDOMIZATION/STRATIFICATION PROCEDURES

Cohorts

Number	Name	Description
1	Safety Run-in Cohort,	The first 6 evaluable subjects enrolled in whom the higher of 2 de-escalating doses of anetumab ravtansine will be evaluated in order to determine the recommended phase 2 dose
2	Phase 2 Cohort	Subjects enrolled after the recommended Phase 2 dose has been determined

Arms

Number	Name	Description
1	Safety Run-in Arm	Subjects will be dosed with the higher of the 2 possible anetumab ravtansine doses (dose level 1) evaluated on the study
2	Phase 2 Arm	Subjects will be dosed with anetumab ravtansine at the recommended phase 2 dose (dose level 1 if no more than 1 DLT occurred in the safety run in arm, or at dose level -1 otherwise)

Stratifications

None

Randomization and Arm Assignment

This is not a randomized study. Subjects in Cohort 1 will be assigned directly to Arm 1. Subjects in Cohort 2 will be assigned directly to Arm 2.

2.5 BASELINE EVALUATION

Screening evaluations performed within 28 days prior and within 7 days prior to treatment initiation will be used as baseline.

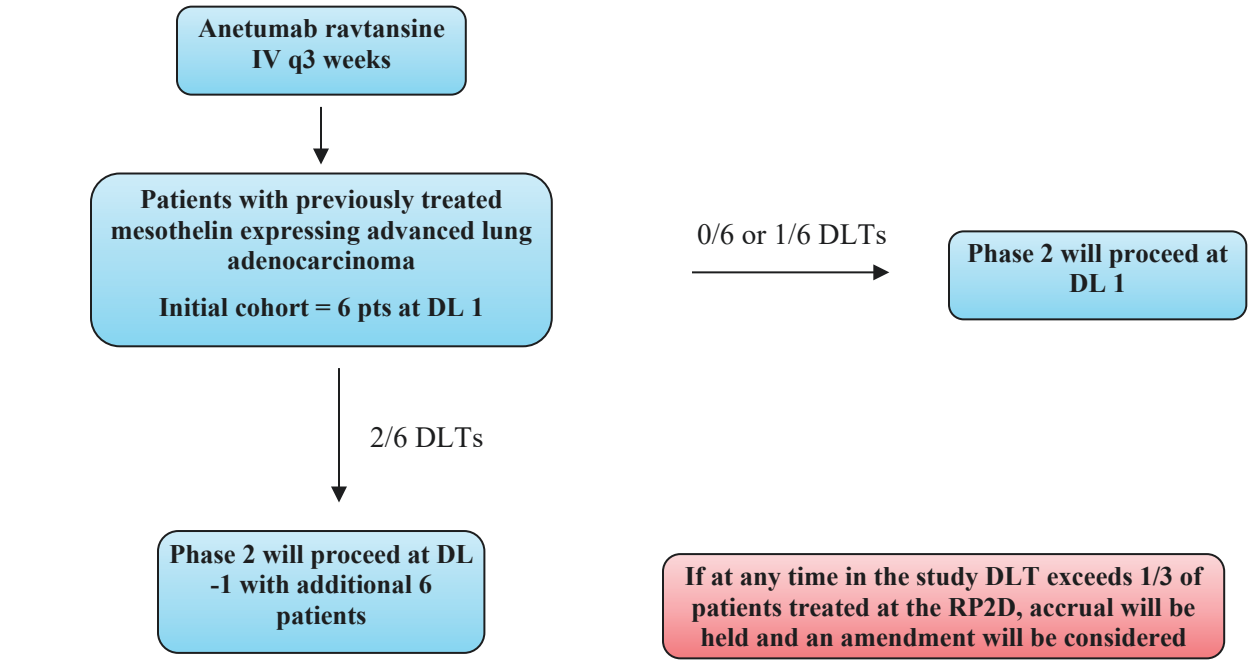
3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

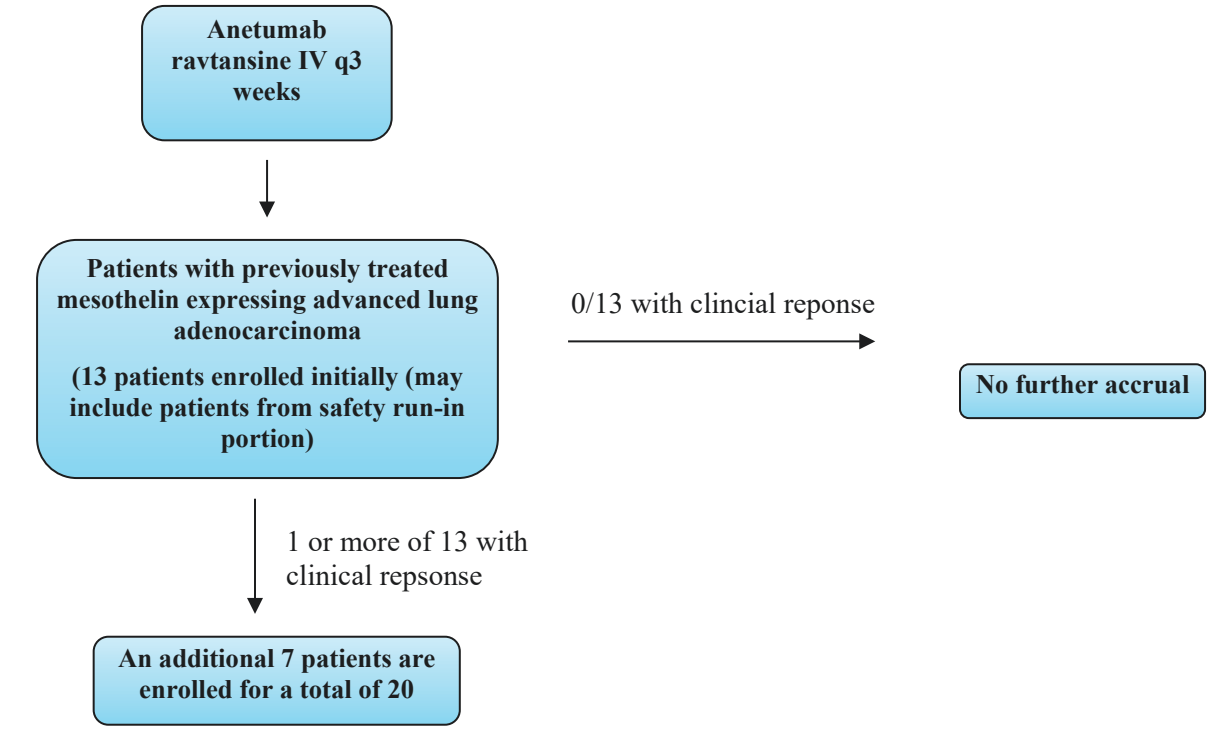
This is an open label, single center, phase I/II study of anetumab ravtansine in subjects with mesothelin positive lung adenocarcinoma. During the safety run-in portion of the study a recommended phase 2 dose (RP2D) will be determined in up to 2 dose levels of up to 6 patients each. In the phase 2 portion of the study, 20 evaluable subjects will be evaluated at the RP2D including the 6 subjects treated at this dose during the dose de-escalation study.

3.1.1 Study Schema

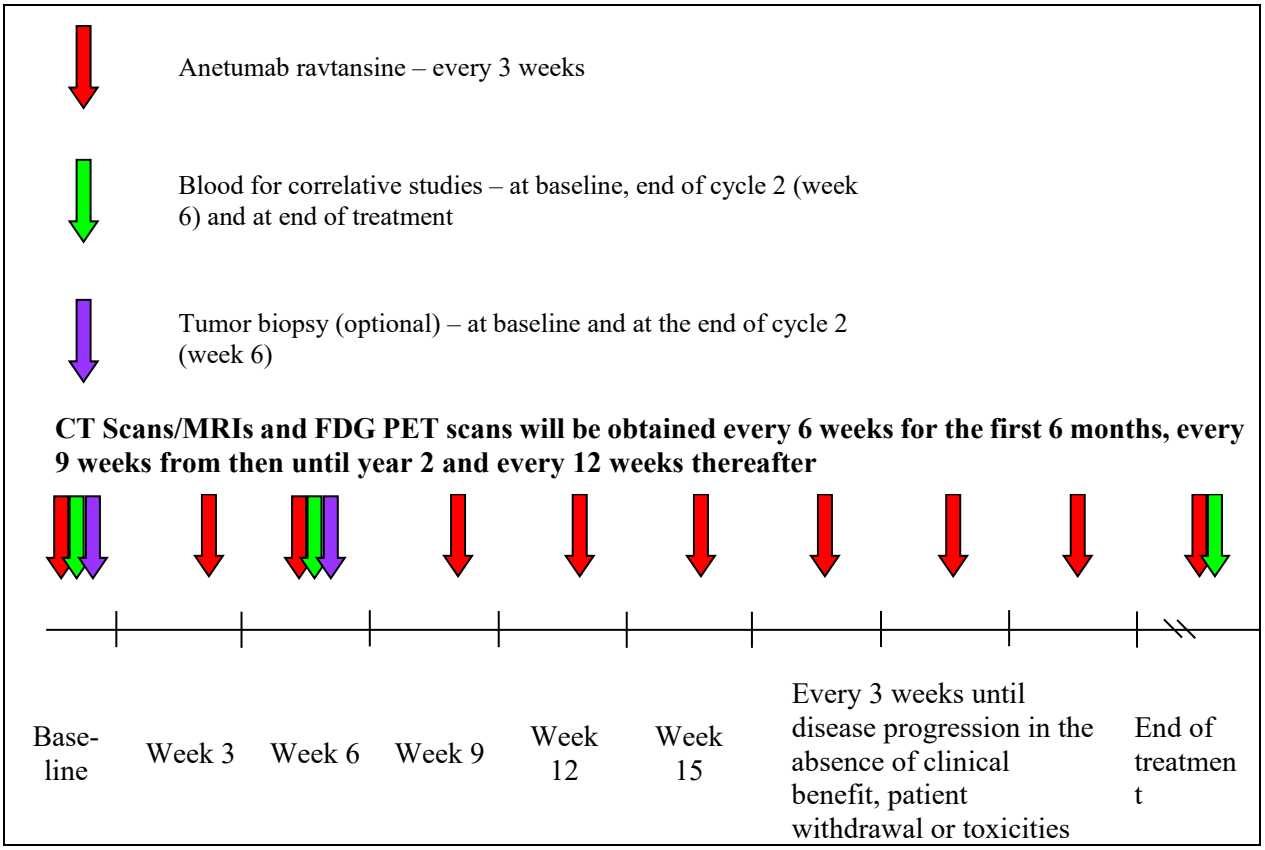
Safety Run-in



Phase 2 – Simon Stage 2 Design



Treatment Schedule



3.1.2 Dose Limiting Toxicity

For the TEAEs of corneal epitheliopathy and the best corrected visual acuity (BCVA) changes potentially fulfilling the DLT criteria for anetumab ravtansine, the grading systems in Table 9 and Table 10 respectively will be used. All other criteria will be assessed per section 6.4.2.

Any TEAE listed below occurring during Cycle 1 and regarded to be at least possibly related to anetumab ravtansine will represent a DLT for anetumab ravtansine treatment.

3.1.2.1 Hematological

- ANC <500/mm3 (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 < 25000/mm3 (CTCAE Grade 4) for ≥7 days regardless of the presence of active bleeding or platelet count <50000/mm^3 (Grade ≥3) with clinically significant bleeding, i.e. bleeding requiring platelet transfusion

3.1.2.2 Non-hematological

- AST and/or ALT increase > 5.0 times ULN (CTCAE Grade ≥ 3)

- AST and/or ALT increase > 3.0 times ULN (CTCAE Grade ≥ 2) with concomitant increase in total bilirubin >1.5 times ULN (CTCAE Grade ≥ 2)
- Total bilirubin > 3.0 times ULN (CTCAE Grade ≥ 3)
- Grade ≥3 corneal epitheliopathy according to the Bayer severity grading for this type of TEAE (Table 9)
- Any other CTCAE Grade ≥ 3 non-hematological toxicity **excluding** the following:
  - Nausea, vomiting, or diarrhea if manageable with antiemetic or antidiarrheal agents within 7 days
  - Hair loss
  - Fatigue lasting ≤ 72 hours
  - Certain asymptomatic laboratory assessments without a clear clinical correlate, if the investigator determines that this TEAE should not be assessed a DLT.
  - CTCAE Grade ≥2 infusion reactions and other CTCAE Grade ≥2 hypersensitivity events deemed at least possibly related to anetumab ravtansine would not be considered a DLT, because hypersensitivity is not directly related to the dose. Nevertheless, these events would require treatment modification or discontinuation.
- Any other toxicity irrespective of the type or severity that represents a clinically significant risk to subject in the investigator's opinion.

If a medically important TEAE not listed above, which is at least possibly related to anetumab ravtansine, has been observed more frequently after Cycle 1, then this TEAE may be declared a DLT in the remainder of the study at the investigator's discretion.

3.1.3 Safety Run-in

The first 6 subjects will be enrolled at dose level 1. If <2 of 6 subjects experience a DLT, dose level 1 will be established as the RP2D and up to 20 evaluable subjects (including the first 6) will be enrolled at this dose level. If 2 or more subjects experience DLT at dose level 1, the RP2D is established at dose level -1 and up to 20 evaluable subjects will be enrolled at this dose level. If a patient did not experience DLT and did not finish treatment, he or she will not be evaluable for toxicity and will be replaced in the dose level. If at any time during the trial, the cumulative fraction of patients treated at the dose used in the phase II portion of the trial who have a DLT exceeds 1/3, then no further accrual will take place unless a treatment modification is provided via an amendment.

Table 3: Dose De-escalation Schedule

Dose Level	Dose of anetumab ravtansine IV q 3 weeks
Level 1	6.5 mg/kg
Level -1	5.5 mg/kg

Table 4: Dose de-escalation will follow the rules outlined in the Table below.

Number of Patients with DLT at Dose Level	De-escalation Decision Rule
0 or 1 out of 6	This will be the recommended phase 2 dose
≥ 2 out of 6	The next lower dose level (DL -1) is established as the recommended phase 2 dose

3.2 DRUG ADMINISTRATION

After reconstitution and dilution as described in section 11.1.3, anetumab ravtansine will be administered at a dose of 6.5 mg/kg or 5.5 mg/kg of body weight every 3 weeks as an intravenous infusion over 1 hour (+/- 15 minutes). **Note**: longer infusions are permitted if following dose modification guidelines; however, diluted anetumab ravtansine must be used within 6 hours. In obese patients, anetumab ravtansine dose should be calculated considering a maximum weight of 100 kg. Patients will continue on treatment until death, or occurrence of progressive disease (PD) in the absence of clinical benefit as defined by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (RECIST 1.1) or drug-related toxicity that requires discontinuation of treatment, or until another criterion for withdrawal from study is met.

3.3 DOSE MODIFICATIONS

Table 5 - Dose modification levels

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

3.3.1 Hematological toxicities

Dose modifications for hematological toxicity

- If treatment modification is required due to a hematological TEAE, and the continuation of treatment is appropriate, the anetumab ravtansine dose will be adjusted as described in Table 6 and Table 7 below.
- G-CSF and other hematopoietic growth factors may be used during the study in the management of acute toxicity such as febrile neutropenia when clinically indicated per ASCO Recommendations for Therapeutic Use of CSF[17] or at the discretion of the investigator; however they may not be substituted for a required dose reduction.
- Blood transfusions and therapy with IV or subcutaneous erythropoietin-stimulating agents (epoetin alpha, darbepoetin alpha) are allowed per institution guidelines but may not be used as substitute for a required dose reduction (see also section 4.1).

- Platelet transfusion may be used during the study in the management of acute toxicity such as hemorrhage or bleeding events, however they may not be used as substitute for a required dose reduction.

Table 6 - Dose adjustments in response to neutrophil and platelet nadir[a] counts of the previous cycle

Absolute neutrophil nadir count of the previous cycle (/mm3)		Platelet nadir count of the previous cycle (/mm3)	Anetumab ravtansine dose adjustment [b]
≥ 500 or < 500 for < 7 days and		≥ 25,000	No change
< 500 for ≥ 7 days	and/or	< 25,000 regardless of the presence of active bleeding (or ≥ 25,000 with clinically significant bleeding, i.e. bleeding requiring platelet transfusion)	Decrease 1 dose level [b]
Febrile neutropenia [c]	and/or	< 25,000 regardless of the presence of active bleeding (or ≥ 25,000 with clinically significant bleeding, i.e. bleeding requiring platelet transfusion)	Decrease 1 dose level [b]

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

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

b) Dose reduction by 1 dose level translates to a change from 6.5 mg/kg Q3W to 5.5 mg/kg Q3W, or from 5.5 mg/kg Q3W to 4.5 mg/kg Q3W. Not more than 2 dose reductions from the starting dose level are permitted. c Febrile neutropenia is defined as ANC < 1000/mm3 and fever (a single body temperature reading of > 38.3°C [101°F] or a sustained body temperature of ≥ 38°C [100.4°F] for more than 1 hour).

Table 7 - Dose adjustments in response to pre-infusion values

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

					dose level [c] (at investigator's discretion)

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

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

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

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

3.3.2 Non-hematological toxicities

3.3.2.1 Non-hematological toxicities requiring dose modification

- CTCAE Grade 2 anetumab ravtansine infusion-related reaction or other CTCAE Grade 2 hypersensitivity events (See section 3.3.3.2)
- AST and/or ALT increase >5.0 x ULN (CTCAE Grade ≥ 3)
- AST and/or ALT increase >3.0 x ULN (CTCAE Grade ≥ 2) with concomitant increase in total bilirubin >1.5 x ULN (CTCAE Grade ≥ 2)
- Total bilirubin ≥ 3.0 x ULN (CTCAE Grade ≥ 3)
- Bayer Grade ≥ 3 corneal epitheliopathy (see below and Table 9)
- Any other Grade ≥ 3 non-hematological toxicity that, in the investigator's opinion, warrants treatment modification (see Table 8), **excluding** the following:
    - Nausea, vomiting, or diarrhea if manageable with anti-emetics or anti- diarrheals within 7 days
    - Hair loss
    - Fatigue lasting ≤ 72 h
- Any other toxicity irrespective of the type or severity that represents a clinically significant risk to patient in the investigator's opinion.

3.3.2.2 Dose modifications for non-hematological toxicity

If treatment modification is required due to Grade ≥ 3 **non-hematological TEAE**, other than corneal epitheliopathy and infusion-related reaction/hypersensitivity events, and the continuation of treatment is appropriate, the anetumab ravtansine dose will be either reduced or maintained as is at investigator's discretion (see Table 8).

Table 8 - Dose adjustments in response to non-hematologic toxicities

CTCAE v4.0 grade	Anetumab ravtansine dose delay / interruption	Anetumab ravtansine dose modification
Grade 1 – 2 [a]	Treat on time	No change required

CTCAE v4.0 grade	Anetumab ravtansine dose delay / interruption	Anetumab ravtansine dose modification
Grade 3	1st appearance: Delay /Interruption until Grade ≤ 2 [b]	Re-start at the same dose or decrease by 1 dose level [c] (at investigator's discretion)
	2nd appearance: Delay /Interruption until Grade ≤ 2 [b]	Decrease by 1 more dose level [c]
	3rd appearance: Permanently discontinue	
Grade 4	Permanently discontinue	

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

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

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

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

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

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

After dose reduction for TEAE, there could be no intra-patient dose re-escalation irrespective of the type of TEAE that has led to dose reduction in this patient with the exception of grade 3 corneal epitheliopathy as per Table 9.

3.3.3 Miscellaneous toxicities

3.3.3.1 IV infusion-related reaction and other hypersensitivity events

If a patient experiences a 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 interrupted.

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

In case of a CTCAE Grade ≥ 3 hypersensitivity and acute infusion reaction, treatment must be permanently withdrawn.

3.3.3.2 Miscellaneous toxicities requiring dose modification

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

3.3.3.3 Dose modifications for corneal epitheliopathy

For the TEAE of corneal epitheliopathy and the best corrected visual acuity (BCVA) changes (blurred vision), the Bayer severity grading system (see Table 9 and Table 10) will be used to assess the severity of TEAEs requiring modification of anetumab ravtansine treatment.

TEAE of corneal epitheliopathy deemed to be at least possibly related to anetumab ravtansine would require modification of anetumab ravtansine treatment (dose reduction or permanent discontinuation of treatment) according to the following principles (see Table 9).

Table 9 - Bayer classification and management of corneal epitheliopathy

	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Corneal morphology	No pathologic changes	Any stage of superficial punctate keratitis[a]	Epithelial opacities Micro-cysts Micro-deposits Corneal erosion Stromal opacity: non-central	Corneal ulcer without risk of acute rupture Stromal opacity: central	Corneal ulcer more severe than Grade 3
Eye treatment[b]	Ocular lubricants at the discretion of investigator in consultation with ophthalmologist/ optometrist	Ocular lubricants; add topical steroids if superficial punctate keratitis shows treatment-emergent progression by ≥ 2 SPK Grades	Intensive treatment with ocular lubricants enhanced with ointments; topical steroids; therapeutic contact lens may be considered at the discretion of investigator in consultation with ophthalmologist/ optometrist	Intensive therapy with ointments; topical steroids; therapeutic contact lens or occlusion recommended at the discretion of investigator in consultation with ophthalmologist /optometrist	Intensive therapy with lubricants, ointments, topical steroids and antibiotics as needed; occlusion or therapeutic contact lens recommended; amniotic membrane transplant and other locally approved therapies to be considered at the discretion of investigator in consultation with ophthalmologist / optometrist

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

SPK = Superficial punctate keratitis

a) Oxford Schema must be used for grading SPK from stage 0 to VI.
b) Other remedial therapies for corneal epitheliopathy may be added or substituted at investigator's discretion or according to the institutional standards.
c) Treatment decisions are based on corneal epitheliopathy only, not on visual acuity changes.

Table 10 - Bayer classification of visual acuity changes

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

ETDRS = Early Treatment Diabetic Retinopathy Study

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

3.3.3.3.1 Recommended measures in case of eye dryness and ocular hypertension

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

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

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

3.3.4 Continuation of treatment with anetumab ravtansine

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

3.3.5 Permanent discontinuation of anetumab ravtansine due to TEAEs

- CTCAE Grade 4 non-hematological AE and Bayer Grade 4 corneal epitheliopathy (see Table 9) (except at the investigator's discretion in case of certain Grade 4 abnormality of laboratory assessments, such as abnormal laboratory assessments without corresponding clinical symptoms, or abnormal laboratory assessments that can be easily clinically managed).
- If any type of TEAE requiring dose modification does not resolve to Grade ≤ 1 (or Hb ≥ 9 g/dL in case of anemia) within 6 weeks after the last dose of anetumab ravtansine.
- Delay in anetumab ravtansine administration of 3 weeks (max. 6 weeks between 2 infusions of study drug).
- TEAE requiring dose reduction when already at the 4.5 mg/kg Q3W dose level (minimum dose).
- More than 2 dose reductions required due to a TEAE.

3.4 STUDY CALENDAR

1 cycle = 3 weeks (21 days)

Screening and baseline evaluations are performed per the timeframes indicated in sections 2.2 and 2.4 respectively.

On therapy assessments may be performed up to 5 days prior to indicated time; safety follow up may occur up to 7 days after indicated time; long term follow up phone calls may be performed within ± 14 days of indicated time.

Dosing cycles after cycle 1 may be delayed for up to two weeks to accommodate schedule conflicts, Federal holidays and inclement weather, etc.

Procedure	Screening/ Baseline	Cycle 1			Subsequent Cycles			End of Treatment	Post Therapy Follow-up	
		Day 1	Day 8	Day 15	Day 1	Day 8	Day 15		30 day safety follow up	Long term follow up
History and PE[1]	X	X	X		X				X	
Weight		X			X				X	
Vital signs	X	X	X		X				X	
ECOG Performance Score	X									
Confirmation of dx and mesothelin expression	X									
Imaging assessments[2]	X	Every 6 weeks (first 6 months), every 9 weeks (until end of year 2), every 12 weeks thereafter								
Echocardiogram	X	Every 6 weeks for the first 6 months, then every 12 weeks thereafter								
12 lead ECG[3]	X	X			X (cycle 2 only)				X	
HBsAg, anti-HCV, anti-HIV	X									
Ophthalmologic exam[4]	X				X				X	

Procedure	Screening/ Baseline	Cycle 1			Subsequent Cycles			End of Treatment	Post Therapy Follow-up	
		Day 1	Day 8	Day 15	Day 1	Day 8	Day 15		30 day safety follow up	Long term follow up
CBC with differential, Hepatic Panel;	X		X	X[5]	X	X[5]			X	
Acute Care Panel	X									
PT/PTT	X				X				X	
Urinalysis	X				X					
β-HCG in women of childbearing potential	X				X				X	
Optional biopsy	X				Cycle 3 only					
Correlative Research Studies[6]		X			Cycle 3 only			X		
NIH Advance Directives Form	X[7]									
Adverse Events		Continuous assessment								
Concomitant Medications		Continuous assessment								
Phone calls q 3 months for survival status and new anti-cancer treatment										X

[1] A complete physical exam is performed at screening. Thereafter, brief physical exams will be performed as per schedule above.

[2] The following imaging assessments will be performed: CT scan, MRI (if appropriate) and FDG PET. Assessments will continue until confirmatory scans for progressive disease have been obtained.

[3] All ECGs will be recorded as single digital 12-lead ECG obtained after 5-10 minutes' rest in supine or semi-recumbent position. Personnel are instructed to ensure a relaxed and quiet environment with the subjects being awake and at complete rest prior and during the recordings. On day

1 of cycle 1, the ECG will be recorded within 1 hour (+15 minutes) after the end of the infusion. On day 1 of cycle 2, an ECG will be recorded at two time points: pre-dose and within 1 hour (+15 minutes) after the end of the infusion.

[4] A detailed ophthalmologic examination (visual acuity, IOP, Schirmer test and slit lamp) will be done for all patients during screening within 3 weeks before the start of study treatment. After study therapy is initiated, visual acuity and slit lamp exam will be repeated before infusion in every cycle except C1D1, and at safety follow-up visit, or more frequently at investigator's and ophthalmologist/ optometrist's discretion. IOP measurement is to be repeated during anetumab ravtansine therapy if the patient receives steroid eye drops as treatment for eye toxicity; dry eye (Schirmer) test may be repeated during treatment at investigator's discretion (e.g. in case of eye dryness during anetumab ravtansine therapy). During treatment period, ophthalmologic examination can be done up to 7 days before anetumab ravtansine infusion.

[5] Assessment may be performed by local laboratory if patient is unable to return to NIH.

[6] At each collection: 4 mL of blood in 10 mL tiger top tube to Figg lab; three 10 mL sodium heparin (green top) tubes to NIH Flow lab.

[7] As indicated in section **10.3**, all subjects ≥ age 18 will be offered the opportunity to complete an NIH advanced directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

3.5 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

3.5.1 Criteria for removal from protocol therapy

- Requirement for therapy prohibited by protocol (see section 4.2)
- Progressive disease; however, treatment may be continued provided that the patient derives clinical benefit as determined by the investigator
- Development of secondary malignancy
- Participant becomes pregnant
- Participant requests to be withdrawn from active therapy
- Unacceptable toxicity as defined in section 3.3
- Investigator discretion

3.5.2 Off-Study Criteria

- Screening failure
- Participant requests to be withdrawn from study
- Lost to follow up
- The investigator decides to stop the study
- Death

3.5.3 Off Protocol Therapy and Off Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

4 CONCOMITANT MEDICATIONS/MEASURES

Any medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study treatment or listed in section 4.2 below, may be given at the discretion of the investigator. In general, patients should be closely monitored for side effects of all concomitant medications regardless of elimination path, especially those with narrow therapeutic indices, such as warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporine, and digoxin. All concomitant medications used while patient is on study therapy (including start/stop dates, dose, frequency, route of administration and indication) must be recorded.

4.1 SUPPORTIVE CARE

4.1.1 Biologic response modifiers, such as filgrastim

Filgrastim and other hematopoietic growth factors may be used during the study in the management of acute toxicity such as febrile neutropenia when clinically indicated per ASCO Recommendations for Therapeutic Use of CSF[17] or at the discretion of the investigator (if medically necessary, growth factors may be administered at recommended doses; however they may not be substituted for a required dose reduction

4.1.2 Blood products

Blood transfusions and chronic therapy with IV or subcutaneous erythropoietin- stimulating agents (epoetin alpha, darbepoetin alpha): These are allowed, but may not be used as a substitute for required dose reduction.

4.1.3 Other

Further supportive per NIH CC Pharmacy guidelines is permitted with the exception of interventions appearing in section 4.2.

4.2 PROHIBITED THERAPIES

- Platinum/pemetrexed/bevacizumab
- Other systemic anti-cancer therapy (cytotoxic therapy, targeted therapies, immunotherapy, hormonal therapy, or any other experimental or approved therapy)
- Acute steroid therapy
- Anti-arrhythmic therapy other than beta blockers of digoxin
- Any drugs with known bone marrow toxicity
- Strong inhibitors and strong inducers of CYP3A4 (listed in Appendix C). Moderate and weak CYP3A4 inhibitors should be used with caution as decrease in plasma concentrations of DM4 cannot be ruled out.
- Any drugs that inhibit renal tubular secretion (e.g. probenecid and cimetidine).

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH

5.1.1 Induction of anti-mesothelin humoral immune response

We have previously shown that in some patients with mesothelioma and ovarian cancer there is loss of tolerance to mesothelin as reflected by development of anti-mesothelin antibodies. We propose evaluating serum samples from all patients enrolled on this study and determine if treatment with anetumab ravtansine induces a humoral immune response to mesothelin and if so correlating induction of anti-mesothelin humoral immune response with tumor characteristics (such as tumor mesothelin expression, serum mesothelin and megakaryocyte-potentiating factor (MPF) levels) as well as clinical outcome including overall survival.

5.1.1.1 Sample Collection

Samples will be collected at baseline, at the end of cycle 2 and at the end of treatment.

All blood samples will be taken by either direct venipuncture or an indwelling venous access. At each sample collection time, blood (4mL) will be drawn into a 10-mL serum separator tube (tiger top tube) labeled as follows:

- Subject ID Number
- Study Number
- Time and date of collection

5.1.1.2 Sample Processing

Please e-mail Julie Barnes at Julie.barnes@nih.gov and Paula Carter pcartera@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact Julie Barnes by e-mail or at 240-760-6044.

Upon arrival in the CPP, each sample should be processed in the following manner:

Allow blood to clot for 10 minutes and centrifuge to separate the serum within 30 minute of collection. If necessary whole blood may be stored in the collection tubes upright and refrigerated at 4-8°C for up to 24 hours prior to centrifugation and processing. Processing within 30 minutes is strongly preferred. Transfer the serum into two (2) pre-labeled cryotubes and immediately freeze by placing on dry ice. Transfer frozen serum samples into a – 80°C freezer for storage.

Autoantibody levels will be retrospectively assessed.

5.1.1.3 Sample Storage

All serum samples will be stored frozen at approximately –80°C in the Clinical Pharmacology Program.

5.1.2 Gene expression-based characterization of the immune landscape before and after treatment with anetumab ravtansine

We will evaluate tumor biopsies before and after treatment with anetumab ravtansine using a hybridization-based digital gene expression platform nCounter (NanoString Technologies). This platform allows for unbiased multiplexed quantification of RNA transcripts achieving sensitivity comparable to quantitative reverse-transcription polymerase chain reaction (Q-RT-PCR), without any enzymatic reaction involved in the process. We have expertise in the use of this technology for the characterization of purified cell subsets and also for the study of the changes that occur in human tumors, as a consequence of a given treatment, using tumor core biopsy tissues. This analysis can be performed on flash frozen biopsies without any further isolation or enrichment of specific cell types. We will also use immunohistochemistry and immunofluorescence techniques to characterize diverse immune cell subpopulations and alterations with tumor biopsies of patients before and after treatment.

For the present study, we will screen pre- and post-treatment samples for the expression of markers of immune cell subsets (CD3, CD8, CD4, etc.), local production of cytokines (interferon-gamma, tumor necrosis factor-alpha, etc.) and chemokines (CXCL13, CCL5, etc.), adhesion molecules and others. The purpose of this study is to characterize the molecular changes that occur within the tumors following treatment with anetumab ravtansine. The ultimate goal is to gain a better understanding of the mechanism of action of this treatment, and to identify molecular correlates of clinical outcomes such as objective responses and/or improved survival.

In order to achieve these goals, flash frozen samples will be subjected to total RNA isolation followed by hybridization with capture and detection probes specific for 620 transcripts, including genes involved in the regulation of the immune function and also markers expressed by tumor cells and tumor stroma. To cover those target transcripts, a combination of a commercially available pre-designed probe set (GX Human Immunology v2, NanoString Technologies) will be used in combination with a custom-designed code set of thirty additional targets (Panel Plus, NanoString Technologies). Hybridization complexes will be quantified using a NanoString nCounter Analysis System, at the Genomics Core Facility of the Center for Cancer Research, NCI.

Results obtained by this approach will be correlated with data obtained from immunohistochemistry and pathology analysis of tumor biopsies as well as with data from analysis of peripheral blood populations, for a comprehensive study of the mechanism of action of anetumab ravtansine in lung cancer and mesothelioma patients.

5.1.2.1 Collection

Optional biopsies will be collected at baseline (if a sample was not collected at screening) and at the end of cycle 2. Archival samples may be used if patient refuses biopsy.

Collection of biopsy should be guided by ultrasound, CT scan, or other method according to the location of the selected lesion using a ≤ 18 gauge needle to provide cores ideally of at least 20 mm in length or equivalent size. At least 2, ideally 4 core biopsies will be obtained. Fine needle aspiration and biopsy of bone lesions are not acceptable.

The first core will be stored in the Laboratory of Pathology. Remaining samples will be stored in the Laboratory of Dr. Raffit Hassan, Building 10, Room 3B51. In general, Betsy Morrow (phone: 301 402 5688; email: morrowbj@mail.nih.gov), a biologist in Dr. Hassan's lab will pick up the samples. If she is unavailable, another biologist will do so.

5.1.3 Assessment of Mesothelin Expression over Time

Fresh tumor tissue collected at baseline (optional) will be compared to archival material in order to determine whether mesothelin protein levels change over time and with disease progression. Mesothelin expression will be assessed by the Laboratory of Pathology using immunohistochemistry. Immunohistochemical staining will be evaluated by a pathologist and scored based on the intensity of staining as weak 1+, moderate 2+, and strong 3+, and the percentage of tumor cells that are positive.

5.1.3.1 Collection

Samples collected at screening (archival) and baseline (optional) as described previously will be used for this analysis.

5.1.4 Assessment of Myeloid Derived Suppressor Cells (MDSC) in Subjects with Lung Adenocarcinoma

5.1.4.1 Sample collection

Samples will be collected at baseline prior to first dose of anetumab ravtansine and the end of cycle 2 and at the end of treatment. All blood samples will be taken by either direct venipuncture or an indwelling venous access. At each sample collection time, blood (30 mL) will be drawn into three 10 mL sodium heparin (green top) tubes.

The tube should be labeled with the following information:

- Subject ID Number
- Study Number
- Time and date of collection
-Specimen type: **peripheral blood**

5.1.4.2 Sample processing

The samples will be sent to NIH Flow Cytometry lab located at 3S240, South part of Building 10.

All specimens for flow cytometry will be scheduled in advance by contacting Dr. Stetler-Stevenson stetler@mail.nih.gov and/or Dr. Yuan yuanc@mail.nih.gov by email. Peripheral blood samples should arrive no later than 1 pm to the flow cytometry laboratory on the day scheduled.

Specimens are received in the laboratory via escort or via delivery by someone from the clinical team. Specimens for delivery AFTER HOURS ONLY may also be placed in the secure specimen drop box located in Laboratory of Pathology 3N hallway. Peripheral blood specimens are collected in sodium heparin tubes, and are stored at room temperature until delivery.

The specimens should be delivered as soon as possible after collection, and cannot be evaluated if > 48 hours old.

Upon receipt in the flow lab, the sample will be checked for correct labeling with appropriate patient identifiers and specimen type (e.g. peripheral blood).

5.2 SAMPLE COLLECTION SUMMARY

Test/assay	**Sample**	**Type of tube (if applicable)**	**Collection point (within)**	**Location of specimen analysis**
Anti-mesothelin humoral immune response	4 mLs blood	10 mL serum Separator	Baseline, C3D1, EOT	Clinical Pharmacology Program
Gene expression characterization of the immune landscape &	Optional tumor biopsy	NA	Baseline, C3D1	Dr. Hassan's lab

Test/assay	Sample	Type of tube (if applicable)	Collection point (within)	Location of specimen analysis
Assessment of Mesothelin Expression Over Time	Archival sample and optional tumor biopsy	NA	Archival sample collected at screening, and on study biopsies collected for Gene expression characterization study	Laboratory of Pathology
Assessment of MDSC	30 mL blood	Three 10 mL sodium heparin tubes	Baseline, C3D1, EOT	NIH Flow Cytometry Lab

5.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without IRB notification and an executed MTA.

5.3.1 Clinical Pharmacology Program

Upon arrival in the Clinical Pharmacology Program (CPP), OCD, CCR, NCI, all samples are barcoded, with data entered and stored in Patient Sample Data Management System (PSDMS), also known as *Labrador*, the system utilized by the CPP. This is a secure program, with access to the PSDMS system limited to defined CPP personnel, who are issued individual user accounts. PSDMS creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without PSDMS access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle, time point, dose, material type, as well as box and freezer location. There are patient demographics that can be obtained to correlate with the samples through PSDMS. For each sample, there are notes associated with processing method (delay in sample processing, storage conditions on the ward, etc.)

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20°C or -80°C according to stability requirements. These freezers are located onsite in the CPP and offsite at NCI Frederick Central Repository Services in Frederick, MD. Samples will be stored until requested by the researcher assigned to the protocol. All requests are monitored and tracked in PSDMS. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per IRB approved protocol) and that any unused samples must be returned to the CPP.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

5.3.2 Laboratory of Dr. Raffit Hassan

This study will follow storage, handling and labeling procedures to ensure that security, confidentiality and sample integrity are maintained. All samples (blood or tissue) are tracked by distinct identification labels generated by Labmatrix that include a unique patient identifier and date of specimen collection. Thus samples will be de-identified of personal data, with access to personal data restricted to the study investigators.

Depending on specimen type, samples are stored in liquid nitrogen, in monitored freezers/refrigerators at either -20 or -80°C according to stability requirements or in a slide cabinet in the research Laboratory of Dr. Raffit Hassan (Building 10, Room 3B51).

5.3.3 Laboratory of Pathology

Tissues designated for clinical diagnostics are transported to the Laboratory of Pathology (LP) where they are examined grossly and relevant portions are fixed, embedded in paraffin and sectioned and stained for diagnostic interpretation. Unutilized excess tissues are stored for up to three months, in accordance with College of American Pathologists/Joint Commission on Accreditation of Healthcare Organizations (CAP/JCAHO) guidelines, and then discarded. Following completion of the diagnostic workup, the slides and tissue blocks are stored indefinitely in the LP's clinical archives. All specimens are catalogued and retrieved utilizing the clinical laboratory information systems, in accordance with CAP/JCAHO regulations. The use of any stored specimens for research purposes is only allowed when the appropriate IRB approval has been obtained. In some cases, this approval has been obtained via the original protocol on which the patient was enrolled.

5.3.4 NIH Flow Cytometry Laboratory

Specimens received in the flow cytometry laboratory are accessible only to the flow cytometry laboratory team, as the laboratory door is locked and key access is only provided to the flow cytometry laboratory members. Additionally, the flow cytometry laboratory is set behind a set of double doors that are accessible only by badge/key card access.

5.3.5 Protocol Completion/Sample Destruction

All specimens obtained in the protocol are used as defined in the protocol. Any specimens remaining at the completion of the protocol will be stored in the conditions described above. The study will remain open as long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or until a subject withdraws consent for their continued use, at which time they will be destroyed and data from the. Once primary research objectives for the protocol are achieved, intramural researchers can request access to remaining samples, provided they have an IRB-approved protocol and patient consent or an exemption from OHSRP.

The PI will report any loss or destruction of samples to the NCI IRB as soon as he/she is made aware of such loss. The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors such as a broken freezer or lack of dry ice in a shipping container, or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples, or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director and the office of the CCR, NCI.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

Data obtained on the study will be stored in C3D and Labmatrix.

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

_X_ De-identified data in an NIH-funded or approved public repository.

_X_ De-identified data in BTRIS

_X_ De-identified or identified data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

_X_ An NIH-funded or approved public repository. _clinical trials.gov.

_X_ BTRIS

_X_ Approved outside collaborators under appropriate individual agreements.

_X_ Publication and/or public presentations.

When will the data be shared?

_X_ Before publication.

_X_ At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

No large scale genomic data will be generated on this study.

6.3 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response every 6 weeks in the first 6 months, every 9 weeks until the end of year 2 and every 12 weeks thereafter. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

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) guideline (version 1.1)[18]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.3.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with anetumab ravtansine.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.3.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm by chest x-ray, as $\geq$10 mm

with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'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.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.3.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers

(e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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 is preferable.

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. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. 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. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. 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.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published[19-21]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer[22]].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

6.3.4 Response Criteria

6.3.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

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

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

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

6.3.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.3.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-	No	SD	Documented at least once ≥4 wks. from baseline**

	PD/not evaluated			
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

6.3.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

6.3.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

6.4 TOXICITY CRITERIA

6.4.1 Corneal Epitheliopathy and Best Corrected Visual Acuity

For the adverse event of corneal epitheliopathy and the best corrected visual acuity (BCVA) changes potentially fulfilling the DLT criteria for anetumab ravtansine, the grading systems in Table 9 and Table 10 respectively will be used. All other criteria will be assessed per section 6.4.2 below.

6.4.2 All Other Adverse Events

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. 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 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Adverse Event

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

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate 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.

7.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.8 Hospitalization

In general, hospitalization means that the subject has been detained at the hospital or emergency ward for observation or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment planned prior to study enrollment is neither an SAE nor an AE.

7.1.9 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.1.10 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.1.11 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**
- 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.

7.2 NCI-IRB AND CLINICAL DIRECTOR (CD) REPORTING

7.2.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report on the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

   NOTE: Grade 1 events are not required to be reported.

7.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

7.3 IND SPONSOR REPORTING CRITERIA

During the first 30 days after the subject receives investigational agent/intervention, the investigator must immediately report to the sponsor, using the mandatory MedWatch form 3500a or equivalent, any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. For serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention, only report those that have an attribution of at least possibly related to the agent/intervention.

Required timing for reporting per the above guideline:

- Deaths (except death due to progressive disease) must be reported via email within 24 hours. A complete report must be submitted within one business day.
- Other serious adverse events as well as deaths due to progressive disease must be reported within one business day.

Events will be submitted to Center for Cancer Research (CCR) at: CCRsafety@mail.nih.gov and to the CCR PI and study coordinator.

7.3.1 Reporting Pregnancy

7.3.1.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately and the pregnancy reported to the Sponsor. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agents (s) should be documented in box B5 of the MedWatch form "Describe Event or Problem".

Pregnancy itself is not regarded as an SAE. However, as patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic, the CCR is requesting that 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.

Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

If any pregnancy occurs in the course of the study, then the investigator should inform the Sponsor within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative will work with the investigator to ensure that all relevant information is provided to the Sponsor within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

7.3.1.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for six months after the last dose of anetumab ravtansine.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 6 months after the last dose should, if possible, be followed up and documented.

7.4 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

All events listed below must be reported in the defined timelines to CCRsafety@mail.nih.gov.

The CCR Office of Regulatory Affairs will send all reports to the manufacturer as described below.

All SAEs must be reported to Bayer within 24 hours of the CCR Office of Regulatory Affair's awareness and must include the following minimum information:

1. The name and contact information of the reporter
2. The name of the study drug(s)
3. A description of the reported SAE
4. A patient identified by one or more of the following:
    a. Patient initials
    b. Patient number
    c. Knowledge that a patient who experienced the adverse event exists
    d. Age
    e. Sex
5. An investigator assessment of study drug causality.

Additional data which would aid the review and causality assessment of the case include but are not limited to:

- The date of onset
- The severity
- The time from administration of study drug(s) to start of the event
- The duration and outcome of the event
- Any possible etiology for the event
- The final diagnosis or syndrome, if known
- Action(s) taken, if any

7.4.1.1 Expedited Reporting of Other Safety Information

The Sponsor shall report to Bayer within 24 hours of the CCR Office of Regulatory Affair's awareness of other events such as:

- An adverse event related to study specific procedures
- Any new and important event related to treatment with the study drug(s).
- Any pregnancy during which a female patient was exposed to the study drug(s)

- Any pregnancy in the partner of a male patient, where the male patient was exposed to study drug at the time of conception or conception occurred within two weeks of the last dose of study drug(s).
- Any other relevant safety information including but not limited to reports on drug interaction, overdose, drug abuse or misuse, drug dependency, withdrawal syndrome, medication error, occupational exposure and lack of drug effect (LODE) occurring at any time during the treatment phase;
- Any communication concerning safety related information to regulatory authorities or ethics committees including but not limited to:
  - Development Safety Update Reports (DSUR) / relevant parts of IND reports for the STUDY;
  - Any other safety related reports, issues and queries that are either raised by or communicated to regulatory authorities or ethics committees.

The Investigator/Sponsor may report SAEs using:

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

All reports shall be sent electronically to:

Electronic Mailbox:	DrugSafety.GPV.US@bayer.com
Facsimile:	(973) 709-2185
Address: Mail only	Global Pharmacovigilance - USA Bayer HealthCare P.O. Box 915 Whippany, NJ 07981-0915
Address: FDX or UPS only	100 Bayer Blvd., Whippany, NJ 07981 67 Whippany Road, Whippany NJ 07981 for UPS

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

Phone:	1-888-842-2937

The Principal Investigator commits to respond promptly to any query from Bayer regarding SAE reports.

7.5 DATA AND SAFETY MONITORING PLAN

7.5.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose de-escalation will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS and to the Sponsor.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.5.2 Sponsor Monitoring Plan

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary study endpoints; adherence to the protocol, regulations, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

This trial will be monitored by personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

8 STATISTICAL CONSIDERATIONS

The primary objectives of this trial are to assess the safety and tolerability of anetumab ravtansine in patients with unresectable mesothelin expressing previously treated advanced lung adenocarcinoma (stage IIIB or IV), and to determine a preliminary estimate of the response rate of the treatment. Based on the mechanisms of action of anetumab ravtansine, at least minimal tumor expression of mesothelin would be required to anticipate clinical activity. As such, patients to be enrolled on the trial will first be screened for the presence of mesothelin membrane intensity score of 2+ or 3+ (on the 0-3 scale) expressed on the membrane of ≥10% of tumor cells. For this assay, subjects must provide sample of archival tumor tissue collected any time before the general screening. Additionally, optional tumor biopsies will be performed before and after 2 doses of anetumab ravtansine.

The first 6 patients enrolled on the trial will receive anetumab ravtansine at a dose of 6.5 mg/kg. If 0 or 1 of the first 6 patients experiences a dose-limiting toxicity (DLT), then the remainder of the patients on the trial will be treated at that dose. If 2 or more patients within the first 6 experience a DLT, then the remaining patients will be treated at 5.5 mg/kg. If at any time during the trial, the cumulative fraction of patients treated at the dose used in the phase II portion of the trial who have a DLT exceeds 1/3, then no further accrual will take place unless a treatment modification is provided via an amendment.

The phase II portion of the trial will be conducted incorporating either the 6 patients treated at 6.5 mg/kg or 5.5 mg/kg as appropriate. Given the expected rarity of responses, the goal would be to determine if using anetumab ravtansine would rule out a 5% response rate and target a rate of 25%. For these patients, the trial will be conducted using a Simon Minimax two-stage phase II trial design in order to rule out an unacceptably low partial response (PR)+ complete response (CR)

rate of 5% (p0=0.05) in favor of an improved response rate of 25% (p1=0.25). With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta = 0.10 (probability of rejecting a good treatment=0.10), this first stage will enroll 13 evaluable patients (including patients treated at the safe dose found in the initial 6 patients), and if 0 of the 13 have a clinical response, then no further patients will be accrued. If 1 or more of the first 13 patients have a response, then accrual would continue until a total of 20 evaluable patients have been treated. As it may take up to several months to determine if a patient has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. If there are 1 to 2 patients with a response out of 20 patients, this would be an uninterestingly low response rate. If there were 3 or more of 20 (15%) who experienced a response, this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (5% response rate), the probability of early termination is 51%.

Assessment of serum samples and tumor biopsies will be exploratory and will be summarized descriptively.

The initial portion of the trial may require up to 6 patients who may not be included in the phase II portion if 2 or more of them experience DLTs at 6.5 mg/kg. The phase II portion may require up to 20 evaluable patients. Thus, if 5.5 mg/kg is the selected dose, then up to 26 evaluable patients may be required while if 6.5 mg/kg is selected, only up to 20 evaluable patients may be required. It is anticipated that approximately 50% of screened patients will have <5% mesothelin level and will not be treated on the protocol. Thus, in order to allow for 50% drop-outs for that reason as well as a small number of inevaluable patients, the accrual ceiling will be set at 55 patients. If 2 patients per month enroll on this trial, accrual would be expected to be completed in approximately 28 months.

9 COLLABORATIVE AGREEMENTS

9.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

The study drug, anetumab ravtansine, will be supplied by the manufacturer, Bayer HealthCare Pharmaceuticals under a CRADA agreement (CRADA #03084) between the manufacturer and the Center for Cancer Research.

10 HUMAN SUBJECTS PROTECTIONS

10.1 RATIONALE FOR SUBJECT SELECTION

This study will be open to all individuals with mesothelin expressing lung adenocarcinoma regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met. The selection criteria reflect all available nonclinical and clinical safety experience with anetumab ravtansine. Further, the selection criteria address the potential pharmacokinetics issues that may confound the reliable assessment of the study objective related to the pharmacokinetic drug-drug interaction.

The treatment of men as well as women is justified because of the severity of the underlying neoplastic disease. Men and women who use appropriate contraception or women who are not of child-bearing potential will be enrolled into this study. The proportion of men and women enrolled into the dose-safety run-in cohorts of this study depends only on the availability of subjects at the NIH Clinical Center.

This study will be recruited through internal referral, our local physician referral base, and will be posted on clinicaltrials.gov.

10.2 PARTICIPATION OF CHILDREN

There are no dosing or adverse event data are currently available on the use of BAY 94-9343 / anetumab ravtansine in patients <18 years of age; therefore, children are excluded from this study.

10.3 PARTICIPATION OF SUBJECTS UNABLE TO PROVIDE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section 10.4), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MAS Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

10.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

10.4.1 Risks

10.4.1.1 Study Drug

Potential risks of the study include the possible occurrence of any of a range of side effects as listed in section 11.1.2 and the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis, provide premedications and supportive therapies as described earlier.

10.4.1.2 Biopsy

Needle biopsy is minimally invasive and is typically a very safe procedure. Depending upon the site being biopsies and the type of biopsy being performed, risks can include infection of the biopsy site, development of a hematoma, and bleeding. Rarely more significant complications can occur when structures near the biopsy target are entered with the needle (e.g. puncture of lung or bowel).

Furthermore, the optional biopsies collected at baseline and after the end of cycle 2 (which may be CT guided) will be for research purposes only. This will result in exposure to approximately 0.27 rem. This amount is below the guideline of 5 rem per year allowed for adult research subjects by the NIH Radiation Safety Committee.

10.4.1.3 Research Blood Sampling

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting.

10.4.2 Benefits

The potential benefit to a patient who enters the study is a reduction in the bulk of his/her tumor, which may or may not have a favorable impact on symptoms and/or survival.

10.5 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

An associate or principal investigator on the trial will inform patients of the purpose, alternatives, treatment plan, research objectives and follow-up of this trial. The patient will be provided an IRB-approved consent for review and signature and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained from the patient at a subsequent visit. The original of the signed informed consent will be placed in the patient's medical record and a copy will be held in the research record.

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before receiving study therapy.

Consent for the optional biopsies on this study will be obtained at the time of the procedure, using the procedure consent. If the patient refuses the optional biopsy at that time, the refusal will be documented in the medical record and in the research record.

10.5.1 Telephone re-consent procedure

Re-consent on this study may be obtained via telephone according to the following procedure: the informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent. The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone. A fully executed copy will be returned via mail for the subject's records. The informed consent process will be documented on a progress note by the consenting investigator.

10.5.2 Informed consent of non-English speaking/writing subjects

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OHSRP SOP 12, 45 CFR 46.117 (b) (2), and 21 CFR 50.27 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation. Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

11 PHARMACEUTICAL INFORMATION

11.1 ANETUMAB RAVTANSINE (IND #: 130915)

11.1.1 Source

Anetumab ravtansine will be supplied by the manufacturer, Bayer Healthcare Pharmaceuticals under a CRADA agreement between the manufacturer and the Thoracic and GI Oncology Branch.

11.1.2 Toxicity

The clinical experience with anetumab ravtansine available to date comes from the ongoing Study 15051 entitled "An open label Phase 1 dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and MTD of the anti-mesothelin ADC anetumab ravtansine in subjects with advanced solid tumors." (NCT01439152)

Data are available from 147 subjects evaluated on this study, including: 10 dose escalation cohorts (45 subjects), two expansion cohorts in mesothelioma and ovarian cancer at a dose of 6.5 mg/kg every 3 weeks (32 subjects); two further expansion cohorts in mesothelioma and ovarian cancer at doses of 1.8 mg/kg weekly (35 subjects, but data from 1 individual was not available) and 2.2 mg/kg weekly (36 subjects).

One hundred nine subjects (74.1%) had treatment emergent adverse events (TEAEs) considered to be at least possibly related to the study drug. The most common TEAEs at least possibly related to anetumab ravtansine are presented in Table 11 by the number of subjects who reported an event in decreasing order.

A total of 16 subjects died within 30 days of the drug being stopped and none of these events were related to the study drug.

Table 11: Treatment-emergent adverse events at least possibly related to anetumab ravtansine, >5% by cohort (with separation of higher and lower dose-escalation cohorts)

Number of subjects with drug related TEAE							
MedDRA Preferred Term	**Escalation 1-8A (n=35)**	**Escalation 9 6.5 mg/kg Q3W (n=6)**	**Escalation 10 7.5 mg/kg Q3W (n=4)**	**Exp 6.5 mg/kg Q3W (n=32)**	**Exp 1.8 mg/kg QW (n=34)**	**Exp 2.2 mg/kg QW (n=36)**	**Total (n=147)**
All	29 (64.4%)	n/a	n/a	30 (93.8%)	26 (76.5%)	24 (66.7%)	109 (74.1%)
Nausea	8 (22.8%)	3 (50.0%)	2 (50.0%)	19 (59.4%)	10 (29.4%)	8 (22.2%)	50 (34.0%)
Fatigue	10 (28.6%)	2 (33.3%)	1 (25.0%)	16 (50.0%)	9 (26.5%)	11 (30.6%)	49 (33.3%)
Diarrhea	1 (2.9%)	3 (50.0%)	0	10 (31.3%)	6 (17.6%)	5 (13.9%)	25 (17.0%)
Vomiting	5 (14.3%)	3 (50.0%)	1 (25.0%)	9 (28.1%)	2 (5.9%)	4 (11.1%)	24 (16.3%)
Decreased appetite	4 (11.4%)	2 (33.3%)	0	10 (31.3%)	2 (5.9%)	3 (8.3%)	21 (14.3%)
AST increase	0	1 (16.7%)	2 (50.0%)	7 (21.9%)	5 (14.7%)	5 (13.9%)	20 (13.6%)

Number of subjects with drug related TEAE							
MedDRA Preferred Term	**Escalation 1-8A (n=35)**	**Escalation 9 6.5 mg/kg Q3W (n=6)**	**Escalation 10 7.5 mg/kg Q3W (n=4)**	**Exp 6.5 mg/kg Q3W (n=32)**	**Exp 1.8 mg/kg QW (n=34)**	**Exp 2.2 mg/kg QW (n=36)**	**Total (n=147)**
Neuropathy peripheral	3 (8.6%)	0	1 (25.0%)	9 (28.1%)	3 (8.8%)	3 (8.3%)	19 (12.9%)
ALT increase	1 (2.9%)	1 (16.7%)	1 (25.0%)	5 (15.6%)	2 (5.9%)	6 (16.7%)	16 (10.9%)
Vision blurred	0	0	2 (50.0%)	6 (18.8%)	2 (5.9%)	4 (11.1%)	14 (9.5%)
Platelet decrease	0	1 (16.7%)	1 (25.0%)	6 (18.8%)	2 (5.9%)	3 (8.3%)	13 (8.8%)
Alk phos increase	0	0	1 (25.0%)	4 (12.5%)	0	5 (13.9%)	10 (6.8%)
Lymphocyte decrease	2 (5.7%)	1 (16.7%)	0	2 (6.3%)	2 (5.9%)	1 (2.8%)	8 (5.4%)
Corneal disorder	0	0	2 (50.0%)	5 (15.6%)	0	0	7 (4.8%)
Dry eye	0	0	0	2 (6.3%)	2 (5.9%)	3 (8.3%)	7 (4.8%)
Asthenia	2 (5.7%)	0	0	5 (15.6%)	0	0	7 (4.8%)
Non cardiac chest pain	1 (2.9%)	0	1 (25.0%)	2 (6.3%)	1 (2.9%)	0	5 (3.4%)
Peripheral sensory neuropathy	0	0	0	1 (3.1%)	3 (8.8%)	1 (2.8%)	5 (3.4%)
Flushing	1 (2.9%)	1 (16.7%)	1 (25.0%)	1 (3.1%)	1 (2.9%)	0	5 (3.4%)
Dyspepsia	1 (2.9%)	1 (16.7%)	0	1 (3.1%)	2 (5.9%)	0	5 (3.4%)
Pyrexia	1 (2.9%)	0	1 (25.0%)	0	1 (2.9%)	2 (5.6%)	5 (3.4%)
Anemia	0	0	0	1 (3.1%)	3 (8.8%)	1 (2.8%)	5 (3.4%)
Hypothyroidism	0	0	0	0	2 (5.9%)	3 (8.3%)	5 (3.4%)
Lipase increase	0	0	1 (25.0%)	2 (6.3%)	1 (2.9%)	1 (2.8%)	5 (3.4%)
Rash	1 (2.9%)	0	0	1 (3.1%)	2 (5.9%)	0	4 (2.7%)
Chills	2 (5.7%)	0	1 (25.0%)	0	0	1 (2.8%)	4 (2.7%)

Number of subjects with drug related TEAE							
MedDRA Preferred Term	**Escalation 1-8A (n=35)**	**Escalation 9 6.5 mg/kg Q3W (n=6)**	**Escalation 10 7.5 mg/kg Q3W (n=4)**	**Exp 6.5 mg/kg Q3W (n=32)**	**Exp 1.8 mg/kg QW (n=34)**	**Exp 2.2 mg/kg QW (n=36)**	**Total (n=147)**
Corneal epithelial microcysts	0	0	0	2 (6.3%)	2 (5.9%)	3 (8.3%)	7 (4.8%)
Hyponatremia	1 (2.9%)	0	0	2 (6.3%)	0	1 (2.8%)	4 (2.7%)
Dyspnea	0	0	0	1 (3.1%)	2 (5.9%)	1 (2.8%)	4 (2.7%)
Arthralgia	0	0	0	2 (6.3%)	1 (2.9%)	1 (2.8%)	4 (2.7%)
Cholesterol increased	0	1 (16.7%)	0	0	0	0	1 (0.7%)
Exp = expansion cohort Cohorts 1 – 8A were dosed every 3 weeks. The doses were as follows: cohort 1 (n=3) - 0.15 mg/kg; cohort 2 (n=3) – 0.3 mg/kg; cohort 3 (n=4) - 0.6 mg/kg; cohort 4 (n=4) – 1.2 mg/kg; cohort 5 (n=4) – 2.4 mg/kg; cohort 6 (n=4) – 3.6 mg/kg, cohort 7 (n=4) – 4.5 mg/kg; cohorts 8+8A* (n=9) – 5.5 mg/kg * including cohort 8A (anetumab ravtansine produced from a new cell line)							

)

Describe all toxicities observed in patients and/or relevant animal studies

11.1.3 Formulation and preparation

The drug product is available as a lyophilizate. Each vial contains 62.5 mg of anetumab ravtansine; the amount available for administration, based on retractable volume of reconstituted solution, is 60 mg of anetumab ravtansine. It should be reconstituted in water for injection and diluted in 0.9% sodium chloride solution (normal saline) or dextrose 5% solution prior to administration as IV infusion.

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

The reconstitution and dilution of the anetumab ravtansine solution and the associated stability information is described in detail in a separate manual "Anetumab ravtansine storage and handling instructions".

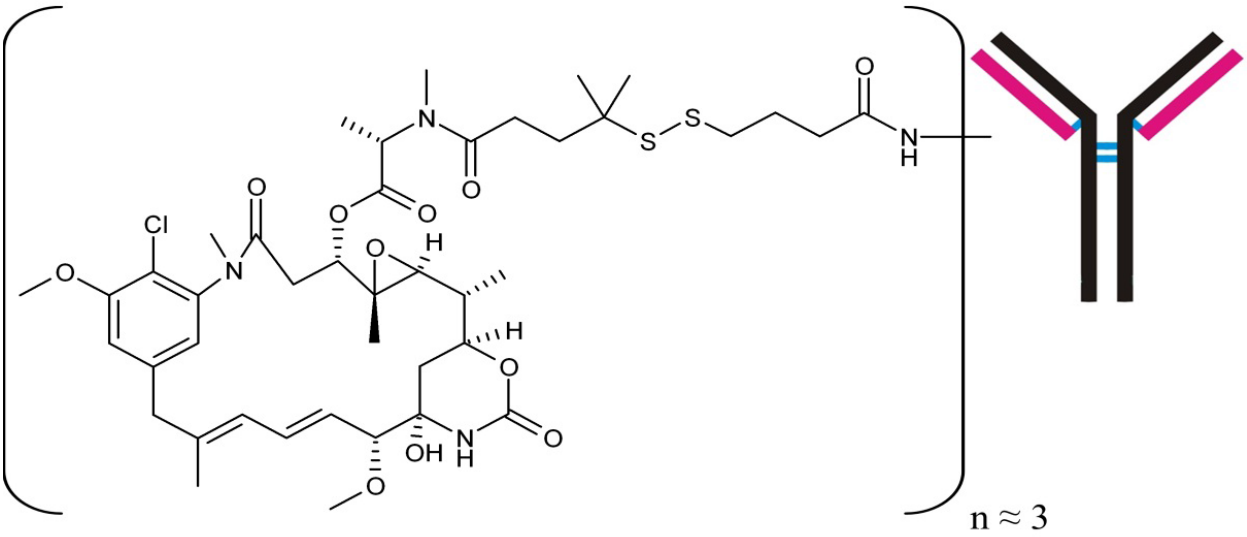
11.1.4 Administration procedures

Please see section 3.2.

11.1.5 Incompatibilities

None have been confirmed in a clinical study.

11.1.5.1 Chemical Structure



Anetumab ravtansine is an ADC consisting of a fully human IgG1 antibody (MF-T, BAY 86-1903) directed at the mesothelin antigen and conjugated to a synthetic cytotoxic anticancer agent, maytansine derivative (DM4, BAY 100-6640) as toxophore through an SPDB.

Based on the reference by Davis et al.[23], DM4 is a substrate of metabolizing enzymes CYP3A4, 3A5, and 2D6. Further the package insert of ado-trastuzumab emtansine, which also uses maytansine (referred to as DM1) conjugated to trastuzumab, indicates that the cytotoxic component is mainly metabolized by 3A4 and to a lesser extent by 3A5. Therefore, concomitant administration of strong inhibitors and inducers of CYP3A4 are prohibited in patients receiving anetumab ravtansine.

DM4-Me is a substrate of P-gp transporter and it is possible that medications that are potent inhibitors of P-gp transporter could alter the pharmacokinetic profile of DM4-Me in plasma.

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13 APPENDICES

13.1 APPENDIX A: NON SIGNIFICANT RISK REQUEST AND DETERMINATION FOR MESOTHELIN EXPRESSION TESTING

13.1.1 NSR Determination Request to FDA

24Oct2015

BAY 94-9343 / 17631, *An open label Phase Ib dose escalation study to evaluate the safety, tolerability, pharmacokinetics, immunogenicity and maximum tolerated dose of anetumab ravtansine in combination with pemetrexed 500 mg/m² and cisplatin 75 mg/m² in subjects with mesothelin-expressing predominantly epithelial mesothelioma or nonsquamous non-small-cell lung cancer*

Dear Insitutional Review Board Members,

The companion diagnostic device used in this research has been assessed by the Sponsor as Non-Significant Risk. The populations enrolled are receiving standard of care in addition to the investigational product can may be chemotherapy naïve or previously treated to be eligible for BAY 94-9343 / 17631:

(1) *Subjects must have histologically confirmed, unresectable, locally advanced or metastatic pleural or peritoneal predominantly (>50% of tumor component) epithelial mesothelioma or nonsquamous non-small-cell lung cancer (NSCLC).* ***Both chemotherapy-naive and previously treated subjects will be eligible; however, newly diagnosed NSCLC subjects eligible for FDA-approved therapies should have received the same before enrollment*** *(e.g. subjects with epidermal growth factor receptor [EGFR]-mutated and anaplastic lymphoma kinase [ALK]-translocated NSCLC should have received FDA-approved targeted therapies).*

Further, there is no significant risk incurred by the subjects to obtain the required specimens for mesothelin expression testing on archival tissue. Therefore, it is the opinion of the Sponsor that the use of this diagnostic device does not pose a serious risk to the health, safety, or welfare of a subject and therefore is considered Non-Significant Risk under 21 CFR 812.3(m). Further, the Sponsor has sought confirmation from the FDA regarding the assessment. FDA's response is pending, and can be provided upon receipt.

If you have any questions or concerns, please do not hesitate to contract our team.

Thank you for your thorough and expert review of this study.

Sincerely,

Katie Andrews

Katie Andrews
INC Research
Project Manager

13.1.2 NSR Designation from FDA

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

Pauline Shand,
Regulatory Affairs Manager, Companion Diagnostics
Ventana Medical Systems, Inc.
1910 E Innovation Park Drive,
Tucson, AZ 85755

Re: Q151839– Study Risk Determination for the use of the VENTANA PD-L1 MSLN (SP74) Immunohistochemistry Assay in the proposed study titled "An Open Label, Phase Ib Dose Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Immunogenicity and Maximum Tolerated Dose of Anetumab Ravtansine in Combination with Pemetrexed 500 Mg/M2 and Cisplatin 75 Mg/M2 in Subjects with Mesothelin-Expressing Predominantly Epithelial Mesothelioma or Nonsquamous Non-Small-Cell Lung Cancer."

Dated: Nov 12, 2015
Received: Nov 13, 2015

Dear Ms. Shand:

The Food and Drug Administration (FDA) has reviewed your submission, dated Nov 12, 2015, requesting a risk determination for the use of the Ventana MSLN (SP74) Immunohistochemistry Assay in the proposed study titled, "An Open Label Phase Ib Dose Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Immunogenicity and Maximum Tolerated Dose of Anetumab Ravtansine in Combination with Pemetrexed 500 mg/m^2 and Cisplatin 75 mg/m^2 in Subjects with Mesothelin-Expressing Predominantly Epithelial Mesothelioma or Nonsquamous Non-Small-Cell Lung Cancer."

FDA has determined that your proposed clinical investigation is a non-significant risk (NSR) device study because it does not meet the definition of a significant risk (SR) device under § 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812).

An IDE application is not required to be submitted to, or approved by, FDA for a NSR study. A NSR study is, however, subject to the abbreviated requirements described in § 812.2(b) of the IDE regulation. The abbreviated requirements stipulate that the sponsor of the investigation must label the device in accordance with § 812.5; obtain institutional review board approval of the investigation as a NSR study; ensure that each investigator obtains informed consent from each subject under the investigator's care; comply with the monitoring requirements of § 812.46; maintain records required under § 812.140(b)(4) and (5) and file the reports required under § 812.150(b)(1) through (3) and (5) through (10); and ensure that participating investigators maintain the records required by § 812.140(a)(3)(i) and file the reports required under § 812.150(a)(1), (2), (5) and (7).

Page 2 –Pauline Shand

Under the abbreviated IDE requirements, a sponsor must also comply with the prohibitions against promotion and other practices as identified in § 812.7. According to this section of the regulation, the sponsor of a NSR study, investigator, or any person acting for or on behalf of the sponsor or investigator is prohibited from promoting or test marketing the investigational device until after FDA has approved the device for commercial distribution; commercializing the device by charging a price greater than that necessary to recover the cost of manufacture, research, development, and handling; unduly prolonging the investigation; and representing the investigational device as being safe or effective for the purposes for which it is being investigated.

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. Please note that, if in the future you submit an application under sections 505, 515, or 520(m) of the FDCA (21 USC §§ 355, 360(e), or 360(j)(m)), or under section 351 of the PHS Act (21 U.S.C. § 262), or you submit a report under section 510(k) of the FDCA (21 USC § 360(k)), the application or submission must be accompanied by a certification that all applicable requirements of section 402(j) of the PHS Act (42 USC § 282(j)) have been met. Where available, such certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC § 282(j)(5)(B). Additional information regarding the certification is available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM164819.pdf . Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information on registering your clinical trial(s) is available at the Protocol Registration System website (http://prsinfo.clinicaltrials.gov/). If you have any questions, please contact Janaki Veeraraghavan at (240) 402-6634.

Sincerely yours,

Reena Philip, Ph.D.
Director
Division of Molecular Genetics and Pathology
Office of *In Vitro* Diagnostics and Radiological Health
Center for Devices and Radiological Health

13.2 APPENDIX B: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

13.3 APPENDIX C: CYP3A4 INHIBITORS AND INDUCERS

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

CYP3A4 = Cytochrome P450, family 3, subfamily A, polypeptide 4